Can assisted reproduction technology compensate for the natural decline in fertility with age? A model assessment

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BACKGROUND: Maternal age is an important factor in reproduction. Can assisted reproduction technologies (ART) fully compensate for the decline in fertility with age? METHODS: We used a computer simulation (Monte Carlo) model of reproduction, combining the monthly probabilities of conceiving, the risk of miscarriage and the probability of becoming age-dependently permanently sterile. RESULTS: Under natural conditions, 75% of women starting to try to conceive at age 30 years will have a conception ending in a live birth within 1 year, 66% at age 35 years and 44% at age 40 years. Within 4 years the success rates will be respectively 91, 84 and 64%. If women turn to ART after 4, 3 or 2 years respectively without conception, and if the rate of success is as observed after two cycles of insemination in IVF, ART makes up for only half of the births lost by postponing a first attempt of pregnancy from age 30 to 35 years, and <30% after postponing from 35 to 40 years. CONCLUSIONS: Even if we relax some of the assumptions, ART in its present form cannot make up for all births lost by the natural decline of fertility after age 35 years.

Key words: fecundity/infertility/ART effectiveness/simulation model

Introduction

Maternal age is clearly an important factor in reproduction. For example, in populations not using birth control, fertility rates (i.e. the number of live births per 1000 women) decline with increasing maternal age when the mother is aged >25 or 30 years, well before menopause is reached (Henry, 1961; Trussell and Wilson, 1985; Menken and Larsen, 1986; Menken *et al*., 1986). Analyses of couples in which both partners are still living together at 50 years confirmed that fertility rates decline with maternal age, especially when the mother is >35 years, and even among women who have another child after the age range used to calculate the rate and who are thus not yet sterile (Henry, 1961; Henry and Houdaille, 1973).

In contemporary populations, time to conception (TTC) also increases with maternal age. This has been shown for naturally occurring conceptions (Spira *et al*., 1979; Joffe and Li, 1994; Dunson *et al*., 2002) but there are possible biases (Juul *et al*., 2000). After conception, the risk of spontaneous miscarriage also increases with the age of the mother, at least after age 30 years (Leridon, 1976, 1977; Wood, 1994; Nybo Andersen *et al*., 2000). The role of paternal age is less clear, partly because of the strong correlation with the mother's age. There might be an independent paternal age effect, but it is less significant than the maternal age effect (La Rochebrochard and Thonneau, 2003; Slama *et al*., 2003). We will not explicitly take this effect into account here, although our model could include it.

The effectiveness of assisted reproduction technology (ART) also depends on age (Fédération CECOS *et al*., 1982; van Noord-Zaadstra *et al*., 1991; Lin Tan *et al*., 1992; Templeton *et al*., 1996): conception rates start declining when the woman is aged >30 years.

Some important practical questions remain: what are the chances of a woman of a given age conceiving within a reasonable period (i.e. 6 or 12 months), longer or never? If the woman does conceive, what is the probability of her delivering a live child? If a woman fails to conceive and to deliver a live child naturally, what is the probability of her doing so thanks to medical techniques, such as hormonal stimulation, IVF, artificial insemination with donor (AID) or ICSI? Answers to these questions would enable efficient family planning advice and more precise information about the potential risks associated with postponing childbirth beyond a given age. This is not easy because all the aspects involved (conceiving naturally, having a live birth in the case of conception, conceiving through ART if needed) are strongly dependent on age, as seen above, and because selection processes (of less fecund women) are at work simultaneously.

Materials and methods

A simulation model

These issues can be addressed by use of aggregate models of reproduction, which take into account the whole reproductive life. Models of this type were intensively developed in the 1970s (Dyke and MacCluer, 1973). We chose a Monte Carlo simulation model (Simula) that was initially developed by Albert Jacquard (Jacquard and Leridon, 1973; Leridon, 1977). This model is explicitly based on the biological components of reproduction, plus nuptiality (including, if needed, divorce, widowhood and remarriage) and birth control variables (e.g. number of children wanted, effectiveness of contraception). We will use the 'marriage' variable as a starting point for exposure to conception for couples deciding to have a child at some age. Risks of death, widowhood and divorce are ignored, as we are interested in existing couples. Contraceptive parameters are also set to zero, but they will be used in another way to take ART into account: after some delay (e.g. 1 or 2 years) couples are presumed to turn to ART to improve their chances of conception.

