1st International Symposium
on Social Egg Freezing

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Dear colleagues

We are pleased to receive you at the 1st International Symposium on Social Egg Freezing, held in Barcelona (Spain)

This one day international symposium, the first of its kind, will promote an open and dynamic discussion on the ethical, demographic, social, medical and psychological implications of elective oocyte freezing in our society.

The symposium is being held in beautiful Barcelona, a city with an open and international personality so typical of Mediterranean cities. It is the perfect city to relax in, stroll around and enjoy. Barcelona has its own way of life which makes it unique.

We wish you all a wonderful Symposium and a pleasant stay.
Dr. Sobotka is senior researcher at the Vienna Institute of Demography (Austrian Academy of Sciences) and the Wittgenstein Centre for Demography and Global Human Capital. He coordinates ERC-funded research project EURREP focusing on fertility reversals and reproduction in contemporary Europe. He belongs to the leading European researchers in the field of fertility and population change. Tomáš Sobotka studies a broad range of topics, including low fertility, changes in family, childlessness, measurement issues, fertility intentions and assisted reproduction as well as the interrelation between migration, fertility and population trends. Together with Joshua Goldstein and Vladimir Shkolnikov he has initiated a Human Fertility Database Project that aims to provide access to detailed and standardised data on fertility rates (http://www.humanfertility.org)
OOCYTE CRYOPRESERVATION AS AN INSURANCE STRATEGY: A SOCIO-DEMOGRAPHIC VIEWPOINT

Introduction
Fertility trends in rich countries have been dominated by a shift towards later age at childbearing. This fertility postponement has been fuelled by multiple factors, in particular by the expansion of university education, massive rise in women’s labour participation, higher partnership instability, economic uncertainty and unemployment in young adulthood, as well as a diffusion of values and lifestyles not compatible with parenthood (Sobotka 2010; Mills et al. 2011; Adsera 2005; Lesthaeghe 2010; Goldin 2006; Ni Bhrolcháin and Beaujouan 2012) A spread of efficient contraception, especially the pill and, in most countries, widening access to legal abortion, were of paramount importance in facilitating this shift to later timing of parenthood: many young adults nowadays enjoy prolonged period of sexual relations without much fear of unintended pregnancy (Goldin and Katz 2002) Mean age of mothers at first birth has reached 28-30 years in most European countries; in Spain and Switzerland it has already surpassed this threshold (VID 2012)

The rising age at childbearing has accentuated a conflict between biological and health rationale to have children at young reproductive ages and the economic and social rationale, which makes it advantageous for most couples to have children much later in life (Sobotka 2010; Schmidt et al. 2012) Specifically, late parenthood has been associated with numerous advantages for the parents (and some for their children), including lower income loss and less severe career interruption for mothers (Miller 2009), more stable partnerships (Sobotka 2010), better financial and housing situation, a stronger sense of “being ready” for parenthood (Mills et al. 2011), and even higher happiness level among the parents (Myrskylä and Margolis 2012) But the postponement transition (Kohler et al. 2002) cannot continue indefinitely: many more women than in the past have postponed family formation past age 35 when rising infertility may endanger the realisation of their plans to have children (Leridon 2008; te Velde et al. 2012)

On this background, assisted reproduction (ART) can be expected to play an increasing role for couples in higher reproductive ages. New reproductive technologies may help
women with poor oocyte quality achieving a pregnancy. Whereas in vitro fertilisation using fresh oocytes has shown low success rates among women at higher reproductive ages (Stolwijk et al. 2000; Leridon 2004; Leridon and Slama 2008, Sullivan et al. 2008; CDC 2012a) oocyte cryopreservation (or “egg freezing”) for non-medical reasons appears to be particularly promising and it may partly erode the boundaries of reproductive age. As N. Hass (2011) noted in the Vogue, “stopping the biological clock through egg freezing has long been the ultimate feminist fantasy.” Media and general public have shown enthusiasm and interest in this rapidly developing technology: Google search of the term “egg freezing” gave 431,000 hits as of December 2012.

This paper discusses the potential role of oocyte cryopreservation (OC) from a socio-demographic viewpoint. I focus on its non-medical or “social” aspect linked to its potential to fulfil fertility plans among the couples who plan to have children later in life. I leave aside the discussion on oocyte cryopreservation for patients with cancer and other medical conditions, including premature menopause, where the OC use is clearly justified and does not raise any ethical issues (Dondorp and Wert 2009).

The paper is structured as follows. Next section gives summarises major trends in the long-term increase of the number women who chose to have children at advanced reproductive ages. Then I analyse the potential demand for oocyte cryopreservation for non-medical reasons, looking at both the number of women who might eventually use IVF treatment with OC as well as the number of women who may consider OC as a precautionary “safety measure” when deciding for later childbearing. Thereafter I discuss the limitations and drawbacks of OC that will limit its use well below its estimated potential. Final section provides concluding discussion on short-term and long-term prospects on social oocyte cryopreservation.

**The rising importance of childbearing at late reproductive ages: intentions, birth rates and use of assisted reproduction**

Many different indicators clearly show that childbearing has been on the rise among women past age 35, in particular among those still remaining childless or having only one child, and among the group with university education (e.g.,
After about a century of declining childbearing rates at higher ages, accompanying the shift to a small family size, birth rates at advanced reproductive ages reached a trough and then started rising steadily across most rich countries during the 1980s-1990s. This reversal has been studied in detail for women aged 40 and older and has also been documented for women at ‘extreme’ childbearing ages of 50 and older (Sobotka et al. 2007; Billari et al. 2007). This study uses selected data for eight rich countries with diverse social policies and institutional backgrounds (Austria, the Czech Republic, the Netherlands, Spain, Sweden, Japan, and the United States) to illustrate trends in childbearing intentions, birth rates and rates of assisted reproduction at ages 35 and older.

**Childbearing intentions among women past age 35**

There are rich sets of period and cohort data on birth rates by age and other characteristics of the mother. However, considerably less comprehensive evidence exists about reproductive plans of women and men. Typically, surveys of reproductive intentions are not carried out regularly and they often rely on different questions about short-term (next 1-4 years) and ‘lifetime’ reproductive plans that are not compatible between countries. I provide an illustration for Austria and the United States, where repeated surveys asked identical questions about future childbearing intentions among women of reproductive age. These data reveal parallel trends in both countries (Figure 1). At age 35-39, when infertility and sterility start increasing rapidly, an ever higher share of women indicate they intend to have a child in the future. In the United States, their share has tripled from 3% to 10% between 1980 and 1998, while in Austria their share almost tripled from 6% to 15% between 1986 and 2006 (excluding uncertain respondents). There are sharp and rising differences in intending a birth at later reproductive ages among women of different parities; among the childless, the declared intentions rose particularly steeply, reaching 28% in the U.S. in 1998 and even 38% in Austria in 2006. Only a few women with two children intend to have another one—a clear indication of a strong orientation towards a two-child family. At the same time, the share of women who are still childless in their late 30s has also risen continually. For instance, in Spain only one out of ten women born in 1945 was childless when reaching age 35; this share then climbed rapidly for the women born
in the 1950s and 1960s and reached over one third for the cohort born in 1973.

Figure 1: Percentage of women aged 35-39 who intend to have another child in the future: United States (1980-1998) and Austria (1986-2006)

Sources: United States: Current Population Survey (published in Hagewen and Morgan 2005, Table 1); Austria: Microcensus survey, author’s computations. Graph excludes responses of uncertain respondents (see also Sobotka 2009)

**Trends in birth rates at ages above 35**

For numerous reasons, only a fraction of reproductive intentions get realised; frequent changes in reproductive intentions have been observed across the life course (Quesnel-Vallée and Morgan 2003; Liefbroer 2009). At higher reproductive ages, the reasons for non-realisation of childbearing plans include infertility, poor health, difficult employment and economic circumstances, partnership dissolution, partner’s disagreement, not having a right partner, inadequate housing, as well as competing careers and incompatible lifestyles (Leridon 2008; Régnier-Loilier and Vignoli 2011; Rosina and Testa 2009; Philipov et al. 2009; NIPSSR 2011). In addition, considerable number of respondents express uncertainty about their desires and intentions or state that they are fine with both possible outcomes, having or not having another child (McQuillan et al. 2011; Ní Bhrolcháin and Beaujouan 2011). Although childbearing intentions change, trends in birth rates at advanced reproductive ages point at the same direction. Sharp increase has been recorded in births rates above age 35, in particular among the childless women. Some of the key trends
are summarised for selected European countries, United States and Japan in Figure 2. Between 1950 and 2010, a U-shaped pattern in the share of birth rates at ages above 35 is visible in most countries, with a lowest share reached in the late 1970s and 1980s (Figure 2a) Since then the share of birth rates realised at higher reproductive ages has doubled in Austria, Spain and the United States, trebled in the Netherlands, Sweden and Japan and quadrupled in the Czech Republic. In Spain, birth rates of women aged 35+ account for more than a quarter of the total fertility rate since 2009, in the other analysed countries it reached between 14% (the Czech Republic) and 21% (Sweden) Yet sharper relative rise in childbearing at higher reproductive ages has been observed for first birth rates. In the past, “late” childbearing has been typical of women having larger families, whereas recently it has increasingly become characteristic of women who have delayed their first or second birth (Sobotka et al. 2007) Consequently, the share of first birth rates at later ages has risen by a factor of 4-6 since reaching the minimum in the 1970s-1980s; this rise has been particularly steep in Spain where almost one out of five first births now occurs at ages 35+ (Figure 2b) Sharp increases have also taken place among women approaching the menopause. At ages 45+, childbearing still remains relatively rare; in most countries there is less than one first birth per thousand women at these ages. Although very low, these birth rates have risen exceptionally fast, especially in Austria, Sweden, and the United States where they jumped by a factor of 10 or more between the mid-1980s and 2007-2010 (Figure 2c) This trend has been in part driven by increasing frequency of ART using oocyte donation (see also below)

