Unexplained infertility and expectant management in women aged 39 or above: is it acceptable to ask couples to wait one year before receiving IVF? A retrospective cohort study

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Research

Keywords: IVF, unexplained infertility, natural conception, expectant management, prediction model, individual prognoses, COVID-19, advanced age

DOI: https://doi.org/10.21203/rs.3.rs-131936/v1

Abstract

Background: in older women, it is difficult to distinguish between ‘true’ unexplained infertility and age-related infertility. Unexplained infertile couples can have further expectant management before starting assisted reproductive treatments to avoid unnecessary, invasive and expensive treatment. However, ovarian reserve rapidly declines after 39 years or more, as the live birth rate after in vitro fertilization. It is thus uncertain if such a waiting policy, is also appropriate for women of advanced age.

Methods: couples who had access to a waiting list for approximately one year before receiving reimbursed public IVF were compared with those paying for access to immediate private treatment at the IVF unit of S. Anna academic hospital and its private appendix. To allow for comparisons between these two strategies, we followed up couples who opted to pay for one year after the last embryo transfer from their first cycle. Clinical procedures regarding diagnosis and treatment were the same for both groups. We calculated the proportion of live births in both groups and compared these using a two-sample Z test for equality of proportions. The imbalance between these groups in terms of prognosis was accounted for using inverse probability weighting.

Results: 635 couples were evaluated. Out of 359 couples in the immediate group, 70 (19.5%) had a live birth of which 11 after natural conception and 59 after IVF. Out of 276 couples in the waiting group, 57 (20.7%) had a live birth of which 37 after natural conception and 20 after IVF. There was no statistically significant difference between the two strategies in terms of the cLBR (19.5% immediate versus 20.7% waiting, 95% CI for difference: -0.07to 0.05), also after weighting (16.8% immediate versus 26.6% waiting, bootstrap 95%, CI for difference: -0.20 to 0.01).

Conclusion(s): the cLBR for the ‘waiting before in vitro fertilization’ and the ‘immediate’ strategies were similar. Further studies are necessary to validate these findings and to better characterize these patients in order to individualize treatment and optimize economic resources, particularly in a setting of publicly-funded IVF.

Trial registration: retrospectively registered

Background

Unexplained infertility is considered as a diagnosis in women who have tried to conceive for at least one year without success, despite the evidence of ovulation, tubal patency, and normal semen parameters [1]. As such, unexplained infertility accounts for approximately 30% of infertility diagnoses in couples presenting for in vitro fertilization (IVF) [2]. On the other hand, up to 50% of couples suffering from unexplained infertility may conceive spontaneously after initial assessment [3].

The diagnosis of unexplained infertility may include a heterogeneous group of conditions [4, 5], including the physiological reduction of fecundity with age (‘age-related infertility’) [6].

In women aged 40 years or more, the cumulative live birth rate with IVF is reported to be around 7% [7]. Due to the well-proven worsening of IVF results with female aging, it is recommended that in these patients action be undertaken as soon as possible, particularly so in women over 40 years [8, 9]. Indeed, the "follicular heritage" of these patients suffers from a rapid physiological decline of oocyte quantity and quality [10].

Taking into account all the above considerations, it is unclear how to proceed in older women with unexplained infertility. A potential overuse of infertility treatments would lead to unnecessary risks for the patient and wastage of financial resources [11–13].

Whether patients in advanced reproductive age with unexplained infertility can benefit from immediate IVF treatment, or could afford a waiting time period in the hope of achieving spontaneous conception, represents an open dilemma [14]. A quite recent study indirectly addressed this issue, showing that in older women with unexplained infertility immediate IVF demonstrated superior pregnancy rates compared to intra-uterine insemination (IUI) [15]. These results seem confirmed by a recent meta-analysis, although the quality of evidence is moderate and limited to 725 couples with poor prognosis of natural conception [16].

Moreover, concern about delayed access to IVF treatments has become dramatically topical following the outbreak of the COVID-19 pandemic [17], which prompted the temporary suspension of treatments due to the limited knowledge on SARS-CoV-2 effects in pregnancy [18–20], generating higher distress in couples on the possible consequences that such "waiting period" could have on treatment outcomes [21, 22].

