FERTILITY AND STERILITY®
VOL. 81, NO. 5, MAY 2004

Published by Elsevier Inc.
Printed on acid-free paper in U.S.A.

A poor response in the first in vitro fertilization cycle is not necessarily related to a poor prognosis in subsequent cycles

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Objective: To calculate the cumulative ongoing pregnancy rate in patients with a poor response in their first IVF cycle.

Design: Retrospective cohort study.

Setting: In vitro fertilization unit of a university hospital.

Patient(s): Two hundred twenty-five women who experienced a poor response in their first IVF or intracytoplasmic sperm injection cycle. These patients were divided into 64 expected (aged ≥41 years and/or elevated FSH level) and 161 unexpected poor responders (aged <41 years and FSH level not elevated).

Intervention(s): In vitro fertilization treatment with a long-suppression protocol with FSH-urofollitropin or recombinant FSH.

Main Outcome Measure(s): Cumulative ongoing pregnancy rate. This rate was calculated in two ways to correct for dropouts: pessimistic (zero chance of pregnancy for the dropouts) and optimistic (the same chance for the dropouts as for patients who continued).

Result(s): The cumulative ongoing pregnancy rate of women with an unexpected poor response in the first cycle was 37% (pessimistic) to 47% (optimistic) after three cycles. Women with an expected poor response had a cumulative ongoing pregnancy rate of 16% (pessimistic) to 19% (optimistic) after 3 cycles. Sixty-four percent of the unexpected poor responders and 31% of the expected poor responders had a normal response in the second cycle, most of them after receiving a higher dose of gonadotropins.

Conclusion(s): Most patients with an unexpected poor response in the first cycle had a normal response in the second cycle, leading to an acceptable cumulative ongoing pregnancy rate after three cycles. Patients with an expected poor response in the first cycle should be advised to withdraw from treatment after the first cycle because of a poor prognosis. (Fertil Steril® 2004;81:1247–53. ©2004 by American Society for Reproductive Medicine.)

Key Words: IVF, poor response, cumulative ongoing pregnancy rates

Received April 28, 2003; revised and accepted October 6, 2003.

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0015-0282/04/$30.00
doi:10.1016/j.fertnstert.2003.10.030

The first successful IVF treatment was performed in a natural cycle, during which one oocyte was retrieved (1). In 1981, ovarian hyperstimulation was introduced to obtain more oocytes to replace more embryos, but some patients responded poorly. Poor response was associated with high cancellation rates and low pregnancy rates. Poor response remains a subject of interest, with the focus being mainly on prediction and treatment (2, 3).

Some patients are more likely than others to respond poorly during IVF treatment. Because ovarian reserve declines with age (4), the risk of a poor response in IVF is higher when the patient is older. Patients aged >40 years are often not treated with IVF because of the poor prognosis, often associated with a poor response (5, 6). However, age is of limited value to assess the ovarian reserve of an individual patient. Therefore, several other markers to predict ovarian response during IVF treatment were introduced, of which basal FSH is most widely used. Patients with elevated FSH levels are known to be at risk for poor response during IVF treatment (7).

Whether it is possible to improve a poor response is still a matter of debate. In the past 2 decades, several strategies have been developed. The most common is to increase the dose of gonadotropins (8–10); however, the quest

continues for a good solution to the problem of poor response. Even when response improves after a change in the hyperstimulation protocol, this does not imply a better probability of pregnancy (11, 12). Thus, when patient and clinician are confronted with a poor response in the first IVF cycle, the question arises of whether it is worthwhile to continue treatment.

The aim of the present study was to determine the cumulative ongoing pregnancy rate after three cycles in patients with a poor response in their first cycle. We also wanted to determine whether there is a difference in prognosis between patients who were already at risk for a poor response because of advanced age or elevated basal FSH and patients who were not.

MATERIALS AND METHODS

Patients

Between January 1, 1998 and December 15, 2001, 1,307 women started their first IVF or intracytoplasmic sperm injection (ICSI) treatment in our IVF center. With our database, all 268 women who experienced a poor response in their first cycle were identified.

