Prioritising IVF treatment in the post COVID 19 era: a predictive modelling study based on UK national data

Siladitya Bhattacharya*®, Abha Maheshwari*, Mariam Begum Ratna*, Rik van Eekelen^,

Ben Willem Mol*+, David J. McLernon*.

*School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, UK

^Centre for Reproductive Medicine, Academic Medical Centre University of Amsterdam, Netherlands

+Monash University, Monash Medical Centre, Victoria, Australia

® Corresponding author

Running title: Modelling post COVID scenarios for access to IVF

Abstract

STUDY QUESTION: Can we use prediction modelling to estimate the impact of coronavirus disease 2019 (COVID 19) related delay in starting IVF or ICSI in different groups of women?

SUMMARY ANSWER: Yes, using a combination of three different models we can predict the impact of delaying access to treatment by 6 and 12 months on the probability of conception leading to live birth in women of different age groups with different categories of infertility.

WHAT IS KNOWN ALREADY: Increased age and duration of infertility can prejudice the chances of success following IVF, but couples with unexplained infertility have a chance of conceiving naturally without treatment whilst waiting for IVF. The worldwide suspension of IVF could lead to worse outcomes in couples awaiting treatment, but it is unclear to what extent this could affect individual couples based on age and cause of infertility.

STUDY DESIGN, SIZE, DURATION: A population based cohort study based on national data from all licensed clinics in the UK obtained from the Human Fertilisation and Embryology Authority Register. Linked data from 9589 women who underwent their first IVF or ICSI treatment in 2017 and consented to the use of their data for research were used to predict livebirth numbers.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Three prediction models were used to estimate the chances of livebirth associated with immediate treatment versus a delay of 6 and 12 months in couples about to embark on IVF or ICSI.

MAIN RESULTS AND THE ROLE OF CHANCE: We estimated that a 6-month delay would reduce livebirths by 0.4%, 2.4%, 5.7%, 9.5% and 11.8% in women aged <30, 30-35, 36-37, 38-39 and 40-42 years, respectively, while corresponding values associated with a delay of 12 months were 0.9%, 4.9%, 11.9%, 18.8% and 22.4%, respectively. In women with known causes of infertility, worst case (best case) predicted chances of livebirth after a delay of 6 months in women aged <30, 30-35, 36-37, 38-39 and 40-42 years varied between 31.6% (35.0%), 29.0% (31.6%), 23.1% (25.2%), 17.2% (19.4%) and 10.3% (12.3%) for tubal infertility and 34.3% (39.2%), 31.6% (35.3%) 25.2%(28.5%) 18.3% (21.3%), and

11.3% (14.1%) for male factor infertility. The corresponding values in those treated immediately were 31.7%, 29.8%, 24.5%, 19.0% and 11.7% for tubal factor and 34.4%, 32.4%, 26.7%, 20.2% and 12.8 % in male factor infertility. In women with unexplained infertility the predicted chances of livebirth after a delay of 6 months followed by one complete IVF cycle were 41.0%, 36.6%, 29.4%, 22.4% and 15.1% in women aged <30, 30-35, 36-37, 38-39 and 40-42 years, respectively, compared to 34.9%, 32.5%, 26.9%, 20.7% and 13.2% in similar groups of women treated without any delay. The additional waiting period, which provided more time for spontaneous conception, was predicted to increase the relative number of babies born by 17.5%, 12.6%, 9.1%, 8.4% and 13.8%, in women aged <30, 30-35, 36-37, 38-39 and 40-42 years, respectively. A 12-month delay showed a similar pattern in all subgroups.

LIMITATIONS, REASONS FOR CAUTION: Major sources of uncertainty include the use of prediction models generated in different populations and the need for a number of assumptions. Although the models are validated and the bases for the assumptions are robust, it is impossible to eliminate the possibility of imprecision in our predictions. Therefore, our predicted live birth rates need to be validated in prospective studies to confirm their accuracy.

WIDER IMPLICATIONS OF THE FINDINGS: A delay in starting IVF reduces success rates in all couples. For the first time, we have shown that while this results in fewer babies in older women and those with a known cause of infertility, it has a less detrimental effect on couples with unexplained infertility, some of whom conceive naturally whilst waiting for treatment. Post COVID 19, clinics planning a phased return to normal clinical services should prioritise older women and those with a known cause of infertility.

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Introduction

IVF is the recommended treatment for those with prolonged unresolved infertility regardless of the underlying cause (NICE, 2023), with a total of just under 70,000 treatment cycles offered across the UK in 2017/18 (HFEA, 2020a). The coronavirus disease 2019 (COVID 19) pandemic had triggered a worldwide suspension of fertility treatments, including all planned IVF in the UK since March 2020. Key reasons behind this have been uncertainty about the impact of COVID 19 on pregnancy, a desire to reduce the burden of non-essential treatments during a national lockdown and the need to release clinical staff and resources from the fertility sector to deal with the pressing demands of COVID-related health problems.

Now that national measures to reduce person to person transmission have succeeded in decreasing rates of infection, emerging health data are starting to reveal the negative impact of prioritising COVID 19 pathways over other clinical areas (AOMRC, 2020) and the UK National Health Service and other health care systems are now planning a recovery phase for fertility clinics (HFEA 2020b). While patients are keen to access IVF and clinics want to treat them as quickly as possible, several months of inactivity have resulted in a sizeable backlog of untreated couples. The volume of activity within each IVF clinic is likely to be reduced by the demands of social distancing and the need to build resilience within the clinical team to cope with staff illness (ESHRE, 2020) and further periods of lockdown. While it is logistically easier to treat the patients in accordance with their position on a waiting list, this may not maximise the net health gain for the individuals, funders and society. Given the significant negative impact of increasing female age on the success of IVF (Templeton et al. 1996; Ratna et al. 2020), a

policy of prioritising older women in their 40s and late 30s could be helpful for this group but carries a risk of compromising outcomes in younger women forced to wait for several months for treatment.

It is therefore critical that any plans to restart fertility treatment are based on a prioritisation system, which aims to identify women who should be treated early in a manner that does not disadvantage those who may need to wait longer. Factors such as increased female age and a longer duration of pregnancy, which can compromise treatment success (Templeton et al. 1996; Lawlor and Nelson 2012; McLernon et al. 2016), and unexplained infertility, which is compatible with a reasonable chance of natural pregnancy (Brandes et al. 2011; Bhattacharya et al. 2008), need to be taken into account in assessing the net benefit of IVF in this group. Alviggi et al, (2020) have recently proposed using female age, ovarian reserve and previous history of ovarian stimulation to stratify women undergoing IVF into prognostic groups based on their chances of live birth. Apart from this, there is very little evidence in the literature to inform a prognosis-based plan for prioritising IVF treatment either at the national or individual clinic level.