Similarly to what happens in other countries, in Italy couples entitled to assisted reproductive technology (ART) treatments supported by the public health care system have to stand in a waiting list. Couples do have the option for paying for treatment themselves, avoiding the waiting period. Therefore, the aim of our study was to compare live birth rates in a retrospective cohort of women who were waiting one year before starting IVF treatment to a cohort of women who received immediate self-paid IVF treatment.

Methods

Patient selection and follow up

The study was performed in accordance with the Helsinki Declaration and with approval of

the Institutional Review Board.

In this retrospective analysis we included a cohort of women aged 39–43 years seeking infertility diagnosis and treatments, who were admitted to the IVF unit of the S. Anna academic hospital and to its private appendix between 2010–2019. Couples who enter a waiting list for publicly funded IVF and those receiving immediate self-paid treatment were compared. In both cases, the same diagnostic and therapeutic protocols were applied.

Only couples with unexplained infertility were selected. In detail, all women included in the study had ovulatory cycles and patency of at least one fallopian tube at hysterosonosalpingography (HSSG), whereas all male partners had normal basic semen parameters according to the indications of WHO 2010. Exclusion criteria were: any known cause of female infertility (i.e. previous history of pelvic inflammatory disease, positive anti-Chlamydia IgG, endometriosis, anovulation, etc), early follicular phase follicle stimulating hormone (FSH) > 20 UI/l and/or anti-Mullerian hormone (AMH) < 0.1 ng/ml, female body mass index (BMI) > 32 kg/m^2.

Couples were considered as part of the 'waiting' group if they abided by national protocol to wait for about one year after diagnosis, before IVF treatment. Couples were considered as part of the 'immediate' group if they opted to pay for access to immediate private IVF. We will also refer to these groups as 'strategies'. Follow up for the waiting group was up to their first IVF cycle. Follow up for the immediate group was one year after their last embryo transfer from their first IVF cycle. Only the first IVF cycle was analysed in order to allow follow up for both groups to be similar. Figure 1 shows the timeline of 12 months plus 1 IVF cycle in total for both groups.

IVF procedure and clinical outcomes

Controlled ovarian stimulation (COS) was performed either with recombinant FSH (rFSH), human Menopausal Gonadotropin (HP-hMG) or rFSH plus recombinant luteinizing hormone (rLH), under pituitary suppression. The choice of the starting gonadotropin dose was based on age, BMI, antral follicular count (AFC), AMH circulating concentrations, as well as on the response to previous COS. In the absence of any pre-fixed criteria, the COS regimen (type of protocol and type of medication) was decided and prescribed by different physicians of the IVF unit, according to their own clinical experience, as per real-life clinical practice.

Both long (Gn-RH agonist for pituitary suppression) and short (Gn-RH antagonist for pituitary suppression) protocols were used. COS was monitored by serial transvaginal US and serum estradiol (E2) measurements performed every second day from stimulation day 6–7. COS continued until at least two follicles reached 18 mm in mean diameter, when ovulation was triggered by injecting subcutaneously either 10,000 international units (IU) of hCG (Gonasi HPfi, IBSA, Lugano, Switzerland) or 250 mcg of rHCG (Ovitrelle, Merck, Darmstadt, Germany). US-guided transvaginal oocyte pick-up (OPU) was performed approximately 36–37 h after hCG administration, under local anesthesia (paracervical block). Conventional IVF or ICSI were performed on all available oocytes within 4 hours after oocytes collection or after 2 h from cumulus cells removal, respectively. Normal fertilization was assessed for the presence of two pronuclei (2PN) and the extrusion of the second polar body after 16–18 h post insemination.

