

Expanding reproductive lifespan: a cost-effectiveness study on oocyte freezing

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BACKGROUND: The average age of women bearing their first child has increased strongly. This is an important reproductive health problem as fertility declines with increasing female age. Unfortunately, IVF using fresh oocytes cannot compensate for this age-related fertility decline. Oocyte freezing could be a solution.

METHODS: We used the Markov model to estimate the cost-effectiveness of three strategies for 35-year-old women who want to postpone pregnancy till the age of 40: Strategy 1: women undergo three cycles of ovarian hyperstimulation at age 35 for oocyte freezing, then at age 40, use these frozen oocytes for IVF; Strategy 2: women at age 40 attempt to conceive without treatment; and the reference strategy: women at age 40 attempt to conceive and, if not pregnant after 1 year, undergo IVF. Sensitivity analyses were carried out to investigate assumptions of the model and to identify which model inputs had most impact on the results.

RESULTS: Oocyte freezing (Strategy 1) resulted in a live birth rate of 84.5% at an average cost of €10 419. Natural conception (Strategy 2) resulted in a live birth rate of 52.3% at an average cost of €310 per birth. IVF (the reference strategy) resulted in a cumulative live birth rate of 64.6% at an average cost of €7798. The cost per additional live birth for the oocyte freezing strategy was €13 156 compared to the IVF strategy. If at least 61% of the women return to collect their oocytes, and if there is a willingness to pay €19 560 extra per additional live birth, the oocyte freezing strategy is the most cost-effective strategy.

CONCLUSION: Oocyte freezing is more cost effective compared to IVF, if at least 61% of the women return to collect their oocytes and if one is willing to pay €19 560 extra per additional live birth. Our Markov model shows that, considering all the used assumptions, oocyte freezing provides more value for money than IVF.

Key words: Markov model / cost-effectiveness / fertility preservation / oocyte freezing / IVF

Introduction

In the past decades, the average age of women bearing their first child has increased strongly (UNECE, 2007). This is an important reproductive health problem, as women steadily lose their oocytes from birth to menopause, with an accelerated loss of oocyte quantity and quality from the age of 35 (Baird *et al.*, 2005). As a consequence, female fertility potential declines rapidly thereafter (van Noord-Zaadstra *et al.*, 1991; Leridon, 2004), resulting in an increase in involuntary childlessness. This risk of involuntary childlessness increases from 2 to 3% for women younger than 30 years, to 36% for women of 40 years or older (te Velde *et al.*, 2008; Steenhof and de Jong, 2009).

Today, IVF is increasingly applied to women of 'advanced female age', i.e. women of 40 years or older. Apart from the costs, the paradox is that

this very indication is also the very reason for the low IVF success rates. Some might even consider it unethical to offer treatment at all, since no other branch of medicine permits an elective operation with a chance of success of <5% (Lockwood, 2009). Yet, in the UK, 19.4% of all IVF cycles performed in 2008 were in women over the age of 40, with a total of 9085 cycles (HFEA, 2009).

Given the recent successes in oocyte freezing (Yoon *et al.*, 2003; Kuwayama *et al.*, 2005; Antinori *et al.*, 2007; Chian *et al.*, 2009; Noyes *et al.*, 2009; Rienzi *et al.*, 2010), fertility preservation for women is now possible. For women with cancer and needing chemotherapy, fertility preservation is already an accepted intervention (ESHRE, 2004; SART *et al.*, 2008), but oocyte freezing could also help women who want to extend their natural reproductive lifespan (Dondorp and De Wert, 2009; Homburg *et al.*, 2009).