Forty-three patients were excluded from the study for various reasons. Twenty patients had been diagnosed with polycystic ovary syndrome (oligo- or amenorrhea, elevated LH levels with normal FSH levels, and/or elevated androgen levels). In these patients, the poor response was probably caused by insufficient stimulation, because the starting dose of gonadotropins was lowered to avoid ovarian hyperstimulation syndrome. One patient was canceled because of a persistent cyst. Six patients had not completed their treatment at the time of evaluation. In 15 patients the basal FSH value was missing, and for one patient the date of birth was unknown. These patients were excluded from the study, leaving a total of 225 women to be analyzed.

The patients were classified into two subgroups. The first group consisted of women with a basal FSH level ≥15 IU/L and/or aged ≥41 years. This FSH level was chosen on the basis of a previous study conducted in our center, in which patients with an FSH level ≥15 IU/L had poor results in IVF (13). The age level is based on our national IVF guidelines. Women aged ≥41 years are not routinely offered IVF treatment in The Netherlands because of the poor results in this group. In our clinic, patients with elevated FSH levels and patients aged ≥41 years are offered IVF treatment in a research setting, after appropriate counseling.

The second group consisted of women aged <41 years with FSH levels <15 IU/L. According to data collected previously in our center and partly published (14, 15) patients aged ≥41 years or with FSH levels ≥15 IU/L had a significantly higher poor response rate than patients aged <41 with normal FSH levels (56% of 93 patients vs. 20% of 136 patients, $P<.001$). We therefore defined the first group of patients as expected poor responders and the second group as unexpected poor responders.

This study did not require approval of our institutional review board because it concerned a retrospective analysis of data that were recorded anonymously and did not imply active involvement of patients.

In The Netherlands, reimbursement is limited to three IVF cycles, so there were no financial restraints to discontinue treatment before the third cycle. Therefore, we decided to limit our follow-up period to three consecutive cycles. Pregnancies resulting from cryopreserved embryos were not included in the calculation of the cumulative pregnancy rates.

Treatment Protocol

All women were treated with a long-suppression protocol. A detailed description of the protocol was published previously (16). In brief, pituitary desensitization was started in the midluteal phase by the administration of leuprolide acetate (Lucrin; Abbott, Hoofddorp, The Netherlands). After menstruation, ovarian stimulation was started.

Before February 1, 1999 patients were stimulated with a standard starting dose of 225 IU of urofollitropin (Metrodin HP; Serono Benelux, ′s Gravenhage, The Netherlands). After this date, our clinic switched to a standard starting dose of 150 IU of follitropin α (Gonal-F; Serono Benelux). The starting dose was lowered to 150 IU because it was found in a randomized study that recombinant human FSH was more effective than urinary human FSH at inducing multiple follicular growth (17). This change in the stimulation protocol did not change the poor response rate in our IVF population. Before the introduction of follitropin α, the poor response rate was 16%, and afterwards it was 20%; this difference is not significant ($P=.10$).

Transvaginal ultrasonography and E_2 measurements were used to monitor ovarian stimulation. In cases of insufficient follicular growth, the dose was adjusted after at least 7 days of stimulation. Thirty-six hours before the ovum pick-up, 10,000 units of hCG (Profasi; Serono Benelux) were administered. A maximum of two embryos was replaced in women aged <38 years. In older women, the maximum number of embryos at transfer was three. Luteal support was provided by hCG (Profasi) or micronized P (Progestan; Nourypharma, Oss, The Netherlands).

Hormone Assay

Follicle-stimulating hormone was measured in plasma with an automated immunometric FSH assay (Chirion Diagnostics, Tarrytown, NY) on the automated ACS-180 immunoassay platform (Bayer, Tarrytown, NY). The observed interassay coefficients of variation were 3.9% and 3.9% at 5.5 IU/L and 26 IU/L, respectively.

Definitions

Poor response after stimulation was defined as the collection of less than four oocytes at retrieval or cancellation of

TABLE 1

Characteristics of the patients with a poor response in the first IVF cycle.