All cleaved embryos were morphologically evaluated under a conventional stereomicroscope, using the IMCS score by Holte [46]. According to the policy of our IVF unit during the time period under study, embryo transfer (ET) was performed either on day 2 or day 3 based on the presence of 1–3 embryos or ≥ 4 embryos, respectively. Embryos were selected and transferred in uterus using a soft catheter, under ultrasound guidance, applying the method previously published by our group [47]. The remaining embryos (if any) were kept in culture until day 6 of development for cryopreservation at the blastocyst stage or discharge. The luteal phase was supported by administering 180 mg/day natural progesterone (Crinone 8, Merck, Darmstadt, Germany) for 15 days. Pregnancy was assessed by serum hCG assay after 14 days from embryo transfer and then confirmed if at least one gestational sac was visualized on transvaginal US after two further weeks.

The primary outcome was the cumulative live birth rate (cLBR). The cLBR was defined as live deliveries (at least one live birth) per women over the full follow up period. The full follow up period was defined as either a period of expectant management up to the first IVF/ICSI cycle (including both fresh and frozen/thawed embryo transfers) or one year after the first IVF/ICSI cycle. Live birth was defined as the delivery of a live-born infant (> 24 weeks of gestation).

Analyses

We tabulated the baseline patient characteristics for the two strategies separately.

As crude analyses, we simply calculated the proportion of live births in both groups and compared these using a two-sample Z test for equality of proportions. In addition, we calculated the odds ratio for immediate IVF versus waiting using a logistic regression model.

Next, we considered emulating a randomized controlled trial [23]. In our study design, the only difference between strategies was the timing of IVF. However, as there was no random allocation to the waiting and immediate strategy, these groups could still differ in terms of prognostic characteristics associated with opting for waiting or immediate IVF. We had to adjust for these characteristics that explained both the chance of live birth and the choice between waiting or immediate IVF. To adjust for these characteristics, we conducted inverse probability weighting that weights some couples more than others to obtain a balance between groups [24]. We regressed the patient characteristics female age, duration of infertility, primary or secondary infertility, previous miscarriage, previous IUI/IVF treatment, AMH, AFC and previous induced abortion on the strategy groups i.e. 'immediate group (a '1') versus the waiting group (a '0')' using a logistic regression model. Other characteristics, such as male age, FSH etc. either do not have a strong effect on live birth or are not as likely to be related to what is essentially a decision based on personal wealth. This model was used to predict the probability of receiving immediate IVF or waiting given a couples' individual characteristics. For couples who received immediate IVF, we divided the proportion of couples who received immediate IVF by a couple's individual probability of choosing immediate IVF [24]. For couples who waited, we divided the proportion of couples who waited by a couple's individual probability of waiting. The result was an individual weight value. This weight value counts certain couples more often than others in order to balance the cohort in terms of the mentioned baseline characteristics. This process was repeated until balance was found, defined as standardized mean differences below 0.1.

Finally, the weights are applied in the cohort or in the logistic regression model to obtain adjusted estimates.

The standard errors obtained from standard software are incorrect as they ignore the weighting procedure [24]. To obtain valid standard errors, we resampled 5000 times, repeated the procedure, calculated the statistic and reported their 2.5th and 97.5th percentile as the bootstrap results.

After we derived the weights, we first checked with a new tabulation whether the patient characteristics were similar between weighted groups, then repeated the previously conducted crude analyses: we calculated the proportion of live births in both weighted groups and compared these using a two-sample Z test for equality of proportions. In addition, we calculated the odds ratio for immediate IVF versus waiting using a logistic regression model including weights.

Sensitivity analysis

Couples who opted to pay for immediate IVF could receive multiple IVF cycles, which leads to follow up timelines that are slightly different. In the primary analysis, we assumed that these couples could still conceive naturally between IVF cycles and after their last IVF cycle. To assess the influence on this assumption on our results, we repeated the primary analyses but now considered couples who received more than one IVF cycle as censored i.e. no longer pursuing expectant management after their first unsuccessful IVF cycle. We estimated the proportion of live birth as the cumulative probability over one IVF cycle and one year of expectant management using the Kaplan-Meier method, then compared proportions between groups like in the primary analysis.

Data were prepared in Microsoft Excel. All analyses were conducted in R version 3.6.0 and RStudio (R Core Team, 2013) using the rms, mice, dplyr and CreateTableOne packages.

