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Short title:

Woman's age and discontinuation of IVF

Abstract

Treatment discontinuations are an important issue in IVF programmes. In the French context, financial constraint does not intervene in discontinuation until older ages. This study examined treatment discontinuation in IVF programmes, according to the woman's age and when there is no financial burden for couples. Medical records were collected for 3037 women who began their IVF programme between 1998 and 2002 in two French IVF units. Up to four attempts were taken into consideration. Cumulative success (delivery) rates were calculated, as well as discontinuation rates. Multiple imputation was applied to estimate a theoretical cumulative success rate as if no woman discontinued treatment before the end of the IVF programme without delivering. Cumulative discontinuation rates at the end of the IVF programme increased with the woman's age (41% for age<35, 56% for age 35–39, 80% for age ≥40). The benefit in terms of delivery rates of pursuing treatment would be smaller for older women (~10% for age<35, 7% for age 35–39, 4% for age ≥40). Even when treatment is reimbursed, the discontinuation rate is high for older women, suggesting that the strong decrease in success rate with age induces older women to discontinue.

Key words

Introduction

Since the middle of the twentieth century, epidemiologists and demographers have presented numerous results showing that the increasing age of a woman causes a decline in the biological ability to give birth to a child, i.e. fecundity (Henry 1961; Tietze 1957). These studies estimated that the age for the start of the fall in the probability of conception lay within the age range 31-35 years (Schwartz and Mayaux 1982; van Noord-Zaadstra et al. 1991).

A similar age effect has been shown for women undergoing *in vitro* fertilization (IVF). A decrease in the live birth rate per cycle started has been demonstrated in older women (Templeton et al. 1996). In particular, the success rate was highest for women aged between 25 and 30 and declined sharply after age 35.

In the light of some recent studies, it seems interesting to consider IVF success not only in relation to each attempt, but also throughout the entire IVF program consisting of several successive attempts (Land et al. 1997; Witsenburg et al. 2005). Witsenburg et al. carried out a cohort study in two centers in The Netherlands that included 1456 patients starting IVF treatment between 1996 and 2000 (Witsenburg, Dieben et al. 2005). They showed that although both centers had the same live birth rate per cycle (24%), their cumulative live birth rate differed significantly (59% vs. 49%). This was explained by the lower number of cycles undergone by the patient (due to a higher discontinuation rate) in the center with the lower cumulative success rate.

Treatment discontinuations are an important issue in IVF programs, as the proportion of women discontinuing treatment before having a child is very high. Land et al. reported a cumulative drop-out rate of 62% after the three cycles that are reimbursed by health insurance in The Netherlands (Land et al. 1997), while La

Rochebrochard et al. reported this cumulative drop-out rate to be 46% and 58% at the end of the fourth and last reimbursed cycle in two French IVF units (La Rochebrochard (de) et al. 2008).

Previous work suggests that the women who discontinue the IVF program may have a poorer prognosis of success than those who persevere (Sharma et al. 2002). In this context, life-table analysis has been shown to overestimate success rates (Daya 2005; Land et al. 1997; Witsenburg, Dieben et al. 2005), and so is considered as an "optimistic" estimation. Conversely, methods considering that patients who discontinue IVF have no chance of success lead to "conservative" estimations (Malizia et al. 2009). Various alternative methods have been developed to give a better estimate (Olivius et al. 2002; Soullier et al. 2008; Stolwijk et al. 2000). A possible solution would be to include the reason for discontinuation in the estimation of the cumulative success rate. The problem is that discontinuation of treatment is a matter of not deciding to continue, rather than deciding not to continue. It is defined a posteriori, when the women did not return to the IVF unit after a long period. Thus, the reason for discontinuation is not entered in the medical records and can be hard to determine. To study the reason for discontinuation, questionnaires must be sent to the women years after their last IVF attempt (Olivius et al. 2004; Rajkhowa et al. 2006). When we wish to estimate the cumulative success rate, it is important to take into account discontinuations of treatment. However, it is not the reason for discontinuation which is most important, but the chances of success that women who discontinued would have had. The two may be linked as women discontinuing for a medical reason are likely to have had poor chances of success if they had continued. However, when the objective is to estimate the success rate, data focus on medical records and do not clarify the reason for discontinuation. Rather, they provide

variables that are linked with both success and discontinuation and can be used to compare women discontinuing and women continuing, as well as to make inferences on the chances of success that women who discontinued would otherwise have had. This appears to be a promising method of providing a better estimation of the IVF success rate than that obtained with "optimistic" or "conservative" methods (Malizia et al. 2009).