In a Monte Carlo model, we reconstruct the reproductive biography of a woman, from marriage to the end of the reproductive period (age 50 years), by submitting her to all relevant risks each month. She is first exposed to the risk of conception (fecundability) during the first month after marriage, then during all subsequent months, except when she is already pregnant or in the anovulatory post-partum period. Based on the value of fecundability for each specific month, a number is drawn at random. If it is greater than that attributed to the probability of the event, the attempt is considered to have failed and a new number is drawn for the next month; in the case of success (conception), the woman enters a period of non-susceptibility, the duration of which depends on the outcome of the pregnancy (a number is drawn to decide whether the pregnancy will end with a live birth or a spontaneous abortion; if the outcome is a live birth, another number is drawn at random to decide the duration of post-partum sterility related with breastfeeding) and so on, until the woman reaches age of 50 years.

A new simulation is then performed for another woman, using the same parameters. Due to the random aspect of the procedure, the new history will differ from the previous one. Exactly as for a survey based on a random sample of the population, we need to use a large sample size to reduce the variance of the estimates. However, here having a large sample has no cost; with modern computers, running a sample of 10^5 women takes just a few minutes.

The inputs of the model, for natural conceptions, are the following: the age-related monthly probability of conception, the probability of having a miscarriage in the case of conception, the duration of the non-susceptible period (pregnancy plus post-partum sterility) for a live birth or a spontaneous abortion, the age at which permanent sterility occurs.

This last distribution has to be defined and estimated. An obvious marker of the end of the reproductive period is menopause. In modern populations, menopause is reached on average at age 50 years, 75–80% of women reaching the menopause between ages 45 and 55 (Treolar, 1974; Stanford et al., 1987). There is no evidence of a strong temporal trend. However, in populations not using contraception, the mean age of the last birth is usually close to 40 years, 10 years before menopause (Henry, 1961; Trussell and Wilson, 1985; Menken et al., 1986): women appear to become unable to start a pregnancy ending in a live birth several years before reaching the menopause. We know that biological parameters change in the years preceding the menopause. For example, menstrual cycles become more irregular, anovulatory cycles occur, the duration of a cycle increases and becomes more variable, and the risk of early and late abortion increases. Te Velde and Pearson (2002) described several possible

steps leading from full fecundity to total sterility. This discrepancy between the ages at last birth and at menopause can be explained by defining an 'age at onset of permanent sterility', the age after which the woman is unable to conceive and to deliver a live birth (Henry, 1961; Leridon, 1977; Trussell and Wilson, 1985; Rahman and Menken, 1993; Wood, 1994). Finally, virtually all data on populations using little or no birth control have shown that a small percentage of married women remain permanently childless (Larsen, 2000). This is true of 2–5% of women marrying at the ages of 20 or 25 years, and we can assume that most of them were sterile from the time of their marriage (or earlier). This proportion increases with age at marriage and we will use it as the starting point for the distribution of sterility at each age of marriage (see below).

Data

For estimating the levels of fecundability and the distribution of ages at onset of permanent sterility, as they will be entered into the model, historical data concerning France gathered by Louis Henry were used. Henry has intensively analysed the demographic behaviour of pre-transition populations. It can be assumed that fertility control did not exist in these populations, or that if it existed it was fairly ineffective (except in a small proportion of the population, such as prostitutes or highly educated women). This situation was called 'natural fertility' (Henry, 1961). Henry carried out a representative survey of the French population between 1670 and 1830 based on parish registers before the Revolution and on civil registrations after the Revolution. All vital events had been counted in a sample of 378 parishes, and all families were fully reconstituted in a sub-sample of 40 parishes. This sub-sample was limited to rural France (86% of the total population was rural in 1750). A computerized file became available recently (Séguy, 2001). This file includes >106 000 children born between 1670 and 1819, and >34 800 marriages during the same period. We used the data for first marriages occurring before 1790, with completed fertility, i.e. where the husband and wife were still living together at age 50 years, and where all dates (births and deaths of both spouses and all children) were known. This provided 3508 families.

