

Natural-cycle in vitro fertilization in poor responder patients: a survey of 500 consecutive cycles

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Objective: To determine the role of the natural cycle for in vitro fertilization (IVF) in poor responder patients.

Design: Retrospective survey.

Setting: Private center for assisted reproduction.

Patient(s): 294 women who were poor responders in a previous IVF cycle.

Intervention(s): Analysis of 500 consecutive natural cycles IVF.

Main Outcome Measure(s): Number of cycles with oocytes, pregnancy rate per cycle, per transfer, and implantation rate.

Result(s): Oocytes were found in 391 cases (78.1%), and cleaving embryos suitable for transfer were obtained in 285 cycles (57.0%). Pregnancy was observed in 49 cases, with a pregnancy rate of 9.8% per cycle, 17.1% per transfer, and 16.7% per patient. The patients were subdivided arbitrarily by the women's age into three groups. Patients 35 years old or younger showed a pregnancy rate of 18.1% per cycle, 29.2% per transfer, and 31.7% per patient. Women aged between 36 and 39 years showed a pregnancy rate of 11.7% per cycle, 20.6% per transfer, and 20.3% per patient. Women 40 years old or older showed a pregnancy rate of 5.8% per cycle, 10.5% per transfer, and 9.7% per patient. No differences were found for any of the evaluated parameters, independent of which cycle was the first, the second, third, fourth, or fifth, or further consecutive cycle.

Conclusion(s): In poor responder patients, natural-cycle IVF is an effective treatment, especially in younger women. (Fertil Steril® 2009;92:1297–301. ©2009 by American Society for Reproductive Medicine.)

Key Words: Natural cycle, IVF, ICSI, poor responder, cumulative pregnancy rate

In vitro fertilization (IVF) in natural cycles or with minimal stimulation has gained worldwide attention and interest for both normal responder and poor responder patients (1–7) because in both groups of patients the treatment offers several advantages: no risk of ovarian hyperstimulation syndrome, very low or no gonadotropin administration, and patient-friendly treatment. In the literature, several studies on natural-cycle IVF or IVF with minimal stimulation have claimed good results in young, normal responder women (8–10). However, several other studies have reported poor results, especially in older women with elevated basal follicle-stimulating hormone (FSH) levels (11).

Although there is no general agreement on this definition, in general poor responder women are the patients who, during controlled ovarian hyperstimulation (COH) for IVF, show poor follicle recruitment despite the high dose of gonadotropins administered, and low levels of serum estradiol peak (12). The incidence of poor responder patients is estimated to be approximately 10% (13). Poor response is often related to patient age, where the low response to gonadotropins re-

flects a decline in the ovarian reserve of primordial follicles (14); thus, in women 40 years old or older it is more frequent, although it may also occur in young women (15). Poor responder patients are generally refractory to any stimulation protocols; although many treatment strategies have been suggested, the results remain poor, and despite the high quantity of gonadotropins administered (16), their chances of pregnancy remain very low (17). In these patients, natural-cycle IVF or IVF with minimal stimulation may be a valid alternative to egg donation or COH in terms of the cost-benefit ratio (1, 18), even though no univocal results have been reported in the literature. In our previous study, we showed that the natural cycle is at least as effective as COH in terms of pregnancy rate in poor responder women, and that this treatment should be preferred to COH in poor responders because of its favorable cost-benefit ratio (19).

In this study, we evaluated IVF outcome in terms of pregnancy rate per cycle started and per transfer in a large group of poor responder women who underwent 500 consecutive intracytoplasmic sperm injection (ICSI) natural cycles in our IVF center.

MATERIALS AND METHODS

Patient Selection

The study was conducted at the IVF program of the Bioroma Center, Rome Italy, between September 2003 and December

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2007 on poor responder patients undergoing IVF. The patients had to have regular menstrual cycles (26 to 39 days) with primary infertility and poor ovarian reserves, as shown by their previous IVF cycle canceled due to the poor response to COH. Inclusion criteria in the study were patient age ≤ 44 years old and a previous IVF cycle performed in our IVF center that was canceled due to no follicle activation or only one follicle recruited, fulfilling our definition of a poor responder (20, 21).

