

Embryo cryopreservation: the clinical outcome and couples' perspectives

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Declaration

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree or diploma of the university or other institute of higher learning, except where due acknowledgement has been made in the text.

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Abstract

Aim: Embryo freezing is a standard practice in most fertility units. According to the latest Human Fertilisation Embryology Authority data, 2,032 babies were born in 2010 from 10,548 cycles using frozen-thawed embryos in the UK. However, the practical benefit of embryo freezing in the National Health Service (NHS) context, and the psychological impact of this practice are unknown, and need to be reviewed in the light of increasing demand for NHS support for assisted conception. Therefore, this thesis investigates the answer to the question, “Should we be freezing embryos?” from two aspects: the influence on *in vitro* fertilization (IVF) success rates from embryo freezing and the decision-making process by which couples decide whether or not to freeze any surplus embryos.

Methods: Analysis of the cumulative pregnancy rate (CPR) following three cycles of IVF treatment including embryo freezing was performed using life table analysis. A qualitative interview study involving IVF couples was performed aiming to explore the personal and social factors that couples consider when deciding about embryo freezing.

Results: It was found that embryo freezing imparts a modest benefit of about 4% increase in the overall CPR.

The qualitative study showed that regardless of the practical benefits of freezing embryos and the ethical and other reservations that couples have about it, the vast majority of IVF couples wish to avail themselves of the opportunity to freeze any surplus embryos, and use every additional opportunity to maximize their chances to have a baby. The decision-making process was complex and nuanced, and was fully appreciated only on reflection.

Conclusion: Findings from this study will inform couples who face the difficult decisions about embryo freezing. Although this study indicates that more detailed information may not have influenced their decision, it provides the basis for further study comparing the influence of more targeted information on freezing decisions.

*Dedicated to the memory of my late grandfather,
Shri Pramod Chandra Goswami, who is my inspiration*

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List of Abbreviations

ART	Assisted reproductive technique
ASRM	American Society for Reproductive Medicine
BMI	Body mass index
CLBR	Cumulative live birth rate
CPR	Cumulative pregnancy rate
eSET	Elective Single Embryo Transfer
FET	Frozen embryo transfer
HFEA	Human Fertilisation Embryology Authority
HMG	Human menopausal gonadotropin
ICSI	Intra cytoplasmic sperm injection
IVF	<i>In vitro</i> fertilization
LBR	Live birth rate
LRM	Law on Reproductive Medicine
NFCL	Newcastle Fertility Centre at Life
OHSS	Ovarian hyper stimulation syndrome
PALS	Patient advice liaison service
PCT	Primary care trust
PEALS	Policy, Ethics and Life Sciences Research Centre
PrOH	1, 2-propanediol
RCT	Randomized Controlled Trial
RR	Relative risk

Chapter 1. Introduction

1.1 A Brief History of *In Vitro* Fertilization

Infertility treatment witnessed a revolution following the pioneering work of Robert Edwards and Patrick Steptoe, which led to the birth of the first *in vitro* fertilization (IVF) baby, Louise Joy Brown, in 1978 (Steptoe and Edwards, 1978). The technique they developed, which literally means “fertilization in glass”, gained popularity globally and resulted in the birth of three million babies worldwide (BioNews, 2006). Commonly, babies born by this technology are termed “test-tube babies”, as fertilization takes place in a Petri dish, using the gametes of the sub fertile couples. According to the latest figures published by the Human Fertilisation Embryology Authority (HFEA), 45,264 women had 57,652 IVF treatments, including intra cytoplasmic sperm injection (ICSI) cycles, in 2010 in the UK alone, and 170,000 babies have been born in the UK since 1991 using this technology (HFEA, 2012a).

1.2 *In Vitro* Fertilization

In IVF, the ovaries are hormonally stimulated to grow multiple follicles, as opposed to the unifollicular development in a natural cycle. The eggs are then retrieved under ultrasound guidance and mixed with the processed sperm of the partner, with the aim of achieving fertilization in an external controlled environment. However, not all follicles contain viable eggs, and not all the retrieved eggs fertilize to give good embryos. Therefore, maximizing the yield of good-quality oocytes is the aim in ovarian stimulation. The embryos are allowed to grow in an artificially controlled environment up to a certain stage, prior to being transferred into the uterus of the patient.

1.3 Regulation on the Number of Transferred Embryos

In 2001, the HFEA introduced a two-embryo transfer policy for women younger than 40 years, with a three-embryo transfer permitted in exceptional situations. In 2004, this policy was revised so that fertility units are permitted to transfer no more than two (three, if the age of the mother is 40 or above) embryos into the uterus of the patient, to reduce the chances of multiple pregnancy and associated risks (HFEA, 2012a). The 2013 National Institute for Health and Clinical Excellence (NICE) guidelines, advises consideration of single- or

double-embryo transfer, depending on the age of the woman, and IVF treatment rank, quality and developmental stage [cleavage (day 2/3) or blastocyst (day 5) stages] (NICE,2013). Again, there is international variation noted in this regard, as the American Society for Reproductive Medicine (ASRM) allows the maximum transfer of five cleavage-stage, or three blastocyst-stage, embryos in women in the 41–42 years age group (Practice Committee for American Society for Reproductive Medicine and the Practice Committee for Society for Reproductive Technology, 2009). This results in the creation of “surplus to immediate requirement” embryos, which are left over following the initial transfer. Nowadays, it is routine practice in most centres to freeze surplus good-quality embryos.

As per the recommendation of the HFEA (HFEA, 2012a), most fertility units are striving to lower their multiple pregnancy rates to less than 10%. With an aim to achieve this, eSET (elective single embryo transfer) policy for all suitable couples is becoming a significant practice in the U.K. However at the time of conducting this study, this HFEA regulation was not yet in place.

With increasing implementation of eSET, offering embryo cryopreservation for the rest of the good quality embryos becomes almost an imperative, not only to preserve the potential of the good quality surplus embryos, but also to optimise the cumulative pregnancy rates including the frozen treatments. A Cochrane database systematic review on the number of embryos to transfer following IVF/ICSI treatments, found that although there was lower pregnancy rates following elective single embryo transfer compared to double embryo transfer strategy in fresh IVF cycles, there was no statistically significant difference in cumulative live birth rate (CLBR) after a double embryo transfer (DET) , compared to that following a single embryo transfer (SET) followed by transfer of a single frozen thawed embryo (Pandian *et al*, 2009).

1.4 Current Assumptions on Why are Embryos Frozen?

The benefits of freezing good-quality surplus embryos include the replacement of stored embryos on several different occasions, and thereby the maximum use of a single IVF procedure (Trounson and Mohr, 1983). It also eliminates the need for repeat ovarian stimulation and egg collection procedures, and the associated risks, but still gives women another opportunity to have a baby.

Furthermore, it gives every good-quality embryo a chance to develop into a baby, rather than being discarded. However, only good-quality surplus embryos can be frozen, as poorer ones would not survive the stressful process of freezing and then thawing. On the other hand, there have been discussions about the possible drawbacks of embryo freezing, including ethical and safety concerns, the secure storage of embryos, and potential legal disputes, which are described in Chapter 5. Whilst the arguments in this paragraph are legitimate, they also smooth over the complex decision making by the couples involved and don't address the actual outcomes of freezing. Addressing these loopholes would be the aim of this thesis.

1.5 Cryopreservation

The freezing of animal embryos has been documented historically. The first pregnancy following the freezing and storage of a human eight-cell embryo for 4 months in liquid nitrogen was reported by Trounson and Mohr in 1983. However, that pregnancy unfortunately terminated at 24 weeks due to sepsis, following the premature rupture of the membranes (Trounson and Mohr, 1983). Since then, approximately 200,000 babies have been born by this technology (ASRM data). According to the HFEA data, there were 8,959 cycles using frozen-thawed embryos in 2008 in the U.K (HFEA, 2010a), which increased to 10,548 cycles in 2010, resulting in 2,032 live births (HFEA, 2012b). However, the cost-effectiveness and psychological impact of this practice are unknown. It is appropriate to review this major practice, particularly in light of increasing demand for National Health Service (NHS) support for assisted conception including embryo freezing, which is discussed later in Chapter 4. Thus, the perspective of clinicians and embryologists, as well as that of the patients, is relevant. NHS treatment buyers are also involved in the decisions from a cost-effectiveness perspective.

Therefore, this thesis entitled 'Embryo cryopreservation: the clinical outcome and couples' perspectives' tries to answer the research question "Should we be freezing embryos?" from two perspectives: (1) the influence on IVF success rates from embryo freezing and (2) the process by which couples decide whether or not to freeze any surplus embryos.

1.6 Cryobiology

The first concept of cell cryopreservation or “freezing of cells”, was proposed by Mazur in 1965 (Mazur, 1965).

Two basic techniques of cryopreservation are applied to embryos: the conventional slow freezing technique and the more contemporary method of “vitrification”.

1.6.1 Slow freezing technique

In this technique, human embryos are exposed to simple salt solutions with cryoprotectants such as 1,2-propanediol (PrOH) and sucrose, and the cells are rapidly cooled to a temperature below their melting point (usually -7°C). The container with the cells is then “seeded” to form ice crystals in the extracellular fluid (controlled formation of ice crystals).

The temperature drops to below -30°C with slow cooling, the cells become dehydrated and the osmolarity of the intracellular solution increases. The cells are then immersed in liquid nitrogen, and the intracellular cryoprotectants prevent intracellular ice crystal formation. During thawing, the cells are exposed to hypotonic solutions and rehydrated. If a cell “lyses” or disintegrates after thawing, the factors held responsible are the formation of intracellular ice crystals and detrimental osmotic effects (Stachecki and Cohen, 2004). Cryoprotective additives, such as phosphate buffered saline solution, PrOH or 9% glycerol are used to reduce cellular damage during freezing by reducing the tonicity by increasing the volume of the residual unfrozen phase (Elder and Dale, 2000).

1.6.2 Vitrification

The term “vitrification” means “achieving a glass-like state”. It was originally described in 1860, and then again by Luyet (1937). Subsequently, it was proposed in the mid-1980s by Rall and Fahy (1985) for freezing cells. In vitrification, cells are exposed to high concentrations of cryoprotectants for a brief period of time near room temperature, followed by rapid cooling to -30°C by immersion in liquid nitrogen. The cells are rapidly dehydrated and then quickly solidified before intracellular ice crystals can form (Stachecki and Cohen, 2004). The samples reach reduced temperature in a glass-like state, thus having the molecular structure of a viscous liquid, rather than a crystal.

This procedure is now gaining popularity as the alternative to the slow freezing method. It has an advantage over the previous technique as it prevents the formation of intracellular ice crystals and the resultant cellular damage. It is also a rapid method, and does not require a controlled-rate cooling apparatus. However, the concern is that the high level of cryoprotectants needed to achieve the procedure can be potentially toxic to cells (Elder and Dale, 2000).

1.6.3 Oocyte freezing

In view of the ethically contentious issue of creation and cryopreservation of surplus embryos, the question that naturally arises is: Why not freeze the surplus eggs instead? The first pregnancy from a frozen-thawed human oocyte was in 1986 (Chen, 1986). However, the procedure failed to gain popularity due to the low success rate and the fear of chromosomal abnormalities in the offspring, as shown in mouse experiments. Although the initial thaw survival of human eggs is 50–70%, it significantly decreases following further cell division. The average number of offspring per number of oocytes frozen is around 1–5% (Stachecki and Cohen, 2004).

Until recently, oocyte cryopreservation was considered experimental. However, the success from oocyte freezing has significantly improved over the last decade, and initial results regarding the safety of the process are reassuring. A recent guideline from the ASRM practice committee has recommended that this practice should no longer be considered experimental (ASRM, 2013). A large RCT (randomized controlled trial) (Cobo *et al.*, 2010) and a meta-analysis (Cobo and Diaz, 2011) also showed no significant differences in fertilization rates, implantation rates, and pregnancy rates per transfer between groups with cryopreserved oocytes, when compared with fresh oocytes. However, all this data need to be interpreted with caution, as the long term data of the clinical outcome from oocyte freezing would not be available until the off-springs born using this technique are at least middle aged.

One RCT compared pregnancy rates of slow freeze with vitrified supernumerary oocytes and showed that vitrification results in better oocyte survival, fertilization, and clinical pregnancy rates per thawed egg, in comparison to slow freeze (Smith *et al.*, 2010).

However, the ASRM practice committee (ASRM, 2013) does admit that the majority of the above data are limited to a good prognosis, young cohort of

patients with oocytes vitrified for a limited duration, and therefore it would be inappropriate to extrapolate this data to the general clinic population.

1.6.4 Safety of freezing

There is good evidence that babies from cryopreserved embryos are generally healthy and have better perinatal outcomes, compared to babies born from fresh embryos (Wang *et al.*, 2010). A recent meta-analysis confirmed better obstetric and perinatal outcomes for pregnancies where frozen embryos were used, including lower antepartum haemorrhages, reduced low birth weight and small-for-gestational-age babies, lower pre-term births and lower perinatal mortality, compared to those using fresh embryos (Maheshwari *et al.*, 2012).

Therefore, there is robust evidence that there are few concerns regarding the health of babies born by the technique of cryopreservation (Wennerholm *et al.*, 2009).

However, concerns have been raised about the potential risks of accidental destruction of embryos in the laboratory, risks related to the mislabelling of embryos or risks of viral contamination of embryos while in the freezer (Bankowski *et al.*, 2005).

1.7 Legal Aspects of Embryo Freezing

There is international and interstate variation in legislation and regulation regarding not only the freezing of embryos, but also the maximum duration of freezing (Hammarberg and Tinney, 2006). For example, embryo freezing was totally prohibited in Switzerland with the introduction of the Law on Reproductive Medicine (LRM) in 2001 (Haimes *et al.*, 2008). Italy has also banned embryo freezing and limits the number of embryos created for transfer to a maximum of three (Fineschi *et al.*, 2005; Robertson 2004). The statutory time limit for storing frozen embryos, and the legislation regarding frozen embryo disposal, also vary from country to country, and are discussed in Chapter 5

In the UK, fertility units need to fulfil the regulations laid down by the HFEA under routine licensing conditions for the freezing of embryos. HFEA guidelines prior to the freezing of embryos require valid consent and negative viral screening blood test results for both partners, which is now included in the routine tests done pre-IVF in most clinics. The HFEA does not set a standard protocol for cryopreservation criteria, though professionally accepted techniques

must be used. Embryos can initially be stored for a period of 5 years, which can be extended to a period of 10 years if the consent of both partners is valid. If the statutory period of 10 years is exceeded, the HFEA requires that the frozen embryos should be allowed to perish (HFEA, 2012a).

Local practice and funding determines each clinic's policy on the number of good-quality surplus embryos needed before any are frozen. The policy of the Newcastle Fertility Centre at Life (NFCL), where this study was conducted, is to offer embryo freezing if at least two or more suitable good-quality surplus embryos are available, following fresh embryo transfer. The rationale against freezing a single embryo is the high likelihood of it not surviving the freeze-thaw process, and hence the low success rate and the issue of the cost-effectiveness of freezing a single embryo.

With regards to NHS-funded treatment, the NICE guidelines (NICE, 2004) advise that frozen embryos be thawed and transferred prior to a fresh stimulation cycle, as this will minimize ovarian stimulation and egg collection, which carry risks and use more resources; this is usually also required by the funding for the treatment provided by the primary care trusts (PCTs).

1.8 National Health Service Attitude Towards *In Vitro* Fertilization and Funding for Embryo Freezing

We now have more than 25 years of experience in freezing embryos. NICE guidelines advise that three cycles of IVF treatment should be offered to women between 23 and 39 years of age, where indicated (NICE, 2004), and the new 2013 guideline recommends that women between 40 and 42 years of age who have tried to conceive naturally for 12 months without success should be offered one cycle of IVF treatment (NICE, 2013). The NHS provides funding for up to three cycles of IVF treatment, including any frozen cycles. Funding for the first year of embryo freezing and storage is also usually provided by the NHS. However, there is variation in the availability of NHS funding, depending on the individual PCT funding the treatment.

1.9 Practical Issues Related to Freezing, Including Success Rates and Cost-Effectiveness

Information regarding the practical aspects of embryo cryopreservation, such as frozen embryo thaw survival rates and the success rate from FET, is important

not only to inform couples faced with the decision of whether to freeze their embryos or not, but also from the perspectives of the NHS funders and service stakeholders, i.e. the clinics offering the service and the PCTs. From the latter's point of view, evaluation of the cost-effectiveness of the programme is also vital. It is also useful to identify the women who are likely to have embryos to freeze at an early point in their IVF treatment, so that the necessary information and support required to make the decision about embryo freezing can be directed at them well in advance.

1.9.1 Survival and transfer rates of thawed embryos

As discussed previously, freeze-thaw techniques are stressful for the embryos and their cells may not survive the impact. Frozen-thawed embryos are classed as "survived" based on morphological parameters, such as when the *zona pellucida* has not been damaged and when at least 50% of the initial number of blastomeres were still intact after thawing, i.e. they showed a smooth cell membrane and a clear cytoplasm without clumping (Van der Elst *et al.*, 1996). Similar parameters were used by De Jong *et al.* (2002). Post-thaw embryo survival figures have ranged from 25 to 77% (De Jong *et al.*, 2002; Emiliani *et al.*, 2003; Fauque *et al.*, 2010; Guerif *et al.*, 2009; Horne *et al.*, 1997; Jones *et al.*, 1997; Mandelbaum *et al.*, 1998; Tiitinen *et al.*, 2001; Toner *et al.*, 1991a; Toner *et al.*, 1991b; Van der Auwera *et al.*, 2002; Van der Elst *et al.*, 1996; Wang *et al.*, 1994). There was, however, no distinct trend of improvement noted with the passing of time, in the survival figures.

Generally, the post-thaw survival rates of the frozen pronuclear zygotes were better, as the delicate metaphase spindle, which is susceptible to temperature changes and freezing and thawing, is not yet present in that stage. Pronuclear zygote thaw survival rates ranged from 74.8% (Fugger *et al.*, 1991) to 80.4% (Senn *et al.*, 2000), 87% (Miller and Goldberg, 1995) and even up to more than 90% (Damario *et al.*, 2000). The survival rates of the early cleavage embryos ranged between 45.1% (Senn *et al.*, 2000) and 76.5% (Gabrielsen *et al.*, 2006). However, blastocyst survival figures have improved with time. Emiliani *et al.* (2003) reported a 27% survival rate, while Guerif *et al.* (2009) reported a 66% survival rate only 6 years later. In general, the thaw survival figures range from 60 to 80% in most fertility units in the UK, and this factor needs to be taken into account when considering the success rates from cryopreservation.

Statistics of transfer rates of thawed embryos were quoted in a few studies as follows: 41.3% by De Jong *et al.* (2002), a 70% replacement rate by Fauque *et al.* (2010) and 97.2% by Joshi *et al.* (2010).

1.9.2 Success rates

The success rate in terms of a live birth from a frozen-thaw cycle is lower than that of a fresh IVF cycle. According to the latest national data from 2009, the live birth rate (LBR) with a fresh IVF cycle is 25.2% per cycle started, whereas it drops to 18.1% per FET cycle started (HFEA, 2012b).

However, there is no standardized parameter of success of the outcome of embryo freezing in the overall treatment cycle. Cumulative pregnancy rates (CPRs), including pregnancies from the fresh and frozen cycles, have been variously represented in the literature. The numerous ways in which the CPR, and the potential biases, have been expressed, are described in Chapter 2. The highest contribution of cryopreserved surplus embryos in increasing the LBR has been quoted by Bergh *et al.* (1995) as 19%. Others have reported an added benefit to the overall CPR or cumulative live birth rate (CLBR) in the region of 2 to 8% (De Jong *et al.*, 2002 and Van der Elst, 1996: 2%; Wang *et al.*, 1994: 4%; Kahn *et al.*, 1993: 5.2%; and Mandelbaum, 1998: 8%). There are no national data from the UK illustrating the CPR including freezing, it is therefore important to analyse this.

Wang *et al.* (1994) estimated the CPR to be increased by 7% in the particular group of women who had embryos cryopreserved, and by 11% for those who returned for frozen-thawed embryo transfer cycles, above the CPR when considering the fresh cycles only. The analysis by this Australian group led by Wang illustrates the selective method of analysis used to project the efficiency of cryopreservation.

Interestingly, however, data regarding the proportion of the total number of generated embryos that were frozen was lacking in most studies. Fugger *et al.* (1991) reported that in 1988, 18.5% of all embryos were frozen, and the corresponding figure for 1989 was 32.1%. Jones *et al.* (1997) quoted similar figures of 27.7 and 32.3% in their two study groups, respectively.

1.9.3 Characteristics of women benefiting from embryo freezing

On reviewing the literature, there was a relationship between a successful pregnancy from embryo freezing and the woman's age, the number of oocytes retrieved following egg collection, the number of frozen embryos and the outcome of the fresh IVF cycle. However, there was no evidence available that tried to characterize the women likely to have embryos to freeze, which would potentially help in providing targeted information.

1.9.3.1 Does the age of the woman influence the benefit of freezing?

There is ample evidence in the relatively old, as well as the comparatively recent, literature of a declining trend in CPR and CLBR with the increasing age of the woman. Borini *et al.* (2008) quoted a CPR of 54% in the ≤ 34 years age group, which progressively declined to 50% in the 35–38 years group, 34% between 39 and 40 years, and plummeted to 26% at or above 41 years. A similar decline in CPR with age was noted by Battaglia *et al.* (2010) as follows: 76.7% at < 36 years, 67.5% at 36–39 years and 50% at > 39 years, and also by Ubaldi *et al.* (2004). The CLBR quoted by Damario *et al.* (2000) and Witsenburg *et al.* (2005) was similar at < 35 years, being 61.2% and 64.6% respectively, and then progressively declining to 18.5% at > 39 years and 31% in the 40–42 years age group.

Considering the success from the FET cycles, Wang *et al.* (2001), reported a significantly reduced chance of pregnancy in the cryo-thawed cycles in the ≥ 40 years group of women, compared to the < 40 years category. Pregnancy rates were 6.5% versus 11.6% in the thaw cycles ($p < 0.05$).

However, there was no evidence available regarding the age of women and the likelihood of their having embryos to freeze.

1.9.3.2 Do oocyte numbers influence the benefit of freezing?

Two studies demonstrated a positive correlation between the number of oocytes and the CPR. The CLBR per stimulation cycle was 28.3% when 6–10 oocytes were retrieved and 41.5% when > 10 were retrieved (Toner *et al.*, 1991a).

Wang *et al.* (1994) reported that in couples with more than 10 oocytes recovered in the fresh treatment cycle, the potential increase in CPR following fresh and frozen cycles was trebled. This could be partially explained by the increase in the number of cryopreserved embryos, along with the rise in the

number of pre-ovulatory oocytes. However, Emiliani *et al.* (2003) did not find any correlation between the number of harvested oocytes or the number of embryos, and the CPR following fresh and frozen cycles.

1.9.3.3 Does the number of cryopreserved embryos influence the benefit of freezing?

Senn *et al.* (2000) quoted increasing CLBRs after fresh and frozen-thawed embryo replacements, associated with a rise in the number of embryos frozen during the initial IVF cycle. This related to the freezing of pronuclear embryos, but the same persistent increase was not demonstrated with the early cleavage embryos.

A retrospective analysis (Prades *et al.*, 2009) showed that freezing single embryos was not beneficial to the CPR. None of the 106 thawed embryos in their series, which were frozen as single embryos, resulted in a pregnancy.

1.9.3.4 Outcome of the fresh IVF cycle

Wang *et al.* (1994) observed that women who had an ongoing pregnancy in the fresh cycle had a significantly higher chance of a further ongoing pregnancy in the thaw cycle, than those who did not (18.8 versus 10%, $p < 0.05$). Miscarriage and ectopic pregnancies, however, did not influence the chances of successful outcome in FET. This finding was confirmed in a further study by the same group of researchers in 2001 (Wang *et al.*, 2001). Similar findings were made by Gabrielsen *et al.* (2006) and Toner *et al.* (1991b); the latter concluded that pregnancy rates were 50% higher in cryo-thaw cycles, after fresh IVF cycles having clinical or ongoing pregnancies.

1.9.4 Cost-effectiveness

There are claims that embryo cryopreservation lowers the cost per live birth to between 25 and 45% of the cost compared to a fresh IVF cycle (Bankowski *et al.*, 2005). Bearing in mind the lower success rate of a frozen cycle, it is possible that embryo freezing actually gives rise to more cycles of treatment, as queried by Haimes and Taylor (2011). In this context, it is important to take into account not only the cost of the number of frozen cycles, but also the cost of freezing and storing the embryos, and compare it with the cost incurred in having another fresh cycle instead of multiple frozen transfers.

Therefore, the relevant question is whether freezing embryos actually saves money for the clinic or not, and if the practice is economically viable.

1.10 Ethical Issues Related to Embryo Freezing

It is important to have background knowledge of the ethical issues related to embryo freezing, and the evidence of couple's views about these issues, as they could potentially influence the decisions that couples make while deciding about embryo freezing. Couples' views are investigated and discussed in detail in Part 2 of this thesis. There are many discussions about whether there are distinctions between the terms 'moral' and 'ethical', and if so, what these might be, but the author of this thesis has used the terms interchangeably.

Embryo freezing has always been a contentious issue and the focus of debate is the moral and social status of the entity, the "embryo". An opposing view related to embryo freezing follows the belief that life begins at conception (Deckers, 2007). Therefore, to some individuals at least, freezing an embryo is "suspending human life" (Hounshell and Chetkowski, 1996), whereas others perceive embryo freezing as no different from freezing any "biological tissue", e.g. freezing eggs. For the latter group, freezing an embryo is equivalent to freezing an "inanimate tissue" that has the potential to become a child only when exposed to a certain environment (De Lacey, 2007b). An embryo, in their opinion, cannot be given the status of an individual as it cannot think, act or communicate (Deckers, 2007). Stem cell scientists add additional dimension to this view by arguing that frozen embryos are "potential sources of stem cells" (Lyerly *et al.*, 2006).

There is evidence that the decision-making involved in disposing of the frozen embryos is stressful and emotionally fraught (De Lacey, 2007b; Nachtigall *et al.*, 2005). It is the "owners" of the frozen embryos who are required to make the difficult decision of whether to thaw and transfer their surplus embryos, or discard or donate them to other couples or to research. Thus, the question "Who should be taking responsibility for the decision of whether to freeze embryos?" arises: should it be the clinicians, the patients, the politicians who formulate policies or regulatory bodies like the HFEA?

Other issues raising concern globally, are the growing number of frozen embryos in storage, many of which are eventually abandoned by their owners and which take up laboratory resources and time (Bankowski *et al.*, 2005; Lyerly

et al., 2006; Newton *et al.*, 2007), and the legal disputes regarding their ownership (De Lacey, 2007b). These aspects are discussed in detail in Chapter 5.

1.11 What Do We Know About Patients' Attitudes Towards Embryo Freezing?

Qualitative research has demonstrated that patients can have conflicting views regarding their frozen embryos. Some perceive their frozen embryos as no different from “virtual children whose development was suspended” or as their “babies” (De Lacey, 2005; De Lacey, 2007a; Haimes *et al.*, 2008; Nachtigall *et al.*, 2005; Parry, 2006; Söderström-Anttila *et al.*, 2001; Svanberg *et al.*, 2001; Svendsen and Koch, 2008). To many individuals, frozen embryos are siblings to their existing children (Nachtigall *et al.*, 2005), whereas others perceive the frozen embryos as “inanimate tissue”, “a bunch of cells” (Fuscaldo *et al.*, 2007) or even “seeds” (De Lacey, 2007a), with the potential to become a child. Most of this research relates to the attitude of patients whose embryos have already been frozen. Little is known about their decision-making process at the time of freezing the embryos, which is important, as the way couples visualize embryos could be very different then; hence, further research is needed in this context.

There is suggestion that the driving force behind deciding to freeze embryos for some couples is “future psychological insurance”, as the reproductive potential of the embryo can be preserved, as well as “genetic insurance”, in terms of any potential medical benefit to their existing children in the future (Nachtigall *et al.*, 2005).

However, such perception has mostly emerged from the theoretical discussion and debates in the literature, and some of the evidence is based on survey-type studies as opposed to qualitative research data (the scarce evidence that is available about decision-making regarding embryo freezing is further discussed in Chapter 5 of this thesis).

Therefore, there is a need to explore this issue by asking patients about their experiences and opinions about the decision-making process involved in freezing their surplus embryos.

1.12 Chapter Conclusion

There are potential overestimations in the claimed benefits of embryo freezing, as evidenced by the diverse methods used and the selective nature of analyses of the success of embryo freezing. However, vital questions linked to the cryopreservation programme remain unanswered in most of the studies. There is limited information available of the percentage of egg retrieval cycles or the proportion of women having IVF who have embryos to freeze. Realistically, the benefit of embryo freezing is limited to this group alone, although the benefits are often extrapolated to the general clinical population. We also know little about the usage rates of frozen embryos, such as how many couples return for cryo-thaw cycles for a fresh or sibling pregnancy. These data would give a better understanding of the efficiency and cost-effectiveness of the embryo freezing programme, especially in view of the increasing demand for NHS support for assisted conception including embryo freezing.

Although past studies have attempted to identify the factors related to a higher CPR, there is no evidence in the literature identifying the characteristics of women who would have embryos to freeze. It is important to try to identify the cohort of couples likely to have frozen embryos so that appropriate advice can be targeted at them. They are the ones who will need to make the complex decision of whether to freeze or not to freeze their surplus embryos, and they may also be faced with the difficult decision of how to dispose of their frozen embryos in the future.

From the preceding discussion, it has been identified that information regarding two key areas needs to be given to couples, to help them make informed decision about embryo freezing. First, there are the practical issues of embryo freezing, including the benefits and success rates, and second, there is the ethical aspect of embryo freezing.

Therefore, we next need to revisit the practice of embryo cryopreservation to assess the benefit in terms of LBR in the general patient population from the point of view of the clinicians and NHS providers who provide the funding for the IVF treatment. We also need to understand the patients' perspective, in terms of their expectations from embryo freezing and their decision-making process in choosing whether to freeze or not to freeze. This is a unique clinical scenario,

where the moral status of the pre-implantation embryo pervades all the decisions made.

It is hoped that analysing the practice of embryo preservation in light of these findings may potentially improve local or national policies and the practice of embryo freezing.

1.13 Aims and Objectives

The aim of this thesis is to find an answer to the key question “Should we be freezing embryos?”

This is a normative research question which can nevertheless be explored empirically by approaching it from two directions. First, by understanding the clinical and scientific procedures and therefore, assessing the influence of embryo freezing on the success rates of IVF treatment. Second, by exploring couples’ views, attitudes and experiences, areas which are best approached through qualitative, interpretivist techniques.

So, the research question is explored from the following two angles:

- How does embryo freezing influence the CPR?
- What are the personal and social factors that patients consider when deciding about freezing embryos?

Exploring the answer to the first question will enable us to decide whether the clinical effectiveness of the embryo freezing process could determine if we should be freezing embryos. Exploring the answer to the second question would tell us whether embryo freezing is beneficial to couples, from their own point of view. Put together, these two sets of data will allow us to address the normative question of ‘should we be freezing embryos?’ Admittedly, by no means this is not a complete approach, as there might be other aspects to address, importantly, the socio-economic aspect of embryo freezing which have not been explored in this thesis. Nevertheless, this is a start to exploring this question, and provides valuable insight.

Therefore, this thesis is broadly divided into two parts. In Part 1, the practical aspects of embryo freezing are discussed, thereby exploring the answer to the first research question. In Part 2, the perspectives of the couples faced with

deciding whether or not to freeze embryos are examined using qualitative interviews, thereby exploring the answer to the second research question. Part 3 is the final discussion following the findings of the two parts.

Part 1: Practical Aspects of Embryo Freezing

In this section, the practical aspects of embryo freezing are explored. It is important to investigate the incidence of embryo freezing in the IVF patient population and the likelihood of the frozen embryo becoming a baby; it is also important to explore the fate of all frozen embryos, and the benefit of embryo freezing to the overall CPR. These are important issues couples need to be aware of when faced with the decision of whether or not to freeze their surplus embryos.

Chapter 2. Statistical Review of Cumulative Pregnancy Rates Following Embryo Freezing

2.1 Introduction

In this chapter, the literature is examined to analyse and critically evaluate how the success rates of IVF treatment, including embryo freezing, have been presented. Before evaluating the outcome of the embryo freezing programme carried out at the NFCL, where this study was conducted, it is important to assess the existing data on CPRs, including FET cycle outcomes.

The success rate from embryo freezing is generally presented as the CPR or CLBR following the fresh oocyte retrieval cycle, together with that following the FET cycles, to achieve the couple's first pregnancy or live birth (Fauque *et al.*, 2010).

There has been considerable debate regarding the best success parameter for an IVF programme, and the CPR has been variously expressed in the literature as follows:

- Cumulative clinical pregnancy rate per stimulation or oocyte retrieval cycle (Fauque *et al.*, 2010; Senn *et al.*, 2000; Veleva *et al.*, 2009);
- Cumulative on-going pregnancy rate per egg retrieval cycle (De Jong *et al.*, 2002);
- CPR per embryo transfer (Rienzi *et al.*, 2002);
- CLBR per cycle, considering only the ones with frozen embryos (Battaglia *et al.*, 2010; Fugger *et al.*, 1988; Jones *et al.*, 1997);
- CPR per couple (Bergh *et al.*, 1995; Chambers *et al.*, 2010);
- Kahn *et al.* (1993) expressed their success rates following embryo freezing as total LBR per oocyte retrieval.

2.1.1 Definitions

Clinical pregnancy was described as the presence of a gestational sac and fetus with cardiac activity at 7 weeks following transvaginal ultrasound (Senn *et al.*, 2000).

On-going pregnancy was defined as positive intrauterine fetal heart activity observed by means of a transvaginal scan 10 weeks after embryo transfer (De Jong *et al.*, 2002).

Pregnancy rates following fresh and frozen-thaw IVF cycles have also been reported as a cryoaugmented LBR. The augmented LBR was defined as the number of live births generated by both fresh and thawed embryos over the number of fresh transfer cycles (Horne *et al.*, 1997).

In a debate published in the *Human Reproduction* journal in 2004, Pinborg *et al.* (2004) suggested that the most relevant standard of success in IVF with cryopreservation of embryos is the cumulative delivery rate per aspiration, which is the delivery rate that combines fresh and FETs, and is the optimal rate to report.

In this literature review, the CPR following fresh and frozen cycles of IVF is reviewed, and the different statistical methodology adopted is analysed.

2.2 Objectives

These entailed finding the answers to the two following questions:

- What are the methods used to assess the CPR or CLBR?
- How is the influence of cryopreservation of embryos on pregnancy or LBR presented in the literature?

2.3 Methods

A search of the online databases PubMed (www.ncbi.nlm.nih.gov/pubmed/), Medline – Ovid and Embase (www.embase.com/), using the keywords and MeSH terms “CPRs”, “CPRs and frozen IVF”, “cryopreservation and pregnancy rates”, was performed. The search was confined to articles written in English, but with no date limitations. Relevant bibliographies of the identified studies were also reviewed.

2.3.1 Search criteria

2.3.1.1 Studies

Randomized controlled trials, prospective observational studies, longitudinal cohort studies and retrospective studies were searched for.

2.3.1.2 Participants

General population of the IVF patients, or a selected cohort of patients included in the studies was identified.

2.3.1.3 Types of intervention

Studies where embryo freezing was offered following egg retrieval, either at the pronuclear, early cleavage or blastocyst stage, were initially included.

2.3.1.4 Outcome measures

Studies quoting success rates following fresh and FET cycles, reported either as CPR or CLBR, were initially included.

2.3.1.5 Exclusion criteria

Studies which reported the outcomes following elective single embryo transfers were excluded, as they constitute a specific category of patients with good prognosis.

2.3.2 Data analysis

From the studies identified following the initial search, the following data analysis was performed.

2.3.2.1 Baseline characteristics of the group studied

Studies that included the general patient population or a selected cohort of patients with the specified baseline characteristics, such as women in a particular age group or women with good prognostic factors, were identified.

2.3.2.2 Methodological characteristics of the trial

The following were noted: whether the analysis was time-limited, or over a specified number of cycles; whether the CPR or CLBR accounted for the first

pregnancies or live births only; or whether siblings were also included in the analysis.

2.3.2.3 Outcome measures

The CPRs or CLBRs following fresh and frozen cycles were noted.

2.3.2.4 Analysis of the statistical methods used in the studies

Analysis of the statistical methods used to assess the CPR or CLBR was performed.

2.4 Results

The following 29 studies were identified and included:

- **Randomized controlled trials:** Emiliani *et al.*, 2003; Horne *et al.*, 1997; Jones *et al.*, 1997; Martikainen *et al.*, 2001; Rienzi *et al.*, 2002; Senn *et al.*, 2000; Van der Auwera *et al.*, 2002.
- **Prospective observational studies:** Bergh *et al.*, 1995; De Jong *et al.*, 2002; Fauque *et al.*, 2010; Fugger *et al.*, 1988; Fugger *et al.*, 1991; Gnoth *et al.*, 2011; Kahn *et al.*, 1993; Le Lannou *et al.*, 2006; Lundin and Bergh, 2007; Ubaldi *et al.*, 2004.
- **Retrospective studies:** Battaglia *et al.*, 2010; Chambers *et al.*, 2010; Criniti *et al.*, 2005; Damario *et al.*, 2000; Kovacs *et al.*, 2001; Mandelbaum *et al.*, 1998; Olivius *et al.*, 2002; Stolwijk *et al.*, 2000; Van der Elst *et al.*, 1996; Van Montfoort *et al.*, 2005; Veleva *et al.*, 2009; Witsenburg *et al.*, 2005.

2.4.1 Participants

Studies considering a general category of patients attending the clinics for treatment, with no specifications, are included.

2.4.2 Types of intervention

From reviewing the 29 studies, the methodology for assessing the CPR or CLBR was broadly categorized into three groups:

- Time-limited studies where the CPR or CLBR was assessed for a specified time period and which considered the outcome from fresh and frozen cycles

were included. Ten studies were identified in this group: Damario *et al.*, 2000; Fugger *et al.*, 1991; Kahn *et al.*, 1993; Mandelbaum *et al.*, 1998; Martikainen *et al.*, 2001; Senn *et al.*, 2000; Ubaldi *et al.*, 2004; Van der Auwera *et al.*, 2002; Van der Elst *et al.*, 1996; Veleva *et al.*, 2009.

- Analysis following a single stimulation cycle: Here, the CPR or CLBR was calculated considering the outcome following a single stimulation cycle and the FET cycles, using the frozen embryos generated from that fresh cycle. Ten studies were identified in this category: Battaglia *et al.*, 2010; Chambers *et al.*, 2010; Criniti *et al.*, 2005; Emiliani *et al.*, 2003; Fauque *et al.*, 2010; Fugger *et al.*, 1988; Horne *et al.*, 1997; Jones *et al.*, 1997; Le Lannou *et al.*, 2006; Rienzi *et al.*, 2002.
- CPR or CLBR calculated over multiple cycles: In this third category, the CPR or CLBR was calculated following a specified number of egg retrieval cycles. The pregnancies or live births resulting from the fresh and frozen embryos derived from that cycle were assigned to the same cycle. Nine studies reported the cumulative outcome following multiple cycles: Bergh *et al.*, 1995; De Jong *et al.*, 2002; Gnoth *et al.*, 2011; Kovacs *et al.*, 2001; Lundin and Bergh, 2007; Olivius *et al.*, 2002; Stolwijk *et al.*, 2000; Van Montfoort *et al.*, 2005; Witsenburg *et al.*, 2005.

2.4.3 Outcome measures

The studies included are the ones which have analysed the CPR or CLBR, taking into account the couple's first clinical pregnancy or live birth only.

2.4.4 Final inclusion criteria

The NHS offers up to three funded IVF treatments with embryo freezing. The aim of this research was to evaluate the outcome evidence following three IVF or ICSI treatments along with the FET cycle outcomes in an unselected population, as is offered by the NHS. Therefore, those studies reporting the CPR or CLBR following three cycles including embryo freezing, were finally included for analysis. Out of the nine studies reporting a success after multiple IVF or ICSI treatments, eight discussed the outcome following three treatments and were thus considered, excepting the one by Lundin and Bergh (2007), which discussed the outcome following two treatments only.

2.4.5 Final exclusion criteria

These were:

- Any study which selected good-prognosis patients only, was excluded. One study (Van Montfoort *et al.*, 2005) consisted only of women younger than 38 years and was thus excluded from the final analysis.
- Any study that included sibling pregnancies in the CPR, like the Gnoth *et al.* (2011) study, which reported the success rates following the inclusion of sibling pregnancies, was excluded.

2.4.6 Results from the studies finally included

Following the final exclusion criteria, six studies were identified as reporting the CPR or CLBR following three IVF or ICSI treatments, including embryo freezing outcome, in the general, unselected population, and taking the couple's first clinical pregnancy or live birth into account. The results are summarized in the following tables.

Table 2.1 represents the CPR in the three studies as demonstrated, presenting the CPR following three treatments including embryo freezing. The mean CPR was 45.7 (SD 2.01). Table 2.2 represents the CLBR in the three studies as demonstrated, presenting the CLBR following three treatments including embryo freezing. The mean CLBR was 55.43 (SD 6.83).

Study	Country	Study type	Sample size	Aim of study	CPR fresh (%)	CPR fresh + frozen (%)
Stolwijk, 2000	Netherlands	Retrospective	1,315	Estimate cumulative probability of pregnancy according to age, subfertility diagnosis		45.50
Kovacs, 2001	Australia	Retrospective	4,225	To assess probability of conception in IVF programme		47.8
De Jong, 2002	Netherlands	Prospective observational	1,251	To calculate the added benefit of embryo freezing on CPR	42.5	43.8

Table 2.1 Cumulative pregnancy rate (CPR) following three IVF/ICSI treatments with embryo freezing. CPR fresh (%) represents the CPR following three fresh IVF/ICSI treatments. CPR fresh + frozen (%) represents the CPR following three treatments including embryo freezing. ICSI: intra cytoplasmic sperm injection; IVF: *in vitro* fertilization. All these studies calculated CPR by Life Table Analysis.

Study	Country	Study type	Sample size	Aim of study	CLBR fresh (%)	CLBR fresh + frozen (%)
Bergh, 1995	Sweden	Prospective cohort	395	Evaluate success rate in Swedish IVF	40.5	50
Olivius, 2002	Sweden	Retrospective observational	974	Evaluate success rate in Swedish IVF		63.1
Witsenburg, 2005	Netherlands	Retrospective cohort study	750	To assess CLBR in cohorts of patients having IVF and ICSI		53.2

Table 2.2 Cumulative live birth rate (CLBR) following three IVF/ICSI treatments with embryo freezing. CLBR fresh (%) represents the CLBR following three fresh IVF/ICSI treatments. CLBR fresh + frozen (%) represents the CLBR following three treatments including embryo freezing. ICSI: intra cytoplasmic sperm injection; IVF: *in vitro* fertilization. The studies by Bergh et al and Witsenburg et al calculated CLBR by summation of the live births from fresh and frozen treatments per couples. Olivius et al used Kaplan Meyer method (survival analysis) to analyse CLBR.

It seems strange that the mean CLBR is higher than the mean CPR following the analyses of the evidence. The possible explanation for this discrepancy is discussed in section 2.5 (Discussion) of this chapter.

2.4.7 Review of the statistical methodology used to calculate the cumulative pregnancy or live birth rate in all the studies

The methodology used to calculate the CPR in the 29 studies reporting a successful outcome including embryo freezing, can be summarized as follows.

2.4.7.1 Cumulative pregnancy or live birth rate per oocyte retrieval cycle

The CPR or CLBR per oocyte retrieval cycle was calculated once the number of pregnancies or live births following fresh and FET cycles within the specified time or cycle interval were added up. Analysing CPR/CLBR per oocyte retrieval cycle is a commonly used standard representation of success rates from IVF treatment. However, the disadvantage is that it constricts the denominator used in calculation by not taking into account the number of cancelled cycles due to poor ovarian response, which do not reach oocyte retrieval. Thus it can potentially overestimate the success rate, when extrapolated to the general population.

Also, not all the studies took into account the first clinical pregnancy or live birth as the end point of analysis, when calculating the CPR/CLBR. The following seven studies considered the couple's first clinical pregnancy or live birth as the end point: Criniti *et al.*, 2005; Damario *et al.*, 2000; Fauque *et al.*, 2010; Kahn *et al.*, 1993; Le Lannou *et al.*, 2006; Van der Auwera *et al.*, 2002; Van Montfoort *et al.*, 2005.

In the following six studies, sibling pregnancies were likely included in the calculations: Emiliani *et al.*, 2003; Fugger *et al.*, 1991; Mandelbaum *et al.*, 1998; Martikainen *et al.*, 2001; Rienzi *et al.*, 2002; Senn *et al.*, 2000).

2.4.7.2 Cumulative pregnancy or live birth rate per oocyte retrieval cycle with frozen embryos

The calculation in this group was similar to that of the previous group, but the denominator consisted of the egg retrieval cycles yielding frozen embryos only (Battaglia *et al.*, 2010; Fugger *et al.*, 1988; Horne *et al.*, 1997; Jones *et al.*,

1997; Le Lannou *et al.*, 2006; Van der Elst *et al.*, 1996). The downside with this method of analysis is that it represents the success rates of the selected cohort who reach oocyte retrieval, and subsequently have suitable embryos cryopreserved. Analysing the CPR/CLBR for this group, and extrapolating their success rates to the general population can grossly overestimate the CPR/CLBR.

2.4.7.3 Cumulative pregnancy or live birth rates per embryo transfer

The outcomes of the fresh and FET cycles in the specified time or cycle interval were calculated per embryo transferred, to derive the cumulative rates (Rienzi *et al.*, 2002). Calculation of CPR/CLBR per embryo transfer is a commonly used practice, but excludes the patients with poor ovarian response, as well the ones with failed fertilisation and poor quality embryos with no suitable embryos to transfer. Thus, their success rates could be potential overestimation, when extended to the general population.

2.4.7.4 Cumulative pregnancy or live birth rate per couple

The CPR/CLBR was calculated as the per couple sum of the fresh and frozen pregnancies or live births in the given time or cycle interval, taking into account all the couples undergoing the initial stimulation cycle. The following five studies used this method: (Bergh *et al.*, 1995; Chambers *et al.*, 2010; Lundin and Bergh, 2007; Ubaldi *et al.*, 2004; Veleva *et al.*, 2009). Witsenburg *et al.* (2005) presented their data in a similar way, though categorizing them into yearly cohorts, and reported the CPR. The advantage of considering the success rates per couple ensures that all the couples starting treatment are considered, thereby minimising the risk of overestimation of success rates that happens when calculating the CPR/CLBR for a good prognosis cohort.

2.4.7.5 Cumulative pregnancy or live birth rate per couple returning for a frozen-thaw cycle

This was obtained by adding up the number of pregnancies in fresh and frozen cycles, with the number of couples returning for a FET cycle for the first or sibling pregnancy included in the denominator (Kahn *et al.*, 1993; Wang *et al.*, 1994). This method of analysis however limits the calculation of success rates to the couples returning for frozen treatments, thereby disregarding the rest of

the population. Such results, when extrapolated to the population at large, can grossly over estimate the CPR/CLBR.