We have previously developed a prediction model based on national IVF data (McLernon et al. 2016) to predict the chance of pregnancy leading to live birth over one or more complete cycles of IVF. This can be adapted to estimate the impact of delaying the start of treatment by 6 or 12 months. Any such estimate also needs to consider the chance of treatment-independent pregnancy in infertile couples with no identifiable barrier to conception using a separate prediction model (van Eekelen et al. 2017). The aim of this study was to adapt these existing fertility prediction models to estimate the impact of delayed treatment on the chances of live birth in different groups of women seeking IVF, based on their age and type of infertility.

Materials and methods

The Human Fertilisation and Embryology Authority (HFEA) collects data on all licensed fertility treatments in the UK. A detailed version of the HFEA database is available for research purposes under strict conditions, which links all IVF treatments to complete cycles and to individual women and allows estimation of the cumulative probability of a live birth (McLernon et al. 2016). Following approval by the North of Scotland Research Ethics Committee, the Confidentiality Advisory Group, and the HFEA register research panel, anonymised data from 2017 on all treatments linked to each woman undergoing IVF or ICSI were made available to the authors.

Study population

Linked data were extracted on consenting women who underwent their first complete IVF and ICSI cycle between January 2017 and December 2017 in the UK. A complete IVF cycle comprised a single episode of ovarian stimulation followed by replacement of all fresh and frozen embryos created from the oocytes retrieved. Women treated with non-autologous gametes, such as donor insemination, egg donation, and surrogacy, were excluded.

Statistical analysis

We used a prediction model we had developed earlier (McLernon et al. 2016) to estimate the probability of live birth over a complete IVF cycle in women who started IVF treatment in 2017. For each woman, we estimated outcomes at three time points – immediate treatment, a 6-month delay and a 12-month delay. This model uses the following characteristics: female age, duration of infertility, previous pregnancy status, IVF or ICSI treatment, and cause of infertility to calculate the chance of live birth over one complete cycle of IVF.

The predictions were initially calculated using data from women who had consented for research. The average predicted probability was then reported for the women treated in 2017 in each of the age

groups 40-42, 38-39, 36-37, 30-35 and < 30 years. For predictions associated with a delay in initiating treatment, we added an extra 6 or 12 months to both age and duration of infertility. In women with unexplained infertility, who have no absolute barrier to conception, we assumed that some would conceive whilst waiting for treatment. To obtain the predicted probability of natural conception leading to live birth in the 2017 patients, we applied a model developed from a cohort of Dutch couples with unexplained infertility (van Eekelen et al. 2017) and externally validated in a Scottish population (van Eekelen et al. 2018). From the point of completion of a couple's diagnostic work up, this model can estimate natural conception over different time periods based on the predictors female age, duration of infertility, primary versus secondary infertility, sperm motility and mode of referral for specialist fertility care (general practitioner versus gynaecologist). Since the last two variables were unavailable in our dataset, we assumed a normal sperm motility of 32% (Barratt et al. 2017) and referral by a general practitioner. To estimate the probability of natural conception over 6 months, we assumed that women with unexplained infertility would receive IVF on average 1 year after completion of their diagnostic workup. This was derived from women's median duration of infertility at the start of IVF (3 years) (Table I) less the median duration of infertility (2 years) at workup completion in a UK cohort (Mclernon et al, 2019). Thus, to derive the woman's age and duration of subfertility at the time of completion of the diagnostic workup, we subtracted 12 months from their age and duration of infertility at the time of starting IVF. As this model updated predictions at repeated time points, we used it to generate predictions from 1 year after completion of diagnostic workup – to reflect the time between diagnosis and the start of IVF treatment. We then predicted the chance of natural conception leading to ongoing pregnancy over the next 6 and 12 cycles that represent the 6- and 12-month delay in treatment. Ongoing pregnancy was defined as the presence of foetal cardiac activity at transvaginal sonography at a gestational age of at least 12 weeks. Since the dynamic model predicts natural conception leading to ongoing pregnancy, we converted these probabilities to the predicted probability of live birth by multiplying them by 0.95 (Braakhekke et al. 2014). This assumes that out of 100 women with an ongoing pregnancy, 95% will go on to have a live birth.

For women with other causes of infertility we used two different estimates for their chance of conceiving naturally. The first was a conservative assumption where we allocated all of these women with a zero chance of conceiving naturally. The second was an optimistic estimate, which was obtained through application of a model developed using a prospective cohort of Dutch couples with different causes of infertility who were registered on a national waiting list for IVF (Eijkemans et al, 2008). This model can estimate natural conception over 1 year based on the predictors female age, duration of infertility, primary versus secondary infertility, and cause of infertility. In order to apply this model to our dataset we had to estimate the baseline survival at 6 months and 12 months because this information was not reported in the original article. However, a later article that provided predictions for women with different characteristics using this model allowed us to estimate the baseline survival at 12 months (Eijkemans et al, 2017). To calculate predicted probabilities at 6 months we multiplied the 12-month predictions by 0.6 (van Eekelen et al, 2017).

We incorporated these chances into the overall impact on delayed IVF using the following equation:

Predicted probability of live birth with Delayed IVF, $P_{delay} = P_{NC} + (1- P_{NC}) \text{ X } P_{IVF}$

where P_{NC} = Predicted probability of conception during delay leading to live birth; and P_{IVF} = Predicted probability of live birth over one complete cycle of IVF which starts after the delay.

Where there was no delay (i.e. immediate IVF), $P_{NC} = 0$.

The difference in live birth predictions between each delay period and immediate treatment were calculated for all women in the linked consented HFEA dataset, then averaged for different causes of infertility and age groups of women. As well as the difference in predictions between scenarios, we also estimated the percentage change in live birth predictions.

When we applied our original IVF prediction model (Mclernon et al, 2016) to the 2017 data the C-statistic was 0.60 (0.59 to 0.61). The calibration intercept was -0.58 (95% CI: -0.63 to -0.52) and the calibration slope was 0.78 (0.70 to 0.87) suggesting that the model did not fit well to the 2017 dataset (Supplementary Fig. S1a). Therefore, the model was recalibrated by multiplying the parameter estimates in the model equation by the calibration slope and then adding the calibration intercept. After recalibration the model showed much better agreement (Supplementary Fig. S1b).

Ethics

Access to the linked anonymised HFEA database for this study was approved by the North of Scotland Research Ethics committee (12/NS/0119) and the HFEA Research Registry Panel.