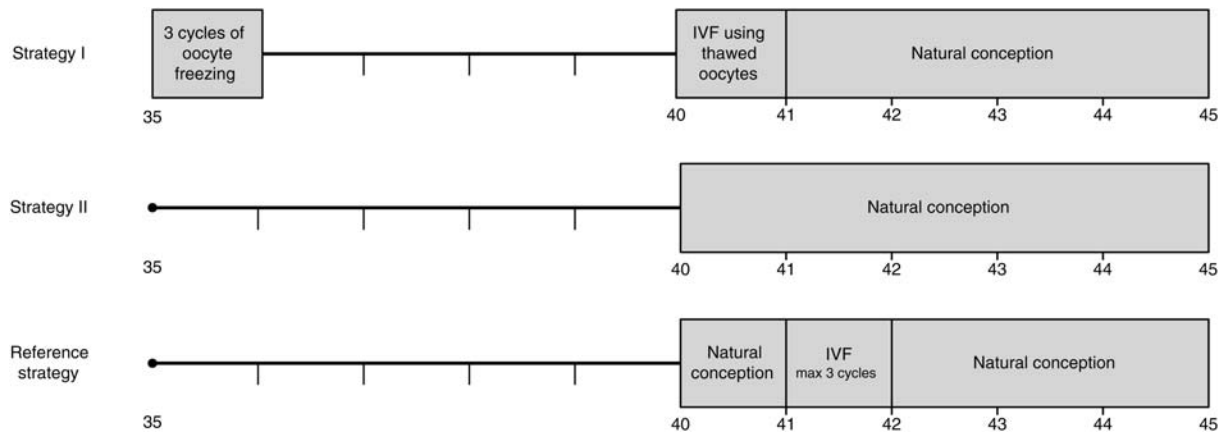


Figure 1 Strategies of treatment.

To obtain oocytes for freezing, these healthy women must undergo IVF treatment, which is burdensome, not without health risk and involves extra costs. As a consequence, this strategy has been criticized (Batty *et al.*, 2006; Henderson, 2007; Khamisi, 2007; ASRM, 2009). This may well have been premature, because oocyte freezing at a relatively younger age could potentially result in much higher pregnancy rates than natural conception or the currently applied strategy, which is IVF treatment at an advanced age.

To facilitate the debate on oocyte freezing for women who want to extend their reproductive lifespan, we performed a cost-effectiveness analysis and determined whether oocyte freezing at age 35 and using these oocytes at age 40 for IVF is cost-effective compared with either IVF at the age of 40 using freshly obtained oocytes or delayed natural conception without treatment.

Materials and Methods

Model design

We used a decision analytical Markov model to mimic three strategies for 35-year-old women who, for various reasons, want to postpone their child-bearing until they are 40. The strategies were selected for clinical relevance. We evaluated three strategies based on the following assumptions. In Strategy 1, women undergo three cycles of ovarian hyperstimulation at the age of 35 to collect and freeze all obtained oocytes. This is in line with current reimbursement of three cycles of IVF in the Netherlands. Between the ages of 35–40, no spontaneous pregnancies occur. The frozen oocytes are thawed at the age of 40 and used for IVF. If the women fail to get pregnant after 1 year of IVF with frozen and thawed oocytes, they attempt to conceive naturally for the remaining 4 years. In Strategy 2, women delay active conception till the age of 40. At the age of 40, they attempt to conceive for the first time. If they do not succeed after 1 year, they are by definition subfertile but, for various reasons, do not seek any treatment. The reference strategy describes the current clinical situation. Women delay active conception till the age of 40 and, if not pregnant after 1 year, start IVF treatment. If they do not conceive after 1 year of IVF treatment, with a maximum of three IVF cycles, they attempt to conceive naturally again in the remaining 3 years (Fig. 1).

Markov models assume that there are finite numbers of health states (Markov states) and at any time patients are assigned to only one health state. The observation horizon of a Markov model is divided into equal

increments of time (the ‘Markov cycle’) that represents the minimum amount of time (cycle length) patients will spend in a health state before transition to another state is possible. At the end of each cycle, there is a probability of a patient moving from one health state to another. All these transitions are defined in terms of probabilities (Fox-Rushby and Cairns, 2005).

We constructed a Markov model to determine the chances of conception and subsequent live birth within a defined period of time (observation horizon). Our model consisted of four main health states: women undergoing IVF with frozen/thawed oocytes or fresh oocytes, live birth after IVF with fresh or frozen/thawed oocytes, live birth after natural conception and no pregnancy. The starting point of the model was age 35. Each cycle in the model comprised a period of 1 year, as we assumed that three cycles of ovarian hyperstimulation to obtain oocytes for freezing, as well as a maximum of three IVF cycles can be completed within 1 year (Eijkemans *et al.*, 2008). The time horizon was set at 10 years as pregnancy chances beyond the age of 45 are close to zero. Women who failed to conceive during a cycle or who had a miscarriage were included in the next cycle. Live birth achieved either spontaneously or by IVF with fresh or frozen/thawed oocytes was the final state of the model; we restricted the model to first pregnancies.

Data sources

Probabilities

The probabilities that were used as input for the Markov model are presented in Table 1. The pregnancy rates after natural conception were calculated with the Hunault prediction model (Hunault *et al.*, 2004). The Hunault model calculates the live birth rate after 1 year of trying to conceive naturally.