The reason for restricting the sample to completed families is that we need unbiased data on age at last birth under natural fertility conditions. This only makes sense if the woman was actually at risk of conceiving until age ≥50 years. More generally, this makes it possible to analyse uncensored data from the last years of the reproductive period and estimate fertility over the whole reproductive period.

Women who married at age 20–24 years between 1670 and 1789 had 7.0 children on average and 3.7% remained childless. Women who married at age 25–29 years had a mean of 5.7 children and 5.0% remained childless. Women who married at 30–34 years had a mean of 4.0 children and 8.2% remained childless. We also looked at the interval between marriage and first birth. If we define the month of marriage as month zero and make a life-table analysis, the birth rate was maximum in month 10, which corresponds to conceptions in month 1. One in 10 (9.8%) births occurred between months 1 and 8, as a result of pre-marital conception. This means that the women giving birth during month 10 (and thereafter) already exhibited slightly reduced fertility relative to the most fecund women who had conceived before marriage. The conception rate was highest for women who married at age 25–29 years: 17.5% during month 10, 17.2% for month 11. To take into account children dying in the very first days and other possible sources of omissions (Henry and Houdaille, 1973), we assume that ~5% of first births were omitted and have corrected the rate of conception accordingly from 17.5 to 18.4%. This estimate must be multiplied by ~1.12 (see below) to include conceptions ending in fetal deaths which are not registered in this source of data. Finally, assuming that the pre-marital conceptions

led to underestimation of fecundity in the population, we used an average value of 23% for age 20–30 years.

Fecundability, like any biological parameter, is not the same for all couples. The 0.23 value was taken as a mean value (for the more fertile part of the reproductive period: F_{max}) and the individual values were presumed to be distributed according to a Gaussian distribution around this mean. According to various estimates of this distribution we took a SD of 0.12. Comparison of the distributions of birth intervals (by birth order and final size of the family) in historical populations with the outputs of an analytical model, suggested that fecundability always declines for some time before the onset of permanent sterility (Leridon, 1977). Instead of considering fecundability as a mere function of age over the entire age range, it is better to assume that the decline with age starts z years before the occurrence of permanent sterility. The best estimate for z is 12.5 years. The profile of fecundability by age is shown in Figure 1. This shows that the age at onset of sterility is the time when fecundability becomes zero, at the end of a continuous process of declining fecundity from an average age of 33 years.

Data on fetal loss were taken from contemporary populations. Most retrospective surveys give rather consistent results for apparent intrauterine mortality, i.e. the proportion of spontaneous miscarriages that are recognized by the woman herself. Mean rates are typically between 12 and 15 per 100 pregnancies (Leridon, 1976, 1977; Wood, 1994). Moreover, this rate increases with the age of the mother, at least after age 30 years (what happens before age 25 years is of no importance here). The rate almost doubles between the ages of 30 and 40 years, as shown on Figure 2 summarizing a set of 12 data (Leridon, 1977). Spontaneous abortions occurring at earlier stages of pregnancy and remaining unknown to the woman are included in the definition of fecundability given above.

In the case of pregnancy ending in a live birth, the mother is presumed to breastfeed the child, as was the case in all traditional populations. In contemporary populations where fertility is still natural, an average duration of lactation of 20 months is common (Leridon and Ferry, 1985). The median duration of post-partum amenorrhoea is 13 months and the range is 1–24 months. In the case of miscarriage, the mean duration of non-susceptibility (including pregnancy) was assumed to be 5 months. These assumptions are necessary for ensuring the validity of the model over the whole reproductive period, but they are not used to estimate success rates in this paper.