2.4.7.6 Calculation of cumulative pregnancy or live birth rate by survival analysis (life table analysis)

Survival analysis methods, such as the life table method, were originally devised to assess light bulb failure times, and were subsequently extended clinically to analyse death rates from cancer, so that a survival estimate could be generated (Berkson and Gage, 1950). The advantage is that this method does not need the subjects to enter the study simultaneously; it can also use the data from subjects who have dropped out or who are lost to follow-up, in calculating cumulative success rates over multiple stimulation cycles (Cox and Oakes 1984; Cutler and Ederer, 1958; Katayama, 1975).

In life table analysis, the cumulative “not pregnant” proportion is initially calculated by multiplying the proportion not pregnant in the initial cycle (frozen embryos derived from a fresh cycle are assigned to the same cycle) or time interval, by the proportion not pregnant in the subsequent cycle or time interval. The cumulative “pregnant” proportion is obtained by deducting the cumulative “not pregnant” proportion from 1 (Cooke *et al.*, 1981).

The following four studies calculated the CPR/CLBR using life table analysis: De Jong *et al.*, 2002; Horne *et al.*, 1997; Kovacs *et al.*, 2001; and Olivius *et al.*, 2002. However, Horne *et al.* (1997) included only the ones who had embryos frozen following fresh transfers in the initial patient population.

Gnoth *et al.* (2011) calculated the CPR and CLBR using the Kaplan–Meier method of survival analysis per treatment cycle and per embryo transferred. The analysis assumed that the dropout couples would have had the same chance of success as those who continued treatment.

2.4.7.7 Projected cryoaugmented cumulative pregnancy rate

The projected (final) cryoaugmented pregnancy rate includes pregnancies among as yet unthawed embryos, on the assumption that the pregnancy rate in the unthawed embryos will be the same as it is in the thawed material (Jones *et al.*, 1997). However, this approach does not appear to be realistic and representative of the actual CPR/CLBR, as it ignores the fact that a reasonable number of frozen embryos are eventually abandoned, or donated to research,

as discussed in Chapter 5. Similar data with different terminology were presented as follows: the anticipated CLBR was the augmented LBR plus the number of live births expected from the potential transfer of embryos still in storage over the number of fresh transfer cycles (Horne *et al.*, 1997).

The expected LBR was calculated by extrapolating the data from the observed delivery rate and the number of cryopreserved embryos still in storage (Senn *et al.*, 2000).

Seven studies calculated the projected CPR or CLBR, which ranged between 24 and 75% (De Jong *et al.*, 2002; Horne *et al.*, 1997; Jones *et al.*, 1997; Miller and Goldberg, 1995; Toner *et al.*, 1991a; Van der Auwera *et al.*, 2002; Wang *et al.*, 1994).

2.4.8 Areas of potential bias

Ten studies calculated the CPR /CLBR in a selected group of patients, such as those with good prognostic indicators (e.g. younger age group), and projected those rates to the general population (Chambers *et al.*, 2010; Criniti *et al.*, 2005; Emiliani *et al.*, 2003; Fauque *et al.*, 2010; Le Lannou *et al.*, 2006; Martikainen *et al.*, 2001; Rienzi *et al.*, 2002; Ubaldi *et al.*, 2004; Van Montfoort *et al.*, 2005; Veleva *et al.*, 2009).

Eleven studies calculated the CPR /CLBR regardless of the couple's first clinical pregnancy or live birth, i.e. they included sibling pregnancies into their calculations (Emiliani *et al.*, 2003; Fugger *et al.*, 1988; Fugger *et al.*, 1991; Gnoth *et al.*, 2011; Mandelbaum *et al.*, 1998; Martikainen *et al.*, 2001; Rienzi *et al.*, 2002; Senn *et al.*, 2000; Ubaldi *et al.*, 2004; Van der Elst *et al.*, 1996; Veleva *et al.*, 2009).

Six studies reported the CPR or CLBR per oocyte retrieval cycle, considering those which only yielded frozen embryos, thereby disregarding the rest of the cycles, though the result was extrapolated to the entire population (Battaglia *et al.*, 2010; Fugger *et al.*, 1988; Horne *et al.*, 1997; Jones *et al.*, 1997; Le Lannou *et al.*, 2006; Van der Elst *et al.*, 1996).

2.5 Discussion

Frozen-thawed embryos account for about 30-40% of all IVF deliveries, while reducing the requirement for pharmacological and surgical interventions (Borini *et al.*, 2008). Recent figures from the HFEA quote that 18.9% of the IVF

treatments in 2010 were frozen treatments (HFEA, 2012b). Reviewing the literature regarding CPRs including embryo freezing is important not only to assess the impact of embryo freezing, but also to evaluate the success rates of individual clinics in the light of the review.

Although there is no standardized method of presenting the CPR and CLBR, different authorities have used diverse methods to project their cumulative success rates. That explains the wide range of figures for the CPR or CLBR. The actual values of the CPR with embryo freezing presented in the literature, have gradually improved over time, possibly reflecting improvement in the freeze-thaw techniques and laboratory infrastructure. Fugger *et al.* (1988) quoted a CPR of 28.3% in 1988, whereas a more recent paper by Fauque *et al.* (2010) quoted a figure of 64.3%. However, it is important to note that the diversity of the methodology employed to calculate the CPR, related to the variable time frames used, the variable number of cycles included and the lack of consistency in the statistical methods employed, make any comparison of the rates quoted in different studies difficult.

Nonetheless, selecting the six studies presenting the success rates over three treatments after eliminating the others with the exclusion criteria, a mean CPR of 45.7 (SD 2) and a mean CLBR of 55.43 (SD 6.8) were obtained, which may appear confusing, though the results are from different sets of studies. None of these selected studies quoted their figures for CPR, as well as CLBR, and hence cross comparison of the values for CPR and CLBR would be difficult. Also, these figures might appear to be relatively lower than expected in the current context, as the studies considered following elimination of others using the exclusion criteria, are relatively old, further justifying the need of a contemporary study.

On analysis of the various studies, multiple factors seemed to interact and influence the CPR, and potentially cause bias, if extrapolated to the general population.

2.5.1 Selected cohort of patients

Some studies have suggested the CPR to be as high as 64.3% (Fauque *et al.*, 2010) and even 90% (day 3 embryos) per cycle (Rienzi *et al.*, 2002) in studies who used a very selected cohort of patients with good prognostic factors for patients, such as age < 36 years, serum Follicle-stimulating hormone levels <

10 mIU /ml and oestradiol levels < 50 pg/ml on day 3, and in their first or second cycle only, or patients having more than eight pronuclear zygotes following fertilization. There is a potential for overestimating the CPR, if these are extrapolated to the general population, as the pregnancy outcome in the good-prognosis group selected by the study would be higher.

2.5.2 Methodological bias

2.5.2.1 Considering only the oocyte retrieval cycles having embryos to freeze

Ubaldi *et al.* (2004) reported a CPR of 76.1% per patient in the < 37 years of age group. A similar figure of 76.7% in the < 36 years of age group was reported by Battaglia *et al.* (2010). These studies factored the cycles or couples having embryos to freeze in the calculation and extrapolated the results generally. This could potentially overestimate the CPR. A similar bias can also be seen in another study, which factored couples having FET only in the calculation (Wang *et al.*, 1994).

2.5.2.2 Using life table analysis to calculate the cumulative pregnancy rate

There has been considerable debate in the past regarding the suitability of life table analysis to calculate the CPR. According to some, the estimation of CPR using life table analysis is not a true representation and is an overestimation of the likelihood of pregnancy (Daya, 2005; Witsenburg *et al.*, 2005).

The requirements of survival analysis studies, which are not satisfied in IVF cycles, are: identifying the precise time of origin of the cycle is problematic; absence of comparability of the subjects; and lack of comparability of the timescale, especially in the presence of cryopreserved embryos. Analysis, in this method, is based on the assumption that dropouts have the same probability of pregnancy as patients proceeding to the next cycle after failed treatment. However, it is not just the financial, geographical and emotional factors that account for patients dropping out; rather it is informative censoring, i.e. couples with poor prognosis being advised not to pursue treatment by clinicians, which plays a major role in IVF treatment. The lack of informative censoring is not satisfied in life table analysis (Daya, 2005).

Land *et al.* (1997) calculated a corrected CPR, where patients who were censored on medical grounds were not considered as dropouts; rather, they were included in the denominator.

However, De Vries *et al.* (1999) found no statistical difference in prognostic factors between patients continuing IVF treatment and dropouts. They concluded that life table analysis for CPR can be considered representative of the whole population of patients for at least the first three treatment cycles. In the continuing debate, Wang *et al.* (2005) reiterated that calculating the CPR only to the second or third cycle within a reasonably short period of 1–2 years may ensure that most patients are included in the calculations, while minimizing the impact of informative censoring.

Olivius *et al.* (2002) calculated the CLBR using the “optimistic method” (65.5%) of calculating life table analysis, where all dropouts are considered to have the same prognosis as the rest of the population, the “realistic method” (63.1%), where dropouts due to informative censoring were considered to have no probability of achieving a live birth and the “pessimistic method” (55.5%), where all dropouts were considered to have no chance of achieving a pregnancy; the results for CPR in the first three treatments are comparable.

2.5.2.3 Projected cryoaugmented cumulative pregnancy rates

Projected or anticipated CPR or CLBR data seem to be an optimistic overestimation, as most of the studies did not take into consideration the thaw rates of the frozen embryos. The issue of abandoning the embryos in storage has been mostly overlooked.

Fauque *et al.* (2010) reported that out of 50 patients who were pregnant in the fresh IVF cycle, two subsequently returned to have FETs. Van der Auwera *et al.* (2002) calculated that, out of all women who delivered from the fresh cycle, 37% of the group with embryos frozen on day 2 and 62% of those with embryos frozen on day 5, did not come back for a second pregnancy. Extrapolating this data, they estimated that 20% of all frozen embryos would be abandoned in storage.

2.5.2.4 Inclusion of sibling pregnancies

As previously discussed, studies that include sibling pregnancies in their calculations potentially overestimate the CPR/CLBR, as the standard definition of CPR takes into account the couple's first pregnancy or childbirth only.

2.5.3 Percentage of embryos thawed in the study period

The quoted figures of CPR and CLBR could potentially vary depending on the percentage of frozen embryos thawed and replaced during the tenure of the study. There is paucity of information regarding the use rate of frozen embryos in the studies. The figures quoted fall within a wide spectrum of between 17 and 78% (Damario *et al.*, 2000; De Jong *et al.*, 2002; Miller and Goldberg, 1995; Senn *et al.*, 2000; Toner *et al.*, 1991a; Van der Auwera *et al.*, 2002; Wang *et al.*, 1994).

2.6 Conclusion

Reviewing the literature, it is apparent that diverse statistical methodologies have been used to analyse CPR or CLBR, and that there is potential for various biases related to either the selection criteria of patients or the methodology used. The ideal standard of efficacy of IVF has been a matter of debate for a long time, but no consensus has been reached.

There has been no evidence of CPR being calculated following the implementation of the three IVF treatments funded by the NHS in the UK, which justifies the need of calculating it to inform patients, clinics and PCTs.

In the light of this review, the CPR in the NFCL has been calculated and compared with the figures quoted in the literature in Chapter 4, to assess the outcome of provision of the three NHS-funded IVF treatments and the impact of embryo freezing. But before that, Chapter 3 reviews the embryo freezing practice in the NFCL, to provide the background to the study.

Chapter 3. Review of the Frozen Embryo Practice at the Newcastle Fertility Centre at Life

3.1 Introduction

This chapter reviews the practice of freezing embryos at the NFCL. This is the clinic from which patients were recruited for interview. It was thus important to understand the background of the clinical environment from which their treatment was provided. The NFCL is a tertiary referral centre of fertility treatment located at the Centre for Life, an international centre for the advancement of science. It is the largest fertility unit in north-east England, catering to a population of 498,000 women in the reproductive age group (Office for National Statistics, 2007). The overall characteristics of this clinic and the workload associated with the freezing of embryos are described. For the purpose of this thesis, the term “IVF cycle or treatment” is used to denote each IVF/ICSI start to completion. The term “fresh cycle or treatment” is used for the IVF cycles involving ovarian stimulation and oocyte retrieval, whereas the term “frozen embryo transfer cycle” or “FET” is used to denote the cycles using frozen embryos. Specific attention is made to address the following issues:

1. Description of the clinic, patient population and treatment outcomes;
2. Evaluation of the outcome of embryo freezing on the LBR in the clinic;
3. Identification of the characteristics of the patients who can benefit from embryo freezing;
4. Decisions that couples make about the fate of their frozen embryos;
5. Practical implications of the freeze-thaw process on the number of embryos in storage;
6. Comparison of implantation rates between sibling fresh and frozen embryos.

3.2 Materials and Methods

3.2.1 Period of data collection

The 5-year time period from January 2005 to December 2009 was chosen, to reflect current practice in the fertility unit, as well as provide a reasonably large amount of data to analyse and present. This time period also witnessed a change in embryo culture systems in the laboratory. The standard open-front

isolators were changed to completely enclosed isolators, and these could have had a potential impact on the success rates of IVF treatment and on the outcome of embryo freezing. The near future will also see a transition from the slow freezing method to the vitrification method of cryopreservation of embryos; therefore, this time period was chosen to analyse and reflect current practice.

3.2.2 Methods of data collection

The electronic database of the NFCL, which recorded the fresh IVF cycles from 2005 to 2009, was analysed retrospectively and the relevant information was collected. The frozen-thaw database was examined up to 5 April 2011, to gather information regarding FET cycles using the embryos frozen between 2005 and 2009. April 2011 was chosen as the end date, as it was hoped that most of the embryos frozen in 2009 would have been thawed by then, based on the calculation of the standard time interval from freeze to thaw. The electronic records of embryo thaws up to 5 April 2011 were analysed to determine the fate of all the embryos frozen from 2005 to 2009.

3.2.3 Statistical analysis

The statistical analysis was done using the SPSS version 17 software (IBM Corporation, Armonk, New York, USA). The data were tested for normality; since they were found not to be normally distributed, a non-parametric Mann–Whitney U test was carried out. A non-parametric correlation test was performed to assess the correlations between different variables. To assess any significant difference in the likelihood of embryo freezing between IVF and ICSI, a chi-square test was carried out using crosstabs, and the relative risk (RR) and odds ratio (OR) for embryo freezing were calculated.

3.3 Description of the Clinic, Patient Population and Treatment Outcomes

Analysis of these data gives us an assessment of the workload, baseline characteristics of the patients and clinic performance. As explained earlier, this provides a snapshot of the clinic and helps in setting the backdrop to the part of this study when patients were recruited and interviewed about their views regarding embryo freezing. The number of IVF or ICSI cycles in those 5 years was calculated, as to also analyse the association between embryo freezing and IVF/ICSI cycles.

The study questions included:

- How many cycles were started?
- How many women had treatment?
- How many IVF/ICSI cycles did each woman undergo?
- What was the pregnancy rate per started cycle?
- Did the pregnancy rate vary between the cycle ranks?
- How many cycles resulted in embryo freezing?
- Did the rate of embryo freezing vary between the cycle ranks?
- What percentage of women had their embryos frozen?

3.3.1 Data collection

To analyse the clinic workload and its performance, the following data were collected from the fresh cycle database: patient's name and age; date of oocyte retrieval. As far as the type of treatment, the following data were collected: IVF or ICSI; cycle number; number of frozen embryos; cycle outcome; outcome of any pregnancies.

3.3.2 Data analysis

The number of initiated cycles of IVF or ICSI and the number of cycles according to cycle rank, i.e. first, second and third treatment, during this time period were calculated from the database. An Excel spread sheet was then sorted according to the names of the patients and the number of women coming for treatment during this period was analysed. The number of women having a number of cycles as according to the cycle rank was also calculated. The number of live births per started cycle and the LBR according to cycle rank were calculated. The number of cycles yielding frozen embryos and the number of women having embryos frozen following the fresh oocyte retrieval cycle were calculated and identified from the database. The frozen embryo yield rate according to the cycle rank was also analysed.

3.3.3 Results

3.3.3.1 Number of in vitro fertilization and intra cytoplasmic sperm injection started cycles from 2005 to 2009

There were 3,399 IVF/ICSI-started cycles from 2005 to 2009. As shown in figure 3.1, there were 2,204 first cycles, 862 second cycles, 247 third cycles, 60 fourth cycles, 20 fifth cycles, five sixth cycles and only one seventh cycle.

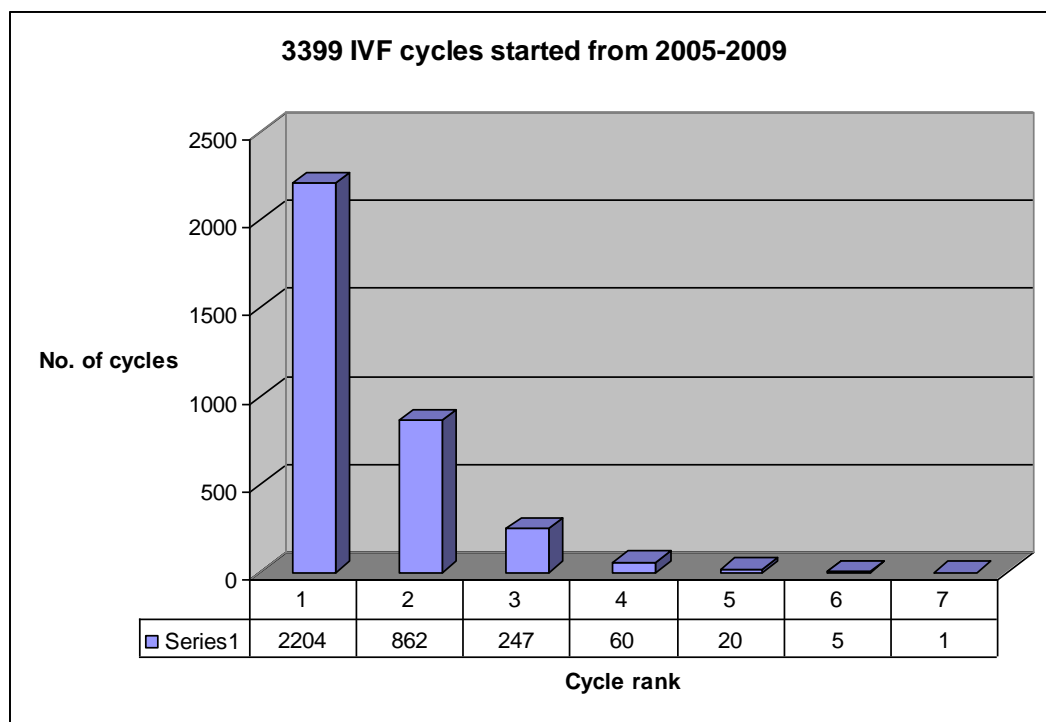


Figure 3.1 Number of cycles per cycle rank, 2005–2009.

3.3.3.2 Number of women having in vitro fertilization treatment from 2005 to 2009

A total of 2,204 women attended the clinic for IVF/ICSI cycles during this time period.

3.3.3.3. Maximum number of in vitro fertilization cycles according to cycle rank attended by individual women

As shown in figure 3.2, 1,342 out of 2,204 women had the first IVF cycle only, while 615 women progressed to the second cycle and 187 to the third, 40 had a maximum of four cycles, 15 progressed to a fifth IVF cycle, four had a maximum of six IVF cycles and only one woman proceeded to a seventh IVF cycle.

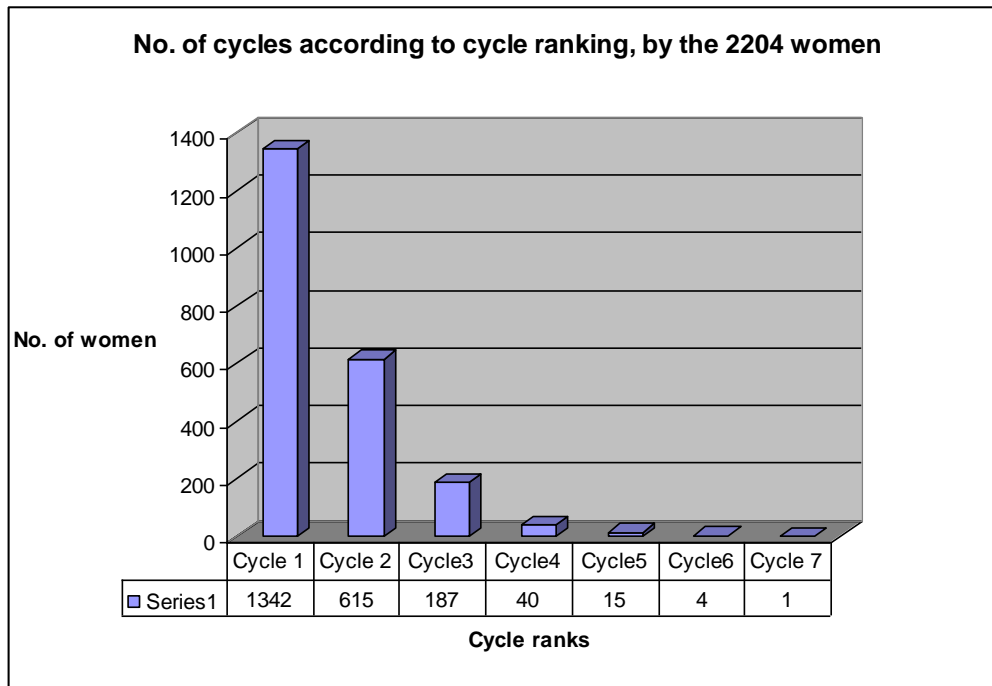


Figure 3.2 Number of cycles according to cycle ranking for the 2,204 women from 2005 to 2009.

3.3.3.4 Number of cycles treated with *in vitro* fertilization and intra cytoplasmic sperm injection

As shown in figure 3.3, 1,554 cycles involved IVF treatment (48.26%), and 1,666 (51.74%) involved ICSI treatment. Egg donors, surrogates and IVF and ICSI split cycles were excluded from this calculation.

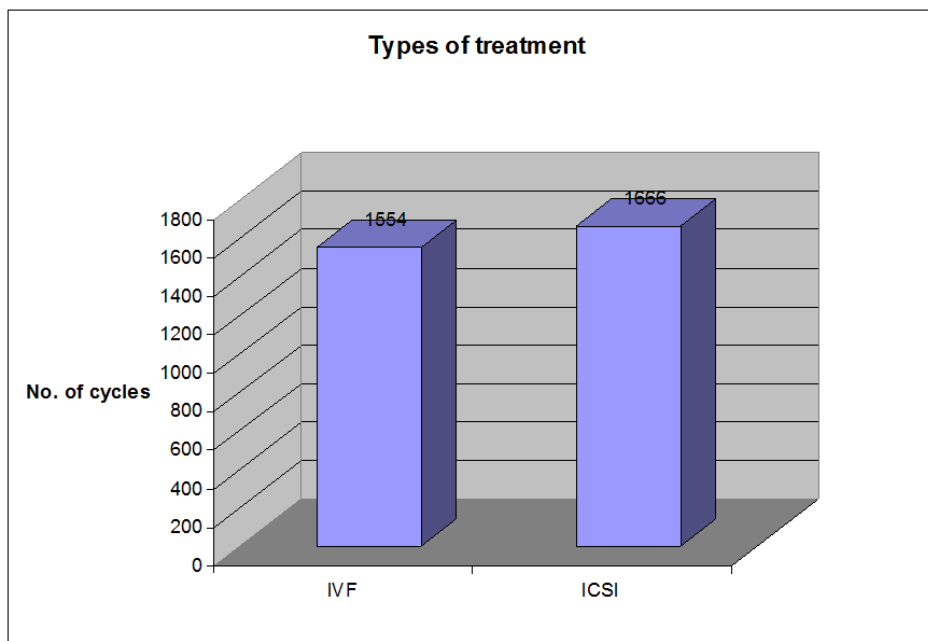


Figure 3.3 Types of treatment by number of cycles. ICSI: intra cytoplasmic sperm injection; IVF: *in vitro* fertilization.

3.3.3.5 Number of women having embryos to freeze

Out of the 2,204 women having IVF from 2005 to 2009, 329 women had embryos to freeze. Therefore, 14.93% women had frozen embryos.

3.3.3.6 Frozen embryo yield in the first three cycles

As shown in table 3.1, 229 of the 2,204 (10.39%) first IVF cycles yielded frozen embryos, 101 of the 862 (11.72%) second IVF cycles had embryos to freeze and 26 out of the 247 (10.53%) third cycles had frozen embryos. Of the 3,399 cycles started, 366 (10.77%) cycles had embryos to freeze.

Cycle number	Number of cycles	Cycles with frozen embryos
1	2,204	229
2	862	101
3	247	26

Table 3.1 Frozen embryo yield in the first three IVF cycles.

3.3.3.7 Live birth rate according to cycle ranking in the fresh cycles

There were 839 live births from the 3,399 cycles of IVF initiated. Therefore, the LBR was 24.68%. There were 561 live births from the 2,204 first cycles, 199 live births from the 862 second cycles, 61 from the 247 third cycles, 12 from 60 fourth cycles, five from the 20 fifth cycles, one from the five sixth cycles and none from the single seventh cycle. The LBR was 25.45% in the first IVF cycles, 23.09% in the second cycles and 24.70% in the third cycles, as shown in figure 3.4.

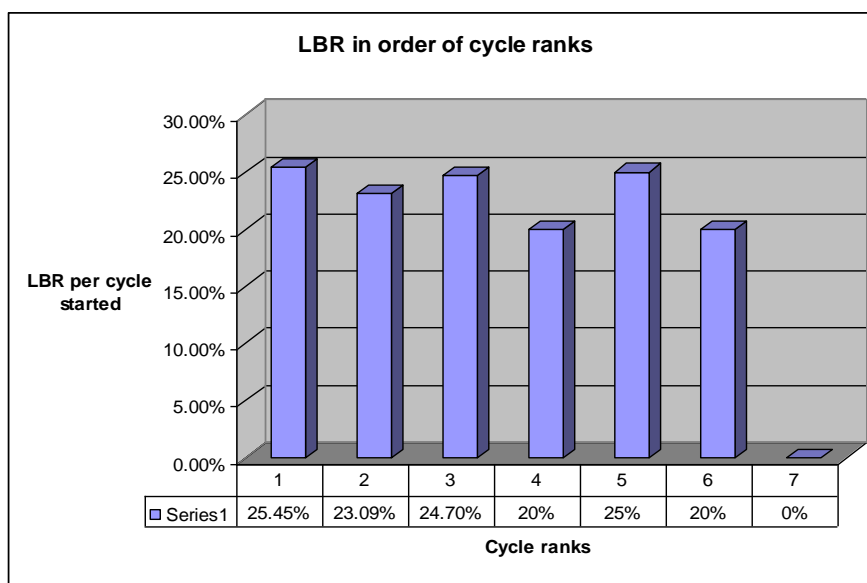


Figure 3.4 Live birth rates (LBRs) according to cycle ranks.

3.3.4 Comment

This snapshot of the clinic presents an overview of its performance and workload. From 2005 to 2009, 2,204 women underwent 3,399 cycles of IVF/ICSI treatment and nearly 11% of the cycles and 15% of women respectively had embryos to freeze. From the analysis of the data over this 5-year period, the trend of frozen embryo yield was fairly constant in the first three IVF cycles. The LBR was also comparable in the first three cycles.

3.4 Evaluation of the Outcome of Embryo Freezing on the Live Birth Rate in the Clinic

In this section of the chapter, the influence of the FET cycles on the overall LBR is assessed.

3.4.1 Data collection

To assess the LBR by combining fresh and frozen cycles, the following data were obtained from the FET database: patient's name; date of freezing; date of thawing; treatment outcome. The number of live births from the fresh cycles was obtained. The FET cycles using the frozen embryos from 2005 to 2009 were identified from the FET database up to 5 April 2011.

3.4.2 Data analysis

The clinical pregnancy rate, as determined from a viable ultrasound scan at 7 weeks of gestation, was analysed. The overall LBR was calculated by adding the live births from the fresh treatments and the ones from the FET cycles, per started cycle.

3.4.3 Results

Figure 3.5 shows the additional benefit of freezing embryos in terms of LBR, following the inclusion of 25 further live births from the frozen-thaw cycles. The total LBR (fresh + frozen) increased to 25.42% per started cycle, compared to 24.68% following the fresh IVF cycles only.

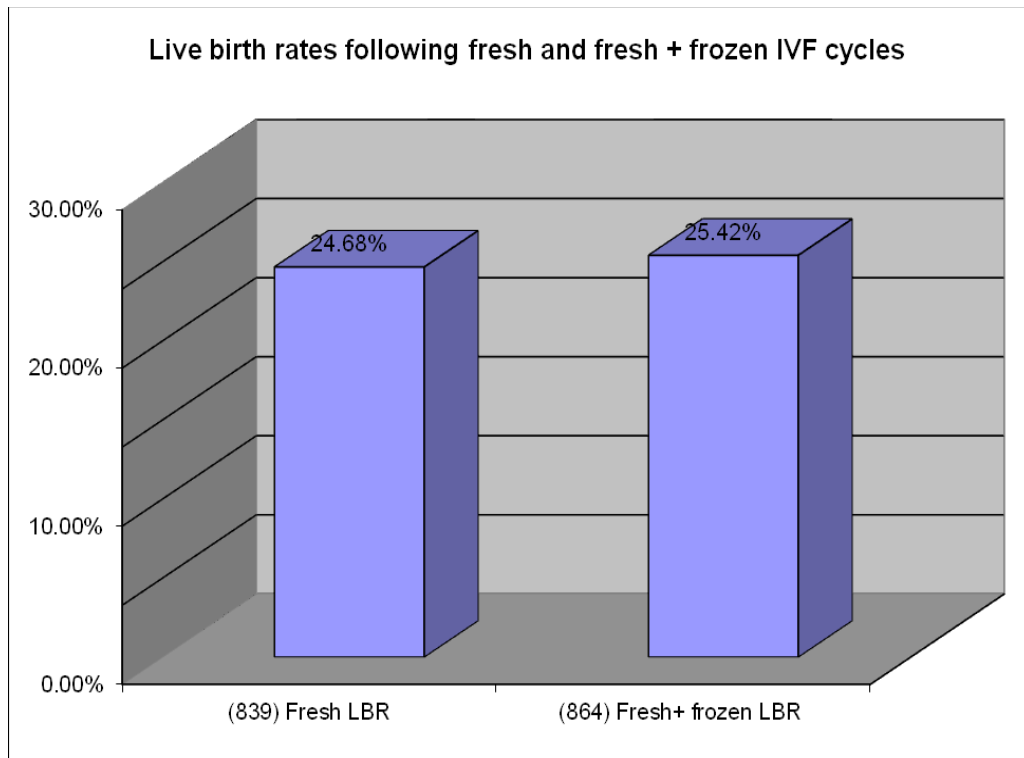


Figure 3.5 Additional benefit to the LBR from frozen cycles. IVF: *in vitro* fertilization; LBR: live birth rate.

3.4.4 Comment

There was a 3.33% increase from the baseline LBR, when births following the FET cycles were included, and an absolute increase of 1%.

3.5 Identification of the Characteristics of Women Likely to Have Embryos to Freeze

This section analyses the characteristics of women who have embryos to freeze. To try to identify women attending treatment who are likely to have embryos to freeze, the following hypotheses were tested:

1. Younger women are more likely to have embryos to freeze.
2. Women with more follicles are likely to have embryos to freeze.
3. Women with more eggs are likely to have more embryos to freeze.
4. Younger women with > 25 follicles are more likely to have embryos to freeze than older women with > 25 follicles.

5. For women with embryos to freeze, having more follicles is associated with more embryos to freeze.
6. For women with embryos to freeze, having more eggs is associated with more embryos to freeze.
7. Women undergoing IVF cycles are more likely to have embryos to freeze than women undergoing ICSI cycles.

It is important to try to identify the women likely to have embryos to freeze early in their cycle, during the stimulation or egg collection phase, to give them the necessary information and support to help them decide whether to freeze their embryos. This would potentially give women more time to decide whether to freeze their surplus embryos and weigh up the pros and cons.

3.5.1 Data collection

To investigate the associations previously mentioned, the following data were collected from the database: patient's age; type of treatment (IVF or ICSI); number of follicles and oocytes; the number of embryos frozen.

3.5.2 Data analysis and results

From the original database, cycles were separated in two groups according to the presence or absence of embryo freezing. Data was then analysed for each group.

3.5.3 Hypothesis 1: younger women are more likely to have embryos to freeze

This hypothesis was tested by:

1. Comparing the mean age in the groups with and without freezing;
2. Analysing whether younger women would have more embryos to freeze.

3.5.3.1 Data analysis

The mean age of women with frozen embryos was calculated and compared to that of women with no frozen embryos. Any significant difference in age in the two groups was calculated. The correlation of the ages of the women in the

group with frozen embryos and the number of frozen embryos was also analysed to detect any possible association.

3.5.3.2 Results

Data on the age of women with no frozen embryos (Gr 1 = NF) and for the group with frozen embryos (Gr 2 = F) were tested for normality using the Kolmogorov–Smirnov test and were found to be not normally distributed. ($p = 0.001$ in Gr 1; $P = 0.002$ in Gr 2). The median age in the group with no frozen embryos was 34 years, whereas the median age in the group with frozen embryos was 33 years, as shown in figure 3.6. The non-parametric Mann–Whitney U test showed that the mean age ranking of women with frozen embryos was significantly lower than that of women with no embryos to freeze ($p = 0.001$).

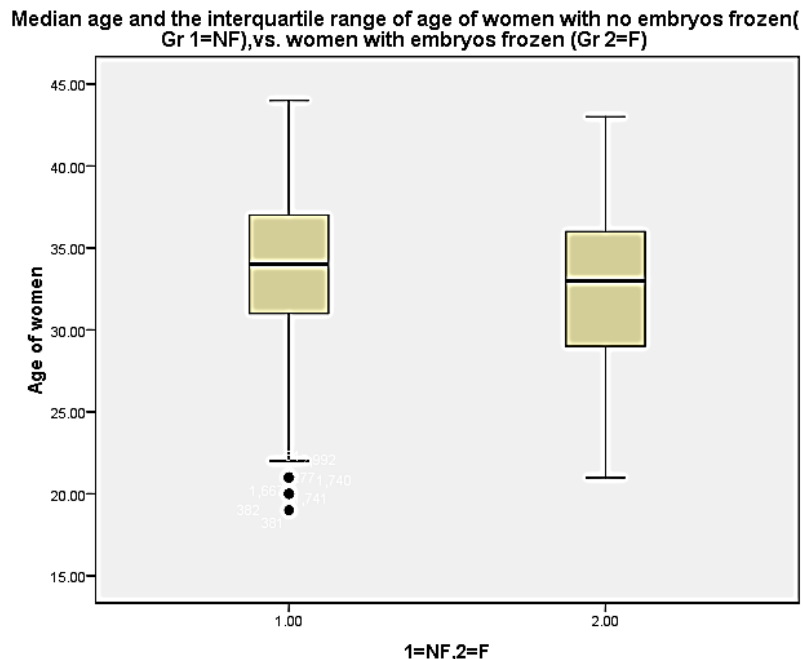


Figure 3.6 Median age of women with frozen embryos versus women with none. The horizontal lines in the box plots show the median age for the two groups. The box plots show the interquartile ranges, the whiskers are the limits of the range of the data at the bottom and the top ends, respectively, and the solid dots are the outliers. Outliers in SPSS are values that are 1.5–3 times the interquartile range.

3.5.3.3 Hypothesis 1(a): younger women have more embryos to freeze

This associated hypothesis was tested as it was assumed that younger women would produce more follicles, and higher numbers of eggs and embryos, and thus would have more embryos to freeze. Figure 3.7 shows the relationship between the age of women and the number of frozen embryos. Correlation

testing showed that there was almost no relationship between the age of women and the number of embryos available to freeze ($R = -0.15$). The result was significant at $P = 0.001$.



Figure 3.7 Relationship between age and the number of frozen embryos.

3.5.3.4 Comment to hypotheses 1 and 1(a)

The trend apparent in this clinic was that women with frozen embryos were younger compared to those with none, thus favouring hypothesis 1. However, there was almost no association with age and number of embryos available to freeze, thereby rejecting hypothesis 1(a).

3.5.4 Hypothesis 2: women with more follicles are likely to have embryos to freeze

3.5.4.1 Data analysis

This analysis was structured as follows:

1. The groups with and without embryos to freeze were compared to determine whether or not there was a significant difference in follicle numbers between the groups.
2. The frequency distribution of the number of follicles in the group of women with embryos to freeze and those without were compared.
3. Cycles were analysed according to the number of follicles and the incidence of freezing was calculated.

3.5.4.2 Results

The data on the number of follicles in the NF group and in the F group were not normally distributed according to the Kolmogorov–Smirnov test for both groups ($p = 0.001$). Figure 3.8 shows the median follicle number in the NF group as 12, versus the median follicle number in the F group being 20. The Mann–Whitney U test shows that the mean ranking of the number of follicles in the group with embryos to freeze was significantly higher than that in the NF group ($p = 0.001$), thus accepting hypothesis 2.

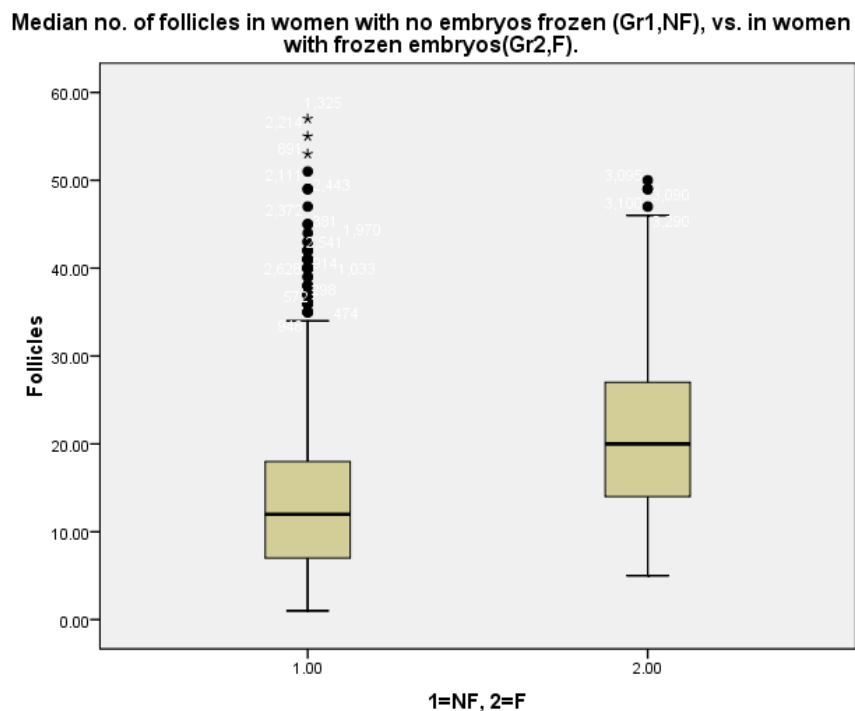


Figure 3.8 Median number of follicles in the group of women with embryos to freeze (F) vs. the group of women with no embryos to freeze (NF). The horizontal lines in the box plots show the median number of follicles for the two groups, while the actual box plots show the interquartile ranges. The whiskers are the limits of the range of the data at the bottom and top end, respectively, while the solid dots represent the outliers and the asterisks denote the extreme values. Outliers in SPSS are those values that are 1.5–3 times the interquartile range, while extreme values are more than three times the interquartile range.

The scatter plot in figure 3.9 shows the relationship between the number of follicles and the number of women having embryos to freeze. The number of follicles in the group of women who had embryos to freeze ranged from five to 50, but the maximum clustering of women, as evident from the scatter plot, was between 10 and 25 follicles.

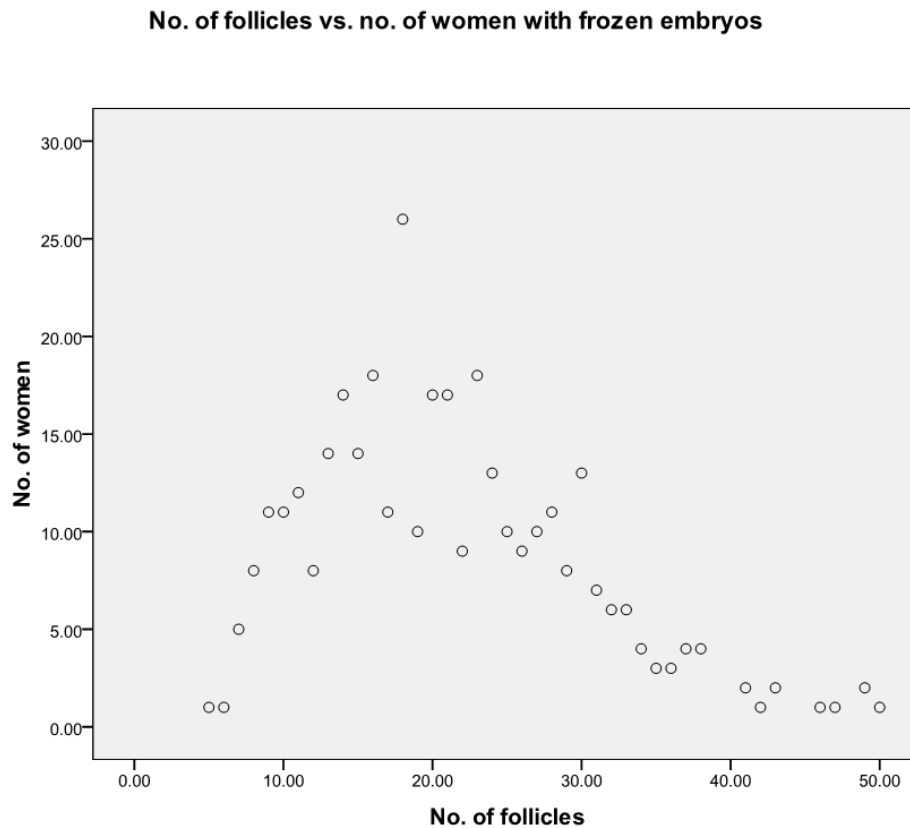


Figure 3.9 Relationship between follicle numbers and the number of women with embryos to freeze.

The same relationship was sought between the number of follicles and the NF group of women, as shown by the scatter plot in figure 3.10. The number of follicles in this group of women ranged from one to 57. The distribution pattern of the number of women was similar to that in figure 3.9, but with a shift to the left of the scatter plot, indicating, as expected, that most women without embryos to freeze tended to have fewer follicles.

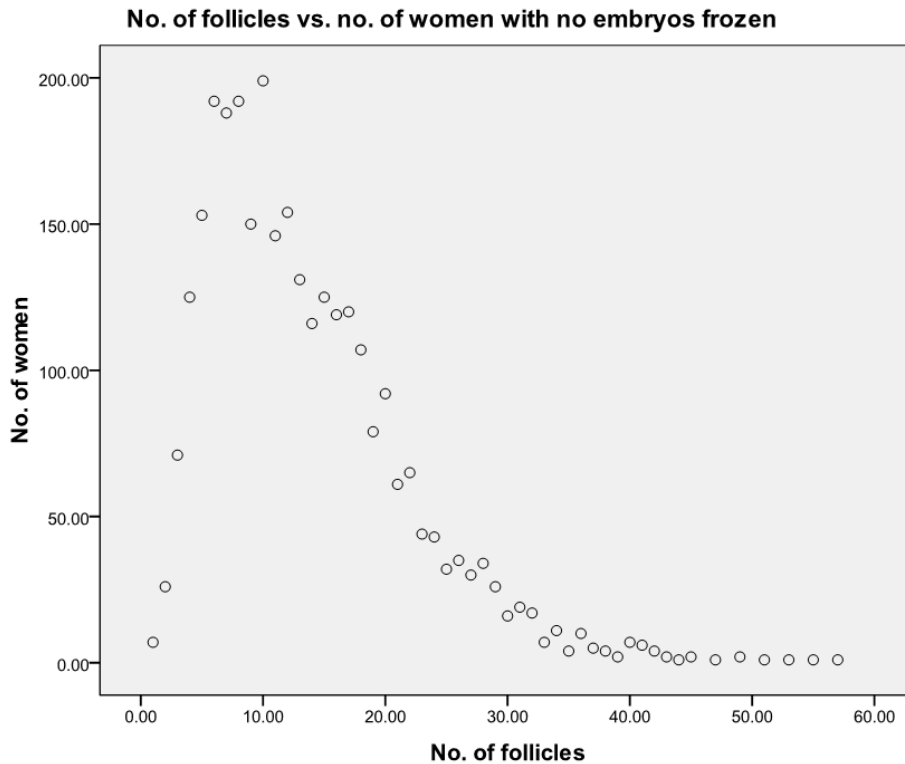


Figure 3.10 Relationship between follicle numbers and the number of women with no embryos to freeze.

Table 3.2 shows the number and percentages of cycles with frozen embryos versus the number without frozen embryos, against the corresponding follicle numbers. A follicle range was used for the easier management of data. As evident from table 3.2, the percentage of cycles resulting in frozen embryos gradually increased up to 25–30 follicles, but then levelled off.

Follicle range	Number of cycles with embryos frozen	Number of cycles without embryos frozen	Total number of cycles	% cycles with embryos frozen	% cycles without embryos frozen
1–5	1	382	383	0.26	99.74
6–10	36	921	957	3.76	96.24
11–15	65	672	737	8.82	91.18
16–20	82	517	599	13.69	86.31
21–25	67	245	312	21.47	78.53
26–30	51	141	192	26.56	73.44
31–35	26	58	84	30.95	69.05
36–40	11	28	39	28.21	71.79
41–60	10	22	32	31.25	68.75

Table 3.2 Incidence of freezing and follicle numbers.

3.5.4.3 Comment to hypothesis 2

The overall trend was that women with embryos to freeze tended to have a higher number of follicles (median number: 20) than women without embryos to freeze (median number: 12), thereby supporting hypothesis 2, although not conclusively proving it. The distribution pattern of the number of follicles in the group with embryos to freeze was essentially similar to that of the NF group, although with a shift to the left in the graph in the latter (figure 3.10), indicating that follicle numbers were higher in the group with embryos to freeze. The incidence of freezing was shown to be greater in cycles where more follicles initially, but then levelled off when reaching a follicle range of 25–30.

3.5.5 Hypothesis 3: women with more eggs are likely to have more embryos to freeze

3.5.5.1 Analysis

The same analyses were carried out using oocyte numbers, also. The importance of separately analysing the data on follicle and oocyte numbers is that the analysis of follicle numbers can inform patients several days in advance, and thus is relevant from the patient's perspective. This analysis is structured in a similar way to that of follicle numbers:

1. The groups with and without embryos to freeze (NF) were compared to determine whether or not there was a significant difference in oocyte numbers between them.
2. The frequency distribution of the number of oocytes in the group of women with embryos to freeze and that of women without embryos to freeze were compared.
3. Cycles were analysed according to the number of oocytes and the incidence of embryo freezing.