Figure 2d further highlights the rising likelihood of first births at advanced reproductive ages. In the early 1980s a woman still childless at age 35 typically had a likelihood of 10-15% that she would become a mother before reaching the end of her reproductive period (measured either at age 50 or 55, depending on data availability) Most recently, in 2007-10 this likelihood has risen in five analysed countries to a range from around 30% (Austria, Czech Republic) up to 45-47% (Spain, Sweden) In addition to that, the share of women remaining childless into their mid- to late- 30s also increased rapidly. This shift has been most pronounced among women with university education, who need many years to complete their studies and to get a foothold on the labour market (Lappegård and Rønsen 2005, Martin 2000, Ekert-Jaffé et al. 2002, Rendall et al. 2005)
Figure 2: Selected indicators of birth rates and first birth rates among women aged 35+ in five European countries, United States and Japan

a) Share of birth rates among women aged 35+ on the total fertility rate, in %, 1950-2010

b) Share of first birth rates among women aged 35+ on the total fertility rate for first births, in %, 1950-2010
c) Sum of first birth rates at ages 45+, per thousand women (smoothed, using 3-year moving averages), 1950-2010

![Graph showing the sum of first birth rates at ages 45+, per thousand women, from 1950 to 2010 for various countries.]

d) Lifetime probability of giving birth to a first child among women still childless when reaching age 35, 1980-2010

![Graph showing the lifetime probability of giving birth to a first child among women still childless when reaching age 35, from 1980 to 2010 for various countries.]

**Infertility, sterility and ART use at advanced reproductive ages**

As ever higher share of births has been shifted into ages when infertility becomes common many women have to make considerable effort to become pregnant and to get a desired child. Many studies have demonstrated that infertility, sterility, the frequency of miscarriages, and pregnancy complications increase gradually among women around age 35 and then skyrocket at ages above 40. Leridon (2008) estimated that by age 40 almost 17% of women are permanently sterile (unable to conceive), while as many as 35% of women will remain childless if starting their pregnancy effort at that age. Different measures based on the National Survey of Family Growth carried out regularly in the United States further illustrate the extent of infertility at ages 35+.

In 2006-10 a quarter of currently married childless women aged 35-39 and 30% of those aged 40-44 have been estimated as infertile (CDC 2012b) Almost a quarter of married childless women aged 40-44 have ever received any infertility service, including advice, tests, ovulation drugs, or artificial insemination. The share of married childless women with impaired fecundity (this includes inability or difficulty of getting pregnant or of carrying pregnancy to term) reached 39% at age 35-39 and 47% at age 40-44. This statistics also suggests that rapidly rising birth rates at ages 35+ mask an equally impressive rise in the number of women and couples who cannot get pregnant at those ages and who may potentially seek infertility treatment. These couples also have considerable potential demand for oocyte cryopreservation (see below)

Some evidence on the rising demand for infertility treatment linked to postponed childbearing is provided by the available reports on ART use at higher reproductive ages. Age 40 can be seen as a boundary where the IVF treatments using women’s own oocytes show low success rates due to a combination of a low pregnancy rate cycle as well as a high rate of pregnancy loss, especially due to miscarriage. In the United States only 20% of ART cycles at age 41-42 using non-donor eggs in 2009 resulted in pregnancy and 12% resulted in live birth (CDC 2012a) In effect, ART use at advanced reproductive ages can be very costly when costs are measured per successful delivery or live birth (Sullivan et al. 2008) In Europe, ART use above age 40 depends in part on legislation regulating access to ART and its reimbursement (ESHRE 2008) Nevertheless, both number of ART cycles initiated to women aged 40+ and live births to these women
have had a rising tendency. Given low success rates of assisted reproduction at higher ages with fresh non-donor oocytes, the use of donor oocytes (OD) has become common among women of advanced reproductive ages. Remarkably stable success rates of ART using OD with age imply that this technique has also been used among women past the usual age of menopause (e.g., Grossman et al. 2012), shifting the limits of childbearing age and leading to a rapid rise in the number of births among women aged 50+, although from very low initial values (Sobotka et al. 2007, Billari et al. 2007, Salihu et al. 2003).

To illustrate the rising relevance of ART at late reproductive ages I review ART trends among women past age 40 in Spain and the United States. Comparability of these data across countries and over time is hindered by a number of factors: lack of comprehensive data collection and reporting, incomplete coverage of ART cycles and, yet more common, of ART pregnancies, live births and deliveries. Furthermore, age-specific data on ART treatments are often not published or different age categories are used in different countries and for different types of ART. Moreover, the data from the national registers are affected by reproductive tourism: they frequently also include women from other countries receiving treatment in national ART clinics, while they exclude treatments their residents receive abroad. Therefore, the data below should be taken as rough illustrations of general trends. In Spain, the number of ART treatments among women aged 40+ skyrocketed between 2002 and 2006, when the number of OD cycles exceeded the use of IVF/ICSI with non-donor fresh oocytes (Figure 3a) The total number of all registered treatments at high reproductive ages, including intrauterine insemination, more than doubled from 5.0 thousand in 2002 to 11.4 thousand in 2010 (this can be compared with 24.5 thousand births to women aged 40+) The estimated number of live births following ART treatment, adjusted for pregnancies that were lost to observation, more than tripled from about 850 in 2002 to around 2,900 in 2010; this fast rise reflects in part an increasing rate of deliveries per ART cycle, achieved especially by a higher use of donor oocytes (Figure 3b) When these numbers of ART births are related to all births among Spanish mothers aged 40 and older, ART turns out to have a sizeable contribution. One out of eight births and one out of five first births at advanced reproductive ages in Spain could be attributed to ART, especially to the use of donor oocytes (assuming that first births make up 60% of all ART births).
Figure 3a: Estimated number of ART cycles in Spain among women aged 40+

![Graph showing the estimated number of ART cycles in Spain among women aged 40+](image)

Figure 3b: Estimated number of births resulting from ART and the share of ART births on total and first births; Spanish mothers aged 40+

![Graph showing the estimated number of births resulting from ART and the share of ART births on total and first births](image)


Similar trends have been observed in the United States, where comparable time series of ART data are assembled by the Centers for Disease Control and Prevention (CDC 2012a) Between 1997 and 2009 the number of ART cycles using donor oocytes tripled to 17.7 thousand thousand, before falling in 2010, possibly as a part of a general slight decline in ART during economic recession. Donor oocytes in the U.S. are used predominantly at advanced reproductive ages when many women have no viable oocytes left. After age 45, ART-OD represents a large majority of ART cycles in the United
States (CDC 2012a, Figure 46) Table 1 compares ART use and ART live births in 1997 and 2009 in the United States at advanced reproductive ages (41 years and older except for donor oocytes where all cycles are included) Over this period, the overall number of ART cycles to women aged 41+ rose from 13.4 to 36.3 thousand and the estimated number of ART births in this category reached 9.3 thousand. This represented one out of nine births and three out of ten first births to women at ages above 40.

Figure 4: Number of ART cycles using donor oocytes in the United States, 1997-2010 (women of all ages)

<table>
<thead>
<tr>
<th>Year</th>
<th>Cycles &amp; treatments at ages 41+</th>
<th>Estimated live births resulting from ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVF + ICSI</td>
<td>6691</td>
<td>16090</td>
</tr>
<tr>
<td>Frozen embryos (FE)</td>
<td>774</td>
<td>2561</td>
</tr>
<tr>
<td>Donor oocytes (OD, all ages)</td>
<td>5980</td>
<td>17697</td>
</tr>
<tr>
<td>Total</td>
<td>13445</td>
<td>36348</td>
</tr>
</tbody>
</table>

| Estimated share on total live births at ages 41+ (%) | 8 | 11 |
| Estimated share on first births at ages 41+ (%) | 22 | 30 |

Note: Share of ART births on total first births at ages 41+ is estimated assuming that 60% of ART births at those ages are first births. Note that no separate statistics by age is published on the use of donor oocytes; therefore, all OD treatments are included in the table.
“Social Egg Freezing”: potential demand and use

Delayed childbearing implies considerable risk of infertility and involuntary childlessness (te Velde et al. 2012), which can only partly be offset by the IVF using non-donor oocytes (Leridon 2004; Habbema et al. 2009). In this context, oocyte cryopreservation appears to be a potential “win-win” strategy, which could expand women’s reproductive lives without presenting them with stark choices between ineffective natural reproduction, IVF/ICSI treatment with own oocytes, ART with donor oocytes, or adopting a child. Unlike biological reproduction and IVF treatment with non-donor oocytes, oocytes preserved early in life—ideally before age 30—and then used at advanced reproductive ages are likely to offer high success rates similar to those for donor oocytes. As of now, OC is still in an early phase to allow a serious analysis of its use. Rather, I estimate its hypothetical use under ideal conditions and then provide a critical appraisal of different forces that will limit its use and potential.