We assumed that the cumulative live birth rate after 1 year of IVF using thawed oocytes is equal to the cumulative live birth rates after three cycles of IVF at the age of 35. This is based upon the balance between the loss of oocyte quantity and quality after the freezing and thawing process (Kuwayama *et al.*, 2005; Lucena *et al.*, 2006; Antinori *et al.*, 2007; Cobo *et al.*, 2008), and the increased chances of success as these women are presumably fertile. These IVF pregnancy rates were based on data from Human Fertilization and Embryology Authority (HFEA, 2007). The pregnancy rates at age 41 after 1 year of IVF, i.e. three cycles, were also based on the HFEA data.

We included miscarriage rates in our analysis, since the chances of a miscarriage increase with increasing female age (Nybo Andersen *et al.*,

Table I Probabilities used as input variables for decision model.

	Source
Spontaneous pregnancy	
Clinical pregnancy rate per year, at age (%)	Hunault et al. (2004)
40	27
41	27
42	23
43	21
44	20
Miscarriage rate per clinical pregnancy, at age (%)	
40	32 CDC (2006)
41	37
42	43
43	50
44	61
Oocyte freezing at age 35 (%)	
Clinical pregnancy rate per year	91 HFAE (2007)
Miscarriage rate per clinical pregnancy	20 CDC (2006)
IVF at age 41 (%)	
Clinical pregnancy rate per year after 3 cycles	60 HFAE (2007)
Miscarriage rate per clinical pregnancy	37 CDC (2006)

2000). We therefore assumed that IVF with frozen/thawed oocytes, which were obtained from women aged 35, would result in lower miscarriage rates than in women aged 40 or older after natural conception or IVF. Miscarriage rates after IVF were based on data from Centers for Disease Control and Prevention (CDC, 2006). We used the same miscarriage rates for the strategies natural conception and IVF at 40 years and older.

Costs

Direct medical costs such as costs of ovarian hyperstimulation, oocyte retrieval, laboratory costs, embryo transfer, costs for oocyte freezing, costs of oocyte storage, costs of transfer of frozen/thawed oocytes and miscarriage cost were included. We included miscarriage cost as miscarriage rates increase significantly with maternal age, which will result in higher costs per strategy. The only costs included in the natural conception strategy were the miscarriage costs.

The costs were converted to Euros and the index year of 2008 according to the consumer price index (CBS, 2008). We assumed that in this period no large cost changes in the treatment protocol occurred except for inflation. The included costs and references are presented in Table II. All costs were based on data from the Netherlands.

Cost-effectiveness analysis

The cost-effectiveness analysis was performed from a healthcare perspective and included direct medical costs. The outcome measures of the economic evaluation were the costs and effectiveness of each strategy. Effectiveness was expressed as the cumulative live birth rate after 5 years. Based on costs and effectiveness of each strategy included in the model, incremental cost-effectiveness ratios (ICERs) were calculated. We determined the ICER of a strategy by dividing the difference in costs between the strategy and the reference strategy, i.e. IVF, by the

Table II Costs used as input variables for decision model.

Costs (€)		Source
Costs per IVF cycle	3042	Merkus (2006)
Costs for oocyte freezing (3 cycles)	9126	Merkus (2006)
Costs for oocyte storage/year	40	Institutional costs
Costs for embryo transfer/cycle	400	Institutional costs
Costs per miscarriage	740	Graziosi et al. (2005)

difference in effect between the strategy and the reference strategy. The ICER for this study therefore expresses the extra costs per additional live birth. The lower the ICER, the more cost-effective the strategy.

Although IVF is a widely used treatment for various indications, there is no evidence that IVF is an effective treatment for age-related fertility decline. To make an optimal comparison, we also calculated the ICERs with a different reference strategy, i.e. delayed natural conception without additional treatment. For this, we calculated the ICER of oocyte freezing and of IVF compared with delayed natural conception without treatment.

The analyses were calculated with and without discounting. Future costs were discounted by 4% annually for a time frame of 10 years (CVZ, 2006). All effects were discounted by 1.5% as recommended by the Dutch Health Insurance board (CVZ, 2006) for a time frame of 5 years, since women delay active conception till 40 and as a result there is no 'effect', i.e. pregnancy till the age of 40.

Sensitivity analysis

Different sensitivity analyses were performed. In the first sensitivity analysis, we evaluated the effect of different percentages of women returning to collect their frozen oocytes. This is important, as we originally assumed that all women would return and collect their frozen oocytes and use them for IVF, which might not be realistic in practice.