3.5.5.2 Results

The data concerning the number of oocytes in the NF group and the group with embryos to freeze were not normally distributed (Kolmogorov–Smirnov test for both groups, $p = 0.001$). As shown in figure 3.11, the median number of oocytes in the group of women with embryos to freeze was 15 versus eight in the NF group. The Mann–Whitney U test also showed a value of $p = 0.001$, denoting

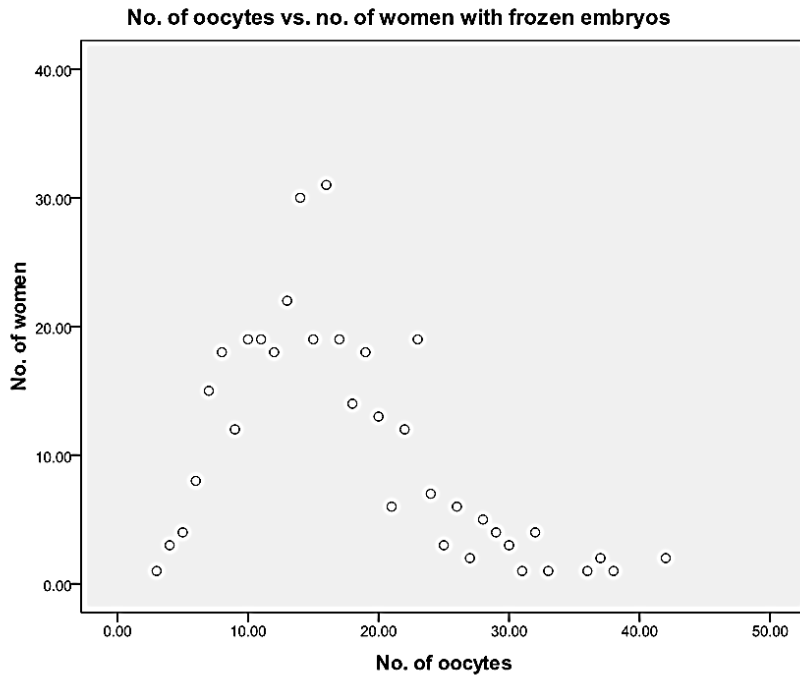


Figure 3.12 Relationship between oocyte numbers and the number of women with embryos to freeze.

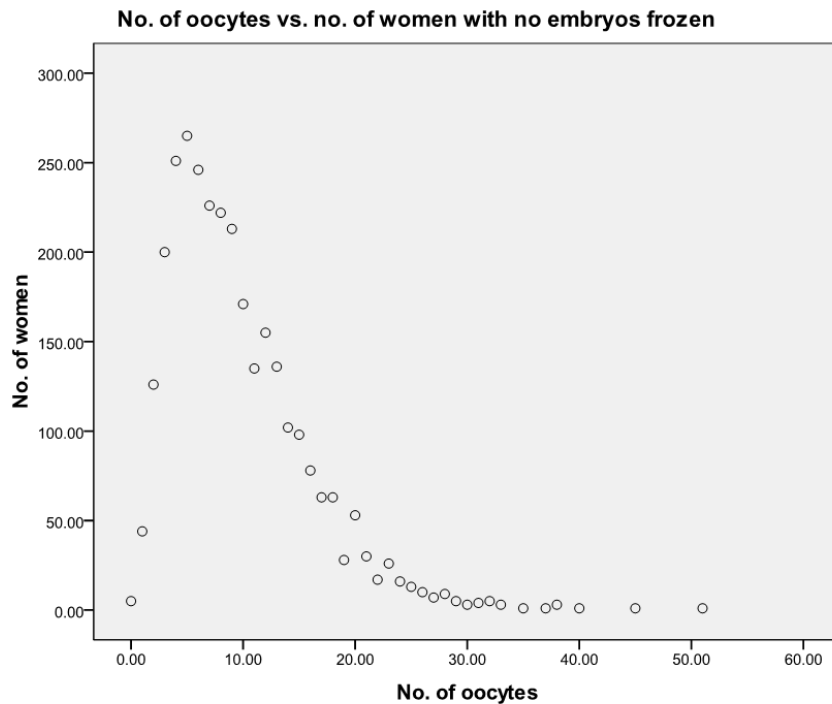


Figure 3.13 Relationship between oocyte numbers and the number of women with no embryos to freeze.

This followed the same trend as the number of follicles and number of women with embryos to freeze.

Table 3.3 shows the number and percentage of women with embryos to freeze versus the number of women without, against the corresponding oocyte number. As clear from table 3.3, the incidence of freezing gradually increases to up to 25–30 oocytes, but then levels off.

Oocyte number/range	Number of cycles with embryos to freeze	Number of cycles with no embryos to freeze	Total cycles	% cycles with embryos to freeze	% cycles with no embryos to freeze
0–5	8	891	899	0.89	99.11
6–10	72	1078	1150	6.26	93.74
11–15	108	626	734	14.71	85.29
16–20	95	285	380	25	75
21–25	47	102	149	31.54	68.46
26–30	20	34	54	37.04	62.96
31–50	12	20	32	37.5	62.5

Table 3.3 Incidence of embryo freezing and oocyte numbers.

3.5.5.3 Comment to hypothesis 3

The overall trend was similar to that of the follicle numbers, and women with embryos to freeze tended to have higher numbers of oocytes (median number: 15) than women with NF (median number: 8), thereby supporting, although not conclusively proving, hypothesis 3. The same trends were noted as with the follicle numbers, in terms of the frequency distribution of oocyte numbers and embryo freezing, and the incidence of embryo freezing and oocyte numbers.

3.5.6 Hypothesis 4: younger women with more than 25 follicles are more likely to have embryos to freeze than older women with more than 25 follicles

Any likely influence of age was analysed to find a possible explanation as to why some women with more than 25 follicles/oocytes had embryos to freeze, whereas others, with an equivalent number of follicles/oocytes, did not.

3.5.6.1 Analysis

The mean age of women with more than 25 follicles was compared and tested for any significant difference between the group of women with embryos to freeze and the group of women without.

3.5.6.2 Results

The median age of women with more than 25 follicles in the “NF” group was 32, whereas the median age of women in the group with embryos to freeze was 31 years. The data on the age of women in the NF group were not normally distributed ($p = 0.001$). However, the data on the age of women in the group with embryos to freeze were normally distributed ($p = 0.159$). Therefore, overall, the data were not normally distributed (Kolmogorov–Smirnov test). The Mann–Whitney U test was performed and gave a value of $p = 0.715$, denoting no significant difference in mean age ranking in the two groups of women.

3.5.6.3 Comment to hypothesis 4

In women with more than 25 follicles, the likelihood of embryo freezing cannot be related to a younger age, thereby rejecting hypothesis 4.

3.5.7 Hypothesis 5: for women with embryos to freeze, having more follicles is associated with more embryos to freeze

3.5.7.1 Analysis

The correlation between the number of follicles and the number of embryos to freeze was tested in the group of women with embryos to freeze, to assess any likely relationship.

3.5.7.2 Results

To address this hypothesis, the relationship between follicle numbers and the number of embryos to freeze was plotted (figure 3.14). The data were not normally distributed ($p = 0.001$). The median number of follicles in this group was 20 and the median number of frozen embryos was 4. Figure 3.14 shows the relationship between follicle numbers and the number of frozen embryos. A non-parametric correlation test (Spearman’s test, $R = 0.460$) was carried out and the result showed a moderately positive correlation, which was significant ($p=0.001$), indicating a rise in the number of embryos to freeze with an increase

in the number of follicles in the group of women who had embryos to freeze.

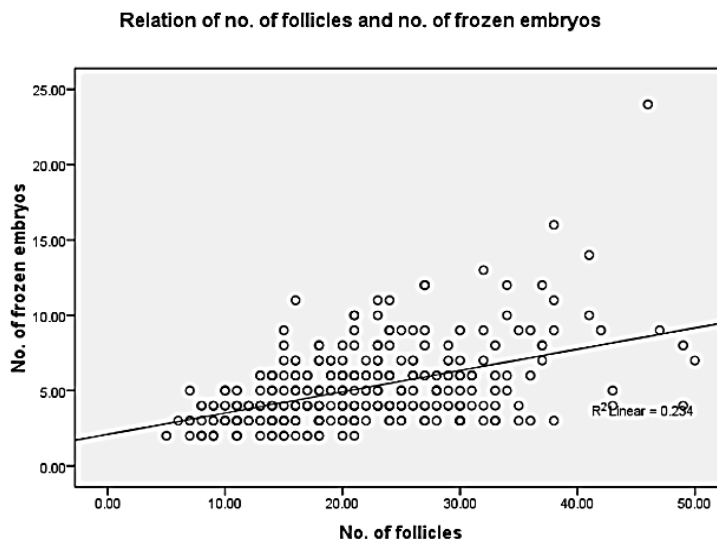


Figure 3.14 Relationship between follicle numbers and the number of frozen embryos, in women with embryos to freeze.

3.5.7.3 Comment to hypothesis 5

In the group of women with embryos to freeze, an increase in follicle numbers corresponded to a higher number of embryos to freeze, thereby supporting hypothesis 5, although not proving it beyond doubt.

3.5.8 Hypothesis 6: for women with embryos to freeze, having more eggs is associated with more embryos to freeze

3.5.8.1 Analysis

A calculation similar to that used for the number of follicles was carried out.

3.5.8.2 Results

The data on the number of oocytes in the group of women with embryos to freeze and the number of frozen embryos were not normally distributed ($p = 0.001$ for both variables). The median number of oocytes in this group was 15 and the median number of frozen embryos was 4. Figure 3.15 shows the relationship between follicle numbers and the number of frozen embryos. A

non-parametric correlation test (Spearman's test, $R = 0.573$) was done, and the result showed a moderately positive correlation between these two variables, indicating a rise in the number of frozen embryos, with an increase in the number of oocytes. The result was statistically significant with $p=0.001$!

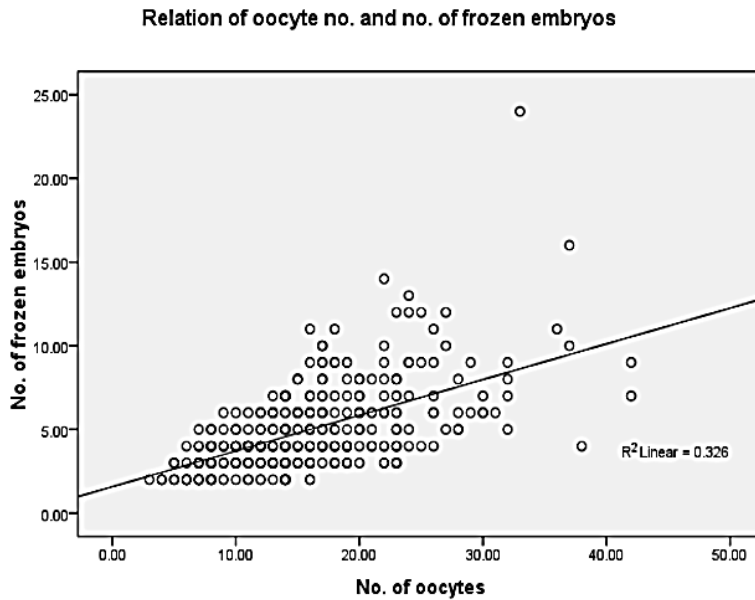


Figure 3.15 Relationship between oocyte numbers and the number of frozen embryos in women with embryos to freeze.

3.5.8.3 Comment to hypothesis 6

A trend similar to that observed for the number of follicles was noted, thus favouring hypothesis 6.

3.5.9 Hypothesis 7: *in vitro* fertilization cycles are more likely to produce frozen embryos than intra cytoplasmic sperm injection cycles

3.5.9.1 Analysis

The number of cycles of IVF and ICSI treatment yielding frozen embryos was calculated, and the proportion of cycles with frozen embryos in the two groups were compared and tested for any significant difference. This was intended to assess the likelihood of having frozen embryos with IVF versus ICSI treatment.

3.5.9.2 Results

Figure 3.16 shows that 213 (13.7%) out of the 1,554 IVF cycles yielded embryos to freeze, whereas 118 (7.08%) out of the 1,666 ICSI cycles had embryos to freeze.

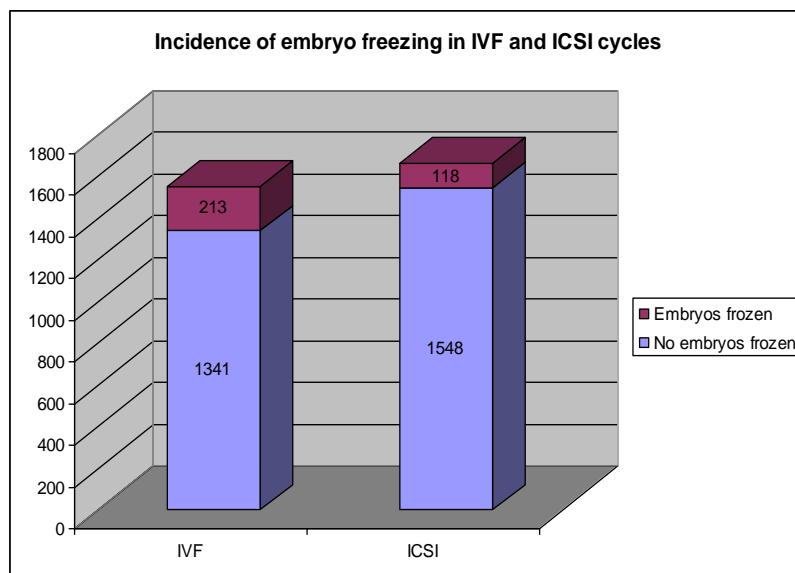


Figure 3.16 Incidence of embryo freezing in IVF and ICSI cycles. ICSI = intra cytoplasmic sperm injection; IVF: *in vitro* fertilization.

A chi-square test using the data in table 3.4 shows that embryo freezing was more frequent in IVF cycles compared to ICSI cycles and that the difference was significant ($p = 0.001$, RR = 1.935). Risk estimation analysis showed that the odds of having frozen embryos with IVF treatment was 0.158 and 0.076 with ICSI treatment [OR = 2.084, 95% confidence interval (CI) 1.645–2.640].

	Frozen	Unfrozen	Total
IVF	213 (13.7%)	1,341 (86.3%)	1,554
ICSI	118 (7.08%)	1,548 (92.9%)	1,666

Table 3.4 Cross tabulation of type of treatment and embryo freezing. ICSI: intra cytoplasmic sperm injection; IVF: *in vitro* fertilization.

3.5.9.3 Comment to hypothesis 7

In this analysis, IVF treatment cycles seemed to have twice the likelihood of producing embryos for freezing compared to ICSI cycles.

The trend derived from this analysis was that younger women, with a higher number of follicles and oocytes, were more likely to have embryos to freeze. IVF cycles were more likely to yield frozen embryos compared to ICSI cycles. There was also a trend towards having more embryos to freeze, with a higher number of follicles and oocytes.

3.6 Decisions That Couples Make About Their Frozen Embryos

The decisions couples make about the fate of their frozen embryos and the decisions they make regarding thawing their frozen embryos, the time interval for attending the FET cycles and the attendance rate depending on the outcome of a fresh IVF cycle, were all assessed here.

3.6.1 Data collection

From the database for the fresh cycles, the following information was obtained: patient's name and age; date of oocyte retrieval; type of treatment; cycle number; number of embryos to freeze; cycle outcome; outcome of any pregnancies; any live births. From the frozen-thaw database (examined from January 2005 to 5 April 2011), relevant data about the following was analysed to trace all the FET cycles using frozen embryos generated from 2005 to 2009: patient's name; date of embryo freezing; date of embryo thawing; number of embryos thawed; and treatment outcome. From the database about thawing, the information collected included: patient's name; date of embryo freezing; and date of thawing for treatment, or data about the number of embryos thawed, or the embryos donated for research, to others, exported, i.e. transferred to other fertility units, or discarded.

3.6.2 Data analysis

Examining the data from the fresh and frozen cycles, the number of women with frozen embryos returning for FET was analysed. The number of women attending for FET cycles for a sibling pregnancy, and also that following unsuccessful fresh cycles, were calculated from the fresh and frozen data sets. The treatment outcome for the women having FET was followed up. The timescale for women to return for their first FET cycle following the fresh cycle was calculated from the fresh and frozen database. The number of women who still had frozen embryos in storage following their FET cycles, and their mean

number of embryos in storage, were analysed from the FET database. Using the data about thawing, the following were calculated: the number of women who thawed embryos for their own treatment; the number of embryos donated to research or other infertile couples; the number of destroyed embryos; and the number of women still having embryos. The fresh and frozen databases were analysed to identify the women who had live births in the fresh or frozen cycles.

3.6.3 Results

3.6.3.1 Decisions made by women with frozen embryos

As shown in figure 3.17, 185 women (56.23%) out of the 329 with frozen embryos, returned for FET cycles until the time of analysis. Figure 3.17 also shows the other decisions made by women regarding the fate of their frozen embryos, as followed up until the time of the study. In total, 40 women (12.16%) chose to discard their frozen embryos, nine of these women after having attended a FET cycle; 37 (11.25%) women donated their embryos to research, and six of them had attended a FET cycle; seven (2.1%) had their embryos exported to other units following relocation of their homes, while only two (0.6%) donated to other infertile couples; 75 (22.8%) women continued to store their embryos.

Of the 37 women who donated their embryos to research, 75.7% had already achieved a live birth (26 had live births in the fresh cycles and two had live births in the FET cycle). Both of the women donating their frozen embryos to others had had live births in their fresh cycles. Sixty per cent of the 40 women who discarded their frozen embryos had achieved live births (23 in fresh cycles, and one in FET). Nine of the 40 women who discarded their frozen embryos had attended a FET cycle, while 54 (72%) of the 75 women still continuing to store their frozen embryos, had already achieved live births in the fresh cycles.

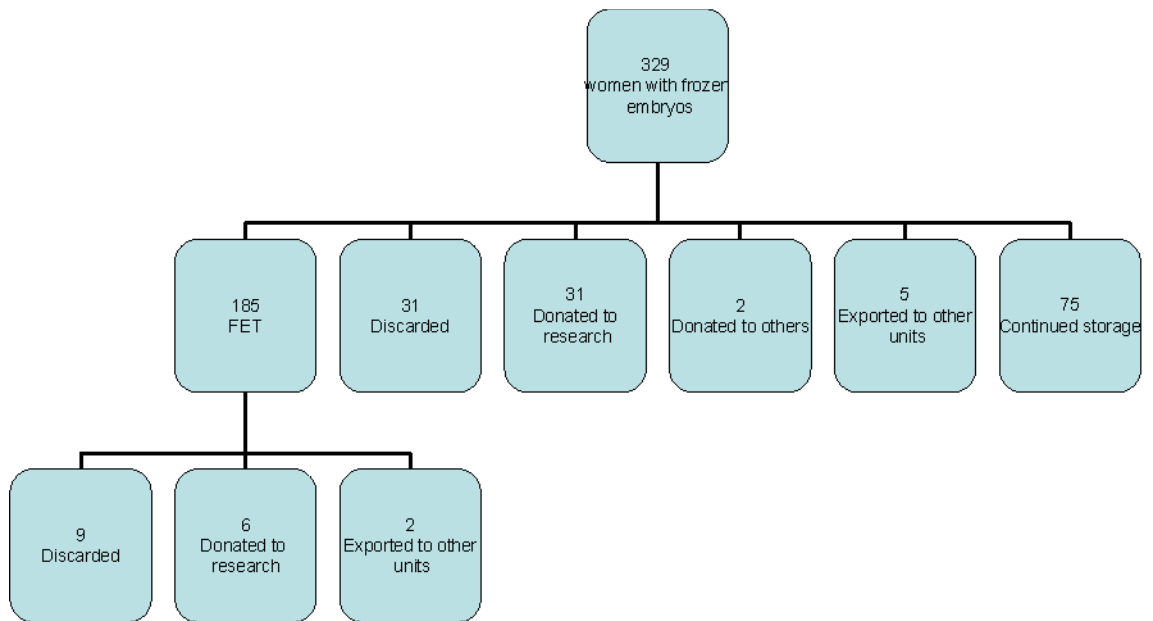


Figure 3.17 Decisions made by women with frozen embryos.

3.6.3.2 Number of frozen embryo transfer cycles, according to cycle ranking, attended by individual women

Figure 3.18 shows that 137 women had one FET cycle only, 42 women went on to have up to two FET cycles, and a further six women ended up having a third FET cycle.

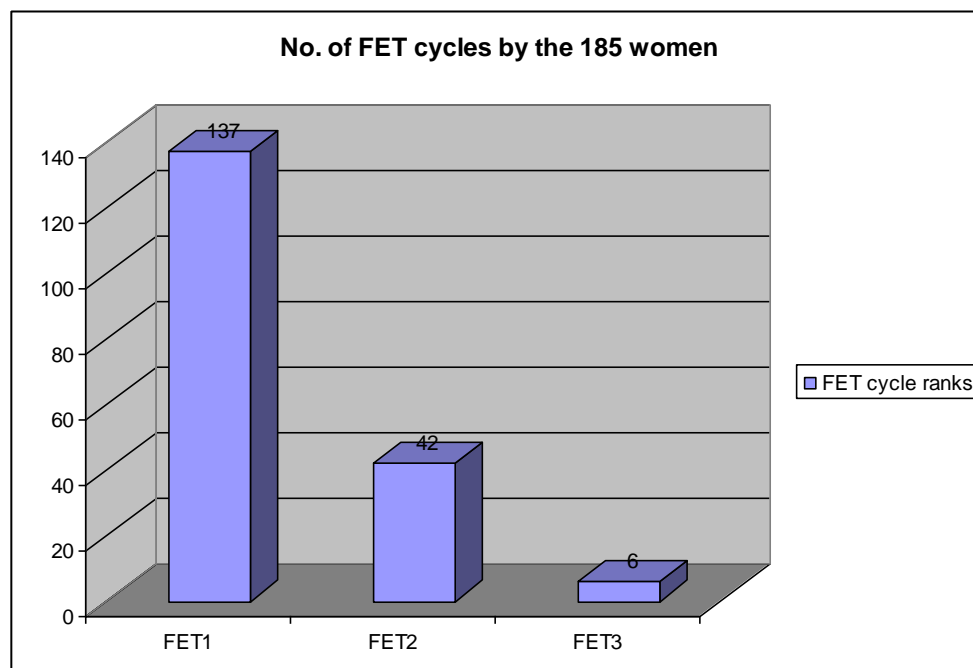


Figure 3.18 Number of FET cycles, according to cycle ranking, attended by individual women. FET = frozen embryo transfer.

3.6.3.3 Clinical outcomes of women returning for frozen embryo transfer

As shown in figure 3.19, 124 of the 329 women with frozen embryos had live births in their fresh IVF cycle, whereas 205 were not successful. Twenty-two (17.74%) of the 124 women who were successful in their fresh cycle attended FET for sibling pregnancies, whereas 102 (82.25%) had not at the time of the study. On the other hand, 163 (79.51%) of the 205 women who were unsuccessful in the fresh cycle attended FET, while only 42 (20.49%) did not. Figure 3.19 also shows the outcomes of the FET cycles for these women.

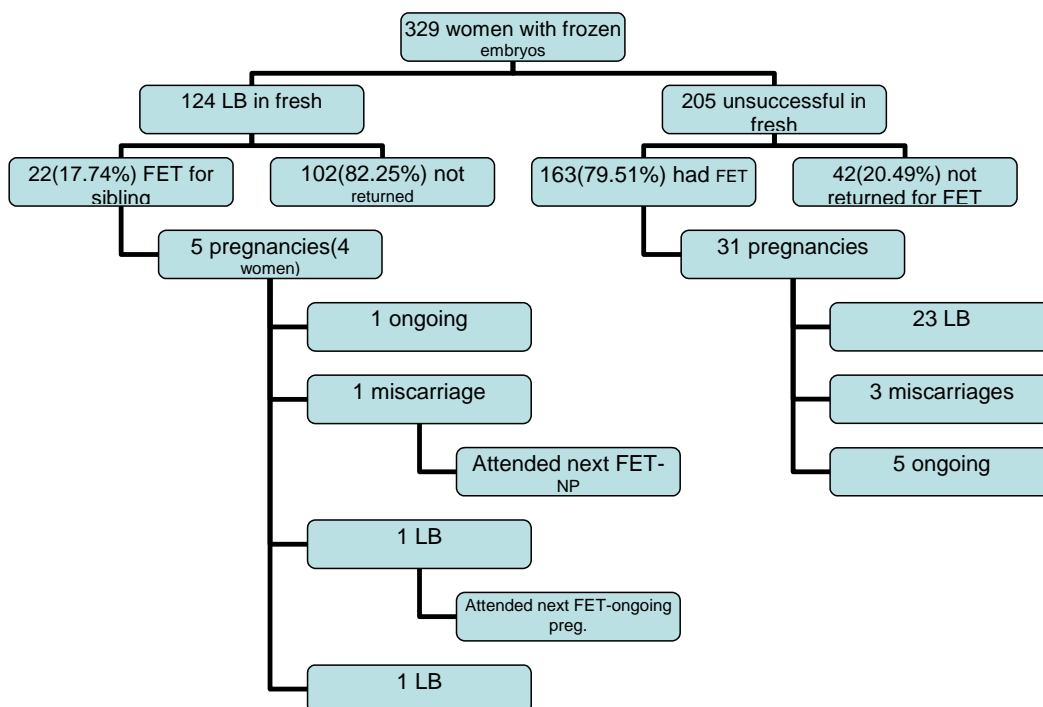


Figure 3.19 Clinical outcomes of women returning for FET. FET: frozen embryo transfer; LB: live birth; NP: not pregnant.

3.6.3.4 Overall outcome of the frozen embryo transfer cycles

There were 239 FET cycles until 5 April 2011 from the embryos frozen between 2005 and 2009. As shown in figure 3.20, 203 cycles did not result in pregnancy, 25 had live births (four had twins), on-going pregnancies were noted in seven, and, sadly, four ended in miscarriage. Therefore, 36 babies were likely to be born, and overall, there was 15.06% clinical pregnancy rate per started FET cycle for the embryos frozen between 2005 and 2009. Also, 36 babies (10.9%) were likely to be born for all the 329 couples who had frozen their embryos in this 5-year period. Figure 3.21 shows the number of clinical pregnancies in the subsequent FET cycles in order of ranking. There were 30 clinical pregnancies

in the 185 first FET cycles (16.22%), five pregnancies in the 48 second FET cycles (10.42%) and one pregnancy in the six third FET cycles (16.7%).

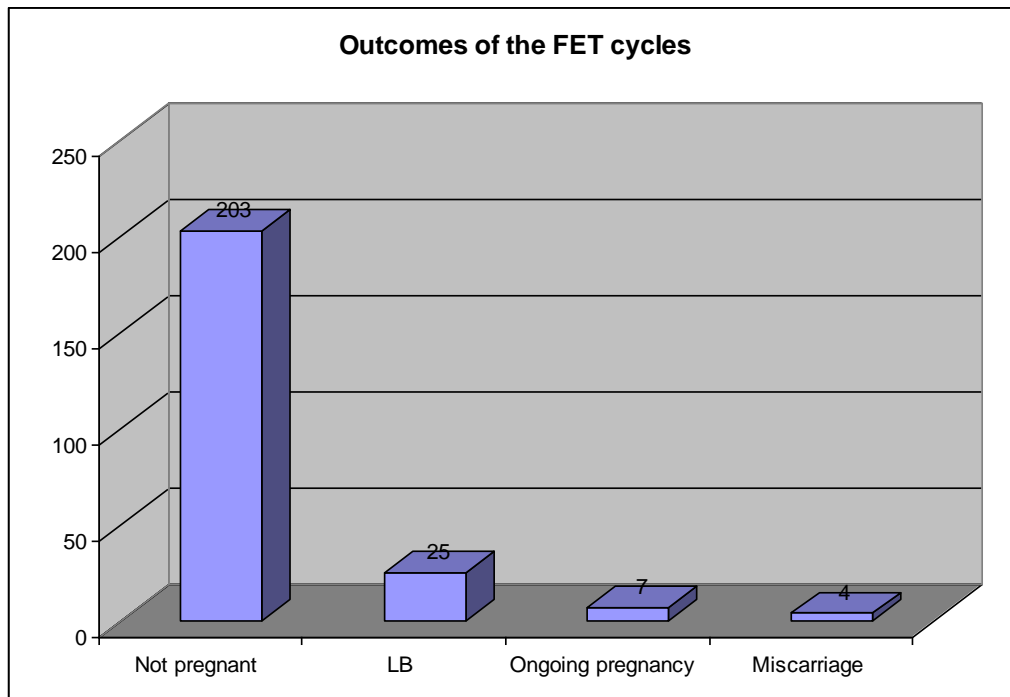


Figure 3.20 Overall outcomes of the FET cycles. FET: frozen embryo transfer; LB: live birth.

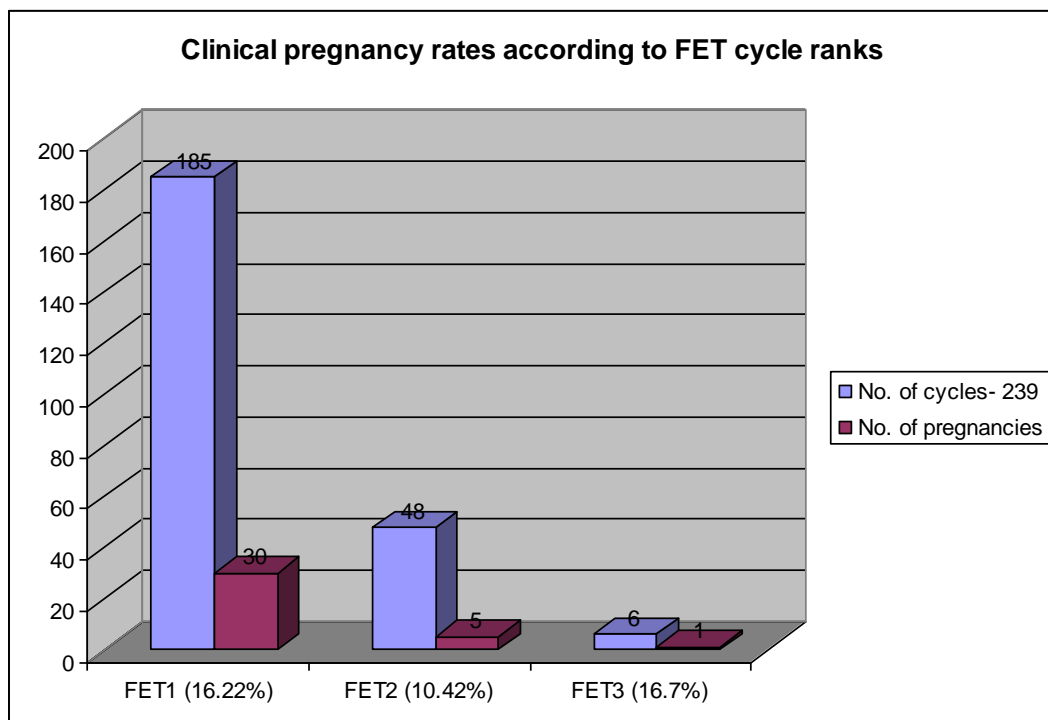


Figure 3.21 Number of pregnancies in subsequent FET cycles. FET: frozen embryo transfer.

3.6.3.5 Timescale for women to return to return for their first frozen embryo transfer

Figure 3.22 shows the timescale for women attending their first FET cycles. As shown, 97 (52.43%) of the 185 women having FET cycles, came back within 6 months of embryo freezing, 171 (92.4%) were back within 2 years, whereas only 14 (7.57%) women returned between 2–5 years. Eight (57.14%) of the 14 women coming for FET between 2–5 years, had attended for a sibling pregnancy.

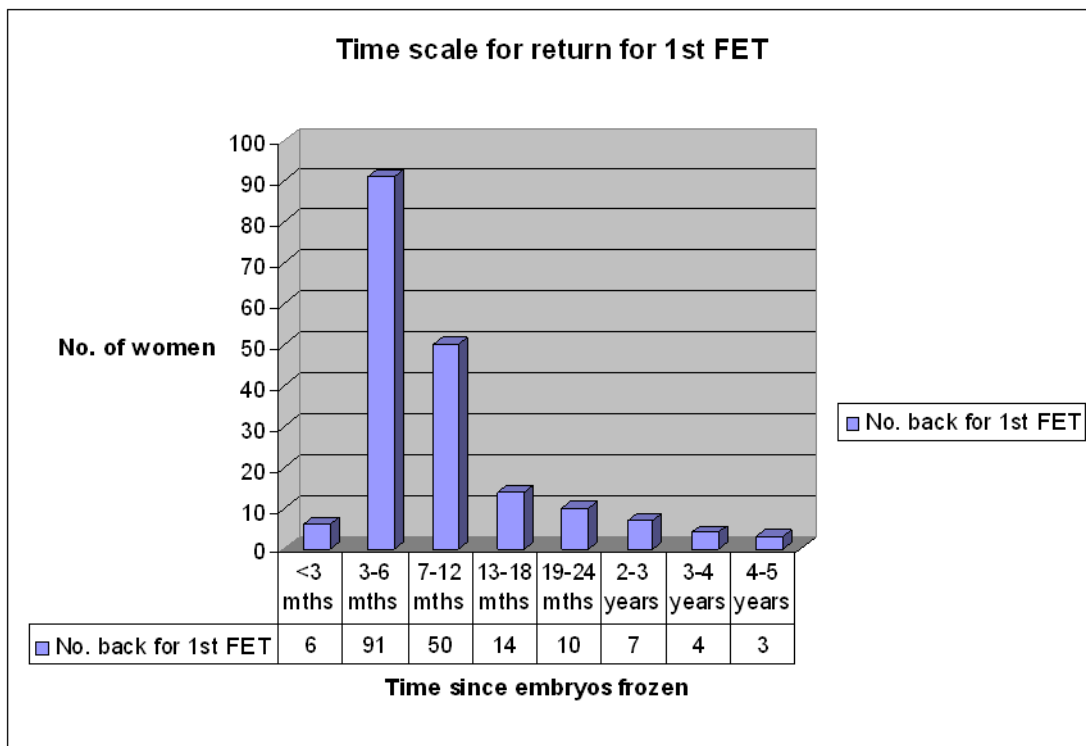


Figure 3.22 Timescale for return for the first FET cycle. FET: frozen embryo transfer.

3.6.3.6 How many women do still have embryos in storage, having attended the frozen embryo transfer cycles?

Table 3.5 shows that 15 women (8.11%) out of the 185 attending FET cycles still had a mean number of 2.8 (SD 1.3) frozen embryos in storage; seven of them did not return for a further FET following a live birth or on-going pregnancy in the last FET or subsequent fresh cycles and two women had their initial FET cycles less than 12 months ago from the time of analysis, thus accounting for 60% of women who still have frozen embryos in storage following FET.

Number frozen embryos following FET cycles	Any LB in the preceding/any subsequent fresh cycle	Outcome of the last FET cycle	Time in months since attended for last treatment
2	0	LB	16
2	0	0	18
5	0	0	13
2	0	0	24
3	0	LB (twins)	58
4	0	0	10
2	0	0	56
2	0	0	13
4	0	0	31
2	0	0	18
2	LB	P	Pregnancy continuing
2 + 4 (next fresh cycle)	LB (next fresh)	0	55
2	LB (next fresh)	0	9 (since FET, from second cycle)
2	0	0	9
2	0	P	Pregnancy continuing
Total = 15 patients	LB in 3 women	LB/on-going pregnancy in four women	

Table 3.5 Individual women still having embryos in storage following FET cycles. FET: frozen embryo transfer; LB: live birth; P: clinical pregnancy.

3.6.4 Comment

More than half of the women with frozen embryos returned for FET during follow-up. Those unsuccessful in the fresh cycle were more likely (80%) to attend than those with a live birth in the fresh cycle. About 18% women who had a live birth in the fresh cycle, returned for a sibling in FET. The overall success rate in terms of clinical pregnancy per initiated FET cycle was 15.06%; nearly 11% of all the couples freezing their embryos were likely to have a baby.

More than half of the women returning for the first FET did so within 6 months, as the unit's policy is to encourage women to have FET cycles prior to having any further fresh cycles, and very few couples were likely to return after 2 years. Only 7.6% of women returned between 2 and 5 years, and more than half of them came for a sibling pregnancy.

Women were more likely to discard or donate to research their surplus frozen embryos, rather than donating them to other infertile couples. The majority of women who donated their embryos to research, or discarded their embryos, had already achieved a live birth. Nearly 23% women continued to store their frozen embryos without having any FET, until the end point of this study, and

the majority of them were already pregnant from the fresh cycle; 8.1% women retained stored embryos after having attended FET cycles, though 60% of them had already achieved a live birth or had been treated recently.

3.7 Practical Implications of Freeze-Thaw on the Number of Stored Embryos

In this section, the implications of cryopreservation of embryos on the total number of embryos are analysed.

3.7.1 Data collection

To assess the number of frozen embryos that had been thawed, and the duration of embryo storage (as on 5 April 2011), the following information as recorded in the fresh cycle database was analysed: patient's name and age; date of oocyte retrieval; and number of frozen embryos that were retrieved. From the frozen-thaw database, the following information was analysed: patient's name; date of embryo freezing; date of embryo thawing; and number of thawed embryos. The electronic records of the thaw database were analysed to gather information regarding the fate of embryos frozen between 2005 and 2009, up to 5 April 2011.

The electronic records of the fate of embryos frozen each year, from 2006 to 2010, were obtained to calculate the number of frozen embryos in the clinic.

3.7.2 Data analysis

Storage duration for the embryos of women who did not attend the FET cycles was analysed from the fresh and frozen databases. Combining data from the fresh, frozen and thaw databases, the following were analysed: the total number of embryos frozen between 2005 and 2009; the number of embryos thawed for treatment until 5 April 2011; the number of embryos donated to others or to research; and the numbers exported or discarded. The number of embryos still in storage was calculated from these data. The cumulative clinic data for the total number of embryos in storage from 2006 to 2010 were also analysed.

3.7.3 Results

3.7.3.1 Fate of embryos frozen from 2005 to 2009

In the time period from 2005 to 2009, 1,651 embryos were frozen. As shown by figure 3.23, 307 (18.6%) embryos were still in storage. Out of the 1,344 (81.41%) embryos that had been thawed till the time of analysis, i.e. 5 April 2011, 925 (68.82%) were thawed for treatment, 172 (12.8%) were donated to research, 200 (14.9%) were discarded, 14 (1%) were donated to other infertile couples and 33 (2.46%) were exported to other units, as requested by the embryo owners.

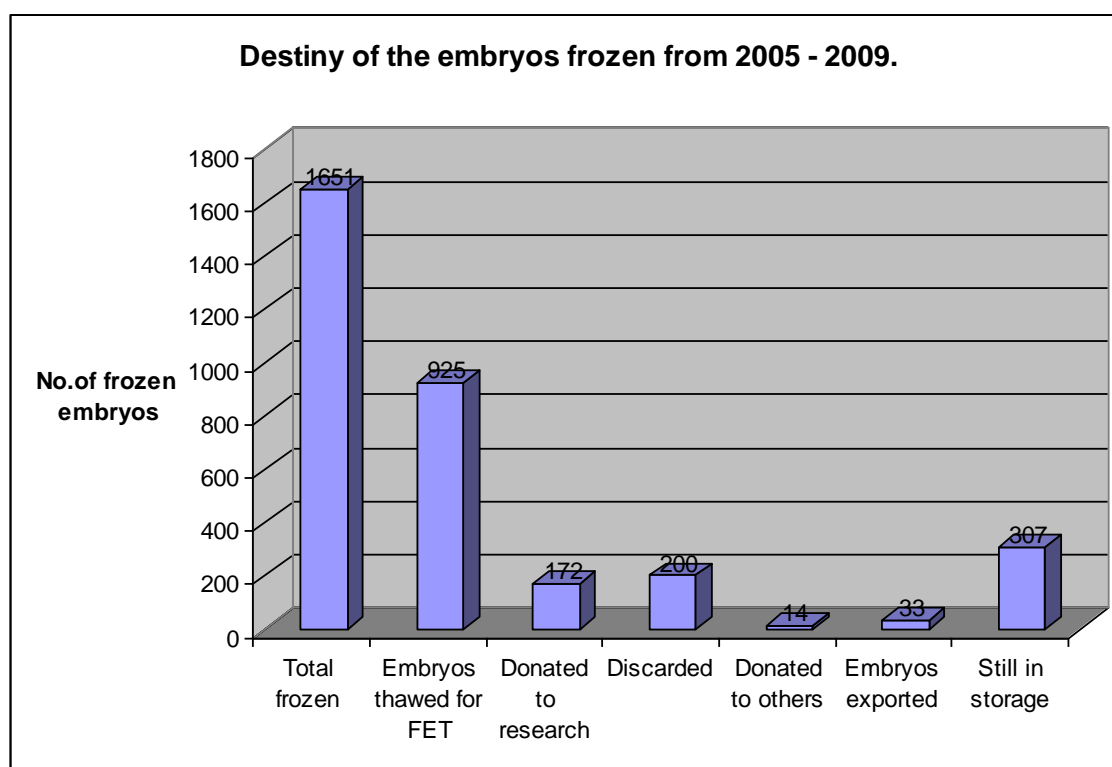


Figure 3.23 The fate of embryos frozen from 2005 to 2009. FET: frozen embryo transfer.

3.7.3.2 Duration of embryo freezing in women who have not attended frozen embryo transfer

Figure 3.24 shows the duration of embryo freezing in the 21 women who have not yet attended FET, despite being unsuccessful in the fresh cycles. Figure 3.25 shows the duration of embryo freezing in the 54 women with live births in the fresh cycles. The majority of women in each group had embryos frozen for up to 36 months. Only 12 (16%) women had stored embryos for more than 3 years, as of the end of this study; 2.67% (one woman in each group) have

had frozen embryos in storage beyond 5 years now, with the rest of the women with embryos frozen for more than 5 years having either donated them to research or discarded them.

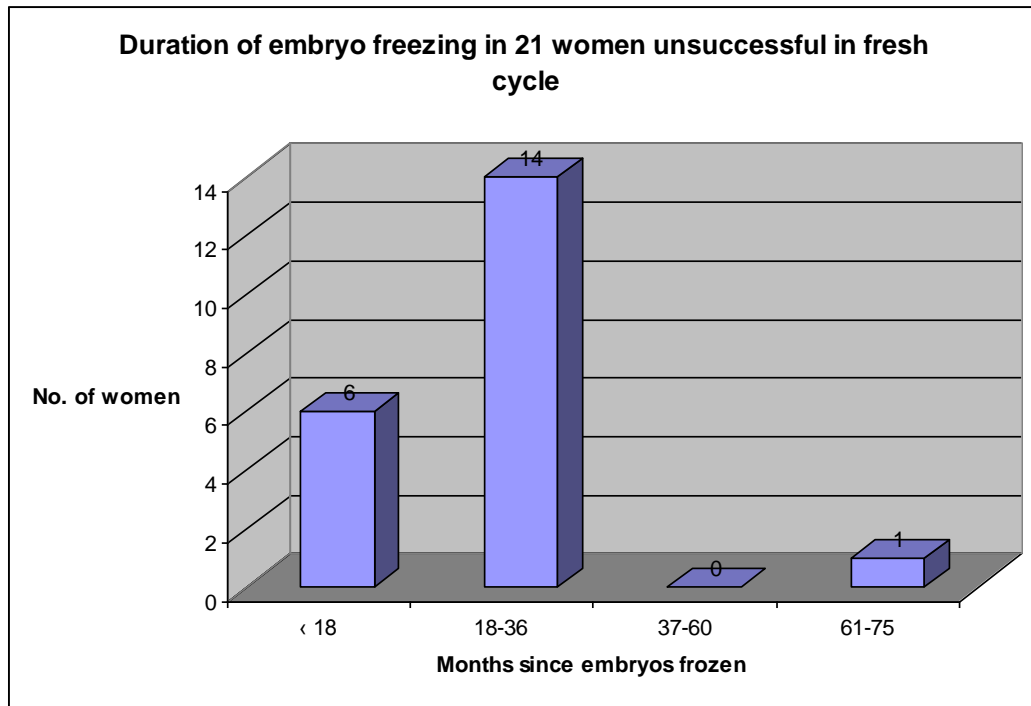


Figure 3.24 Duration of embryo freezing in women who were unsuccessful in the fresh cycle and who had not yet returned for FET.

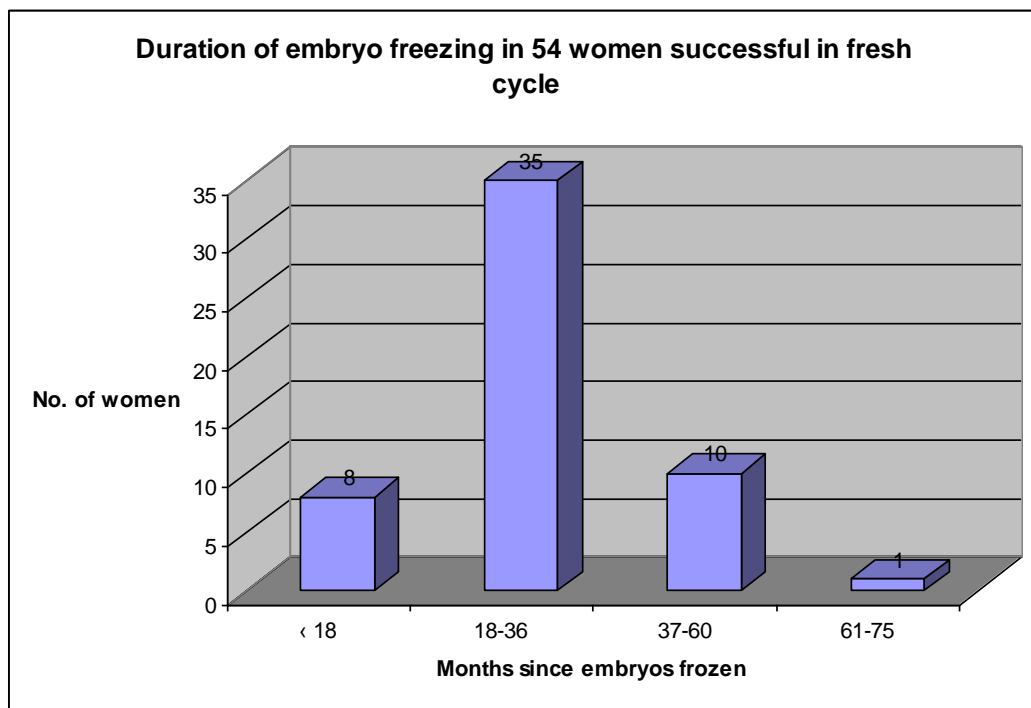


Figure 3.25 Duration of embryo freezing in women who were successful in the fresh cycle and who had not yet returned for FET.

3.7.3.3 Trend of the total number of embryos in storage

Figure 3.26 shows the overall clinic data of the total number of frozen embryos in storage from 2006 to 2010. There has been more than a 140% rise in the total number of embryos stored since 2006–2010.

