Human Reproduction, Vol.24, No.6 pp. 1414–1419, 2009
Advanced Access publication on February 20, 2009 doi:10.1093/humrep/dep004

human reproduction

ORIGINAL ARTICLE *Infertility*

The effect of *in vitro* fertilization on birth rates in western countries

J. Dik F. Habbema[1,7], Marinus J.C. Eijkemans[1], Geeta Nargund[2], Gijs Beets[3], Henri Leridon[4,5,6] and Egbert R. te Velde[1]

[1]Department of Public Health, Erasmus MC, University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, The Netherlands [2]Department of Obstetrics and Gynaecology, St George's Hospital and Medical School, London, UK [3]Netherlands Interdisciplinary Demographic Institute, PO Box 11650, 2502 AR, The Hague, The Netherlands [4]INED, Paris F-75020, France [5]INSERM, Unit 822, Le Kremlin-Bicêtre F-94276, France [6]Univ Paris-Sud 11, Faculté de Medicine, Le Kremlin-Bicêtre F-94276, France

[7]Correspondence address. E-mail: j.d.f.habbema@erasmusmc.nl

BACKGROUND: We will assess to what extent *in vitro* fertilization (IVF) is effective in increasing the number of births overall and whether earlier application of IVF will increase this number.

METHODS: We simulate 100 000 women trying for their first and second child. Natural and IVF pregnancy rates and infertility rates are age-dependent and based on published data. The age at which women start trying for their first child is based on the Netherlands 2002 data. Three cycles of IVF are given during a 12-month period after 1 or 3 years of trying to conceive unsuccessfully. Main outcome measures are live born deliveries and children, both naturally conceived or after IVF, as well as numbers of singletons, twins and triplets, the total fertility rate (TFR) and the number of IVF cycles performed.

RESULTS: Full access to IVF after 3 years increases the TFR by 0.08 children. Applying IVF after 1 year leads to an additional TFR increase of 0.04, with double the number of IVF cycles and twin and triplet children, and a shift from naturally conceived children to IVF children.

CONCLUSIONS: Full access to IVF after 3 years is important. It does increase the TFR. Early availability of IVF would further increase the TFR, but with side-effects and high costs.

Key words: *in vitro* fertilization / assisted reproduction / total fertility rate / multiple pregnancies / IVF policy

Introduction

Since the contraceptive revolution of the 1960s, having children has become an issue of personal choice in Western societies, and most women in Europe currently want one, two or no children. As a consequence, the total fertility rates (TFRs—the mean number of children per woman for a given country) have dropped in most countries from three or more in 1965 to below the replacement level of 2.1 within the following 10–15 years. For the European Union as a whole, the TFR is presently 1.5. The aim of our study is to investigate to what extent the application of IVF would increase the number of children born and consequently the TRF of a population. The British NICE guidelines and the Dutch IVF guidelines recommend that in couples with no obvious cause of sub-/infertility, IVF should not be applied before they have attempted to conceive naturally for at least 3 years (Dutch Society for Obstetrics and Gynaecology, 1998; NICE, 2004).

However, the mean age at first delivery has increased by 4–5 years since the 1960s. Since the ability to achieve a natural pregnancy decreases with age (van Noord-Zaadstra *et al.*, 1991), couples may benefit from earlier application of *in vitro* fertilization or intracytoplasmic sperm injection (jointly abbreviated as IVF) than presently recommended.

Therefore, we determined what the effect of IVF is on the TFR, and whether earlier application of IVF, than that recommended by present guidelines, would further increases the TFR.

We developed a model simulating the reproductive events of a cohort of 100 000 women trying for a first and second child. The model takes account of the age-related decline in both natural pregnancy chances and pregnancy chances after IVF. The model is used to simulate two scenarios in which three IVF cycles in 1 year are applied either after 1 or after 3 years of infertility. The two scenarios are compared with each other, and also with a situation in which IVF is not applied.