Patients and the public were not involved in designing this study, analysing the results or writing this paper.

Results

A total of 24,839 couples underwent their first IVF or ICSI treatment in 2017. After excluding women who did not provide consent for their data to be used for research, our linked anonymised version of the HFEA dataset included 11,575 couples. We excluded 1,039 couples with no recorded cause of infertility and 947 couples with more than one cause of infertility. This left 9,589 couples whose characteristics are shown in Table I. The profile of women whose linked data were used to calculate our predictions resembled that of the whole population embarking on IVF in 2017 (Supplementary Table SI).

Table II shows the predicted probability for immediate treatment versus a 6-month delay in IVF or ICSI in women of different age groups. A 6-month delay in access to a complete IVF cycle was estimated to result in an absolute reduction in live birth chances by 0.1% (0.4%), 0.8% (2.4%), 1.5% (5.6%), 1.9%

(9.5%) and 1.5% (11.8%) in women aged <30, 30-35, 36-37, 38-39 and 40-42 years, respectively. Table II also shows the corresponding absolute and relative percentage reduction in the chance of live birth caused by delaying the start of treatment by 12 months to be 0.3% (0.9%), 1.6% (4.9%), 3.2% (11.9%), 3.8% (18.8%) and 2.9% (22.4%) for those same age groups.

Table III compares the outcomes of immediate treatment with those associated with a 6-month delay in hypothetical women with no previous pregnancy and a 2-year duration of infertility. For example, in a 30-year-old woman with tubal infertility, the chance of an IVF live birth falls from 31.5% if treated immediately to 31.1% if treated at 6 months in the conservative scenario, where we assume that she has no chance of conceiving naturally during those 6 months. However, an optimistic scenario predicts her chances of a live birth to be as high as 34.3% if treated at 6 months. In a 30-year-old woman with unexplained infertility, the chance of an IVF live birth falls from 34.2% if treated immediately, to 33.8% if treated after 6 months. However, this is more than compensated by a 10.2% chance of treatment independent pregnancy whilst waiting, such that overall predicted chance of a live birth following delayed treatment is 40.6%. The corresponding predictions associated with a 12-month delay in hypothetical women are presented in Table IV.

Tables V and VI report on predicted chances of live birth in women with unexplained as well as other types of infertility. In women with infertility associated with tubal disease, endometriosis, male factor or ovulatory disorders, if the chances of conceiving naturally are assumed to be nil, the impact of delay on predicted live birth worsens in women from the age of 30 years (Tables V and VI). A more optimistic approach reverses this trend, but the effect is modest in all except women under 35 years.

In women with tubal infertility, conservative (optimistic) chances of predicted live birth rates after a 6-month delay are 31.6% (35.0%), 29.0% (31.6%), 23.1% (25.2%), 17.2% (19.4%), and 10.3% (12.3%) in women aged <30, 30-35, 36-37, 38-39, and 40-42 years, respectively (Table V): in contrast, the

corresponding live birth rates associated with immediate treatment are 31.7%, 29.8%, 24.5%, 19.0%, and 11.7% in the corresponding age groups.

In women with endometriosis facing a delay of 6 months, even an optimistic approach is unable to show an increase in live birth rates in women over 35 years (Table V). While the absolute chances of live birth range from a 0.8% reduction to a 1.0% increase in women aged 30-35 years, for those aged 40-42 years the same delay would cause an absolute decrease ranging from -0.5% to -1.9% (see Table V).

A 12-month wait is associated with a fall in the anticipated live birth rate - from 31.5% to 29.8% in women with endometriosis aged 30-35 and 12.4% to 9.6% in those aged between 40 and 42 years (Table VI). An optimistic estimate improves the chance of live birth by 1.4% in women aged 30-35 years, but not for those who are older (Table VI).

In women with tubal infertility, a 12-month delay is associated with a decrease in the chance of live birth from 29.8% to 28.3% in those aged 30-35 and 11.7% to 9.1% in those aged between 40 and 42 years, assuming a 0% chance of natural pregnancy (Table VI). However, an optimistic prediction would see these chances increase to 32.5% and 12.4%, respectively.

In women with unexplained infertility, the negative impact of a delay in starting IVF is compensated by the chance of conceiving without treatment whilst waiting. Thus, the predicted chance of a live birth in those facing a 6-month wait, which includes the chance of conceiving naturally during those 6 months followed by the chance of conceiving with IVF, is 36.6% in women aged 30-35 years and 15.1% in women aged 40-42 years compared to 32.5% and 13.2% in women treated without any delay. (Table V). A 12-month delay shows similar projections, with a live birth rate of 39.4% in women aged 30-35 years and 16.3% in women aged 40-42 years compared to 32.5% and 13.2% in women treated without any delay.

Discussion

Principal findings

Our results show that delaying the start of IVF by 6 or 12 months has relatively little impact on the chances of live birth in younger women but substantially compromises outcomes in women over 40 years of age. In those with unexplained infertility, a delay of up to 1 year may not be detrimental as couples can conceive whilst waiting for treatment, with IVF being available later for all those who do not. This holds true for older women as well, although the additional benefit is small in those who wait. In other types of infertility, predictions assuming no chance of natural pregnancy suggest compromised outcomes in all those who have to wait 6 or 12 months. A more optimistic prediction, which is based on the expectation of some treatment independent conceptions whilst waiting for IVF or ICSI, show a modest rise associated with delay, especially in younger women.

Strengths and weaknesses

This is the first study to use national data to predict the consequences of delaying the start of IVF in different groups of women, whilst incorporating the chances of natural pregnancy in couples with different categories of infertility. This is a critical step in assessing the additional value of IVF (NICE, 2013) but is often missing in previous studies, as is the use of a model that can estimate live birth after a complete cycle (McLernon et al.2016).

This study has several limitations. Our predicted live birth rates need to be validated in prospective studies to confirm their accuracy. Major sources of uncertainty include the use of prediction models generated in different populations and the need for a number of assumptions. Although the models are validated and the bases for the assumptions are robust, it is impossible to eliminate the possibility of imprecision in our predictions. We have combined IVF and its variant ICSI in a single model under the broad term “IVF” as the most pragmatic approach in the present context, although observational

work has reported slight differences in outcomes between the two (Lawlor and Nelson 2012). As ICSI has not been shown to be more effective than IVF for non-male infertility and is not recommended for any other situations (NICE,2013), this approach should not compromise our predictions in the unexplained cohort where this diagnosis has been excluded.