Under ideal (and purely hypothetical) conditions social OC would offer a smooth procedure with high success rates, would be widely available at little or no cost to the users (e.g., as a part of health insurance coverage), would raise few ethical objections, and would be widely accepted by the public. If such conditions are fulfilled, how many women should be “storing their eggs” for the future? How many women would eventually use IVF with their cryopreserved oocytes? This thought exercise allows estimating the potential limits of OC use. For that purpose, I work with the data on birth rates and ART treatments in Spain, which has progressed far in the transition to late parenthood and currently has, alongside Switzerland, the highest age at first birth globally (VID 2012, Schmidt et al. 2012).

First I estimate the potential IVF use with cryopreserved oocytes, assuming that all women who need to undergo assisted reproduction have enlisted in OC earlier in life. Next, I provide estimates of the number of women who might consider OC as a safety strategy because their plan to have children later in life puts them at a high risk of impaired fecundity. To estimate the potential of OC use I present a series of alternative scenarios based on different thresholds for its use, starting from the most restrictive definition (IVF with OC use replacing only the ART with donor oocytes among women past age 40) up to the widest definition, including all women considering
having first birth after age 35 or any birth after age 40 (Table 2) These different scenarios give a wide range of numerical estimates of the share of women who might chose OC and who might eventually use IVF with their preserved oocytes.¹

If all women planning to have a child later in life had “stored” their oocytes at younger ages, how many may actually use them for assisted reproduction? If we start from the narrowest and most obvious option—an IVF with women’s own cryopreserved oocytes replacing the use of donor oocytes at ages 40+—the share would amount to 0.7% in each birth cohort. If all ART treatments (including artificial insemination which also has a very low success rate at ages 40+) were replaced by IVF using OC, 1.4% women would make use of the procedure. If all childless women who ever try getting pregnant after age 40 would use it, their share would amount to 0.8-2.4%, depending on whether only those definitely sterile would turn to IVF, or also those with infertility or impaired fecundity. Including all women who are trying to get pregnant (also those who already have a child), the share would range from 2.7% to 3.7%. Finally, including also childless women aged 35-39 who are infertile or assuming that the trend of postponing childbearing will further continue provides the highest share of women who may eventually use IVF with OC, between 4.0% and 7.6% in each cohort.

¹ These scenarios combine diverse demographic and biomedical data. Birth rates and first birth rates by single years of age among women aged 35 and older are based on the data for Spain in 2010 (own computations from the data of INE 2012 and EUROSTAT 2011) Recent ART use by age and by ART method as well as the estimates of the number of ART births by age are computed from registered data for Spain in 2008 and adjusted for pregnancies lost to observation (computations based on Registro SEF report for 2008 and ESHRE 2012; see also Figures 3a and 3b) The estimated share of women intending to have children after ages 35 and 40 is estimated separately by parity and is based on Austrian data (the 2006 Microcensus survey analysed in Figure 1) The estimates of permanent sterility (inability to conceive) by single year of age are based on Leridon (2008, Table 2) Data on infertility and impaired fecundity (which includes difficulties in carrying pregnancy to term) by age (5-year age groups) are based on a sample of married childless US women surveyed in 2002-2006 in the National Survey of Family Growth (CDC 2012b) A number of additional assumptions have been applied in these scenarios, including the split of ART births into first births and higher-order births; 65% of ART births at ages 35-39 and 60% of ART births at ages 40+ are assumed to be
first births. Additional assumptions have also been made about the number of women ever undergoing ART treatment after age 40, as this figure cannot be directly estimated from the statistics on total treatments (ART cycles) or on the number of successful treatments (deliveries, live births) Further details about the OC use scenarios and the underlying data and assumptions can be provided by the author upon request.

To achieve any of these rates of IVF-OC use, women would first need to use the option of oocyte cryopreservation at younger ages. How many women might potentially consider using the technology? Again, I present a range of scenarios depending on whether this “hedging strategy” is used only by childless women or by all who plan to have a child, whether the age threshold is 35 or 40, and also depending on different estimates of pregnancy attempts and reproductive intentions later in life. When only childless women past age 40 are included, the potential demand for oocyte cryopreservation reaches from 2.4% to 4.5% with current age-specific first birth rates in Spain and 3.7%-7.5% if parenthood is further shifted to later ages. If all women attempting to become pregnant after age 40 are included, the potential demand for OC reaches between 7.8% and 11.6% with current birth rates and 11.7%-12.5% with additional shifts in childbearing age (“shifting age model” in Table 3) Finally, if also all women planning to become mothers after age 35 are included, the share of potential OC users skyrockets to 16.6%-22.8% in each cohort and 20.8%-28.2% if additional shifts in childbearing age take place.

Table 2: Percentage of women who would use IVF with own cryopreserved oocytes according to different scenarios.

<table>
<thead>
<tr>
<th>Model / assumption</th>
<th>Share of the female birth cohort (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Current pattern</td>
</tr>
<tr>
<td>1. Replacement of donor oocytes</td>
<td>0.67</td>
</tr>
<tr>
<td>2. Replacement of all other ART treatments after age 40</td>
<td>1.37</td>
</tr>
<tr>
<td>3. All women who intend to have a child and cannot conceive / carry pregnancy to term after age 39</td>
<td></td>
</tr>
<tr>
<td><strong>Childless women:</strong></td>
<td></td>
</tr>
<tr>
<td>Sterility model</td>
<td>0.83</td>
</tr>
<tr>
<td>Infertility model</td>
<td>1.12</td>
</tr>
<tr>
<td>Impaired fecundity model</td>
<td>2.37</td>
</tr>
<tr>
<td><strong>All women:</strong></td>
<td></td>
</tr>
<tr>
<td>Sterility model</td>
<td>2.68</td>
</tr>
<tr>
<td>Infertility model</td>
<td>3.66</td>
</tr>
<tr>
<td>Infertility model, including childless women after age 35</td>
<td>5.04</td>
</tr>
</tbody>
</table>
Table 3: Percentage of women who might consider oocyte cryopreservation as a back-up option (women potentially at risk of impaired fecundity due to postponed childbearing)

<table>
<thead>
<tr>
<th>Model / assumption</th>
<th>Share of the female birth cohort, in %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Current pattern</td>
</tr>
<tr>
<td>1. Childless women aiming to get pregnant after age 40</td>
<td>2.4-3.5</td>
</tr>
<tr>
<td></td>
<td>Intention-based model</td>
</tr>
<tr>
<td>2. All women aiming to get pregnant after age 40</td>
<td>7.8-8.3</td>
</tr>
<tr>
<td></td>
<td>Observed birth rates model</td>
</tr>
<tr>
<td></td>
<td>Intention-based model</td>
</tr>
<tr>
<td>3. Childless women aiming to get pregnant after age 35 and all women aiming to get pregnant after age 40</td>
<td>16.8-23.9</td>
</tr>
<tr>
<td></td>
<td>Observed birth rates model</td>
</tr>
</tbody>
</table>

Notes and data sources for tables 2 and 3: See footnote 1 for methods, assumptions and data sources.

The “real world”: forces that will limit the expansion of oocyte cryopreservation

The scenarios presented in the previous section are hypothetical estimates based on the assumption that all women fulfilling a given set of conditions would opt for an OC at younger ages or would later use IVF with OC when facing infertility at advanced reproductive ages. This exercise should be seen as mapping the potential use of the new technology (or, defining the potential set of “consumers”), while in reality a number of factors will limit the actual use of OC to considerably lower levels. At present, the OC is too recent to appreciate its risks, costs, effectiveness, acceptance, and advantages and this discussion will rather give an overview of different factors affecting its future use rather than a more precise quantitative estimate on the impact of each individual force.

Uncertainty about long-term success rates, potential pregnancy complications, and health risks for mother and child. While OC has been spreading rapidly in the last years and the number of births resulting from the transfer of cryopreserved oocytes has risen exponentially (Noyes et al. 2009), it will take another decade or so before sufficient amount of data accumulates to study long-term success rates of IVF-OC for long periods of time and identify all the potential pregnancy complications and health risks for...
mothers and their children. As IVF using OC is still in its “experimental” phase (although this has been debated, see Noyes et al. 2010), there are many reasons to be careful about embracing or recommending its use for social reasons (Dondorp and Wert 2009).

Costs. Choosing an OC and, eventually, using it in order to achieve pregnancy later in life is a costly strategy, involving payment for oocyte retrieval, regular payments for storing the oocytes and, eventually, also all the costs of IVF treatments. Cost assessment is tricky and two studies using widely different assumptions arrived at diverging cost estimates, putting a price tag of one live-born child after IVF-OC at 24,600 US Dollars (van Loendersloot et al. 2011) vs. 135,520 US Dollars (Hirshfeld-Cytron et al. 2012a; see also the discussion in Hirshfeld-Cytron et al. 2012b) The main difference between these studies was that the model users in Hirshfeld-Cytron et al. 2012a tried first to achieve natural conception before turning to IVF, while the model users in van Loendersloot et al. 2011 were first pursuing an IVF use, before eventually attempting to achieve natural pregnancy. The potential OC users should weight these high costs against the likelihood that they may achieve spontaneous pregnancy or that the ART use may not result in the delivery of live birth. The spread of OC will also depend on who will be paying most of the costs of OC for social reasons. If governments or health insurance companies were to subsidise the technology, the annual costs may reach hundreds of millions EUR in a country such as Spain.