Results

Data on 635 couples were available. Out of 359 couples in the immediate group, 70 (19.5%) had a live birth of which 11 after natural conception and 59 after IVF. Out of 276 couples in the waiting group, 57 (20.7%) had a live birth of which 37 after natural conception and 20 after IVF. Couples in the waiting group started their first IVF cycle after a median of 12 months (25th-75th percentile: 11–14).

Characteristics in both groups are depicted in Table 1.

Table 1
Baseline characteristics of couples in the immediate or waiting group.

Baseline characteristics of couples	Couples who received immediate IVF (n = 359)	Couples who waited before IVF (n = 276)	P value
Female age at diagnosis (years)	40.6 (39.0–42.0)	40.2 (39.0–42.0)	< 0.05
Male age at diagnosis (years)	42.1 (34.0-53.1)	41.7 (31.9–52.0)	< 0.05
Duration of infertility at diagnosis (years, median)	2.0 (1.0–8.0)	3.0 (1.0-12.1)	< 0.05
Percentage of progressive motile sperm (median)	40.0 (30.0–48.0)	38.5 (32.0-49.1)	< 0.05
Female smoking status (yes versus no)	44 (12%)	31 (11%)	0.78
AFC	11.2 (3.0–28.0)	9.5 (2.0-28.2)	0.05
AMH (ng/ml, median)	1.1 (0.1–5.8)	1.1 (0.1-8.0)	1.00
FSH (IU)	8.9 (3.9–17.9)	8.4 (3.7–16.6)	0.15
Primary infertility (versus secondary)	260 (72%)	116 (42%)	< 0.05
Previous miscarriage:			< 0.05
None	294 (82%)	153 (55%)	
1	49 (14%)	78 (28%)	
2	11 (3%)	27 (11%)	
3 or more	5 (1%)	18 (7%)	
Received previous ART			< 0.05
None	234 (65%)	43 (16%)	
IUI	18 (5%)	190 (69%)	
IVF	107 (30%)	43 (16%)	
Previous induced abortion (yes versus no)	14 (4%)	31 (11%)	< 0.05

Legends: Data are mean unless specified as median. Between brackets depicts the percentage for categorical data or the 5th-95th percentile for continuous data. AFC, antral follicle count; AMH, Anti-Müllerian hormone; FSH, follicle stimulating hormone

There was no statistically significant difference between the two groups in terms of the cLBR (19.5% immediate versus 20.7% waiting, 95%CI for difference: -0.07 to 0.05). In addition, the odds ratio (OR) did not significantly differ from 1 (OR 0.93, 95%CI: 0.63 to 1.38).

After weighting, there was an adequate balance between groups in terms of female age, duration of infertility, AMH, AFC, primary or secondary infertility, previous miscarriage, previous IUI/IVF treatment and previous induced abortion as shown by the point estimates provided in the Table 2.

Table 2
Baseline characteristics of couples in the waiting or immediate group after weighting.

Baseline characteristics	Couples who received immediate IVF (n = 344)	Couples who waited before IVF (n = 291)
Female age at diagnosis (years)	40.3	40.3
Male age at diagnosis (years)	41.6	41.7
Duration of infertility at diagnosis (years, median)	2	2
Percentage of progressive motile sperm (median)	42	36
Female smoking status (yes versus no)	54 (16%)	37 (16%)
AFC	10.8	10.8
AMH (ng/ml, median)	1.2	1.2
FSH (IU)	8.7	8.1
Primary infertility (versus secondary)	218 (63%)	184 (63%)
Previous miscarriage:		
None	257 (75%)	216 (75%)
1	63 (18%)	54 (19%)
2	15 (4%)	12 (4%)
3 or more	9 (3%)	8 (3%)
Received previous ART		
None	150 (44%)	125 (43%)
IUI	91 (27%)	79 (27%)
IVF	103 (30%)	86 (30%)
Previous induced abortion (yes versus no)	21 (6%)	17 (6%)

Legends: Data are mean unless specified as median. AFC, antral follicle count; AMH, Anti-Müllerian hormone; FSH, follicle stimulating hormone

In the weighted cohort, there was no significant difference between the two groups in terms of the cLBR (16.8% immediate versus 26.6% waiting, bootstrap 95%CI for difference: -0.20 to 0.01). In addition, the OR did not significantly differ from 1 (OR 0.56, bootstrap 95%CI: 0.32 to 1.08).