Estimating age at permanent sterility

As the distribution of age at onset of permanent sterility is always estimated indirectly (Leridon, 1977; Trussell and Wilson, 1985), we decided to derive empirically the sterility distribution (in terms of proportions of women unable to conceive, whatever the fate of the pregnancy) that fits best with the observed distribution of age at last birth. The result is shown in Figure 3, together with a distribution of age at menopause. The curves for age at last birth with the model and with Henry's data are almost perfectly superposed. This adjustment is very sensitive to the choice of the distribution of age at sterility, which gives some confidence for the estimation of this distribution. The median age at onset of sterility (inability to conceive) is 44.7 years, compared to 50.5 for menopause and 41.2 for delivery of the last birth.

Taking ART into account

When taking ART into account, we assume that medical treatments have two effects. The first is to increase the fecundability of hypofertile couples. It is indeed very likely that ART is particularly efficient on hypofertile women or men. It is clear, however, that ART also allows some totally sterile couples to have a child, as IVF was first
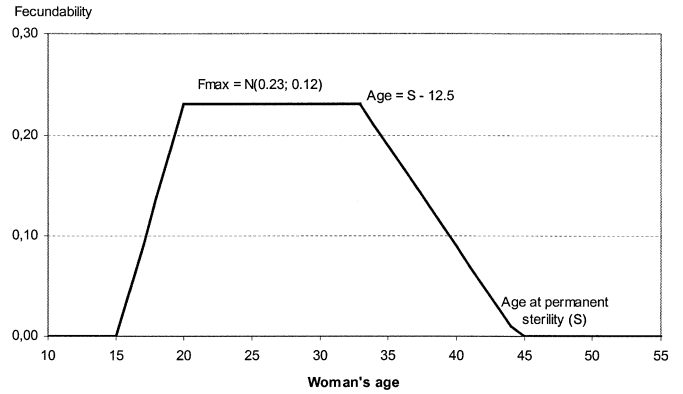
Figure 1. Fecundability as a function of woman's age and age at onset of permanent sterility. An example for a woman with S = 45 years
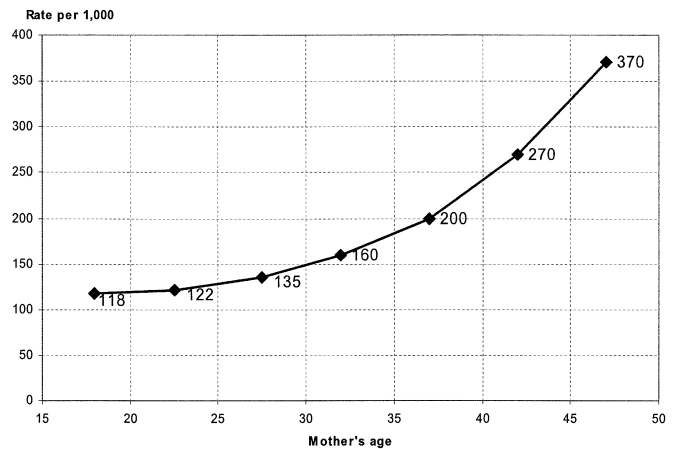

Figure 2. Mean rates of fetal death according to the age of the mother (per 1000 pregnancies). Average from 12 studies (Leridon, 1977).

used for women suffering from tubal sterility and as the new ICSI technique allows some virtually sterile men to have a child. Consequently, we must include two new parameters in our model: (i) the proportion of sterilities overcome by ART (OS), and (ii) a multiplicative factor for fecundability with ART (MF), both of which may depend on age.

In practice, a woman is considered to start trying to become pregnant at a given age, A, with a fecundability, p, defined as above; p depends on F_{max} and changes with age. After D months without conception, it is assumed that the woman uses some medical technique to improve her fecundity, and her current fecundability becomes $p*MF$. If she was already sterile at age A or becomes sterile between A and $A + D$, her risk of conception is null until she reaches the end of the delay D. She has then an OS% chance of recovering a positive fecundability, which is again calculated as $p*MF$. The 'current' value of p still depends on F_{max} and age, but in any case the woman is presumed to reach permanent sterility at 50 years of age.

