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Postponing pregnancy seeking and anticipating infertility treatments: an unwise combination

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ABSTRACT

Research Question: Natural fecundity and IVF-ICSI success rate both decrease with age. For this reason, in women older than 35, it is generally recommended to initiate the infertility work-up earlier. However, this assumption may expose couples to over-diagnosis and over-treatment.

Design: To shed light on this issue, we developed a theoretical model aimed at assessing the effects of starting the infertility work-up after 6 rather than 12 months of pregnancy seeking The assumptions of the model were: 1) infertile women are straightly treated with IVF-ICSI for up to three cycles; 2) IVF-ICSI success rate at first cycle linearly declines with age (3% per year), 3) the drop-out rate after the 1st and 2nd cycle is 18% and 25%, respectively, 4) the relative reduction of the success rate at 2nd and 3rd cycle is 16% and 26%, respectively.

Results: On these bases, the anticipation moderately improved the cumulative chances of live birth of a full IVF-ICSI program. This improvement depended on age. Specifically, it increased from 2.0% at age 35 to 3.0% at age 43. Conversely, the incremental success rate per single IVF cycle was mainly stable, varying only from 1.4% at age 35 to 1.3% at age 43.

Conclusions: In women older than 35, anticipation of the infertility work-up is associated with only a modest increase in the rate of success of IVF-ICSI. In most scenarios, this advantage may compare unfavorably with the chances of natural conception during the 6 months period.

Key words: motherhood; aging; IVF, cost-benefit

Key message

In older women, it is generally recommended to anticipate the infertility work-up after only 6 months of pregnancy seeking but this may expose couples to over-diagnosis and over-treatment. Based on a theoretical model, we actually showed that anticipating clinical management may not be justified and can cause wastage of resources.

Introduction

Postponing motherhood is a common demographic trend in the Western world (Schmidt *et al*., 2012). It is driven by a range of social processes such as the utilization of effective contraception, increases in women's education and labor market participation but also value changes and economic uncertainty (Mills *et al*., 2011). From a clinical perspective, it is a worrying phenomenon because women's fecundity declines with age and, in contrast to common beliefs, infertility treatments do not overcome the detrimental effects of women's aging (Mills *et al*., 2011; Schmidt *et al*., 2012; ESHRE Capri Workshop Group, 2017). Indeed, both natural fecundity and the rate of success of Assisted Reproductive Techniques (ARTs) decrease at a similar rate after age 35 and definitely end at about age 45. Live births after this age are anecdotal (Leridon, 2004; Van Voorhis, 2007; Somigliana *et al*., 2016).

Understanding and overcoming the detrimental effects of women aging represents a main research priority in reproductive medicine. However, up to now, efforts have been unfruitful and clinical applications disappointing (Crawford and Steiner, 2015; Igarashi *et al*., 2015). On these bases, the main scientific Societies engaged in the field, including the American Society of Reproductive Medicine (ASRM), the American College of Obstetrics and Gynecology (ACOG) and the National Institute for Health and Care Excellence (NICE) claim for the anticipation of clinical management (performing diagnostic tests and, if needed, treatments) for women who start seeking pregnancy after age 35 (NICE, 2013; ACOG and ASRM; 2014). In particular, the guidelines recommend to initiate the infertility diagnostic work-up after only 6 months of pregnancy seeking rather than the usual one year period. ASRM and ACOG also recommend to anticipate the initiation of treatments (ACOG and ASRM, 2014).

We argue that these recommendations actually generate a paradox with potential relevant public health consequences. In fact, it is recommended to anticipate clinical management in a population characterized by reduced fecundity, thus in a population that would conversely need a longer rather

than a shorter duration of pregnancy seeking to reach a reliable diagnosis of infertility (Somigliana *et al*., 2016). This situation can engender over-diagnosis and over-treatment and the well-known associated wastage of resources and undue exposure to risks (Carroll, 2017; Korenstein *et al*., 2018). Noteworthy, this tricky situation is complicated by the limited accuracy of the diagnostic work-up of infertility (Evers, 2012). Indeed, in the vast majority of cases, results of diagnostic tests alone do not enable us to reach an accurate diagnosis. Duration of regular sexual intercourses remains essential for a definitive diagnosis of infertility (Evers, 2002; ESHRE Capri Workshop Group, 2017).