Another potential weakness is the fact that we were only able to use linked data from consenting couples for our predictions, although the characteristics of participants do not appear to be different to those of the complete cohort. As data for 2020 are not yet available, our predictions for those facing IVF treatment delay are based on couples treated in 2017.

In conditions other than unexplained infertility, we have assumed the chances of natural conception to range between nil and an optimistic value obtained from a prognostic model (Eijkemans et al, 2008; Eijkemans et al, 2017). This is because a small proportion of women with other causes, such as unilateral tubal block, endometriosis, irregular ovulation and partners with deranged semen parameters, have been known to get pregnant without treatment (Arce et al. 2005; Collins et al. 1995) but these chances are generally perceived to be low enough to recommend active treatment rather than an expectant approach (NICE, 2013).

Findings in context of the literature

Our results are consistent with the conclusions of previous studies (Ratna et al. 2020; van Eekelen et al. 2018; van Loendersloot et al. 2010; van Loendersloot et al. 2014), which have all highlighted the importance of female age and duration of infertility in determining the chances of success following IVF treatment. The impact of age is likely to be mediated by its effect on ovarian reserve but recent data from women with diminished ovarian reserve suggest that delaying the start of IVF by up to 180 days has had little impact on success rates (Romanski et al, 2020).

Less well researched, owing to the paucity of relevant data, is the chance of natural conception in untreated couples with unexplained infertility. Limited data from the literature indicate that couples who have been trying for a relatively short duration have a good chance of natural conception and thus may not benefit from immediate access to IVF (Brandes et al. 2011). Few previous models have been able to compare individualized chances of conception associated with IVF relative to chances of natural conception in the same population (van Eekelen et al. 2019). Those which have done so have reported live birth outcomes in couples embarking on a strategy of expectant management or IVF without the ability to report separately on the chances of treatment- related and treatment-independent pregnancies at different points in time (Barratt et al. 2017). The predicted live birth rates in our study may appear optimistic, but it is worth noting that these not only include the chance of natural conception whilst waiting, but also the additional benefit of IVF in those who start treatment at 6 or 12 months. As such they are not inconsistent with the 24.5% (95% CI: 20-29%) chance of natural conception over 12 months in a randomised cohort of couples (van Eekelen et al. 2018) or a 17% chance of natural live birth over 5 years following unsuccessful IVF treatment (Romanski et al. 2020). The literature contains few recent studies on natural chances of conception in couples with known causes of infertility. A prospective cohort study on Dutch couples awaiting IVF or ICSI in The Netherlands showed that although the chances of treatment-independent pregnancy were lower in this group they were not insignificant (Eijkemans et al, 2008). The likelihood of natural conception varied according to the type of infertility, and provided the basis for our optimistic predictions of natural pregnancy in this group.

Our primary aim was to investigate the impact of delaying treatment in different groups of couples registered to start IVF in order to inform a strategy for sequencing treatment in the post pandemic recovery period. The results are therefore not comparable to those from studies modelling the chances of live birth following immediate IVF compared to a 1-year delay (El Mokhallalati et al. 2019). As our aim is to explore the consequences of disruption of IVF services, we report outcomes following

different waiting times for access to IVF. Our analysis therefore focuses on the period between the decision to have IVF and the start of treatment and does not mandate a similar time horizon for follow-up for all couples. This approach disregards the chance of natural conception following unsuccessful IVF in those who have immediate treatment as our question was formulated to aid decision making around starting IVF rather than to explore the value of IVF in couples with unexplained infertility. From a clinical perspective, the answer is unlikely to influence decision making in couples already committed to active treatment.

From a methodological point of view, any assumptions around the appropriate time horizon for follow up will be imprecise as the length of time needed for a complete cycle of IVF treatment is variable. In addition, the use of our dynamic model, which was developed to estimate pre-treatment natural conception, may not be valid for predictions in a post IVF cohort of couples in whom the chance of conceiving naturally after failed IVF may be lower.

Clinical implications

We anticipate that our results will help to inform a process of phased access to IVF in a post COVID 19 recovery period. The estimates of live birth in different categories of infertile women is expected to help patients understand the rationale for decisions made by clinics, funders and policy makers in formulating a strategy for re-starting IVF treatment.

Our predicted estimates show that older women, particularly those with a low chance of natural conception, are at highest risk if left untreated for 6 months or more. Whilst the impact is highest on women over 40 years, this is true for women in their mid and early thirties with known causes of infertility: an age-based sequencing would appear to be the logical approach in this group.

The situation is different in couples with unexplained infertility whose background rate of natural conception can offset any reduction in IVF success rates associated with a delay of 6-12 months. Our estimates show an age-linked trajectory, with greater gains in younger women. As with all predictions, these values need to be interpreted with caution and while this information may be reassuring for some patients, others might feel that a policy of deferred treatment does not acknowledge their personal preferences. Previous research has revealed that many in this group tend to find an expectant approach frustrating and seek to commence early treatment (Kersten et al. 2017; van den Boogaard et al, 2011).

It is worth noting that in couples who fail to conceive during the waiting period of 6-12 months, the delay will impact on their future chances of live birth. As most couples are unlikely to conceive after their first complete cycle of IVF, this delay is likely to have consequences for the cumulative chances of having a baby over a series of treatments.

Our results challenge the current policy of applying access criteria based on a fixed duration of unexplained infertility for couples with different prognostic profiles (NICE, 2013) and support recent guidance (RCOG, 2020) advising earlier hospital appointments for older women. In addition to prognostic profiles, individual clinics may have to consider the size of their backlog, anticipated volume of activity and the proportion of women in different age and diagnostic categories in order to prioritise access to treatment.

Research recommendations

This research exposes the limitations of the literature in providing a robust evidence base for individualised, prognosis-based decision making in assisted reproduction and the limitations of interpreting IVF success rates in couples with unexplained infertility without factoring in the chance of treatment-independent pregnancies. In the absence of suitably powered randomised trials

comparing IVF with expectant management (Pandian et al, 2015), future research should focus on large population-based studies, which can generate data on conception with and without IVF. Further refinement of dynamic models, which allow repeated predictions over time, are needed to inform decisions to transition from an expectant approach to active treatment. This can only be possible through widespread use of general fertility registries, which are rare in comparison with IVF data collection systems.

Conclusion

Delay reduces IVF success rates in all couples. This results in a lower chance of live birth in older women, especially those with a known cause of infertility. In women with unexplained infertility, the impact of delay is more than compensated by the chance of natural conception during a 6-12month treatment-free interval. In the post COVID 19 recovery period, clinics planning a phased return to normal clinical services should prioritise older women, particularly those with a known cause of infertility.

