human reproduction

ORIGINAL ARTICLE *Infertility*

Delay in IVF treatment up to 180 days does not affect pregnancy outcomes in women with diminished ovarian reserve

Phillip A. Romanski*, Pietro Bortoletto, Zev Rosenwaks, and Glenn L. Schattman

Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medical College, New York, NY, USA

*Correspondence address. Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medical College, 1305 York Avenue, New York, NY 10021, USA. Tel: 813-785-0773; E-mail: par9114@med.cornell.edu

STUDY QUESTION: Will a delay in initiating IVF treatment affect pregnancy outcomes in infertile women with diminished ovarian reserve?

SUMMARY ANSWER: A delay in IVF treatment up to 180 days does not affect the live birth rate for women with diminished ovarian reserve when compared to women who initiate IVF treatment within 90 days of presentation.

WHAT IS KNOWN ALREADY: In clinical practice, treatment delays can occur due to medical, logistical or financial reasons. Over a period of years, a gradual decline in ovarian reserve occurs which can result in declining outcomes in response to IVF treatment over time. There is disagreement among reproductive endocrinologists about whether delaying IVF treatment for a few months can negatively affect patient outcomes.

STUDY DESIGN, SIZE, DURATION: A retrospective cohort study of infertile patients in an academic hospital setting with diminished ovarian reserve who started an IVF cycle within 180 days of their initial consultation and underwent an oocyte retrieval with planned fresh embryo transfer between 1 January 2012 and 31 December 2018.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Diminished ovarian reserve was defined as an anti-Müllerian hormone (AMH) <1.1 ng/ml. In total, 1790 patients met inclusion criteria (1115 immediate and 675 delayed treatment). Each patient had one included cycle and no subsequent data from additional frozen embryo transfer cycles were included. Since all cycle outcomes evaluated were from fresh embryo transfers, no genetically tested embryos were included. Patients were grouped by whether their cycle started 1–90 days after presentation (immediate) or 91–180 days (delayed). The primary outcome was live birth (≥24 weeks of gestation). A subgroup analysis of more severe forms of diminished ovarian reserve was performed to evaluate outcomes for patients with an AMH <0.5 and for patients >40 years old with an AMH <1.1 ng/ml (Bologna criteria for diminished ovarian reserve). Logistic regression analysis, adjusted *a priori* for patient age, was used to estimate the odds ratio (OR) with a 95% CI. All pregnancy outcomes were additionally adjusted for the number of embryos transferred.

MAIN RESULTS AND THE ROLE OF CHANCE: The mean ± SD number of days from presentation to IVF start was 50.5 ± 21.9 (immediate) and 128.8 ± 25.9 (delayed). After embryo transfer, the live birth rate was similar between groups (immediate: 23.9%; delayed: 25.6%; OR 1.08, 95% CI 0.85–1.38). Additionally, a similar live birth rate was observed in a subgroup analysis of patients with an AMH <0.5 ng/ml (immediate: 18.8%; delayed: 19.1%; OR 0.99, 95% CI 0.65–1.51) and in patients >40 years old with an AMH <1.1 ng/ml (immediate: 12.3%; delayed: 14.7%; OR 1.21, 95% CI 0.77–1.91).

LIMITATIONS, REASONS FOR CAUTION: There is the potential for selection bias with regard to the patients who started their IVF cycle within 90 days compared to 91–180 days after initial consultation. In addition, we did not include patients who were seen for initial evaluation but did not progress to IVF treatment with oocyte retrieval; therefore, our results should only be applied to patients with diminished ovarian reserve who complete an IVF cycle. Finally, since we excluded patients who started their IVF cycle greater than 180 days from their first visit, it is not known how such a delay in treatment affects pregnancy outcomes in IVF cycles.

WIDER IMPLICATIONS OF THE FINDINGS: A delay in initiating IVF treatment in patients with diminished ovarian reserve up to 180 days from the initial visit does not affect pregnancy outcomes. This observation remains true for patients who are in the high-risk categories for poor response to ovarian stimulation. Providers and patients should be reassured that when a short-term treatment delay is deemed necessary for medical, logistic or financial reasons, treatment outcomes will not be affected.