Characteristic	All poor responders (n = 225)	Unexpected poor responders (n = 161)	Expected poor responders (n = 64)	*P* value
Age (y)	36.7 (29.9, 42.4)	35.4 (29.6, 40.0)	41.5 (32.7, 44.5)	NA
Primary infertility (%)	56.9	62.1	43.8	.01[a]
Duration of infertility (mo)	38.0 (16.0, 90.6)	42.6 (23.0, 95.7)	28.3 (12.0, 77.1)	<.01[b]
Cause of infertility (%)				
Tubal	23.3	26.5	15.6	.09[a]
Male	36.3	41.7	23.4	.01[a]
Unexplained	40.5	31.8	60.9	<.01[a]
Basal FSH (IU/L)	8.4 (5.2, 16.7)	8.0 (5.0, 11.3)	12.1 (5.8, 21.3)	NA
Total no. of ampules	32.0 (18.6, 62.0)	30.0 (18.0, 62.0)	39.0 (22.0, 64.0)	<.01[b]
No. of ampules per stimulation day	2.5 (2.0, 3.8)	2.1 (2.0, 3.8)	2.9 (2.0, 3.8)	<.01[b]
Cancels (%)	32.9	34.8	28.1	.34[a]
No. of oocytes	2 (1, 3)	2 (1, 3)	2 (0, 3)	<.01[b]
No. of embryos	1 (0, 2)	1 (0, 2)	1 (0, 2)	.91[b]
No. of embryos/ET	1 (0, 2)	1 (0, 2)	1 (0, 2)	.24[b]
Ongoing pregnancies per cycle (%)	10	9	11	.73[a]

Note: Data are presented as median (10th percentile, 90th percentile) or %. NA = not applicable.

[a] χ^2 test.

[b] Mann-Whitney *U* test.

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the cycle due to insufficient follicular growth (less than three follicles). This definition is based on the assumption that a minimum of four oocytes is needed to have an average of two embryos available for transfer, given a mean fertilization rate of 50%–60% in IVF (14). The same definition was used in many other studies (10, 18–24) and seems to be the most widely used definition of poor response.

The outcome measure of this study was ongoing pregnancy, which was defined as the presence of a vital pregnancy beyond 11 weeks' gestation. Patients who did not become pregnant after IVF and did not return for a new treatment within 1 year were considered dropouts.

Statistical Methods

Cumulative ongoing pregnancy rates were calculated by life table analysis (Kaplan-Meier method). Most studies overestimate the cumulative pregnancy rate because they assume that women who drop out have the same probability of becoming pregnant as those who continue IVF treatment. However, patients who stop treatment are known to have a less favorable prognosis than those who continue (25, 26).

In 1996, a method was proposed by Stolwijk et al. (27) to estimate a more realistic cumulative pregnancy rate, by taking the reason for an early cessation of treatment into account. They assumed that women who stopped treatment for medical reasons had no chance of pregnancy, whereas women who stopped for other reasons had the same chance of pregnancy as those who continued. In the study presented here, we used an adapted version of this method, which resulted in "pessimistic" and "optimistic" cumulative ongoing pregnancy rates. In the pessimistic scenario, the dropouts were assumed to have zero chance of becoming pregnant, whereas in the optimistic one they were considered to have the same probability of pregnancy as patients who continued. We assumed that the real chance of pregnancy for dropouts was somewhere between the optimistic and pessimistic scenarios.

To compare the characteristics of the patients with an expected and an unexpected poor response, the χ^2 test and the Mann-Whitney *U* test were used, when appropriate. A *P* value of <.05 was considered statistically significant. The data were analyzed with commercial software (SPSS 10.0; SPSS, Chicago, IL).

RESULTS

We studied 225 patients who experienced a poor response in their first IVF cycle; 64 (28%) of them were expected poor responders, according to our definition. Of these, 35 women were aged ≥41 years but had a basal FSH level <15 IU/L and 7 were aged ≥41 years and had a basal FSH level ≥15 IU/L. Twenty-two patients were aged <41 years and had a basal FSH level ≥15 IU/L. The remaining 161 patients had an unexpected poor response (72%), as defined.

Table 1 shows the characteristics of the 225 patients. The unexpected poor responders were more often primary infertile and had a longer duration of infertility. The expected poor responders, who by definition were older and had higher FSH levels, were twice as often diagnosed with unexplained infertility. Regarding treatment characteristics,

TABLE 2

Ongoing pregnancy rates of the unexpected and expected (basal FSH ≥15 IU/L and/or aged ≥41 years) poor responders.