Success not guaranteed. As is the case of any ART treatment, the success of OC is far from being guaranteed. Research so far suggests IVF-OC success rates comparable to IVF using fresh oocytes (Dondorp et al. 2012) Among older women, its success rate in terms of the number of live-birth deliveries per one IVF cycle might eventually approach success rates of ART with donor oocytes (there are not yet enough data to support this conjecture) In the model by van Loendersloot et al. 2011, IVF-OC users aged 40 achieve a cumulative live birth rate of 73.7% after four cycles of IVF with frozen and then thawed oocytes and another 10.7% through natural conception following unsuccessful IVF. Even this high success rate implies that one out of six women postponing childbearing until age 40 would never achieve live birth despite putting considerable effort (and money) into preserving their oocytes.
Stress surrounding OC and IVF. Oocyte retrieval and IVF treatments, especially when repeated or unsuccessful are stressful experiences, physically and psychologically taxing. Many women may prefer avoiding such experience.

Early decision necessary for successful outcome planned much later in life. To achieve highest success rate with IVF using oocyte cryopreservation the oocytes should be collected relatively early in life, preferably until age 30, as ART cycles performed with more mature oocytes display a gradual decline in success rates with age (e.g., CDC 2012a, Figure 47). This implies that women should make a decision to preserve their oocytes at an age when they are often uncertain about their reproductive plans or when their future plans seem to be too distant to act on them and commit considerable resources into OC. Many women will tend, in economic terminology, to “discount the future”, and to ignore the future threat of infertility and involuntary childlessness in a similar way as young smokers often ignore the abstract threat of getting cancer later in life. Moreover, many women are not well aware of the pace of age-related increase of infertility (Mac Dougall et al. 2012) Women may also not be able to envision their partnership, career and health later in life, risking that they will make use of their preserved oocytes if they face unforeseen and difficult life circumstances.

Acceptance. As any other advanced medical technology related to reproduction, oocyte cryopreservation may not be universally accepted for religious, ethical, cultural and other reasons, or simply because of fear of possible side effects or of trying an unfamiliar procedure. An online survey of Belgian respondents aged 21-40 found only a low proportion (3.1%) declaring they would consider freezing oocytes for social reasons, with a much higher share (28.4%) responding “maybe” and more than a half saying “no” (Stoop et al. 2011) This rather low acceptance may change, however, as the new OC technology matures, spreads, becomes more effective and more familiar to wider public.

Ethical concerns. A number of ethical concerns regarding OC for social reasons can be voiced. One is potentially unequal access. Due to high costs involved in OC, women with lower income and disadvantaged social background may not be able to cover the costs necessary for OC and, eventually, IVF using OC. Second are possible risks from
having children late in life. While using IVF with OC may limit some of the risks of late motherhood associated with natural reproduction or with the IVF using fresh non-donor oocytes, some risks remain and need to be better monitored. Older mothers are likely to have children with older fathers and higher paternal age (>40) has been associated with pregnancy complications and selected adverse outcomes in children (Sartorius and Nieschlag 2009). Very old parents (>50) may also have physical difficulties in coping with childrearing demands and risk experiencing poor health, cognitive decline and other age-related adverse outcomes well before their children reach adulthood. However, no consistent evidence exists on the adverse outcomes of very late parenthood on psychological and physical outcomes and wellbeing of children (e.g., Schmidt et al. 2012). Third concern pertains to the possible effect of OC on fuelling further postponement of childbearing and contributing to infertility and childlessness. Many women erroneously believe that ART is highly effective in giving women a chance of achieving pregnancy at late reproductive (or even post-reproductive) ages (Maheshwari et al. 2008, Wyndham et al. 2012). The same misperception may be stimulated by a spread of oocyte cryopreservation: many women will falsely believe that the new technology will allow them to have child at any age. This believe may lead to an additional shift in childbearing age, both among the women choosing OC as well as among other women not making an advantage of this new technology.

**Discussion and conclusions**

As the length of human life has continually expanded during the last century (Oeppen and Vaupel 2002) and many markers of the life course such as finishing studies, entering labour market, or starting a family have been delayed (Lee and Goldstein 2003), the boundaries of reproductive age, marked by menopause, remained remarkably stable. Many couples have to seek a careful balance between economic, cultural, and social rationale of having children later in life and a biological rationale of reproducing at younger ages. Remarkable percentage of childless women in their late 30s still intend to have a child later in life and many will not be able to achieve this goal via natural conception.

Will “social egg freezing” revolutionise assisted reproduction and blur the boundaries of reproductive span? Will eggsurance become a routine exercise and motherhood
beyond age 50 an accepted matter of choice, just another lifestyle on offer in the post-modern variety of living arrangements and family relations? Only the future will tell. For now, oocyte cryopreservation represents a rapidly evolving technology with considerable potential, but also many practical and ethical repercussions. It may soon move from an “experimental” stage to a fully recognised ART option (Noyes et al. 2010).

On the positive side, women and couples who are in difficult life situation or are not simply ready to have children in their thirties may choose a “safe strategy” of preserving their oocytes for a possible use later in life. This should give them some extra “breathing space” (Dondorp et al. 2012) This strategy is likely to yield high success rate and, for the first time, offer women at ages above 40 with impaired fecundity, a high chance of having a child of their own, rather than deciding between involuntary childlessness, ART use with donor oocytes, and an adoption. In addition, oocyte cryopreservation is less objectionable practice for the Catholic Church than embryo cryopreservation, which may lead to its faster adoption in some countries, especially when they enacted legal restrictions on embryo cryopreservation, as was the case in Italy (Noyes et al. 2010).

On the negative side, OC requires considerable resources, its long-term success rates and potential negative effects are still unknown, and there are many psychological and practical barriers to its use. Most of all, if oocyte cryopreservation is to become successful and relatively common, many women would have to make an important decision to “freeze and store their eggs” early in life, without knowing whether they will eventually make any use of their preserved oocytes at higher ages, whether they will still intend to have children, whether they will still be able to get naturally pregnant or will have to use IVF, or, indeed, if they turn to IVF use, whether it will help them achieving live birth. Therefore, OC is a long-term investment with uncertain outcome. It potentially provides a significant, but only partial protection against reproductive aging and involuntary childlessness.

This study has demonstrated that in light of the progressing postponement of parenthood to higher reproductive ages, OC has a considerable potential. Assisted reproduction already contributes significantly to the observed number of births and birth rates among women past age 40, despite low success rates of fresh non-donor IVF cycles or the need to give up the idea of “reproducing own genes” in the ART with donor oocytes. In vitro
fertilisation with cryopreserved oocytes appears to be a more effective option offering higher pregnancy rates achieved with non-donor oocytes. Therefore, it should soon start replacing some of these “traditional” ART methods among women at advanced reproductive ages. In the long-term, the potential share of women who may make use of IVF with cryopreserved oocytes has been estimated in the range of up to 5% (or even 7.6% if the postponement of childbearing further continues) and the share of women who may potentially consider oocyte cryopreservation ranged from 2.4% to 29.9%, depending on models, assumptions and data used. This is a potential demand, which will not be fully realised; nevertheless it points out at potentially huge and rapidly expanding opportunities for health professionals and IVF clinics offering OC. Tests of ovarian reserve will allow women to obtain individual assessment of their ovarian reserve which will in turn help them to make informed decision about OC, in part independently of their age. As the cryopreservation of oocytes spreads, more research should accumulate on its long-term risks and advantages. As soon as possible, proper monitoring of OC use, IVF-OC cycles and their outcomes should be established across Europe and in other countries in order to effectively evaluate this technology as it rapidly evolves. Also, a debate should ensue about most effective regulation of oocyte cryopreservation for non-medical reasons, especially with regard to its ethical aspects, age limits, access rules, and possible cost coverage for economically disadvantaged women.

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IS THERE A NEED FOR OOCYTE CRYOPRESERVATION: ATTITUDES AND INTENTIONS AMONG WOMEN

Jaime Knopman et al., published a case report in 2010 describing what they call ‘a novel model for egg donation’. The authors reported a pregnancy achieved at the age of 41 years, but with oocytes that have been harvested after ovarian stimulation at the age of 38 (Knopman et al., 2010) Some time after cryopreservation, the patient was confronted with infertility, which could not be overcome with intrauterine insemination or in-vitro fertilisation. The cryopreserved eggs served as an alternative for heterologous oocyte donation. The preventive freezing of oocytes enabled the patient to perform autologous oocyte donation.

The woman in this case report is far from the only one that might benefit from preventive egg freezing. We have been witnessing a trend to delay motherhood in all western countries and the phenomenon is also present in the emerging economies around the world. This evolution based on societal and economical changes unfortunately leads to an increase of age related infertility.

The introduction of efficient oocyte cryopreservation in the last decade made autologous oocyte donation an alternative for the classical fresh oocyte donation. This new approach requires the women to take action before she is being confronted with infertility. Therefore, it should be performed in women that are considered at risk for age related infertility. However, few are really sure whether they will need the frozen eggs or whether it will help them in case they do have to rely on them. Therefore, the question discussed here is what do young women think about this option and would they consider doing it.

A survey among young women

We performed an electronic survey aimed at evaluating the opinion of women between 20 and 40 years with regard to social egg freezing. The questionnaire was completed by 1049 women with representation of all social classes and geographic locations within Belgium. 3.1% answered ‘yes’ as to the question whether they would consider freezing their oocytes in the future, another 28.4% answered ‘maybe’. These potential freezers are more likely to be younger and not married. We did not observe a
difference in awareness with regard to age related infertility between those interested in freezing and those who are not. Another interesting finding is that the women that would potentially consider freezing oocytes are more open to the idea to donate oocytes. Egg donation programs, often short of oocyte donors, could therefore use the already available oocyte pool when the social freezers no longer need them.