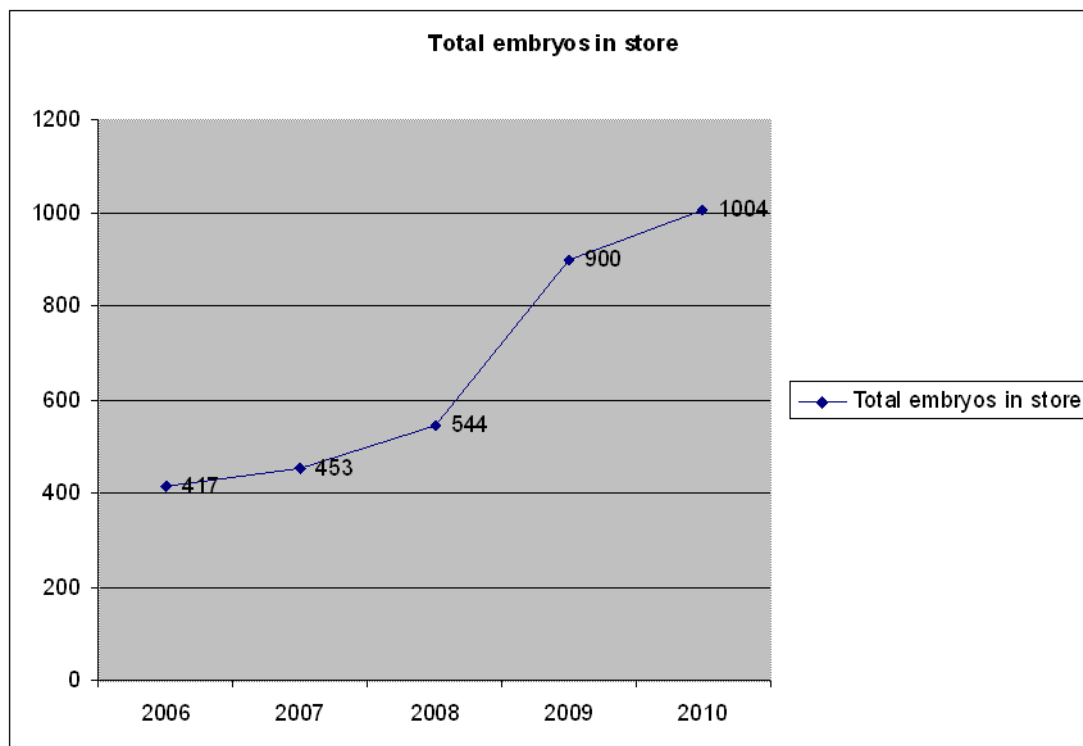


Figure 3.26 Trend of the total number of frozen embryos in storage from 2006 to 2010.

3.7.4 Comment

During the study period, more than two-thirds of the frozen embryos that had been thawed were thawed for treatment. The majority of the rest were either discarded or donated to research, in between 3 to 5 years. From the analysis of the freeze-thaw practice in this time period, 18% of the frozen embryos were found to be still in storage. Forty-nine (65.33%) women with stored frozen embryos had stored these for up to 36 months and two (2.67%) had stored them for 5 years, at the time of this study. Analysis of the overall clinic data shows that there has been more than a 140% increase in the number of embryos stored from 2006 to 2010.

3.8 Comparison of Implantation Rates Between Sibling Fresh and Frozen Embryos

The implantation rate of the fresh embryos and that of the frozen embryos derived from the same IVF treatments were compared. This information is important for couples when making the decision of whether to freeze their surplus embryos or not.

3.8.1 Data collection

To calculate the implantation rate of the fresh embryos, the number of fresh embryos transferred in the couples who had frozen treatments between 2005 and 2009 was noted from the fresh database, and the number of implantations from the treatment outcome was noted. Analysing the frozen-thaw database up to 5 April 2011, the number of frozen embryos thawed and then transferred for those couples attending FET and the implantations were also noted.

3.8.2 Data analysis

The fresh embryo implantation rate was calculated using the total number of fresh embryos transferred and the total number of implantations from them. The frozen embryo implantation rate was calculated using the number of frozen embryos transferred during FET treatment and the number of implantations from them. The two implantation rates were compared using a chi-squared test.

3.8.3 Results

The outcomes of all 329 couples who had frozen embryos were considered; 185 couples had 239 FET cycles, 206 (86.2%) of which had thawed embryos transferred. Of the 925 embryos that had been thawed, 369 were transferred in the FET treatment resulting in 40 implantations. By contrast, a total of 620 embryos transferred in the fresh treatments resulted in 158 implantations in this group of patients. Thus, the implantation rate for the fresh embryo transfer was 25.5% compared with 10.8% for the frozen embryos arising from the same egg collection ($p < 0.0005$).

3.8.4 Comment

Cryopreservation resulted in lower implantation rates, i.e. a reduced likelihood of making a baby, for comparable embryos.

3.9 Discussion

3.9.1 Description of clinic, patient population and treatment outcomes

In this section, the workload of the clinic is discussed to create the backdrop for data analysis and subsequent patient interviews. From 2005 to 2009, the LBR from fresh cycles was 24.68% per cycle started. The success rate is comparable to the national average LBR, as published in 2009 by the HFEA, which is 25.18% per cycle started (HFEA, 2012b). The LBRs in the first three IVF cycles were very similar: 25.45%, 23.09% and 24.70%, respectively. Although the largest body of evidence regarding the success rates in repeated IVF cycles shows a decline (Crosignani and Rubin, 2000), this finding was consistent with that of other studies, which showed a stable success rate in the first three IVF cycles (Croucher *et al.*, 1998; Meldrum *et al.*, 1998).

Eleven per cent of IVF cycles yielded frozen embryos and 15% of women had embryos to freeze, which seems lower compared to the figures quoted in the literature. The quoted figures for embryo freezing rates in egg retrieval cycles vary in between 21 and 76% (Battaglia *et al.*, 2010; Damario and Dumesic, 2000; De Jong *et al.*, 2002; Fugger *et al.*, 1991; Ubaldi *et al.*, 2004; Van Montfoort *et al.*, 2005; Walsh *et al.*, 2010). The percentage of IVF patients having frozen embryos is quoted to be in between 20 and 44% (Fugger *et al.*, 1991; Horne *et al.*, 1997; Jones *et al.*, 1997; Kahn, 1993; Ubaldi *et al.*, 2004).

It would appear that the slightly lower results in this study could be attributed to the frozen embryo yield rate being expressed as “per cycle started” or “per woman initiating treatment”, which also takes into account the cancelled cycles not reaching the egg collection stage, whereas in the literature, the figures are quoted as per egg retrieval episode, thus accounting for the higher values. Variation in the criteria for freezing in different units can be another cause of lower freezing rates. In the NFCL, the criterion for freezing is the presence of at least two surplus top or good-quality embryos.

3.9.2 Evaluation of the outcome of embryo freezing on live birth rates in the clinic

The improvement in the LBR following summation of the frozen-thaw live births in the NFCL was 3.33%. The various methods used to assess the CPR or

CLBR are discussed in Chapter 2. In Chapter 4, the CPR of this clinic will be evaluated in comparison to the evidence found in the literature.

3.9.3 Characteristics of patients who are likely to have frozen embryos

There is a considerable body of literature regarding the various prognostic factors determining the success of FET cycles, e.g. protocol type, fresh cycle outcome, endometrial thickness, number of follicles, numbers of oocytes and embryos and the quality of embryos transferred (Ashrafi *et al.*, 2011; Mark Hirst *et al.*, 2011; Zhu *et al.*, 2001). However, there is lack of evidence defining the characteristics of women who are likely to have embryos to freeze.

Identification of the characteristics of women who are likely to have embryos to freeze, based on their age, number of follicles or eggs retrieved and their type of treatment, namely IVF or ICSI, have been attempted in this study.

3.9.3.1 Age and embryo freezing

There is a wealth of evidence that conclusively proves the negative correlation between advanced age and fertility success, due to ovarian and endometrial factors (Hull *et al.*, 1996; Meldrum, 1993; Navot *et al.*, 1994). Yeung *et al.* (2009) noted an increased pregnancy rate in frozen-thaw cycles in women < 35 years. Although there is no evidence directly linking women's age and embryo freezing, in this analysis, the anticipated trend of women with frozen embryos being younger when compared to women with no frozen embryos, was found.

3.9.3.2 Number of follicles/oocytes and embryo freezing

The trend noted in this analysis was that women with frozen embryos had higher number of follicles and oocytes, compared to women with NF. There was a negative trend of embryo freezing seen with the highest number of follicles and oocytes. There can be at least two explanations for this observation. First, generally speaking, fewer women have very high follicle or oocyte numbers, which is clear from the similar patterns shown in figures 3.9 and 3.12.

Second, as suggested by Toner *et al.* (1991a), the retrieval of large number of oocytes (> 10) can have a small negative impact on oocyte quality as judged by fertilization rates (4% lower), which would resultantly yield lower numbers of embryos to freeze. The pathophysiology of reduced fertilization rates with > 10

oocytes, as hypothesized, could be related to gonadotropin releasing hormone agonists re-recruiting the follicles originally destined to undergo atresia, or high levels of oestrogen and progesterone disturbing healthy endometrial development.

The percentage of cycles with frozen embryos, as noted in this study, increased with an increase in the number of follicles and oocytes initially, but then levelled off following about 25–30 follicles or oocytes. This trend can again probably be explained as above. In this context, Toner *et al.* (1991a) have, however, witnessed a progressive increase in the percentage of egg retrieval cycles yielding frozen embryos, along with a rise in the number of oocytes (10% in the group with 1–5 oocytes, 62% in the group with 6–10 oocytes and 88 % in the group with > 10 oocytes).

In women with follicle numbers > 25, no association was noted with younger age and embryo freezing. In this group of women, the author has not been able to define the characteristics of the women who would have embryos to freeze. However, it may be speculated that quite a few of these women with no embryos to freeze have Polycystic ovarian syndrome (PCOS), and hyper stimulate to ovarian stimulation yielding immature, or poorer quality oocytes, which do not make good embryos suitable for freezing. It is suggested that there is disruption in folliculogenesis leading to poorer oocyte development in PCOS, caused by intrinsic molecular defect in the oocytes and the androgen excess in this condition (Patel and Carr, 2008).

In women with embryos to freeze, the number of frozen embryos actually increased along with a rise in follicle or oocyte numbers. This could be accounted by the fact that good-quality oocytes yielded good embryos suitable for freezing in these women. This observation corroborates the findings of two studies, where there was a progressive increase in the number of frozen embryos with a rise in the number of oocytes (Toner *et al.*, 1991a; Wang *et al.*, 1994). Wang *et al.* (1994) have reported that 1.5 cryopreserved embryos were generated in the group of patients with < 6 oocytes; the number of frozen embryos then doubled in the group with 6–10 oocytes and trebled in the group with > 10 oocytes. Similar figures were quoted by Toner *et al.* (1991a).

3.9.3.3 *In vitro fertilization or intra cytoplasmic sperm injection treatment and the likelihood of embryo freezing*

In this analysis, there was a higher trend for women having IVF to have embryos to freeze, compared to women having ICSI treatment (OR = 2.084, 95% CI 1.645–2.640). There is paucity of evidence in the literature associating assisted reproductive technique (ART) with embryo freezing. The observed association could be attributed to the fact that, generally, IVF embryos are of better quality, compared to ICSI embryos. A previous study demonstrated that the number of grade A(1) embryos was significantly higher in the IVF than in the ICSI group (46.4 versus 29.0%, respectively, $p = 0.02$) (Yoeli *et al.*, 2008). In another study, embryos from frozen-thawed IVF zygotes cleaved more rapidly and were more regular compared to frozen-thawed ICSI zygotes (Macas *et al.*, 1998).

Overall analysis of the trends indicate that younger women (median age: 33 years) with a good number of follicles (median number: 20) and a good number and quality of oocytes (median number: 15), having IVF treatment, were more likely to have embryos to freeze. However, this being a descriptive study, further study is required, prior to making any conclusive comment.

3.9.4 *Decisions couples make about the fate of their frozen embryos*

3.9.4.1 *Decisions made by couples with frozen embryos*

Of the 329 women with frozen embryos, 185 (56.23%) returned for FET, until the date of analysis of this study. This is a reflection of the use of the embryo freeze-thaw service. There is limited information about the return rate for women with frozen embryos in the literature. Ubaldi *et al.* (2004) presented a similar return rate of 49.6% for FET in women < 38 years and 50% in women \geq 38 years. In a long-term follow-up, Elford *et al.* (2004) similarly reported that 60% of women were back for FET over a period of 11 years. Others have quoted slightly higher figures of 64–86.8% (Horne *et al.*, 1997; Kahn *et al.*, 1993; Lornage *et al.*, 1995; Tiitinen *et al.*, 2004).

A literature review of the decision-making process by couples when deciding of how to dispose of frozen embryos, and of the factors influencing such decisions, is described in Chapter 5. Briefly, 11.25 % of couples with frozen embryos choose to donate to research, a percentage which is similar to that

quoted by Lornage *et al.* (1995), where 12% of couples donated their frozen embryos to research and 0.06% of couples donated their embryos to other infertile couples. This is similar to the experience of others, with donating to other infertile couples being the least popular option (Elford *et al.*, 2004). In this study, 12% of couples discarded their surplus frozen embryos and 60% of these couples had already achieved a live birth. The financial factor that accompanies the storage of those embryos could be one of the reasons behind this, as yearly storage fees are charged beyond 12 months of storage. There was a similar finding by Nachtigall *et al.* (2009, 2010). The finding of this study is similar to that of Elford *et al.* (2004), where 8% of couples discarded their frozen embryos, and that of Lornage *et al.* (1995), where 17.5% of couples destroyed their embryos, after storing them for 1 year. In the author's own analysis, 22.8% of couples continued to store their frozen embryos until the end of the study period, 72% of them having already achieved a pregnancy from the fresh cycle. Comparable figures have been quoted in the study by Elford *et al.* (2004), where 26% couples chose to continue storing their frozen embryos, and in a recent study, where 22.8% couples continued freezing their embryos (Provoost *et al.*, 2012). The reasons why couples continue to store their frozen embryos are going to be explored further in Chapter 5.

3.9.4.2 Frozen embryo transfer success

Clinical pregnancies were achieved in 15.06% of the FET cycles that had been started. Exploring the HFEA database, similar figures ranging from 14 to 19.5% were reported in the period from 1991 to 2006 (HFEA, 2007).

3.9.4.3 Attendance in relation to success in the fresh cycle

As shown by figure 3.19, about 18% of women having a live birth in the fresh cycle returned for a sibling pregnancy in the FET cycle, whereas the rest did not. There is paucity of information in the literature regarding this aspect. Fauque *et al.* (2010) reported even lower figures, with only two of 50 patients who were pregnant in the fresh IVF cycle returning to have FETs. Van der Auwera *et al.* (2002) quoted that 37% of the group with embryos frozen on day 2 and 62% of women with day 5 frozen embryos did not come back for a second pregnancy.

The trend of comparatively fewer women who were successful in the fresh cycle returning for FET, can be at least partially attributed to the financial aspect, as couples with a child do not have access to NHS funding.

3.9.4.4 Timescale of frozen embryo transfer

Fifty-two per cent of all women coming for FET did so within the first 6 months of embryo freezing. This is an expected observation, as the NFCL policy is that women with frozen embryos are required to go through a frozen cycle first, prior to any further fresh cycles. The vast majority (92%) of women, who returned for FET, came back within 2 years, whereas only 7.6% returned in the 2–5-year period. More than half (57%) of the delayed attendees came for FET to achieve a sibling pregnancy. Wang *et al.* (1994) also reported that following a successful fresh cycle, very few women would return for FET within 2 years, but subsequently, those who returned did so in the period of 4–5 years. Hence, they suggested that embryos should be left in storage for a minimum period of 5 years. In this context, the HFEA recommends that embryos should be frozen for an initial period of 5 years, which can subsequently be extended to a period of 10 years, with the agreement of each couple (HFEA, 2012a). The end point of this study being 5 April 2011 meant that women freezing their embryos in December 2009 were followed up for only 16 months. The complete picture, however, will only be available if followed up for 10 years.

3.9.4.5 Embryos still in storage following frozen embryo transfer

As shown in table 3.5, 8.1% of women still have embryos in storage, even after attending FET cycles. This can partially be explained by the fact that 60% of these women had either achieved a live birth in the FET cycle, or in a subsequent fresh cycle, or had been through FET recently, within the last 12 months.

3.9.5 Practical implications of freeze/thaw on the number of embryos in storage

3.9.5.1 Frozen embryo thaw rate

In this study, 68.8% of all the embryos thawed, were thawed for treatment until the time of analysis, which is higher than the figure of 51.6% quoted by Miller and Goldberg (1995), and by the figure of 46.9% quoted by Tiitinen *et al.*

(2004). However, a thaw rate of 68.8% is similar to that reported in a few other studies, which ranges from 65 to 77% (Damario *et al.*, 2000; De Jong *et al.*, 2002; Senn *et al.*, 2000; Toner *et al.*, 1991a; Wang *et al.*, 1994). The different thaw rates could be at least partially attributed to the variations in the time period of the studies, and by the varying number of FET cycles in the studies.

3.9.5.2 Duration of frozen embryos in storage for women not undergoing frozen embryo transfer

Only 2.67% of women not undergoing FET had embryos in storage beyond 5 years, up to the end point of this study, as possibly most of the frozen embryos not used for treatment were either discarded or donated to research in between 3 to 5 years of storage. However, Elford *et al.* (2004) found that after 11 years, 26% couples still preferred to retain their embryos in storage for future use.

In light of these findings, where 92% of women returning for FET did so within the first 2 years of freezing, there is probably little hope for those women who have frozen embryos in storage beyond a period of 3 years (16% not undergoing FET) to return for FET. Mandelbaum *et al.* (1998) noted that the fate of most of the frozen embryos was determined within the first 5 years of storage. Data regarding couples abandoning their stored embryos with no contact with the freezing unit or actually deciding to discard their embryos, is also limited in the literature. The figures quoted are in the range of 6–51%, and have been reported as follows: 6% (Mandelbaum *et al.*, 1998); 8% in 11 years (Elford *et al.*, 2004); 10.3% after 2 years of freezing (Luna *et al.*, 2009); 17.5% after a 1-year storage period (Lornage *et al.*, 1995); 25.2% following 2 years of storage (Walsh *et al.*, 2010); and 51% (Moutel *et al.*, 2002).

The reason why the 21 women (figure 3.24) have not yet returned for FET, despite being unsuccessful in their fresh cycles, is left to speculation. The probable causes could include: having a recent fresh IVF cycle; the couple splitting up; fulfilment of family goal by other means, such as adoption; and personal choice. The reasons why couples default treatment will be examined in the next chapter.

3.9.5.3 Fate of the embryos frozen from 2005 to 2009

Up to 5 April 2011, 12.8% of thawed embryos had been donated to research. Lower figures were reported in other studies, where 2–3% of frozen embryos were donated to research in the USA and Canada (Baylis *et al.*, 2003; Hoffman *et al.*, 2003). However, Newton *et al.* (2007) reported that 39% frozen embryos in their unit were donated to research; in this study, 14.7% unused frozen embryos were discarded in this time frame. Our experience is slightly higher than that of Mandelbaum *et al.* (1998), who calculated a 4.7% rate of embryo disposal in their unit, during a follow-up of 10 years. Van der Auwera *et al.* (2002) estimated that 20% of all frozen embryos would be subsequently destroyed and Darlington and Matson (1999) quoted a similar figure of 18.8% following 3 years of cryopreservation.

Only 1% of frozen embryos have been donated to other infertile couples during this study. There is scarce information regarding this aspect in the literature, but there is some evidence that a very small percentage of stored embryos are actually donated for use by other couples. Nachtigall *et al.* (2005) reported that 3–5% of frozen embryos were donated to other couples, and a similar figure of 2% was cited by Hammarberg and Tinney (2006). The decision-making process used by couples when disposing of frozen embryos, as discussed in the literature, will be discussed in Chapter 5.

3.9.5.4 Increase in the number of stored embryos

The increase in the number of frozen embryos has been dramatic since 2009, as more embryos were frozen due to a change in the freezing policy, when day 3, rather than day 2, embryo freezing was started, and the freezing of two good surplus embryos, instead of three, was offered. This, compounded by relatively few couples deciding to discard their surplus frozen embryos, has led to the growing storage of frozen embryos. There has been worldwide concern about the growing number of frozen embryos in storage (Bankowski *et al.*, 2005; Lyerly *et al.*, 2006; Newton *et al.*, 2007), which are eventually abandoned by their owners.

3.10 Conclusion

This chapter has described the scope and practice of the NFCL, from where couples for the interviews discussed in Chapter 7 were recruited. The findings

from this study should help identify the women who are likely to have embryos to freeze and give them the necessary practical facts about embryo freezing, thereby facilitating their decision-making with regard to this issue.

Later sections of this thesis will assess the influence of cryopreservation of embryos on the CPR and explore the actual decision-making process of couples considering embryo freezing; this will help evaluate this practice from the perspective of the service provider and the point of view of couples undergoing IVF.

Chapter 4. Cumulative Pregnancy Rates Including Embryo Freezing in the Newcastle Fertility Centre at Life

4.1 Introduction

The previous chapter provided a snapshot of the work of the NFCL clinic, attempted to identify the characteristics of women with embryos to freeze, and traced the decisions of couples with frozen embryos, and the fate of frozen embryos. The aim of this chapter is to answer the research question: “How does embryo freezing influence the CPR?” This thesis attempts to answer this question by analysing the CPR following three NHS-funded IVF treatments, and then again by following the inclusion of pregnancies from FET. A secondary aim is to evaluate the reasons why couples drop out from IVF treatment. It is hoped that information about these facts will inform their decision-making before they embark on treatment.

The 2004 NICE fertility guidelines on the management of infertile couples recommended that all eligible sub fertile women between 23 and 39 years should be offered up to three IVF treatments funded by the NHS (NICE, 2004). Since 2009, the PCTs in north-east England provide funding for the full NICE treatment recommendations. These are mostly provided at the NFCL within 18 weeks of referral for investigation. This includes the provision of the three IVF treatments including embryo freezing. This study relates to a well-defined geographical population in the north-east of England only.

As discussed in Chapter 2, the CPR for three treatments has been reported to be between 43.8 (De Jong *et al.*, 2002) and 65.5% (Olivius *et al.*, 2002). These studies relate to potentially selected populations with good prognosis, whereas the NHS population reflects everyone who requires treatment irrespective of their ability to pay.

There being no statutory guidelines, PCTs in the UK have implemented the NICE recommendations inconsistently. A survey by the All Party Parliamentary Group on Infertility (2011) reported that 73% of PCTs in the UK were not complying with the NICE recommendations and only 27% of PCTs in the UK offer the recommended three NHS-funded IVF treatments. This report, backed by all MPs, urged all PCTs in the UK to fully implement the NICE recommendations. PCTs normally fund embryo freezing for the first 12 months,

and the subsequent FETs within that time period. Couples with frozen embryos are usually encouraged to attend for frozen treatments prior to having further fresh treatments. Information about the outcome of treatment provision according to the NICE criteria, i.e. assessing the CPR following three NHS-funded treatments including embryo freezing, will inform this debate.

The dropout rate following successive IVF treatments has been reported as ranging from 17% (Verberg *et al.*, 2008) to 47.8% (Pelinck *et al.*, 2007). The reasons why women drop out from IVF treatment have been identified as being of a financial, geographical, physical and emotional nature; informative censoring has also been identified as playing a role (Daya, 2005; Witsenburg *et al.*, 2005). Informative censoring is when clinicians dissuade couples from pursuing further treatment due to anticipated poor response (Pelinck *et al.*, 2007). Within an NHS setting, there is no financial impact for couples, thus a significant negative factor against further treatment is removed. It is thus appropriate to study the dropout rate for NHS-funded patients, as this is important in resource planning.

4.2 Materials and Methods

This is a retrospective observational study, where the electronic databases for fresh and frozen treatments were analysed from August 2009 to July 2011, until there were 100 women undergoing the third NHS treatment, to get a reasonable number to calculate the CPR following three treatments. This resulted in the analysis of 812 women undergoing the first NHS treatment. The end point was the first clinical pregnancy for the couple, defined as the presence of a fetal heartbeat in the pregnancy scan. The timescale for this analysis was chosen as the full implementation of the NICE guidelines, including the provision of embryo freezing, started from this period.

4.2.1 IVF treatment

All women in this study had standard IVF or ICSI treatments, using sperm from the ejaculate or following surgical retrieval. Following conventional fertilization by standard IVF or ICSI procedure, a maximum of two day 3 embryos were transferred. More than one good-quality surplus embryos were frozen using slow freezing techniques and were later transferred to stimulated frozen-thawed treatments.

4.2.2 Treatment intervals

From the database of fresh IVF treatments, the 812 women were followed up to identify the dates of their first, second and third treatments. Treatment outcomes (clinical pregnancy) were noted for all the treatments. The median time intervals and SD between the first and second treatment and second and third treatment were calculated.

4.2.3 Defaulters

Couples were classified as defaulters if they had not returned for their next planned treatment within the mean +2 SDs of the interval time for the group. The clinical records of the defaulting women were analysed to identify the causes of the default.

4.2.4 Calculating the cumulative pregnancy rate

The CPR following the three NHS-funded IVF treatments, respectively, were calculated using life table analysis, as mentioned by Cooke *et al.* (1981), and as described in Chapter 2. The CPR was calculated taking into account the couple's first clinical pregnancy following three fresh treatments and the total number of pregnancies following fresh and frozen treatments, to evaluate the impact of embryo freezing.

4.3 Results

4.3.1 Treatment outcomes

Eight hundred and twelve women had their first IVF treatment during the analysis period, 298 progressed to their second IVF treatment and 100 women had their third treatment. One hundred and ninety-five out of 1210 (16.1%) egg collections resulted in embryos being frozen. The outcomes following fresh and frozen treatments are shown in figure 4.1; 381 women were pregnant following either fresh or frozen treatments.

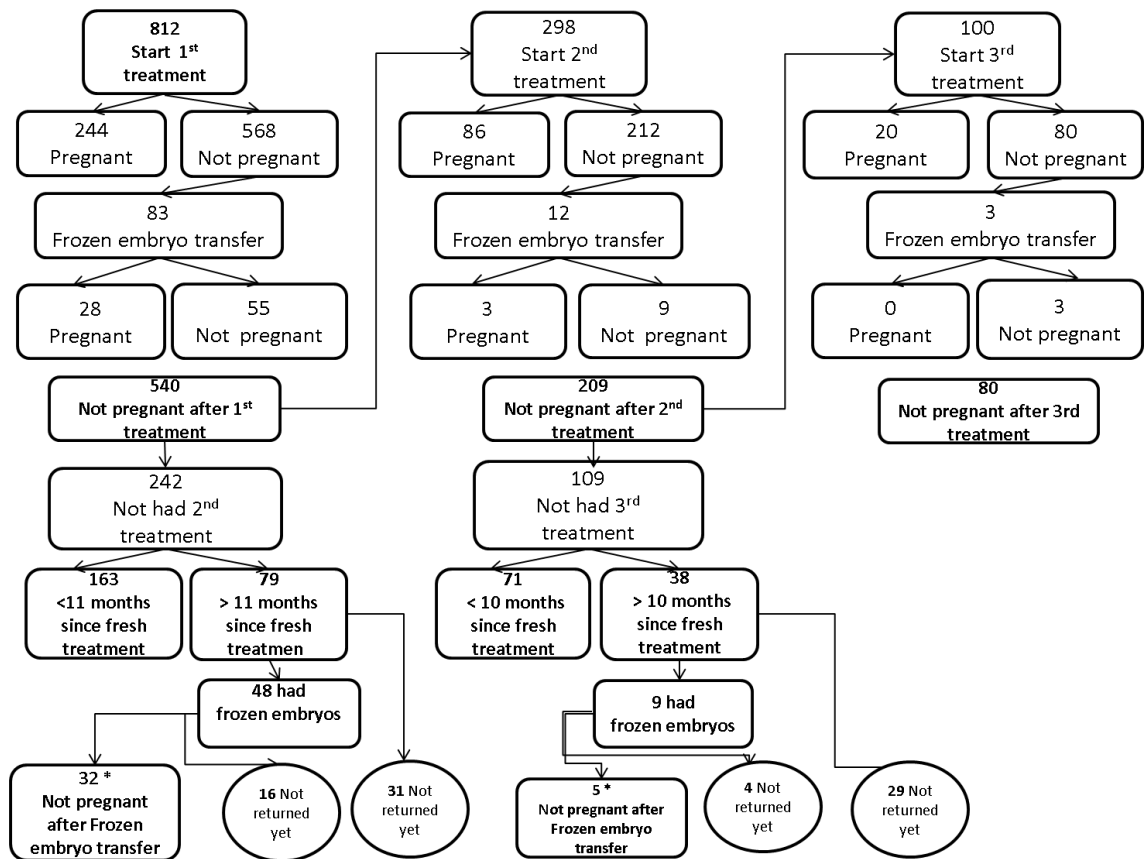


Figure 4.1 Flow chart of the treatment outcomes for all the patients. Eight hundred and twelve women, starting with their first treatment and all the way to the end of their third treatment, were followed up. The oval boxes refer to the women deemed to have defaulted. *Women who were not deemed to have defaulted as they had attended FET for less than 11 months (*32 women) and 10 months ago (*five women), respectively. FET: frozen embryo transfer.

4.3.2 Time intervals and defaulters

The median time intervals ± 2 SD and between the first and second fresh treatment was 5 months ± 2.97 ; that between the second and third treatment was 5 months ± 2.53 SD. The median $+2$ SD, i.e. 11 months and 10 months, was taken as the anticipated time for 95% of women to return for their second and third treatment respectively.

Figure 4.1 shows the status of women not returning for their subsequent treatments, despite not achieving pregnancy; 242 women had not as yet returned for their second NHS-funded treatment despite having no success with the first treatment. When these 242 women were followed up, it was found that 163 of them had had their first treatment less than 11 months previously. Of the remaining 79 women, 48 had frozen embryos, 32 had actually returned for their FET treatments but were not pregnant and 16 were yet to come back. It was interesting to note that 31 women had not returned for the second fresh IVF treatment beyond the expected time interval and for no apparent reason.

One hundred and nine women have so far failed to attend their third fresh NHS treatment despite being unsuccessful in the previous fresh treatment. Out of these, 71 were found to have had the previous fresh treatment within the last 10 months. Nine women out of the remaining 38 had frozen embryos and had attended FET treatments, albeit without success. However, 29 women were deemed defaulters, as they were beyond the anticipated time interval of 10 months.

Figure 4.1 shows that 80 women (circular blocks) failed to return for fresh or frozen treatments within the expected time period and were thus deemed to have defaulted.

4.3.3 Cumulative pregnancy rate

Table 4.1 shows the life table analysis used to calculate the CPR following the fresh treatments only and the fresh combined with the frozen treatments. The CPR per fresh treatment was 30.1%, 50.2% and 60.2%, respectively, and that including the FET was 33.5%, 53.4% and 62.7%, respectively, following the three consecutive treatments (figure 4.2).

Treatment ranks	No. not pregnant at start	Pregnant during treatment		“Drop outs”	Proportion pregnant in treatment		Proportion not pregnant in treatment		Cumulative proportion not pregnant		Cumulative proportion pregnant	
		F	F + FET		F	F + FET	F	F + FET	F	F + FET	F	F + FET
1	812	244	272	242	0.30	0.33	0.69	0.66	0.69	0.66	0.3005	0.335
2	298	86	89	109	0.28	0.29	0.71	0.70	0.49	0.46	0.5024	0.5337
3	100	20	20		0.2	0.2	0.8	0.8	0.39	0.37	0.6019	0.627

Table 4.1 Life table analysis showing the cumulative pregnancy rate following fresh and frozen treatments. F: fresh; FET: frozen embryo transfer. “Dropouts” represent the number of women not attending for the next treatment, despite being unsuccessful in the previous treatment.

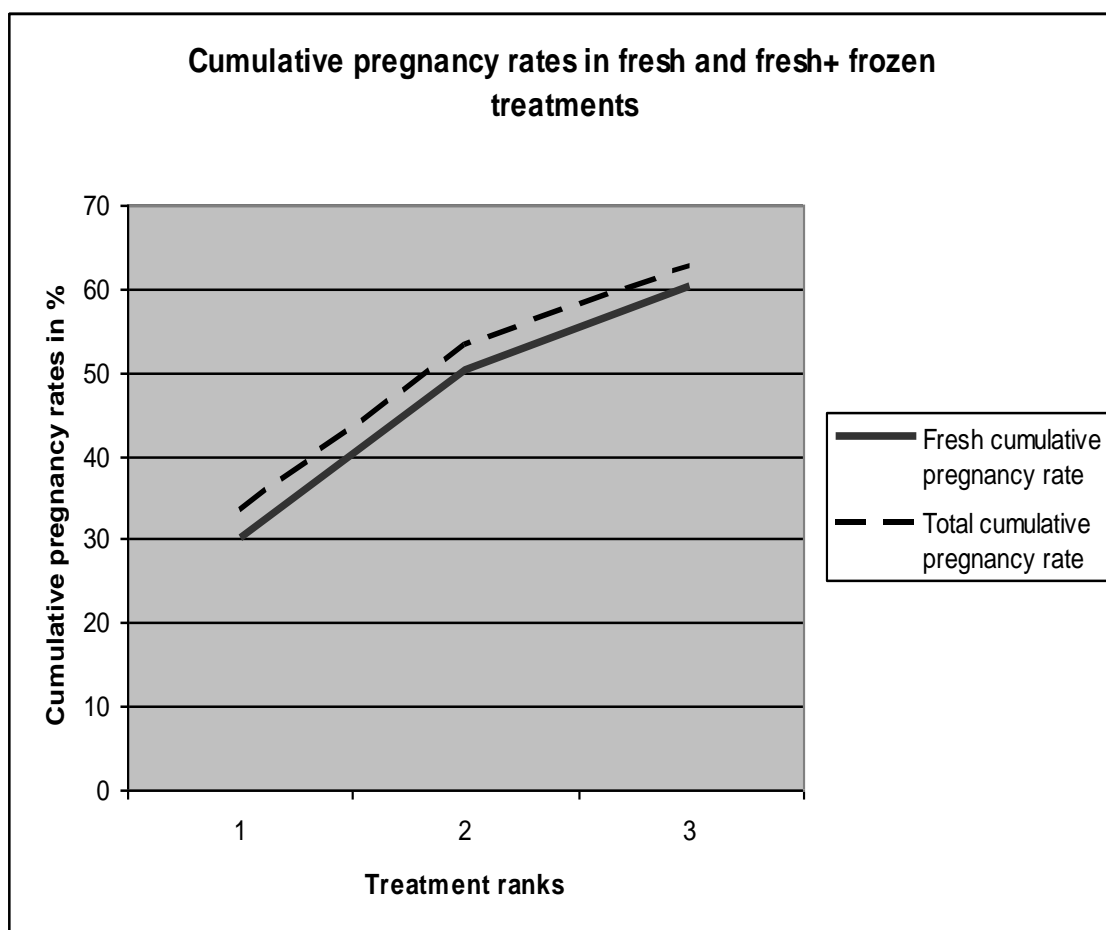


Figure 4.2 Cumulative pregnancy rate (CPR) following three fresh cycles and including frozen IVF treatments. This is the graphical representation of the CPR following three treatments. The solid line represents the CPR following the fresh IVF treatments only, while the broken line represents the CPR including the pregnancies from the frozen treatments.

4.3.4 Reasons for default

Eighty women (9.8%) did not complete the three NHS-funded treatments. Table 4.2 shows the various reasons why couples defaulted in the second, third or frozen treatment.

Therefore, 90.2% couples are likely to complete three NHS-funded treatments until they achieve a pregnancy within the anticipated time interval of approximately 2 years.

Reason	Second treatment	Third treatment	FET
Age	6	4	
Informative censoring*	10	7	
Emotional	5	6	3
Geographical	3	1	2
Spontaneous pregnancy	3	3	9
Couple separated	3		3
Failed clinic appointment	1	1	
Fertility preservation in cancer			2
Medical contraindication			1
No funding		1	
Miscellaneous**		6	
Total	31	29	20

Table 4.2 Reasons for patients defaulting treatment. *Poor ovarian response, retrieval of no oocytes and failed sperm retrieval; ** High body mass index, medical issues, desire to try naturally.

4.4 Discussion

The outcome of this study not only shows the influence of embryo freezing, but also illustrates the outcome of providing three NHS-funded IVF treatments along with embryo freezing, as recommended by NICE.

The CPR following the three fresh treatments was 60.2%, while the CPR including the frozen treatments was 62.7%. The CPR in the NFCL after the third treatment including embryo freezing was higher than that quoted in some studies: 47.8% (Kovacs *et al.*, 2001) and 43.8% (De Jong *et al.*, 2002). However, figures from this study are quite comparable to more recent statistics of CLBR following a third treatment, as presented by Olivius *et al.* (2002; 63.1%), Witsenburg *et al.* (2005; 53.2%) and Gnoth *et al.* (2011; 52%).

The incidence of freezing per egg collection in our study was 16.1%. Analysis of the HFEA anonymous data set for 2010 (HFEA, 2010b) found that 13,139/47,863 (27%) of egg collections were associated with embryos being frozen; 918 (7%) of these were related to blastocyst transfer treatments. Excluding those who had only one embryo frozen (the clinic policy at the time of this study), there were 10,349/47,863 (21%) of egg collections associated with embryo freezing. This indicates that the protocol of this clinic for the selection of embryos suitable for freezing was consistent with contemporaneous practice. It is recognized that freezing only one embryo has a poor prognosis for success; thus, the overall results in this study are unlikely to be changed if we had frozen one embryo only (Prades *et al.*, 2009).

There was a 4.15% increase in CPR after the third treatment and an absolute increase of 2% following the inclusion of the pregnancies from the FET, which is a modest benefit to the overall CPR. This is similar to reports in previous studies where the additional benefit to the CPR or CLBR following embryo freezing was quoted as being between 2% and 8% (De Jong *et al.*, 2002; Kahn *et al.*, 1993; Mandelbaum *et al.*, 1998; Van der Elst *et al.*, 1996; Wang *et al.*, 1994). This statistical analysis probably reflects the accepted understanding that the couples with the best prognosis for pregnancy are those with several best-quality embryos. Such couples have the highest chance of conceiving after FET and the highest chance of having frozen embryos. This “best-prognosis cohort” is small, but disproportionately represents those who conceive after FET. Since the end point of our analysis is pregnancy, the impact of freezing on the overall cumulative outcome is small.

Regarding the outcome of thawed embryo transfers, there were 31 clinical pregnancies from 98 FET treatments (31.6%); this compares favourably with national data of 22.8% CPR per FET (HFEA, 2012b). Therefore, it is not deemed that the low contribution of FET to the overall CPR was due to poor freezing techniques. This study did not include embryos frozen at the blastocyst stage, nor those frozen using vitrification technology. The FET pregnancy rate per embryo transfer is higher for blastocysts, in comparison to early cleavage-stage transfer (30.3% vs. 23.1% for double-embryo transfers) (HFEA, 2012b). The added value of FET may increase as the technology improves but this is unlikely to change the CPR unless we are able to provide embryos suitable for freezing for more patients.

The main statutory requirements by the PCTs for NHS-funded treatment include: the woman’s age, from 23 years until her 40th birthday; the man’s age > 23 years; the woman’s body mass index (BMI) being between 19 and 30; the couple having had a stable union for at least 2 years; at least 2 years of unexplained subfertility (> 1 year if the woman > 35 years old); neither partner having a living child (including an adopted child) from current or past relationships; neither partner having being sterilized. Thus, the results are based on a population that is selected primarily by geography, primary infertility and age.

The median interval between successive IVF treatments was purely determined by patient choice, as there was no clinic waiting list for treatment.

The anticipated time limit for completion of the three NHS-funded treatments is approximately 2 years, based on the median +2 SDs (i.e. 11 months and 10 months between the successive treatments). However, in the experience of Witsenburg *et al.* (2005), 90% of all pregnancies occurred within the first three treatments and 95% of all treatments were within a time frame of 3 years. They suggested that, to derive the final live birth outcome rates, a minimum follow-up period of 3 years is warranted.

In this study, almost 9.85% of the 812 women starting the first treatment were no longer likely to return for further treatment. Other studies have reported higher dropout rates (Pelinck *et al.*, 2007; Verberg *et al.*, 2008); however, in our experience, women were keen to complete the three IVF treatments funded by the NHS until they achieved a pregnancy. The low rate of treatment defaults may also be a positive reflection on the quality of the service, since dropout rates are a vital marker of quality control (Schröder *et al.*, 2004).

When reviewing the causes of couples defaulting IVF treatment, most had significant reasons. The main factors reported elsewhere as being responsible for patient dropping out are financial, geographical, physical and emotional aspects, as well as informative censoring (Daya, 2005; Witsenburg *et al.*, 2005). Pelinck *et al.* (2007) reported that where there was a poor ovarian response, no oocyte retrieval, failed fertilization and failed surgical sperm retrieval, the effects of informative censoring by clinicians dissuaded couples from pursuing further treatment. The decision to try to achieve pregnancy spontaneously or couple separation were noted in our study and reflected other reports (Olivius *et al.*, 2002). Psychological and physical stress-related dropouts were one of the major factors in our experience, as also reported in other studies (Pelinck *et al.*, 2007; Schröder *et al.*, 2004; Witsenburg *et al.*, 2005). Occasional failed marriages and relationship breakdowns in couples undergoing IVF treatment bear testimony to the emotional cost incurred in undergoing IVF treatment (Boivin and Takefman, 1995; Gourounti *et al.*, 2012; Newton *et al.*, 1990).

Stress-related issues of patients dropping out of IVF treatment were analysed in an Australian study, where the major reasons why unsuccessful couples ceased to have further treatment were found to be: "I had had enough" (66%); "emotional cost" (64%); "could not cope with more treatment"(42%); and "physical cost" (39%) (Hammarberg *et al.*, 2001). This study reports similar findings to other reports, with only finance being excluded as a default reason.

Other practical aspects were identified that withdrew their eligibility for NHS funding, e.g. a rise in BMI or reaching the age limit of 40.

The end point of this study was clinical pregnancy. While the ideal end point is the LBR, the analysis was restricted to cumulative clinical pregnancy rates due to time constraints. Based on the author's previous analysis at this centre, it can be concluded that there would be about 8% attrition rate when considering live births, which would give an estimated CLBR of around 57%.

5.4 Conclusion

Thus, the results, albeit pertaining to one particular geographical area, would convey the realistic outcome of having three NHS-funded IVF treatments. It would also inform couples of the modest influence of embryo freezing on the CPR, when the overall picture is considered. It is hoped that this will assist couples in making an informed decision when facing the complex decision-making of whether or not to freeze their surplus embryos.

Conclusion of Part 1

In the preceding chapters, the literature regarding the CPR was reviewed, including that related to embryo freezing, and the methods and potential biases of its calculation were evaluated. A snapshot of the clinic where this thesis was researched and from where the couples were recruited for interview was also provided. The analysis shows that only about 15% of IVF couples have embryos to freeze. The majority of couples use frozen embryos for the purpose for which they were created, i.e. thaw them with the intention to have a baby. However, on evaluation of the NHS-funded embryo freezing programme, there is a modest improvement of about 4% in the overall CPR at the end of the third NHS-funded IVF treatment, including embryo freezing. This is important information that couples need to be given when making decisions about embryo freezing.

The difficult decision-making behind embryo freezing is possibly dependent not only on practical and statistical information, but also on other multiple personal and social factors interrelated in a complex matrix, which will be explored in the following chapters.

Part 2: Investigating Patients' Experiences When Faced with the Decision of Whether to Freeze Embryos

There is evidence in the literature that the decision of surplus frozen embryos disposal is difficult and emotionally fraught, but there is very little evidence regarding how couples make the complex decision of whether to freeze or not to freeze their surplus embryos in the first place. In this section of the thesis, the literature about embryo freezing is reviewed and any gaps in our current knowledge are identified. Then, the findings from interviews conducted with couples who have been through at least one cycle of IVF are presented. Through these findings, data is put forward that shed light on previously unexplored areas, leading to an understanding of how couples make the complex decision to freeze embryos and their views on this subject.

Chapter 5. Literature Review on Couples' Experiences of Embryo Freezing

5.1 Introduction

Cryopreservation of embryos is now a standard practice in most fertility units. A review of the literature regarding the practical aspects of embryo freezing has been detailed in Part 1 of this thesis. The overwhelming majority of patients are known to accept, given the option, to freeze their surplus embryos (Hug, 2008; Laruelle and Englert, 1995; Svanberg *et al.*, 2001). Some relatively old data reported that 0.4% (Lornage *et al.*, 1995) to 2% (Laruelle and Englert, 1995) of couples declined embryo freezing. In this chapter, evidence presented in the literature about the attitudes of couples towards the practice of embryo cryopreservation is reviewed.

Prior to examining the attitudes of couples towards embryo freezing in the literature, it is important to understand that the embryo can have different meanings to different individuals and groups.

5.1.1 *The moral status of the embryo*

The elusive entity of the “embryo” has a contentious moral status and has been at the crux of various debates, although, as we shall see, in most public debates the nuances are lost in favour of seeing the embryo either as “fully human” or as “a bunch of cells”. The debates stem from the perception of the embryo as the beginning of “life” by various sections of society; some ethicists and philosophers, and the “pro-life” debates, argue for the entitlement of the same “rights, respect and protection” for an embryo, as for an individual (Lyerly *et al.*, 2006; Parry, 2003). Perceiving embryos as living entities results in contention regarding the practice of embryo freezing, which is seen as “suspending life” (Hounshell and Chetkowski, 1996), and the use of embryos in research, such as in stem cell research (Parry, 2006).

Previous studies indicate that to some IVF couples the embryo is equivalent to a person, and should have the same rights as an individual (Laruelle and Englert, 1995), while some perceive embryos as virtual children whose interests need to be protected (De Lacey, 2005; Laruelle and Englert, 1995; McMahon, 2001; Nachtigall *et al.*, 2005; Svendsen and Koch, 2008). Some couples see embryos as living entities, capable of feeling pain and suffering (Nachtigall *et*

al., 2005). In a study by Haimés *et al.* (2008), several people interviewed in the UK viewed their embryos as babies, whereas others disagreed. However, all started their deliberations with “baby talk”, as IVF treatment frames discussions in terms of babies, but subsequently agreed or disagreed on their views of embryos as babies.

On the other hand, many couples conceptualize embryos as nothing more than a cluster of cells, with no moral status (Bankowski *et al.*, 2005; Fuscaldo *et al.*, 2007; Haimés *et al.*, 2008; Lyerly *et al.*, 2006). Some patients even described embryos as a developing multicellular entity (Mitzkat *et al.*, 2010), whereas to others they are just like any other biological tissue (Van Montfoort *et al.*, 2005).

Many couples perceive the embryo as similar to a “seed”, or even as an inanimate tissue with the potential to grow into a child (De Lacey, 2007a).

However, couples’ conceptualisation of frozen embryos can be different when the embryos have been frozen for some time. This was evident when Swiss couples (Scully *et al.*, 2010), who had embryos frozen prior to 2001, and with changing legislation in the country with the introduction of the new law on stem cell research (LSCR) in 2004 (Scully and Rehmann-Sutter, 2006), were faced with the options of either discarding their unused embryos, or donating them to stem cell research. These couples perceived the frozen embryos as potential research material and clearly distinguished them from ‘babies’; a few described them as ‘little Eskimos’ or ‘little polar bears’. The emotional attachment to these embryos seemed to have disappeared, and these were perceived by the couples as related to the biomedical domain. Thus, the ‘embryo’ had different meanings to individuals in different socio-cultural time and space (Haimés *et al.*, 2008).

As well as giving consideration to lay perspectives on the human embryo, it is worth giving consideration, given the focus of this thesis, to the distinctions between social scientists’ and moral philosophers’ analysis of the human embryo.