To shed light on this potentially relevant issue, we developed a theoretical model to estimate the consequences of the anticipation of the clinical management of infertility in women older than 35 years.

Methods

The aim of the model was to explore the effects of starting the infertility work-up after 6 months of pregnancy seeking rather than the usual 12 months' period. We mainly aimed at determining whether the detrimental impact of a 6 months' delay on the chances of success of ARTs could justify this clinical position. The model was based on cost-beneficial considerations, ie on the balance between the potential benefits of anticipation in terms of increased live births on one hand and the exposure of undue risks and the incremental use of resources on the other hand. The perspective was the one of the health provider. The study was based on a theoretical model and was thus exempted from acceptance of the Institutional Review Board.

The main assumptions of the model were: 1) infertile women older than 35 years are straightly treated with *in vitro* fertilization or intra-cytoplasmatic sperm injection (IVF-ICSI) for up to three cycles (NICE, 2013); 2) IVF-ICSI success rate at first cycle linearly declines with age from 30% at 35 years up to 0% at 45 years (3% constant reduction per year) (ACOG and ASRM, 2014;

Sunderam *et al*., 2018) , 3) the drop-out rate after the 1st and 2nd cycle is 18% and 25%, respectively (Gameiro *et al*., 2013), 4) the relative reduction of the success rate at 2nd and 3rd cycle of IVF-ICSI is 16% and 26% (compared to first cycle), respectively (McLernon *et al*., 2016), 5) the detrimental impact of the time passing for the performance of the three attempts of IVF-ICSI was not considered because deemed poorly relevant and expected to similarly impact at any age.

Calculations of the total number of live births after IVF-ICSI treatments according to age are explained and illustrated in Figure 1. The impact of the anticipation is calculated as the difference between the number of live births that can be obtained at age X + 0.5 years and those that can be obtained at age X years. The Number need to be treated (NNT) is calculated as the ratio between 100 and this difference: it represents the number of patients that should be treated in advance to obtain one additional live birth. In the analyses, age ranged between 35 to 43 years because infertility treatments beyond 43 are not justified (NICE, 2013; ESHRE Capri Workshop Group, 2015; Devesa *et al*., 2018). Then, we ran sensitivity analyses for the chances of live birth, moving the basal probability at first IVF-ICSI cycle at 35 years (30% in the basal model) from 20% to 40% but keeping the reduction with time linear up to 0% at 45 (thus corresponding to a yearly reduction of 2% and 4%, respectively).

Finally, we calculated the incremental success rate (ISR) per IVF-ICSI cycle associated with the anticipation of treatment. The formula was:

$$ISR = (\text{Proc. at age } X / \text{LB at age } X) - (\text{Proc. at age } X+0.5 / \text{LB at age } X+0.5)$$

Where Proc. and LB represent the number of IVF-ICSI procedures and the number of live births, respectively. To support a beneficial effect of the anticipation, this ISR had to be superior to 7% (range 4-10%) which is the proposed thresholds of live birth rate to consider IVF-ICSI cost-beneficial (ESHRE Capri Workshop Group, 2015).

Calculations were done in an Excel file which is available as an additional material for those interested in adapting the analyses to their own setting.

Results

The increase of the success of the IVF-ICSI program associated to an anticipation of 6 months in the initiation of treatments changed with age, increasing from 2.0% at age 35 to 3.0% at age 43. The corresponding NNTs decreased from 49 at age 35 to 34 at age 43. These results are shown in Figure 2.

Figure 2 also illustrates the results of the pre-specified sensitivity analyses that modified the basal live birth rate at 35 years (30% in the basal model) to 20% and to 40%. In the former, the beneficial effects of the 6 months' anticipation on the success of the IVF-ICSI program increased from 1.6% at age 35 to 2.0% at age 43. The corresponding NNTs decreased from 63 to 49, respectively. For the latter (basal rate of success of 40%), the improvement progressively increased from 2.3% at age 35 to 3.9% at age 43. The corresponding NNTs decreased from 44 to 26, respectively.