The study was reviewed and approved by the institutional review board. All patients undergoing IVF and participating in the study gave their informed consent. All patients underwent a standard infertility evaluation, including hormonal evaluation on the third day of the menstrual cycle (FSH, LH, estradiol, etc.), hysteroscopy, hysterosalpingogram, complete blood examination, and semen analysis.

The patients from the 7th day of the cycle underwent daily monitoring of follicle size by transvaginal ultrasound scan, which was performed to measure follicular structures within the ovary, endometrial thickness, and morphologic features. The criteria used for triggering ovulation with 10,000 IU of intramuscular human chorionic gonadotropin (hCG, Gonasi HP 5000; AMSA, Rome, Italy) was a follicle size of ≥ 16 mm in mean diameter.

Oocyte retrieval was performed under ultrasound control by the transvaginal route, 36 hours after the injection of hCG. Either local or general anesthesia was used. Generally only the dominant follicle was aspirated because the other smaller antral follicles were too small or they contained immature oocytes not suitable to be fertilized. We performed ICSI in all cases according to published procedures (22) to obtain a higher fecundation rate and to maximize the chances of embryo transfer because of the very low number of oocytes harvested (only one) in these patients and to avoid differences in the fertilization rate among patients treated with different techniques. Patients were informed of the possible risks to offspring from ICSI. Oocytes were observed 18 hours after ICSI for their pronuclei and 44 hours after insemination for embryo development.

The embryos obtained were categorized on day 3 into three categories, depending on their morphologic appearance. Grade A had equal and regular blastomeres without the presence of cytoplasm fragments. Grade B had unequal blastomeres with or without cytoplasmic fragments. Grade C were totally fragmented embryos (23).

Embryos were transferred 72 hours after insemination using the Sydney embryo transfer catheter (Cook Ltd, Brisbane, Queensland, Australia). All transfer procedures were performed by the same physician to avoid interoperator variability. All pregnancies were confirmed by a rising titer of serum β -hCG from 12 days after embryo transfer and by ultrasound demonstration of the gestation sac 4 weeks after the transfer. Biochemical pregnancies only have not been included.

The same luteal phase support was used in all cycles: 50 mg daily of intramuscular progesterone (Prontogest; AMSA) from the day of replacement.

Statistical Analysis

Statistical analysis was performed using the Fisher exact test and chi-square test for comparison of proportions, when appropriate. Parameters analyzed were: number of cycles with oocytes, number of cycles with embryos, number of embryo transfers, pregnancy rate (per cycle started and per embryo transfer), implantation rate (number of embryos observed by ultrasound per number of embryos transferred), and abortion rate. All statistical analyses were performed using the SPSS statistical package (SPSS, Inc., Chicago, IL).

RESULTS

The study included 294 women who were poor responders in a previous IVF cycle: their mean age was 39.3 ± 3.6 years (range: 30 to 43 years), their duration of infertility was 4.6 ± 2.7 years (range: 2.8 to 12.1 years), and the age of their male partners was 42.1 ± 3.9 years (range: 32 to 49 years). The women underwent 500 consecutive oocyte retrievals for IVF natural cycles. The causes of infertility were tubal factor in 27.9%, endometriosis in 11.9%, male factor infertility in 38.4%, and idiopathic in 21.8%.

Oocytes were found in 391 cases of oocyte retrieval (78.1%). After the ICSI procedure, cleaving embryos suitable for transfer were obtained in 285 cycles (57.0%), but no fertilization or cleaving embryos were obtained in 106 cycles (21.0%). Pregnancy was observed in 49 cases, with a pregnancy rate of 9.8% per cycle, 17.1% per transfer, and 16.7% per patient. The implantation rate was 17.1%. The birth rate was 8.2%, and no twin or multiple pregnancies were observed. The data are reported in Table 1.