The embryo has been recognized by certain philosophers as a “morally laden, but abstract entity ... deserving respect” (Haimés and Taylor, 2009), although different philosophers take different stances, as shown later in this section. Moral philosophers tend to debate the moral status of the human embryo because of a concern with the nature and the distinctiveness of human

life and dignity, and deal with the abstract notion of 'the embryo', from the points of view of any anonymous or generalized 'persons', as opposed to considering the accounts describing the lived experiences of individuals (Scully et al, 2010). More recently social scientists have become involved in these discussions less because they are concerned about the moral status of the embryo itself and more because they are interested in analysing how debates about the moral status of the human embryo reveal wider social positionings and structures. They are interested in the social positioning of the embryo itself, (e.g. some argue that it is at the "margin of human life" and has an "ambiguous and contestable" status) and in the social positioning of those debating the embryo (Haimés and Luce, 2006; Waldby and Squier, 2003). Social scientists will also tend to investigate the lived experiences of the individuals and groups involved (whether patients, doctors, bioethicists, regulators etc.) to explore whether these perspectives are distinct or similar, and in what way (how and why) they are distinct or similar. They will often have an interest in patients' perspectives as these have tended to be neglected in formal discussions by policymakers, professionals and bioethicists (Scully *et al*, 2010). Thus, social scientists analyse why others take an interest in the moral status of the human embryo as part of social scientists' wider interests in the structuring of distinct social domains.

The following shows how the moral status of the human embryo has been debated. The 1984 Warnock report, on which the legislation permitting research on human embryos up to 14 days was based (Human Fertilisation and Embryology Act 1990), summed up the moral status of the embryo as having a "special status, but not the same status as a living child or adult", but, at the same time being "entitled to a measure of respect, beyond that accorded to an embryo of other species" (Warnock, 1985). Steinbock (2001) argued in support of the permission to use the early human embryo in research by suggesting that its moral status is questionable, since it is an entity lacking sentience, i.e. any sensory perception or consciousness, though this fact does not imply an absence of any moral value (Steinbock, 2001). However, Gibson (2007) argued that for those individuals who attribute a human status to the embryo from right after conception, it is failure of respect of the embryo as a person. In this context, Meyer and Nelson (2001) argued that since the human embryo is "alive", it does have a moral status, but it is weak in comparison to that of other

sentient beings, though the embryo deserves genuine respect. The weak moral status allows, on the one hand, the killing of the embryo for research, but on the other hand, the respect for it dictates that it cannot be harmed or killed without “good reason”, i.e. not for the purpose of trivial research. Therefore, Callahan (2001) recommended that the goal for research should be an important one, and that the destruction of the embryo should be associated with an acknowledgement of regret and an appropriate sense of loss.

UK legislators, while permitting the use of embryos for research, were persuaded by these arguments about the embryo: the “argument from suffering”, as embryo research can potentially develop the treatment for diseases; the “argument of twinning”, as the embryo can split and grow into two individuals; the “argument from capacities”, which denies it the same status of a human being, as it does not have human attributes and cannot think, act or feel any pain; and the “argument from potentiality”, appreciating its capacity to grow into a human being, but only under specific conditions (Haimes *et al.*, 2008; Lizza, 2007).

Further elucidating the issue of the status of and respect for the human embryo, Robertson (1995a) stated that even if the embryo lacks any moral status, it deserves genuine respect as it is the “potent symbol of human life”. Gibson (2007) explained that, regardless of the capacities of the human embryo, it is its “humanness” that imparts it its special moral status.

Regarding the aspect of respect for the human embryo, Callahan (2001) suggested that the respect is of no value to the embryo itself, but only “makes the researchers and embryo donors feel better”. In the continuing debate, Meyer and Nelson (2001) argued that the moral status of the embryo should also consider the respect of the attributes of the embryo by other “moral agents”, i.e. the individuals concerned in its making (the couple). Acknowledging the uncertain moral status of the embryo, Cohen (2001) recommended that there should be appropriate ethical uses of the human embryo, and that too with extreme caution.

Thus, there has been much debate regarding the moral standing of the human embryo, though no consensus has been reached.

Gibson (2007) concluded that the human embryo is an enigmatic symbol and warrants further endeavour to find out the meaning of “humanness” and “moral status”.

5.1.2 The concept of the embryo: dynamic and nuanced

Interestingly, in one paper, the concept of the embryo was a dynamic one, from the perspective of the patients of the U.K. and the Swiss cohorts, and varied with the stage of IVF treatment (Haimes *et al.*, 2008). To many, it was the symbol of hope prior to the pregnancy test result (Svanberg *et al.*, 2001). Once transferred inside the uterus, it acquired the status of a baby in the perspective of some (Mitzkat *et al.*, 2010). Haimes and Taylor (2009) described a complex system of classification of embryos in the view of IVF couples. Initially, all embryos were perceived as equally important and precious because rare entities, but following embryo gradation, the couple's focus shifted to the viable "good embryos" and the others became less important. At the time of the study, that IVF clinic had the criteria of having at least four surplus, good-quality embryos for freezing. On later reflection, when couples realized that some good embryos might have been denied freezing based on clinic regulations and had gone to research instead, they were distressed. Those good-quality embryos which were declined freezing were termed "the troubling third (or potentially fourth or fifth) embryo" by the researchers. This reflected how the embryos were perceived differently by IVF couples at different stages of treatment, and hence had a dynamic nature.

The nuanced nature of the embryo has been captured in various studies, which are described here; the nuances of the embryo related to their allocated gradation are evident in this study. The embryos were distinguished by the IVF couples as "good-" and "bad-" quality, based on embryo grading (Mitzkat *et al.*, 2010). Viable and non-viable embryos were not given the same status by couples, and the viable ones were deemed "precious", due to their potential to make a baby. However, some couples did not approve of the gradation of embryos, as they felt it was associated with a sense of disrespect towards the embryos. A few also thought gradation was inappropriate, as it did not give due respect to their personal, emotional, physical or even financial investment in creating the embryos (Parry, 2006).

The effect of cultural values and norms has been recognized in a social science study of the Chinese population, where any surplus frozen embryos lost their importance in the couple's perspective after having a child, due to the Chinese one-child policy (Mitzkat *et al.*, 2010). Therefore, embryos were seen

not as fixed biological entities, rather by having a nuanced character defined by social contexts (Haimés and Taylor, 2009; Haimés *et al.*, 2008).

The use of embryos in stem cell research has added a new dimension to the nuanced concept of embryos, as they were identified as having “dual reproductive” value by developing into babies and transforming into stem cells (Franklin, 2006). They are deemed a precious resource to stem cell scientists (Lyerly *et al.*, 2006; Nachtigall *et al.*, 2005; Newton *et al.*, 2007; Niskér and White, 2005; Van Voorhis *et al.*, 1999) and their contribution to scientific research imparted value to the ones not used for reproduction purposes, as opposed to just discarding and wasting them (Haimés *et al.*, 2008). As evidenced from past research, scientists perceived embryos as “moral work objects”, to reconcile their personal values and conflicts, adding a completely new dimension to the embryo concept (Ehrich *et al.*, 2008; Porter *et al.*, 2010).

Authors have also debated the right of ownership over embryos. It is an important question related to this thesis, in terms of who is authorized to make decisions about embryo freezing – is it the IVF couple or is it the decision of the IVF unit. Is it statutory legislation or does the decision rest on the verdicts of the ethicists? In the context of the use of embryos in research, Chan and Quigley (2007) have debated the ownership of embryos and the right to property over genetic material. The authors concluded that even if there were property-based rights over one’s embryos created using IVF, there was no right of an individual in preventing those embryos from being brought to birth on the ground of having the right over genetic information.

It is important to set the background for the views of IVF couples regarding the embryo from previous studies, and be informed of the debates about its moral status, as these would potentially be key factors influencing couples’ decisions of freezing embryos in the study which is the subject of this thesis..

5.2 What is a Frozen Embryo?

In previous studies from Australia, Europe, the UK and the USA, frozen embryos were perceived by couples as no different from their “virtual children whose development was suspended” or their “babies” (Boivin and Takefman, 1995; De Lacey, 2005; De Lacey, 2007a; Haimés *et al.*, 2008; Nachtigall *et al.*, 2005; Parry, 2006; Söderström-Anttila *et al.*, 2001; Svanberg *et al.*, 2001; Svendsen and Koch, 2008). To many individuals, frozen embryos are siblings to

their existing children (Nachtigall *et al.*, 2005). In another study, several individuals identified them as frozen entities, not having the same status as an embryo or fetus. In a study by Haimes *et al.* (2008), Swiss interviewees, who had embryos frozen for some time prior to the interview and were considering donation to research, perceived the frozen embryos as their “dormant body part” and as a symbol of their relationship. To some couples in a US study, the frozen embryos were the symbol of their past infertility (Nachtigall *et al.*, 2005). To quite a few Chinese IVF couples, they were perceived as “hope”, as the possibility of a future pregnancy (Mitzkat *et al.*, 2010). Frozen embryos were viewed by US couples as a “security blanket” in the study by Lyerly *et al.* (2006), or as a genetic/psychological insurance policy (Nachtigall *et al.*, 2005), as it gave them reassurance that they could, at any time in the future, have their frozen embryos thawed and replaced for the purpose of having more children.

Understanding previous studies of the perspectives of IVF couples and their views about their frozen embryo helped the author of this thesis with incorporating these nuances in the semi-structured questionnaire, and to delve into them further during the interviews. Thus, in these studies from Australia, Europe, the UK and the USA, the couples’ views on their frozen embryos mostly related to the framework of “virtual children”, symbol of hope or seed, or similar to an “insurance policy”. Some of the couples connected the frozen embryo to their past infertility, and to a few, it was the symbol of their relationship. To others, however, the frozen embryo was similar to a frozen bunch of tissue. It is important to remember that all these studies related to couples who already had their embryos frozen for years, and that many of them had already achieved a pregnancy, which could have modified their views of the frozen embryos. There has been no study conducted on couples’ conceptualization of frozen embryos at the time of embryo freezing, while they were still going through the IVF journey. It is important to find out the views of couples at that point of time, and to investigate to what extent their conceptualization of frozen embryos influences their freezing decision.

5.3 Legislation Regarding Embryo Freezing and the Disposal of Frozen Embryos

The legislation regarding embryo freezing, storage duration and frozen embryo disposal options varies from country to country. It is vital to have an overview of the legislative framework, as it underpins not only the disposal decisions of couples with frozen embryos, but also potentially the views of IVF couples regarding their frozen embryos in the first place.

5.3.1 Legislation regarding the freezing and storage of embryos

There are legal limits imposed on the maximum duration of embryo freezing, which dictate the disposal of frozen embryos. Italian law forbids any embryo freezing (ESHRE, 2012). In the UK, the HFEA legally limits the storage of embryos to a maximum period of 5 years, which can be further extended to 10 years with the consent of the couple (Department of Health, 2007). The ESHRE Task Force also advocated standard time limits for the storage of frozen embryos, which can be renewed, such as in Austria and Belgium, as discussed later (Shenfield *et al.*, 2001). In Switzerland, there is a high degree of safeguarding the human embryo, and the LRM has totally prohibited the freezing of embryos since 2001 (Haimés *et al.*, 2008). In the USA, there is no legal maximum time limit for storing embryos, and this is left to the decision of the individual clinic (Van Voorhis *et al.*, 1999), whereas in Australia, the legal limit varies between the different states (Burton and Sanders, 2004). Surplus embryos in Austria (1992 Act; ESHRE, 2012) can be frozen for a maximum period of 1 year, following which they need to be destroyed, if they have not been used. A recent law (2007) in Belgium limits the storage time to 5 years, which can be extended, and patients are required to make decisions about the disposal of their frozen embryos prior to their first treatment (Provoost *et al.*, 2012). It could be debated whether it would be fairer to have a uniform international policy on this matter, where all couples going through IVF treatment in the various nations would have equal opportunities.

5.3.2 Legislation regarding frozen embryo disposal

International legislation about the disposal and storage of embryos governs the disposal of frozen embryos in many countries (Hammarberg and Tinney, 2006). It is important to be familiar with the international regulatory framework, as this

will determine what the studies on frozen embryo disposal might find. Table 5.1 shows the options available for the disposal of frozen embryos in different countries, e.g. in Denmark (Bangsbøll *et al.*, 2004), Sweden (Burton and Sanders, 2004), Brazil and Italy (Dickey and Krentel, 1996) donation of embryos to other couples is prohibited, and hence the options for disposal include discarding or donating to research, as per the legislation. On the other hand, countries like Austria, Germany, Israel, Italy and Norway (Fasouliotis and Schenker, 1996; De Lacey, 2007a) forbid embryo research, leaving couples with the options of donating to others or discarding their frozen embryos. Countries like Belgium, the Czech Republic, Denmark, Spain and Sweden, have various restrictions regarding the use of frozen embryos in research and permit it only for specific types of research, such as research for improving the knowledge of how to cure diseases. Embryo research in those countries is permitted under stringent regulation, as opposed to that in the UK, which has more liberal views on the use of embryos and frozen embryos in research (ESHRE, 2012). In Switzerland, since 2005, frozen embryos can be donated to embryonic stem cell research only (Haimes *et al.*, 2008). The USA promotes donation of frozen embryos to other couples, encouraging it by perceiving the practice as “embryo adoption” (Dickey and Krentel, 1996; Frith *et al.*, 2011). However, the laws regarding frozen embryo disposal can vary from one US state to another (National Conference of State Legislatures, 2007). The law in Brazil, Germany and Spain prohibits discarding embryos (Klock, 2004; Robertson, 1995b).

Research		Donation to others		Discard	
<i>Prohibited</i>	<i>Permitted</i>	<i>Prohibited</i>	<i>Permitted</i>	<i>Prohibited</i>	<i>Permitted</i>
Austria	Belgium*	Brazil	Finland	Brazil	Austria
France	Bulgaria	Denmark	Greece	Germany	UK
Germany	Czech Republic*	Italy	Russia	Spain	
Israel	Denmark*	Sweden	Spain		
Italy	Greece		UK		
Norway	Hungary		USA		
	Portugal*				
	Russia				
	Spain*				
	Sweden*				
	Switzerland (heSCR)*				
	UK				

Table 5.1 International legislation on frozen embryo disposal. *Countries permitting research with frozen embryos only for certain specified purposes. Donation to research options as per the ESHRE legal guidelines (ESHRE, 2012). heSCR: human embryonic stem cell research.

5.4 Views of Societies Regarding the Use of Embryos in Research

The ethics surrounding the use of embryos in research is a fiercely debated issue (National Bioethics Advisory Commission, 1999), and there has been negative moral and political reaction to the creation of any embryos for use in research. The UK was the first country to permit human embryonic stem cell research (Haimes *et al.*, 2008) and also to allow the creation of human embryos by somatic cell nuclear transfer, or “cloning” for research (Hug, 2008), which is regulated by the HFEA Act 1990, 2001 revision (Wellcome Trust, 2002).

However, there have been conflicting views regarding the use of embryos and frozen embryos in research, even within a society with liberal legislation and views. There has been opposition from the advocates of “beginning of life at conception” (Deckers, 2007). Some endorse the use of only frozen embryos for stem cell and other research (Thomson *et al.*, 1998). Embryo research is disapproved of by certain religious and cultural groups (Porter *et al.*, 2010; Sandel, 2004; Weissman, 2006). For example, the Roman Catholic view

attributes the same rights as a human being to an embryo from the moment of fertilization, and embryo research is disapproved of.

5.5 Perception of Problems Associated with Embryo Freezing

Previous research has identified potential problems resulting from embryo cryopreservation for IVF couples, as well as for fertility units and laboratories.

5.5.1 Safety and security of embryo freezing

The concerns voiced by couples in previous studies relate to the safety of the cryopreservation procedure and any harmful effect on the potential children born from the thawed embryos (Check *et al.*, 2003; Svanberg *et al.*, 2001). Couples have also expressed worries regarding the risks of viral contamination in laboratories; technical or accidental errors relating to mislabelling of the embryos; or embryos being inadvertently destroyed (Bankowski *et al.*, 2005; Siegel-Itzkovich, 2003).

5.5.2 Future moral and legal problems

Frozen embryos could also potentially create moral or legal problems in the future related to contention over their legal custody, in case of the separation or death of the partners (Bennett, 2000; De Lacey, 2007b; Haimes and Taylor, 2011; Newton *et al.*, 2007).

Other potential problems with embryo freezing that have been highlighted by previous researchers include the risk of raising “false hopes” in couples, with regard to the capacity of a frozen embryo to make a baby (Lyerly *et al.*, 2006).

With the “thaw survival rates” of frozen embryos reported as being between 60 and 70%, and with the success rates from “frozen-thaw” cycles being 15–20%, there is a concern that the practice would lead to having a higher number of cycles, with logistical and financial implications.

Concerns have also been raised regarding the associated emotional and social costs when couples make personal emotional investments when freezing their embryos, but the embryos then fail to survive the thaw, or do not make a baby. There may also be ethical costs involved, which are unaccounted for. (Haimes and Taylor, 2011).

5.5.3 Mounting numbers of stored embryos

The problem of the mounting numbers of stored embryos has been discussed. In the USA, in 2003, there were 400,000 surplus frozen embryos (Hoffman *et al.*, 2003), and 15,615 embryos in 13 Canadian clinics (Baylis *et al.*, 2003). In 2009, in Spain, there were 50,000 surplus frozen embryos (Luna *et al.*, 2009).

Information about the potential problems associated with embryo freezing is important, and it guided the author of this thesis to formulate the aide-memoire for the interviews, with the idea to elicit the views of IVF couples on these topics.

5.6 Frozen Embryo Disposal

There has been substantial information in the literature regarding patients' decisions about the disposal of their frozen embryos, involving couples who have surplus embryos frozen in laboratories. Disposal options include: frozen embryos to be used for personal reproductive purposes; donated to other infertile couples; donated to research; stored indefinitely; discarded; or even used in uterine transfer at a time not conducive of pregnancy (De Lacey, 2005; Nachtigall *et al.*, 2005). It might be important to make couples aware of the choices of frozen embryo disposal that are available to them, right at the time of embryo freezing, as it might influence their decision of whether to freeze their embryos. However, from the author's interviewing experience, it seemed that most couples were not keen to make any hypothetical disposal decision at that point. Nonetheless, it would be worth warning couples of the possible difficult disposal decision-making scenario in the future.

The decisions made by couples who already have surplus frozen embryos, or their intended decisions, as presented in the literature, are discussed in the following sections.

5.6.1 Couples' intentions and decisions about the disposal of frozen embryos

Evidence here is patchy and not presented in a systematic manner. Some studies report the final destinations of frozen embryos using variable time intervals (Appendix F). Others are qualitative research (interviews and surveys) to illustrate couples' intentions regarding their disposal choices when embryos are not used for their own treatment (Appendix G). Although most patients

indicated that they intended to use their frozen embryos for personal reproduction purposes (Darlington and Matson, 1999; De Lacey, 2007a; Luna *et al.*, 2009), there is a huge range of 8–77% couples who planned to thaw their embryos to have a baby (Boada *et al.*, 2003; Elford *et al.*, 2004; Hoffman *et al.*, 2003; Hounshell and Chetkowski, 1996; Luna *et al.*, 2009; Nachtigall *et al.*, 2009; Svanberg *et al.*, 2001).

Donation to other couples was generally the least common option chosen in the reported literature, as mentioned by Hammarberg and Tinney (2006); 2–39% of couples intended to donate their surplus frozen embryos to other infertile couples, whereas 1–21% actually did so. Wide international variation is noted, probably due to cultural and ethnic differences, or related to legislation in different countries, as discussed earlier. Couples in Belgium, Finland and France had higher donation rates to other sub fertile couples, compared to their Australian, Canadian or US counterparts. However, the Australian and US studies are relatively old, and more recent data are needed to illustrate the current scenario.

Studies relating to different timescales and different socio-geographical areas show complexity in data comparison. Nonetheless, the author of this thesis has attempted to make a crossover comparison of the different destinations of the frozen embryos.

Recent studies noted an increasing enthusiasm in donation to research, including stem cell research. A very wide range of 10–76% couples wished to donate their frozen embryos to research, though in reality, 5–41% of couples actually did so. Interestingly, 40–90% of couples in Australia and Europe were willing to donate their stored embryos to research, whereas in the USA and Canada, only 2–3% of the total number of frozen embryos were available for research (Hug, 2008). The importance of legislation is demonstrated in one Swedish study, where 92% of Swedish couples wished to donate their fresh or frozen embryos to stem cell research, as donation to another infertile couple is prohibited in Sweden (Bjuresten and Hovatta, 2003).

Choudhary *et al.* (2004) found that white couples were more likely to donate fresh embryos to research, compared to an ethnic minority group. However, the number of couples recruited for this study was small, and hence the results are to be interpreted with caution.

In older studies, destroying unused stored embryos was the most frequently chosen disposal option; 1–34% of couples wished to discard their frozen embryos, but studies reported a higher range of 8–89% of couples actually discarding them. Only 3–4% of couples intended to continue storing their frozen embryos, though 10–64% actually continued to do so.

The decision to dispose of frozen embryos was found to be an “unresolved issue” in the lives of many respondents (Nachtigall *et al.*, 2005). Indeed, 3–72% of couples were undecided regarding their disposal choice. The various factors influencing a couple’s disposal choices are discussed later in this chapter.

There were low rates of spouse discordance noted in the different studies regarding the decision of how to dispose of frozen embryos (Boada *et al.*, 2003). One study quoted a discordance rate of 7% (Bankowski *et al.*, 2005). However, as many studies report non-contact with the couples with frozen embryos, the reliability of these data can be questioned. Moreover, it can be speculated that couple disagreement could be one of the reasons for non-contact by the couples.

In a study conducted by Svanberg *et al.* (2001) regarding the intended use of frozen embryos at the time of embryo freezing, women respondents expressed higher rates of desire to personally use their frozen embryos, compared to their male partners, before the pregnancy test result. However, there was no difference noted in the intentions following the results of the pregnancy test.

5.6.2 Unclaimed frozen embryos

Several studies suggest that up to more than half of couples apparently “abandoned” their frozen embryos following 3–5 years of storage, despite several attempts by the clinics to communicate with the embryo owners, who did not give any updated directive regarding their disposal (Bangsbøll *et al.*, 2004; Brzyski, 1998; Lornage *et al.*, 1995; Newton *et al.*, 2007). Qualitative research revealed that the non-response of couples did not mean they abandoned the embryos, but allowed exercising their autonomous rights not to take difficult decisions (McMahon *et al.*, 2001). Dawson *et al.* (1997) found that couples avoided making difficult decisions in the hope that clinics, on their behalf, would discard the frozen embryos or donate them to others.

The explanations provided by the couples for non-response were being content with their family size and being too busy with childcare (Svanberg *et al.*,

2001; Lornage *et al.*, 1995; Newton *et al.*, 2003). In the opinion of some, there was a lack of suitable disposal options, such as a little private ceremony where couples could bid farewell to their frozen embryos, which they perceived as their “children who will never exist”, or have the embryos replaced in the womb and absorbed by their body (Lyerly *et al.*, 2006).

To tackle the growing number of unclaimed frozen embryos, the ASRM committee allowed clinics to dispose of them after 5 years of no contact with the couples, despite repeated attempts (ASRM, 2004). In the UK, 3,000 frozen embryos were discarded by the clinics in 1996, fuelling criticism of the handling of cryopreserved embryos by clinics (Edwards *et al.*, 1997). For the same reason, by the end of 1998, in Manchester alone 904 (67%) of embryos frozen for over 5 years had to be destroyed to comply with the Human Fertilisation and Embryology Act, 1990 (Oghoetuoma *et al.*, 2000).

5.6.3 Factors influencing couples' decision of how to dispose of frozen embryos

Abundant evidence in the literature suggests that the decision-making process regarding the disposition of frozen embryos is difficult and “emotionally fraught” (De Lacey, 2007b; Fuscaldo *et al.*, 2007; Hammarberg and Tinney, 2006; McMahon *et al.*, 2003; Melamed *et al.*, 2009; Nachtigall *et al.*, 2005; Söderström-Anttila *et al.*, 2001; Svanberg *et al.*, 2001).

Nachtigall *et al.* (2009) identified four major factors determining the fate of frozen embryos.

5.6.3.1 Embryo conceptualization and personal values

Embryo conceptualization and personal values, such as the decision to dispose of frozen embryo, reflected the couple’s view of the embryo as a “life” and having a right to live (De Lacey, 2007a; Fuscaldo *et al.*, 2007; Melamed *et al.*, 2009).

5.6.3.2 Personal life circumstances

Not using the frozen embryos was linked to life events, such as: complicated labour or a difficult parenting experience could dissuade couples from using their frozen embryos for a sibling pregnancy (De Lacey, 2007a); or due to the achievement of the desired family size (Bangsbøll *et al.*, 2004; Svanberg *et al.*,

2001; Newton *et al.*, 2003). In others, the decision-making was not affected by the presence of any existing children, or the successful outcome of IVF (Burton and Sanders, 2004; Haimes and Taylor, 2009; Klock, 2004; Lornage *et al.*, 1995; Lyerly *et al.*, 2006).

5.6.3.3 Embryo characteristics

There was evidence of donation to research of poorer-quality, post-thaw embryos, due to the reduced likelihood of successful reproductive outcome (Lyerly *et al.*, 2006). Relatively fewer frozen embryos were frozen for a longer period of time compared to larger numbers of frozen embryos (Brzyski, 1998).

5.6.3.4 Clinic information and support

The information provided by the clinic played a vital role in the couple's disposal decision (Nachtigall *et al.*, 2010), and the rapport with clinic personnel facilitated donation to research (Lyerly *et al.*, 2006).

The issue of trusting the professionals, or the lack of it, was also thought to play a role in decision-making (Lyerly *et al.*, 2006).

5.6.3.5 Other factors

The importance of variations in the legislations about embryo freezing and disposal in different countries has already been discussed. Other influences important in the decision-making behind the fate of frozen embryos are as follows:

- **Religious beliefs:** These (De Lacey, 2007a) influenced views, such as the concept of the "sanctity of life", from the Catholic belief, influenced couples' views of embryos having a 'right to life', and influenced their decision against donation to research (Burton and Sanders, 2004) or discarding embryos (Melamed *et al.*, 2009).
- **Continuation of insurance policy:** Frozen embryos were deemed similar to having an insurance policy and the opportunity to maintain the couple's embryo potential for the future (Bankowski *et al.*, 2005).
- **Financial factors:** Having to pay the annual storage fees to continue storing the embryos motivated many couples to take the decision to dispose of them (Brzyski, 1998; Nachtigall *et al.*, 2009; Nachtigall *et al.*, 2010).

- **Use of donor gametes:** In the study by Luna *et al.* (2009), the use of donor gametes in the creation of the embryos was associated with a higher likelihood of donating to other couples.
- **Duration of freezing:** Luna *et al.* (2009) found that couples with embryos frozen for a short period of time mostly chose to continue freezing; those who had embryos stored for 5–10 years often decided to donate to others or to science; and those couples whose embryos were frozen for longer than 10 years usually decided to discard them (Luna *et al.*, 2009).

5.6.4 Deciding how to dispose of frozen embryos: Research outcome

Nachtigall *et al.* (2005) explained a couple's decision-making to dispose of their frozen embryos as involving four steps. First, there was reassurance at having many frozen embryos. This was followed by a phase of avoiding thinking about them once a pregnancy was achieved. The third step involved confronting the decision of how to dispose of them with uneasiness, and finally, a phase of resolution following taking the decision (Nachtigall *et al.*, 2005). In the study that is the subject of this thesis, the availability of embryos to freeze was noted to be also associated with a feeling of reassurance, which will be elucidated in the next chapter.

De Lacey *et al.* (2007a) observed a process entailing an initial rejection of the “morally abhorrent” option by the couples, leading to acceptance of the remaining options. On interviewing couples with frozen embryos, the group donating to others viewed discarding as similar to pregnancy termination, which was morally unacceptable to them, and chose to donate their embryos to others, perceiving it as similar to organ donation. On the other hand, the “discard” group used the “embryo adoption” metaphor for donating to others, and viewed it as giving away their own child for adoption, and thus preferred to discard those embryos.

It was widely recognized that the difficult decision was related to couples having a “conflict of interest and moral values” (Lyerly *et al.*, 2006), which could be related to religious, emotional, social and moral aspects, and was increasingly difficult following the birth of a child (De Lacey, 2005; Fuscaldo *et al.*, 2007; Hug, 2008). The restriction of the time limit was thought to add to the stress of making the difficult decision (Svanberg *et al.*, 2001). It was also presumed that because of “cognitive–affective dissonance”, i.e. during the

stressful IVF treatment, the emotional or “affective” state of the couples is disturbed, and the ability to meet the cognitive demands regarding the fate of the frozen embryos can be compromised (Lyerly *et al.*, 2006). In contrast to this view, there is evidence that although IVF patients are primarily focused on their own treatment, they handle issues such as donating their embryos to research as part of the process of the numerous decisions that have to be made in their journey to achieve a baby (Franklin, 1990; Haimes and Taylor, 2009).

5.7 Factors Affecting how Frozen Embryos are Disposed of

How couples choose to dispose of their frozen embryos from the available options is described in the sections that follow. Understanding the perspectives of couples could potentially shed light on their decision-making to freeze embryos in the first place.

5.7.1 Factors influencing couples donating to others

In qualitative interview studies, there was evidence that couples keen on donating frozen embryos to other couples perceived it as a way of “helping other” infertile couples and “giving back” to society, and to allow the embryos to fulfil the purpose for which they were originally created (Nachtigall *et al.*, 2009).

Researchers found that couples likely to donate to others laid more emphasis on the role of social bonding and nurturing in the upbringing of a child, as opposed to genetic lineage (De Lacey, 2007a; De Lacey, 2007b; Fuscaldo *et al.*, 2007). De Lacey *et al.* (2007a) found that couples willing to donate to others perceived the frozen embryos as “reproductive material” or “seed”, as opposed to “a child”. When donating, the couples relinquished their rights over their embryos and conditioned themselves to perceive them as the children of others (Nachtigall *et al.*, 2009). In a recent US paper (Frith *et al.*, 2011), the authors advocated use of the term “conditional relinquishment”, as opposed to the more politically charged term “embryo adoption”, and found that the factors influencing embryo donation were the couple’s conceptualization of the frozen embryos, a sense of responsibility towards them and facilities of conditioned relinquishment, with varying grades of “openness” in information sharing and contact arrangements between the donor and recipient couples.

Some qualitative study respondents agreed to only “conditional donation”, i.e. deciding to donate only to suitable recipients, emanating from a sense of

responsibility towards their embryos (Fuscaldo *et al.*, 2007; Nachtigall *et al.*, 2010), which was similar to the findings of a postal questionnaire survey (McMahon and Saunders, 2009).

In studies based on postal surveys, researchers found that acceptance of being identified in the future by their genetic offspring, was one of the important determining factors influencing couples towards embryo donation (Hammarberg *et al.*, 2001; Newton *et al.*, 2003). In certain countries, such as the UK, the 2005 law empowers children born using donor gametes to access identifying information regarding their biological parents from the age of 18 (HMSO, 2004).

Concerns of “wastage” of their personal efforts in creating the embryos, as well as wasting the embryo potential, also influenced their decision (De Lacey, 2007b).

5.7.2 Factors influencing couples against donation to others

Conceptualization of the embryos as virtual children, leading to the allegory of child relinquishment or adopting out one’s own children, prevented couples from donating to others, which was evident not only from the qualitative interviews (De Lacey, 2007a; Fuscaldo *et al.*, 2007), but also in questionnaire-based research (McMahon and Saunders, 2009). In a survey, the couples donating their embryos to other couples felt distinctly different from the oocyte donors. Embryo donors perceived embryo donation as giving away a child, whereas oocyte donors perceived it as donation of a cell (Söderström-Anttila *et al.*, 2001). Embryo donors, in qualitative (Lyerly *et al.*, 2006) and survey-based research (Söderström-Anttila *et al.*, 2001), expressed concerns about the suitability of the recipients as parents and preferred to donate to research, or even discard their frozen embryos. Researchers saw this as an interesting paradoxical view of couples, in perceiving the embryo as a life and yet discarding it (De Lacey, 2005; De Lacey, 2007b; Laruelle and Englert, 1995; Melamed *et al.*, 2009).

Several questionnaire-based surveys (Burton and Sanders, 2004; McMahon and Saunders, 2009; McMahon *et al.*, 2003) identified the concern of couples about potential risks of consanguinity between their offspring or even the disconcerting thought of meeting an unknown child in the future, which were further elaborated in social science interviews (De Lacey, 2005; Fuscaldo *et al.*, 2007; Melamed *et al.*, 2009; Nachtigall *et al.*, 2005; Nachtigall *et al.*, 2010).

5.7.2.1 Areas of debate

Researchers have debated the value of “conditional donation”, as there is the risk of discriminating against recipients. Also, it could fuel the contention regarding the moral status of an embryo, as in conditioned donation the couples seem to be treating the frozen embryo as a child (McMahon and Saunders, 2009). Another hugely debated area is embryo donation being similar to adoption, which again promotes the concept of the embryo as a child with rights, but simultaneously puts its status into sharp contention when donated to research or discarded (Bankowski *et al.*, 2005; Robertson, 1995b).

5.7.3 Factors influencing couples to donate to research

Couples agreeing to donate their surplus frozen embryos to research often have the desire “not to waste”, both in survey studies and qualitative research (De Lacey, 2007a; Fuscaldo *et al.*, 2007; Hammarberg and Tinney, 2006; Melamed *et al.*, 2009; McMahon *et al.*, 2003). Interviewers found that the keenness to donate to research often stemmed from a desire to “reciprocate” and a sense of obligation to previous research (Fuscaldo *et al.*, 2007; Parry, 2003; Parry, 2006). The desire to donate to fertility research originated from a sense of solidarity with other subfertile couples (Mitzkat *et al.*, 2010) and altruistic intentions (Hug, 2008; Lyerly *et al.*, 2006). “Directed research”, where the aim of the research was informed (Fuscaldo *et al.*, 2007), was important to some, whereas others were happy regardless of the type of research, as long as it was beneficial to mankind (Lyerly *et al.*, 2006). In couple interviews, Porter *et al.* (2010) found four main themes driving couples to donate frozen embryos to research: “utilitarianism” of embryo research, i.e. for a bigger benefit, such as developing the treatment of diseases; “ecology” or the efficient use of the embryos as opposed to wasting them; “moral duty” – for the benefit of society; and “eugenic” – the belief that embryo research would eliminate the diseased and the frail.

Donation to research also prevents the uncomfortable scenario of meeting with genetic offspring in the future, or complex family dynamics, as in the case of donation of embryos to other couples, as identified in one postal questionnaire survey (Hammarberg and Tinney, 2006; Nachtigall *et al.*, 2010).

A few social scientists voiced concerns of whether the donation of embryos to science was originating from a sense of obligation and gratitude, and the

potential risk of it (Parry, 2006). However, in a recent study, researchers found evidence that the donation of embryos – fresh or frozen – to research was generated from a feeling of solidarity with other patients and the desire to “give something back” to research, and interpersonal gratitude had little direct role to play in their decision (Scully *et al.*, 2012).

In previous studies, some researchers voiced concerns that institutions or clinicians could exploit the gratitude of couples and fulfil their vested interest, over the informed decisions of couples, i.e. couples could be coerced into donating to other couples, or to research, in the private and academic settings, respectively. In their paper on donation of fresh embryos to stem cell research, McLeod and Baylis (2007) expressed concerns about female IVF patients misunderstanding various important aspects of the donation decision, being coerced to donate or potentially being exploited during the consenting process, and therefore advocated that patients should not be invited to donate their fresh embryos to stem cell research. Therefore, the involvement of an independent agency counselling women about decisions regarding embryo donation has been recommended (Heng, 2006). However, the genuineness of these concerns and the actual perceptions of couples can be subject to further studies. On this note, in a recent study, Haines *et al.* (2012) examined the issue of “exploitation” by interviewing women about an egg sharing scheme, where their fees for IVF treatment would be reduced on agreement of sharing half of the harvested eggs with research. Women, although acknowledging the potential for exploitation in theory, emphasized that they did not feel exploited, as they were able to exercise their autonomy if participating in that scheme.

5.7.4 Factors influencing couples against donation to research

Qualitative research data has also revealed that those with legal or moral values against the use of embryos in research, and with specific cultural or religious views, e.g. those conceptualizing the embryo as a human being, were against the donation of embryos to research (Melamed *et al.*, 2009; Porter *et al.*, 2010). Other factors, detected using qualitative interviews, responsible for non-donation were: not knowing the aim of the research (Fuscaldo *et al.*, 2007; Hug, 2008; Melamed *et al.*, 2009; Mitzkat *et al.*, 2010); concern regarding the trustworthiness of the scientists; and worry about embryos being misused (Melamed *et al.*, 2009; Nachtigall *et al.*, 2010; Parry, 2006). Another interesting

factor was reluctance to donate one's frozen embryos to research because of concerns with privacy of genetic information and its misuse (Fuscaldo *et al.*, 2007).

5.7.5 Factors influencing couples to discard embryos

Couples disposing of frozen embryos perceived waste in reproduction as natural, and being similar to having a miscarriage or a termination of pregnancy, according to the postal survey data collected by McMahon *et al.* (2003) and from qualitative research (De Lacey, 2007b). They found that the decision to discard was often made at the last minute by couples who could not donate to other couples or to research (Hammarberg *et al.*, 2001; Melamed *et al.*, 2009). In interviews, Nachtigall *et al.* (2010) found that couples with grown-up children, who no longer needed to store embryos as an "insurance policy", mostly discarded them. Financial factors, as discussed previously have also been implicated (Nachtigall *et al.*, 2009; Nachtigall *et al.*, 2010).

The interesting paradox raised in interviews, where some couples having respect and concerns for their embryos chose to discard of them, has also been discussed (Lyerly *et al.*, 2006).

5.7.6 Factors influencing couples against discarding embryos

Couples who were against discarding their frozen embryos were concerned about "wasting a valuable resource" (De Lacey, 2007b; Nachtigall *et al.*, 2009; Nachtigall *et al.*, 2010). The roles of embryo conceptualization as life, and religious views have been discussed.

5.8 Changing Decisions

In view of the growing number of frozen embryos in storage, and to avoid the large numbers of unclaimed embryos, various clinics asked couples to indicate their surplus frozen embryo disposal preferences, as a "pre-freeze agreement" or "advance directives" (Jones *et al.*, 1992; Schuster *et al.*, 2003). However, various studies quote a huge range of figures, from 28 to 71%, where couples change their decisions subsequently and the decisions were deemed as "dynamic" and "volatile" (Bankowski *et al.*, 2005; De Lacey, 2007b; Hug, 2008; Klock *et al.*, 2001; Lornage *et al.*, 1995; Lyerly *et al.*, 2006; Newton *et al.*, 2007; Thomson *et al.*, 1998). The initial choice, such as the decision to donate to

other couples, was quite often the morally acceptable one; however, this was subsequently altered due to the experience from having children, and conceptualizing the frozen embryos as “virtual children” (Bankowski *et al.*, 2005; De Lacey, 2005; Lornage *et al.*, 1995). Subsequently changed preferences, such as discarding frozen embryos, rather than donating them to research or to other couples, was also noted by other researchers (Lyerly *et al.*, 2006; Newton *et al.*, 2007). Therefore, the advance directive was not deemed a reliable indicator of a couple’s final decision (Haimes and Taylor, 2011; Klock *et al.*, 2001; Newton *et al.*, 2003), as it changed with the changed circumstances of life, and with renewed information (Bankowski *et al.*, 2005; Lyerly *et al.*, 2006). Hence, the validity of “advance directives” has been contested as “uninformed decisions” (Bankowski *et al.*, 2005).

In sections 5.6 and 5.7, previous studies showed how and under what circumstances and influences couples make the decision to dispose of their surplus frozen embryos left in the clinics. The following section shows how the views and disposal decisions change over time. Thus, it is important to elicit the views of couples at the time of making the decision to freeze their embryos.

5.9 Decision-Making: to Freeze or not to Freeze?

5.9.1 What do we know?

Although there has been abundant information in the literature about the disposal choices made by couples regarding their frozen embryos, little is known about the actual decision-making process.

In the sparse evidence available, couples have cited reasons for embryo freezing as having security and hopefulness (Lyerly *et al.*, 2006; Nachtigall *et al.*, 2009; Svanberg *et al.*, 2001), reducing stress (Bankowski *et al.*, 2005; Koryntová *et al.*, 2001; Stoléru *et al.*, 1997) and “buying time” (Haimes and Taylor, 2009). Various authors have interpreted the perceptions of couples freezing embryos as having an “insurance policy” for the future, as having backup embryos in case the current IVF treatment failed, or in the situation of anything happening to their existing children (Bankowski *et al.*, 2005; Koryntová *et al.*, 2001; Stoléru *et al.*, 1997). It is also understood that couples freeze embryos as it “extends choice, chances, prevents regret” (Ehrich *et al.*,

2010) and imparts a “degree of reversibility” to their decisions (Haimes and Taylor, 2011).

The decision to freeze embryos was facilitated by clinic information of the perceived advantages of embryo freezing in supplementing the CPR and the avoidance of surgical egg retrieval and its associated risks. The benefits portrayed included the prevention of destruction of surplus embryos created during IVF, the reduction of multiple pregnancy rates as embryo freezing allows the storage of surplus embryos (Cattoli *et al.*, 2004; De Lacey, 2007b) and as it is also deemed to be cost-effective (Damario and Dumesic, 2000).

As discussed previously, there is some evidence that some couples are sceptical about embryo freezing; there are also concerns regarding the health of the potential children (Svanberg *et al.*, 2001) and worries about laboratories mishandling embryos (Bankowski *et al.*, 2005) which could impact the decision-making process.

One study looking at the decision time needed to freeze embryos, found that some couples needed more time than others who decided almost immediately whether to freeze their embryos or not. Some of them left the decision-making till the very last minute, until informed about suitable surplus embryos on the day of FET (Svanberg *et al.*, 2001).

5.10 Summary and Observations

To conclude, embryo freezing has been in clinical practice for more than 25 years. The relatively old data that is available suggest that the vast majority of couples accept embryo freezing, if offered to them.

However, there is great uncertainty about the conceptualization of this elusive entity, the “embryo”, by IVF couples, and the embryo concept has nuanced attributes. Embryo freezing is also a contentious area, especially in the eyes of ethicists and philosophers, and is related to the embryo being considered in the framing of “life” and hence having a disputed moral status. Nonetheless, all agree that it has a special moral status, deserving respect. In the literature, the evidence about couples’ conceptualization of the frozen embryo is all within the context of frozen embryos that have been in storage for a significant period of time. It is important to know how couples perceive a frozen embryo on a different timescale, at the point when making the decision to

freeze, as it could potentially impact the decision-making process to freeze. This information is lacking in the literature.

Embryo cryopreservation is associated with multiple complex and contentious issues, and there are raging debates regarding issues such as: the use of frozen embryos in research, including stem cell research; and ethically acceptable options of how to dispose of frozen embryos. There is no unanimity of legislation in different countries, regarding embryo freezing and the disposal of frozen embryos, which often makes the available choices of how to dispose of frozen embryos ethically unacceptable and difficult for couples.

In the light of the review, it is evident that there is abundant evidence in the literature about how couples view embryos and to inform patient choices regarding the disposal of their frozen embryos. From the little evidence available in the literature, it is known that the practice of freezing the embryos in the first place can be associated with various ethical dilemmas. There are also certain safety issues associated with the practice. Little is known about how couples make the complex decision of whether to freeze their surplus embryos. Of the information that is available, it is not clear to what extent it illustrates the actual perceptions of couples, and the potential role of speculations of the researchers. The expectations of couples from embryo freezing and their disposal plans for surplus frozen embryos in the future could have an impact on their decision-making to freeze in the first place.

The sparse information available in the literature regarding the decision-making process about embryo freezing reinforces the need to conduct further study in this area, to inform the decisions of couples confronted with this difficult decision. The little evidence about couples' views on embryo freezing as a symbol of security is also useful as it serves as a stepping stone on the way to further research. It guided the author of this thesis to formulate the semi-structured questionnaire used in her research, so that these topics could be introduced to her interviewees to elicit their views. It is important to understand how couples approach the complex decision-making process of embryo freezing, and it is hoped that in the light of the information and evidence gained, it will be possible to provide better information and support to patients seeking IVF treatment.

Chapter 6. Investigating Patients' Experiences of Making Decisions About Embryo Freezing: Methodology

This qualitative study was aimed at exploring the personal and social factors that couples consider when making their decision whether to freeze their surplus embryos during IVF treatment.

Qualitative research has been defined as multi-method in focus, and involving an interpretative, naturalistic approach to its subject matter (Denzin and Lincoln, 1998). As an epistemological framing, interpretivism is generally seen as being in contrast to positivism. Positivism generally involves taking the ontological status of the physical (and social) world as unproblematic and pursues knowledge about that world through systematic testing of hypotheses about relationships in that world. By contrast, the interpretative approach sees the ontological status of the social world as emergent and changing and therefore tends not to approach analysis of that world with fixed categories or variables but rather tracks emergent categories and theories from data derived from non-experimental research in naturally occurring settings (naturalistic). Clearly analysis is informed by pre-suppositions and understandings of the social world but these are regarded as tentative and contingent rather than as fixed aspects of that social world. In this study certain themes came to light from the literature review and were included into the semi-structured questionnaire to initially guide the interviews.

The importance of conducting a qualitative study is that it allows us to reach areas usually less accessible to quantitative studies, such as lay and professional health beliefs, as it explores the views and perspectives of the subjects being studied, and lays emphasis on eliciting detailed meanings of their experiences. It is also a prerequisite for good quantitative research, especially in previously unexplored areas (Pope and Mays, 1995). Unlike quantitative methods, where 'reliability' i.e. the capacity to generate identical results if used on a different occasion, is an essential criterion (achieved through the use of tools such as standardized questionnaires), qualitative methods use non-standardized, semi-structured or unstructured methods and are concerned with accessing the perspectives of those being studied. The strength of qualitative research is 'validity', i.e. the extent of truly reflecting the

phenomenon under scrutiny. The ethos of qualitative work is “inductive theorizing”, i.e. moving from observation to hypothesis

6.1 Study Plan

The study was planned as part of the author’s research project as a Clinical Research Fellow at the NFCL, as it was thought that analysing the quantitative and the qualitative aspects of embryo freezing was needed. The author also registered for a Doctor of Medicine degree at Newcastle University. The initial study plan was made and the research proposal for the project approval was written in November 2010, under the guidance of the author’s supervisors.

6.2 Ethics Committee and National Health Service Site Approval

The study was commenced following the favourable opinion from the Newcastle ethics committee and NHS Trust approval.

6.3 Funding

The project was funded by the NFCL Fertility Research Fund.

6.4 Recruitment of Patients

6.4.1 Sample

The intention was to conduct “purposive or systematic sampling” which involves the deliberate, theoretically led choice of respondents, as opposed to statistical sampling, which aims to obtain a representative sample to serve as a framework of the total population (Pope and Mays, 1995). Owing to the dearth of available evidence regarding the different categories of interviewees to be selected, and as very little work had been done with regards to decision-making for embryo freezing, the categories for sampling were tentative. The initial aim was to recruit couples who had been through at least one cycle of IVF treatment, and who thus had had to consider the prospect of freezing any surplus embryos. The target was to recruit 15 such couples, as it was anticipated that thematic saturation would be reached by then. The interviewees were to be recruited from patients attending the IVF follow-up clinics, thus allowing for the opportunity to include couples both for and against embryo freezing. The author also intended to get the views regarding embryo freezing from couples who were successful following the IVF treatments, because their

views on embryos and embryo freezing could potentially change after achieving a pregnancy. Therefore, patients attending clinics for early pregnancy scans following IVF treatment were also recruited.