Materials and Methods

Using computer simulation with a previously published model (Leridon, 2004), a cohort of 100 000 women with a partner and trying for their first and second baby is followed over time. Pregnancies occur either

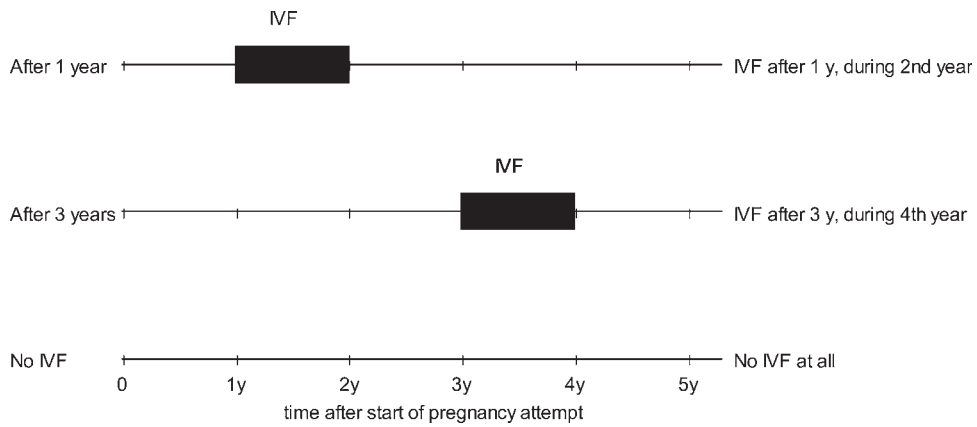

Figure 1 Three scenarios: IVF after 1 year of unsuccessfully trying to conceive, IVF after 3 years of unsuccessfully trying to conceive, and no IVF.

naturally or after IVF. Only pregnancies leading to a live born delivery (LBD) are taken into account. From each woman, a record is made of all children she delivers during her reproductive life.

In two IVF scenarios, IVF is applied either after 1 or after 3 years of unsuccessfully trying to conceive (Fig. 1). All couples who did not conceive naturally receive three IVF cycles during a 1-year period unless a pregnancy has occurred in the first or second cycle. We assume that there are no drop-outs during treatment. Thus, all women have three IVF cycles, unless they are pregnant earlier. The model assumes that after each IVF cycle there is one cycle in which natural conception is not possible, leaving six cycles during the year of IVF treatment in which natural conception may occur. For comparison, there is also a scenario where no IVF is applied.

We define subfertility as a state in which the chance of natural conception leading to LBD, although lower than normal, is still present. Infertility is defined as a complete failure to have a natural conception leading to LBD. Assumptions are required for the age-dependent rates of infertility and the distribution of monthly fertility chances of couples who are not (yet) infertile. Some couples are infertile right from the beginning of their union, whereas others become infertile later as a result of ageing (Menken *et al.*, 1986). For estimating this age-dependent onset of infertility, we used data on the age at last childbirth in a natural non-contraceptive population where infertility increases from 3% at age 25 to 6% at age 30, 17% at age 35, 50% at age 40 and 85% at age 45 (Henry, 1965; Leridon, 2004). Conception is a matter of chance depending on numerous male/female factors of which the quality of oocytes and spermatozoa, and the patency of the fallopian tubes are the most important ones. With regular intercourse, a woman has a new chance of conception leading to LBD each month, until she becomes infertile. The monthly pregnancy chances of couples who are not (yet) infertile vary widely. The most fertile couples will conceive early, leaving progressively less fertiles in the pool of not (yet) pregnant couples. Bongaarts (1975) demonstrated that the distribution of the monthly fertility rates of these couples fits a β-distribution with a constant coefficient of variation of 0·56. The average chance of conception during the first month of exposure—which is the second variable defining the β-distribution—varies across populations and primarily depends on female age (Bongaarts, 1975; Schwartz and Mayaux, 1982). We assumed this average value to be 0.23 for women of young age, with a standard deviation (SD) of 0.12 (Leridon, 2004). Instead of considering pregnancy chances as a mere function of age over the entire age range, it is better to assume that the decline with age starts a number of years before the occurrence of infertility. The best estimate found was to start the decline 12.5 years before infertility (Leridon, 2004). From that time onward, the monthly chances decline, to become zero at the time of infertility.

Data on fetal loss, which increases with advancing female age, at least after age 30, were taken from contemporary populations (Leridon, 1977). The rate almost doubles between the ages of 30 and 40 years (Leridon, 2004). Spontaneous miscarriages occurring at earlier stages of pregnancy and remaining unknown to the woman are included in the definition of monthly pregnancy rates given above.