The patients were subdivided arbitrarily by the women's age into three groups. In patients aged 35 years old or younger, oocytes were found in 81.9% cycles, cleaving embryos suitable for transfer were obtained in 61.8% cycles, but no fertilization or cleaving embryos were obtained in 19.1% cycles; the pregnancy rate was 18.1% per cycle, 29.2% per transfer, and 31.7% per patient; the implantation rate was 29.2%. In women aged between 36 and 39 years, oocytes were found in 81.4% cycles, cleaving embryos suitable for transfer were obtained in 56.1% cycles, but no fertilization or cleaving embryos were obtained in 23.5% cycles; the pregnancy rate was 11.7% per cycle, 20.6% per transfer, and 20.3% per patient; the implantation rate was 20.6%. In women aged 40 years or older, oocytes were found in 76.0% cycles, cleaving embryos suitable for transfer were obtained in 55.4% cycles, but no fertilization or cleaving embryos were obtained in 20.6% cycles; the pregnancy rate was 5.8% per cycle, 10.5% per transfer, and 9.7% per patient; the implantation rate was 10.5%. The differences for pregnancy rates among the three groups were statistically significant ($P < .01$), but the other parameters were similar among the three groups of patients (see Table 1).

Table 2 describes the performance of natural cycles in the first cycle performed in patients, in the second consecutive cycle, third consecutive cycle, fourth consecutive cycle, fifth

TABLE 1**Data on poor responder women treated with natural-cycle IVF in all cases, stratified by women's age.**

Parameters	All cases	≤ 35 years	36–39 years	≥ 40 years
No. of patients	294	60	69	165
No. of cycles	500	105	120	275
Cycles without oocytes	21.9%	19.1%	19.6%	24.0%
Cycles without embryos	21.0%	19.1%	23.5%	20.6%
Cycles with transfer	57.0%	61.8%	56.9%	55.4%
No. of embryos	285	65	68	152
Embryo A type	37.0%	43.1%	49.0%	30.7%
Embryo B type	51.9%	41.1%	41.5%	58.7%
Embryo C type	11.1%	15.7%	9.4%	10.6%
No. of embryos/transfer	1.0	1.0	1.0	1.0
Pregnancy/cycle	9.8%	18.1%	11.7%	5.8%
Pregnancy/transfer	17.1%	29.2%	20.6%	10.5%
Pregnancy/patient	16.7%	31.7%	20.3%	9.7%
Implantation rate	17.1%	29.2%	20.6%	10.5%
Abortion rate	16.3%	10.5%	14.3%	25.0%

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consecutive cycle, and further cycles. No differences were observed in terms of oocyte recovery or pregnancy rate in the entire series of cycles.

DISCUSSION

The management of women who are poor responders to COH remains a challenge for physicians in assisted reproduction despite the large number of protocols proposed for ovarian hyperstimulation in these patients and the attempts to improve their outcome (24). It is generally accepted that both young and old poor responders have a reduced number of follicles remaining in the ovary (17). Their treatment is generally approached in different ways, either by trying different

stimulation protocols using high levels of gonadotropins associated with different dosages and timing of GnRH analogs or antagonists, or trying IVF in a natural cycle (24) or with minimal stimulation, or as a last resort suggesting egg donation. Our previous study found that the natural cycle works at least as well as the COH in poor responder women who failed previous ovarian hyperstimulation, with a pregnancy rate per cycle of 6.1% and 14.9% per transfer (19).