The French social security system reimburses up to four IVF attempts to all couples until the woman is 43 years old. In this context, financial constraint does not intervene in discontinuation until older ages.

We aimed to examine treatment discontinuation in IVF programs, according to the woman's age and when there is no financial burden for couples.

Materials and methods

The Institutional Review Board (CNIL) approved the project in September 2005. Population and methods have been detailed in a previous article (Soullier et al. 2008) and are briefly described below.

Materials

Data were provided by two French IVF units (Cochin in Paris and Clermont-Ferrand, a medium-sized city in the center of France). All 3037 women beginning an IVF program between 1998 and 2002 in these two units were included. Data were collected from medical records and concerned all conventional IVF procedures and intracytoplasmic sperm injections (ICSI) undergone by the woman in the IVF unit, as well as data on frozen embryo transfers (FET) up to 2005. Data were collected until the woman's fourth attempt, four being the number of attempts which is refunded by the French social security system.

Definitions

An IVF program was therefore defined as a maximum of four successive attempts undergone by the woman in the IVF unit. An attempt was defined as an aspiration, i.e. an oocyte pick-up from the patient (cycles cancelled before oocyte retrieval were not included). Success of an attempt was defined as a delivery resulting from fresh or frozen embryo transfer. Only the first delivery was considered. Discontinuation of treatment was defined as no subsequent attempt in the IVF unit for at least two years at the time of data acquisition, whatever the reason for discontinuation (decision to stop IVF treatment, relocation to another area, decision to pursue treatment in

another IVF center, etc). Age was defined at the beginning of the IVF program and was considered as a categorical variable divided into 5 groups: <25, [25 – 29], [30 – 34], [35 – 39], and ≥40 years.

Methods

The observed cumulative delivery rate corresponded to the percentage of women entering the IVF unit and delivering during the IVF program.

The cumulative discontinuation rate corresponded to the proportion of women discontinuing treatment before the end of the IVF program without delivering expressed as a percentage of the women entering the IVF unit..

To evaluate the efficiency of the IVF technique, the theoretical cumulative delivery rate was calculated. This is the delivery rate which would be achieved if no woman discontinued treatment before the end of the IVF program. It was calculated by reconstituting a whole program for women who discontinue treatment as if they had in fact continued. Outcomes of attempts posterior to discontinuation were treated as missing and were estimated with multiple imputation (MI). The MI method consists of replacing each missing value by a set of plausible values in order to take into account the uncertainty about the correct value to impute. This method has been presented in detail elsewhere (Soullier et al. 2008; Soullier et al. 2010). The MI estimation was made using the known characteristics of women and of their previous aspirations: IVF unit, woman's age, number of oocytes retrieved and total number of embryos (defined as the sum of the number of transferred embryos and the number of frozen embryos). Following Rubin's recommendations, we made 5 imputations by

attempt (Rubin 1996). Multiple imputation was carried out using the SAS MI

procedure (SAS/STAT® 9.1 User's Guide. Cary, NC: SAS Institute Inc., 2004).

Results

Of the 3037 women included, 716 (24%) were aged between 25 and 29 years at the beginning of their IVF program, 1215 (40%) were aged between 30 and 34 years and 807 (27%) were aged between 35 and 39 years. The younger and older age groups were much smaller: at the beginning of the IVF program, 80 women (3%) were aged less than 25 years and 219 (7%) were aged ≥40 years. Median age at the beginning of the program was 32 years. On average, women were aged 33 years at the first and second attempts, 34 years at the third attempt and 35 at the fourth attempt.

The decrease in observed delivery rates with the woman's age is shown in Figure 1 (solid line). The three groups of women starting an IVF program before age 35 had similar chances of delivery. In older women, the observed cumulative delivery rate decreased for age 35-39 and declined sharply for age ≥40. These observed delivery rates at ages 35-39 and ≥40 differed significantly both from each other and from those of the age groups <35 years (p-values < 0.03).

On the other hand, cumulative discontinuation rates at the end of the IVF program increased with the woman's age (Table 1). Indeed, 41% of women starting an IVF program before age 35 years discontinued treatment before completion without delivering. This proportion increased to 56% for women starting a program between age 35 and 39 and was twice as high (80%) for women aged ≥40 at the beginning of the IVF program. Concerning the time of discontinuation, half of all women discontinuing treatment did so after the first attempt, 32% after the second and 18% after the third. This distribution was similar in the five age groups.