The distribution of the age at which the 100 000 women start trying to have children is based on the age distribution at first childbirth in the Netherlands in 2002, which has been corrected for the age-dependent time to pregnancy, for the age-dependent infertility percentage and for the 9 months which elapse between conception and birth.

The distribution of IVF births over singletons (75.5%), twins (23.2%) and triplets (1.3%) is taken from the 2002 European ESHRE registers (The European IVF monitoring programme for the European Society of Human Reproduction and Embryology *et al.*, 2006). Thus, an IVF delivery gives on average 1.26 children. The twin and triplet rates in natural pregnancies add to an average of 1.01 children per delivery. For the age-dependent ongoing pregnancy rates after IVF, results of IVF cycles performed in the Netherlands during 2003 and 2004 (Lintsen *et al.*, 2007) were used. We assume that after 1 year of non-conception, a diagnostic fertility work up is performed, by which couples with an absolute or severe cause of infertility, such as two-sided tubal blockage or very poor semen quality, are identified and treated by IVF without delay.

For calculating the impact of IVF on the TFR of the 100 000 women, we simulate first and second children. We assume in all scenarios that all women wish to have two children, have a partner, and will use IVF if indicated. With two children, a family is considered complete. Because of spacing between first and second child, we assume in our simulation that 15 months after the birth of a first singleton, couples start trying for their second child. This will be in a natural manner if the first child was conceived naturally, and by direct application of IVF if the first child was conceived by IVF. Women who already had more than one child from the first LBD because of a multiple birth, do not proceed to have more children.

For a description of the original model, see Leridon (2004). The IVF option has been added to the model. The model makes it possible to simulate the dynamic interplay between naturally occurring pregnancies and those obtained by IVF.

Results

First LBDs and first children

The number of first LBDs occurring naturally and after applying IVF after 1 and 3 years are given in Fig. 2. There are many natural pregnancies leading to LBD during the first year after stopping birth control; 76% of the women conceive spontaneously. Of those who do not become pregnant during the first year, ~50% will still succeed during the following year. About 92% of the women achieve a natural pregnancy within 10 years. Thereafter, still very few natural pregnancies will occur during the reproductive lifespan of a woman. As a result of the IVF treatment, the number of pregnancies leading to LBD increases steeply during the year of treatment. Thereafter, the graph resumes the shape of the natural conception curve.

Figure 3a shows that the total number of LBDs hardly differs between the two IVF scenarios. Apparently, many of the LBDs obtained by pregnancies after IVF with the early scenario are 'replaced' by natural pregnancies obtained with the late scenario during the following 2 years. In contrast, Fig. 3b shows that the number of children born in the 1-year IVF scenario is considerably higher than in the 3-year scenario, because more children from multiple pregnancies are born after IVF.

First and second LBDs and first and second children

We assume that all couples want two children. Thus, all couples who have achieved a first child try for a second one, except those who have two or three children from the first LBD. The results are given in Table I. The total number of children born to the 100 000 couples ranges from 178 720 without IVF to 186 400 when IVF is applied after 3 years and 190 400 when IVF is applied after 1 year. This corresponds to a TFR increase of 0.04 with IVF after 1 year instead of after 3 years and a TFR increase of 0.08 with IVF after 3 years relative to no IVF. There is a noticeable effect of increasing the number of children by early application of IVF due to the large proportion of multiple pregnancies. For achieving the increase of 4000 more children with IVF after 1 year compared with after 3 years, ~55 000 more IVF cycles are needed resulting in 17 500 more IVF children born, and nearly 7000 more twin and triplet children.