The parameters OS and MF are difficult to estimate independently. The values used were chosen in such a way that the success rates after ART matched those observed in IVF data at the same ages (Templeton et al., 1996; FIVNAT et al., 1997). We assume that women will have an average of two IVF attempts. Taking the mean of the two series, the success rate (in terms of live births) after two retrievals is 29.7% at age 34 years, 23.5% at age 38 years and 15.3% at age 42 years. With the

1550

Per 1,000 women
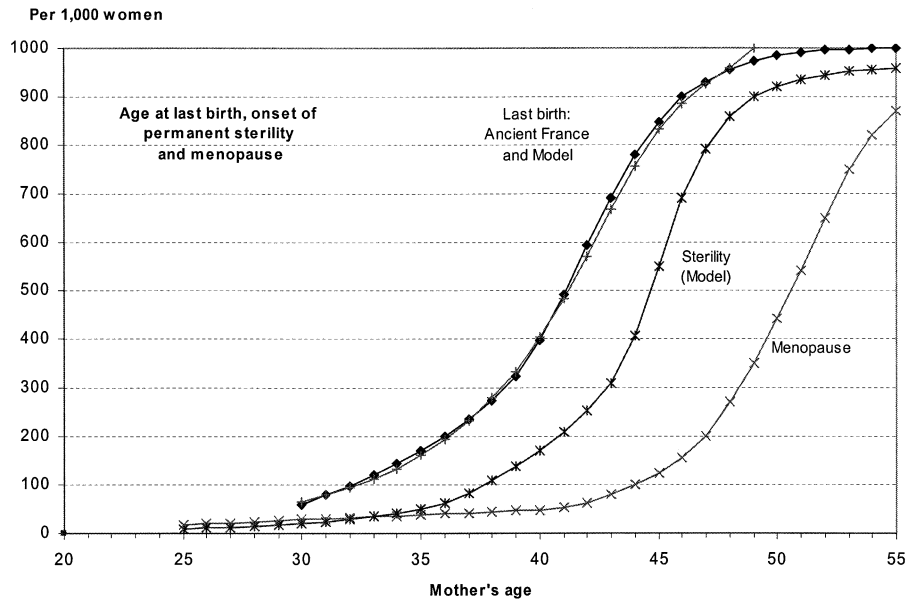
Figure 3. Cumulative proportions of women by age at last birth (historical French data and results of the model), at onset of sterility and of menopause. (Sources: Henry's survey, INED: Séguy, 2001; Treolar, 1974; and present author.)

Table I. Success rates (pregnancies ending in live birth per 100 women of each age) for conception without assisted reproduction technology (ART): results of the model

	Woman's age when starting pregnancy attempt		
	30 years	35 years	40 years
Success:			
Conception (LB) within 12 months	75.4	66.0	44.3
Delay:			
Conception (LB) in 12–23 months	10.9	12.3	12.7
Conception (LB) in 24–35 months	3.0	3.9	4.7
Conception (LB) in 36–47 months	1.4	1.7	2.0
Total conceptions (LB) within 4 years	90.7	83.9	63.7
Total conceptions (LB) ever	93.9	85.9	65.1
At least one miscarriage before LB	14.4	15.7	16.3
Age Y when starting ART (in case of failure)	34 years	38 years	42 years
No conception at age Y	9.3	17.8	43.0

values chosen for OS and MF, we obtain very similar values within 2 years: 30.1, 23.6 and 16.5% respectively. It is clear, however, that similar results can be obtained with different combinations of the two parameters.

Results

Trying to have a child at 30, 35 and 40 years of age

We run the model with our newly derived estimates of women permanently sterile according to age, assuming that a woman is exposed to the risk of conceiving at exact ages 30, 35 or 40 years. Table I shows the estimated proportions of women who start a pregnancy ending in a live birth (conception–LB) within 12 months of attempting (regarded as a 'full success'), or within 12–23, 24–35 or 36–47 months (considered as 'delayed' pregnancies).

The full success rates (within 1 year) are rather low: 75% when starting attempts to conceive at age 30 years, 66% for age 35 years and 44% for age 40 years. However, if we include the conceptions delayed by <4 years the success rates are respectively 91, 84 and 64%.