In order to shed light on the incremental cost-beneficial ratio of the anticipation of treatment we calculated the incremental success rate per cycle (Figure 3). In the basal situation (live birth rate at 35 years of 30%), it decreased from 1.4% to 1.3% from age 35 to age 43. When setting the live birth rate at 35 years at 40%, the incremental success rate per cycle decreased from 1.9% to 1.8% from age 35 to age 43. Finally, for a live birth rate at 35 years set at 20%, it also slightly decreased but remained approximately 0.9%. In all the scenarios, the estimated impact is well-below the 4-10% thresholds used to define IVF-ICSI as cost-beneficial (ESHRE Capri Workshop Group, 2015).

Discussion

The diffused and shared idea that women older than 35 who are seeking pregnancy should anticipate the infertility work-up is questionable. Indeed, in our model, respecting the common definition of infertility (i.e. maintaining the limit of 12 rather than 6 months of regular sexual intercourses prior to initiate clinical management) was associated with only a marginal reduction in

the chances of success of ARTs (below 4% for all conditions tested corresponding to a NNT above 25). In addition, in all scenarios, the incremental rate of success per cycle associated to anticipation was < 2%, thus well-below the thresholds generally used to define IVF-ICSI as cost-beneficial (4-10%) (ESHRE Capri Workshop Group, 2015). Noteworthy, one should consider that a consistent proportion of women could conceive naturally in the 6 months interval, in particular for those aged 35 to 40 years. Regardless of any economical consideration, anticipation does not seem reasonable if the estimated chances of natural conception exceed the net benefit of an earlier treatment. One has to balance the calculated NNT with the natural pregnancies that can occur during these 6 months (Somigliana *et al*., 2016; van Eekelen *et al*., 2018). In other words, if the cumulative chance of pregnancy at 6 months are >4%, anticipation appears unwise. This threshold is presumably significantly lower if one were to include additional costs and risks associated to IVF-ICSI. To note, natural pregnancies in women seeking pregnancy for only a short period of time are relatively common. For instance, Van Eekelen *et al*. (2018) recently showed that in 38 years' old women seeking pregnancy for one year and without significant obstacles to conception, the chances of natural pregnancies over the following year is 25%. Moreover, Eijkemans *et al*. (2017) failed to observe any detrimental effect on the overall chances of pregnancy when comparing women with immediate access to IVF-ICSI to those with a delayed access. Importantly, this observation was not influenced by women's age.

One could argue that these considerations are merely speculative because of the common belief that IVF-ICSI could overcome age or could increase the chances of pregnancy compared to natural conception. However, this popular beliefs are unproven. A biological rationale is lacking and, up to now, there is no scientific evidence supporting this view, either directly (RCTs) or indirectly (ESHRE Capri Workshop Group, 2017). To our knowledge, there is only one RCT recruiting women of advanced reproductive age with "unexplained infertility" (age 38-42 years, pregnancy seeking > 6 months and unremarkable diagnostic work-up) (Goldman *et al*., 2014). The authors compared three different therapeutic approaches and failed to document any difference. Even if a

study group of women treated with expectant management was lacking, it is noteworthy that 37 out of the 177 eligible women (21%) had natural pregnancies, corresponding to 39% of all the recorded pregnancies (Goldman *et al*., 2014). Albeit indirect, this observation fuels the concerns against the indiscriminate anticipation of IVF-ICSI in this group of women.

A second possible concern against our view is related to the accuracy of the diagnosis. If the accuracy of the diagnostic armamentarium was high, anticipation would not be harmful. However, this is not the case. If on one hand an earlier diagnosis of patent causes of absolute infertility (such as severe male factor or bilateral tubal occlusion) could be beneficial because no pregnancies can occur in the delay of 6 months, on the other hand this could be detrimental for all the other causes of subfertility which represent the vast majority (Evers, 2002). A definite diagnosis is a difficult achievement in reproductive medicine. For this reason, there is now a commitment to use the term subfertility rather than infertility (Evers, 2002). The duration of the period of pregnancy seeking plays an essential role in the diagnosis, even when some causes of infertility emerge in the diagnostic work-up. For instance, the semen analysis is highly fluctuating and a remarkable overlap exists between fertile and infertile men (Guzick *et al*., 2001). With the exception of severe cases, the diagnosis of male infertility cannot be drawn in couples who have not sought for pregnancy for a relatively long period of time (1-2 years). Endometriosis is a cause of infertility but a significant proportion of women (up to 50%) can conceive naturally even in advanced stages (Vercellini *et al*., 2009; Leone Roberti Maggiore *et al*., 2015; Leone Roberti Maggiore *et al*., 2017). Most importantly, unexplained infertility is a common condition (it affects one quarter of couples) that is intrinsically linked to the duration of pregnancy seeking. Two thirds of young couples seeking pregnancy for one year who have an unremarkable diagnostic work-up are erroneously labeled with this diagnosis (Somigliana *et al*., 2016). They were just unlucky. Due to the natural decline of fecundity with age, this rate of false positive diagnoses boosts in women older than 35. It reaches 80% at age 37 and 90% at age 40. As a matter of fact, a reliable of diagnosis of unexplained infertility cannot be done in old women (Somigliana *et al*., 2016). More in general, drawing a