6.4.2 Site

The plan was to recruit patients from the NFCL, which is a tertiary care centre and the largest fertility treatment unit in the north-east of England.

6.4.3 Invitation to participate

An invitation letter and information about the research (copies in Appendix C), were handed out by the doctors and nurses of the NFCL to all patients attending for review following treatment. The successful couples attending for pregnancy scans in the scan lists were also invited.

Two hundred invitation letters were sent out over a period of 2 months from the end of May 2011 to the end of July 2011. A stamped addressed envelope (SAE) was enclosed in the invitation pack for the interested couples to return the signed invitation letter. Couples interested in participating in the research were requested to sign the letter and tick a box indicating their willingness to take part, document their contact telephone numbers, and return it in the SAE. Sixteen letters expressing an interest in participating in the research were received. The response rate was 8%, which was interestingly at a less than encouraging level. The reasons for the relatively poor recruitment could be speculated as: time constraints on the part of the couples to take part in the interviews; reluctance in participating as it was not directly related to their treatment outcome; IVF treatment being their main focus; or couples not feeling emotionally ready to participate, as they were going through a stressful time.

6.4.4 Scheduling interviews

Respondents were contacted by telephone and a mutually convenient time and venue for the interviews was set up. Couples were encouraged to participate in the interviews jointly, as both members have been involved in the IVF treatment. Therefore, it would be interesting to look out for any differences or similarities in opinion, or any areas of couple discordance.

6.5 Formulating an Aide-Memoire for the Interviews

A literature search was conducted to identify relevant past papers and to also identify any gaps in our knowledge in this area. A semi-structured questionnaire with open-ended questions was designed, covering the areas intended to elicit the couple's views: the demographics of the patients; their detailed IVF history; their background knowledge about embryo freezing; their concept of a frozen embryo; their perceived advantages and disadvantages of embryo freezing, including any ethical or moral reservations; their decision-making process regarding embryo freezing and the reasons behind freezing, including the issues identified from the literature, such as embryo freezing as an "insurance policy" or avoiding the difficulties of fresh IVF treatment; their decision-making experience and the consent process; and the information received regarding the practical aspects of embryo freezing, e.g. the safety and security of the process, regulations, funding; and lastly the experience of couples who had been through a frozen-thaw cycle (aide-memoire copy in Appendix D). The aide-memoire allows flexibility and acts as a reminder of the various issues to be discussed; it was written under the guidance of the author's supervisor, and was approved by the ethics committee.

6.6 Interviews

Sixteen interviews with couples were conducted in the period between the end of June and the beginning of August 2011. Unfortunately, one of the interviews was only partially recorded due to a technical glitch with the recording equipment.

Couples were given the options for a convenient venue (including their homes) for the interviews. All the couples were happy to be interviewed at the NFCL. All interviews were done out of hours in the evenings, as suited to the couples, in a quiet room so that the interviewees felt relaxed and uninhibited.

Prior to interviewing, the couples were told the aims and procedure of the interview. They were assured of the anonymity of all data, and informed that they could withdraw their consent, if they chose to do so, at any point of the study. The researcher reiterated that she was not there as a doctor, that they could express their opinions freely without any hesitation, and that their views would not influence their treatment in any way. The researcher attempted to be sensitive to the way she conducted the interviews and being aware that her

status as a doctor could have a modifying effect on the responses of the interviewees. This is a part of practising 'reflexivity', which involves reflecting on the way in which research is carried out and understanding how the process of doing research shapes its outcome (Hardy *et al*, 2001). In essence, reflexivity entails engaging in critical appraisal of one's own practice.

Informed consent was thus obtained and the couples signed two copies of the consent form, one of which they retained; the forms were also counter signed by the researcher. Each interview was recorded with an Olympus DS-30 digital voice recorder.

Each interview lasted between 60 and 90 min. During the interviews, both partners were encouraged to participate and express their views without any inhibitions. All the participants seemed to have a sufficient understanding and command of English. The interview was "semi-structured", with an open-ended approach and the aide-memoire was only used from time to time to guide the interview. The interviewees comprised couples with (five couples) and without (11 couples) frozen embryos. The couples without frozen embryos were not because they declined embryo freezing, but because they lacked any suitable embryos to freeze. During the interviews, the researcher was mindful of not asking any leading questions, but instead following up cues and remarks. She paid attention to any new ideas emerging during the interviews, which she raised in the subsequent interviews for discussion. Towards the end of the interviews, no further new themes appeared to emerge. The researcher's supervisor listened to the first recorded interview and appraised it, and then provided the necessary feedback on technique, style and content. The interviews were transferred as electronic sound files and saved on the Trust and university computers with secure log ins. The interviews were also transferred to audio CDs as additional backup, and stored under lock and key to ensure confidentiality.

The interviews were fully transcribed verbatim by a transcriber trained in protecting medical confidentiality. The transcribed interviews were then checked and corrected for any transcription errors; any gaps were filled in and the transcripts were anonymized by the researcher. Each woman and her partner interviewed were assigned to non-identifiable codes and any identifiable data was de-identified, so as to prevent revelation of the identity. All the corrected interviews were then electronically saved.

6.6.1 Listening notes

All the recorded interviews were individually listened to in open-ended way and listening notes were taken, which were used as “field notes” by the researcher. The aim was to listen without any attempt to organize the data but rather simply to “hear” the interviews afresh and to note anything that occurred to the researcher that she might not have noticed while conducting the interviews. Also, she could identify any other remarks relevant to her research question, any interesting or unusual comments, and any associations or connections between different issues. Summaries of each interview were made at the end of listening to each interview, to assist as a further reminder of the individual interviews.

6.6.2 Annotation of transcripts

The final interviews were printed and the hard copies of the transcripts were carefully read to mark up the parts of speech as part of the process of identifying emerging themes in an open-ended way, also enabling the emergence of new themes not previously thought of to be recognized. The repetition of themes and any unanticipated themes were noted in the interviews, and subthemes were designated, based on the similarity, dissimilarity, conflict, variations and ambiguity of the content. The different themes were grouped together and assigned to various codes, to identify them.

After coding the first five interviews, the researcher had a meeting with her supervisor who cross-examined the thematic mapping of a transcript and gave further guidance. The rest of the corrected interviews were then coded according to the major themes, and all the hard copies of the final interviews were filed separately.

6.6.3 Coding list

The initial coding list included as many nuances in the data as possible. From the very broad, open-ended list of the emerging themes, a refined, concise coding list was developed, incorporating the nuanced variations of related themes under common codes and identifying the ones relevant to the research question. The annotations were discussed with the researcher’s supervisors to gain further insight.

6.7 Thematic Analysis

Prior to embarking on the thematic analysis of data, it is important to understand the meaning of 'phenomenology', and the 'interpretative approach'. The goal of 'phenomenology' is to understand a person's 'lived experience' of an event, stressing the view that only those who have experienced the phenomenon can communicate it to the outside world (Mapp, 2008).

In addition, the researcher interprets the data of the interviews using his or hers background knowledge and preconceptions (Mapp, 2008). Therefore one has to acknowledge the epistemological limits of the double hermeneutic, as what the researcher presents is his/her interpretation of the interviewees' interpretation of their experiences, as there is no way of accessing the experiences directly. A 'hermeneutic circle' develops, as the researcher deploys their own presuppositions of the relevant experience, and eventually develops further understandings following interaction with the interviewees, who have actually lived through those experiences (Ricoeur, 1991).

The thematic analysis was performed with guidance from the researcher's supervisor, and with the help of a past study (Pope *et al.*, 2000) and textbook (Silverman, 2001) on qualitative research analysis. Possible relationships of the data were interpreted by "inductive theorizing" or through generating hypotheses from the available data (grounded theory), through "constant comparison" and analysis of "deviant" or negative cases (Pope *et al.*, 2000). Relevant data from a particular category were identified from the text, and the data were constantly compared to check for similarities, contrasts, different nuances and variations. Data of similar category were assigned to the same themes.

6.7.1 Segregation of themes

The segments of text from the annotated individual themes were cut, pasted and electronically saved in separate folders, and labelled in such a way so as to identify the source, interview number and line numbers. Segments of text having multiple themes were inserted in all the relevant folders. The font of the text was then reduced, so that all the extracts from one particular interview could ideally fit in a single page, for ease of use.

6.7.2 Content analysis

The thematic content of all the interviews was carefully read several times to identify, through constant comparison, the similarity and differences between the interviews, any variations and the “deviant cases”. Deviant cases are the cases which are contradictory to the apparently emerging explanation of the phenomenon under study (Pope *et al.*, 2000).

Subthemes, with subtle variations of the contents of the main themes, were identified. Attention was paid to not only “what” was being said, but also to “how” it was being said, to pick up the different nuances, connotations and meanings of the deliberations. Following analysis of the data, a few hypotheses were derived, using ‘inductive theorizing’, which involves repeated testing of the data and moving towards the construction of hypotheses. In further cases, the hypotheses can be tested, i.e. in future research done in this field.

6.8 Conceptual Mapping

The relevant themes of the research question were enumerated and a graphical representation of their interrelationships was mapped, highlighting how the themes were interlinked and how they influenced one another. The conceptual map (figure 6.1) is the overview derived from the interviews of the couples regarding their decision-making, and their views of embryo cryopreservation. The aim of this map was to identify the core themes that emerged from the interviews and their interrelationships. The broad categories of the emergent themes and the ones used to answer the research question are shown in the conceptual map. At the centre of the map, connecting the major themes, is the primary goal to have a baby:

- the context of the infertility experience;
- fertility treatment history;
- the couple’s concept of the frozen embryo;
- their views regarding the perceived benefits and difficulties of embryo freezing;
- technical factors influencing their decision on embryo freezing;
- information that the couple obtained about embryo freezing;
- the decision-making the couple’s experience of making the decision to freeze their embryos; and

- trusting the clinic professionals.

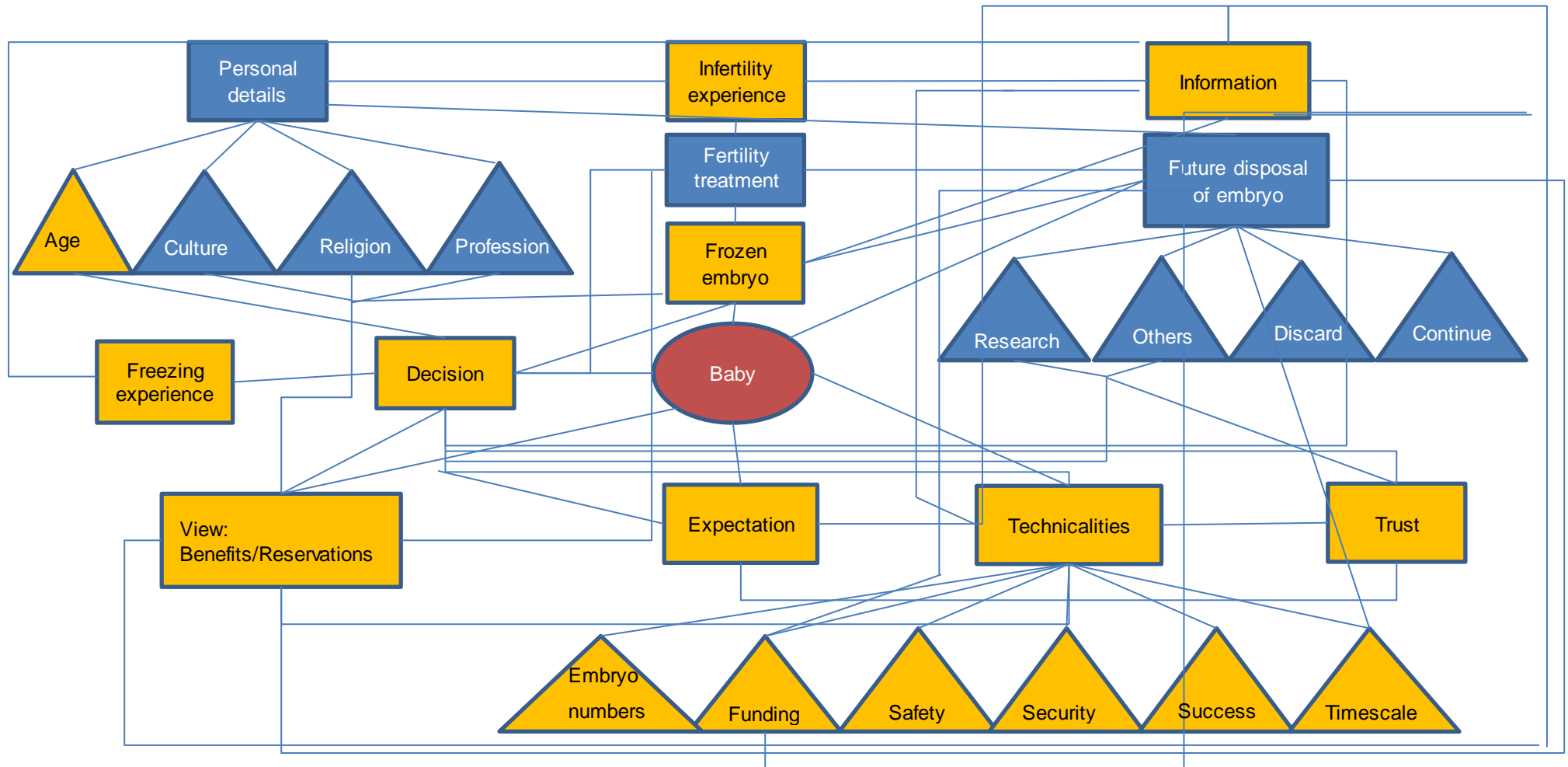


Figure 6.1 Conceptual Map showing the interrelationship of the various themes. The elements in gold are the themes that have been discussed, as they were relevant to the research question. The elements in blue represent themes that have not been discussed. “Expectation”, denoting the expectation to freeze, has been included under the theme “Information”, in the data section. “Frozen embryo” denotes each couple’s concept of embryo or frozen embryo.

Chapter 7. Couples' Decision-Making on Embryo Freezing

7.1 Introduction

The aim of this chapter is to explore the decision-making process of the interviewed couples regarding embryo freezing. The research question was: "What are the personal and social factors that couples consider when making decisions about embryo freezing?" This study is unique in terms of the time scale of the interviews, as all previous studies in this context consisted of interviewees who had had frozen embryos in storage for several years. This study is important, as its interviewees were "active IVF patients", in so far as they all had had at least one cycle (in which embryo freezing might have been a consideration), and all were in the process of considering future cycles. Therefore, embryo freezing was a "live" issue for them, as they may well be producing surplus embryos in future cycles. All 16 couples interviewed had experienced at least one cycle of IVF treatment and thus had had to consider the possibility of freezing any surplus embryos. Five couples had actually frozen their embryos following treatment.

A clinician interviewing 'active IVF patients' in his/her own clinic could create ethical dilemmas. For example, there is potential for IVF couples to fear their future clinical care could be compromised, as a result of saying anything unfavourable about the unit. Thus there is a chance that the interviews could be biased, and lacking in spontaneity and authenticity. Moreover, there is the risk of the couples' clinical decisions in the future being affected by anything said in the interviews. However, as mentioned earlier, the interviewer was conscious of trying not to influence the opinion of the interviewees as far as possible. Also, she was not involved in the direct management of the majority of these couples, and clinical care was provided by other members of the team.

From the interpretation of couples' experiences during the interviews, the broad categories of the themes that emerged and that were relevant to the research question are presented again here. Since there is no obvious way to claim a 'complete' interpretation of interviews, this study focused on achieving thematic saturation; that is, reaching a point where no new themes emerged from a detailed analysis.

- the context of the infertility experience;
- fertility treatment history;
- the couple's concept of the frozen embryo;
- their views regarding the perceived benefits and difficulties of embryo freezing;
- technical factors influencing their decision on embryo freezing;
- information that the couple obtained about embryo freezing;
- the decision-making;
- the couple's experience of making the decision to freeze their embryos; and
- trusting the clinic professionals.

The author has not dealt separately with the “personal characteristics of the patients” and the “couple's infertility history”, as they were not directly related to the research question, though these are shown in the conceptual map (figure 6.1). The theme of the future disposal decision has been extensively discussed in previous studies, and has not been dealt with separately, though it has been briefly touched upon, whenever relevant to the research question.

7.2 Data

7.2.1 The context of infertility and in vitro fertilization treatment

Before starting to analyse the various factors influencing the decision-making of couples, it is important to understand how the IVF journey, which finally led them to confront this complex decision, started. The desperate desire to have a baby was the key driving force leading couples with fertility problems to seek IVF treatment in the first place:

I think I wanted very much my wife to have a baby ... and err I really looked at y'know, okay, a desire to just have a baby ... to have a child ... and then, this whole [process started] – there's so many dynamics involved into deciding on IVF ... (11:927–960).

Embarking on IVF treatment after their prolonged pursuit for a family was the crucial decision that couples had to make, as exemplified by this statement: *[Freezing decision] it wasn't really a massive big ... decision for us to make. The big decision is to do IVF ... (19:596–603).*

The complexity of the IVF treatment, especially in the first cycle, demanded the intense attention of the couples, and embryo freezing seemed secondary at that point:

We've never, we've honestly, all the way through we've never really thought about embryo freezing, what that, what implications that will have or benefits that will have ... you had the egg collection ... at that point he gave us a detailed explanation as to how many it is but even from that point of when you had the eggs [embryos] inserted back in ... we, we still didn't think about those eggs[embryos] being frozen ... you know because we were just taking one step at a time. We weren't thinking about too much because it was so much to take on board at the time ... So anxious of getting to the next stage (I2:236–334).

Couples with NHS funding for up to three IVF cycles seemed to be keener on freezing embryos with increasing cycle ranks, i.e. with subsequent numbers of IVF cycles. Possibly, they were more aware and worried about their diminishing opportunities, in view of the limited number of free NHS-funded attempts:

I think the more treatment cycles that we did, the more it probably would have ... affected [decision to freeze embryos] because ... – certainly the second cycle I was very aware: this is my second cycle and my chances ... Her partner agreed: ... yeah, I agree – I think I'd have got a bit wobbly by the time we got to number three ... because it would have been "last chance saloon (I7:1685–1740).

The desperation to maximize any opportunity to have treatment is voiced by one individual with a past history of malignancy having treatment with frozen sperm, who was ready to freeze embryos, even at the cost of some potential risks. The desperation of couples is also evident from the repeated use of the phrase "last chance saloon":

... because I've been through erm two bouts of testicular cancer in the last ten years ... I've got samples stored here ... because this was erm – to coin a phrase "last chance saloon", ... so for me, I think it was very much about, all about maximising all opportunities and keeping as many opportunities open as we could get erm even if there were potential risks around the freezing process in terms of what might happen to the embryos (I7:457–496).

Through the experience of IVF, and the information gained in the process, couples realized the uncertainty and the limited chances of success of IVF treatment and started viewing embryo freezing as an additional resource to be relied on. One interviewee commented: *There are no guarantees about the process and at least y'know if you had some frozen embryos you know your*

chances are higher than somebody starting a fresh cycle – the unknown [outcome] ... (I12:482–491).

A very interesting new finding in this study was how the experience of the process of IVF influenced the view of many couples, who saw embryo freezing as a “medical aid” or a tool to achieve a pregnancy. This couple initially had ethical reservations about the process, but changed their view:

... what made us change our mind ... on the issue was ... circumstances ... And this is when we paused and ... we had a second look at this and we thought: let's just see these things now with a different – having had the experience of IVF – ... put things into perspective (I1: 273–290).

The male partner later continued: *... we came to view IVF and even the freezing part – just as a “medical aid” ... to someone who can't really naturally have babies (I1: 927-960).*

This view was echoed by another interviewee, who had an interesting development in the conceptualization of embryos following the experience of IVF. She learned to perceive embryos as mere cells, and the freezing process as similar to storing tissue:

... I now, for instance, understand how small it [embryo] was – seven cells or something [laughs]. You know I imagined it as a half formed sort of erm – but yeah, I didn't realize sort of how small it would be and so by the end it kind of just seemed a, a way of storing cells y'know ... I half felt like storing some storing tissue ... (I12:316–387).

Thus, the circumstances of the couples, their desperation for a baby and the experience of the journey of IVF drove them to consider the option of freezing embryos, because it gave them an additional opportunity to have a baby.

On that note, this interviewee, following the journey through IVF and achieving success from the fresh cycle, valued embryo freezing even more. She commented:

... I'm pregnant now – obviously I haven't had the baby yet ... – but ... having been through the process, I very strongly believe that you need to maximise your chances now as I very strongly believe that you should freeze embryos if you get the opportunity... (I7: 1741–1772).

On the other hand, frozen embryos seemed to be of secondary importance to a couple who were now pregnant following the fresh cycle. The partner said:

... We haven't looked into it [embryo freezing] either – we haven't asked the question ... – with everything being successful – we've just left it at that (I2:736–758).

Although all the interviewees generally were in favour of embryo freezing, there were some interesting caveats to that decision in the light of pregnancy following the fresh IVF treatment.

This interviewee, pregnant with twins following the fresh treatment, on hindsight, would not freeze any embryos, as she would now not plan to have any more babies. She also now took into account the risks of a future pregnancy associated with advanced age, using a frozen embryo. She said:

... I think now obviously with us having twins erm ... I think we wouldn't ... freeze them now ... if they're both healthy erm and obviously if I go ... like full term ... I think it's pretty much really we wanted to didn't we? [3-s pause] I think, 'cause I mean this has been amazing for us to have [twin pregnancy] and I think, think age as well. ... thinking ... obviously the older you are, erm I think there's a lot more risks involved [in future pregnancy]] (I13:379–442).

Another interviewee, pregnant from the fresh cycle, in retrospect was relieved not to have any frozen embryos. As described later (I8:1014–1047), she would have had a moral conflict regarding the selection of the embryos to be transferred or frozen. Nonetheless, in view of the benefits of embryo freezing, she was not certain about her decision in any future IVF cycle. She said:

... I'm pleased we didn't have that opportunity [to freeze embryos] [laughs] because it would have really messed with my mind. ... I know it's an extra chance and y'know if I had to go through this again and we got the choice to have them frozen I probably would have them frozen erm but hopefully – I don't know (I8:1219–1241).

This is an interesting contradiction to the 'choice is good' rhetoric, depicting how at times having a choice can lead to moral conflict and dilemma in the future. There was a definite sense of relief on retrospection, at not having the option to freeze any embryos. The relief at having no frozen embryos after achieving a pregnancy, and hence avoiding any ethical dilemma, was an important finding in this study.

7.2.2 The couples and their conceptualization of the frozen embryo

The way the couples envisaged an embryo, or a frozen embryo, i.e. as a life or baby, or as tissue, played a pivotal role in their decision-making process. The interviewees, although not able to articulate properly the nuanced nature of the embryo, were at times not paralysed by the uncertainty of its concept.

7.2.2.1 The embryo: a living entity?

To the following interviewee, the embryo was a living entity. He combined a scientific awareness of the embryo as being the result of the fusion of two cells; he ascribed the status of an actual or potential person to it:

That's how I view an embryo to me – it's life. There's been the fusion between the two cells and it's a life ... it's growing and it's a person (I1 493–498) ... you try to imagine ... that's a potential life, potential person – somebody who in ... 15, 20 years' time could be sat ... in front of you and you could have a conversation – that's how I think of embryos – not just y'know something that happens in a lab or under a microscope (I1: 611–619).

Although the majority of the couples recognized the embryo as a potential baby, they were convinced that it did not have the same moral status as a baby. The following interviewee sounded unsure about the nature of this entity, as it did not have the attributes of a living being, and vacillated between “the beginning” and a “cluster of cells”:

... as far as being a living object and understanding and ... feeling and smelling and things like that I'm still not convinced. ... I might be completely wrong ... yes, it's the very, very beginning – it's not actually a baby, ... – well it's an object but it's an undeveloped object y'know, it's a bigger cluster of cells isn't it? [laughs] (I5:1174–1218).

7.2.2.2 Conceptualizing the frozen embryo

The couples who saw embryos as “babies” held the same view for frozen embryos, and the “frozen” prefix did not impart any connotation to them. The following interviewee perceived his frozen embryos as his “babies in waiting”:

... they'd [frozen embryos] been through this extra period of waiting ... they were hardy souls: they'd made it through; they'd successfully gone through the freezing procedures, successfully ready for erm transfer ... Really proud of them ... Just my babies in waiting ... waiting to get a place to grow ... so I don't think the word “frozen” really matters in that context (I11:844–861).

How appropriate it would be to approach a couple for embryo research who perceive their frozen embryos as “babies in waiting”, is a matter of debate. As a caveat to this finding, it might be recommended that prior to approaching couples to ask them to donate their embryos to research, it would be appropriate to first discuss with couples their views on embryos.

There were also couples who were not quite comfortable with the paradoxical concept of freezing their babies, as this interviewee expressed:

I would be thinking: I've frozen my kids. [Laughs] ... I really would think that and I don't think I would like that very much to be honest ... they could turn into children and we've actually got them frozen. It's a very strange thing to think about ... (18:975–1013).

Many learned to perceive the process of creating or freezing embryos as a scientific exercise in pursuit of the goal of a baby. The deliberation of the following interviewee testifies how she started viewing the frozen embryos as part of a scientific process, as opposed to them being living entities:

... and I got to know a bit more about what embryos were, what they looked like, what good ones were, about fragmentation and all that kind of thing so it became much more of a scientific exercise – they were creating ... some child in the early stages (16:1437–1467).

Later on, she continued: *I imagine them to be ... in tubes and frozen in kind of little ice cubes or crystals. I'm not sure about how they thaw them out though ... but I'm sure it's quite amazing science (16:1650–1684).*

Another interviewee similarly described the frozen embryos as being part of the scientific process, and as a tool to have a baby: *... it's just part of the process ... (14:1881–1893) ... it's a means to an end, isn't it? (14:2601–2614).*

The development of the view of perceiving frozen embryos as “a part of the process” or as a “means to an end”, was an important finding in this study, and in keeping with the previous deliberations where couples conditioned their perception regarding embryo freezing as a medical aid, or a means to an end, namely, to have a baby.

Another interviewee visualized the frozen embryos as siblings of an existing child: *Those two spare embryos ... I'm not thinking about them as an insurance – I'm thinking about them: well that's like brothers and sisters for the first child ... (119:641–651).*

Many interviewees perceived the frozen embryos as a symbol of hope, to have a baby, as the following couple stated: *... I just think it's just err not ... life but another chance that we've got that* His partner commented: *Yeah – another seed of hope, really (13:1367–1385).*

They developed this idea further:

... it's like seeds. It's y'know – if you get a packet of seeds and some flowers grow y'know ... It's just that you've got a good packet of seeds ... so yeah that, that, this is what it grows into ... The woman explained: “... if you give birth to ... a baby and you have still got some frozen y'know you would still see that as ... positive that the rest [frozen embryos] – yeah (13:1554–1576).

There were a few couples who perceived the frozen embryos as objects and were not worried about them being mistreated in any way, as the following couple commented:

We also don't feel a connection to it [frozen embryo] because ... it hasn't been produced into anything so I wouldn't feel bad if it was – the way it was treated – I wouldn't think too much about that.” Her partner added: “It's a nothing at the moment (I2:1102–1115).

Many conceptualized the frozen embryo as being a cellular entity with suspended development, as described by the following interviewee:

It's just held in suspension basically, isn't it? Well if it's frozen, as far as I understand, it can't actually continue to grow can it? ... So, it's still just ... six or seven cells, or eight cells or whatever, but rather than being in real time and continuing to develop and get bigger and bigger, it's in suspension – its ... not changing ... it's not being allowed to move on – y'know ... (I5:990–1010).

7.2.2.3 Frozen versus fresh embryos

For some couples, frozen embryos had identical status as fresh embryos, as this interviewee commented: ... *it never even crossed my mind that they were anything other than exactly the same as the first two [fresh embryos] ... (I11:1778–1785).*

However, there were a few who were more analytical and assessed the status of the frozen embryos based on their quality:

If they're all identical then I think I would y'know ... I'd take that at face value and say y'know okay, ... they're all the same ... but if I got the feeling we were taking the best two [for transfer] and we'll keep these other two [frozen] just in case then ... you'd be thinking and trying to calculate and things ... there would be a different way of looking at them ... (I15:1856–1907).

The frozen embryos of this interviewee had not survived the thaw. She still appreciated their potentiality, but to her, there was a subtle difference in the status of the frozen and freshly transferred embryos. She commented:

Yeah, [I see them in a] slightly different way – only because it wasn't going inside I suppose. They were just four little guys that were gonna chill out there. ... I still saw them as like, as potential little beings. but ... I'm not grieving for the fact that three haven't survived (I14:1778–1815).

The IVF journey influenced the view of another interviewee, who saw the frozen embryos as “backup”, as opposed to babies. However, the status of those frozen embryos transformed into a view of an actual baby closer to the

thaw and transfer time. To this interviewee, the intention of using the frozen embryo to have a baby imparted the meaningful status of a baby to the frozen embryos, as opposed to viewing them just as a backup: *... if you freeze them it's sort of like in the back of your mind... you've got a back-up ... they are not exactly your babies ... until ... we require them (I13:1008–1050).*

7.2.2.4 Embryo concept: uncertainty and dynamicity

The uncertainty of the concept of the embryo echoed in many of the interviews. It was the abstract conceptualization of the embryo, and the various attributes given to it, that added nuances to its concept. It was evident from the comments of the following interviewee, who realizing the dichotomy of her embryo concept, called it “ridiculous”. Following the unsuccessful outcome of IVF, she was grieving for the “hope”, rather than grieving for the embryo or for a child. She commented:

... y'know you could see the cells ... it's the potential – that's going to be a child. I think it's just incredible... I know they're a bunch of cells but they're kind of our cells ... and when it didn't work it almost felt that it was grief that I was feeling in a way which was y'know, in a way it sounds ridiculous because it wasn't a child but it could ... it could have been y'know so I suppose ... (I14:1681-1699). She later continued: Yeah, it was almost [sounding uncertain] I suppose it almost was a child (I14:1708–1727).

It is not just the uncertainty of the concept of the embryo, but interestingly, its dynamic nature also, which has emerged from the interviews. The perceptions of the following interviewee drifted between the personified and the cellular concept of embryo, about which she had full cognition:

... I probably contradicted myself because I remember saying earlier that y'know – I don't know – you can't think of it [embryo] like that [a baby], but once they were transferred ... this sounds mad– I would talk to them [laughs] in my tummy and say, like will them to implant, implant y'know and feel my tummy. (I4:1494–1524).

She further clarified:

To me, when I've got sort of rational, sensible head on ... it's cells. When I'm on the Menopur [stimulating hormone] [laughs] ... and hormones are kicking in ... you're coming to egg collection and you're coming to embryo transfer and things – then it becomes, I think, a life ... (I4:1632–1677).

7.2.3 Views on embryo freezing

Perceiving the major benefits or disadvantages of freezing their embryos influenced the decision-making of the couples.

7.2.3.1 Provides an extra chance and backup for a baby

An appreciation of the extra chance of having a baby from frozen embryos propelled the decision-making of the majority of the interviewees, and some described it as a “bonus”: ... *you only have a limited number of goes on the NHS and by freezing embryos you potentially circumvent that a little bit ... (17:953–973).*

Another interviewee, who had embryos to freeze, described: *At that point for me it [embryo freezing] was a bit of a bonus really so that y'know it's – I'm always one for looking for second chances really ... (19:410–425).*

Having embryos frozen was seen as having a “backup”, in case of failure of the fresh cycle. One interviewee termed it as having “belt and braces”: ... *if something went wrong or if ... we suddenly changed our minds in the future and thought: let's give it one more go – there is that back up. (14:740–752).* She carried on: *Again it's like I suppose what you call belt and braces – isn't it ... (14:1375–1402).*

Another interviewee drew the similarity to a safety net, but at the same time recognizing the absence of any guaranteed success:

... it's [embryo freezing] kind of like a safety net I suppose because obviously I really hoped that, the one at that time [fresh cycle] would work. (114:842–857).... It's like ... another half chance within that first chance [laughs] y'know? But it's not really a safety net because [laughs] it still might not work, y'know. (114:921–954).

Whereas another interviewee compared it to having embryos in the bank: *I suppose it would have been very nice to have some in the bank if you like [laughs] – if I can put it that way (115:460–465).*

One interviewee even had the very interesting view of perceiving frozen embryos as having a backup in the situation of loss of an existing child. This idea of replacement of an existing child with the help of frozen embryos, in case of an accident and subsequent loss of the child, was not seen in the deliberations of any of the other interviewees. This interviewee said: ... *maybe y'know ... because the child had an accident or something and you just feel,*

y'know, that's part of your life missing – well let's have another child ... y'know to put that part back. (I12:1664–1690).

When the concept of embryo freezing as an insurance policy was introduced to the interviewees, there was a polarized response, with some supporting and others refuting it on ethical and other grounds. The following interviewee said in support: *Well you're just insuring yourself aren't you? ... If this doesn't work it's your – you fall back on your insurance policy, isn't it? (I7X:948–978).*

Another interviewee agreed with the concept, but disliked the term:

Insurance policy" ... I wouldn't say ... insurance. I can see why the terminology would be used. It's a bit too cold ... But a couple of times while we've been talking, the words backup have gone round my head – which isn't a million miles from insurance is it? (I11:884–982).

The following interviewee disapproved of the term, not only because it failed to respect the emotions or aspirations of the couples, but also because it had business and financial connotations. In her view, the term was a misnomer, as there was no reimbursement, as with an insurance policy:

... that kind of terminology to me just sounds very, very err – shows a lack of understanding about why people go through this ... it sounds like the kind of business decision you make about budgeting in the home, ... not something you make as a decision as a couple about starting a family. So the terminology kind of doesn't fit really ... an insurance policy... when this one goes wrong it's an immediate swap and an immediate replacement which obviously ... it isn't really for this kind of process (I7:849–905).

The following interviewee acknowledged the benefit of embryo freezing to couples in having an extra opportunity to have a baby, but at the same time had guarded hopes or a “healthy scepticism” regarding the success from the frozen cycles. This seemed to be a kind of coping mechanism to face an unsuccessful treatment, and was echoed by other interviewees. However, this interviewee justified it based on the information of lower success rates from frozen treatments. She said:

I'm sure that it [frozen cycle] brings great benefits to ... lots of people erm but ... just, it's really not trying to be sceptical, it's, it's just trying not to build up hopes ... when you know there's a greater chance of not succeeding than succeeding ... (I15:849–865).

7.2.3.2 Desire for autonomy and having options open

Some couples felt that with embryo freezing, they would have the opportunity to exercise a certain amount of control in deciding their fates, as the embryos

belonged to them. This was interpreted as desire for autonomy of the couples in controlling the destiny of their embryos. This interviewee commented:

... so if I wasn't allowed to freeze them, ... I would have a lot of problem with ... that – not knowing what was going to happen to them ... whether they would just be destroyed ... or ... taken off me for research or whatever then I've lost ... that control of that decision erm and it's then taken out of my hands so it's ... because they're my embryos ... they're ours so surely it's for us to make that decision as to what happens to them ... (19:677–752).

Another interviewee talked about not feeling restricted by the imposition of government policy of the limited number of IVF chances: *you don't get limited on the number of opportunities you've got based on a government policy, you get – there's more chances – as many chances – bite at the cherry you can get. (17:974–984).*

Another major advantage with freezing embryos was seen as having all avenues open, either as a backup, or for a sibling, or for embryo donation, and this was also related to the desire of exercising one's autonomy. This interviewee said:

... it [frozen embryo] is there in case you change your mind in the future in case you want to have more children ... you don't know what the future holds and I think I would feel risk to taking that option away ... Her partner added: ... I would want a second child anyway (17:1057–1084).

Another view was that freezing embryos buys you time and prevents any regrets in the future, as the door to all the options is still open. One interviewee commented in this context: *... there probably wouldn't be any regrets about freezing them because I'd rather freeze them and have time to think about what to do with them ... than to discard them (16:753–759).*

7.2.3.3 Avoiding further fresh treatment

A common reason for couples to support embryo freezing was avoidance of the complications and hazards associated with a fresh IVF cycle. The driving force was to avoid the painful step of egg retrieval, and complications such as ovarian hyperstimulation syndrome (OHSS), which are absent in a frozen-thaw treatment. One interviewee commented:

... so it was to save going through the ... egg collection, because that was awful. ... well I can remember waking up half way through it and the pain was horrendous ... So I think if it was to save that then it would be bloody marvellous (18:322–379).

A few couples recognized the aspect of reduced emotional stress with having frozen embryos, because of the reassurance of having a backup. This interviewee said: *... it [embryo freezing] does take the stress off a bit ... the mental stress. You've got something to fall back on ... (17X:432-496).*

The following interviewee perceived the advantages of frozen treatment, as opposed to those of the fresh. She saw the frozen cycle as shorter and closer to being more natural:

... it [fresh IVF] takes a big chunk out of your life for about ... seven weeks... ... and I think to not have to go through that and just be able to have an embryo put back in would probably seem a bit more like a natural process where you haven't got to go through a regime for seven weeks before you get pregnant y'know ... (17:925-948).

7.2.3.4 Maintenance of the embryo potential

Maintenance of the embryo potential was an important consideration for some interviewees, especially for those who viewed embryos as living beings. This interviewee said: *... it would be criminal not to [freeze] and there was a life you were playing with, there was no way it wasn't going to get every chance to ... become that life (111: 856-861).*

Some couples perceived embryos as not only life, but also as a valuable resource, and therefore viewed discarding them as a waste, and hence, as ethically unacceptable. This interviewee said:

... all what we're doing here is trying to create a life and all of this is the start of life and you can't just discard that ... and we've also been explained how rare it is to get a lot of follicles, to get a lot of eggs, to get a lot of erm successful fertilisations and to have lots available ... (111:813-861).

Another interviewee explained how freezing was a way to avert discarding and wasting embryos: *But freezing, definitely, there's more of a chance they're gonna live than not using them because if you don't use them, they're wasted aren't they (114:1501-1506).*

Even after achieving the primary goal of having a baby in the fresh cycle, couples viewed the scope of maintaining the embryo potential for having a sibling with frozen embryos, as this interviewee said: *... and then there's also the chance of having y'know a second child or maybe a third y'know so you have the option of the normal type family (110:460-468).*

7.2.3.5 *Potential harm to the embryo*

One of the key objectives of a few couples when considering embryo freezing, was doing no harm to the embryos. The different clusters of opinions regarding having any difficulties or reservations about this practice ranged from concerns about causing any physical harm to the embryos or to the future offspring, or having concern from the moral or ethical aspect of freezing the embryos.

The following couple, as discussed earlier, had initial ethical and moral reservations about embryo freezing, but following the IVF experience, viewed the practice as a medical tool to achieve a pregnancy. Despite that, the male partner had reservations about the potential harm to embryos, as there is uncertainty surrounding the fate of frozen embryos, almost giving them the status of complete individuals. His deliberation echoed respect for the embryo by seeing it as an individual. He said:

... I think somehow morally it's not right. Because ... what happens if those embryos are not placed in a womb where they can grow ... and ... develop and become babies? What happens with them? (I1:418–437) ... Because we wouldn't like any spare embryos just left somewhere – you know, kind of waiting in limbo (I1:384–386).

On this note, and as documented earlier, interviewee 14 P had argued that there were more chances of an embryo surviving when frozen, as opposed to not freezing and discarding it (I14:1501–1506).

The repertoire of deliberations of the couples in the context of safety of the embryos, showed their concerns of causing any harm to the embryo or to the resultant offspring, either by the freezing process, or the length of time being frozen, or the risks of them not surviving the thawing process. Several couples had concerns about any potential harm to the embryos, and the resulting babies, from the freezing process. One interviewee said: *... I worried about how they were going to defrost the eggs [embryos] and put them back in ... How would they develop? Would they develop the same, y'know – as a normal baby and that? (I7X:497–511).*

The association with freezing food in the freezer was a common theme and added to the concern. This interviewee thought her worry was related to not having sufficient information about the process. She said:

I mean beyond the concept of freezing I would never have known what was involved – what was going to happen y'know to the ... embryo so I guess perhaps some of it [the worry] was y'know I didn't have a very good

understanding of it ... It sounded a little bit scary I guess. (112:253–267) ... I know it's not done in the same way but if you put something in your freezer and it's not wrapped up properly you get freezer burn and therefore it's useless ... afterwards y'know so there was this sort of ... how do you store it safely and you hear about it stored for a number of years; well you don't store things like food for a number of years ... (112:359–379).

The worry about the safety of the process was related to the concerns of freezing life. The following interviewee was sceptical about the concept of freezing an embryo, which she visualized as a life, and for it to “spring back to life” following the thaw. Interestingly, she drew the analogy of freezing her cat: *... I don't know – if I picked up my cat and stuck it in the freezer y'know I wouldn't expect it to be there when it came out again ...* Her partner added: *Sprung to life, yeah ... (112:1185–1309).*

Another interviewee had concerns about the frozen embryos not surviving the thaw, and hence the potentially lower success rate from the process, and had initially decided against freezing: *... I read that erm y'know – quite often the embryo doesn't survive the ... thawing process ... that's probably as well why we said no [would not freeze] (14:536–560).*

Another interviewee was sceptical of the quality of the embryos following the thaw and thought that they would deteriorate with time, with a resultant reduction in the success rate. The repeated use of the word “defrosted” by a number of interviewees is interesting, as people extrapolated their knowledge from their own domestic freezing experiences:

... it's [embryo] been out and then it's frozen ... then it's got a longer journey really because it's then gotta be defrosted sort of thing and then put back. (18:265–293) ... it must take ages to defrost something that's been frozen that length of time, it must take longer erm and I would just think that it's been frozen that long that ... it will have deteriorated at some point ... Yeah, I would think that the chances would be slimmer ... the longer it's frozen (18:1569–1582).

A few interviewees had worries about the nature of the process of freezing embryos, and wondered if it would be traumatic for them. However, these doubts would not deter them from freezing embryos. One interviewee said:

... Yeah – the whole process of that and I don't know if it was a harsh process or anything like that in terms of your embryos – I wasn't 100% sure on that. (13:306–309) I mean things cross your mind. I mentioned about the whole erm ... the kind of process of them being frozen thinking: oh, will they be as good and all that. You obviously have reservations. However, I was really... devastated at the fact that we didn't have any to freeze (13:550–564).

Another interviewee's concern about the severity of the process of freezing was reflected in the use of the phrase "bruised and battered": ... *the frozen ones have already been bruised and battered coming in and out of freezing – that can't be an easy process (I11:311–348).*

In the view of one interviewee, embryo freezing and suspending their development seemed an unnatural process, and one that bore a connotation to the term "freezing". There was an interesting reversal in her thought process: use of the term "cryopreservation" was better in her view, but also conjured up an image of science fiction in her mind. In her opinion:

... the freezing thing does seem to be a stage further in terms of being unnatural ... yeah, just ... stopping the development for hours/months/years whatever ... It just seems to be a stage a bit far so (I15:611–629) She continued: ... and it's just, maybe it's just the simple terminology of freezing I, y'know, it's a different sort of thing actually isn't it? ... Well it [using "cryopreservation"] might be ... it might help people ... Although that does veer towards the science fiction ... (I15:2509–2534).

Some interviewees had fleeting security concerns about frozen embryos getting mislabelled or mixed up, though all of them perceived the risk of that happening to be low. Nonetheless, that would not deter them from embryo freezing, and this decision also rested on an element of trust. This couple commented:

I did jokingly say what happens if ... the embryos get mixed up. [Laughs] ... It shouldn't happen [laughs] you have to trust that it shouldn't happen. Her partner commented: I know you do hear stories ... I don't know, mistakes happen everywhere don't they ... That would be awful. It would be terrible but that's a risk ... it's not a nice thought. But no – yeah, I don't think it would have made any difference in our decision. (I14:1382–1461).

Another interviewee provided an interesting input. He wanted to see the embryo storage facility and compared it to storing valuables in the bank safe. He said:

... in effect it's a belonging of yours and you like to know where your belongings are y'know ... if you know it's in the bank, the bank safe, if you've got your jewellery at home it's in the drawer ... If it was just somewhere – where is it, y'know? ... Again, not having had too much information on it if I found it was y'know a little fridge/cupboard style thing somewhere y'know in the corner of the, the building ... I'd be more worried y'know ... what happens if you have a power cut so that sort of thing ... whereas if you seen some proper storage facility ... it reassures ... you I think. (I12: 2035–2141).

The following interviewee had concerns about any potential harmful effect on the psyche of the offspring born from a frozen embryo: ... *would you then tell that child and what kind of implications would it have on the child knowing that the child started out as a frozen embryo ... (I7:560–623).*

It is quite interesting and thought provoking to contemplate whether the disclosure to a child about him or her starting the life's journey as a frozen embryo would have any adverse psychological influence.

7.2.3.6 Risk of forgetting the embryos

Interestingly, the following couple brought up the issue of the risk of forgetting that the frozen embryos remained in storage, which is a unique finding in this study. The male partner mentioned: *I guess, long term would be more of an issue y'know if they were there for three, four, five, six years ... would you forget yourself and would somebody else forget they're there ... (I12:592–611).*

7.2.3.7 Potential legal problems

A few couples were aware of potential dispute over frozen embryos, in case of death or legal separation of the couple, but that was not perceived as a serious concern. The following interviewee observed: ... *it's [embryo freezing] only a potential future problem if, if that y'know ... if the couple splits up ... If they're likely to argue over the CD collection they're certainly going to argue ... over the embryo you know [laughs]. (I10:469–528).*

7.2.3.8 Benefit to research

Many of the couples appreciated the value and use of frozen embryos in research and had a sense of obligation in recognizing that they were reaping the benefits of past research. This interviewee said:

... if something actually [one could] learn [from frozen embryo research], or they [frozen embryos] can be used to help somebody else ... if somebody hadn't done it [research] in the past and the research and development hadn't been done in the past, we wouldn't have been able to go through the ICSI treatment (I5:311–332).

7.2.3.9 Helping other subfertile couples

A few couples also felt that frozen embryos could be donated to other couples in a similar situation. The following interviewee, pregnant following the fresh treatment, was empathetic towards other infertile couples and wanted to give

them the same opportunity. She said: ... *having been through this I guess, the thought that you ... could give that opportunity [to have a baby] to somebody else ... feels like quite a nice thing to do (I12:1705–1713).*

7.2.3.10 Medical indications

The following couple appreciated the importance of embryo freezing for certain medical indications. The woman had a slightly thin lining of the womb on the day of the embryo transfer, and in the couple's opinion, freezing all the embryos for later transfer could have given them the opportunity to investigate the problem. Her partner said:

... So for example, going back to the point about the lining of the womb being a bit thinner ... so ... that [embryo freezing] would have actually given us the chance to test those things. Meanwhile you've got these stored in the bank to come back and use after you've gone through and worked out what the issue might have been ... (I7:813–842).