If we take into account the pregnancies that occur after 4 years, the final proportions of women who deliver a live baby reach 94% for women starting at age 30 years, 86% for those starting age 35 years and 65% for those starting at age 40 years.

How much can ART help unsuccessful couples?

We concentrated on the proportions of women who conceive within 4 years because this is the mean delay before women turn to the most advanced forms of medical assistance (IVF or ICSI) in France. According to the national data on IVF (FIVNAT, 2001), women were aged 34 years on average at the time of the oocyte recovery and they had been trying to achieve pregnancy for 5 years. We used a slightly shorter delay because in our model the estimates of times to conception with ART are longer than in actual IVF practice. Moreover, we assumed that the delay (D) before turning to ART decreases for older women: 3 years after age 35 years and 2 years after age 40 years. The absence of conception–LB during this delay is considered to be a failure of natural reproduction.

According to the model (Table II, line b), out of 100 women who originally tried to conceive, 2.8% will give birth to a live child within 2 years of treatment started at age 34 years, 4.2% if started at age 38 years and 7.1% at age 42 years. The proportions increase with age because older women are less likely to conceive spontaneously and therefore more likely to use ART than younger women. If we relate these values to the number of women using ART (line a), the success rates of ART are 30, 24 and 17% at these ages respectively. As mentioned above, these rates are fully consistent with those reported after two IVF cycles.

Table II. Success rates [pregnancies ending in live birth (LB) per 100 women of each age] for conception with assisted reproduction technology (ART): results of the model

	Woman's age when starting pregnancy attempt		
	30 years	35 years	40 years
Age Y when starting ART (in case of failure)	34 years	38 years	42 years
(a) No conception at age Y (failure)	9.3	17.8	43.0
Total conceptions (LB) with ART			
Success: conception (LB) within 12 months	2.0	3.0	5.1
Delay: conception (LB) in 12–23 months	0.8	1.2	2.0
(b) Total conceptions (LB) within 2 years	2.8	4.2	7.1
(c) Apparent rate of success for ART (%) = 100*b/a	30.1	23.6	16.5
No conception at age $Y + 2$ (= $a - b$)	6.5	13.6	35.9
Spontaneous conceptions (no treatment)			
(d) Within 2 years	1.4	2.5	6.7
(e) Net rate of success for ART (%) = 100*$(b - d)/a$	15.1	9.6	0.9
Hypotheses for ART			
Months without conception when starting treatment	48	36	24
Fecundability of non-sterile women multiplied by (MF)	3	2	1.2
Percentage of sterilities overcome (OS)	50	25	3

Note, however, that the success rates given in Table II are only 'apparent', because some hypofertile women may conceive without any treatment (Collins *et al*., 1995). The number of such 'spontaneous' conceptions is small at ages 34 and 38 years (Table II, line *d*: 1.4 and 2.5 per 100 women respectively within 2 years), because the number of women having not yet succeeded by these ages is small (9 and 18%). However, for the third cohort (i.e. women aged 42 years), the number of spontaneous conceptions is far from being negligible (6.7%) for two reasons: (i) 43% of women are still trying to conceive at age 42 years; (ii) the selection of hypofertile was less severe in this cohort because we consider the situation after only 2 years without conception instead of 3 years in the 35 year group and 4 years in the 30 year group.

In summary, out of 100 women trying to become pregnant at age 30 years, 91 will have a child within 4 years without ART, another three will do so during the next 2 years thanks to ART (IVF) and the remaining six will remain childless. Out of 100 women starting at age 35 years, 82 will have a child after 3 years, plus four thanks to ART, and 14 will remain childless. Out of 100 women starting at age 40 years, 57 will have a baby after 2 years, plus seven after using ART, and 36 will remain childless. In this latter case, the number of births with ART is only slightly higher than what would be observed in 2 additional years without ART.

Discussion

The validity of our model has been carefully checked in two ways. First, we compared its results (mean number of live births and proportion of women remaining childless as a function of the age of the woman at the time of marriage) with those for a large and representative sample of families where fertility could be regarded as natural (uncontrolled). Second, we chose parameters for ART leading to 2 year success rates (in live births) identical to that associated with two IVF attempts. The results of the models appear to be quite robust to

the choice of the parameters: a small variation in one parameter usually resulted in small differences in the output. Random variations were limited by using large cohorts of 10^5 women.