Data availability

The data underlying this article were provided by the Human Fertilisation and Embryology Authority by permission. Data may be shared on request to the corresponding author with permission of Human Fertilisation and Embryology Authority.

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Authors' roles

SB, DJM and AM designed the study. DJM and MBR conducted the statistical analysis and SB wrote the article. All authors contributed intellectually to the writing or revising of the manuscript and approved the final version. SB is the guarantor.

SB affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; the study has been conducted as planned and no important aspects of the study have been omitted.

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We plan to disseminate the results to patient organisations and the Human Fertilisation and Embryology Authority.

Conflict of interest

Authors declare that no support was received from any organisation for the submitted work; there are no financial relationships with any organisations in the past three years that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work. Authors with conflicts outside the submitted work have completed the ICMJE uniform disclosure form. B.W.M. is supported by an NHMRC Practitioner Fellowship (GNT1082548) and reports consultancy work for ObsEva, Merck, Merck KGaA, Guerbet and iGenomics. SB is Editor-in-Chief of *Human Reproduction Open*.

References

Academy of Medical Royal Colleges Effects on health from non-COVID-19 conditions and moving forward to deliver healthcare for all 2020

AOMRC 2020 https://www.aomrc.org.uk/wp-content/uploads/2020/05/200515_COVID19_moving_forward_to_deliver_healthcare.pdf

Alviggi C, Esteves SC, Orvieto R, Conforti A, La Marca A, Fischer R, Andersen CY, Bühler K, Sunkara SK, Polyzos NP, Strina I, Carbone L, Bento FC, Galliano D, Yarali H, Vuong LN, Grynberg M, Drakopoulos P, Xavier P, Llacer J, Neuspiller F, Horton M, Roque M, Papanikolaou E, Banker M, Dahan MH, Foong S, Tournaye H, Blockeel C, Vaiarelli A, Humaidan P, Ubaldi FM; POSEIDON (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number) group. COVID-19 and assisted reproductive technology services: repercussions for patients and proposal for individualized clinical management.

Reprod Biol Endocrinol. 2020 May 13;18(1):45. doi: 10.1186/s12958-020-00605-z

Arce JC, Nyboe Andersen A, Collins J. Resolving methodological and clinical issues in the design of efficacy trials in assisted reproductive technologies: a mini-review.

Hum Reprod 2005;**20**:1757-71.

Barratt CLR, Björndahl L, De Jonge CJ, Lamb DJ, Osorio Martini F, McLachlan R, Oates RD, van der Poel S, St John B, Sigman M, Sokol R, Tournaye H. The diagnosis of **male infertility**: an analysis of the evidence to support the development of global WHO guidance-challenges and future research opportunities.

Hum Reprod Update 2017;**23**:660-680. doi: 10.1093/humupd/dmx021.

BBC 2020 https://www.bbc.co.uk/news/health-52504522

Bhattacharya S, Harrild K, Mollison J, Wordsworth S, Tay C, Harrold A, McQueen D, Lyall H, Johnston L, Burrage J, Grossett S, Walton H, Lynch J, Johnstone A, Kini S, Raja A, Templeton A. Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for

unexplained infertility: pragmatic randomised controlled trial. BMJ 2008;**337**:a716. doi: 10.1136/bmj.a716.

Braakhekke M, Kamphuis EI, Dancet EA, Mol F, van der Veen F, Mol BW. Ongoing pregnancy qualifies best as the primary outcome measure of choice in trials in reproductive medicine: an opinion paper. Fertil Steril 2014;**101**:1203-4.

Brandes M, Hamilton CJ, van der Steen JO, de Bruin JP, Bots RS, Nelen WL, Kremer JA. Unexplained infertility: overall ongoing pregnancy rate and mode of conception. Hum Reprod 2011;**26**:360-8. doi: 10.1093/humrep/deq349. Epub 2010 Dec 16.

British Fertility Society 2020 https://www.britishfertilitysociety.org.uk/2020/05/06/arcs-and-bfs-u-k-best-practice guidelines-for-reintroduction-of-routine-fertility-treatments-during-the-covid-19-pandemic/

Collins JA, Burrows EA, Wilan AR. The prognosis for live birth among untreated infertile couples. Fertil Steril 1995;**64**:22-8.

Eijkemans MJC, Lintsen AME, Hunault CC, Bouwmans CAM, Hakkaart L, Braat DDM, Habbema JDF. Pregnancy chances on an IVF/ICSI waiting list: a national prospective cohort study. Hum Reprod 2008; 23: 1627-32.

Eijkemans MJC, Kersten FAM, Lintsen AME, Hunault CC, Bouwmans CAM, Hakkaart-van Roijen L, Habbema JDF, Braat DDM. Cost-effectiveness of 'immediate IVF' versus 'delayed IVF': a prospective study. Hum Reprod 2017; 32: 999-1008.

El Mokhallalati Y, van Eekelen R, Bhattacharya S, McLernon DJ. Hum Reprod 2019;**34**:1470-1478. doi: 10.1093/humrep/dez099. Hum Reprod. 2019.PMID: 31306480

ESHRE 2020 European Society for Human Reproduction and Embryology https://www.eshre.eu/Home/COVID19WG

HFEA 2020 (a) https://www.hfea.gov.uk/media/2716/the-state-of-the-fertility-sector-2017-2018-final-accessibility-checked.pdf

HFEA 2020 (b) https://www.hfea.gov.uk/treatments/covid-19-and-fertility-treatment/coronavirus-covid-19-guidance-for-professionals/

Kersten FA, Hermens RP, Braat DD, Hoek A, Mol BW, Goddijn M, Nelen WL. Improvement Study Group. Overtreatment in couples with unexplained infertility. Hum Reprod 2015;**30**:71-80. doi: 10.1093/humrep/deu262. Epub 2014 Oct 21. PMID: 25336712

Kersten FAM, Lintsen AME, Hunault CC, Bouwmans CAM, Hakkaart-van Roijen L, Habbema JDF, Braat DDM. Cost-effectiveness of 'Immediate IVF' versus 'Delayed IVF': A Prospective Study. Hum Reprod 2017;**32**:999-1008. doi: 10.1093/humrep/dex018.

Lawlor DA and Nelson SM. Effect of age on decisions about the numbers of embryos to transfer in assisted conception: A prospective study. Lancet 2012;**379**:521.

McLernon DJ, Lee AJ, Maheshwari A, van Eekelen R, van Geloven N, Putter H, Eijkemans MJC, van der Steeg J, van der Veen F, Steyerberg EW, Mol BW, Bhattacharya S. Predicting the chances of having a baby with or without treatment at different time points in couples with unexplained subfertility. Hum Reprod 2019;**34**:1126-1138.