7.2.3.11 Freezing for social purposes

The following couple recognized the potential social indications of embryo freezing. The woman said:

...Times have changed... She added: I can understand why people – they meet a partner late in life ... they marry late in life or they've had an illness and it's through ... no fault of their own ... this freezing thing would be an amazing opportunity for them to grasp at y'know (I4:1006–1028).

Egg freezing is not yet a common or standard practice in most fertility units. Therefore, for a single woman in the previous scenarios, freezing the embryos created with the help of donor sperm for future use could be an option.

A few interviewees objected to the concept of embryo freezing for social reasons, such as deferring pregnancy for a career. One interviewee commented: ... *you read in some magazines people freeze them [embryos] because they want kids like another ten years down the line to suit their lifestyle which I just think is ridiculous. I don't agree with that at all (I8:1599–1626).*

7.2.4 Technical factors influencing the decision to freeze embryos

7.2.4.1 Embryo numbers

Some of the interviewees would give consideration to the number of suitable embryos present when making the freezing decision. Most couples would

freeze any suitable embryos, regardless of the numbers. This interviewee commented: *I don't think it would matter how many [embryos] there were (16:1218–1241).*

However, another interviewee commented that they would be more inclined to freeze a single embryo, if the number of embryos were few, due to the uncertainty of the scenario:

... if you had ... a small number like what happened with me and I4 [his partner] ... then I think that we'd might ... make you more inclined to, to freeze one. ... because it, it's obviously not working very well whereas I think if I4 ... produced more eggs and we didn't have a problem producing embryos then, y'know ... I think I would be less inclined to freeze them because that's not where there's a problem.

Nevertheless, his partner would still have frozen. She commented: *... – no I totally agree with what you're saying but I think you would still do it if you had y'know – say you produced, what, I don't know – ten, eight, – pick a number out of the air ... (14:1229–1402).*

One couple expressed scepticism in freezing a single embryo, especially in younger people, due to the uncertainty of its thaw survival following a longer freeze period. Though the woman would freeze a single embryo, her partner did a mental calculation of storage fees over the years, versus fees for a private treatment, and regarded a fresh cycle as a prudent option. She said:

... erm I think it would have made me less confident if we'd only had one erm to freeze because of sort of the thawing ... the s-survival rates ... but I would still have frozen them. While her partner commented: ... that scenario when you're in your late twenties ... if you've only got one ... you probably wouldn't. Because ... – the chances of it – so you freeze it, keep it for ... years and defrost it and it doesn't survive ... what's the point? You could have saved that money ... There's half your money towards your full IVF treatment so you might get a better chance (19:1451–1566).

There was just one interviewee who took into account the aspect of the cost-effectiveness of freezing a single embryo, who had been denied that option in a past cycle. He appreciated that it was the prerogative of the fertility unit to make such decisions, but demanded involvement in the decision-making. His view was that:

... it's basically cost effective to freezing one. How much? Obviously I don't know the numbers. I know the injections – that's a lot of money ... and would that freezing outweigh the cost ... of the drugs ... Basically there are a lot of factors to be considered ... the cost of drugs and how many [embryos] did you get, did you get one, did you get twenty-five? Y'know it all depends on

each case by case. Now, if it [is] more effective to freeze that one, good – if that's going to work out better, but obviously I think ... that's kind of the centre's type of decision really ... we should be, we should be able to ask, we should be able to be informed on this type of decision if we want to appeal against that ... (I7X:1093–1247).

7.2.4.2 Views about the clinic's freezing policy

Most couples were not certain if they were permitted to freeze a good-quality single embryo, but were keen to do so. The following interviewee was aware of the clinic requirement of meeting the quantitative and qualitative criteria of having at least two embryos of suitable quality for freezing. However, this individual expressed moral difficulty at not being able to freeze his single embryo. He said: *... one difficulty we still have is that basically you can only ... you can't have just one single embryo frozen. I believe these are the rules ... (I1:372–416).*

He elaborated his ethical dilemma in a hypothetical scenario:

... if for example next cycle we are going to have ... three of them [embryos], yes, and we think: right, what do we do now? Are we going to have one put back in and two frozen or have two put back in and then none frozen? That would be a very difficult decision and therefore that's why we would like to have ... the option given where one embryo is frozen (I1:1411–1454).

7.2.4.3 Funding issues

A key finding in this study was that financial issues were found to have a major impact on the decision-making for embryo freezing, especially in the context of private funding. The majority of the couples appreciated the NHS funding for embryo freezing to be of huge benefit, especially in view of the economic climate. This interviewee viewed the storage time of 12 months to be a useful period for decision-making:

We don't have enough free money in this country to ... pay for everything ... yeah. Twelve months, eighteen months yeah – it gives you a chance to move on and research and make ... your decisions ... it gives you a window of time. I think you need to keep that if, if there was a financial penalty from day one I think it would put a lot more people in a lot more stressful position and, and the people at the lower end of the market ..., would be in a far worse position ... (I5:1372–1421).

One interviewee had a different opinion. He had reservations about embryo freezing as a routine practice and indicated that free funding for freezing could potentially dilute the embryo freezing decision-making process. He said: *... so*

you know err people have this – oh if it's free ... I think [if] it would be costs involved – maybe not huge costs but something that is affordable I think people would give it a second thought err for doing that (I1:560-580).

Another aspect that emerged from the interviews was that couples not having the opportunity to freeze were mostly not aware of the regulations regarding embryo freezing, and about NHS funding, its duration and the fees subsequently involved. This couple sounded unsure:

... Some cost [for freezing], yeah. Unless it's free for a little time. I don't know – I can't remember. Her partner added: You had to pay the initial fee for [sounds unsure] – was it the freezing and then you had to pay them ... yearly or something? I think that's what it was? (I3:737–773).

Another couple assumed they could have the frozen-thaw cycles only following the three funded fresh treatments. Therefore, the woman was concerned about the practical feasibility of having three funded IVF treatments within the span of 12 months, the duration of NHS funding for embryo freezing. She said: ... *So they would pay for the eggs [embryos] to be frozen for twelve months? Erm ... if, if it hadn't work, to do three rounds [fresh cycles] in twelve months is a lot to ask ... (I8:492–573).*

In the opinion of another interviewee, it was reasonable to fund embryo storage for medical reasons, but not for social reasons. He said:

... if there was a medical reason, I think that should come first ... I think if it's just purely [to] have a career or I want to travel the world and then come back to it but I think if, if there's a medical reason that someone needed ... to do that, I think that should be funded – yes (I4:1086–1177).

The legitimacy of drawing the distinction between the “medical” and “social” reasons for embryo freezing can be debated. NHS funding for embryo freezing is available for up to 12 months for subfertile couples undergoing IVF treatment, and having suitable surplus embryos to freeze. It is also funded for medical reasons, such as fertility preservation in cancer patients, or in patients having complications during treatment, such as severe OHSS, where pregnancy carries a risk of aggravating the condition. NHS funding for social embryo freezing, for example, to have a career, is not currently allowed.

7.2.4.4 Embryo storage time limit

Interviewees had a range of views about the time limit for NHS-funded storage or any maximum time for embryo storage. This information was relevant from the point of view of planning the thawing and use of frozen embryos.

Again, many couples with no frozen embryos had no idea about the existence of any time limits: ... *about the time limits. I err ... I don't think that ..., there are, I don't know of any (I1:1055–1071).*

A few couples thought that the funded 12-months storage was inadequate for couples who have a baby following the fresh cycle. They would feel the pressure of deciding to use their embryos for a sibling within the next few months of the remaining storage time, while not being ready for another pregnancy physically or mentally. This interviewee said:

... but if there is a child then if that period can be extended to six months after the first child is born because I could see that as being quite a bit of pressure on the parents erm because of a sudden ... you're now thinking ... we've only got three months to decide. ... so [ideally should have] like twelve to fifteen month sort of window... ...because then ... it's better for the health of the mother ... (I10:1544–1767).

On the other hand, this interviewee appreciated the fixed time for funded storage, in view of the limited resources: ... *because ... there's only so much money in the NHS system. I think it would be very difficult to make the rule as to, to when ... I guess invariably there would be some people who – yeah – couldn't pay, could get quite upset ... (I12:972–998).*

Another interviewee felt the need for a planned time limit for storage even in case of privately funded embryo freezing, not only for financial reasons, but also to draw a closure to the journey. She said:

Not just from a monetary perspective but I think it's y'know, you've got to get closure at some point to decide how long are you going to allow this journey ... to go on ... we, I would say – would have to make some decisions. It's not something we could just leave for forever (I9:872–960).

7.2.5 Information couples obtained about embryo freezing

It is important to explore what prior knowledge and initial impression about embryo freezing the couples had when attending for IVF treatment, and any further information they received, which potentially could have influenced their decision of whether to freeze their embryos.

7.2.5.1 Knowledge prior to attending the clinic

It emerged from the interviews that most couples were aware of the practice of embryo freezing as general knowledge derived from the media: *I've heard about it like through the news and stuff like that ... so it wasn't anything that I hadn't heard of before (I9:389–406).*

Other interviewees had some knowledge gained from personal research on the internet, or from colleagues, friends and relatives:

I gathered it from the computer... – yeah, Internet – because when I start my IVF I'm a bit curious about what was happening so I did a little bit of research about that ... I've got one working colleague erm I think it's her daughter as well, had the same situation and she had frozen erm [embryos] – so that's where I found out it was and things (I10:283–302).

However, some people had not heard of it at all and were newly introduced to this idea in the fertility clinic. This interviewee was a bit nervous to start with when first introduced to this concept and made a negative association with the term “embryo freezing”. She, however, related her feeling to her lack of knowledge about the process:

I think at that stage I was possibly a little bit nervous ... at the thought of it – at that early stage. Erm. I think it's just, sometimes it's just hearing the term... sometimes the way the term is used is usually in ... quite a negative way erm ... so yeah, the term made me a little, perhaps a little nervous at ... that point. (I12:211–232) ... and I mean beyond the concept of freezing I would never have known what was involved – what was going to happen y'know to the ... embryo so I guess perhaps some of it was y'know I didn't have a very good understanding of it ... at that point (I12:253–267).

The initial impression about embryo freezing that couples had when they first came to the clinic, was based on their general knowledge about the process and on the information gained from various sources, including the media, the internet, friends and relatives. This was before they received any information from the clinic. The following couple had a positive opinion regarding embryo freezing, as it would keep their options open in view of the uncertainty of the IVF outcome: *We didn't know ... how things were going to go ... you don't want to shut any doors at, at the start. You can always change your mind later on. (I5:216–239).*

However, there were others who had initial reservations about freezing embryos due to various reasons. The following couple had initial ethical

reservations about “freezing a baby”, which they later changed following the IVF experience, and perceived their initial opinion as “uneducated”:

I think we were a bit reserved to begin with. Because err ..., it just did not sound right y'know. Just putting it very plainly y'know – having a baby frozen ... but that was obviously, it was an ... uneducated opinion, err that was kind of just when I had a general idea – why would someone do that? ... because an embryo – we imagined as very, very small baby [laughs] – they were being frozen so [trails off] (11:211–260).

7.2.5.2 Information sources

Couples obtained their knowledge and information about embryo freezing mainly from the IVF clinic, and also from other sources, which influenced their decision to a certain extent.

This interviewee described how the clinic information was broken down so that it was not overwhelming, and talked about the information leaflet:

... I think the way the kind of consultations are broken down as well – I think it was just enough at that time in each meeting – step by step. ... And I think y'know it could have certainly been handled in a different way when it was too informative and this was continuously put on to you as pressure and I think that's when it would start kind of being the “pulling your hair out” times y'know ... (12:407–426). ... it was explained that depending on how many good eggs they got and how many fertilised, we could have them frozen then there was, I think – we had a sheet of paper where it explained all ... (12:183–222).

Again, a few couples, especially the ones who did not have any embryos to freeze, did not remember much about the freezing information, or had false impressions regarding different aspects of it. One interviewee commented: *I don't remember that, it seems so long ago, a lot has happened since then (15:240–268).*

Another couple had no idea that the frozen cycle imparted additional chances, over the three NHS-funded treatments. The woman, who had been through two IVF cycles, seemed surprised:

... So that (frozen-thaw cycle) wouldn't class as a third go? ... I don't know, you think you're listening, don't you and sometimes too much information ... I thought that the frozen embryos would be used in your official three cycles if you like ... Her partner added: I didn't know that ... Well of course, it makes sense now – doesn't it? (14:760–842).

Appreciating the huge volume of information, especially for those new to IVF treatment, the following interviewee advocated a separate session to discuss

embryo freezing information: ... *I think ... you'd need a separate appointment about freezing embryos and you'd really need to go through that whole decision. I think it would add a lot ... info, for you to consider ...* (I11:1490–1546).

The internet, although being one of the other major sources of information, was misleading and confusing at times. This interviewee talked about his experience of getting contradictory information from the internet: ... *everything we were reading was contradicting on-line ...* (I7X: 593–617).

A few couples also discussed the process with their friends and colleagues, but most did not have any opportunity to discuss it with any other patients in the clinic.

7.2.5.3 Expectation to freeze

Couples also described whether they actually expected to freeze their surplus embryos. The following couple, having high expectations to freeze, talked about their devastated feeling at having no suitable embryos: ... *we were, quite devastated at the fact that we didn't have any, any spare embryos ... to freeze because ... we would have actually, absolutely made that choice to freeze them* (I3:344–376).

The majority of couples, however, did not consider the possibility of having embryos to freeze, being too preoccupied with their current treatment, as discussed previously (I2:236–334).

Very few couples had realistic expectations and did not hope to freeze embryos during their fresh IVF cycle. The following interviewee, who did not have any embryos to freeze, commented: ... *and it didn't cross my mind actually [that] we'd lost out on something ... we hadn't been going in sort of ... with the, an expectation of, of putting something in the bank or anything like that ...* (I15:1535–1572).

Most couples received an explanation for why there were no embryos to be frozen, their understanding of it being exemplified by this interviewee: ... *that the cells didn't divide well and that there was perhaps fragmentation of the cells ... It [embryo] just didn't take very well, didn't grow ...* (I7:149–229).

7.2.6 Decision-making

The factors that couples, who were contemplating the future, considered when confronted with the decision whether to freeze or not to freeze embryos, either hypothetically or in reality, are explored in this section. An important and interesting finding was that the decision making of the couples who actually froze their embryos seemed to be an automatic and straight forward decision. It was common sense to them to freeze any suitable embryos, and it was, as one interviewee said, 'a no brainer'. However, for others reflecting on their IVF experience and making a decision for the future, it involved intricate thought processes of balancing the roles of various factors.

Before reviewing the different ramifications of the decision-making process, it is important to understand who, in the eyes of the couples, owned the right to make the decision.

7.2.6.1 Who makes the decision?

It appeared that couples thought that they had the ultimate right to make the decision about freezing "their embryos", which can be interpreted as them exercising their autonomy, as explained below. The various quotes that follow illustrate the justification of their decision to freeze embryos. The following interviewee explained that since the ultimate goal of embryo freezing is to create life, he had no ethical reservations about it. However, he appreciated concerns of certain individuals about freezing life. He said:

... ultimately, what you're ... trying to do there is then thaw that [frozen embryo] life with a hope to that life growing and becoming a baby. Your end goal is still to have the baby so to freeze the embryo ... I don't have an ethical issue there but I can understand why people look at it and say ethically you're taking a life and then you're freezing that life (I7:1156–1235).

Another interviewee appreciated the objections of some, from the religious point of view, but viewed the desperation for a baby to be a stronger driving force and therefore giving him the right to decide what to do : ... *I can understand how maybe people who have a religious faith and ... think that it's wrong ... y'know because you do want a child you think well no, I think you would ... continue y'know – even if you had thoughts like that ... (I4:945–978).*

In the opinion of quite a few couples, moral critics of embryo freezing would change their view if they were placed in a similar situation to theirs. Although

being fully aware of the moral criticisms to embryo freezing, this interviewee proclaimed her view and justification to embryo freezing. This shows how the couples perceived themselves to be the rightful authorities in making the freezing decision, and is thus being interpreted as reflecting their 'autonomy'! This interviewee also argued and expressed his view that since an embryo has no independent survival, no ethical reservation arises from freezing it:

... I know, I know what people have said about it [embryo freezing] ... and I still think ... if they were in the same situation as us they would have a different view on it because you're just keen for any chance that you've got ... And at that early stage the embryo was not going to survive. If you don't freeze it to preserve it for later on and you don't transfer it, it doesn't successfully implant well it doesn't survive anyway (15:670–732).

An interesting view was expressed by the following interviewee, who said that using the term “embryo” instead of “fertilized egg” might fuel moral controversy regarding freezing, as the term embryo conjures a mental image of a miniature baby. He said:

... to me ... what you used to see in the little diagrams where it's [embryo] like a little baby sort of thing ... whereas when they did the IVF ... they didn't call it a fertilised egg ... and they called it an embryo with eight cells ... I thought ... how doesn't that influence debate more? The people doing the procedures, it's like as soon as it's fertilised ... it then becomes an embryo ... which you would say would be a fundamental Christian point of view ... that's what really surprised me – that the doctors themselves had actually subscribed to that point of view ... (110:896–988).

7.2.6.2 Instinctive decision-making

As mentioned earlier, the decision-making process was presented as an instinctive or automatic one for most of the couples who had actually frozen their embryos, especially the ones having their first treatment. Embryo freezing was an imperative to increase their pregnancy chances; it did not involve complex decision-making, and the couples were also preoccupied with the complexities of the fresh IVF treatment. One interviewee said: *Erm I think we would just very instinctively just have them [frozen] ... there wouldn't be much thinking ... (16:672–721)*. He then went on to say: *Yeah, it's a no brainer. (16:1196–1205)*

Another interviewee said: *... as I say, it seemed a practical thing to do ... it's common sense you know? (110:599–609).*

7.2.6.3 Balancing risk versus benefit

When presented with a hypothetical decision-making setting, a few couples made a mental calculation, which involved weighing the risks of freezing. These couples had already gained the experience and insight following their IVF experience. For example, a few considered any potential harm to the offspring on the one hand, and the benefits of the procedure on the other, before making the decision to freeze, as the following interviewee did. He viewed the desire to have a baby versus compromising its health as a result of the freezing process, as “selfishness”:

... We ... asked the questions: what are the facts? you'd make an estimated guess, wouldn't you? I'd be wanting to know more the risk factor ... success of a ... full term [pregnancy] ... (I5: 1538–1571) ... The risk of terminal sort of illness ... for the baby, because obviously ... I wouldn't want to – don't get me the wrong way ... bring a child into the world who was so severely disabled due to a factor that I wanted a baby so much that I was going to put their lives in such a lot of trauma ... and bad health, because of my, my err ... selfishness ... (I5:1572–1603).

However, when told that embryo freezing was not associated with any increased health risk to the offspring, he was keen on embryo freezing.

To another interviewee who was paying for her treatment, the slight reduction in success rate was compensated for by the benefits of the frozen cycle:

I don't see what that extra ten per cent lower [success rate] is going to make any difference. And it's almost counter balanced by the fact that the frozen cycle is ... for me – so much less intrusive ... and there's less trips back here for scans and ... that I'm paying less [in frozen cycle, compared to the fresh] so yes, the success rates aren't that good but, all the other part of it is actually much easier ... (I9:1607–1639).

7.2.6.4 Considering the success rate

Considering the success rate from frozen-thawed embryos would be the most important and decisive issue, when making the decision of whether to freeze or not to freeze, for a few interviewees.

The following interviewee was quite calculating, and judged the process by the exact success rate. He also viewed the potential of raising false hopes among couples with frozen embryos, if the success rate was actually very low. However, he did not have the precise information regarding the success rate from frozen cycles. He commented:

... If you're only going from twenty-five [assumed success rate in fresh cycle] to twenty [per cent success rate] you're not going from twenty-five to five ... then you have a reasonable chance, ... whereas erm ... if it was from twenty-five to five ... that really is ... not worth doing y'know? Yeah ... it would be more debatable as to whether that was actually y'know creating more false hope rather than being a viable prospect (I10:1812–1853).

Notwithstanding the lower success rates, most couples were inclined to freeze as long as there was a chance of having a baby. One interviewee argued that a reduction in the success rate was counterbalanced by the potential multiple chances, as there are no limitations on the number of frozen cycles. They said:

... your chance may be lower, but you've got more of those chances. ... so when you get down to the stage where you've maybe exercised all your normal options and the only option left is the one that you've already frozen, you'd be pretty desperate by that point ... and I think ... the practice should be continued even if, if your chances reduce as you go through that, that journey [laughs] – you're still, you're trying to take ... advantage of that. His partner added: ... as long as there is A chance, you're still going to ... take it (I7:1819–1851).

The majority of couples believed that the success rate with a frozen cycle would be lower than with a fresh cycle, but were not quite certain as to what extent. It did not seem from the interviews that they overestimated the success rate from embryo freezing. A few were not sure of the exact success rate: *The success rates ... obviously reducing because if they [embryos] are frozen, but I'm still unsure – is there actually ... a depreciation of the success rate? I'm still unsure (I7X:794–815).*

7.2.6.5 Considering other options

A few couples made their decision after considering other available disposal options of the surplus embryos, and eliminating the ones not acceptable to them. One interviewee said:

... At the end of it, you're left with some embryos so ... what do you want to do with them: do you want to give them over for research or do you want to keep them or do you want them destroyed? So for us, the – it was a simple question of well, we'd rather keep them and try ... we don't want to y'know destroy them. If we didn't freeze them we would give them to research so ... so for us it was quite easy (I9:515–540).

7.2.6.6 Decisions made by the couples

The ultimate verdict given by all the interviewees was that given the opportunity, all would freeze their embryos. One interviewee said: ... *Yeah, definitely. I don't think I would think twice about it [embryo freezing] if the opportunity's there. (I14:498–508).*

As discussed previously, one couple, who had ethical reservations about freezing embryos, subsequently modified their view by perceiving the practice as a medicalized process to achieve a pregnancy (I1:927–960). They would have ideally chosen to freeze a single embryo, but since it was not permitted, they would freeze two, because of their concern of any unused surplus embryo being wasted. Their original plan, it seemed, was to have two children, assuming one from the fresh IVF treatment, and a sibling from the single frozen embryo. However, since clinic regulations allow freezing with at least two suitable embryos, they would have to freeze two embryos and have three children, assuming one from the fresh treatment, and two from the frozen treatments. Clearly, they were probably being a bit overoptimistic in hoping that all the treatments would be successful. The male partner said:

... we would consider to have two embryos frozen ... but no more than two. We'd actually like one [embryo frozen] but y'know because ... one is not possible, one would be ideal or one would be our first option but because one is not really [an option] then two [we'll freeze two embryos] then we'd have to try and have three children [assuming one from the fresh cycle] (I1:968–993).

7.2.6.7 Variation with stage of treatment

The following interviewee made an honest admission about how her freezing decision-making process changed with the stage of the IVF cycle. Her initial thought of embryo freezing driven by altruism was replaced by the predominant reassuring thought of having a backup for her goal of a baby, closer to the time of the embryo transfer. She said:

... at the time of ticking the box it's for research ... but ... being in the immediacy of having your embryos being transferred and then being told you may or may not have some to freeze ... it would be definitely: well thank goodness we've got two embryos frozen because y'know we might want to use these in cycle two or cycle three ... so it depends on which stage – ... Whether or not it's filling the forms out or whether or not it's in that moment where ... I'm having embryos transferred (I6:844–861).

7.2.6.8 Age of the woman

Of the patient characteristics, the issue that played quite an important role in the decision-making process was the age of the female partner. The emphasis on the age of the woman was an important aspect in the decision-making, as understood from this study. One couple was initially not keen on embryo freezing due to the woman's advanced age, and decided to draw a closure on their pursuit of a pregnancy if the fresh cycles did not work:

I was just about thirty eight ... and I think because of my age, I thought that we'd have the three, the three goes of IVF ... if it didn't work now it wasn't something that I would go back to in the future ... I've met women who've had IVF that hasn't worked and ... It's become an obsession to have a baby ... and I never wanted to get into that situation (14:305–360).

In contrast, another woman who was in her late thirties and who was aware of the NHS regulation of eligibility up to one's 40th birthday, considered a cycle with frozen embryos as recourse, to save time. She said:

I'm not that far from being thirty-nine so y'know [laughs] with the ... mathematics we thought that y'know if we weren't fortunate first time we'd be, we'd be lucky for instance to get through y'know to the end of a third cycle in ... before my fortieth birthday ... so it was probably, I guess, a time issue as well ... speed it up a bit [with frozen cycle] (112:510–532).

The following woman perceived embryo freezing as a backup with advancing age and uncertainty in future cycles: ... and also obviously you know as I get older I suppose the chances of success get less and less so from that point of view it's quite, it probably would have been an attractive option ... (115:275–286).

Another interviewee keen on freezing, was aware that frozen embryos used in later cycles were likely to have higher success, having being frozen at her younger age. She said:

... my original cycles are just thirty-six ... that was when I was younger so that's another bonus in that if I wanted to wait a couple of years [for the frozen cycle] then that [frozen embryos] was from ... when I was a bit younger so that's, got to be a plus ... when you look at the statistics that ... it's better when you're younger (19:816–864).

7.2.6.9 Further fresh versus frozen cycle

Clinic regulations for couples who have frozen embryos are to have a FET cycle, before embarking on further fresh treatment. The logic behind this is not only to use the frozen embryos for the purpose for which they were already

created, but in NHS patients, it is also a requirement for PCT funding for the treatments. It also prevents the build-up of a bank of unused embryos.

The interviewees were asked if, hypothetically, they would prefer to use their frozen embryos in a next cycle, or would rather have another fresh cycle first. When given the option of going for a further fresh cycle or a frozen cycle using one's frozen embryos, most interviewees opted to have the fresh cycle next. The main reason cited was: *I think I would go for a fresh cycle. Given that, I know that the fresh eggs [embryos] are usually better than the frozen (I6: 991–1003).*

Nonetheless, there was one interviewee who would have opted to have a frozen cycle next, in view of having already completed half the journey in having frozen embryos, and because of the uncertainty of a further fresh cycle. He said: *I think because you already have, your half way through the process ... A fresh cycle ... maybe there is no any good quality [eggs or embryos] ... (I1:1494–1515).*

The factor of age was considered by the following couple, who wondered about the feasibility of having a further fresh treatment before her 40th birthday, and conserving her frozen embryos for future use, in view of the higher success rate of fresh cycles. Bearing in mind the clinic regulations, she referred to this attitude as “playing a bit of a game”. She said:

... I think though I still might have been inclined to try for a second, full cycle erm before my fortieth birthday and keep the frozen embryos for a later ... I don't know if that sort of playing ... playing ... a bit of a game or whatever... ...if, if that would be allowed but erm, err I suppose just because of having heard that with a frozen embryo your chances are even less than with a fresh one so that, that would have been my thinking there ... (I15:466–500).

7.2.7 Experiences of couples

In the following sections, couples' interpretations of their experiences of freezing embryos are presented.

7.2.7.1 Circumstances of embryo freezing

The five couples who had frozen their embryos described their experience. They made the final freezing decision on the day of embryo transfer, when the embryologist selected any suitable surplus embryos for freezing; however, the planning for the decision had started way back. This interviewee said:

... it was on the day of implantation when we were told there was four ... [embryos] that were good quality... ...these two were your better ones, there were another two [that could be frozen] ... and I can't remember if we'd signed something before already ... but I think it was the day. It [decision] was a question and an answer ... But ... actual contemplation of the decision we were given months y'know – from the first time we spoke to Dr ... (I11:565–604).

7.2.7.2 Experience of decision-making

This interviewee emphasized that the decision of freezing any suitable surplus embryos was entirely up to the couple, with no coercion from the clinic:

... It wasn't forced upon us if that's y'know, if that's what you think – somebody saying: oh, you know, you've got to get it done, you've got to do this ... No, it was totally up to us. So if we didn't want to get them done y'know – the form itself, I think, said what do you want to do with any embryos [spare] ... (I9:667–676).

7.2.7.3 Couple discordance

There was no difference in opinion between the interviewees participating in this study regarding the embryo freezing decision. As one interviewee commented:

... No it was pretty much a snap, the same decision (I14:677–685).

However, when considering embryo numbers and freezing, the men seemed to be more calculating, whereas the women were more inclined to freeze regardless of the numbers and the practical aspect of thawing survival.

7.2.7.4 Time given to decide

When asked, the couples decided almost instantaneously. As this interviewee explains, there was no pressure experienced, as the decision was contemplated beforehand:

... we just made that decision there and then when we knew ... we had to ring up the day ... after they [the eggs] had been taken out and we found out how many had fertilised ... so we knew how many extra we had then and I think we always knew that we were going to freeze them (I2:335–361). He explained further: ... people know what to expect – because it is explained earlier on in the treatment and they have had time to think about it ... (I2: 386–436).

7.2.7.5 Influence of others

For most couples, the freezing decision was solely made by them, with minimal influence from others, as this interviewee mentioned: *I think one thing again*

from start, middle and finish is, is every decision made by I2 [his partner] and myself. There hasn't been any influential figures ... (I2:519–543).

However, a few couples were guided by friends and family who had been through the same experience:

... my sister and brother-in-law are going through IVF... and they've had embryos frozen... so I know from her experience ... So I suppose it's that kind of knowledge that feeds and guides women, couples like us. It's not so much the advice you get from centres, it's your friends, peers ... (I6:945–972).

7.2.7.6 Consenting

The couples had to sign a consent form for freezing on the day of the FET, as this interviewee explained:

It was erm the day the embryos were put back in – it was after the procedure ... We were on the ward for a little while and one of the nurses came over and ... went through it and explained everything with us and that's when we signed ... [the consent form] (I2:437-464).

The consent form for embryo freezing was straightforward and well written, according to the interviewees: *...It [The consent form] was quite straightforward, yeah. All of the topic – free for twelve months and then after that it was explained pretty well (I14:725-745).*

7.2.7.7 Advance directive

The clinic did not require the patients to state any advance directives about the future disposal of their unused frozen embryos. One interviewee said: *We did have a form that informed us of the options but we weren't asked to sign anything or make a decision ... because they were just informing us of what we could do (I2:1167–1181).*

7.2.7.8 Future disposal dilemma

A few also appreciated the potential future dilemma of making the difficult decision of disposing of the frozen embryos. This interviewee commented: *... when you do get to a decision at the end of the day y'know how long do we keep these for – do we need them anymore then it feels like you're ... making quite a difficult decision really (I12:592–611).*

7.2.8 Trust

7.2.8.1 Trusting the professionals

Most interviewees were explicit in singing the praises of the fertility clinic and its staff and trusted the expertise of the professionals in the decision-making process. One couple felt almost like having delegated some of their responsibility of making difficult decisions to the professionals, as they graded the embryos and assessed their suitability for transfer or freezing. The man stated: *... I suppose that there's an element of trust and faith in the process and the doctors ... that when they're advising you and talking about the grading of embryos ... there's a bit of erm trust in their expertise about what that means.*

The woman added: *... [the advice] did take some of the decision away from you because you think: oh well that's not very good is it, that decision has already been made ... (I7:1587–1684).*

Nevertheless, there were rare occasions when the couples reflected on their experiences and had fleeting shadows of doubts. The following interviewee experienced a momentary suspicion of whether the “slow-growing” embryos, which were not frozen, could have made babies, given a chance. It seemed that there was occasional doubt about trusting the professionals' capacity in predicting the outcomes. However, it did not appear as if the interviewee was questioning the integrity or honesty of the professionals. They promptly held their lack of knowledge about the process responsible for their concern:

... To me, it seemed a bit strange in terms of it's [embryos] usually described as some may be slow growing and I'm thinking yeah, but they may start slow and speed up y'know like, like anything else. If you plant a plant and it starts off slow sometimes ... [it] suddenly shoots up from nowhere so ... Not understanding that process I guess (I12: 1105–1162).

7.2.8.2 Doubts and subsequent moral conflicts

While making their journey through the complex process of IVF treatment, it was not until later reflection that crucial moral doubts and debates crept into the mind of certain couples. This interviewee later contemplated the process and admitted that there would be occasional suspicion about the suitability of the embryos chosen to be frozen or transferred and about the selection process. She commented:

I don't think it would be till afterwards that you'd have time to reflect on y'know – these embryos: what are they and what are they doing and could they be the better ones to put in and how do they choose the best ones and what happens if they don't – are never used, that could be a child of ours and all those bigger questions (16:732–751).

Another interviewee talked about her moral dilemma if asked to select the embryos to be frozen or the ones to be given a chance to be a baby, if all were of identical quality:

... not that you would ever want to have six kids all at the same time but erm I think because you've got two in you now, why have we picked those two and ... put back in and how do you decide on the three that you freeze? (18:1014–1047).

7.3 Summary

7.3.1 Clarity, confusion and conflicts

From analysing the repertoire of perceptions, certain key issues of clarity, confusion and conflicts in the psyche of the couples regarding the decision whether or not to freeze embryos were unravelled.

7.3.1.1 The desire to have a baby eventually overcame all ethical concerns

The main issue clear in the mind of all the couples was the desperation for a baby being the dominant drive for freezing embryos. Despite having various issues, given a chance, all would freeze their embryos to maximize the opportunities to have a baby.

7.3.1.2 Confusion about the concept of embryo

There were a few issues regarding which of the couples were confused. The embryo seemed to be an enigmatic entity, whose nature couples struggled to comprehend, and they vacillated from one perception to the other. Couples that usually envisaged the embryo as a life, shifted their conceptualization to “cellular”, or as a “part of a process” when freezing their embryos.

7.3.1.3 Misinformation

There was confusion regarding the information about the practical aspects of embryo freezing, namely its safety and success rate, freezing and thaw cycle regulations, duration of NHS funding for embryo freezing, any freezing fees, and

so on. This was predominantly noted among the majority of couples who had not had the opportunity of freezing their embryos, and occasionally had preconceived misconceptions, such as the belief that the frozen cycle would be using one of their three NHS-funded IVF treatments.

Many were not keen to seek any further information regarding these issues from the clinic, being focused on the demanding IVF treatment. This is evident from the case of the couple who initially decided against freezing embryos, but changed their mind when they realized that the frozen cycle imparted extra chances outside the three NHS-funded opportunities. The relevant information regarding all these aspects of embryo freezing is given to all couples at the start of their treatment, when they attend the information session. The fact that couples are still confused and have misinformation, indicate that they are probably too preoccupied with the complexities of IVF treatment. Therefore, they are not able to process this additional information, as embryo freezing is not their primary focus at that point.

7.3.1.4 Conflict of freezing babies

The major conflict that many couples initially encountered was the paradox of 'freezing babies'. That is, couples who conceptualised embryos as their potential babies faced the moral conflict of therefore perceiving embryo freezing as freezing babies; this was the cause of some reservations about freezing. The conflict is best illustrated in the case of the couple who, although agreeing to freeze embryos to achieve a pregnancy, decided not to freeze more than two embryos (the minimum allowed by the clinic), even if there were more suitable to freeze. This also reflects a conflict between maximising their chances of having a baby on one hand, and the ethical reservations of freezing their embryos on the other .

7.4 Conclusion

In this section, the deliberations of the interviewees regarding their decision-making process of embryo freezing, and their nuanced views, their perceived benefits and reservations about the process have been presented. In the next chapter, the key findings from this study and their relevance to the existing literature are discussed.

Chapter 8. Comparing the Data from the Couples with the Literature Review and the New Findings

This chapter focuses on the key findings from this study with patients and also draws on the similarities and dissimilarities of the findings in comparison to the past literature on embryo freezing.

8.1 Comparison of This Study with Others

8.1.1 Key drive: the baby

The key factor in the decision-making about embryo freezing is the goal to have a baby, which connects all the themes, and demonstrating that all the themes in the interview were linked to the overwhelming desire and goal of having a baby. The aim to have a baby being the primary focus of IVF couples is an obvious fact in its own right. It has been neglected by past researchers in connection with embryo donation for research, but was upheld in a study carried out by Haines and Taylor (2009).

8.1.2 Role of information provided by the clinic

Nachtigall *et al.* (2010) observed that clinic information played a vital role in the decision made by couples to dispose of their frozen embryos; in our experience, clinic information also influenced the view regarding freezing embryos in the first place. It helped couples appreciate the benefits of having frozen embryos, in being given an extra chance, or in bypassing the difficulties and complications of the fresh cycle, such as ovarian stimulation, oocyte retrieval and the associated risks. Information derived from the clinic regarding egg numbers, embryo numbers and the clinic's practices and regulations, influenced the expectation to freeze embryos in the fresh cycle and assisted in decision-making. However, many couples harboured confusions despite receiving detailed information regarding embryo freezing. And the question remains whether further detailed information would have influenced their decision making at all.

8.1.3 Complexity of the first treatment

Most couples were preoccupied with the complexities of going through the fresh cycle, especially the first one, as also discussed in other papers (Carroll and

Waldby, 2012; Haimes and Taylor, 2009; Haimes and Taylor, 2011), and embryo freezing did not seem to be the focus, rather a bonus at that point. Many who did not have embryos to freeze were not interested in enquiring further regarding embryo freezing, and sometimes had misconceptions about it.

8.1.4 Concept of embryo

The conceptualization of the elusive entity, the “embryo”, played a key role in the decision-making. The subtleties in the nuanced characters of the embryo concept emerged from this study also, as in previous ones (Bankowski *et al.*, 2005; Boada *et al.*, 2003; Haimes *et al.*, 2008; Svanberg *et al.*, 2001), along with the uncertainty and the dynamic nature of its character, as reported by other researchers (Haimes and Taylor, 2009). Frozen embryos were perceived by many as “virtual children” or siblings to existing ones, but with suspended development (Laruelle and Englert, 1995; Nachtigall *et al.*, 2005; Svendsen and Koch, 2008), as seeds or as tissue with a potential, as mentioned in some studies (De Lacey, 2007a), and as emblems of hope, as found in other studies (Mitzkat *et al.*, 2010; Svanberg *et al.*, 2001). A few, however, although recognizing the frozen embryo as a valuable resource, attributed a lesser status to it compared to a baby or a fetus, as witnessed by De Lacey *et al.* (2007b). No relation could be drawn with the conceptualization of the status of frozen embryos and having pre-existing children, as none of our interviewees had children.

8.1.5 Ethical concerns

Some interviewees argued that there was no moral objection to embryo freezing, as the embryo is an entity with no senses or higher human attributes, such as capacity of thinking, as argued by the UK legislators when legalizing the use of embryos in research (Haimes *et al.*, 2008). To some couples, it was ethically acceptable to freeze embryos, as the embryo cannot be compared to an individual, since it does not have any independent survival if not transferred into the uterus under congenial circumstances. A similar argument was presented in one study (Deckers, 2007), when discussing the debate regarding the use of embryos in research. Others had no concerns, since the ultimate goal was to create life anyway.

8.1.6 Benefits of freezing

All interviewees appreciated the additional chance to achieve a pregnancy with embryo freezing. It was frequently perceived as a backup in case of an unsuccessful fresh cycle. Although in essence conveying a similar perception, many interviewees had moral objections to the term “insurance policy”, when quoted, as a term used by researchers in previous studies (Bankowski *et al.*, 2005; Koryntová *et al.*, 2001; Stoléru *et al.*, 1997). The disapproval of the term insurance policy could be because of the implied association between babies and money. The term “security blanket” used by other interviewees in another study was similar to the allegories of “belt and braces” and “safety net” used by our couples (Lyerly *et al.*, 2006).

Couples appreciated the potential future benefits of avoiding the invasive steps of stimulation, egg retrieval, and the related complications of a fresh cycle, as also mentioned by interviewees in other studies (Cattoli *et al.*, 2004; De Lacey, 2007a). They also perceived the benefits of having all the avenues of use of frozen embryos open, as mentioned in other studies (Ehrich *et al.*, 2008; Ehrich *et al.*, 2010; Haimes and Taylor, 2009), which prevented future regret from closing all options, as also seen by Ehrich *et al.* (2010). The aspect of reduced emotional stress associated with embryo freezing, as mentioned by one of the interviewees, was reported by participants in previous interviews and led researchers to conjecture that reduced stress with frozen embryos, perceived as a backup, could be associated with increased success rate in IVF cycles (Koryntová *et al.*, 2001; Stoléru *et al.*, 1997).

As mentioned by interviewees in the past, other perceived benefits of embryo freezing in this study were “maintenance of embryo potential” by freezing them, and also prevention of “relinquishing control” in determining the fate of the embryos (Nachtigall *et al.*, 2009).

For many couples, freezing was an acceptable option as opposed to discarding embryos, which they considered as “waste” of a valuable resource. Similar views were expressed by interviewees in other studies, who regarded discarding their good-quality frozen embryos as wasting a precious resource (Nachtigall *et al.*, 2009; Nachtigall *et al.*, 2010).

8.1.7 Concerns about freezing

As mentioned by interviewees in the past, other perceived benefits of embryo freezing in our study were “maintenance of embryo potential” by freezing them, and also prevention of “relinquishing control” in determining the fate of the embryos (Nachtigall *et al.*, 2009).

The concerns with embryo freezing were mainly related to worries about the quality of the thawed embryo and the health of a future offspring, as also found by Svanberg *et al.* (2001); they noted a gender bias, with men worrying more regarding the negative effect of cryopreservation as opposed to women, which was not seen in our interviewees. Most couples anticipated a lower success rate from the frozen-thawed embryos, drawing reference from their domestic experience of freezing food. However, they were ready to compromise with a lower success rate, as embryo freezing potentially would give them more additional opportunities. One interviewee, however, raised the issue of the risk of generating “false hopes” if thaw survival and frozen cycle success were far too low, as also discussed in another past study (Haimes and Taylor, 2011).

Some of the interviewees had fleeting anxieties regarding the clerical mislabelling of embryos, as highlighted in other studies (Bankowski *et al.*, 2005; Siegel-Itzkovich, 2003). The potential for future legal problems regarding custody of frozen embryos in case of death of a partner or separation of couples was a concern raised by few researchers (Bennett, 2000; De Lacey, 2007a), but did not seem to be a major issue for the couples in this study. A few couples anticipated having to make a difficult decision when disposing of their unused frozen embryos in the future, as per the experience of a large number of couples reported in the literature (De Lacey, 2005; Fuscaldo *et al.*, 2007; Hug, 2008). Nevertheless, none of these potential drawbacks would dissuade the couples from freezing their embryos.

8.1.8 “Calculus of conception”

As reported by Nachtigall *et al.* (2010), information about the number and grade of the embryos were important decisive factors in the decision to freeze. There was evidence of mental calculation made by couples when determining the number of embryos to be transferred and frozen, in view of the clinic’s regulations requiring a minimum of two good surplus embryos to freeze. The scenario of having three suitable embryos to freeze posed a dilemma, as to

whether to have one embryo transferred and two frozen, or to try and maximize the pregnancy chances by having two embryos transferred, but the third one wasted. This was consistent with the experience of Haimés and Taylor (2009), who witnessed relentless mental calculation by couples, who tried to calculate their success chances from the number of follicles, eggs and embryos, and their quality, which Haimés and Taylor (2009) termed the “calculus of conception”.

8.1.9 *Trusting the professionals*

The information and advice provided by the professionals about the grading of embryos, when assessing the suitability for freezing, guided the decision-making of couples. However, there were occasional flickers of doubts regarding the decisions made by the experts, as also witnessed by previous researchers (Haimés and Taylor, 2009).

8.2 What is New in This Study?

Contrary to the other studies about couples with frozen embryos, this study is at a different point in time, interviewing couples just following their IVF treatment, when they had just confronted the option of whether or not to freeze any surplus embryos, which could possibly have been influenced by the conceptualization of embryos at this point, as mentioned earlier. The interviewees consisted of both groups of women, those who had the opportunity to freeze and those who did not. The following issues were identified as new findings in this study.

8.2.1 *Transformation of view*

It was very interesting to note that quite a few couples had ethical reservations about embryo freezing, but overcame them by envisaging the embryos as “medicalized” or scientific entities, as opposed to a “baby”, and perceived embryo freezing as “part of a process” of IVF, i.e. as a means to an end (= a baby). So, rather than seeing the embryo as the beginning of a baby, which could potentially lead to ethical and moral dilemmas when considering freezing it, couples started to view the frozen embryo in a slightly mechanical or scientific way as part of the IVF process, with the ultimate goal of having a baby. Thus, freezing is viewed as just another step towards achieving their ultimate objective. This change in view seems to be a “transformation” process happening in the IVF journey, to achieve the goal of having a baby. Therefore, it

can be hypothesized that experiencing the IVF journey made couples appreciate the benefit of embryo freezing in imparting additional opportunities to have a baby. Moreover, it influenced their views on how they perceived the frozen embryos and also influenced their embryo freezing decision. On this note, it is also worth wondering if the prospect of freezing embryos during IVF influenced their views of the embryos themselves, i.e. seeing them as a means to an end. This transformation or the metamorphosis of the views of IVF couples is a key finding of this study. Couples who initially had reservations about freezing embryos due to perceiving them as 'life', through the journey of IVF, switched their views. Conceptualising the embryo as a scientific or medicalized entity enabled them to overcome their moral dilemma and sense of guilt regarding freezing 'life'. This is kind of a tool they developed to maximise their opportunities of being a parent on one hand, and overcoming any ethical reservations on the other.

8.2.2 Age of the female partner

The age of the woman was identified as an important factor in the decision-making process of embryo freezing. Anticipating the uncertainty of a good response in future IVF cycles with advanced age, and the hope of having better success with frozen embryos at an advanced age in the future, were taken into account in appreciating the importance of frozen embryos as a backup. NHS-funded IVF treatments are generally offered only up to the 40th birthday. Therefore, embryo freezing could practically offer additional opportunities for women approaching such a birthday, who could come for a funded frozen cycle within the following year. Therefore, women in their late thirties perceiving freezing embryos as leading to extra chances of availing themselves of NHS-funded treatment, was relevant from the NHS perspective.

8.2.3 Funding for freezing

The funding scenario had implications in the decision-making, as the decision to freeze any surplus embryos for the future became almost automatic in the presence of NHS funding. However, in couples funding their treatment privately, the decision-making was more discretely thought out, as the financial factors of freezing and storing expenses, and the cost of a frozen-thaw cycle versus a fresh IVF cycle were calculated before taking the decision. This probably

implies that the automatic availability of funded freezing of suitable embryos in NHS patients, probably and partly takes away the burden of decision-making, at least from the financial point of view.

8.2.4 *Feeling of being in control*

One of the striking reasons for having embryos frozen that has emerged from these interviews, is that embryo freezing can boost the feeling of being in control in couples who seem to be suffering from a feeling of lack of control, due to their subfertility. Their deliberations also suggest that embryo freezing helps them to exercise their autonomy regarding the fate of “their” embryos, which couples distinctly see as belonging to them. There seems to be also a sense of freedom in being able to extend chances beyond the regulated three NHS-funded treatments.

8.2.5 *Risk of forgetting the frozen embryos*

A genuine concern raised by one of the interviewees was the risk of the owners forgetting the frozen embryos that had been stored for a number of years, especially after achieving a live birth. His concern could be related to the high number of frozen embryos abandoned by couples, as mentioned in the literature review, with the resultant growing number of stored embryos in laboratories, causing problem for the laboratories. In an attempt to avoid such a scenario of forgotten frozen embryos, the practice in most units is to send annual reminder letters to the couples, asking them to make a decision about the disposal of their embryos.

8.2.6 *Effect on child's psychology*

Another interesting revelation from this study is anxiety of the couples regarding any adverse psychological effect on the children on being disclosed that they started life as frozen embryos. Would it potentially lead to any identity crisis or influence the perception of their selves in being different from so called ‘normality’? The worry of the potential parents in this context would probably call for future research involving the off spring from frozen embryos and an exploration of any psychological impact.