diagnosis of unexplained infertility in women older than 35 who are seeking pregnancy for only 6 months is clinically meaningless.

Based on our model, a mild increase in the proportion of women who could benefit from anticipation occurred with age, i.e. anticipation would be more justified in older women (above 40). This mild increase in the beneficial effects emerging from our analysis is due to the extremely low rate of success of the procedure in this age group, a situation that determines a significant increase in women persisting in the program (very few become pregnant and thus most remain in the program) and thus an increase in the number of procedures (and some more pregnancies). This is thus a kind of artifact that should not be used to claim a benefit of anticipation of treatment in this extreme age group. On the other hand, it has to be recognized that, theoretically, women older than 40 may particularly benefit from the anticipation because the proportion of those expected to conceive naturally is lower. Albeit plausible, this inference is speculative and would deserve to be validated with clinical evidence. Indeed, to date, IVF-ICSI has not been shown to overcome the detrimental effects of age (ESHRE Capri Workshop Group, 2017).

Some limitations of our model should be recognized. First, as a treatment, we exclusively took into consideration IVF-ICSI. One could argue that other treatments could also be used, including surgery or intrauterine insemination. However, the cost-beneficial balance of these interventions is debated and NICE does not recommend their use (NICE, 2013). Second, the assumption that IVF-ICSI success rate linearly declines with age may be argued. Even if at prima faces the reduction seems linear, this may be a simplistic view. On the other hand, we believe that the sensitivity analysis that varied the annual decrease in the rate of success from 2% to 4% may have overcome this possible criticism. Third, our model was very focused. We did not adopt a comprehensive approach as our model did not include the costs to perform diagnostic tests and treatments, the risks of IVF-ICSI and, most importantly, the chances of natural pregnancies. Such type of analysis would have enabled us to better estimate the detrimental effects of the anticipation. However, such

model would also be very complex and would require several assumptions that could ultimately affect its reliability. For instance, a validated model to calculate the chances of natural pregnancy over a 6 months period after 6 months of pregnancy seeking is lacking in the literature. To note, there is also no mean to disentangle the magnitude of the overlap between pregnancies obtained with IVF-ICSI and those occurring naturally. One may even argue that IVF-ICSI could not add new pregnancies if aging is the underlying cause of the 6 months delay in conceiving. In fact, there is no evidence to support that anticipated IVF-ICSI could really increase the chances of pregnancy in couples with unremarkable infertility work-up. Moreover, we judged that including in the model costs, risks and natural conceptions was not essential since anticipation emerged as poorly acceptable even without considering these additional aspects. On the other hand, we believe that future more articulated analyses can be foreseen to investigate another related issue, i.e. whether the duration of pregnancy seeking should be prolonged rather than reduced in women older than 35. Given the reduction of natural fecundity with age, the reliability of any diagnostic tests in old women is inevitably reduced. One might consider to raise the minimal duration of pregnancy seeking in women older than 35 up to two years. Interestingly, NICE recommends the anticipation of the diagnostic work-up in women older than 35 but does not recommend prompt IVF-ICSI in couples whose tests are unremarkable. Even in this group, the procedure is not indicated up to two years of pregnancy seeking (NICE, 2013). In other words, NICE guidelines are more aware of the risk of overtreatment, at least for couples without patent obstacles to conception.