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Introduction

A novel coronavirus (SARS-CoV-2) that can infect humans and cause severe respiratory tract illness was first identified in Wuhan, China in December of 2019 (Zhu et al., 2020). Since this virus emerged, it has spread throughout the world, with the first case in the USA reported on 19 January 2020 (Holshue et al., 2020). The virus has since spread to all 50 states, resulting in shortages of life-saving medical supplies and equipment. This has led to unprecedented changes to the healthcare system, including limitations on non-urgent patient visits and procedures in order to preserve resources needed to combat the virus and slow its spread (Toner and Waldhorn, n.d.; Cavallo et al., 2020; Hollander and Carr, 2020; Ranney et al., 2020).

In response to the SARS-CoV-2 pandemic, the American Society for Reproductive Medicine (ASRM) convened a task force to provide interim guidance for patient management (Coronavirus/COVID-19 TaskForce of the American Society for Reproductive Medicine). One of the key recommendations was to 'suspend initiation of new treatment cycles, including ovulation induction, intrauterine inseminations, in vitro fertilization including retrievals and frozen embryo transfers, as well as non-urgent gamete cryopreservation'. In addition, a joint statement from the ASRM, the American College of Obstetricians and Gynecologists, the American Association of Gynecologic Laparoscopists, the American Urogynecologic Society, the Society of Family Planning, the Society of Gynecologic Oncology, the Society of Gynecologic Surgeons and the Society for Maternal-Fetal Medicine was released that endorses the suspension of medically indicated procedures except in cases where a delay in treatment would negatively affect the health and safety of the patient (COVID-19: Joint Statement on Elective Surgeries).

There is disagreement among reproductive endocrinologists about whether delaying IVF treatment for a few months can negatively affect patient outcomes. In particular, some clinicians are concerned that women with diminished ovarian reserve may experience worse pregnancy outcomes if their treatment is delayed during this pandemic. Since estimates of peak infections vary depending on the adoption of and compliance with measures used to combat spread, such as stay-at-home orders and social distancing, estimates of infertility treatment delays range from weeks to months. Currently, there are no data to indicate whether patients are negatively affected by delays in infertility treatment for up to 6 months. This study was performed to determine whether women with diminished ovarian reserve have worse pregnancy outcomes when their treatment is delayed up to 180 days compared to women who undergo immediate infertility treatment.

Materials and methods

Study population and design

This was a retrospective cohort study of women at our institution who underwent their first IVF cycle resulting in an oocyte retrieval with a planned fresh embryo transfer from 1 January 2012 to 31 December 2018. For each patient, all subsequent cycles that occurred in this time range were excluded. Since all cycle outcomes evaluated were from fresh embryo transfers, no genetically tested embryos were included in this study. Data were collected from our hospital electronic medical record system. IVF cycle and embryology data are prospectively entered into the electronic medical chart. Key data points were verified in the electronic medical records. This study was approved by the institutional review board at Weill Cornell Medical College.

Definition of study groups

All patients with diminished ovarian reserve, defined as an anti-Müllerian hormone (AMH) level of <1.1 ng/ml, at the time of initial presentation to our office were included in this study. At our center, the AMH level was determined using the AMH Gen II ELISA (Beckman Coulter Inc., Brea, CA, USA) up until 10 May 2016, at which time we transitioned to using the Access 2 AMH assay (Beckman Coulter Inc., Brea, CA, USA). A minority of patients had their AMH level processed at an outside laboratory (14.6%) for which information about assay type was not available.

Patients were stratified by whether they initiated an IVF cycle immediately after their first visit or whether their treatment was delayed. At our center, once patients are given a full evaluation and a treatment recommendation is made, they can start their IVF cycle on a timeline of their choice. Some patients begin their IVF cycle as soon as possible after their initial visit, while others may take longer to complete their evaluation or schedule their treatment cycle. In our cohort, immediate treatment was defined as initiating their first IVF cycle within 90 days of their first patient visit, and delayed treatment was defined as initiating their first IVF cycle between 91 and 180 days after their first patient visit.