**What would make women more likely to freeze?**
The main concern among potential social oocyte freezers (75.2%) is the effect that such treatment may have on their future fertility. We have therefore examined the effect of ovarian stimulation and oocyte retrieval on the reproductive outcome in oocyte donors (Stoop et al., 2012a). This study suggests it does not affect the short-term reproductive health. The second and third most important concern is the health safety of the children (70.9%) and the financial cost of the treatment (65.9%). Obviously, there is debate on whether or not such treatment is cost effective. A recent study suggests that social freezing is more cost effective compared to IVF, but only if a significant proportion of the women return to collect their oocytes at a substantial additional cost. (van Loedersloot et al., 2011) Another relevant question is who should pay for the treatment (Mertens and Pennings, 2012).

**Guarantees for success**
The fourth concern among women that are open to the idea to freeze oocytes is the guarantee for success. The individual chance for an oocyte retrieved after ovarian stimulation to ultimately result in a live birth is relatively low. A recent study calculated that 23 eggs are needed on average per child in women up to 37 years of age (Stoop et al., 2012b). This means that the individual chance of an oocyte is 4 to 5%. Women of a more advanced age see their chances drop spectacularly. Unfortunately, many of the women that visit fertility centres for elective oocyte cryopreservation are actually too late to safeguard their fertility (Gold et al., 2006; Nekkebroeck et al., 2010). Many of these women do however proceed with the treatment as they realise that doing nothing gives them even less chances for a genetically own child.

**Conclusion**
There is definitely a need for elective oocyte cryopreservation. Many women
are currently performing the procedure and many will probably do so in the future. The general trend to delay motherhood and the risk of age related infertility are here to stay. One of the main challenges is the cost of the treatment, as women need multiple treatment cycles. Secondly is it important that candidate social freezers are aware that at some point they turn even too old to freeze.

References


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IS THERE A NEED FOR OOCYTE CRYOPRESERVATION: THE PSYCHOLOGICAL VIEWPOINT

Increasingly more and more women and men are delaying parenthood until their thirties and forties (Sobotka, 2004). Reasons for delay are mostly social (e.g., education, career development, achieving a higher standard of living) and relational (e.g., lack of a suitable partner) (Mills et al., 2011). Delaying parenthood can result in unintentional childlessness due to the fact that female fertility declines with age. For instance, in the UK, 44% of women who reported an intention to have children remained childless six years later, when reaching the end of their reproductive years (i.e., at 35–39 years) (Berrington, 2004).

Fertility preservation through oocyte cryopreservation may be an effective choice for women to avoid age-related subfertility and the subsequent unintentional childlessness. As such, oocyte cryopreservation is yet another technique to add to the already existing vast list of contraceptive (e.g., the pill) and reproductive (e.g., in vitro fertilization) technologies that started to become available since the 1960s and that allow women to control their own reproduction. And as the previous techniques, oocyte cryopreservation may become widely used. Research shows that currently at least around one in three childless women in their twenties or thirties would consider freezing their oocytes so that they could have children in the future (Stoop et al., 2011, Proudfoot et al., 2009, Gorthi et al., 2010). While oocyte cryopreservation represents a potential solution for these women, it should be ensured that women have the full necessary information and decisional support to make such complex and future orientated decisions (ESHRE Task force on Ethics and Law, 2012).

Present research shows that this is not the case and that, in fact, most women lack fertility knowledge and vastly overestimate the success of assisted reproductive technologies. For instance, in a study with 3345 Canadian women between the ages of 20 and 50, 57% of these women believed that, for women over 30 years old, overall health and fitness level is a better indicator of fertility than age, and 65% that prior to menopause the Assisted Reproductive Technologies (ART) can help most women to have a baby using their own eggs (Daniluk et al., 2012). However, the success rates per cycle of ART are 27% up to 29 years of age, 26% between 30 and 34, 19% between 35 and 39 and 6.4% between 40 and 44 (e.g., Wang et al., 2008).
Almost nothing is known about women’s perception of oocyte cryopreservation and their motivations to use it. In the Canadian sample (Daniluk et al., 2012), 52% of women believed that oocyte cryopreservation can prolong a woman’s fertility. A study with 1049 Belgian women (Stoop et al., 2011) showed that, when compared with non-users of oocyte cryopreservation, potential users were more likely to be in their twenties, not married and childless. Facilitators of oocyte cryopreservation usage were having more information about the risks that oocyte cryopreservation implied to the women and the health of the child. In addition, this study also showed that awareness of the relationship between age and fertility was not related with these women’s intentions to use oocyte cryopreservation (Stoop et al., 2011). This is a worrisome fact, as results from a qualitative study suggest that the average age of those women who actually opt for egg freezing is around 38 (Gold et al., 2006). Although this is very preliminary data with a small sample of 20 women, it does suggest that the use of oocyte cryopreservation may be linked with delays in parenthood beyond the age of 40. These and other studies (e.g., Bunting and Boivin, 2008, Maheshwari et al., 2008) indicate significant gaps of knowledge upon which many women may be basing their decisions to delay parenthood.

Opting for oocyte cryopreservation may simply be seen as an option for women to safeguard their fertility, but it is probable that it may implicitly contain a marked motivation for parenthood delay. This, however, is a much more complex decision with broader implication than the simple oocyte cryopreservation. Counseling for fertility preservations due to social factors should thus include (beyond the medical and financial issues of oocyte cryopreservation) the implications of using oocyte cryopreservation as a mean to postpone parenthood and the burden of undergoing ART treatment.

Indeed, the effects of delayed parenthood go much further than its impact on the women’s fertility. From a medical perspective, older mothers have considerably more problems during gestation and delivery, have a higher risk of birth defects and have more complications after delivery, all resulting in higher morbidity and healthcare costs. From a psychosocial perspective, delayed parenthood reduces the chance that both parents will survive until their children reach adulthood, marry or become parents themselves and it increases the likelihood of the need to provide care to both child and parents. On the other hand,
delayed parenthood is associated with a more stable family environment, higher socio-economic position, higher income and better living conditions, as well as better parenting practices (see Schmidt et al., 2012 for a review of the consequences of parenthood delay).

Finally, women need to understand that oocyte cryopreservation later implies using ART to conceive. Although hormonal stimulation is not needed at this point, women may still experience significant distress associated with the uncertainties of treatment success (Boivin et al., 1998) and depressive symptoms after failure (Verhaak et al., 2007).

In conclusion, oocyte cryopreservation is yet another technique that offers women increased control over their reproductive decisions. It is as (nor more, nor less) needed as the previously existing techniques. However, it should be noted that such increased reproductive control (some would label freedom) cannot be dissociated from the current reproductive trend of delayed parenthood and its multiple clinical, demographic and psychosocial implications. The question arises of how to help women achieving parenthood at an optimal age from both a medical, social and psychological perspective. Oocyte cryopreservation may be another helpful option for the effect, but it is essential that it is framed within a broader educational approach to increase fertility awareness and informed childbearing decisions.

References


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OOCYTE CRYOPRESERVATION: WHAT ARE THE EVIDENCES?
Recent studies suggest that oocyte vitrification significantly improves oocyte survival, embryo development and pregnancy rates compared to slow freezing procedure (Oktay et al., 2006, Gook et al., 2007, Smith et al., 2010) The most efficient and reproducible protocol being today the “minimum volume open system approach”, in which oocytes are directly exposed to liquid nitrogen in a very small volume to maximize ultra-rapid cooling and minimize ice crystal formation. However, there is a theoretical concern regarding such direct contact, that potentially exposes oocytes to infectious organisms present in the liquid nitrogen (although infectious transmission has never been observed in ART) To avoid this theoretical cross-contamination, methods have been developed to sterilize liquid nitrogen by microfiltration or ultraviolet irradiation (Parmegiani et al., 2011) Closed systems approaches have also been suggested for oocyte vitrification (Stoop et al., 2012), but it is not clear whether they are associated with equivalent reproducibility and success rates. Cryopreservation protocols involve removing cumulus cells from oocytes in order to assess oocyte maturity, and maximize cryoprotectants penetration (Minasi et al., 2012) Intracytoplasmic sperm injection is thus used to fertilize vitrified oocytes.

To evaluate the success rate of oocytes vitrification different randomized controlled trials comparing outcomes with vitrified and fresh oocytes in ICSI cycles have been conducted (Cobo et al., 2008; 2010; Rienzi et al., 2010, Parmegiani et al., 2011) All these studies have used a similar minimum volume open system protocol. Overall, oocyte survival after vitrification and warming was >90%, fertilization rate was similar to the one obtained with fresh oocytes, and implantation rates ranged between 17%-41%. These studies and a recent meta-analysis (Cobo et al., 2011) suggest that the reproductive outcome of vitrified/warmed and fresh oocytes are similar.

The impact of important factors such as maternal age, ovarian reserve and embryo quality on cryopreservation success rate should also be considered. A longitudinal cohort multicentre study to assess the efficacy and reproducibility of oocyte cryopreservation, as well as the effect of patient and cycle characteristics on the delivery rate has been conducted (Rienzi et al., 2012) The study included 486 cycles performed in 450 couples, in which 2721 oocytes were warmed and 2304 survived (84.7%) Of the 2182 oocytes
inseminated by ICSI, the fertilization and developmental rates to top-quality embryos were 75.2 and 48.1%, respectively. There was a total of 128 deliveries (26.3% per cycle and 29.4% per transfer) in 450 patients (28.4%), with 147 liveborn babies from 929 embryos transferred (15.8%). The number of oocytes vitrified was correlated with outcome, with a higher delivery when >8 oocytes were vitrified (22.6 versus 46.4%). Furthermore, when fewer oocytes were available in women aged >38 years, the delivery rate was dramatically reduced (12.6 versus 27.5%). Conversely, when >8 oocytes are available, blastocyst culture represents the most efficient policy (62.1% delivery rate; data from one centre only). These results demonstrate the reproducibility of oocyte vitrification and should be of value when counselling patients for fertility preservation.