8.2.7 Relief at not having embryos frozen, if pregnant

A few couples, successful from IVF treatment, who although initially in favour of embryo freezing, on retrospection, felt relieved not to have any embryos frozen, on ethical considerations. This is strongly connected to the ethical reservation of viewing frozen embryo as freezing “life”, a difficulty which was overcome by the overwhelming desire to avail all opportunities to have a baby. However, couples who were successful following a fresh cycle, on retrospection, heaved sighs of relief at not having to deal with the difficult scenario of what to do with the frozen embryos, which would pose a moral dilemma for them. As one of the interviewees commented, on reflection, one could face very disconcerting ethical questions of potential discrimination against those embryos frozen, in giving them a chance to fulfil their potential. This probably suggests that, following reassurance of the fulfilment of the primary goal of having a baby, the issues of morality and ethics, which were previously considered secondary, gain prominence. Hence, the decision-making, however nuanced, is associated with a sense of relief at not having embryos frozen, which is intriguing and a revelation from this study.

8.2.8 Decision-making process

To most couples who had an opportunity to freeze their embryos, it was a “common sense”, “straightforward”, almost instinctive decision to maximize their chances of having a baby. Retrospective accounts of couples who had the opportunity to freeze their embryos seemed to convey that such a decision appeared an easy decision to make. This could be due to at least two reasons. First, the availability of free NHS funding for freezing embryos reduced the difficulty of any complex decision-making, as the NHS funded embryo freezing for the first twelve months in suitable cases who met the embryo freezing eligibility criteria. For NHS patients, embryo freezing was perceived as a free facility, which did not involve any complex financial planning or budgeting; this easily available option made the embryo freezing decision almost an automatic one. Second, the deliberations of quite a few couples testified to the fact that they were preoccupied with the complexities of the fresh IVF treatment, and almost automatically perceived embryo freezing as a part of the process. However, other couples who had not had the opportunity to freeze their embryos, when reflecting on the IVF process, had more discretely analysed

their considerations, and taken into account the success rate and alternative options for the disposal of surplus embryos, balancing the risks versus the benefits of freezing the embryos. Therefore, prospective thinking about the possibility of embryo freezing shows that in fact it is a nuanced and complex decision to make, as do the data that suggest relief at not having frozen embryos once one has got pregnant.

8.2.9 “Deviant case” analysis

One particular couple (I1 & I1P) had strong ethical reservations about embryo freezing as they perceived the embryos as living beings. Having realized the uncertainty of IVF treatment following their experience of unsuccessful IVF attempts, and keen to have a baby, the couple appreciated the importance of maximizing their chances. Thus, they developed the view of comparing the embryo freezing process to the medicalized framing, to have a baby. However, driven by their strong ethical outlook, they declined freezing more than two embryos, the minimum number of embryos required for freezing, as opposed to others, who had no such limitations and wished to maximize their opportunities almost at all costs. This couple felt strongly against “playing with the fate” of the unused frozen embryos, who were “waiting in limbo” and did not approve of the concept of freezing as “buying time”. Unlike other couples, they would embark on a frozen cycle before having any further fresh, not only to have the easier frozen cycle, but mainly because of their strong views against wasting any frozen embryos. They also felt that a reasonable fee for embryo freezing ought to be enforced, as couples would then give well-contemplated and due respect to the process, as opposed to having it for free, where there is the potential of diluting the decision-making.

8.3 Unexpected Comments from the Interviewees

Unexpected comments in this study included the slightly uncanny comment of freezing embryos as a strategy to replace the existing children, in case of an accident and loss of a child. This context, though theoretically possible, is probably unlikely to be the intention behind embryo freezing in an individual with a child. Also, the question arises as to what duration of time storage for such purpose would be continued; as this kind of decision would need to take into

account not only the legal time limits of storage, but also the age of the couple and whether still in the acceptable age limits of parenthood.

Another interesting facet that emerged from the interviews is the reservation about using the term “embryo freezing”, as it has connotation with the process being far from “natural”. It is debatable whether the term “cryopreservation” would impart a more “medico-scientific” tuning to the process, but there was interesting reversal of ideation noted, as the same interviewee had thought that the term “veered towards science fiction”.

The interviewee who suggested that the use of the term “embryo” could potentially fuel more ethical debate about embryo freezing, correlated the term with the image of a baby. In his view, freezing “fertilized eggs” would have a more scientific and professional connotation and could potentially reduce the ethical dilemmas regarding embryo freezing. It is an interesting thought indeed, and warrants further in-depth study.

8.4 Strengths and Weaknesses of the Study

The main strength of this study is that it sheds light on areas that are deficient in the literature, with regards to the decision-making behind embryo freezing, and the personal and social factors influencing that decision. A good kernel of original data has emerged from these interviews, which can form the basis of further in-depth research.

The author accepts that not all aspects of embryo freezing were covered in this study, such as the views of those couples who already have a baby, or opinions of women in the older age group, or views of those who strongly decline embryo freezing. Also, no relationships with religion, education, profession and ethnicity have been captured in this study, and further work needs to be done to explore the relationships in these areas.

Nonetheless, the framework of data generated from this study can potentially guide future work in two different directions: first, further in-depth study to tease out more ideas of couples’ views. Second, this study generates hypotheses that could now be tested further in another study. The hypotheses derived from this study can be summarized as follows:

- IVF couples transform their views on embryo freezing to overcome any reservations.

- The desire for a baby overcomes all ethical concerns about embryo freezing.
- More information regarding embryo freezing may not influence the decision making of couples.
- NHS funding for embryo freezing may potentially dilute the decision making for embryo freezing.

Conclusion of Part 2

Part 2 started with a review of the literature on embryo freezing, proceeded to highlight the gaps in our knowledge and then described the methodology of the interview-based study; data from the interviews was also presented. Finally, the data were interpreted and compared with the existing literature; new and interesting findings and the hypotheses generated from the study were highlighted, which could lead further research in the future.

Part 3: Discussion

This is the final discussion section of this thesis, which draws from the findings, summaries and conclusions of Part 1 and Part 2.

Chapter 9. Discussion

In this thesis, entitled “Embryo cryopreservation: the clinical outcome and couples’ perspectives?”, the answer to the question “Should we be freezing embryos?” has been explored from two key perspectives. In Part 1, the practical aspects of embryo cryopreservation, including the impact of embryo freezing on the overall CPR in the unselected NHS population, were evaluated. In Part 2, the views of couples about this practice were explored, and their decision-making-process behind embryo freezing was investigated.

To provide a summary of the key findings of this study, the presentation of the CPR in the literature was found to be quite commonly biased; as in most cases, the successful outcomes of a selected, good-prognosis patient group were extrapolated to the general population, and therefore, IVF patients may not be receiving the actual facts regarding embryo freezing. In reality, approximately 15% of NHS IVF couples have embryos to freeze and embryo freezing imparts a modest benefit of about 4% increase in the CPR. This overall assessment is from the entire NHS perspective, not undermining the benefits to the individual women who have babies from frozen embryos. Nevertheless, regardless of the practical benefits of freezing embryos, and ethical and other reservations that couples may have about it, the vast majority of IVF couples have a positive view regarding embryo freezing and wish to avail themselves of the opportunity to freeze any surplus embryos. Undoubtedly, the decision is driven by their overwhelming desire to have a baby, and to use every additional opportunity to maximize their chances towards that goal, as well as allowing them the freedom to exercise their rights regarding deciding the fates of ‘their’ embryos. It also emerged that most couples considered in detail the intricacies and complexities of the embryo freezing practice and the various ethical and moral nuances, on reflection, after having gone through the IVF process. Although all the relevant information about embryo cryopreservation was given by the clinic at the start of the IVF process, many couples were unable to retain and process that information at that point in time, either because the whole process was new and overwhelming to them, or possibly because embryo cryopreservation was not their focus at that stage.

In this thesis the author is attempting to answer the normative question 'Should we be freezing embryos?' This is essentially trying to find a relationship between empirical data, and the answer to the 'normative' (Hare, 1952) question as a basis for making policy and practice recommendations. In a paper by Rehmann-Sutter et al (2012), the authors have elucidated the relationship between empirical research and answering a normative question. According to them, the various aspects relevant to any particular practical scenario can best emerge from a detailed investigation of that context (which might include interviews with participants but also includes detailed engagement with the setting and other practices that occur there). It is the ethical argument and logical explanation of the researcher that makes the normative conclusion convincing. In the above cited paper (Rehmann-Sutter, 2012) the authors justify the use of empirical research findings for developing ethical propositions, provided the recommendations are not purely based on the descriptive findings.

In this thesis the normative question, 'should we be freezing embryos?' (which is essentially a value-laden question) has been addressed first by analysing the practical benefits of embryo freezing and , second, by understanding MF patients' views on this question. From an analysis of both aspects several hypotheses have been developed which can be tested in future studies (see below). Whilst it is debatable whether it is possible to derive from an empirically demonstrated demand for embryo freezing, the claim that there is a moral obligation to provide embryo freezing, nonetheless, insights into the practicalities of embryo freezing and into patients' views on the topic provide a clearer basis for any normative discussion since at the very least this means that the purported 'facts' that inform such a discussion are evidence based, rather than derived from hypothetical speculation or assertion. (It is also worth noting that not all authors accept the apparently clear distinction between the 'normative' and 'empirical', 'value'/'fact', that is often asserted (Haimes and Williams, 2007) and might debate this issue from a different starting point). Several perspectives that would facilitate an exploration of the answer to the normative question, 'Should we be freezing embryos' cannot be covered in this thesis; e.g. the cost-effectiveness of embryo freezing could not be analysed. However, the pros and cons of several propositions are debated below.

In light of the findings of this study, and in view of the increasing NHS support for embryo freezing, the following issues need to be considered:

- The decision of the providers of the service to freeze any embryos;
- The most appropriate time to inform IVF couples regarding all aspects of embryo freezing; and
- The issue of NHS funding for freezing embryos and the cost-effectiveness of the practice.

Regarding the service provider's decision of freezing any embryos, the following options could be considered in view of the difficulties faced by couples while making the decision, and also taking into account the modest practical benefit from this practice. The following is a discussion of the pros and cons, and not actual recommendations:

1. In NHS clinics, embryo freezing consent can be taken from all couples about to start the IVF process, and all suitable embryos could be frozen in the first place. Following completion of the IVF cycle, couples could reflect on the process and decide if they wished to continue freezing or not. The advantage of this is that couples would be able to make a more discretely thought-out decision at that point, as evident from this study. On the other hand, this would potentially use more resources in freezing all suitable embryos, many of which might be subsequently discarded if their owners decided against freezing them; therefore, this might turn out to be an expensive exercise.
2. The next theoretical option could be not having the option to freeze embryos. It can be argued that embryo freezing offers little benefit to the overall pregnancy rates, and that very limited number of couples actually benefit from this practice in terms of having a baby. This would resolve all the complexities of making the difficult decision, and would prevent the unnecessary use of resources and a build-up of embryos in storage. In light of the evidence from this study, it appears that there is a high demand for freezing embryos from couples, and hence there is great doubt whether the option of not offering it would be morally acceptable.
3. Another theoretical option to remove the difficulty of decision-making would be to routinely freeze all the embryos that are not freshly transferred, but there would be cost implications for this practice.
4. Recently, many fertility units are moving to blastocyst (day 5 embryo) stage transfer, in view of the evidence of higher implantation rates compared to

early cleavage stage (day 2/3 embryos) transfer (Blake *et al.*, 2007). Implementation of a new policy of freezing only those embryos which progress to the blastocyst stage could be introduced, as it would be hoped that those self-selected cohort of embryos progressing to the blastocyst stage would be associated with an improved clinical outcome. This would possibly remove the burden of clinical decision-making of selecting the suitable embryos for freezing, and would potentially reduce the expenses of the embryology laboratory in reducing the load of freezing the embryos associated with a poorer prognosis.

About the second issue of selecting the most appropriate time to give couples detailed information regarding embryo freezing, there could be two options:

1. As mentioned by one of the interviewees, there could be a benefit in organizing a separate information session to discuss the different issues about embryo freezing at the beginning of the IVF treatment. It is thus hoped that splitting the IVF information into two sessions would prevent any information overload and would allow couples the opportunity to better understand the complex issues of embryo freezing. However, there are two major concerns with this option. First, organizing an additional clinic session for each couple would have logistical and cost implications. Second, it is questionable whether it is appropriate to unnecessarily overload all couples with so much detailed information in what is already a stressful time for them, especially in view of the fact that most of them would not be encountering the scenario of having to decide whether to freeze their embryos. It could also raise the expectation of freezing embryos in many couples, a hope which may not be realized.

The second option would be to hold a joint debriefing session for the couples at the end of the IVF treatment, where the issue of embryo freezing would be revisited in detail. This would give couples the opportunity to reflect and make informed decision for the future, and also would facilitate interaction with others and the exchange of views. Arranging such group debriefing sessions would be relatively cost-efficient. The recommendations to the fertility clinics based on the emergent data would also include: clinics to take the initiative in facilitating discussion and communication among patients, for

example, developing a Web-based forum, which could be a platform for patients to share information, views and experiences, and which would boost a feeling of solidarity.

The third and final issue is the discussion regarding the appropriateness of NHS funding for embryo freezing. The key factor influencing that decision would be assessing the cost-effectiveness of embryo freezing, which unfortunately, this study was unable to perform due to time constraints. However, in the current scenario of a financial crisis, where the majority of the NHS trusts are still struggling with funding the three NICE-recommended IVF treatments, how appropriate is it to fund embryo freezing, especially in the light of the limited clinical benefit of it?

1. In this present economic climate, restricting NHS funding for embryo freezing could theoretically be used to purchase more fresh IVF treatment, which would potentially be associated with a better clinical outcome. However, this policy of denying couples funded embryo freezing is bound to be associated with ethical and moral contentions.
2. Another option to explore could be offering embryo freezing on an ability to pay basis for a reasonable sum of money. There could be two justifications for offering NHS-funded fresh IVF treatment, but not embryo freezing. First, this would still offer the option of private embryo freezing, while maintaining the funded IVF treatments. However, this is contrary to the principles of the NHS and the existing NICE recommendations (National Institute for Health and Clinical Excellence, 2004). Second, this practice might be socially acceptable, as this was suggested by one of the interviewees. In his view, levying a reasonable tariff on embryo freezing would give more weight to the embryo freezing decision, rather than making it a routine exercise available for free. However, again it can be argued that the concept that payment for freezing equals greater thought and critical decision-making might only be applicable to individuals for whom private funding might be a struggle.

This research is unique as it has made a maiden attempt to address an area of key importance, which has not previously been visited. The wealth of information available from this study will hopefully guide couples confronting the decision to freeze their embryos in the future. This study could also usher

further in-depth work in this field. Of the different options discussed previously, further study could be carried out in the future with blastocyst freezing to assess if alteration in freezing policy would make any significant improvement to the CPR. Another possibility would be to evaluate the CPR following a switch to the vitrification technique of embryo freezing, to assess any significant difference with the changed laboratory practice. Regarding the most appropriate timing for informing couples about embryo freezing, it would be best left to the judgement and discretion of the individual clinics, based on their local practice and preferences. With respect to the issue of NHS funding for embryo freezing, the policy should ideally be based on consideration of the triple issues of: the impact of embryo freezing on the general CPR; the demand of IVF couples to be given the option of embryo freezing; and the cost–benefit of the freezing practice. This thesis has addressed the first two aspects.

The main shortcoming of this study is that it has not been able to evaluate the cost-effectiveness of the embryo freezing practice due to time limitations. Analysing the cost efficiency of the programme is a vital aspect to further support or refute the practice, from at least the point of view of the funders and stakeholders. If embryo freezing is not deemed cost-effective on economic analysis, given the modest benefit to the general clinic population, the funders of IVF treatment would possibly seriously think twice prior to offering NHS-funded freezing, especially in view of the current economic climate. On the other hand, if it is proven to be economically viable, it might be justified to promote funded embryo freezing, especially in the light of IVF couples' desire to maximize their chances of having a baby. However, evaluating the cost-effectiveness of this practice would only be meaningful from the NHS perspective, as the option of private funding may always be provided to couples who wish to pay for the service themselves. The practical benefits and couples' views would be the main determining factors to provide the service for couples paying for their own treatment and for embryo freezing. Future work regarding this point would help inform this debate.

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Appendix A

Protocol

(Version number /date- 01/150211)

Title

Should we be freezing embryos?

Investigators

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Background

Cryopreservation or freezing of embryos has been a well-established practice since the first human pregnancy following the transfer of cryopreserved embryos was described in 1983 by Trounson and Mohr.(Trounson and Mohr ,1983). In the UK, in 2007 there were 8,541 treatments that used cryopreserved embryos (www.hfea.gov.uk). Standard IVF creates many embryos to give the maximum chance of pregnancy. It is only permitted to transfer up to 2 embryos (HFEA regulations). Good-quality surplus embryos have a chance of pregnancy if frozen and transferred later. The decision to freeze embryos is made by patients following professional advice. Little is known about the processes by which patients make these decisions, but we are aware that it causes considerable anxiety.

Understanding these processes will (i) help clinics provide the necessary information to help patients understand the process and assist their decision-making and (ii) inform clinics develop their freezing policies.

Purpose of the Study

To understand the personal and social factors that influence the patient decisions to freeze embryos.

Design

Time Period

April–July 2011

Study Group and Setting

This study involves interviews with 15 couples who have had IVF treatment at this centre and have thus had to consider the option of freezing surplus embryos. We want to understand the personal and social factors that underpin their decisions. The interviews will take place at the residence of the participants, where they will be at ease to express their views. Dr. Goswami and a trained social scientist will be conducting the interviews.

Size

We plan to interview 15 couples.

Eligibility

Any couple who have had IVF treatment at this centre and have thus had to consider the option of freezing surplus embryos are eligible to participate in this study.

Method

Recruitment:

An invitation to take part in the proposed research would be handed out to 50 couples attending the NFCL clinic for follow-up, who have been through the IVF treatment and had egg retrieval. The information leaflet would be handed to the couples by the doctors or nurses, who would be reviewing the couples in the clinic but they will not discuss the project at that time.

Information about the research project would be given in the invitation letter. Interested couples would be asked to express their willingness in taking part in this project by ticking an appropriate box in the letter, along with their contact details and return it enclosed in an addressed envelope.

Procedure

Dr. Goswami would then contact the willing research participants, and set up a mutually suitable appointment for interview. The interview will take place in a quiet secluded area, preferably in the residence of the participants, where they

would feel relaxed, and at- ease to talk about their views. Prior to the interview, informed consent will be taken and the participants will be assured of confidentiality.

We aim to interview 15 couples. Both the partners would be encouraged to take part in the interview. Our previous experience in recruiting fertility patients for similar studies suggested that we will need to approach 50 couples to recruit 15 participants.

Dr Goswami and a trained social scientist will interview the couples. The interview would be semi structured, where the couples would be encouraged to spontaneously express their views and speak freely, without any restraints. Specific issues would only be raised with the intention of guiding the interview in the right direction. The interviews would be conducted in a sensitive way, taking care not to cause emotional stress to the couples.

The interview would be tape recorded, and the interviewees would be assigned unique codes. The transcribed interviews will be analysed to identify the various emerging themes that shed light on the complex process of decision-making of the couples and the factors underpinning them related to their consideration of embryo freezing.

Data storage

The interviews would be transcribed, and the information stored in the departmental NHS and university computers with secure logins, which would be accessible only to the researchers and supervisors.

Confidentiality

The participants would be anonymised and assigned unique codes while recording their interviews, and any identifiable information would be deleted from the recorded tape. The interviews would be transcribed, and the information stored in the departmental NHS or university computers with secure personal logins, which would be accessible only to the researchers and supervisors.

The tapes would be erased following transcription of the interviews.

Following analysis of the interviews, the transcribed interviews would be deleted from the computers.

Analysis and Outcome

The data would be analysed with the help of my supervisors using social science methodology. The primary outcome would be to understand the personal and social factors that influence the patient decisions to freeze embryos.

References

www.hfea.gov.uk

Trounson, A.O. and Mohr.L. (1983) 'Human pregnancy following cryopreservation, thawing and transfer of an eight-cell embryo', *Nature*, 305(5936), pp. 707–709.

Appendix B

Information leaflet

Should we be freezing embryos? (Version number /date- 03/20.05.11)

Information for potential research participants

We would like to invite you to take part in research. Before you decide it is important that you understand why the research is being done and what it will involve.

This information sheet is yours to keep. It tells you the purpose of the study and explains what will happen to you if you take part.

Please take time to read the following information carefully and discuss it with others if you wish.

Ask us if there is anything that is not clear or if you would like more information.

Your standard NHS care will not be affected whether or not you decide to help in this study.

What is the purpose of the study?

In IVF treatment we are only allowed to transfer up to 2 embryos. Good surplus embryos can thus have a chance of pregnancy if frozen and used later. We are aware that it is a stressful time and having to take the difficult decision of freezing the surplus embryos adds on to it. We may not fully understand all the personal and social factors that couples consider when taking this complex decision. In this research we will try to understand how couples make this difficult decision. It is hoped that this understanding will help us give appropriate information and support to the couples having IVF treatment in the future.

What am I asked to do?

We are asking you to read this leaflet and decide if you want to participate in this research. If you are willing, please tick the appropriate box in the enclosed sheet and sign it, and write your contact telephone or mobile number in the indicated space. You can hand this sheet in the enclosed envelope at the reception desk or post it back to us. We will contact you and set up an appointment for interview at your home, according to your convenience.

What are the possible benefits of taking part?

We cannot promise this study will help you directly. However you may feel psychologically better having expressed your views and concerns. It is hoped that the information we gather from this research will help us inform and support our future IVF patients.

What will happen to me if I take part?

We would contact you and set up a time for interviewing you at your home, or any other place, at your convenience. Dr. Goswami, one of the research fellows in this unit, will be taking the interviews. You would sign a consent form prior to the interview. We encourage both of you to take part in the interview. It would be about your views and concerns about freezing your embryos. The interview would last for about an hour but may be longer if needed, and would be tape recorded. We would not use your name or any personal identifiable information at any stage.

Taking part in this research will not alter your future treatment.

What are the possible disadvantages or risks of taking part?

We are aware that going through IVF treatment is not easy. Discussing about it or reflecting on it can add to the stress at times. We would be careful about it during the interview. Feel free to stop the interview if you find it disturbing at any stage.

If you feel you need to talk to somebody following the interview, feel free to contact the Fertility Centre any time on the telephone number given below or the independent counselling service that is provided.

Will participating in research affect our treatment?

No. You can be assured that your treatment always comes first. Whatever views you express in the interview will not have any negative impact on your future treatment.

Data and results

Will my taking part in research be kept confidential?

All information collected in the interview will be kept strictly confidential to those involved in the research. Only members of the research team in the Fertility clinic and social scientists involved from the Newcastle University and some regulatory authorities may view any information from your interview.

The taped interviews will be transcribed as written documents and the tapes would be erased. The data would be saved for about 6-12 months by the researchers after the completion of the study, for analysis.

What will happen to the results of the study?

Whenever possible we will publish the results of the research in scientific journals. We will also present data in scientific conferences. You will not be identified personally in any way in any publication or presentation.

Will we get any results that you will need to know about?

It is unlikely that we will get any information from this research that we would need to give you. You will not be given information about what data we derive from the interview. However, the findings of the study will be published in peer reviewed journals, and we can direct you to the published information, if you are interested.

Management of this research

Who is funding the research?

The research is supported by the Department of Reproductive Medicine, Newcastle Fertility Centre at Life.

How is the research overseen?

Research is overseen by the Newcastle upon Tyne NHS Hospitals Foundation Trust.

What if something goes wrong?

It is highly unlikely anything could go wrong in this study but in the rare event that you are harmed by someone's negligence then you may have the grounds for a legal action for compensation against Newcastle upon Tyne Hospitals NHS Foundation Trust but you may have to pay your legal costs. If you wish to complain, or have any concerns about any aspect of the way you have been treated or approached during the course of the study, the normal NHS complaints procedure are available to you. You could also discuss any issues with PALS (Patient Advice Liaison service).

Address:

North of Tyne PALS,

The Old Stables,

Grey's yard,

Morpeth,

NE61 1 QD.

Phone-0800 032 0202

Text- 01670 511260

Email: northoftynepals@nhct.nhs.uk

Contact for further information

For further information you can contact Dr. Mohar Goswami during 9AM to 5PM, Monday to Friday on 0191 2138213.

Who is leading the research?

Prof. Alison Murdoch

Professor and Head of the Department

Newcastle Fertility Centre at Life

Contact No: 0191 2138225

Prof. Erica Haines

Professor of Social Policy

Policy Ethics and Life Sciences Centre (PEALS),

Contact No: 01912430780

Dr. Mohar Goswami,

Clinical Research Fellow,

Newcastle Fertility Centre at Life,

Contact No: 07886967972

Should we be freezing embryos?

I am interested in taking part in this research project †

I am not interested in taking part in this research project

I agree to be contacted in the following telephone / mobile number:

Signature:

Signature:

Name:

Name:

Date:

Date:

Appendix C

Invitation Letter for participation in interviews

Dear

We would like to invite you to be interviewed as part of some research that is being carried out in this department.

One of the most difficult times during IVF treatment is when the embryos are transferred. At that time you need to make decisions about what happens to any embryos that remain. We are trying to understand the issues that you consider in reaching your decisions so that we can improve the service and make sure that we meet your needs. Therefore we would like to interview couples who have gone through treatment recently.

This research is being carried out in collaboration with Professor Erica Haimes and colleagues in PEALS (Policy Ethics and Life Science Centre) at the University. Further details are in the attached Information Sheet.

If you are interested in being interviewed about this, please complete and return the form. Dr. Mohar Goswami (Clinical Research Fellow in this department) who is undertaking this research will then contact you.

Yours sincerely,

Alison Murdoch

Appendix D

Aide-memoire for “Embryo cryopreservation: the clinical outcome and couples’ perspectives”

I. Some introduction of the project by the interviewer

(The following acts as aide-memoire for me, and outlines the structure of the interview. I will not read it out in its entirety, but this indicates what I will say before the recorder is started.)

a) Introduction

Thank you for agreeing to help with our research.

(Introduction of myself and my supervisors, who are involved in this project, and who funds it.)

As you will know there are many decisions that need to be made during IVF treatment and some of those relate to what happens to embryos that are ‘left over’ after a course of treatment.

Our study mainly focuses on the experiences and views of the couples in your position who had IVF treatment, and have had to consider the option of freezing their surplus embryos. I would like to talk with you for about an hour about how you came to make the decisions you did regarding freezing, or not freezing, embryos.

We hope to understand how people take the difficult and complex decisions of freezing their surplus embryos, and what are the factors underpinning their decisions. The findings of this study might influence in the future the freezing policies locally, or even nationally.

b) About the general structure of the interview

As I said, the interview will last about an hour and although I have what looks like many questions, these notes are actually just to remind me of the key points I’d like to cover. I might, from time to time, look at this to keep myself on track through the interview but really I’d like to hear about your experiences. It’s not a questionnaire, more a discussion.

c) [About *the content of the interview*]

We are aware that you have been through IVF treatment, and at some point probably the issue of freezing any surplus embryos was discussed. As I say, we want to know your experiences and views in this regard, and what factors influenced your decision.

d) [Consent to record]

In order to ensure we don't make mistakes in interpreting what our interviewees tell us, I'd like to record our discussion. Later on the recording will be transcribed and anonymized and de-identified, and will remain confidential. I can assure you, that this interview, and whatever views you express today, is not going to alter your relationship with the doctors in the fertility clinic, and would not influence your former or future treatment. Only myself and my supervisors will have access to this data.

If there are any questions I ask that you don't want to answer, just say so and remember we can stop the recording or even the interview any time, if you wish so.

At this point I should ask: Do you have any questions?

(If not ...)

So can I please switch the recorder on?

If that's OK then what we do now is get you to sign another consent form while I get the recorder set up.

Assuming yes – get two copies of consent form signed.

II. Demographic details

As I said, the idea is that this is a chance to talk about your experiences, but if you don't mind I'd like to start with a few short, factual questions, so that we can build up a picture of the range of people we are talking to. So...

May I ask your date of birth please?

Do you have a current partner?

May I ask his/ her date of birth please?

How many of you are there in your household, and could you elaborate on that please?

What is the highest qualifications you and your partner have got?

What is your current or most recent job?

What is your approximate annual household income?

Under £ 20,000

Between 20,000-30,000

Between 30,000-40,000

Between 40,000-50,000

Between 50,000-60,000

Above £ 60,000

How would you describe yourself in terms of ethnicity or nationality?

Do you have a religious faith, and if so, may I know what it is?

Thank you. That's the short answer questions out of the way, so can we move on and talk a bit about your fertility treatment.

III. IVF treatment

Can you please remind me about the facts and the sequence of cycles of your IVF treatment ?

How long have you been having fertility treatment?

How many cycles of IVF treatment have you had? When approximately?

Can you remember which of these were NHS funded ?

Did you have to privately fund any of those treatment cycles?

Did you freeze any embryos in any of those cycles? If so, in which cycle? How many embryos did you have frozen?

Have you used any/all of these?

And what about the cycles where you have used frozen embryos, how were they funded?

Have you had any success with fertility treatment?

Discussing freezing embryos

Can we now talk about how the topic of embryo freezing was first brought up?

Do you remember when the option of freezing surplus embryos was first mentioned?

{We are looking for responses such as; Information session, first meeting with doctor or nurse , during consenting for IVF treatment, or during the treatment cycle?}

What was it like , when the topic of embryo freezing was first raised? Did you have lots of questions to ask?

(Possible prompts could be ...)

How was it explained?

What information were you given?

Did you ask any specific questions?

Had you heard about embryo freezing before? From whom?

Did you have any views about it then?

Did you have any reservations about freezing or did it seem a good idea? What did you think about it? Why did you think so?

How was it explained?

Did you look up any more information about embryo freezing? If yes, what did you find out?

Do you know anyone else who has frozen embryos? Or anybody who decided not to freeze embryos?

Was it a possibility that interested you?

V. Decision time

(For those who were offered the option of freezing embryos)

At what point in your treatment did you have to decide whether to freeze your embryos or not?

How long were you given to decide?

Do you think the timing of having to decide about freezing was right for you?

Did you feel any pressure to make this decision?

VI. Consenting

Can we talk about the time when you actually signed the consent form to freeze embryos?

(For those who have frozen embryos)

Were you asked if you wanted to freeze your surplus embryos? If so, when, and by whom?

Do you remember when you actually signed the consent form to freeze your embryos?

Do you recall who was the person who took you through the consent process?

Did you have any questions?

What was the form like? Could you understand it?

Did anyone in the clinic help you understand the information in the consent form?

Did you know for how long you could freeze the embryos?

Were you responsible for paying your own freezing charges? Had you realised there was a charge?

Did you sign the consent for paying the freezing charges at the same time?

Decision making

Let's now talk about what was going on in your mind, when you actually took the decision to freeze, or not to freeze any spare embryos.

(This section is aimed at exploring the process of how couples make the decision to freeze or not to freeze.)

(Questions for all)

What do you think about the practice of 'embryo freezing'?

What to you are the benefits of freezing your embryos?

What, if any, difficulties, does embryo freezing raise for you?

Did any of the given information help you to decide for or against freezing of embryos?

How did the given information influence you?

Was it the information itself, or do you think the person giving the information influenced your decision?

Any other factors, either in the clinic, or outside, that influenced you to decide to freeze or not to freeze ?

(Reasons for freezing embryos)

[Notes for myself, to look out for and explore further answers like 'future insurance', 'buying time', avoidance of the stress and risks of ovarian stimulation and egg collection in the frozen cycle, or availability of NHS funding].

In your view, what is the advantage of freezing embryos?

There is some evidence in the literature suggesting that people may want to freeze their surplus embryos, as it is like having an 'insurance policy'. Would you agree to this view?

Many people also perceive it as a chance to have a baby in the future, without having to go through all the hassles and risks of ovarian stimulations, egg collection. How would you look at it?

Often couples are quite confused and stressed at this stage of IVF treatment, and don't know what to do with their surplus embryos. With the option of embryo freezing, they seem to be able to 'buy time', while they can take their time to reflect, await the outcome of the fresh cycle, and decide what to do with their surplus embryos. Has any similar thought influenced your decision?

To some individuals, availability of the NHS funding for the first year of freezing, is the driving force behind their decision to freeze. What are your thoughts about it?

Did anything during the treatment influence your decision regarding this matter?

If so, in what way?

Did you talk to other people in your situation before taking the decision?

In the respective IVF cycles, how many follicles or eggs did you have?

How many embryos did you have?

Was there any relation between your number of eggs or embryos and your decision to freeze the embryos?

(Questions for couples who had embryos frozen in any of the IVF cycles)

What was going on in your mind when you were trying to decide about freezing embryos, and how did you come to that decision?

Was it an easy one, or was it hard to decide? Did you need to take a quick decision?

Did you have any concerns about freezing?

Did you and your partner have similar or different views about freezing embryos?

Was there anybody else (family / friends) who had an important influence in your decision making?

Have you made the same or different decisions in different cycles? (If applicable?)

(Questions for couples who did not have any surplus embryos available for freezing)

How did you feel, when you realised you did not have any embryos available for freezing? (Prompt: had you assumed you would have some left over?)

If you had had any embryos suitable for freezing, would you have considered freezing those ?

Why do you think you would have frozen the embryos?

(Question for those who declined freezing)

[Notes for myself- , to look out for any of the issues regarding ethics of freezing 'life', not able to trust the clinic, fear of lab errors, financial burden, or avoidance of a future difficult situation of not knowing what to do with them].

Why did you decide not to freeze your surplus embryos?

Do you have any reservations about freezing in general? What are these?

Why do you think this?

You might be aware that there have been debates about embryo freezing: have you heard about any of these?

Prompts: for example, some people think of it as freezing living beings. What are your views about this?

Also, occasionally there are reports about labs making mistakes while handling the frozen embryos and this can put some people off : did this occur to you at all?

Rarely there is news in the media, linking birth defects to embryo freezing. Are you worried of the safety of the procedure?

Financial burden can be a factor as well, if somebody needs to privately fund the freezing: was this an issue for you?

VIII. Cycles using the frozen embryos

As you mentioned you had your frozen-thaw cycle, is it alright to ask a questions about that?

How many frozen cycles did you have? When, and in what sequence were they?

What were the results of the fresh cycles preceding the frozen ones?

Are there any more embryos in storage, or have all been used up? How many of the frozen embryos survived the thaw process? Is this what you expected?

What was the outcome of the frozen-thaw cycle?

What was your experience like in the frozen cycle, compared to that of a fresh IVF cycle?

Is there any difference in the way you look at your fresh and frozen embryos?

Has your view changed in any way from before and following the frozen cycle?

IX. What are embryos?

Can I ask you a few questions about embryos themselves because, as you know, there are lots of discussions about embryos, and what they are.

Views about specific embryos:

Were there any embryos left after the initial transfer?

Do you know what happened to them?

Did you get an opportunity to have a look at the embryos which were being transferred on the screen?

How do you think of each sort of embryo- the ones that are transferred, and the ones that are not , and the embryos that are frozen , and the ones that are not?

Did the way you look at these categories of embryos change during the course of the IVF treatment? Or did your views change following the treatment?

Do you still have any frozen embryos in storage? How do you look at them?

Are you aware of the possible uses of frozen embryos?

Views about embryos in general:

Are you aware of these debates surrounding embryos? If so, what is your reaction to these debates?

What do you understand by the term 'embryo'?

Some people think of embryos as the start of 'life', whereas to others, they are like any other biological tissue – what are your views on this debate?

Some People have looked at frozen embryos as their 'virtual children', whereas others have described them as just 'seeds'. What are your thoughts about this debate?

Does your own experience of IVF treatment influence your views about embryos?

Do you think your views about frozen embryos would change following the experience of pregnancy, child birth or parenting?

Did your own views about embryos changed in any way following IVF treatment?

Do you think the fresh embryos, the ones which are for freezing, and the ones which are not so good, look the same ?

What is your understanding about what can be done with the embryos which are not good enough to be frozen?

Did anyone discuss the options of disposition of the embryos not good enough to be frozen with you? What did you think of those options?

X. Financing for freezing

For couples with frozen embryos.

You have got embryos in storage. Can we just talk about the financing of the freezing?

Who is paying for your embryo freezing? If it is you who are paying, may I ask how much it is?

Were you surprised that you had to pay?

How easily could you afford it?

Can you continue paying? What happens if you are not able to pay for freezing anymore?

In your opinion, what are the alternatives about who should pay? Why do you think so?

XI. Duration of freezing

Are you aware of the length of time the embryos can be frozen for legally, as well as technically?

What are your views on this? Why do you think so?

XII. Successful outcome of thawed embryos

Are you aware of the chances of survival of the frozen embryo following the thaw?

Do you know anything about the likely chances of a successful outcome from a frozen cycle?

What are your expectations from the practice of embryo freezing? How hopeful are you of having a baby from a frozen-thaw cycle?

Do you think bearing in mind the lower success rate of a frozen-thaw cycle, compared to that of a fresh one, it is worth freezing embryos?

XIII. Future decision making

(For couples with frozen embryos)

(The options available for use of the frozen embryos in the future are- thaw and transfer, otherwise donation to other couples, donation to research, dispose of , or continuation of storage for a further length of time.)

Are you aware of the possible uses of frozen embryos, if not used for personal reproductive purpose?

There have been debates about the various options of disposition of the frozen embryos in the future. There is evidence that it is difficult to decide about the destiny of one's frozen embryos.

Some people are happy to donate their frozen embryos to other infertile couples, whereas others perceive it as 'giving away' their children or worry about their genetic offspring growing up in unknown circumstances. There are also concerns of their identity being disclosed and consanguinity of siblings in the future. What are your views about this?

As you can imagine, donating frozen embryos to stem cell or other research is a hugely contentious issue. People have concerns of the embryos being mistreated by scientists, and the ethics of the practice, but the proponents of it argue about the importance of advancement of science by using embryos for research.

People willing to donate to others, or to research, have altruistic views, and a desire 'not to waste'. I would like to know your thoughts about these issues.

Of course, there is the option of discarding the unused embryos, and it is often chosen by couples who have concerns about donating their embryos to others, or donating to science.

To many, wastage in reproduction is natural, and compared to a miscarriage, whereas others have serious misgivings about wasting embryos.

Do you have any idea what you would like to do with your frozen embryos, if they are not thawed and transferred?

Why do you think you would take that particular decision?

Did the clinic ask you to make any decisions about what to do with frozen embryos at the end of the storage time?

If you had already decided about the disposition of your unused embryos at the beginning of treatment, do you think your decision might change in the future? If so, why? Is it the experience of the IVF treatment, or a successful treatment outcome behind it?

XIV. Further queries

Any other views or experiences you would like to share?

Do you have any questions about anything else at all?

Thank you for taking part in this interview.

Appendix E

Consent form

Should we be freezing embryos?

Consent Form

(Version no./Date: 02/220211)

I have read and understood the information sheet and the consent form about the study; and have had the opportunity to discuss it. †

I understand that I would be interviewed by the research team, on one occasion,

lasting for about an hour. † †

I understand that I am under no obligation to take part in this study and that a decision not to participate will not alter any future treatment that I would normally receive.

I am aware that I can withdraw my consent at any time. † †

I understand my interview data can be accessed by any member of the research

team from the NHS Trust or the social scientists belonging to the team, and may be looked at by the regulatory authorities. I give permission to these individuals to have access to my interview records. † †

I consent to be reminded about the interview appointment by

letter/phone/email/text messages. † †

I consent to the storing and processing of data collected about me. I understand

the data will be kept for 6-12 months after the completion of the study. I

understand data will be kept secure and confidential. I am aware that electronic database will not have any identifying information and is coded. †

I understand that I can stop the interview and withdraw my consent, if I find it upsetting. †

I understand that I will not benefit financially from this research and its outcome. † †

I understand that I will not be given any individual feedback about the outcome of this study. † †

I consent to my participation in this study. † †

Patient's name-..... Signature-..... Date-
.....

Partner's name-.....Signature-.....Date-
.....

Name of the person taking consent -

Signature-Date-.....

Appendix F

Destination	Author(s)	Year	Actual		Country	
			Actual (% couples)	(% frozen embryos)		
Research	Oghoetuoma <i>et al.</i>	2000	21		UK	
	Baylis <i>et al.</i>	2003		2	Canada	
	Hoffman <i>et al.</i>	2003		< 3	USA	
	McMahon <i>et al.</i>	2003	29		Australia	
	Newton <i>et al.</i>	2003		2.3	Canada	
	Elford <i>et al.</i>	2004	5		USA	
	Newton <i>et al.</i>	2007	33	39	Canada	
	Provoost <i>et al.</i>	2012	40.8		Belgium	
	Other Couples	Lornage <i>et al.</i>	1995	17		France
		Saunders <i>et al.</i>	1995	3.4		Australia
Hounshell and Chetkowski		1996	4		USA	
Darlington and Matson		1999	6		Australia	
Oghoetuoma <i>et al.</i>		2000	10–11		UK	
Söderström-Anttila <i>et al.</i>		2001	18		Finland	
Elford <i>et al.</i>		2004	1		Canada	
Newton <i>et al.</i>		2007	13	10	Canada	
Provoost <i>et al.</i>		2012	21.5		Belgium	
Discard		Hounshell and Chetkowski	1996	23.5		Australia
	Darlington and Matson	1999	19		Australia	

	Oghoetuoma <i>et al.</i>	2000	29	67	UK
	Svanberg <i>et al.</i>	2001	26.8		UK
	Kovacs <i>et al.</i>	2003	89.5		Australia
	Elford <i>et al.</i>	2004	8		USA
	Newton <i>et al.</i>	2007	44	40	Canada
	Provoost <i>et al.</i>	2012	37.8		Belgium
Continue storage	Darlington and Matson	1999	64		Australia
	Oghoetuoma <i>et al.</i>	2000	39		UK
	Elford <i>et al.</i>	2004	26		USA
	Newton <i>et al.</i>	2007	10	7	Canada
	Provoost <i>et al.</i>	2012	22.8		Belgium

Table AF1 Frozen embryo disposal decisions by couples. The reported figures of the actual fate of frozen embryos, as documented in the literature, are illustrated in in this table. The “Couples %” column shows the percentages of all the couples with frozen embryos choosing the disposal option. The “Frozen embryos%” column shows the percentage of the total number of frozen embryos donated to that particular destination.

Appendix G

Destination	Author(s)	Year	Couples %
Research	Van Voorhis <i>et al.</i>	1999	10
	Boada <i>et al.</i>	2001	31.5
	Moutel <i>et al.</i>	2002	12
	Boada <i>et al.</i>	2003	75.5
	McMahon <i>et al.</i>	2003	10–34
	Bangsboell <i>et al.</i>	2004	60
(heSCR)	Burton and Sanders	2004	29
	Burton and Sanders	2004	27
(heSCR)	Hammarberg and Tinney	2006	42
	Hammarberg and Tinney	2006	69
(heSCR)	Luna <i>et al.</i>	2009	30
	Melamed <i>et al.</i>	2009	31.1
	Nachtigall <i>et al.</i>	2009	22
	Nachtigall <i>et al.</i>	2010	39
Other couples	Cooper	1996	2
	Laruelle and Englert	1995	39
	Van Voorhis <i>et al.</i>	1999	12
	Moutel <i>et al.</i>	2002	9.1
	Newton <i>et al.</i>	2003	12
	Bangsboell <i>et al.</i>	2004	29
	Burton and Sanders	2004	15
	Hammarberg and Tinney	2006	16

	Luna <i>et al.</i>	2009	20.2
	McMahon and Saunders	2009	4
	Melamed <i>et al.</i>	2009	10.3
	Nachtigall <i>et al.</i>	2009	6
Discard	Nachtigall <i>et al.</i>	2010	7
	Van Voorhis <i>et al.</i>	1999	34
	Hammarberg and Tinney	2006	30
	Luna <i>et al.</i>	2009	10.3
	Melamed <i>et al.</i>	2009	24.1
	Nachtigall <i>et al.</i>	2009	1
	Nachtigall <i>et al.</i>	2010	3
Continue storage	Van Voorhis <i>et al.</i>	1999	44
	Moutel <i>et al.</i>	2002	23.6
	Hammarberg and Tinney	2006	3
	Luna <i>et al.</i>	2009	33.3
	Melamed <i>et al.</i>	2009	31.1
	Nachtigall <i>et al.</i>	2009	33.3
Undecided	Nachtigall <i>et al.</i>	2010	24
	Saunders <i>et al.</i>	1995	8.7
	McMahon <i>et al.</i>	2001	70
	Nachtigall <i>et al.</i>	2005	72
	Hammarberg and Tinney	2006	7
	Newton <i>et al.</i>	2007	32
	Nachtigall <i>et al.</i>	2009	29

Melamed <i>et al.</i>	2009	3.4
Nachtigall <i>et al.</i>	2010	21

Table AG1 Frozen embryo disposition intentions of couples. This table illustrates the reported intentions of couples with frozen embryos regarding their frozen embryo disposal decision, as expressed in the different interviews or surveys. Human embryonic stem cell research (heSCR) denotes the percentage of couples with frozen embryos expressing their intention to donate to stem cell research. The “Couples %” column shows the percentages of all the couples with frozen embryos intending for the particular disposal option (Bangsbøll *et al.*, 2004; Baylis *et al.*, 2003; Boada *et al.*, 2001; Boada *et al.*, 2003; Burton and Sanders, 2004; Cooper, 1996; Darlington and Matson, 1999; Elford *et al.*, 2004; Hammarberg and Tinney, 2006; Hoffman *et al.*, 2003; Hounshell and Chetkowski, 1996; Kovacs *et al.*, 2003; Laruelle and Englert, 1995; Lornage *et al.*, 1995; Luna *et al.*, 2009; McMahon and Saunders, 2009; McMahon *et al.*, 2003; Melamed *et al.*, 2009; Moutel *et al.*, 2002; Nachtigall *et al.*, 2009; Nachtigall *et al.*, 2010; Newton *et al.*, 2003; Newton *et al.*, 2007; Oghoetuoma *et al.*, 2000; Provoost *et al.*, 2012; Saunders *et al.*, 1995; Söderström-Anttila *et al.*, 2001; Svanberg *et al.*, 2001; Van Voorhis *et al.*, 1999).

Appendix H

My achievements from this study so far ...

Oral Presentations

“Should we be freezing embryos?”, oral presentation at the “Fertility 2013”, joint conference of the BFS and the ACE in Liverpool on 3 January 2013. Awarded “Best Junior Clinician Award” for the oral presentation.

“Destiny of frozen embryos in Newcastle”, oral presentation as Frank Stabler award finalist in Annual Training Day of Northern Deanery, on 29 June 2012.

“Implementation of NICE Guidelines in fertility treatment: outcome”, oral presentation at the British Fertility Society Annual Conference in Leeds on 6 January 2012.

“Consequences of implementation of NICE Guidelines in NFCL: outcome”. Best oral presentation award in the North of England Obstetrics and Gynaecology Society Meeting in Sunderland Royal Infirmary on 11 November 2011.

Publication in peer reviewed journal

Publication entitled "NHS Funded IVF: Consequences of NICE Implementation" published in *Human Fertility* in June 2013, 16 (2), pp 121-127.

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