Clinical protocols

Controlled ovarian stimulation, trigger timing and dose, oocyte retrieval, embryo culture, embryo transfer and cryopreservation of supernumerary oocytes and/or embryos were performed per the standard protocols at our institution. Stimulation protocols utilized GnRH antagonists or GnRH agonist flare protocols (Surrey et al.,

1998; Cheung *et al.*, 2005). Letrozole or clomiphene citrate was added to some GnRH antagonist protocols at the treating physician's discretion (Tummon *et al.*, 1992; Yarali *et al.*, 2009). Patients who received priming in the mid-luteal phase of the cycle preceding the ovarian stimulation cycle were treated with either 0.1 mg estradiol patches or oral contraceptive pills (Dragisic *et al.*, 2005).

Once two leading follicles had reached 17 mm in size (20 mm for letrozole or clomiphene-based protocols), oocyte maturation was triggered with either an hCG (Novarel [Ferring Pharmaceuticals Inc., Parsippany, NJ, USA] or Pregnyl [Merck, Whitehouse Station, NJ, USA]) trigger or a dual trigger with hCG and GnRH agonist (leuprolide acetate) according to a sliding-scale regimen for hCG dose (Pereira *et al.*, 2015, 2016). Oocyte retrieval was performed transvaginally under ultrasound guidance ~35–37 h after the trigger was administered. The method of insemination, embryo evaluation and day of embryo transfer was determined based on internal protocols, patient history, embryo numbers and embryo development assessed using morphokinetics. Luteal support was provided with 50 mg daily i.m. progesterone in oil injection beginning the day after oocyte retrieval. Patients who received a dual trigger with <3300 units of hCG also received two 0.1 mg estradiol patches every other day. Luteal support was continued until documentation of a fetal heartbeat identified around 7 weeks of gestation.

Demographics and outcomes

Key demographic variables were collected (Table I). Clinical pregnancy was defined as the presence of at least one intrauterine gestational sac observed on ultrasound. Spontaneous abortion was defined as a failed pregnancy after the observation of at least a gestational sac on ultrasound. Live birth was defined as delivery of a live-born infant at ≥24 weeks of gestation.

Statistical analysis

The primary outcome of this study was live birth. The secondary outcomes included implantation, biochemical and miscarriage rates. The size of our cohort is powered to detect a 5.7% difference in live birth per cycle with a 5% level of significance and 80% power. Logistic regression analysis was used to estimate the odds ratio (OR) with a 95% CI among the study groups for pregnancy outcomes listed in Tables II, III and IV. This analysis was adjusted *a priori* for patient age, and all pregnancy outcomes were additionally adjusted for the number of embryos transferred. A subgroup analysis of more severe forms of diminished ovarian reserve was performed to evaluate outcomes for patients with an AMH <0.5 ng/ml (Table III) and for patients >40 years old with an AMH <1.1 ng/ml (Bologna criteria for diminished ovarian reserve; Table IV) (Ferraretti *et al.*, 2011). Statistical analyses were performed using StataSE 16 (StataCorp LLC, College Station, TX, USA).

Results

This study consisted of 1790 patients with diminished ovarian reserve. Overall, 1115 patients initiated an IVF cycle within 90 days of initial evaluation (immediate), and 675 patients initiated an IVF cycle between 91 and 180 days of initial evaluation (delayed). Among the study

Table I Demographic characteristics for immediate and delayed treatment groups.

Characteristics	Immediate treatment (1–90 days), $n = 1115$	Delayed treatment (91–180 days), $n = 675$
Time from initial visit to IVF start (days)	50.5 ± 21.9	128.8 ± 25.9
Age at IVF start (years)	39.1 ± 4.4	38.9 ± 4.3
BMI (kg/m^2)	24.8 ±5.3	24.3 ± 4.7
Race		
Caucasian	538 (48.3%)	342 (50.7%)
Asian	137 (12.3%)	100 (14.8%)
Black	43 (3.9%)	21 (3.1%)
Other/declined	397 (35.6%)	212 (31.4%)
AMH (ng/ml)	0.56 ± 0.29	0.57 ± 0.29
Antral follicle count		
0–5	520 (46.6%)	317 (47.0%)
6–10	494 (44.3%)	301 (44.6%)
11–15	79 (7.1%)	45 (6.7%)
≥16	22 (2.0%)	12 (1.8%)
Prior IVF cycles at outside institutions	1.3 ± 2.1	0.8 ± 1.6
Stimulation protocol		
Gonadotrophin/antagonist	847 (76.0%)	504 (74.7%)
Gonadotrophin/agonist flare	145 (13.0%)	105 (15.6%)
Gonadotrophin+CC or letrozole/antagonist	115 (10.3%)	56 (8.3%)
Other	8 (0.7%)	10 (1.5%)
Day of embryo transfer		
None	133 (11.9%)	69 (10.2%)
Day 3	913 (81.9%)	555 (82.2%)
Day 5	69 (6.2%)	51 (7.6%)
Number of embryos transferred	2.0 ± 1.3	2.1 ± 1.2
Oocytes retrieved	6.3 ± 3.9	6.6 ± 4.4
Oocytes mature	4.9 ± 3.4	5.3 ± 3.7
Oocytes fertilized	3.5 ± 2.8	3.7 ± 3.1