The theoretical cumulative delivery rate estimated what the cumulative delivery rates would be if no woman discontinued before the end of the IVF program

without delivering (Figure 1). This would increase the chances of delivery for women starting IVF before age 35 years by about 10%. Thus, younger women would have a more than 50% chance of delivery during the IVF program if none of them discontinued treatment. For women starting IVF when older than 35 years, the increase would be smaller: 7% for women starting between age 35 and 39, and 4% for women starting at 40 years or later. Overall, the delivery rate would increase from 37% to 46% if no woman discontinued treatment before the end of the IVF program without delivering.

Differences were also noted in the time elapsing between successive attempts according to the woman's age. On average, the time elapsing since the beginning of the IVF program was 1.0 year at the time of the second attempt, 1.8 years at the third attempt and 2.6 years at the fourth attempt (Table 2). However, the intervals between attempts were shorter for older age groups. Women beginning an IVF program before age 35 completed the fourth attempt approximately 2.7 years later, whereas women starting a program at age ≥40 took 1 year less to complete a program of four attempts (1.7 years). Carrying out the same analysis but including only the women who did not have frozen embryo transfers between aspirations, the same significant trend was observed at each attempt (p-values < 0.002). This result was therefore not due to a greater number of frozen embryo transfers for the younger women.

Discussion

Studying the effect of the woman's age on discontinuation of IVF treatment is a new and important topic. It is particularly interesting to study this issue in the French context, where four attempts are reimbursed by the French social security system for all women aged less than 43 years. Indeed, financial burden did not intervene in the decision to discontinue. We observed that the cumulative discontinuation rate was high and that it strongly increased with the woman's age.

We also noted a strong decrease in cumulative IVF success rates with the woman's age: from 44% at 25-29 years to 14% at over 40 years old. This decrease may be even greater if not only oocyte pick-up cycles but also all cycles where women started stimulation are included. In our study, this decrease can be explained both by a decrease in delivery rates following embryo transfer and by a decrease in the number of frozen embryo transfers following an IVF attempt. Indeed, after the first IVF attempt, 40% of women aged <35 years who did not obtain a delivery after fresh embryo transfer had at least one frozen embryo transfer, but this proportion decreased to 29% among women aged 35-39 years and 18% among those aged 40 years and older. In our analysis, the effect of the center's frozen embryo policy was controlled by including a center effect in the imputation model.

Both women and physicians are well aware of this decrease. Two results suggested that IVF success rates were being taken into account by the women who discontinued. First, the difference between the theoretical and the observed cumulative delivery rates was smaller for older women than for younger women. The theoretical cumulative delivery rate - the rate as if no woman discontinued unless she delivered - was estimated using multiple imputation based on variables

characterizing the main biological factors explaining IVF success and discontinuation for medical reasons (Sharma et al. 2002; Soullier et al. 2008; Templeton et al. 1996). The small difference between the observed and the theoretical cumulative success rates for older women might then suggest that most of these discontinuations were due to poor chances of success. Second, older women completed an IVF program more quickly than younger women: women aged <35 when they started the IVF program completed the whole program in almost three years, whereas women aged between 35 and 39 completed it in two years and women aged ≥40 in a year and a half. This difference was not due to a greater number of frozen embryo transfers undergone by the younger women. This could reflect the fact that physicians and/or women are aware that IVF efficiency decreases markedly after age 35. Therefore, physicians and their patients may be more likely to conduct IVF cycles in rapid succession, to diminish the effect of further age-related decline on IVF success. The hypothesis that women beginning an IVF program after age 35 received more rapid treatment has been suggested in a study in a French unit (Tain 2002). Such a possibility deserves more detailed research.

In a brand-new perspective, this work suggests that when financial constraint does not intervene, another process leads older women to discontinue treatment. Further research should be done to determine how this process originates: does the woman/couple make the decision to discontinue or do the medical staff strongly recommend it? In the latter case, the couple may consider pursuing treatment in another IVF unit. Further work should address the reasons and consequences of the decision to discontinue IVF treatment. Moreover, it will be important to develop these results by examining how cycles cancelled before oocyte pick-up affect the treatment discontinuation process. These cancelled cycles could represent 10% to 15% of all

cycles (Min et al. 2004) and center policies regarding cancellation of IVF treatment before oocyte pick-up may vary. This issue could not be dealt in the current study as data on all cycles where women started stimulation were not collected.

In a context of state reimbursement for all, the increase in discontinuation rates with the woman's age suggests that IVF care self-regulates. Even when the IVF attempts are reimbursed, the discontinuation rate is very high for older women, suggesting that the strong decrease in success rate with age induces them to discontinue treatment.