McLernon DJ, Steyerberg EW, Te Velde ER, Lee AJ, Bhattacharya S. Predicting the chances of a live birth after one or more complete cycles of in vitro fertilisation: population- based study of linked cycle data from 113 873 women. BMJ 2016;**355:**i5735. doi: 10.1016/S0140-6736(11)61267-1. Epub 2012 Jan 12.

NICE National Collaborating Centre for Women's and Children's Health. Fertility: assessment and treatment for people with fertility problems. 2013. https://www.nice.org.uk/guidance/cg156/evidence/ full-guideline-188539453.

Pandian Z, Gibreel A, Bhattacharya S. In vitro fertilisation for unexplained subfertility. Cochrane Database Syst Rev 2015;**2015**:CD003357. doi: 10.1002/14651858.CD003357.pub4.

Ratna MB, Bhattacharya S, Abdulrahim B, McLernon DJ. A systematic review of the quality of clinical prediction models in in vitro fertilisation. Hum Reprod 2020;**35**:100-116. doi: 10.1093/humrep/dez258.

Romanski PA , Bortoletto P , Rosenwaks Z , Schattman GL. Delay in IVF treatment up to 180 days does not affect pregnancy outcomes in women with diminished ovarian reserve. Hum Reprod 2020;deaa137. doi: 10.1093/humrep/deaa137. Online ahead of print.

RCOG 2020 https://www.rcog.org.uk/en/guidelines-research-services/coronavirus-covid-19-pregnancy-and-womens-health/reset-recovery-and-restoration/

Templeton A, Morris JK, Parslow W. Factors that affect outcome of in-vitro fertilisation treatment. Lancet 1996;**348**:1402-6. doi: 10.1016/S0140-6736(96)05291-9.

van den Boogaard NM, Oude Rengerink K, Steures P, Bossuyt PM, Hompes PG, van der Veen F, Mol BW, van der Steeg JW. Tailored expectant management: risk factors for non-adherence. Hum Reprod 2011;**26**:1784-9. doi: 10.1093/humrep/der123. Epub 2011 Apr 30.

van Eekelen R, McLernon DJ, van Wely M, Eijkemans MJ, Bhattacharya S, van der Veen F, van Geloven N. External validation of a dynamic prediction model for repeated predictions of natural conception over time. Hum Reprod 2018;**33**:2268-2275.doi: 10.1093/humrep/dey317.Hum Reprod 2018 PMID: 30358841

van Eekelen R, Scholten I, Tjon-Kon-Fat RI, van der Steeg JW, Steures P, Hompes P, van Wely M, van der Veen F, Mol BW, Eijkemans MJ, Te Velde ER, van Geloven N. Natural conception: repeated predictions over time. Hum Reprod 2017;**32**:346-353. doi: 10.1093/humrep/dew309. Epub 2016 Dec 18.Hum Reprod. 2017.PMID: 27993999

van Eekelen R, Tjon-Kon-Fat RI, Bossuyt PMM, van Geloven N, Eijkemans MJC, Bensdorp AJ, van der Veen F, Mol BW, van Wely M. Natural conception rates in couples with unexplained or mild male subfertility scheduled for fertility treatment: a secondary analysis of a randomized controlled trial. Hum Reprod 2018;**33**:919-923. doi: 10.1093/humrep/dey051. Hum Reprod. 2018.PMID: 29538638

van Eekelen R, van Geloven N, van Wely M, Bhattacharya S, van der Veen F, Eijkemans MJ. McLernon DJ. IVF for unexplained subfertility; whom should we treat? Hum Reprod 2019;**34**:1249-59.

van Loendersloot L, Repping S, Bossuyt PM, van der Veen F, van Wely M. Prediction models in in vitro fertilization; where are we? A mini review. J Adv Res 2014;**5**:295-301. doi: 10.1016/j.jare.2013.05.002. Epub 2013 May 9. PMID: 25685496

van Loendersloot LL, van Wely M, Limpens J, Bossuyt PM, Repping S, van der Veen F. Predictive factors in in vitro fertilization (IVF): a systematic review and meta-analysis. Hum Reprod Update 2010;**16**:577-89. doi: 10.1093/humupd/dmq015. Epub 2010 Jun 25. PMID: 20581128 Review.

Figure legends

Supplementary Figure S1 Calibration plots showing the association between the predicted probability of live birth and observed proportion of live births over the first complete cycle of IVF in women who started their treatment in 2017.

Predicted probability of live birth and observed proportion of live births for **(a)** the original pre-treatment model as described by McLernon et al. (2016) applied to women who started IVF in 2017 and **(b)** recalibrated pre-treatment model with adjustment of the intercept and the slope applied to women who started IVF in 2017.

Table I Characteristics of women who started IVF treatment in 2017.

Characteristic		**N (%)**
Number of patients		9589
Female age (years), mean (SD)		34.1 (4.0)
Duration of infertility (years), median (IQR)		3 (2-6)
Previous pregnancy	Yes	3885 (40.5)
	No	5704 (59.5)
Cause of infertility	Tubal	921 (9.6)
	Endometriosis	523 (5.5)
	Unexplained	4037 (42.1)
	Male factor	3235 (33.7)
	Anovulation	873 (9.1)
Treatment type	IVF	5018 (52.3)
	ICSI	4571 (47.7)

IQR: interquartile range

Table II Predicted chance of live births by age group for immediate treatment versus 6-month delay in IVF or ICSI *.

Age group (years)	No of women	Scenario 1: Treat now	Scenario 2: Treat in 6 months			Scenario 3: Treat in 12 months		
		Average predicted chance of live birth (%)	Average predicted chance of live birth (%)	Difference in average chance	% change in average chance	Average predicted chance of live birth (%)	Difference in average chance	% change in average chance
<30	1370	34.2	34.1	-0.1	-0.4	33.9	-0.3	-0.9
30-35	4520	32.1	31.3	-0.8	-2.4	30.5	-1.6	-4.9
36-37	1478	26.6	25.1	-1.5	-5.6	23.4	-3.2	-11.9
38-39	1328	20.4	18.4	-1.9	-9.5	16.5	-3.8	-18.8
40-42	893	12.9	11.4	-1.5	-11.8	10.0	-2.9	-22.4

* using only predictions from the OPIS IVF model (McLernon et al 2016)

Table III Example of predictions considering a 6-month delay for women undergoing IVF with no previous pregnancy and 2 years duration of infertility.