Data are mean ± SD or *n* (%).
AMH, anti-Müllerian hormone; CC, clomiphene citrate.

cohort, 785 patients (43.9%) had an AMH <0.5 ng/ml, and 829 patients (46.3%) were >40 years old and had an AMH <1.1 ng/ml.

Demographic characteristics are shown in Table I. The mean ± SD and median (interquartile range) number of days from initial presentation to the start of an IVF cycle was 50.5 ± 21.9 and 48 (33–69) days in the immediate treatment group and 128.8 ± 25.9 and 125 (107–149) in the delayed treatment group, respectively. Figure 1 displays the length of duration, in 30-day increments, from the initial visit to IVF cycle start for the study cohort. A plot of each study year that displays the length of duration from the initial visit to IVF cycle start for both groups is shown in Fig. 2. The mean AMH was 0.56 ± 0.29 ng/ml in the immediate treatment group and 0.57 ± 0.29 in the delayed treatment group. The number of oocytes retrieved was 6.3 ± 3.9 (immediate) and 6.6 ± 4.4 (delayed), and the number of mature

Table II The association between time to treatment and IVF treatment outcomes.

Outcome	Immediate treatment (1–90 days), n = 1115	Delayed treatment (91–180 days), n = 675
No transfer*	133 (11.9%) 1.00 (Ref)	69 (10.2%) 0.84 (0.62, 1.15)
Pregnancy rate among all IVF cycles	385 (34.5%) 1.00 (Ref)	264 (39.1%) 1.23 (0.99, 1.51)
Live birth rate among all IVF cycles[a]	235 (21.1%) 1.00 (Ref)	155 (23.0%) 1.11 (0.88, 1.42)
If embryo transfer	(n = 982)	(n = 606)
Pregnancy rate after embryo transfer	385 (39.2%) 1.00 (Ref)	264 (43.6%) 1.20 (0.97, 1.48)
Live birth rate after embryo transfer[a]	235 (23.9%) 1.00 (Ref)	155 (25.6%) 1.08 (0.85, 1.38)
If clinically pregnant[b]	(n = 385)	(n = 264)
SAB[c]	66 (17.1%) 1.00 (Ref)	43 (16.3%) 0.96 (0.62, 1.48)
Live birth[a]	235 (61.0%) 1.00 (Ref)	155 (58.7%) 0.91 (0.65, 1.26)

Data are n (%) with OR (95% CI). Logistic regression models adjusted *a priori* for age and number of embryos transferred to estimate the OR of pregnancy outcomes.
*Adjusted for age only. The reason for no transfer was due to unplanned upfront cryopreservation in six patients in the immediate treatment group and in six patients in the delayed treatment group. The reason for no transfer in all other patients was due to a lack of oocytes, sperm or embryo development.
[a]Live birth was defined as delivery at $\geq$24 weeks of gestational age.
[b]Clinical pregnancy was defined as the visualization of at least one gestational sac on ultrasound.
[c]Spontaneous abortion (SAB) was defined as a failed pregnancy after the observation of at least one gestational sac on ultrasound.

Table III The association between time to treatment and IVF treatment outcomes in patients with AMH <0.5 ng/ml.