Anticipation of diagnosis and treatment of infertility in women above 35 years is a clinical attitude that could expose a large proportion of couples to over-diagnosis and over-treatment. The situation is even more troublesome in the Western World where women typically postpone pregnancy seeking in the late thirties or even in the forties (Mills *et al*., 2011; Schmidt *et al*., 2012). If applied, a systematic policy of investigations and treatment after only 6 months of pregnancy seeking in women older than 35 can have a relevant impact, from both a clinical (undue exposure to risks) and economical perspective. In this regard, it has however to be highlighted that, in real life, physicians

and patients do not stringently follow the suggestions of the major scientific Societies and duration of pregnancy seeking is generally well-above 6 months. Nevertheless, we believe that there is the need for a more in-depth reasoning on this point. A blind plea for anticipation is not justified and evidence is required. To note, one could also maintain the indication for anticipation after 6 months in women older than 35 but this should be accompanied by a precise fertility workup to be used in these cases. It should be limited only to the most informative tests (mainly assessing tubal patency testing and semen quality) and should foresee stringent criteria for drawing an indication to IVF-ICSI. More in general, there is the urgent need for well-designed economical studies and RCTs aimed at disentangling the best approach for older women older than 35 who are seeking pregnancy rather than a blinded plea for anticipation of the clinical management.