Cause of infertility	Female age (years)	Scenario 1 Immediate IVF	Scenario 2 Delay by 6 months†			Difference in chance†
		% Chance of IVF live birth, $P_{immediate}$¶	% Chance of natural conception over 6 months, P_{NC_6m}	% Chance of IVF live birth if begin in 6 months, P_{IVF_6m}	% Chance of live birth if delay IVF for 6 months, P_{delay_6m}±	P_{delay_6m} - $P_{immediate}$
Unexplained	30	34.2	10.2	33.8	40.6	+6.4
	35	29.6	7.8	28.6	34.2	+4.6
	40	15.3	5.5	13.5	18.3	+3.0
Endometriosis	30	33.2	0.0 to 3.4	32.8	32.8 to 35.1	-0.4 to +1.9
	35	28.6	0.0 to 2.6	27.7	27.7 to 29.6	-1.0 to +0.9
	40	14.7	0.0 to 2.1	13.0	13.0 to 14.8	-1.7 to +0.1
Anovulatory	30	34.0	0.0 to 5.4	33.6	33.6 to 37.2	-0.4 to +3.2
	35	29.4	0.0 to 4.2	28.4	28.4 to 31.5	-1.0 to +2.0
	40	15.2	0.0 to 3.3	13.4	13.4 to 16.3	-1.7 to +1.1
Tubal	30	31.5	0.0 to 4.6	31.1	31.1 to 34.3	-0.4 to +2.8
	35	27.1	0.0 to 3.6	26.2	26.2 to 28.8	-0.9 to +1.7
	40	13.8	0.0 to 2.8	12.2	12.2 to 14.6	-1.6 to +0.8
Male factor	30	31.4	0.0 to 7.0	31.1	31.1 to 35.9	-0.4 to +4.5
	35	27.1	0.0 to 5.5	26.1	26.1 to 30.2	-0.9 to +3.1
	40	13.7	0.0 to 4.3	12.1	12.1 to 15.9	-1.6 to +2.2

¶ Predicted probability of live birth over the first complete cycle of IVF (i.e. fresh and/or frozen embryo transfers associated with first egg retrieval).

† For causes of infertility that are not unexplained, the conservative and optimistic range is given. The conservative prediction for natural live birth is 0% while the optimistic is calculated from a prediction model (Eijkemans et al, 2008).

± Cumulative chance of conceiving naturally over 6-month delay and following one complete cycle of IVF.

Table IV Example of predictions considering a 12-month delay for women undergoing IVF with no previous pregnancy and 2 years duration of infertility.

Cause of infertility	Female age (years)	Scenario 1 Immediate IVF	Scenario 3 Delay by 12 months†			Difference in chance†
		% Chance of IVF live birth, $P_{immediate}$¶	% Chance of natural conception over 12 months, P_{NC_12m}	% Chance of IVF live birth if begin in 12 months, P_{IVF_12m}	% Chance of live birth if delay IVF for 12 months, P_{delay_12m}±	P_{delay_12m} - $P_{immediate}$
Unexplained	30	34.2	17.6	33.3	45.1	+10.9
	35	29.6	13.6	27.5	37.3	+7.7
	40	15.3	9.7	11.9	20.4	+5.2
Endometriosis	30	33.2	0.0 to 5.7	32.3	32.3 to 36.1	-0.9 to +2.9
	35	28.6	0.0 to 4.4	26.6	26.6 to 29.8	-2.1 to +1.2
	40	14.7	0.0 to 3.4	11.4	11.4 to 14.5	-3.2 to -0.2
Anovulatory	30	34.0	0.0 to 9.0	33.1	33.1 to 39.2	-0.9 to +5.2
	35	29.4	0.0 to 7.1	27.3	27.3 to 32.4	-2.1 to +3.0
	40	15.2	0.0 to 5.5	11.8	11.8 to 16.7	-3.3 to +1.5
Tubal	30	31.5	0.0 to 7.7	30.7	30.7 to 36.0	-0.9 to +4.5
	35	27.1	0.0 to 6.0	25.1	25.1 to 29.6	-2.0 to +2.5
	40	13.8	0.0 to 4.7	10.7	10.7 to 14.9	-3.1 to +1.1
Male factor	30	31.4	0.0 to 11.7	30.6	30.6 to 38.7	-0.9 to +7.3
	35	27.1	0.0 to 9.2	25.0	25.0 to 32.0	-2.0 to +4.9
	40	13.7	0.0 to 7.2	10.7	10.7 to 17.1	-3.1 to +3.4

¶ Predicted probability of live birth over the first complete cycle of IVF (i.e. fresh and/or frozen embryo transfers associated with first egg retrieval).

† For causes of infertility that are not unexplained, the conservative and optimistic range is given. The conservative prediction for natural live birth is 0% while the optimistic is calculated from a prediction model (Eijkemans et al, 2008).
± Cumulative chance of conceiving naturally over 12-month delay and following one complete cycle of IVF.

Table V Predicted chance and number of live births by cause of infertility and age group for immediate versus 6-month delay in IVF.