In the sensitivity analysis in which we censored couples in the immediate group after their first unsuccessful IVF cycle if they received at least one addition cycle, the cLBR was 20.8% for the immediate group instead of 19.5%. There was no statistically significant difference between the two groups in terms of the cLBR (20.8% immediate versus 20.7% waiting, 95%CI for difference: -0.07 to 0.06). In the weighted cohort, there was no significant difference between the two groups in terms of the cLBR (17.8% versus 26.6%, bootstrap 95%CI for difference: -0.20 to 0.03).

Discussion

In couples with unexplained infertility and female age between 39–43 years, we found that the average chance of success in terms of cumulative live birth rate over one year and one IVF cycle is similar between waiting and immediate IVF.

Recent studies in large cohorts of infertile couples with varying female age, support the notion that IVF increases the probability of an ongoing pregnancy as compared to expectant management. However, this benefit attenuates with increasing female age [9]. More importantly, the clinical question is more often: can we delay treatment for a certain period of time without causing harm to the patient and perhaps have them conceive spontaneously? A recent retrospective study shows that in patients with reduced ovarian reserve a delay of no more than six months is not associated with worse IVF outcomes [25], but the chances of achieving pregnancy without IVF have not been investigated. So, our dilemma is still open.

Treatment strategies in women of advanced reproductive age are of major interest, given the current societal norm to start having children later on [26, 27]. However, whereas Scientific Societies agree on recommending a rapid diagnostic procedure starting from the age of 35 years, there is no shared consensus regarding the best treatment strategies when common causes of female and male infertility are ruled out [16, 28, 29]. Doubts are rising that IVF could overcome the age-related subfertility in women as the quality of oocytes cannot be changed in the IVF procedure and the responsiveness of the ovaries decreases over the years increasing the risk of poor results from ovarian stimulation [30–32].

Therefore, such patients remain a controversial challenge in clinical decision making.

Our study can be reassuring for patients in the age range considered, who are cared with expectant management of at least eleven months before IVF as we did not find evidence that waiting has a negative influence on their live birth rate. These findings may also reassure couples who have experienced or will experience delays in accessing IVF treatments due to the COVID-19 pandemic, according to similar results reported by other groups [25].

However, couples should be advised that beyond age 39, both strategies can lead to a high probability of not reaching a live birth, confirming the importance of reproductive counselling in younger women wishing to obtain motherhood at an older age.

This finding adds to the current debate about the optimal therapeutic approach to unexplained infertility, as couples that conceive after IVF might have otherwise conceived naturally [1, 12, 33]. Thirty-seven couples (13%) included in the waiting group obtained a live birth spontaneously during the observation time. This chance was similar as the chance obtained in the only available study with the same design as the present one [34], but including younger patients and only 6 months of observation. In a different study regarding the waiting list for IVF in the Netherlands, the cumulative live birth rate over one year was 14%, thus also similar to our result [35].

In both early studies [34] and more recent and larger ones [9] IVF has proven overall to be a better approach than expectant management, even in unexplained infertility. However, as these couples can still conceive naturally, the question is thus not if couples should be treated with IVF, but when. If treatment is started later and couples might conceive naturally, they are spared unnecessary, expensive and invasive treatment [1, 36, 37]. In the present study, only one third of the live births in the waiting group were obtained after IVF. The implications would be that a certain number of IVF treatments are currently carried out without a true indication, as the live births after IVF might have occurred after prolonged expectant management anyway, thereby exposing offspring of these couples to the potential risks related to ART treatments [38, 39].

Should these findings be confirmed in larger series of patients, the protocol for treating unexplained infertility in women of older age should be reconsidered. Waiting before treatment or selecting those women who are expected to benefit most from IVF would save couples from unnecessary invasive treatments, while at the same time optimizing the allocation of economic resources.