However, it is important to recognize that success rates may not be generalizable, and clinic-specific success rates should be used to counsel patients. As suggested in the Alpha consensus document about cryopreservation (Alpha scientists, RBM online, 2012) it is important to remind that benchmarks for clinical outcomes (i.e. pregnancy, implantation, miscarriage and birth rates) are subject to variables associated with clinical practice. Thus, to evaluate the post-thaw development and implantation of cryopreserved oocytes, the outcomes from equivalent fresh oocytes/embryos within the individual clinic are a crucial reference point.

Limited number of established pregnancies and deliveries derived from cryopreserved oocytes are reported in the literature. However, perinatal outcome data are reassuring. A review of over 900 live births derived from cryopreserved oocytes, suggests that there is no increased risk of congenital anomalies compared to the general population (Noyes et al., 2009). Moreover, the incidence of chromosomal abnormalities in human embryos obtained from cryopreserved oocytes is no different from that of control embryos (Cobo et al., 2001). Long-term data on developmental outcomes are lacking. In conclusion, there is good evidence that excellent fertilization and pregnancy rates can be obtained with vitrified/warmed oocytes (similar to those obtained with fresh oocyte in expert centres). Although data are limited, no increase in chromosomal abnormalities, birth defects, and developmental deficits has been reported in the offspring born from cryopreserved oocytes. As recently stated by “The Practice
Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology” the evidence indicates that oocyte vitrification and warming should no longer be considered experimental (ASRM pages, in press)

References


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EXPANDING REPRODUCTIVE LIFESPAN: A COST-EFFECTIVENESS STUDY ON OOCYTE FREEZING


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;

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 €7,798. 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 (UNICEF, 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).

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; Khamsi, 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 childbearing 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 I. 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., 2000) We therefore

<table>
<thead>
<tr>
<th>Table 1 Probabilities used as input variables for decision model.</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Spontaneous pregnancy</td>
</tr>
<tr>
<td>Clinical pregnancy rate per year, at age (%)</td>
</tr>
<tr>
<td>40</td>
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<tr>
<td>41</td>
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<td>42</td>
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<tr>
<td>43</td>
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<tr>
<td>44</td>
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<tr>
<td>Miscarriage rate per clinical pregnancy, at age (%)</td>
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<tr>
<td>40</td>
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<tr>
<td>41</td>
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<tr>
<td>42</td>
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<td>43</td>
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<tr>
<td>44</td>
</tr>
<tr>
<td>Oocyte freezing at age 35 (%)</td>
</tr>
<tr>
<td>Clinical pregnancy rate per year</td>
</tr>
<tr>
<td>Miscarriage rate per clinical pregnancy</td>
</tr>
<tr>
<td>IVF at age 41 (%)</td>
</tr>
<tr>
<td>Clinical pregnancy rate per year after 3 cycles</td>
</tr>
<tr>
<td>Miscarriage rate per clinical pregnancy</td>
</tr>
</tbody>
</table>
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 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

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**Table II Costs used as input variables for decision model.**

<table>
<thead>
<tr>
<th>Costs</th>
<th>Source</th>
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</thead>
<tbody>
<tr>
<td>Costs per IVF cycle</td>
<td>Merkus (2006)</td>
</tr>
<tr>
<td>Costs for oocyte freezing (3 cycles)</td>
<td>Merkus (2006)</td>
</tr>
<tr>
<td>Costs for oocyte storage/year</td>
<td>Institutional costs</td>
</tr>
<tr>
<td>Costs for embryo transfer/cycle</td>
<td>Institutional costs</td>
</tr>
<tr>
<td>Costs per miscarriage</td>
<td>Graziosi et al. (2005)</td>
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consequences of each parameter on the results of the study. All parameters are listed in Supplementary data, Table SI.

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

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cumulative live birth rate (%)</th>
<th>Cumulative live birth rate discounted (%)</th>
<th>Miscarriage rate (%)</th>
<th>Costs per strategy (€)</th>
<th>Cost per strategy discounted (€)</th>
<th>Cost per live birth (€)</th>
<th>Cost per live birth discounted (€)</th>
<th>ICER (€)</th>
<th>ICER discounted (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy 1</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Freeze oocytes at age 35, IVF with frozen oocytes at age 40</td>
<td>84.2</td>
<td>84.5</td>
<td>26.8</td>
<td>10 195</td>
<td>10 419</td>
<td>12 111</td>
<td>12 326</td>
<td>19 524</td>
<td>13 156</td>
</tr>
<tr>
<td>Strategy 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural conception (no additional treatment)</td>
<td>51.2</td>
<td>52.3</td>
<td>35.9</td>
<td>266</td>
<td>310</td>
<td>519</td>
<td>593</td>
<td>47 874</td>
<td>60 717</td>
</tr>
<tr>
<td>Reference strategy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women age 40, IVF after 1 year of subfertility</td>
<td>63.5</td>
<td>64.6</td>
<td>41.1</td>
<td>61 54</td>
<td>7798</td>
<td>9694</td>
<td>12 071</td>
<td></td>
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</tr>
</tbody>
</table>
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 €7,798 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 €5,058 or the IVF costs are €4,475, 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.

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).

![Image](image.png)

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

<table>
<thead>
<tr>
<th>Table IV</th>
<th>The results of the probabilistic sensitivity analysis (Monte Carlo simulation).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean costs per strategy (€), mean (95% CI)</td>
</tr>
<tr>
<td>Strategy 1</td>
<td>Freezing oocytes at age 35, IVF with frozen oocytes at age 40</td>
</tr>
<tr>
<td>Strategy 2</td>
<td>Natural conception (no additional treatment)</td>
</tr>
<tr>
<td>Reference strategy</td>
<td>Women age 40, IVF after 1 year of subfertility</td>
</tr>
</tbody>
</table>
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 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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IS OOCYTE CRYOPRESERVATION FOR SOCIAL REASONS ETHICALLY DEFENDABLE? AGAINST

The sociological trends that encourage women to pursue higher education and enter the workforce in significant ways combined with the inflexibility of the industrialized countries workplace, tacitly encourage women to push the boundaries of their fertility. As a result, increasing numbers find themselves over age 35 and confronting fertility challenges. Over the last 20 years, major advances in assisted reproductive technologies have markedly improved the success rates. In addition, development and recent improvements in oocyte cryopreservation have offered women the possibility of greater control of their reproductive future by potentially extending their fertility. Indeed, a growing number of women who either desire or foresee delaying their childbearing years may consider the social egg freezing. Despite its advantages, this strategy raises some social, ethical, medical, psychological and political questions that are still unresolved. The present article summarizes some of the main arguments against the development of a routine program of social egg freezing.

Sociological implications

Oocyte cryopreservation offers women the potential to extend their biological time clock and delay childbearing for social or career reasons. Actually, the development of social egg freezing programs has socio-political consequences. Indeed, it may encourage women to delay marriage and increase the number of older parents, therefore modifying the demographic characteristics of industrialized countries. The process of egg freezing implies the administration of high doses of exogenous gonadotropins followed by oocyte retrieval and cryopreservation. Despite recent improvements in cryopreservation techniques, it is possible that oocyte may not survive the thawing procedure. Further, failure in fertilization of frozen-thawed oocytes may also occur. Finally, embryos transferred into the uterus may fail to implant or/and develop. It is therefore important for women to understand that having eggs frozen, even before they are 35 years of age does not guarantee successful pregnancy and live birth. Currently, a woman’s best chance of having a child is still through timely and natural conception. The possibility of freezing eggs for lifestyle reasons will possibly conduct women to make important life decisions based on false assumptions that their fertility
is safeguarded that wind up limiting their ability to become a mother in the future. Another key issue is the possible occurrence of natural conception in many patients having cryopreserved eggs, leading to an accumulation of unused frozen oocytes. Apart from the cost of freezing, the outcome of these eggs will be a major concern.

**Safety**

Social egg freezing requires medical procedures to be performed on healthy women. The maternal risks associated with egg freezing for non-medical reasons are twofold. Primo, collecting eggs for cryopreservation requires the use of controlled ovarian hyperstimulation followed by transvaginal ovarian puncture. Although long-term risks of exposure to high doses of exogenous gonadotropins appear minimal, there remains a dearth of research. However, it is noteworthy that some serious complications may be associated with FSH administration, in particular ovarian hyperstimulation syndrome, which could be life threatening in severe cases. In addition, intraperitoneal bleeding, ovarian torsion, ruptured ovarian cyst and infection may also occur in rare cases. Secondo, becoming pregnant in one’s 40’s carries with it a higher chance of complications, including developing preeclampsia, diabetes, chronic hypertension and cardiac diseases.