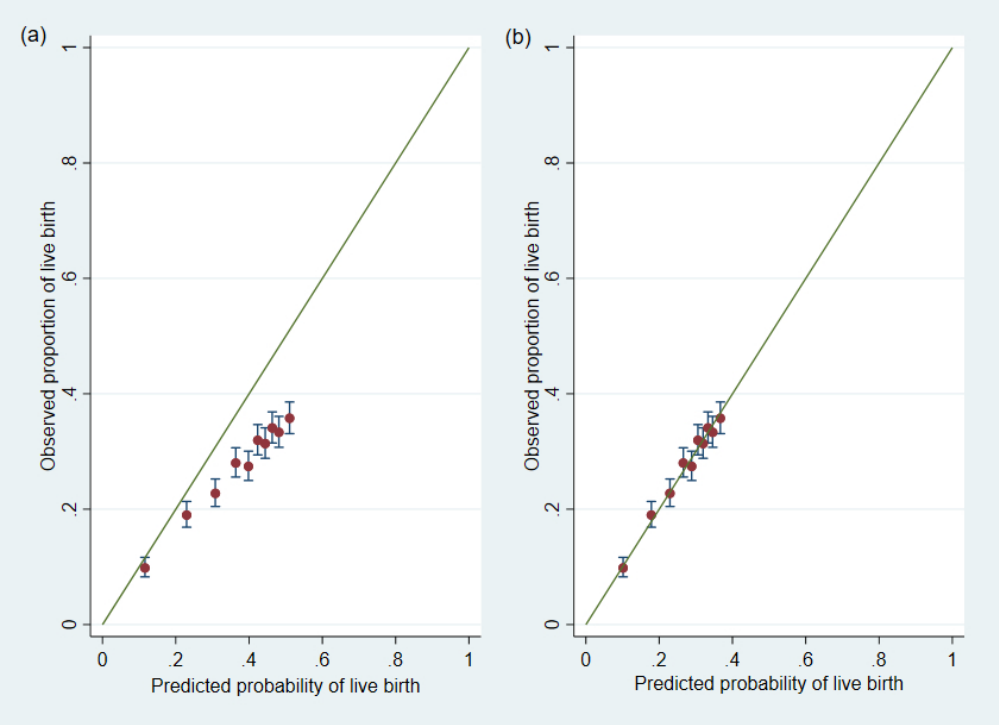
Cause of Infertility	Age group (years)	No of women	Scenario 1: Treat now	Scenario 2: Treat in 6 months		
			Average predicted chance of live birth (%)	Average predicted chance of live birth (%)	Difference in average chance (Scenario 2 – Scenario 1)	Percentage change in chance (Difference / Scenario 1)*100
Unexplained	<30	432	34.9	41.0	+6.1	+17.5
	30-35	1858	32.5	36.6	+4.1	+12.6
	36-37	654	26.9	29.4	+2.5	+9.1
	38-39	635	20.7	22.4	+1.7	+8.4
	40-42	458	13.2	15.1	+1.8	+13.8
Endometriosis	<30	56	33.5	33.3 to 35.6	-0.1 to +2.1	-0.4 to +6.4
	30-35	268	31.5	30.7 to 32.5	-0.8 to +1.0	-2.5 to +3.3
	36-37	81	25.8	24.3 to 25.8	-1.5 to -0.0	-5.9 to -0.0
	38-39	81	19.9	18.0 to 19.4	-1.9 to -0.5	-9.5 to -2.5
	40-42	37	12.4	10.9 to 12.2	-1.5 to -0.2	-11.9 to -1.5
Anovulatory	<30	171	34.6	34.5 to 38.1	-0.1 to +3.5	-0.4 to +10.2
	30-35	442	32.4	31.7 to 34.5	-0.7 to +2.1	-2.3 to +6.3

	36-37	120	27.1	25.6 to 28.1	-1.5 to +1.0	-5.4 to +3.6
	38-39	95	20.9	18.9 to 21.3	-2.0 to +0.4	-9.4 to +1.8
	40-42	45	13.3	11.7 to 14.1	-1.6 to +0.8	-11.8 to +6.1
Tubal	<30	150	31.7	31.6 to 35.0	-0.1 to +3.3	-0.3 to +10.4
	30-35	443	29.8	29.0 to 31.6	-0.7 to +1.8	-2.4 to +6.1
	36-37	149	24.5	23.1 to 25.2	-1.4 to +0.7	-5.8 to +2.7
	38-39	112	19.0	17.2 to 19.4	-1.8 to +0.3	-9.6 to +1.7
	40-42	67	11.7	10.3 to 12.3	-1.4 to +0.6	-11.9 to +4.7
Male factor	<30	561	34.4	34.3 to 39.2	-0.1 to +4.8	-0.4 to +14.0
	30-35	1509	32.4	31.6 to 35.3	-0.8 to +3.0	-2.3 to +9.2
	36-37	474	26.7	25.2 to 28.5	-1.5 to +1.8	-5.7 to +6.6
	38-39	405	20.2	18.3 to 21.3	-1.9 to +1.1	-9.5 to +5.4
	40-42	286	12.8	11.3 to 14.1	-1.5 to +1.4	-11.8 to +10.7

Table VI Predicted chance and number of live births by age group and severity of infertility for immediate treatment versus 12-month delay in IVF.

Cause of Infertility	Age group (years)	No of women	Scenario 1: Treat now	Scenario 3: Treat in 12 months		
			Average predicted chance of live birth (%)	Average predicted chance of live birth (%)	Difference in average chance (Scenario 3 – Scenario 1)	Percentage change in chance (Difference / Scenario 1)*100
Unexplained	<30	432	34.9	45.3	+10.4	+29.9
	30-35	1858	32.5	39.4	+6.9	+21.4
	36-37	654	26.9	30.9	+3.9	+14.6
	38-39	635	20.7	23.4	+2.8	+13.5
	40-42	458	13.2	16.3	+3.1	+23.4
Endometriosis	<30	56	33.5	33.1 to 36.9	-0.3 to +3.5	-1.0 to +10.4
	30-35	268	31.5	29.8 to 32.9	-1.6 to +1.4	-5.1 to +4.5
	36-37	81	25.8	22.6 to 25.2	-3.2 to -0.6	-12.3 to -2.4
	38-39	81	19.9	16.1 to 18.5	-3.7 to -1.4	-18.8 to -6.8
	40-42	37	12.4	9.6 to 11.8	-2.8 to -0.6	-22.6 to -5.0
Anovulatory	<30	171	34.6	34.3 to 40.4	-0.3 to +5.8	-0.9 to +16.8
	30-35	442	32.4	30.9 to 35.6	-1.5 to +3.2	-4.8 to +9.8
	36-37	120	27.1	24.0 to 28.1	-3.1 to +1.1	-11.4 to +3.9

	38-39	95	20.9	17.0 to 21.0	-3.9 to +0.1	-18.6 to +0.6
	40-42	45	13.3	10.3 to 14.3	-3.0 to +1.0	-22.4 to +7.9
Tubal	<30	150	31.7	31.5 to 37.1	-0.2 to +5.4	-0.8 to +17.2
	30-35	443	29.8	28.3 to 32.5	-1.5 to +2.8	-5.0 to +9.2
	36-37	149	24.5	21.5 to 25.1	-3.0 to +0.6	-12.1 to +2.3
	38-39	112	19.0	15.4 to 19.1	-3.6 to 0.0	-19.0 to +0.3
	40-42	67	11.7	9.1 to 12.4	-2.7 to +0.6	-22.7 to +5.4
Male factor	<30	561	34.4	34.1 to 42.4	-0.3 to +8.0	-0.8 to +23.1
	30-35	1509	32.4	30.8 to 37.1	-1.6 to +4.7	-4.9 to +14.6
	36-37	474	26.7	23.5 to 29.1	-3.2 to +2.4	-12.0 to +9.0
	38-39	405	20.2	16.4 to 21.6	-3.8 to +1.3	-18.8 to +6.6
	40-42	286	12.8	9.9 to 14.8	-2.9 to +2.0	-22.5 to +15.7



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