Outcomes of 1503 cycles of modified natural cycle in vitro fertilization: a single-institution experience

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Abstract

Purpose A retrospective cohort study was conducted in a single academic center to determine if modified natural cycle in vitro fertilization (mnIVF) is an acceptable treatment for the infertile couple.

Methods Cycles performed between July 2005 and December 2011 were included. In our center's mnIVF protocol, a GnRH antagonist, gonadotrophin, as well as Indocid are given on a daily basis from detection of a dominant follicle until ovulation induction. The primary outcomes were clinical pregnancy rates (CPR) per cycle started and per embryo transfer (ET). Outcomes were stratified by female patient age (≤ 35 years and ≥ 36 years). They were further stratified in each age group by ovarian response status according to the 2011 Bologna criteria.

Results A total of 1503 cycles of mnIVF, performed in 782 patients, were analyzed. CPRs were 13.7 % per started cycle and 32.5 % per ET. Stratification by ovarian response status (normal or poor) in each age group showed similar CPRs in patients ≤ 35 years ($p=0.373$), and divergent CPRs per ET in patients ≥ 36 years old (26.26 vs 6.25 %).

Conclusion MnIVF is an acceptable treatment option for patients considering IVF, particularly for women ≤ 35 years old and for women ≥ 36 years old with normal ovarian response.

Keywords Assisted reproduction · Modified natural IVF · Clinical pregnancy rates

Introduction

Conventional stimulated IVF involves various different ovarian stimulation protocols to increase the yield of retrieved oocytes to then increase the chance of fertilized embryos and ultimately to increase the chance of pregnancy. This stimulated form of IVF carries with it a physical and psychological burden for the patient, high cost, a risk of ovarian hyperstimulation syndrome (OHSS), and a risk of multiple pregnancies when more than one embryo is transferred at once. Although the increasing use of antagonist cycles in IVF with a GnRH agonist trigger and a freeze-all strategy has lowered the risk of OHSS, reports in the literature of severe OHSS in these cases are still appearing [1–3]. Also, repeated stimulated IVF cycles are not usually performed in consecutive menstrual cycles in order to allow time for ovaries to recover. For these non-negligible reasons, natural cycle IVF has regained popularity in recent years. Despite the ideal advantages it offers, natural cycle IVF is also associated with high risk of cancelation, which varies in the literature from 15 to 71 % [4]. As this type of IVF revolves around a single follicle, there are several reasons for which the cycle can be canceled: abnormal follicular maturation, premature ovulation of the single follicle, failed oocyte retrieval or empty follicle at retrieval, as well as failed fertilization. However, in contrast to conventional stimulated IVF, repeated cycles can be performed in consecutive months.

Capsule Modified natural IVF is a low-cost, patient-friendly treatment and is a reasonable option for infertile couples considering IVF, particularly for women ≤ 35 years old.

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Several variations have been put on the spectrum of natural IVF, as described in the literature. These range from a purely natural cycle with no additional medication involved, to a modified natural cycle with the addition of certain agents to prevent premature ovulation and to maintain follicular growth, to mild or minimal stimulation IVF where there is some form of ovarian stimulation with clomiphene citrate or letrozole.

Modified natural IVF (mnIVF), which is used in our center, follows the course of the natural female menstrual cycle. The addition of a GnRH antagonist will help in preventing premature ovulation, and the addition of a gonadotropin will aid in maintaining estradiol concentrations and avoid dominant follicle atresia induced by the GnRH antagonist [5]. Indomethacin has also proved to be beneficial in mnIVF by decreasing premature ovulation rates, and this is when it is initiated prior to the LH surge [6–8]. It does so probably by delaying or preventing spontaneous ovulations through cyclooxygenase blockade, which plays an important role in follicle rupture. Our fertility clinic is a leading center in North America performing modified natural IVF [9], and this technique represents more than 25 % of the IVF activity in this center [10].

It is still vague in the literature which patients should be selected for mnIVF. Evidently, only those with regular cycles should be considered since mnIVF depends on the natural dominant follicle. The indication for mnIVF does not seem to affect efficacy of the treatment [11]. Several studies show that natural IVF yields favorable results in poor responders [12–15]. A randomized controlled trial by Morgia et al. [16] comparing purely natural IVF with controlled ovarian stimulation in poor responders demonstrates that natural cycle IVF is a suitable option especially in the younger patients. In 2011, the Bologna criteria for poor ovarian response were established [17] to make it possible to compare different studies on this subject. Following this, a retrospective cohort trial [18] comparing poor responders, defined by the Bologna criteria, to normal responders in natural cycle IVF showed contradictory results to the studies previously stated. Also, a recent study looking at outcomes of mnIVF in poor responders, with a protocol very similar to the one used in our center, showed that this treatment yields poor outcomes in this patient population [19].