To take into account ART in our model, we included two parameters: one for subfertile women (considering their increased monthly chance of conception) and one for sterile women (to allow for their restored chances of conception). The balance between these two parameters is somewhat arbitrary. We need, however, to include these parameters because we want to include all kinds of ART treatments. Hormonal stimulations can only help subfertile women, and the fact that our model calculates monthly rates of conception makes it easy to analyse the effects of such treatments. IVF is also used for subfertile women. However, IVF among women with tubal occlusion, and AID or ICSI in couples where the male partner is almost azoospermic, can allow totally sterile couples to have a child. In our model, the second effect is increasingly important as the woman becomes older. One reason for the very low effectiveness of ART after age 42 years is that the percentage of sterile couples is proportionally high (close to 50% in the model). In our simulation, only 3% of these sterile couples had some chance of conceiving.

Our results show that the chance of giving birth to a live baby decreases between ages 30 and 35 years, and even more so between ages 35 and 40 years. In both cases, ART only partly reduces the gap. If a woman postpones an attempt to become pregnant by 5 years, from age 30 to 35 years, her chances of conceiving will be reduced by 9% (91–82%) and ART will make up for only 4%. If she postpones from age 35 to 40 years, the chances will be reduced by a further 25% (82–57%) and ART will make up for only 7%. In other words, ART makes up for only half of the births lost by postponing an attempt to become pregnant from 30 to 35 years (4.2/8.5), and <30% of the births lost by postponing from 35 to 40 years (7.1/25.2).

More optimistic results might be reached by encouraging women aged 35–40 years to turn to ART faster than assumed in

the model, after 3 and 2 years respectively. Note, however, that this delay includes the time to decide to visit a doctor plus the time to make the necessary medical investigations, plus the time to start ART. It does not mean that the woman is not doing anything before 2 or 3 years.

The chances of conceiving spontaneously (natural fecundability) were estimated on the basis of data from non-contraception populations. It can be assumed that these populations were not doing anything to avoid a pregnancy, especially in the months following marriage. However, it is also true that they did not know anything about the daily probabilities of conception during a cycle. Modern couples wishing to conceive might use their knowledge of the most fertile part of the cycle to increase their fecundability. This would increase the rate of spontaneous conception and decrease the number of women turning to ART. Based on estimates of the probability of conceiving on each day of the menstrual cycle (Schwartz *et al.*, 1980), and assuming that the couple had intercourse every other day, we made new simulations with a mean fecundability of 0.40. The proportion of women still childless after the treatment dropped from 6 to 4% for those starting at age 30 years, from 14 to 10% for those starting at age 35 years, and from 36 to 30% for those starting at age 40 years.

It could also be assumed that couples might decide to have more than two attempts at IVF. Our simulations, however, aim to see what would happen if a large proportion of the couples decided to postpone childbirth. Not all of them would accept to turn to medically assisted reproduction if they failed, and among those using ART not all women would decide to continue after two failures. An average of two attempts seems a reasonable assumption.

Other techniques might also be used. Success rates with ICSI are similar to those with traditional IVF, and there are no less constraints for the couple. Success rates with AID depend on the specific technique used, and cumulative rates of conception after a large number of insemination cycles are sometimes impressive (Fédération CECOS *et al.*, 1982; van Noord-Zaadstra *et al.*, 1991). However, once again we must remember that only a minority of couples consider the possibility of an insemination with a donor and that not all couples will endure a long series of attempts.

We draw two general recommendations. The message for a woman aged <35 years trying to conceive is: be patient. If the woman fails to conceive within a year, the chances of conceiving subsequently are still substantial: more than half of those still childless after 1 year will conceive during the next 2 years. The message for women aged ≥35 years is: be impatient. The chances of a rapid spontaneous conception are still significant, but in case of failure, ART will not fully compensate for the years (and the chances of conceiving) lost.

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