Outcome	Immediate treatment (1–90 days), n = 506	Delayed treatment (91–180 days), n = 279
No transfer*	76 (15.0%) 1.00 (Ref)	38 (13.6%) 0.90 (0.59, 1.37)
Pregnancy rate among all IVF cycles	154 (30.4%) 1.00 (Ref)	86 (30.8%) 1.01 (0.72, 1.41)
Live birth rate among all IVF cycles[a]	81 (16.0%) 1.00 (Ref)	46 (16.5%) 1.02 (0.67, 1.54)
If embryo transfer	(n = 430)	(n = 241)
Pregnancy rate after embryo transfer	154 (35.8%) 1.00 (Ref)	86 (35.7%) 0.99 (0.70, 1.39)
Live birth rate after embryo transfer[a]	81 (18.8%) 1.00 (Ref)	46 (19.1%) 0.99 (0.65, 1.51)
If clinically pregnant[b]	(n = 154)	(n = 86)
SAB[c]	35 (22.7%) 1.00 (Ref)	18 (20.9%) 0.97 (0.50, 1.89)
Live birth[a]	81 (52.6%) 1.00 (Ref)	46 (53.5%) 0.99 (0.57, 1.72)

Data are n (%) with OR (95% CI). Logistic regression models adjusted *a priori* for age and number of embryos transferred to estimate the OR of pregnancy outcomes.
*Adjusted for age only.
[a]Live birth was defined as delivery at $\geq$24 weeks of gestational age.
[b]Clinical pregnancy was defined as the visualization of at least one gestational sac on ultrasound.
[c]SAB was defined as a failed pregnancy after the observation of at least one gestational sac on ultrasound.

oocytes was 4.9 ± 3.4 (immediate) and 5.3 ± 3.7 (delayed). The number of fertilized oocytes was 3.5 ± 2.8 (immediate) and 3.7 ± 3.1 (delayed).

Among the 1790 patients, an embryo transfer was not performed in 133 cycles (11.9%) in the immediate treatment group and in 69 cycles (10.2%) in the delayed treatment group. There were six cycles per group that resulted in unplanned cryopreservation of embryos. Otherwise, the reason for no embryo transfer was an unexpected lack of oocytes, sperm or embryo development. Among all patients with an AMH <1.1 ng/ml, the pregnancy rate was comparable between the immediate and delayed treatment groups when evaluated among all patients in the cohort (34.5% versus 39.1%; OR 1.23, 95% CI 0.99–1.51) and when evaluated among only patients who had an embryo transfer (39.2% versus 43.6%; OR 1.20, 95% CI 0.97–1.48). The live birth rate was also comparable between the immediate and delayed treatment groups when evaluated among all patients in the

cohort (21.1% versus 23.0%; OR 1.11, 95% CI 0.88–1.42) and when evaluated among only patients who had an embryo transfer (23.9% versus 25.6%; OR 1.08, 95% CI 0.85–1.38). For women who achieved a pregnancy, the live birth rate was also similar between the immediate (61.0%) and delayed treatment groups (58.7%) (OR 0.91, 95% CI 0.65–1.26). Additionally, there were no differences between the proportion of biochemical pregnancies or miscarriages that were observed in pregnant patients (Table II).

Subgroup analysis for women with an AMH <0.5 ng/ml is displayed in Table III. The pregnancy rate was comparable between the immediate and delayed treatment groups when evaluated among all patients in the cohort (30.4% versus 30.8%; OR 1.01, 95% CI 0.72–1.41) and when evaluated among only patients who had an embryo transfer (35.8% versus 35.7%; OR 0.99, 95% CI 0.70–1.39). The live birth rate was also comparable between the immediate and delayed treatment groups when evaluated among all patients in the cohort (16.0% versus

Table IV The association between time to treatment and IVF treatment outcomes in patients >40 years old.