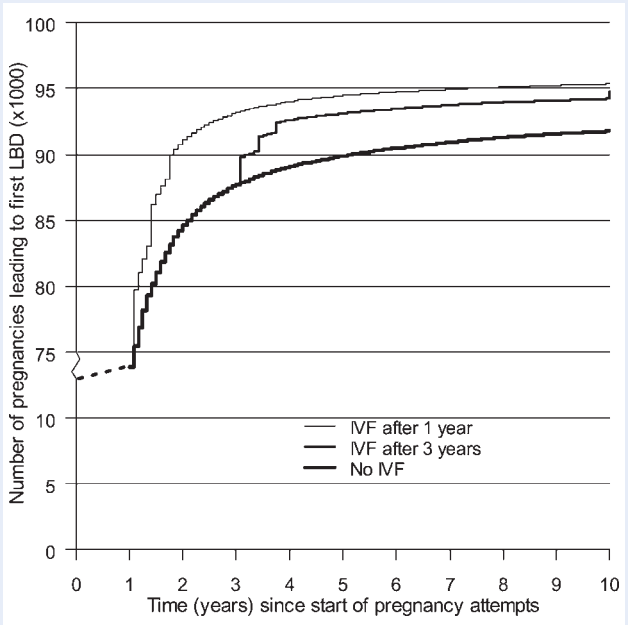

Figure 2 Number of first LBDs by year since start of pregnancy attempts in the 100 000 women trying for their first baby during the following 10 years.

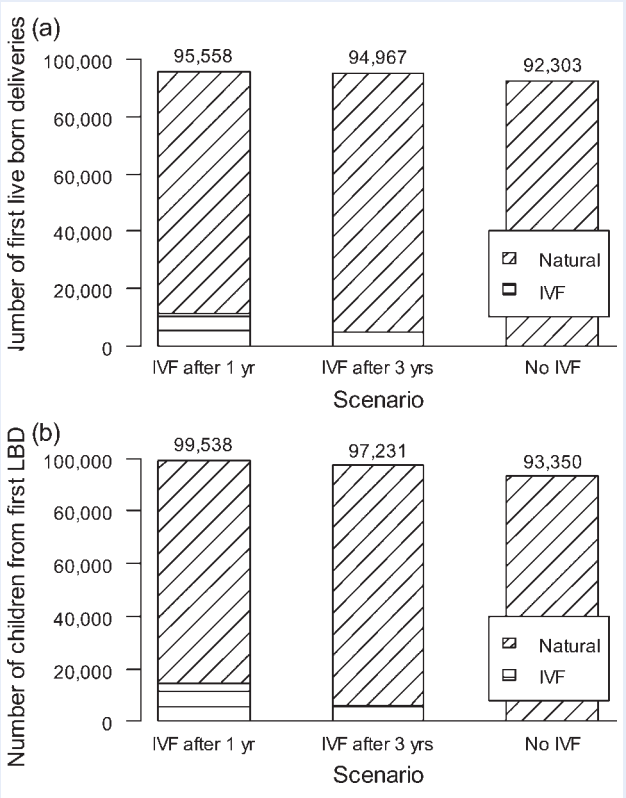

Figure 3 (**a**) Number of first LBDs and (**b**) number of children born therefrom in the cohort of 100 000 women.The total numbers are broken down into numbers due to natural pregnancy and numbers due to IVF-pregnancy.

Discussion

Our results in Table I demonstrate that when applying IVF after 1 instead of after 3 years, 4000 more children would be born in the cohort of 100 000 couples wishing to have two children, a TFR increase of 0.04. In our opinion, this limited increase in TFR does not justify the extra 55 000 IVF cycles to be performed and the almost 7000 more twin- and triplet children being born.

RAND Europe published a study on the potential impact of wider and earlier access to IVF (Grant *et al.*, 2006; Hoorens *et al.*, 2007). Their model showed that if the high IVF-intensity of Denmark is applied to the UK, the TFR would rise from 1.62 to 1.66. Moreover, if IVF was applied to all couples after 1 year of non-conception, the TFR in the UK would rise by 0.24–1.86 and in Denmark by

Table I Outcomes and differences in outcomes of the three scenarios, with IVF after 1 year, IVF after 3 years and no IVF

Number of:	IVF after 1 year	IVF after 3 years	No IVF	Difference between IVF after 1 and 3 years	Difference between IVF after 3 years and no IVF
Live born deliveries	182 700	182 140	176 720	560	5420
All children	190 400	186 400	178 720	4000	7680
Naturally conceived	161 670	175 170	178 720	−13 500	−3550
After IVF	28 730	11 230	0	17 500	11 230
Singletons	175 000	177 880	174 730	−2880	3150
Twins and triplets	15 400	8520	3990	6880	4530
IVF cycles	102 830	48 100	0	54 730	48 100
Total fertility rate (TFR)	1.90	1.86	1.79	0.04	0.08

0.22–1.96 when compared with no IVF. These figures indicate large effects compared with other policy measures (Gauthier, 2007), and the authors conclude that IVF and other assisted reproductive technologies have the potential to increase birth rates considerably, thereby helping to reverse the trend of population ageing.