	Unexpected poor responders			Expected poor responders		
	Cycle 1	Cycle 2	Cycle 3	Cycle 1	Cycle 2	Cycle 3
No. at risk						
Optimistic	161	120	75	64	32	15
Pessimistic	161	146	120	64	57	54
No. of pregnancies	15	26	19	7	3	0
No. of dropouts	26 (18%)	19 (20%)	—	25 (44%)	14 (48%)	—
Pregnancy rate per cycle (%)						
Optimistic	9	22	25	11	9	0
Pessimistic	9	18	16	11	5	0
Cumulative pregnancy rate (%)						
Optimistic	9 (5–14)	29 (22–37)	47 (38–56)	11 (3–19)	19 (8–31)	19 (8–31)
Pessimistic	9 (5–14)	26 (19–32)	37 (30–45)	11 (3–19)	16 (7–25)	16 (7–25)

Note: For cumulative pregnancy rate, values in parentheses are 95% confidence intervals.

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the expected poor responders used more ampules of FSH during stimulation.

Although the median number of collected oocytes was the same in both groups, there was a significant difference because distribution was not normal. The number of oocytes was 2.3 ± 0.7 (mean ± SD) for the unexpected poor responders and 1.8 ± 1.0 for the expected poor responders. The ongoing pregnancy rate after the first cycle was 9% for the unexpected poor responders and 11% for the expected poor responders.

The cumulative ongoing pregnancy rate of all women with a poor response in their first cycle was between 31% (pessimistic) and 42% (optimistic). The cumulative ongoing pregnancy rate after three cycles in women with an unexpected poor response was between 37% (pessimistic) and 47% (optimistic) (Table 2). The pregnancy rate per cycle in this group doubled, from 9% in the first cycle to 18%–22% in the second cycle and 16%–25% in the third cycle, which is comparable to the 24% ongoing pregnancy rate per cycle in the entire IVF program during the same period. In women with an expected poor response in the first cycle, the pregnancy rate per cycle remained low in the second cycle, whereas no pregnancies occurred in the third cycle (Table 2). In this group, the patients aged <41 years with an FSH level ≥15 IU/L (n = 22) had a cumulative ongoing pregnancy rate after three cycles between 18% (pessimistic) and 23% (optimistic). The patients aged ≥41 years with normal FSH levels (n = 35) had an ongoing pregnancy rate after three cycles between 17% (pessimistic) and 20% (optimistic). All patients aged ≥41 years with a basal FSH level ≥15 IU/L (n = 7) dropped out before the third cycle was reached. None of them became pregnant, also not in the first cycle.

There was a noticeable difference in dropout rates between the unexpected and expected poor responders: 18% vs. 44%, respectively, after the first cycle and 20% vs. 48% after the second cycle.

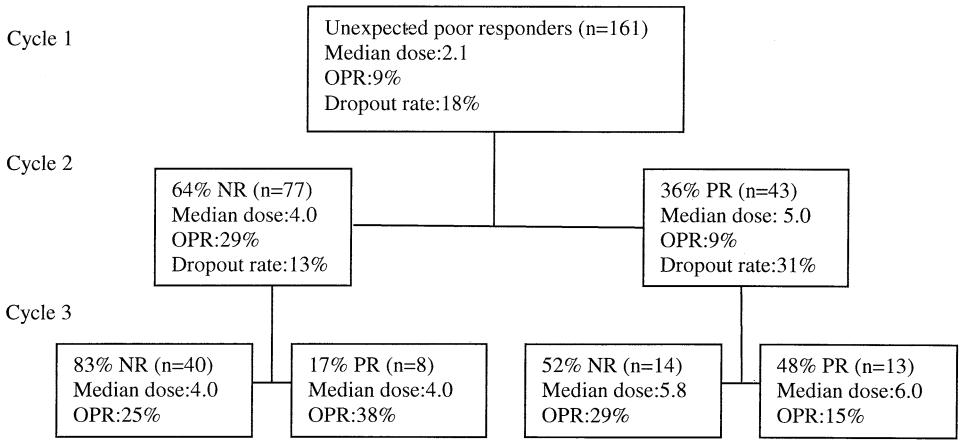
Figures 1 and 2 show the response, median dose of gonadotropins, pregnancy rates, and dropout rates of the unexpected and expected poor responders undergoing a second and third cycle. All expected poor responders and almost all of the unexpected poor responders received a higher dose in the second cycle. The majority of the unexpected poor responders turned into normal responders in the second and third cycle. In the expected poor responders group, only one third of the patients responded normally in the second cycle. In the third cycle, most of these patients fell back to a poor response. In the unexpected poor response group, 45 of 120 patients (38%) continuing IVF treatment after the first cycle became pregnant in the second or third cycle; most of them had a normal response. In contrast, in the expected poor response group, 3 of 32 patients (9%) continuing treatment became pregnant in the second cycle. In the third cycle, no more pregnancies occurred.