The second analysis was a one-way simple sensitivity analysis to evaluate the robustness of the model. In this analysis, each model parameter is varied individually to isolate the consequences of each parameter on the results of the study. All parameters are listed in Supplementary data, Table S1.

The third analysis was a probabilistic sensitivity analysis (Monte Carlo simulations). In probabilistic sensitivity analysis, it is assumed that the uncertainty of an input variable possesses probability distributions, i.e. a baseline estimate and a upper and lower bound of the 95% confidence interval. In the probabilistic sensitivity analysis, the probability distributions of input variables are incorporated into the evaluation model. Thus, probabilistic sensitivity analysis characterizes, quantitatively, the uncertainty and variability in estimates of the results.

In our analysis, all major model parameters were simultaneously and randomly varied over the appropriate probability distributions using Monte Carlo simulation with 1000 runs. On the basis of the simulation results, we constructed cost-effectiveness acceptability curves at different willingness-to-pay thresholds as well as 95% confidence limits for the calculated ICER.

The sensitivity analyses were performed with undiscounted costs and effects. All computations were performed using a commercially available decision analysis software package (TreeAge Pro 2009, Tree Age, Inc., Williamstown, MA, USA). No medical ethical approval for this research was needed.

Results

Effectiveness and costs

After 10 years, at the age of 45, the discounted cumulative live birth rate for Strategy 1, freezing oocytes at age 35 years and using them at age 40, was 84.5% (73.7% after IVF with frozen and thawed oocytes and 10.8% after natural conception). The costs for this strategy were €10 419 per woman and the costs per live birth were €12 326 (Table III). The discounted cumulative live birth rate for Strategy 2, women delaying active conception till the age of 40 and receiving no treatment, was 52.3%. The costs for this strategy were €310 per woman and the costs per live birth were €593 (Table III).

For the reference strategy, women of 40 years receiving IVF treatment after 1 year of attempting natural conception, the discounted cumulative live birth rate was 64.6% (31.4% after IVF and 33.2% after natural conception), the costs for this strategy were €7798 per woman and the cost per live birth were €12 071 (Table III). The average number of IVF cycles performed was 2.35. The results without discounting are also listed in Table III.

Cost-effectiveness

The discounted ICER for Strategy 1, oocyte freezing at 35, was €13 156 per additional live birth when compared with the reference strategy (Fig. 2 and Table III). For Strategy 2, delayed natural conception without treatment, the ICER was €60 717. This implicates that one saves €60 717 at the cost of one live birth (Fig. 2 and Table III). The results without discounting are also listed in Table III.

When we changed the reference strategy from IVF to delayed natural conception without additional treatment (Strategy 2), the ICER without discounting for Strategy 1, oocyte freezing, was €30 091 per additional live birth when compared with delayed natural conception without treatment and after discounting €31 339. The ICER of IVF compared with delayed natural conception without additional treatment was €47 874 undiscounted and €60 716 after discounting per additional live birth.

Sensitivity analysis

In the first sensitivity analysis, we varied the percentages of women returning to collect their frozen oocytes. The threshold at which Strategy 1 remains cost-effective compared with the other strategies is 61%.

The second one-way simple, sensitivity analysis showed that two model inputs had considerable influence on the model, i.e. pregnancy rates after oocyte freezing and the costs for oocyte freezing. If cumulative live birth rates after oocyte freezing drop <53%, the reference strategy becomes more cost-effective. If the costs for oocyte freezing are <€5058 or the IVF costs are >€4475, Strategy 1 is more cost-effective.

The third, probabilistic, sensitivity analysis showed that oocyte freezing remains the preferred strategy (Table IV).

Cost-effectiveness acceptability curves

Until the ceiling ratio (expressing the willingness to pay for an additional live birth) reaches €19 560, the probability that the reference strategy is most cost-effective, is the highest.

Table III Cumulative live birth rate, miscarriage rate, costs and estimated ICERs.