However, we find a smaller impact of early IVF on TFR than that found by the RAND model. For example, we estimate that IVF after 1 year of non-conception leads to a TFR increase of 0.11 compared with no IVF (1.90–1.79; Table I), which is only half the effect predicted by the RAND model. This difference in results can be traced back to an important difference in assumptions. The RAND authors apply an all-or-nothing fertility concept assuming normal fertility when a natural pregnancy leading to an LBD occurs within 1 year, and infertility when couples do not conceive within that first year. This assumption ignores the chance of natural pregnancies occurring in subsequent years. This ability has not only been demonstrated in non-contraception practicing populations (Henry, 1965; Leridon, 1977; Rochon, 1986; Spira, 1986; Wood, 1989), but also in contemporary populations of couples consciously trying to become pregnant (Tietze, 1950; van Balen *et al*., 1997; O'Connor *et al*., 1998; Dunson *et al*., 2004), and also in patients assigned for infertility treatment (Collins *et al*., 1983). In four independent prospective studies of subfertile couples in which the chance of natural conception was followed for various lengths of time, the 12-month chance of a natural conception leading to live birth agreed with the chances of natural pregnancy depicted in Fig. 2 in all four studies (Eimers *et al*., 1994; Collins *et al*., 1995; Snick *et al*., 1997; van der Steeg *et al*., 2007) and this emphasizes the robustness of our assumptions on the likelihood of natural pregnancy. Another study estimates that 10% of couples in whom IVF was not successful, later on had a child after a natural pregnancy leading to LBD (de La Rochebrochard *et al*., 2008). In our simulations, we found a comparable percentage of natural pregnancies following unsuccessful IVF after 3 years (results not shown).

We cross-validated our model with the RAND model by re-running the scenarios, but now with the RAND assumption of no natural pregnancies after 1 year. In this case, we obtained a TFR increase of 0.25 when applying IVF after 1 year, which is similar to the estimates of the RAND model. This confirms that the difference in results between the two models can be entirely explained by this one crucial assumption. By ignoring natural conceptions after 1 year, the RAND report overestimates the impact of early IVF.

When only counting the number of children, the many multiple pregnancies with IVF are an advantage as they lead to many more children. From such an exclusively quantitative perspective, the best strategy would be to start IVF immediately after stopping birth control. In such a 'Brave New World' scenario, we calculated that ~20 000 more children would be born in the cohort of 100 000 couples in comparison with no IVF, an impressive TFR increase of 0.20, for a considerable part due to twins and triplets. However, from a medical perspective, multiple pregnancies are a serious complication of IVF because of the high chance of premature births associated with increased risks of infant mortality, morbidity and cognitive and neurological problems later in life (Helmerhorst *et al*., 2004; Fauser *et al*., 2005; Hille *et al*., 2007). The medical consequences of multiple births have a greater impact on healthcare costs than the IVF treatment itself (Collins, 2002; Evers, 2002). Furthermore, application of IVF after 3 years rather than 1 year of non-conception results in halving the number of IVF cycles being performed (Table I) because of natural pregnancies occurring during these 2 years, which reduces the number of women requiring IVF by ~50%. More IVF increases the morbidity of the female partner (Allen *et al*., 2006), and also increases the financial costs either to the couple or the state.

Our results also demonstrate the importance of IVF as an excellent treatment for couples who have little or no chance of obtaining a natural pregnancy. In the cohort of 100 000 women, nearly 3000 couples who would have remained childless without IVF will have at least one child with IVF after 3 years (Fig. 3a). Moreover, the TFR increased by a non-negligible 0.08 compared with no IVF (Table I) in couples wishing to have two children, thus demonstrating the potential value of IVF as one of the measures to increase national birth rates.