DISCUSSION

The three-cycle cumulative ongoing pregnancy rate of all patients with a poor response in the first cycle seems quite acceptable. The cumulative rates were calculated with pessimistic and optimistic approaches. In the pessimistic approach, we assumed that the patients who dropped out of treatment had no chance of pregnancy. In the optimistic scenario, they were assumed to have the same chance as those who continued. Especially in poor responders, it is important to take dropouts into account when calculating the cumulative pregnancy rates, to avoid an overestimation. It is likely that patients who drop out of treatment are those with the least favorable prognosis; but even in the pessimistic scenario, the cumulative ongoing pregnancy rate after three

FIGURE 1

Response, dose, pregnancy rate, and dropout rate of the unexpected poor responders. OPR = ongoing pregnancy rate per cycle; NR = normal response; PR = poor response. Median dose = total number of ampules/duration of stimulation.



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cycles is still reasonable, especially in unexpected poor responders.

It can be concluded from this study that a poor response in the first IVF cycle is not sufficient reason to stop further treatment. Much depends of course on the definitions applied. There is no generally accepted definition of poor response, although the definition we applied is the one most widely used (10, 18–24). Even if we were to apply stricter definitions of poor response, our conclusion that a poor response in the first cycle is not necessarily a reason to stop further treatment would not change. If, for example, we define poor response as cancellation due to insufficient follicular growth (n = 74), the cumulative ongoing pregnancy rate was between 26% (pessimistic) and 38% (optimistic). At a cut-off level of less than two oocytes (n = 109), the cumulative rate was between 25% (pessimistic) and 39% (optimistic), and at a cut-off level of less than three oocytes, the cumulative rate was between 25% (pessimistic) and 37% (optimistic).

We differentiated between expected and unexpected poor responders. By "unexpected" we mean that before the start of stimulation, there was no reason to expect a poor response. In contrast, "expected" poor responders were defined as patients estimated to have a high probability of poor response because of elevated FSH levels or advanced age. Naturally, other definitions of expected poor response are feasible and might be more clinically useful. In several studies, the antral follicle count seemed to be a better predictor of IVF outcome than age or basal FSH level (15, 28–30).

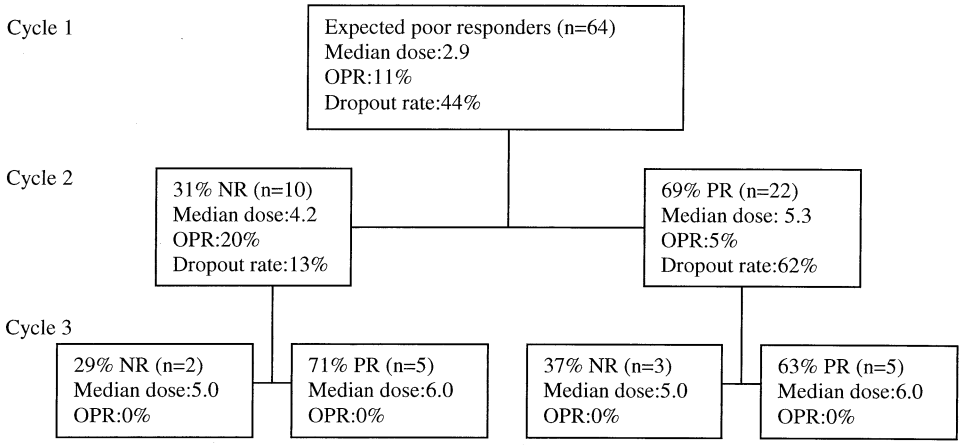
The results of this study demonstrate that the differentiation between expected and unexpected poor responders is clinically useful. Despite a poor result in the first cycle, the three-cycle ongoing pregnancy rate of the unexpected poor responders was quite acceptable, even in the most pessimistic scenario. If pregnancy has not occurred after three cycles, it might be reasonable to encourage such patients to go on for a fourth or even a fifth cycle, to give them the opportunity to compensate for the poor result in the first cycle.