	Cumulative live birth rate (%)	Cumulative live birth rate discounted (%)	Miscarriage rate (%)	Costs per strategy (€)	Cost per strategy discounted (€)	Cost per live birth (€)	Cost per live birth discounted (€)	ICER (€)	ICER discounted (€)
Strategy 1									
Freezing oocytes at age 35, IVF with frozen oocytes at age 40	84.2	84.5	26.8	10 195	10 419	12 111	12 326	19 524	13 156
Strategy 2									
Natural conception (no additional treatment)	51.2	52.3	35.9	266	310	519	593	47 874	60 717
Reference strategy									
Women age 40, IVF after 1 year of subfertility	63.5	64.6	41.1	6154	7798	9694	12 071		

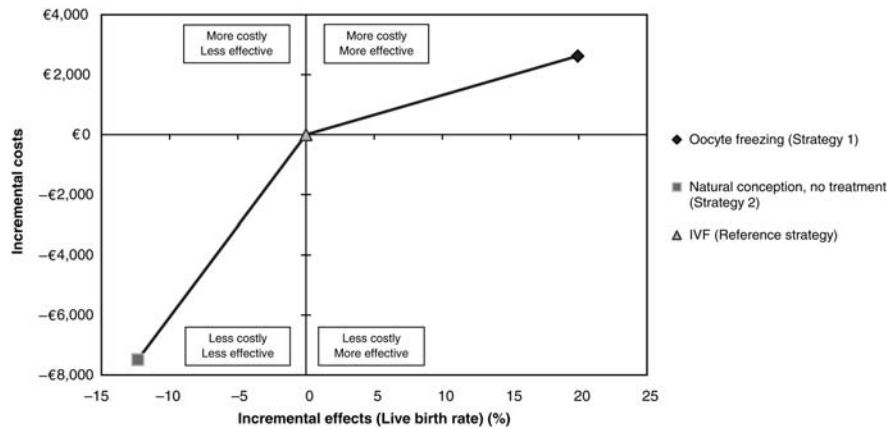


Figure 2 Incremental cost-effectiveness plane for Strategy 1 and 2.

Table IV The results of the probabilistic sensitivity analysis (Monte Carlo simulation).

	Mean costs per strategy (€), mean (95% CI)	Mean ICER (€/effect), mean (95% CI)
Strategy 1 Freezing oocytes at age 35, IVF with frozen oocytes at age 40	8764 (4369–13 123)	19 587 (–12 728 to 111 841)
Strategy 2 Natural conception (no additional treatment)	271 (166–389)	50 137 (17 888 to 221 021)
Reference strategy Women age 40, IVF after 1 year of subfertility	5303 (2903–7828)	

If one is willing to pay more €19 560 extra for an additional live birth, the probability that Strategy 1 is most cost-effective compared with IVF is the highest (Fig. 3).

Discussion

Our society at large creates the economic, educational and professional conditions that encourage deferred maternity (Gosden et al., 2000). Fertility starts to decline more than a decade before menopause (Menken et al., 1986). As a consequence, postponement of maternity results in an increase in involuntary childlessness (te Velde et al., 2008; Steenhof and de Jong, 2009). Oocyte freezing is able to circumvent the natural decline of fertility and to extend women's natural reproductive lifespan.

In this study, we evaluated the cost and effects of oocyte freezing compared with IVF treatment. Our study showed oocyte freezing at age 35 to be cost-effective if the return rate after oocyte storage is >61% and one is willing to pay €19 560 extra per additional live birth compared with our reference strategy, IVF. When changing the reference strategy to delayed natural conception without treatment, the ICER of oocyte freezing was €31 339 per additional live birth when compared with delayed natural conception and the ICER of IVF was €60 716. Oocyte freezing is therefore more cost-effective than IVF.

This study has some limitations. First, although empirical data and true healthcare costs were used as input parameters for the model, data on natural conception at 40 years or older are limited. For our Markov model, pregnancy and miscarriage rates of women aged between 40 and 45 were necessary. Large epidemiological studies only provide these rates till the age of 41 (van Noord-Zaadstra et al., 1991; Dunson et al., 2004; Leridon, 2004). We therefore used a validated prediction model to calculate pregnancy rates after natural conception (Hunault et al., 2004). These calculated pregnancy rates may not precisely reflect the 'real' pregnancy rates for women of 40 or older, but our sensitivity analyses showed that, even with higher or lower spontaneous pregnancy chances, the model remained stable.

Another limitation is that data on oocyte freezing are still limited. Most of the published papers have used data on frozen oocytes of subfertile women (Yoon et al., 2003; Kuwayama et al., 2005; Antinori et al., 2007; Chian et al., 2009; Noyes et al., 2009). The women in our hypothetical cohort were not subfertile, but women of unproven fertility. The published data could therefore result in an underestimation of pregnancy rates, but we believe that this potential underestimation is equalled out by the potential decline in quality and quantity of oocytes after freezing/thawing.