We have to realize that the results of our scenarios are an upper bound of what can be expected from IVF in 100 000 women of an actual population. In our scenarios, we assume that all women want to have two children, but in reality some women remain childless voluntary. Others want only one child or have no partner. This is only partly counterbalanced by women with more than two children. Moreover, not all women with a fertility problem are going to use IVF even when there is a good indication and IVF is freely available. When not all women would make use of IVF, the impact of IVF will be proportionally reduced. For example, with 50% uptake, only half of the IVF effects in Table I will be achieved. When some women do not

complete three cycles but stop earlier, the effects of IVF will also be reduced.

So the impact of IVF on the TFR will be smaller than the cohort impact in Table I suggests.

Currently, there is agreement among European IVF professionals that one of the greatest challenges of the coming years is to reduce multiple pregnancy rates by transferring fewer embryos, preferably only one (elective single embryo transfer). Multiple pregnancy rates after IVF in Europe are already decreasing (Andersen *et al*., 2008). We expect that, in 10 years time, this favourable downward trend will continue further resulting in multiple pregnancy rates of maybe 10% or less. With such a decrease in the number of IVF twins and triplets, a considerable part of the impact on the number of children of IVF after 3 years would be maintained, but the additional impact of early IVF after 1 year will shrink.

We have assumed the same IVF policy for all ages. However, older aged women may benefit from shorter and younger women from longer periods of time before IVF is applied. More extensive studies using scenarios with age-dependent times to IVF should clarify this issue.

In conclusion, the initial purpose of IVF is to solve individual problems of infertility, and it is indeed the most important treatment for couples who have no or little chance of conceiving naturally. All such couples should have the opportunity to have IVF and if they would accept, a small but significant impact on national birth rates would result. Making IVF available early with the intention to boost national birth rates would be a largely ineffective policy measure with serious costs and side-effects.

References

Allen VM, Wilson RD, Cheung A, Genetics Committee of the Society of Obstetricians and Gynaecologists of C and Reproductive Endocrinology Infertility Committee of the Society of Obstetricians and Gynaecologists of C. Pregnancy outcomes after assisted reproductive technology. *J Obstet Gynaecol Can* 2006;**28**:220–250.

Andersen AN, Goossens V, Ferraretti AP, Bhattacharya S, Felberbaum R, de Mouzon J, Nygren KG, European IVFmC European Society of Human Reproduction and E. Assisted reproductive technology in Europe, 2004: results generated from European registers by ESHRE. *Hum Reprod* 2008; **23**:756–771.

Bongaarts J. A method for the estimation of fecundability. *Demography* 1975;**12**:645–660.

Collins J. An international survey of the health economics of IVF and ICSI. *Hum Reprod Update* 2002;**8**:265–277.

Collins JA, Wrixon W, Janes LB, Wilson EH. Treatment-independent pregnancy among infertile couples. *N Engl J Med* 1983;**309**:1201–1206.

Collins JA, Burrows EA, Wilan AR. The prognosis for live birth among untreated infertile couples. *Fertil Steril* 1995;**64**:22–28.

de La Rochebrochard E, Quelen C, Peikrishvili R, Guibert J, Bouyer J. Long-term outcome of parenthood project during in vitro fertilization and after discontinuation of unsuccessful in vitro fertilization. *Fertil Steril* 2008; Epub ahead of print August 13.

Dunson DB, Baird DD, Colombo B. Increased infertility with age in men and women. *Obstet Gynecol* 2004;**103**:51–56.

Dutch Society for Obstetrics and Gynaecology. NVOG-Guideline no 09. Indication for IVF, 1998; http://nvog-documenten.nl/.

Eimers JM, te Velde ER, Gerritse R, Vogelzang ET, Looman CW, Habbema JD. The prediction of the chance to conceive in subfertile couples. *Fertil Steril* 1994;**61**:44–52.

Evers JL. Female subfertility. *Lancet* 2002;**360**:151–159.

Fauser BC, Devroey P, Macklon NS. Multiple birth resulting from ovarian stimulation for subfertility treatment. *Lancet* 2005;**365**:1807–1816.

Gauthier AH. The impact of family policies on fertility in industrialized countries: a review of the literature. *Popul Res Policy Rev* 2007; **26**:323–346.