In this study, we analyzed the outcome of 500 consecutive unstimulated IVF cycles in 294 women who were poor responders in previous IVF cycles; this is the largest study to our knowledge of poor responder women who have undergone natural-cycle IVF. We found that in these women natural cycles showed a pregnancy rate per cycle of approximately

TABLE 2**Data on poor responder patients treated with natural-cycle IVF stratified by first, second, third, fourth, or further cycle.**

Parameters	Number of consecutive cycles				
	1	2	3	4	≥ 5
No. of cycles	294	103	50	39	14
Cycles with oocytes	77.9%	78.6%	78.0%	79.5%	64.3%
Cycles with transfer	57.5%	57.3%	58.0%	56.4%	42.9%
No. of embryos obtained	169	59	29	22	6
No. of embryos/transfer	1.0	1.0	1.0	1.0	1.0
Pregnancy/cycle	9.5%	9.7%	12.0%	10.2%	7.1%
Pregnancy/transfer	16.6%	16.9%	20.7%	18.2%	16.7%
Implantation rate	16.6%	16.9%	20.7%	18.2%	16.7%
Abortion rate	14.3%	20.0%	16.7%	25.0%	0

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10%, and 18% per transfer. The pregnancy rate was different depending on the women's age: in younger women (≤ 35 years old), the pregnancy rate was 18% per cycle and 30% per transfer; in women aged >35 to 39 years, it was 11% per cycle and 20% per transfer; in women aged ≥ 40 years, it was 6% per cycle and 10% per transfer. The correlation between the women's age and the IVF outcome is well known; in poor responding younger women, the remaining follicles seem to be of good quality though low in number, but the opposite is true of women aged 40 years or older. Our data agree with what has been reported in the literature (1–7) and further confirm the results that had been obtained with natural-cycle IVF in poor responders in our previous study (19).

Our data evidenced that the results of all the parameters evaluated were similar, independent of whether they were the first, second, third, fourth, or further consecutive cycle. The pregnancy rate per cycle and per transfer always remained approximately 10% and 16% to 18%, respectively. Also, the rate of cycles with egg recovery and with transfer were similar, independent of the consecutive cycle. These results agree with those published by others recently in normal responder women (8–10). This may be explained by the fact that in poor responder women the few remaining follicles have the same chance to arrive at ovulation and to achieve pregnancy, according to the woman's age, of a physiologic cycle in healthy normal responder women. Consequently, each IVF cycle has the same chance of success as the previous and the future ones. These data show that IVF in natural cycles is an affordable and valid alternative in poor responder patients. These results agree with the data reported in a meta-analysis study (7) and in an earlier study published by Daya et al. (25).

Furthermore, in recent years several studies have reported that the use of minimal stimulation, a GnRH antagonist from 6th day of the cycle plus mild gonadotropin administration, lead to a relatively good pregnancy rate (8–10). In a recent study of patients aged 36 years or younger with subfertility who were generally normal responders, the investigators reported results similar to our pregnancy rate. It is noteworthy to emphasize that we obtained a pregnancy rate of 10% per cycle in older women, all whom were poor responders.

In light of our results, minimal stimulation does not seem to have any advantage over natural cycles in terms of pregnancy rate improvement. Minimal stimulation also is expensive because GnRH antagonists and gonadotropins, even if in low doses, are additional costs as well as stressful for the woman, without adding any improvement to the expected outcome. The literature offers no studies comparing natural cycles and minimal stimulation; consequently, no conclusions can be drawn on the cost-effectiveness of these two different strategies. An earlier study reported that in poor responder women with high day-3 FSH levels, minimal stimulation IVF did not offer a realistic chance of parenthood as the investigators did not obtain any pregnancies in 78 cycles started in 32 women (11).

Natural-cycle IVF is a suitable, feasible alternative to ovarian hyperstimulation in poor responder patients, and it should be suggested by physicians as an alternative to expensive ovarian stimulation with gonadotropins or before proposing egg donation, especially in women younger than 40 years. Furthermore, at least four consecutive attempts may also be suggested in the counseling of these patients because the chance of oocyte recovery and pregnancy per cycle remains the same for each consecutive attempt. Further studies are needed to determine whether natural cycles or minimal stimulation work better in these women, to establish the role of natural-cycle IVF in poor responders, and to improve its efficacy.

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