A last limitation is that medical costs of the pregnancies and deliveries were not taken into account. One should bear in mind that these costs exist for all pregnancies despite the mode of conception

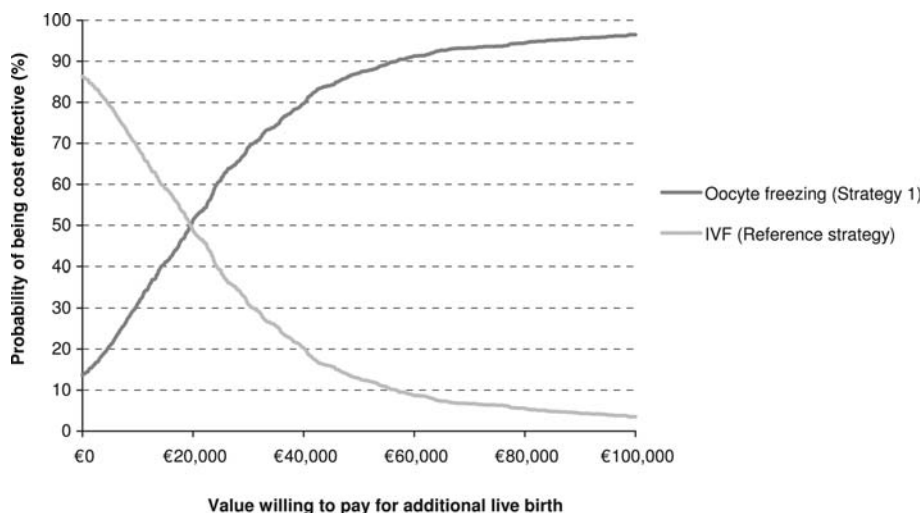


Figure 3 Cost-effectiveness acceptability curve showing the threshold for the willingness to pay for an additional live birth.

and the goal of fertility treatment is to attain a pregnancy/child and therefore generate these costs. Yet, the costs of IVF pregnancies are higher than after natural conception since the chances of multiple pregnancies and premature birth are also higher (Ledger *et al.*, 2006), but in the current IVF practices embryo transfer policies are shifting towards single embryo transfer which results in much lower multiple pregnancies rates and lower costs.

A strong point of our study is that we compared oocyte freezing with two strategies of relevance to women wishing to conceive at age 40, i.e. delayed natural conception without additional treatment or IVF. Also, our model simulates all relevant clinical events and the use of health services, reflecting a real clinical setting. The costs used in our model were based on a recent publication on costs of IVF (Merkus, 2006) resulting in an optimal approach to a real clinical setting and resulting in a more robust model. Furthermore, in this study, we made great effort to be transparent in our reporting, which should allow researchers and decision-makers to judge the applicability of this work to their own setting.

Our study substantiates that oocyte freezing results in higher live birth rates compared with IVF or natural conception without additional treatment, but is also more costly. Our study also shows that oocyte freezing will be more cost-effective if women use their frozen oocytes later in life, as older women have lower chances of conceiving naturally, but it will be less cost-effective if women use their frozen oocytes at a younger age as they will then still have reasonably high chances of conceiving naturally.

In cost-effectiveness studies, the most important outcome is the ICER. This ratio is calculated if there are established norms for what is considered cost-effective, i.e. in our situation how much society is willing to pay for an additional child. However, there are no established norms for how much society would be willing to pay for an additional child. Yet, IVF is used extensively for the indication of age-related fertility decline and therefore the costs for the IVF treatments are already accepted by society. The magnitude of the ICER, indicating the difference in costs and effectiveness of IVF and oocyte freezing, provides evidence of the amount of money involved.

Hopefully, the data from this study are helpful in progressing the debate on reproduction in women who for various reasons have to defer their pregnancy.

In conclusion, the present study demonstrates that oocyte freezing is cost-effective, if at least 61% of the women return to collect their oocytes and if there is a willingness to pay €19 560 extra per additional live birth. Our Markov model shows that oocyte freezing provides more value for money than IVF, considering all used assumptions.

Supplementary data

Supplementary data are available at <http://humrep.oxfordjournals.org/>.

Authors' roles

L.L.L. contributed to the design of the study, acquisition of the data and analysis of the data; also drafted the manuscript. L.M.M. contributed to the design of the study and analysis of the data; also participated in interpretation of the data and revised the manuscript critically. B.W.J.M. contributed to the design of the study, interpretation of the data and to the revisions of the manuscript. S.R. contributed to the design of the study and to the revisions of the manuscript. F.V. contributed to the design of the study, interpretation of the data and to the revisions of the manuscript. M.G. contributed to the design of the study and revised the manuscript critically.

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