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Figure legend

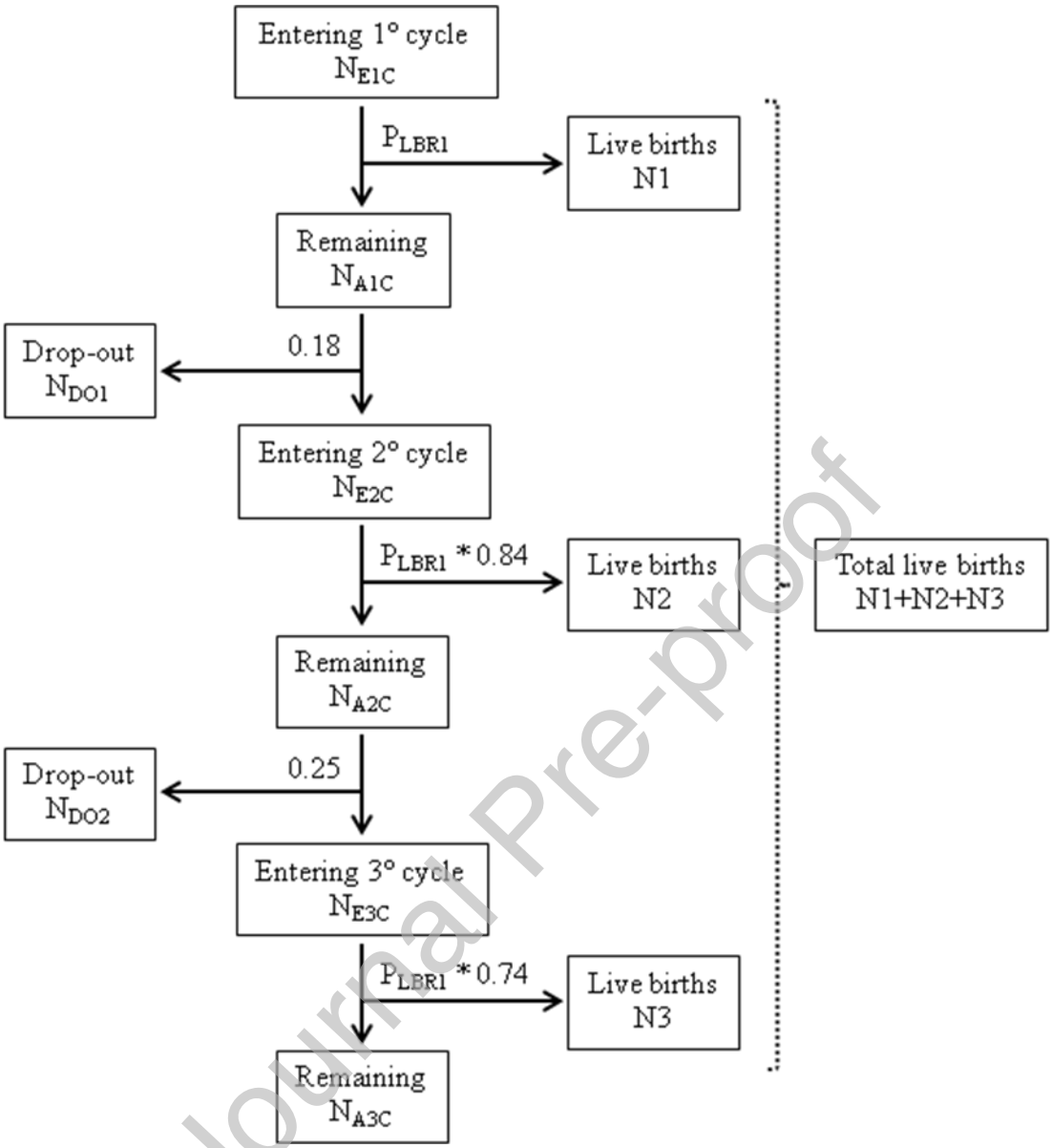

Figure 1: Calculations of the total number of live births that can be obtained in three IVF-ICSI cycles. $N_{E1C,}$ N_{E2C} and N_{E3C} represent the number of women entering the first, second and third cycle, respectively. N_{A1C}, N_{A2C} and N_{A2C} represent the number of women failing to become pregnant after first, second and third cycle, respectively. N_{DO1} and N_{DO2} represent the number of drop-outs after the first and second cycle, respectively. P_{LBR1} is the probability of live birth at first cycle. N1, N2 and N3 represent the number of live births that are obtained at first, second and third cycle, respectively. As an example, considering 100 women aged 35 years with P_{LBR1} a of 0.30, the calculated numbers of live births is 51.6. Six months later, at age 35.5, P_{LBR1} drops to 0.285 and the

calculated numbers of live births becomes 49.6. Anticipation of treatments from age 35.5 to age 35 thus leads to an overall increase of the chances of live birth with IVF-ICSI of 2% (51.6 - 49.6).