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Table 1. Cumulative discontinuation rates at the end of the IVF program according to the woman's age at the beginning of the program

Woman's age *(years)*	N	Cumulative discontinuation rate[a] %
< 25	80	41
25 - 29	716	41
30 - 34	1215	41
35 - 39	807	56
≥ 40	219	80
Overall	*3037*	*48*

[a] Proportion of women discontinuing treatment before the end of the IVF program without delivering expressed as a percentage of the women entering the IVF unit

Table 2. Length of time (in years) between the beginning of the IVF program and subsequent attempts, according to the woman's age at the beginning of the program

Woman's age (years)	Length of time (years) since the beginning of the IVF program					
	Attempt 2		Attempt 3		Attempt 4	
	N	*Mean*	*N*	*Mean*	*N*	*Mean*
< 25	49	1.1	20	2.0	12	2.7
25 - 29	433	1.1	230	2.0	108	2.8
30 - 34	759	1.0	424	1.8	219	2.7
35 - 39	443	0.8	221	1.5	118	2.2
≥ 40	104	0.6	38	1.2	12	1.7
p-value for trend	*<0.0001*		*<0.0001*		*<0.0001*	

Figure 1. Cumulative delivery rates according to the woman's age at the beginning of the IVF programme. Triangles with solid line = observed rates; squares with dotted line = theoretical rates.
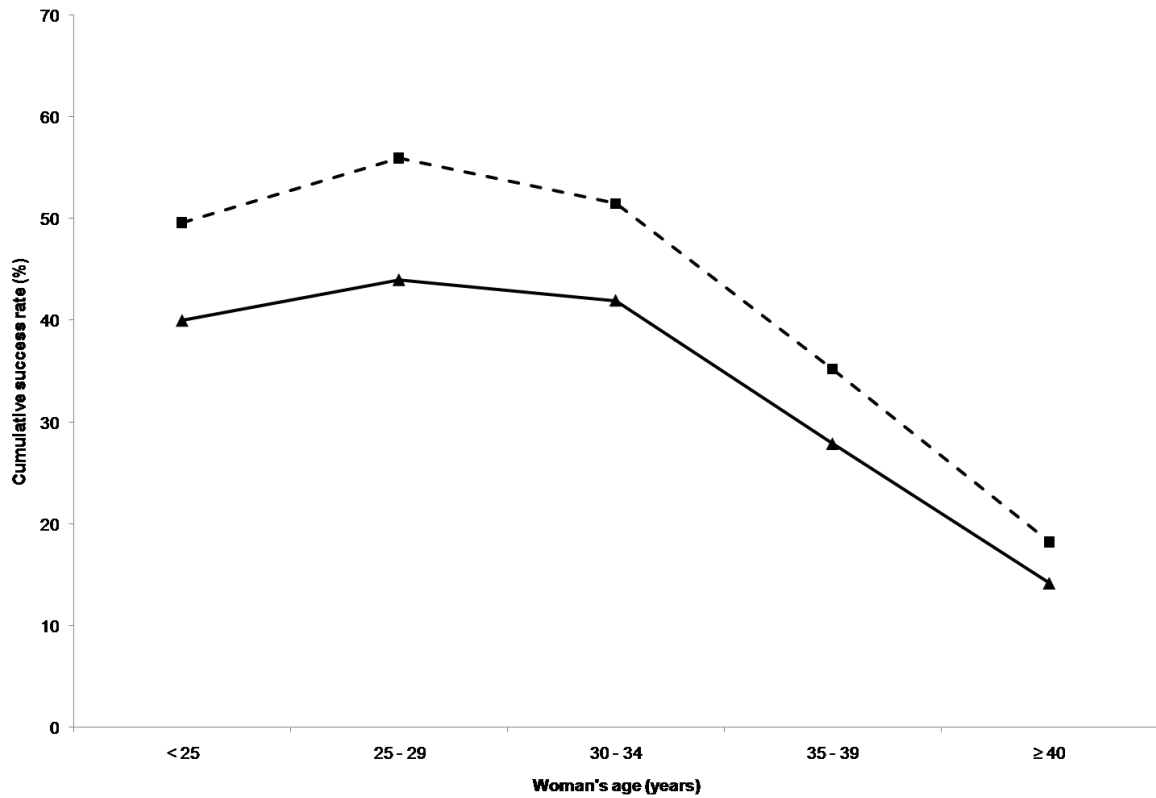
Data for figure 1

Age at the first attempt (years)	N	Observed rates	Theoretical rates
< 25	80	40.00	49.59
25 - 29	716	44.00	55.94
30 - 34	1215	41.98	51.46
35 - 39	807	27.88	35.19
≥ 40	219	14.16	18.19
Overall	*3037*	*36.78*	*45.74*