The major strength in our study is that patients from both groups were handled by the same medical and embryologist team, following identical diagnostic and therapeutic protocols. Furthermore, in Italy the option to wait or pay for immediate access to IVF constitutes a condition that cannot be easily carried out in a prospective randomized controlled trial (RCT). Even if our study is limited by its retrospective design, RCTs on unexplained infertility that include ‘no treatment’ i.e. expectant management are lacking as clinicians might be reluctant to include such an arm. Couples may perceive further expectant management as a waste of time and are unlikely to be volunteer in a study in which they might be allocated to expectant management whereas they will receive IVF if they refuse to enter the study [40]. Because of this lack of evidence from RCTs, most studies published so far compared different treatment arms or separate observational databases [15, 41, 42].

However, the major limitation to our methodological approach pertains to the potential selection bias associated with choosing either strategy. Although the ovarian reserve of our groups was similar (see AFC and AMH in Table 1), the study groups differed in a few baseline characteristics, which are known to be related to the chances of pregnancy, namely the prevalence of primary/secondary infertility, a history of previous miscarriage, and previous IUI/IVF. By using inverse probability weighting [24], these confounding variables were reasonably accounted for as shown in the Table 2 after weighting.

Couples having multiple IVF cycles in the paid group might have led to follow up timelines that are not strictly comparable. However, most of the couples in the immediate group who received multiple IVF cycles were still ‘at risk of natural conception’ for most of the year. This is likely considering that the majority of couples who received multiple cycles in the immediate group did not conceive after their first IVF cycle and remained free for several months between cycles for a potential spontaneous conception. We thus think our primary analysis remains realistic. Our sensitivity analysis on this subject showed an estimated (unadjusted) proportion of live birth of 20.8% instead of 19.5% that did not lead to different conclusions. Thus, we argue that this issue might not have a large influence on results given our study design.

Conclusions

Our study showed that a waiting strategy instead of immediately receiving IVF in couples with unexplained infertility, with advanced female age, resulted in similar cumulative live birth rates. Therefore, we did not find evidence that couples on a waiting list should have reasons to be concerned. This might be comforting for couples for which treatment was or will be delayed due to the COVID-19 pandemic. Further studies are needed to validate these findings and to optimize economic resources, particularly in a setting of publicly-funded IVF.

Abbreviations

IVF
in vitro fertilization
IUI
intrauterine insemination
COVID-19
coronavirus disease-2019
SARS-CoV-2
SARS coronavirus 2
ART
Assisted reproductive technology
HSSG
hysterosonosalpingography
WHO
world health organization
IgG
Immunoglobulin G
FSH
follicle stimulating hormone
AMH

anti-Mullerian hormone
BMI
body mass index
COS
controlled ovarian stimulation
rFSH
recombinant FSH
HP-hMG
human menopausal gonadotropin
rLH
recombinant luteinizing hormone
AFC
antral follicular count
Gn-RH
gonadotropin-releasing hormone
US
ultrasound
E2
estradiol
IU
international units
hCG
human chorionic gonadotropin
ICSI
intracytoplasmic sperm injection
2PN
two pronuclei
IMCS
integrated morphology cleavage score
ET
embryo transfer
cLBR
cumulative live birth rate
GP
general practitioner
CI
confidence interval
AIC
akaike’s Information Criterion
RCT

randomized controlled trial

Declarations

Ethics approval and consent to participate: The study was performed in accordance with the Helsinki Declaration and with approval of the City of Health and Science Institutional Review Board Review Board (n. 0040486, 23/04/2020).

Consent for publication: not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors report no conflict of interest

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions: Andrea Carosso conceived the study and wrote the manuscript. Rik van Eekelen performed the data analysis and co-wrote the manuscript. Alberto Revelli contributes to interpretation of the data and critically revised the manuscript. Stefano Canosa, Noemi Mercaldo and Ilaria Stura collect the data and contributes to data analysis. Sara Cesarano, Stefano Cosma, Carlotta Scarafia and Marta Sestero contributed to execution of the study and critically revised the manuscript. Chiara Benedetto and Gianluca Gennarelli contribute to conceive the study, coordinate the study and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Acknowledgements: We thank Paolo Caselgrandi for helping in data collection.