Outcome	Immediate treatment (1–90 days), n = 524	Delayed treatment (91–180 days), n = 305
No transfer*	60 (11.5%) 1.00 (Ref)	39 (12.8%) 1.18 (0.76, 1.83)
Pregnancy rate among all IVF cycles	135 (25.8%) 1.00 (Ref)	85 (27.9%) 1.11 (0.79, 1.55)
Live birth rate among all IVF cycles[a]	57 (10.9%) 1.00 (Ref)	39 (12.8%) 1.19 (0.76, 1.87)
If embryo transfer	(n = 464)	(n = 266)
Pregnancy rate after embryo transfer	135 (29.1%) 1.00 (Ref)	85 (32.0%) 1.13 (0.81, 1.59)
Live birth rate after embryo transfer[a]	57 (12.3%) 1.00 (Ref)	39 (14.7%) 1.21 (0.77, 1.91)
If clinically pregnant[b]	(n = 135)	(n = 85)
SAB[c]	43 (31.9%) 1.00 (Ref)	16 (18.8%) 0.51 (0.26, 0.98)
Live birth[a]	57 (42.2%) 1.00 (Ref)	39 (45.9%) 1.10 (0.63, 1.93)

Data are *n* (%) with OR (95% CI). Logistic regression models adjusted *a priori* for age and number of embryos transferred to estimate the OR of pregnancy outcomes.
*Adjusted for age only.
[a]Live birth was defined as delivery at ≥24 weeks of gestational age.
[b]Clinical pregnancy was defined as the visualization of at least one gestational sac on ultrasound.
[c]SAB was defined as a failed pregnancy after the observation of at least one gestational sac on ultrasound.

Figure 1. Days from initial visit to IVF cycle start.

16.5%; OR 1.02, 95% CI 0.67–1.54) and when evaluated among only patients who had an embryo transfer (18.8% versus 19.1%; OR 0.99, 95% CI 0.65–1.51). For women who achieved a pregnancy, the live birth rate was also similar between the immediate (52.6%) and delayed groups (53.5%) (OR 0.99, 95% CI 0.57–1.72). Additionally, there were no differences between the proportion of biochemical pregnancies or miscarriages that were observed in pregnant patients.

Subgroup analysis for women who met the Bologna criteria for diminished ovarian reserve by age >40 years old and an AMH <1.1 ng/ml is displayed in Table IV. The pregnancy rate was comparable between the immediate and delayed treatment groups when evaluated among all patients in the cohort (25.8% versus 27.9%; OR 1.11, 95% CI 0.79–1.55) and when evaluated among only patients who had an embryo transfer (29.1% versus 32.0%; OR 1.13, 95% CI 0.81–1.59). The live birth rate was also comparable between the immediate and delayed treatment groups when evaluated among all patients in the cohort (10.9% versus 12.8%; OR 1.19, 95% CI 0.76–1.87) and when evaluated among only patients who had an embryo transfer (12.3% versus 14.7%; OR 1.21, 95% CI 0.77–1.91). For women who achieved a pregnancy, the live birth rate was also similar between the immediate (42.2%) and delayed treatment groups (45.9%) (OR 1.10, 95% CI 0.63–1.93). Additionally, the proportion of biochemical pregnancies was similar between the immediate (24.4%) and delayed treatment groups (34.1%) (OR 1.75, 95% CI 0.95–3.24). However, the proportion of pregnancies that resulted in a miscarriage was significantly higher for women in the immediate (31.9%) compared to the delayed treatment groups (18.8%) (OR 0.51, 95% CI 0.26–0.98).

Discussion

The aim of this study was to identify whether a delay in initiating IVF treatment has a negative effect on outcomes for women with diminished ovarian reserve (AMH <1.1 ng/ml). In our cohort of patients who initiated an IVF cycle within 6 months of their first consultation, there was no difference in the live birth rate among women who initiated their IVF cycle within 90 days of their first visit compared to those who did so 91–180 days after initial consultation. There was also no difference in the live birth rate for the immediate or delayed treatment groups for women with an AMH <0.5 ng/ml or for women who met Bologna criteria for diminished ovarian reserve who were >40 years old with an AMH <1.1 ng/ml.

In clinical practice, treatment delays can occur due to medical, logistical or financial reasons. In a more extreme scenario, treatment delays also can occur as the result of natural disasters or pandemics, at which time resources are often temporarily reallocated to manage the disaster at hand. The SARS-CoV-2 pandemic is one such example that prompted both the ASRM and ESHRE to recommend the suspension of new infertility treatment cycles, and that fertility patients should avoid becoming pregnant until more information about the virus is known (Coronavirus Covid-19: ESHRE statement on pregnancy and conception; Coronavirus/COVID-19 TaskForce of the American Society for Reproductive Medicine).