In contrast, the expected poor responders should be advised to stop treatment after the first cycle. The pregnancy rate in the second and third cycles was between 3% (pessimistic) and 6% (optimistic). Taking into account the balance between risks, costs, and benefits, further treatment is not justified, in our opinion. Perhaps this policy would harm the interest of expected poor responders with a normal response in the second cycle, because their pregnancy results seem remarkably good. Unfortunately, the number of patients in this group is too small for firm conclusions to be drawn. Further research is needed to determine whether further treatment in this subgroup of patients is useful and whether we can identify these patients before treatment by using, for example, the antral follicle count (28–30).

Most of the studies evaluating the significance of increasing the gonadotropin dose after a poor response in a first cycle or an anticipated poor response during the course of stimulation focused on patients who were more or less expected to respond poorly, although the term "expected" was never used, and different definitions were applied (8, 10–12, 31). All these studies agreed that increasing the gonadotropin dose in such patients is not beneficial, because pregnancy prospects remain poor. The results in our expected poor response group are completely in line with this conclusion. The impaired reaction to ovarian hyperstimulation with go-

FIGURE 2

Response, dose, pregnancy rate, and dropout rate of the expected poor responders. OPR = ongoing pregnancy rate per cycle; NR = normal response; PR = poor response. Median dose = total number of ampules/duration of stimulation.



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nadotropins in this group of patients is likely to be caused by a decline of the quantity of the oocyte pool, which parallels a decrease in quality (32). This cannot be overcome simply by increasing the dose of gonadotropins (33, 34).

But what about the unexpected poor responders? In our experience, an unexpected poor response occurs more often than an expected poor response, at least when the latter definition is based on FSH level and age, as in our study. At first sight, the results shown in Figure 1 suggest that increasing the dose in unexpected poor responders results in a high proportion of normal responders who have good pregnancy prospects. However, biological data, such as ovarian response, are subject to random fluctuations above and below a mean. Therefore, patients with a poor response in the first cycle might fluctuate back to the mean (i.e., normal response) in a subsequent cycle, irrespective of the dose given. This phenomenon, known as "regression to the mean" occurs because the low response group might have included women who usually have a normal response but by chance were low in the first cycle. Regression to the mean has been mentioned previously as an explanation for the spurious effect of increasing the dose after a poor response in the first cycle (35).

Whether the favorable results in the second and third cycles of the unexpected poor responders can be completely explained by regression to the mean or is (partly) due to the increased dose of gonadotropins, can only be evaluated in a prospective study in which unexpected poor responders who received a normal dose in the first cycle are randomly assigned to increased-dose and normal-dose groups. Such a study has never been performed. The randomized studies that have been performed on different starting doses in IVF stimulation showed that more oocytes were retrieved in young patients who received a higher dose of gonadotropins, but not in older patients (33, 34). The results of the present study suggest that increasing the dose might only be beneficial in young poor responders when the poor response is unexpected. Of course, this is a retrospective study, and the numbers of patients in the third cycle are small, so no firm conclusions can be drawn.

Perhaps there are patients among the unexpected poor responders in whom the poor response is not as unexpected as we thought. Such patients might be revealed by a look at other characteristics besides age and FSH level, such as antral follicle count (29), FSH-receptor polymorphism (36), or low diffusion of exogenous gonadotropin (37).

In conclusion, this study showed that an unexpected poor response in a first IVF-ICSI cycle is not sufficient reason to deny a patient further treatment. The prognosis of these patients is not altered by a poor response in the first cycle. On the other hand, the treatment of patients with elevated basal FSH levels or aged ≥41 years who experience a poor response should be limited to one IVF cycle because of the poor pregnancy prospects in subsequent cycles.

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