At present, oocyte cryopreservation is still an experimental procedure, but this classification is increasingly contested. Recent data are very encouraging, both concerning the health of the resulting offspring (especially for vitrification), oocyte survival after freezing and thawing and the subsequent success rates which are comparable to those of fresh oocytes. Long-term follow-up data on children born from vitrified oocytes are not yet available due to the novelty of the technique and thus the possibility remains that oocyte freezing may affect the long-term health of the offspring. However, while it is currently uncertain whether such risks are involved in oocyte cryopreservation, they are certain to exist in aged oocytes. Thus, definitive conclusions regarding either the efficacy or the safety of this procedure cannot be drawn at present. The most relevant difference between ‘medical IVF’ and ‘social IVF’ would be that if there was an increased risk of disease in the offspring, this might be acceptable in medical IVF, since IVF would the ‘only’ way to have children of one’s own, though it would be less acceptable in social IVF, since fertile couples could have a child in the usual way at an earlier time.
**Age**

The reproductive aging process is thought to be dominated by a gradual decrease in both the quantity and the quality of the oocytes residing within the follicles present in the ovarian cortex. It is currently established that the rate of oocyte decline follows a biphasic pattern, with a distinct acceleration at about age 38 years as women age toward the menopause. Therefore the potential of fertility may be altered after the age of 35 years, both naturally and after assisted reproductive technologies. Although it is well established that oocyte cryopreservation should be performed before 35 years. Some fertility clinics offer this procedure beyond this age limit, which is ethically questionable. In addition, questions regarding the limit of age to use these oocytes remain represent another issue. Moreover, patients seeking conception between 38 and 45 years after having previously cryopreserved eggs at younger age, will have to deal with the question of a natural conception with possible diminished quality eggs, leading to potential increased miscarriage and aneuploidy rates, or a conception through IVF/ICSI using frozen-thawed oocytes.

**Psychological risks**

Cryopreservation of oocytes for lifestyle reasons may be associated with many psychological concerns. The opportunity to postpone motherhood may lead to a generation disruption. In addition, the possibility that frozen oocyte may survive the patient can also be perceived as a life insurance, a denial of death. Women having their eggs frozen may feel all-powerful, with the ability to control time. What does women project into egg cryopreservation is also an important issue. The development of social egg freezing programs at a large scale may induce in women a feeling of pressure to prophylactically store their oocytes. Although patients had been informed on the absence of guarantee offered by oocyte cryopreservation at the time of the initiation of the procedure, they may feel disappointed in case of failure after thawing.

**Cost**

At present, the cost of a procedure of egg freezing tends to run between $12,000 – $20,000 per cycle. In addition, women are likely to require several cycles to have the suggested, but actually unknown, number of eggs frozen to optimize the
chance of success. Furthermore, although the storage costs for the cryopreserved oocytes are often included for the first year, several hundred dollars per year have to be added. Egg freezing for social reasons is currently not covered by insurance.

The question of who should pay for social egg freezing remains a major concern, in particular in countries in which infertility treatments are usually covered by health care. Unlikely, most women will ever need to use their frozen eggs, yet accrue the cost of freezing.

**Political issue**

On a political standpoint, offering women the opportunity to freeze their eggs and delay motherhood until their 40’s, will enable them to compete in a professional environment designed by and for men. However, changing the climate of industrialized countries workplace will require more women in positions of power and influence and that is still a long way off. Routine social egg freezing may allow society to ignore problems in workplace that lead to women having babies later in life and not address the need for societal support for working mothers.

Social egg freezing may also be associated with potential manipulative and dishonest marketing. Indeed, private cryobanks have a financial benefit in informing women about a decline in their fertility with age and about the option of oocyte cryopreservation as more ‘customers’ will generate more revenue. Many fertility clinics’ websites offer correct information and are upfront about what their potential customers can expect. However, in some cases commercial interests can also taint the information that is conveyed and lead to an overly optimistic representation of social freezing. Even the use of terms such as ‘fertility preservation’ may create the impression that, by freezing oocytes, a status quo is offered as far as a woman’s reproductive options are concerned.

An important concern is the possible commercialization of the fertility field, especially before randomized and long-term studies offer solid data on efficacy and safety for both women and children created.
Conclusions

Given the increased efficiency of oocyte freezing by vitrification and given the reassuring data on the health of resulting offspring, the possibility for women to store their oocytes theoretically expands their reproductive options and allows them to overcome the increasing gap between the optimal age to reproduce from a gynecological point of view and the optimal age to reproduce from a socioeconomic point of view. However, there is not enough accumulated data for women to make truly informed judgments and derive conclusions as to whether this technique can meet their needs and expectations. As it stands now, oocyte cryopreservation offers a possibility, not a guarantee. Women should aware that the best chance of having a baby still remains doing it naturally, before the age of 35. In addition, sociological, psychological and political questions should be discussed before offering a routinely program of egg freezing for lifestyle reasons.
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IS OOCYTE CRYOPRESERVATION FOR SOCIAL REASONS ETHICALLY DEFENDABLE? IN FAVOUR

Introduction

Vitrification of oocytes has lead to major changes in the perception of oocyte freezing. Soon after the introduction, the debate started on the possible use of this technology for healthy women. Very soon, clinics all over the world offered fertility preservation to women who feared not to be in the right circumstances to build a family before their fertility will have dropped below the threshold. People’s fantasies about future scenarios went wild. All kinds of concerns were raised against these applications: it would encourage women to further postpone their pregnancies, it would be inappropriate use of medical technology, etc. We will look at these objections in more detail to see whether they stand scrutiny.

Discussion

Medical techniques have been applied for non-medical applications for ages. However, the distinction between medical and non-medical applications has never been clear-cut. Moreover, analysis of the use of the label reveals that the concept ‘medical’ is used as a normative concept: it sanctions the use of a technique for certain problems and it justifies reimbursement from public funds. The principle behind this is that desires, contrary to needs, are a matter of personal choice and autonomy and thus elective treatment. However, a strong argument can be made to extend coverage to social freezing in countries with publicly funded IVF on the basis of justice considerations (Mertes & Pennings, 2012).

A key question is whether medical technology (fertility preservation) should be used to cure a health problem (infertility) that is caused by individual behaviour (postponed parenthood) that in turn is strongly determined by the social and cultural context (career, education, value changes …) An analogy can be made with other medical interventions that are employed in similar circumstances (e.g., gastric bypasses for morbidly obese persons) Some people argue that one should alter the social and cultural context so that women can have and want to have their children earlier. Even if we believe that this is the way forward, this does not tell us what we should do in the meantime. Moreover, the main determining factors for postponement may be difficult to change...
(such as the desire of women and men to enjoy other things in life before starting a family) or change may be undesirable (such as higher education for women). This point shows that a real danger of adapting policies to ‘allow’ women to have their child earlier is that progress made in the last decades to improve the general position of women in society is reversed. Having your child when you are young may put women back into the kitchen. Although social freezing is clearly neither the ideal, nor the only solution, it is surely a solution worth looking into. Autonomy is a strong argument to allow women to decide for themselves whether the chance of having genetically related children in the future is worth the effort of the medical intervention. In addition, postponement may well be in the best interest of the future children.

Although the opponents of social freezing argue that age is not a disease, treatment of age-related infertility is considered fully acceptable. It is also remarkable that an argument against social freezing, namely that it will lead to an unacceptable increase in health care costs, is rarely given the same weight when older women are considered. It is important that the cost argument is not taken for granted without research. A number of studies have been performed (with hugely different results) to determine cost effectiveness (Van Loenderschoot et al., 2011; Hirshfeld-Cytron et al., 2012). The discrepancies in results could be attributed to different cost estimates and different probabilities of success. Whatever the final result, this argument should be based on empirical evidence and well-argued points of comparison.

An interesting exercise of prospective ethics is to work out the (unlikely?) scenario of a large scale uptake of this option. What will be done with the oocytes if they are not requested by the progenitors for their own reproduction? There are at least two other options: donation to others or donation to science. This raises several ethical questions, including the question of reimbursement of the original stimulation cycle (Mertes, Pennings, Dondorp & De Wert, 2012). In order to find an answer to this question, an analogy can be made with either oocyte donation as such or with donation of supernumerary embryos.

**Conclusion**

Fertility preservation for non-medical reasons is a highly complex issue that touches
upon general views on the appropriate use of medicine, beliefs about motherhood and women’s role in society, long-term consequences for society etc. The blunt rejection of these applications that dominates the present discussion in Europe is too simplistic. We need stronger arguments than those offered at the moment to made a convincing case for a prohibition of egg freezing for social reasons.

**References**


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PRESERVATION OF FERTILITY WITHOUT MEDICAL INDICATION

Female reproductive issues often have ethical implications. For example, such medical procedures as uterine subrogation and oocyte donation can provide no immediate health benefit, but they do involve health risks.

A recent example involves the possibility of using oocyte vitrification to preserve fertility at ages when the oocytes may be of better quality than at the desired time of pregnancy.

While oocyte vitrification is highly regarded in patients with cancer, the procedure has been met with resistance in healthy patients for several reasons:

- Oocyte cryopreservation is an experimental technique that involves the medicalisation of reproduction; there are no guarantees that the procedure will be successful, and the risks increase with maternal age.

- There are emotional objections to oocyte vitrification related to the representation of healthy women as career-focused and victims of a sexist society.

The recent appearance and increased demand for fertility preservation, often for personal, professional, and social reasons, has led the scientific community to address the topic of oocyte vitrification. The procedure involves women with or without partners who wish to postpone reproduction until their situation makes conception more favourable.

The first ethical implication of the procedure is that the ovarian reserve is finite and has an expiration date. If this were not the case, gamete preservation would be unnecessary. Sociocultural changes in our society have led to increases in life expectancy and changes in gestational age.

According to the National Institute of Statistics, in 1986, women tended to give birth to their first child between the ages of 20 and 24. By 2006, women having their first child were most often between the ages of 30 and 34. In 1996, only
2% of couples had their children between 34 and 39 years of age; in 2006, there were 10 times more women who had their children during this age range.