Regardless of the reason for treatment delay, both patients and providers express concern when infertility treatment cycles are unable to start in a timely manner. This is particularly true for patients with diminished ovarian reserve due to the shorter timeframe these patients
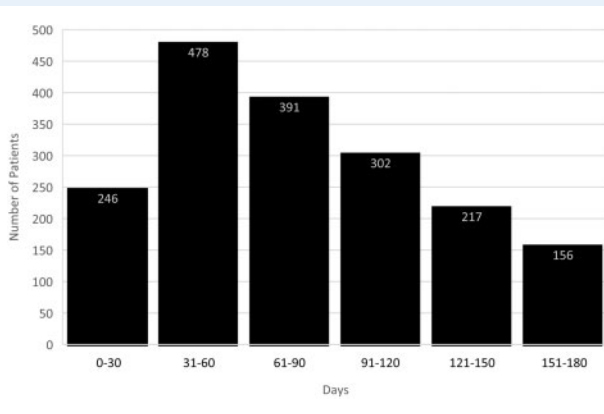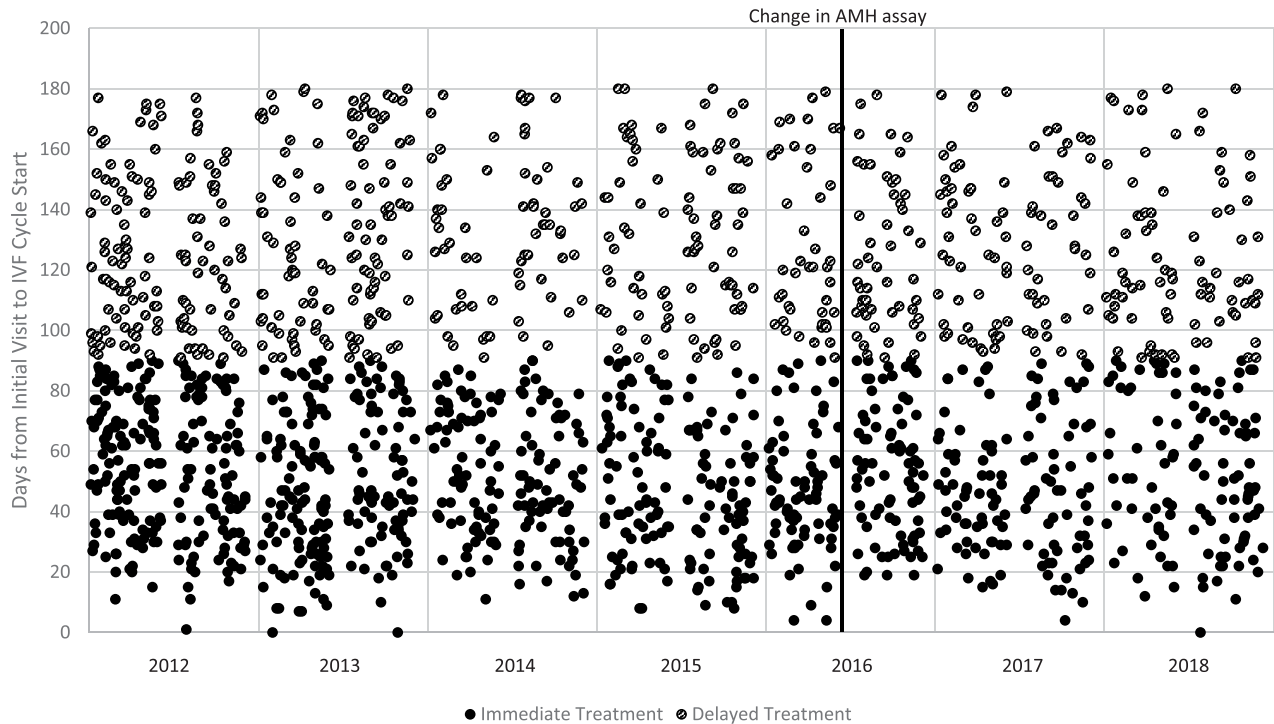
Figure 2. Length of duration from initial visit to IVF cycle start, by year. The solid black line marks the change in our laboratory from using the anti-Müllerian hormone (AMH) ELISA assay to the Beckman Coulter Access AMH assay (10 March 2016).

have to achieve a pregnancy compared to age-matched women with normal ovarian reserve. It is well understood that over an interval of several years, women experience a gradual decline in ovarian reserve and fecundability (Schwartz and Mayaux, 1982; Wilkosz *et al.*, 2014). However, in infertile patients, the length of time that it takes for a clinically meaningful decline in ovarian reserve or the likelihood of a successful treatment outcome is not known.