Grant J, Hoorens S, Gallo F, Cave J. *A Preliminary Assessment of the Demographic and Economic Impact of Assisted Reproductive Technologies*. Santa Monica, CA: RAND Corporation, 2006.

Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. *Br Med J* 2004;**328**:261.

Henry L. French statistical work in natural fertility. In: Sheps M, Ridley JC (eds). *Public Health and Population Change*. Pittsburg: University of Pittsburg Press, 1965, 333–350.

Hille ET, Weisglas-Kuperus N, van Goudoever JB, Jacobusse GW, Ens-Dokkum MH, de Groot L, Wit JM, Geven WB, Kok JH, de Kleine MJ *et al*. Functional outcomes and participation in young adulthood for very preterm and very low birth weight infants: the Dutch Project on Preterm and Small for Gestational Age Infants at 19 years of age. *Pediatrics* 2007;**120**:e587–e595.

Hoorens S, Gallo F, Cave JA, Grant JC. Can assisted reproductive technologies help to offset population ageing? An assessment of the demographic and economic impact of ART in Denmark and UK: Case Report. *Hum Reprod* 2007;**22**:2471–2475.

Leridon H. *Human Fertility: The Basic Component*. Chicago: Chicago University Press, 1977.

Leridon H. Can assisted reproduction technology compensate for the natural decline in fertility with age? A model assessment. *Hum Reprod* 2004;**19**:1548–1553.

Lintsen AM, Eijkemans MJ, Hunault CC, Bouwmans CA, Hakkaart L, Habbema JD, Braat DD. Predicting ongoing pregnancy chances after IVF and ICSI: a national prospective study. *Hum Reprod* 2007;**22**:2455–2462.

Menken J, Trussell J, Larsen U. Age and infertility. *Science* 1986; **233**:1389–1394.

NICE. *Clinical Guideline 11: Fertility—Assessment and Treatment for People with Fertility Problems*. London: NICE, 2004.

O'Connor KA, Holman DJ, Wood JW. Declining fecundity and ovarian ageing in natural fertility populations. *Maturitas* 1998;**30**:127–136.

Rochon M. [Sterility and infertility: two concepts] Sterilite et infertilite: deux concepts. *Cah Que Demogr* 1986;**15**:27–56.

Schwartz D, Mayaux MJ. Female fecundity as a function of age: results of artificial insemination in 2193 nulliparous women with azoospermic husbands. Federation CECOS. *N Engl J Med* 1982;**306**:404–406.

Snick HK, Snick TS, Evers JL, Collins JA. The spontaneous pregnancy prognosis in untreated subfertile couples: the Walcheren primary care study. *Hum Reprod* 1997;**12**:1582–1588.

Spira A. Epidemiology of human reproduction. *Hum Reprod* 1986; **1**:111–115.

The European IVF monitoring programme for the European Society of Human Reproduction and Embryology, Andersen AN, Gianaroli L, Felberbaum R, de Mouzon J, Nygren KG. Assisted reproductive technology in Europe, 2002. Results generated from European registers by ESHRE. *Hum Reprod* 2006;**21**:1680–1697.

Tietze C. Time required for conception in 1727 planned pregnancies. *Fertil Steril* 1950;**1**:338–346.

van Balen F, Verdurmen JE, Ketting E. Age, the desire to have a child and cumulative pregnancy rate. *Hum Reprod* 1997;**12**:623–627.

van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, Broekmans FJ, van Dessel HJ, Bossuyt PM, van der Veen F, Mol BW *et al*. Pregnancy is predictable: a large-scale prospective external validation of the prediction of spontaneous pregnancy in subfertile couples. *Hum Reprod* 2007;**22**:536–542.

van Noord-Zaadstra BM, Looman CW, Alsbach H, Habbema JD, te Velde ER, Karbaat J. Delaying childbearing: effect of age on fecundity and outcome of pregnancy. *Br Med J* 1991;**302**: 1361–1365.

Wood J. Fecundity and natural fertility in humans. In: Milligen S (ed). *Reviews of Reproductive Biology*. Oxford: Oxford University Press, 1989, 61–109.

Submitted on October 31, 2008; resubmitted on December 19, 2008; accepted on January 2, 2009