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Figures

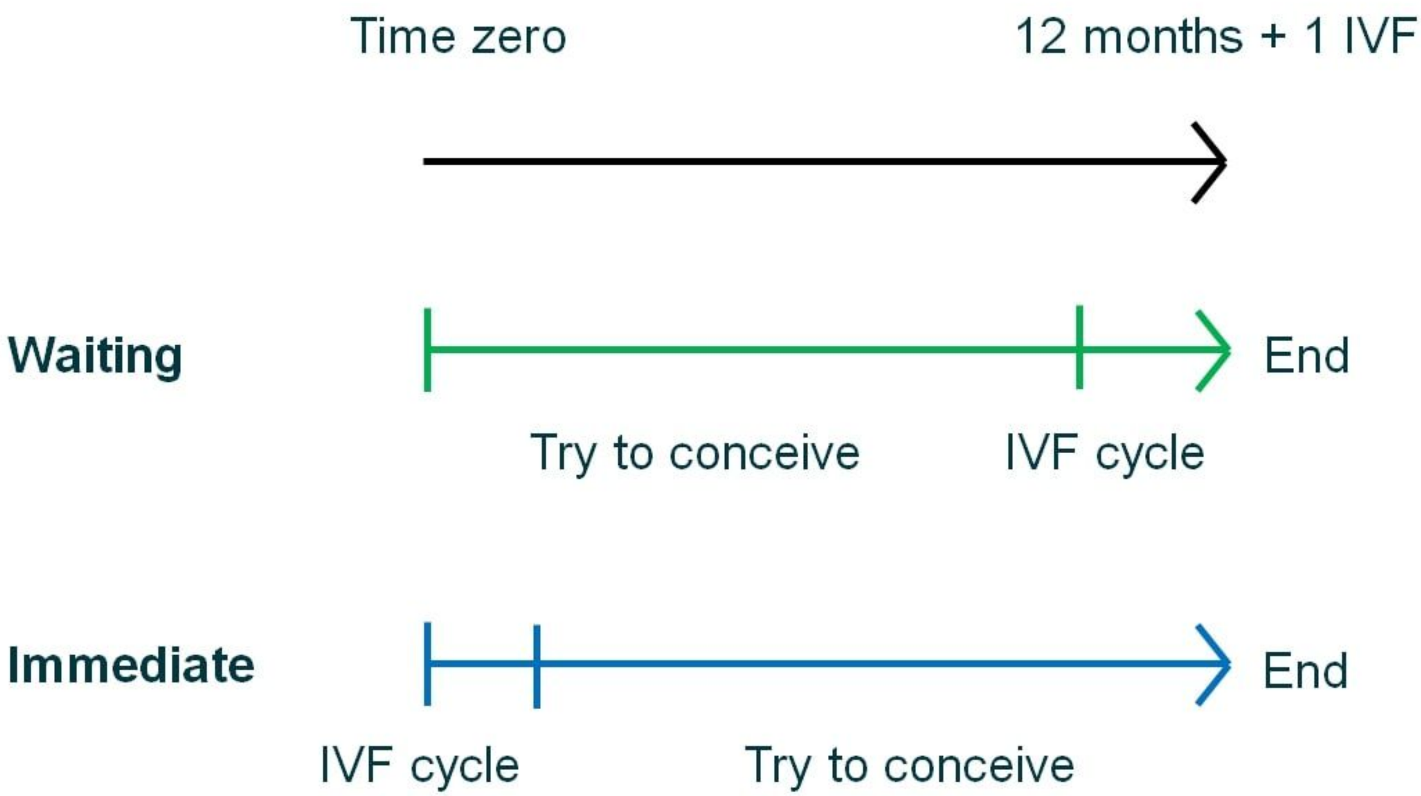

Figure 1

timeline of 12 months plus 1 IVF cycle in total for both groups