The results of our study are reassuring in that women with an AMH <1.1 ng/ml were not observed to have a decline in pregnancy rate or live birth rate after a delay of up to 180 days in initiating IVF treatment. This observation remained true when pregnancy and live birth rates were assessed among all patients in the cohort, among only patients who had an embryo transfer and among only patients who achieved a pregnancy. These findings suggest that a short delay in treatment does not have a clinical effect on implantation or fetal and pregnancy development. A similar proportion in both groups did not have an embryo transfer due to no oocytes retrieved, no sperm available or poor embryo development. This finding suggests that embryo development is also not affected by a short delay in IVF treatment.

Furthermore, for patients with an AMH <0.5 ng/ml and for patients who were >40 years old with an AMH <1.1 ng/ml, there were no differences observed for pregnancy or live birth rate analyses. Since both of these subgroups may be considered particularly poor-prognosis patients, providers may feel there is an urgent need to start their treatment as soon as possible. While prioritizing treatment for all patients, including those with diminished ovarian reserve, is important in the normal clinical

setting, it is reassuring that a delay in treatment of up to 180 days did not lead to a decline in pregnancy outcomes, even in patients who are among the highest risk for poor response to ovarian stimulation.

The increased rate of miscarriages observed in the immediate treatment group in patients >40 years old was an unexpected finding and warrants a more detailed evaluation in a larger patient cohort. In terms of the study objective, it is reassuring that this outcome was not observed in women in the delayed treatment group. Furthermore, the overall similar pregnancy and live birth rates between the two groups in these women support the overall findings of this study that a short delay in infertility treatment does not affect the goal outcomes of infertility treatment.

We acknowledge the limitations of this study. There is the potential for selection bias with regard to the patients who started their IVF cycle within 90 days compared to 91–180 days after initial consultation. It is possible that for patients with severely diminished ovarian reserve, there may have been an urgency in starting their treatment. However, the mean AMH levels and the proportion in each antral follicle count category were comparable between the two groups, which partially mitigates this concern. In addition, we did not include patients who were seen for initial evaluation but did not progress to IVF treatment with oocyte retrieval; therefore, our results should only be applied to patients with diminished ovarian reserve who complete an IVF cycle. We were unable to determine the assay used in cases where the AMH level was processed at an outside laboratory, which may lead to some inter-assay variation between the reported AMH levels. Finally, since we excluded patients who started their IVF cycle greater than

180 days from their first visit, it is not known how such a delay in treatment affects pregnancy outcomes in IVF cycles.

Conclusion

In summary, a delay in initiating IVF treatment in patients with diminished ovarian reserve (AMH <1.1 ng/ml) up to 180 days from the initial visit does not affect pregnancy outcomes. This observation remains true for women who are considered the highest risk for poor response to ovarian stimulation (either having an AMH <0.5 ng/ml or being >40 years old with an AMH <1.1 ng/ml). Overall, these results are reassuring to providers that when short-term treatment delays are deemed necessary for medical, logistic or financial reasons, treatment outcomes will not be affected. Additionally, these results are reassuring to patients who may feel anxious to begin their treatment and become frustrated when unexpected delays occur. Future studies should seek to identify the length of time over which clinical outcomes are affected by treatment delays, particularly to help counsel patients in whom a treatment delay of greater than 180 days is expected.

Authors' roles

P.A.R.: Participated in study design, execution, analysis planning, manuscript drafting and editing. P.B.: Participated in study design, analysis planning, manuscript drafting and editing. Z.R.: Participated in study design, analysis planning and manuscript editing. G.L.S.: Participated in study design, analysis planning and manuscript editing.

Conflict of interest

The authors do not have any conflict of interest disclosures.

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