On the contrary, several studies have reported a decline in fertility that begins at the age of approximately 35 years. Variation in these data may be related to genes, follicular endowment at the time of birth, or environmental and toxic factors that women are exposed to throughout their lives. With sufficiently verified methods, they may be options for preventing age-related fertility decline. However, regulation or consensus is necessary before these methods can be utilised.

The Spanish Fertility Society (Sociedad Española de Fertilidad-SEF) should use health education to promote individual, family, and social interests related to reproductive health. Thus, the SEF should educate individuals regarding the consequences of conception delay.

**Age limits in women**

The law permits egg donation in women who are up to 35 years old (Royal Decree 412/1996, Chapter I, Article 2, Point 1), which is based on data showing a decrease in fertility at age 35. Thus, “fertility preservation is advised when an adequate oocyte reserve still exists, which is generally before age 35-38 years and preferably between 30 and 35 years of age.”

The decision to preserve fertility at older ages is evaluated by the physician. Physicians inform their patients who pregnancy rates are directly related to age, oocyte reserve (OR) at the time of consultation, and individual variation. The following is an approximation of the pregnancy rate by age:

<table>
<thead>
<tr>
<th>AGE</th>
<th>PREGNANCY RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>7.7 %</td>
</tr>
<tr>
<td>43</td>
<td>5.4 %</td>
</tr>
<tr>
<td>44</td>
<td>1.9 %</td>
</tr>
<tr>
<td>45</td>
<td>0 %</td>
</tr>
</tbody>
</table>
Techniques for fertility preservation without medical indication

Oocyte freezing (vitrification)

Oocyte freezing relies on pharmacological ovarian stimulation to induce multiple follicular development and oocyte maturation. Gametes are subsequently extracted through ovarian aspiration and cryopreserved. The primary risks associated with the procedure affect the patient and the integrity and quality of the gametes. The risks for patients are associated with undergoing anaesthesia and follicular puncture.

The risks for gametes, which can limit the efficacy of their reproductive use, are derived from the damage that can occur during the freezing and thawing processes. The promising results that have been obtained with oocyte vitrification present a new perspective regarding their use. Vitrification is the process of cryopreservation that relies on high concentrations of cryoprotectant to solidify cells without causing ice crystals to form in their interior. The post-thawing survival rate, fertilisation rate, and later embryonic development are similar to those of fresh oocytes. However, the number of gestations and newborns is still insufficient to evaluate whether the procedure is associated with any specific risks. Certain potential risks may be derived from an osmotic stress effect that is created by the cryoprotectant or from direct exposure of the cryoprotectant to liquid nitrogen. Furthermore, nonsterile environments can lead to viral contamination.

Article 11.2 of Law 14/2006 refers to assisted human reproduction techniques. The law states that the use of oocytes and cryo-conserved ovarian tissue requires authorisation by the corresponding health authority.

In conjunction with the National Commission on Assisted Human Reproduction, which considers there to be sufficient scientific evidence for the safety of oocyte vitrification, the autonomous communities grant general reproduction authorisations (non-specific) to perform these techniques. Facilities must be formally trained and accredited and must comply with certain requirements (e.g., consent forms, describing the technical procedures to the patient).

The possibility that women will freeze their oocytes to postpone their maternity for personal convenience is not addressed in the assisted reproduction law. While the law does not
expressly assume that women will use the procedure to preserve fertility before a surgical or chemotherapeutic treatment, there is a difference between using the procedure for personal convenience and using the procedure to address a medical problem.

However, a woman’s choice to secure quality oocytes to delay her maternity is understandable from a personal point of view and can serve other interests, such as professional interests or a desire to be independent or establish other priorities. These interests are respectable, but they are not pathological. In this sense, women should be reminded of the need for assisted reproduction techniques for medical indications (Article 1).

The Sexual and Reproductive Health and Voluntary Interruption of Pregnancy Law (Organic Law 2/2010) supports a wide conception of reproductive health, and sociocultural factors are explicitly considered in the language: “Everyone has the right to freely adopt decisions affecting their sexual and reproductive life without limitations other than respecting the rights of others and the public order guaranteed by the Constitution and the law” (Article 3).

In any case, reproductive rights are controversial, so clinics must meet a minimal set of conditions, such as approval from the National Commission on Assisted Human Reproduction.

**Embryonic freezing**

Another procedure that has demonstrated efficacy and safety is the cryopreservation of embryos from the patient’s oocytes. The fundamental limitation of this alternative is the need for male gametes.

When considering the possibility of preserving gametes, preserving embryos with embryonic freezing does not seem reasonable. Therefore, embryonic freezing should not be used for the preservation of fertility without a medical indication.

Law 14/2006 on assisted human reproduction expressly considers that the techniques may be used by married couples (heterosexuals and female homosexuals), couples (heterosexual), and single women (Articles 6 and 8). Consequently, individuals requesting the technique must be classified into one of these groups.
If a couple decides to use a technique, the male must sign an informed consent before receiving treatment, and he must agree to be the father of the offspring whether the gametes are his or they come from a donor (Article 8). However, because of the incidence of the principles of gradualism and because the interventions are becoming less invasive, the use of a donor’s semen requires a medical indication. Medical indications include the male having problems donating his own gametes or being unable to respond to petitions from the interested parties. These indications reflect the fact that assisted reproduction is not an a la carte medicine (Article 1 stipulates that the techniques be medically indicated).

A woman can have her oocytes fertilised with a donor’s semen if she agrees to the technique as a single individual; in other words, a donor’s semen can be used in the absence of a male partner signing the consent protocol. In this case, the children are only the woman’s. However, a woman cannot be classified as single and later use the gametes of a sentimental partner, as this would involve gamete donation that is not anonymous, which is prohibited by the reproduction law (Article 5).

The Assisted Reproduction Law does not consider the use of frozen embryos for fertility preservation at an unspecified future date, especially in the case of women in clinical situations in which some embryos are created with donor semen and others are created with partner semen. In fact, the regulation only refers to the possible freezing of leftover embryos with the technique (Article 11.3), rather than embryos’ being used as a personal reserve.

In addition to the ethical controversy, personal, rather than medical, use of these techniques is contrary to the requirement of our Constitutional Tribunal (Sentences 212/1996 and 116/1999) to recognise the dignity of “in vitro” embryos, which have juridical rights. The Tribunal requires that there be a concrete reproductive purpose for creating embryos (even when the embryos are created for clinical purposes, one must consider that a woman may discard a portion of them, as she may not remain with her current partner).
For the purposes of postponing maternity, oocyte freezing has fewer ethical and judicial problems, as early ovarian failure is a medical indication. Because oocytes are associated with fewer ethical and judicial problems compared to embryos, and despite the lack of coverage in the Reproduction Law regarding the technique, oocyte freezing should be considered for postponing maternity for women. However, if the intention is to generate a couple’s embryos to postpone maternity, more rigorous protection is necessary to ensure the ethical creation, conservation, possible destiny, and destruction of embryos.

**Freezing ovarian tissue for auto-graft**

The ovarian tissue graft is another option for preserving female fertility. However, research on the technique is in the early stages. The heterotopic auto-graft uses in vitro fertilisation techniques to achieve gestation, but the orthotopic model is theoretically compatible with natural reproduction. Additional research on these methods may lead to clinically applicable procedures in the relatively near future.

The most relevant risks for the patient are associated with the surgical procedures for extracting and re-implanting the ovarian tissue.

Ovarian deterioration is caused by ischaemia in the transplanted tissue, which occurs while the ovarian implants are revascularised. The majority of the primordial follicles lose their viability because of ischaemia, rather than tissue cryoinjury.

The positive gestational results that have been obtained are anecdotal at best. The actual performance of this technique has not been established, although the technique will benefit from future advances. **The ovarian tissue graft should not be used** for the preservation of fertility without medical indication.

Article 11.2 in Law 14/2006 stipulates that the use of oocytes and cryo-conserved ovarian tissue requires prior authorisation from the corresponding health authorities, such as the health ministry of the autonomous community.
As of January 31, 2003, the subsequent use of ovarian tissue is regulated by Royal Decree 120/2003. The law regulates procedures that involve oocyte fertilisation, previously frozen ovarian tissue, or assisted human reproduction techniques. The regulation establishes requirements similar to those of clinical trials, including committee reports and ethical requirements, to avoid gratuitousness and improve safety.

According to the 2008 National Commission on Assisted Human Reproduction, a procedure cannot be authorised outside of the context of an experimental or research project. For this reason, corresponding documentation must be presented for the development of a procedure. The experimental or research project must be submitted to the National Commission on Assisted Human Reproduction for approval.

Centres should formally request authorisation from their autonomous community. Certain requirements, such as the presentation of a consent form and description of the technical procedures, must be approved by the autonomous community.

**In vitro oocyte maturation**

The techniques for the in vitro maturation of immature oocytes have been applied with oocytes that were obtained with and without prior ovarian stimulation and from samples of ovarian tissue, regardless of whether they are surrounded by follicular units. The technical modalities that appear to be the most accessible are based on the final in vitro maturation of oocytes in prophase I. Research on this process has derived from in vitro fertilisation in the general sterile population. The terminal maturation of immature oocytes (primordial and primary) that constitute the majority of the follicular reserve in the ovarian tissue is not yet feasible.

The most feared risk associated with this procedure is associated with a possible increase in chromosomic and genetic alterations. These alterations may occur during the maturation process, but research is in the early phases.
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