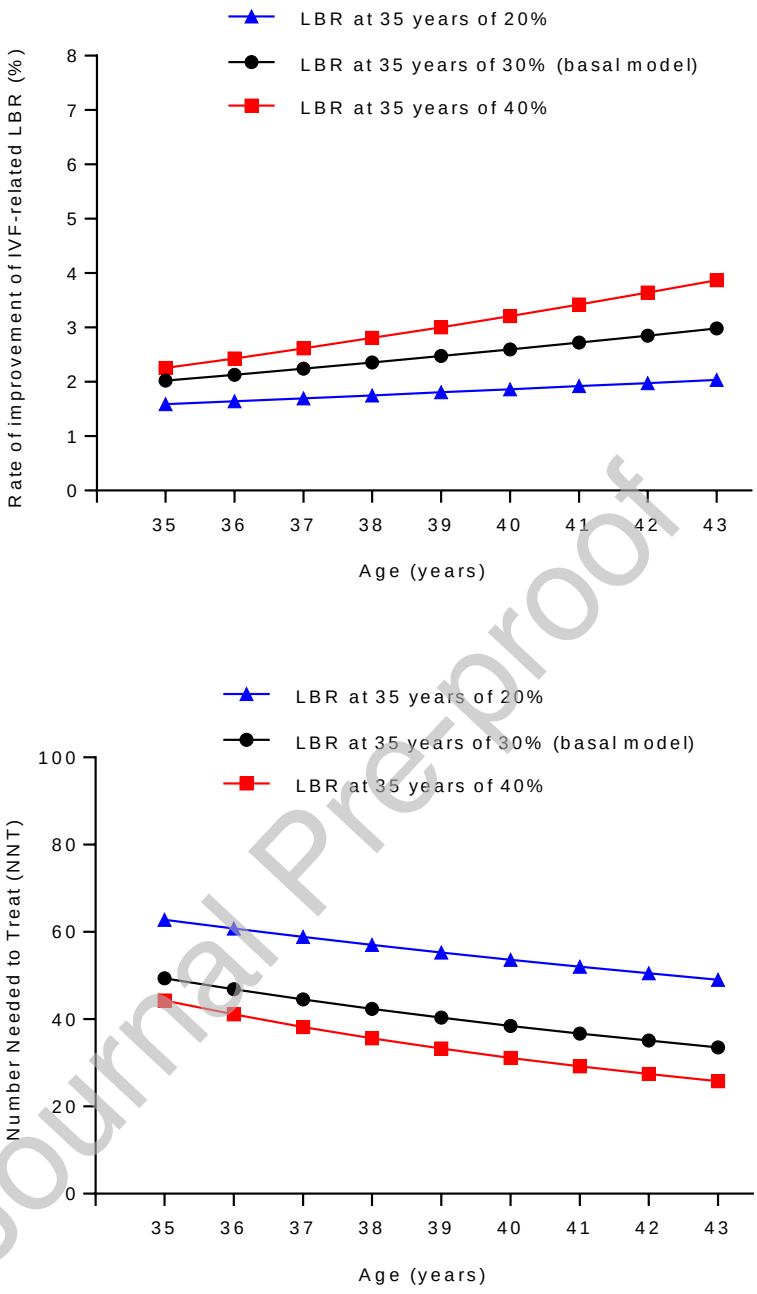

Figure 2: Impact of a 6 months anticipation on the effectiveness of a 3 cycles program of IVF-ICSI. The *upper panel* shows the absolute increase in the rate of success of the program in the basal condition (black line, corresponding to a 3% annual loss per cycle) and in the situations of an annual loss of 2% (blue line) and 4% (red line). In the lower panel, the same data is presented as Number Needed to be treated (NNT).

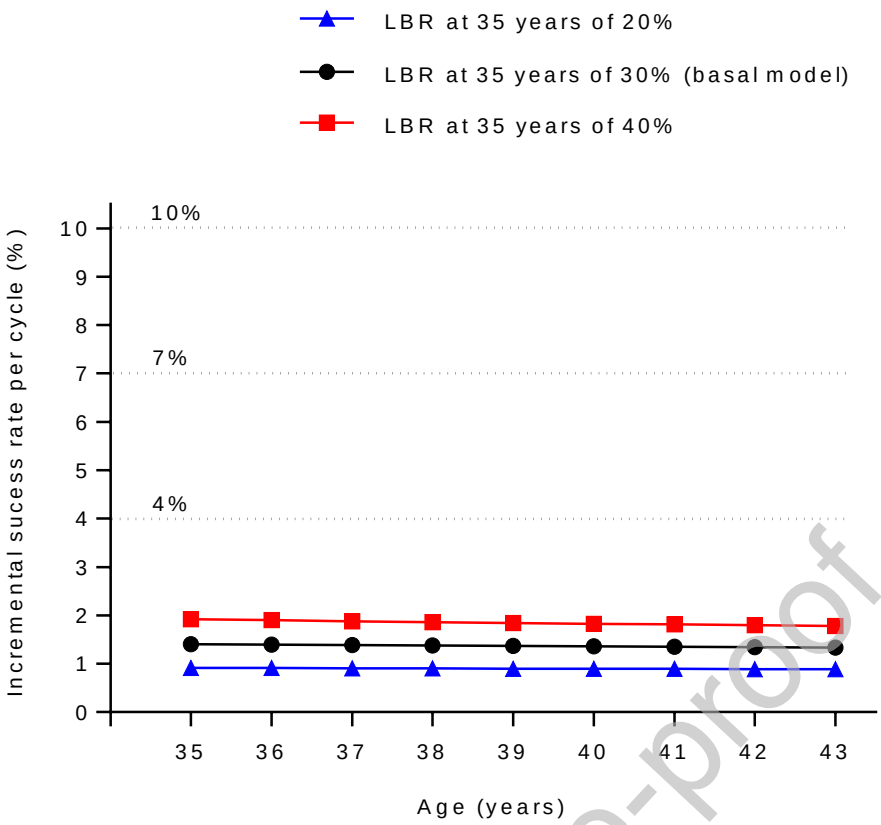

Figure 3: Impact of a 6 months anticipation on the incremental success rate per cycle. The figure shows the absolute percentage of increment in the three conditions (basal condition in black, 2% annual loss in blue line and 4% annual loss in red). The dotted lines refer to the thresholds used to consider IVF-ICSI cost-beneficial, i.e. a success rate of 7% (range 4-10%).