The objective of the present study is to describe the outcomes of a large number of cycles of mnIVF cycles performed in our center and then analyze them according to patients' age and ovarian response status as per Bologna criteria.

Materials and methods

Study design

A single-center retrospective cohort study was performed using all mnIVF cycles performed between July 2005 and

December 2011, according to the current mnIVF protocol used in our center. Cycles that diverged from this protocol were excluded.

The decision to undertake mnIVF is a shared decision between the healthcare professional and the patient. Some patients had undergone stimulated cycles beforehand, and some patients were undergoing mnIVF as their first IVF treatment. In our practice, mnIVF is strongly recommended as a first-line treatment for young patients with poor ovarian reserve testing and with an indication for IVF [9, 20].

The primary end points studied were clinical pregnancy rates per cycle started and per embryo transfer. A clinical pregnancy was defined as the visualization of a positive fetal heartbeat on ultrasound. Secondary endpoints were cancellation rates, successful oocyte retrieval rates, fertilization rates, and embryo transfer (ET) rates.

Outcomes were stratified by female patients' age (≤ 35 years and ≥ 36 years) and were further stratified in each age group by poor ovarian response according to the 2011 Bologna criteria (Ferraretti et al., 2011). Women are classified as poor responders when at least two of three criteria are met: (i) advanced maternal age (≥ 40 years) or any risk factor for poor ovarian response, (ii) a previous poor ovarian response (≤ 3 oocytes with a conventional stimulation protocol), (iii) an abnormal ovarian reserve test (i.e., antral follicle count < 5 – 7 follicles or AMH < 0.5 – 1.1 ng/ml). Patients who had undergone previous stimulated IVF cycles were evaluated based on all three criteria, and patients not having done so were evaluated based only on the first and third criteria.

Details of the cycle protocol

In our mnIVF protocol, an ultrasound is performed on day 9 of the cycle to detect the presence of a dominant follicle. Monitoring is then continued with ultrasound. Once the dominant follicle reaches 15 mm, a 0.25-mg subcutaneous injection of a GnRH antagonist (Orgalutran®—MSD Canada or Cetrotide®—EMD Serono Canada), a 150-IU subcutaneous injection of a gonadotrophin (Repronex® or Menopur®, Ferring Canada), as well as a 50-mg suppository of Indocid (Merck Canada) three times daily are given on a daily basis until ovulation induction day. Ovulation is induced by a 5000-IU hCG injection when the dominant follicle attains maturity (18–19 mm). Oocyte retrieval is then performed 34 h later under minimal or no sedation according to patient preference, and the embryo is transferred at cleavage stage on day 2. Patients were offered ICSI if male factor contributed to the infertility. Cycles were canceled when an ovarian cyst was detected during follicular surveillance, if the dominant follicle failed to progress normally, or if ovulation happened prior to oocyte retrieval. Luteal phase support was given in the form of intravaginal progesterone.

Statistical analysis

Proportion comparisons were performed by chi-squared test or Fisher's exact test when indicated. A p value <0.05 was considered to be statistically significant. Statistical analysis was performed using STATA version 10.0 (Stata Corporation, College Station, TX, USA).

This retrospective study was approved by the institutional Research Ethics Committee on 4 January 2012.

Results

Overall outcomes

A total of 1503 cycles of mnIVF were included in this analysis, which were performed in 782 patients. Baseline patient characteristics are shown in Table 1. Primary infertility was the case in 494 patients, and the most frequent cause of infertility was male factor. The mean number of days that the antagonist, gonadotrophin, and indocid were given was 2.61 days, with a range of 1 to 8 days. A maximum of 5 cycles was performed per patient; however, the number of cycles performed decreased from 782 to 21 from the first to the fifth rank.

Of the 1503 cycles, 279 were canceled (18.6 %). The two most common causes of cancellation were absent or abnormal follicular recruitment in 94 cycles and premature ovulation in 86 cycles. The rest were due to other causes (e.g., cyst formation) or not specified.

Table 1 Characteristics of patients undergoing up to five cycles of mnIVF

Number of patients (N)	782
Female patient age, mean (SD)	32.5 (3.2)
≤35 years old, n (%)	657 (84.0)
≥36 years old, n (%)	125 (16.0)
Male patient age, mean (SD)	36.7 (6.0)
Type of infertility, n (%)	494 (63.4)
• 1°	286 (36.6)
• 2°	
Ovarian reserve by Bologna criteria, n (%)	704 (90)
• Normal	70 (10)
• Poor	
FSH (IU/L), mean (SD)	8.5 (5.5)
• FSH<10 IU/L, n (%)	598 (76.5)
• FSH≥10 IU/L, n (%)	184 (23.5)
Cause of infertility, n (%)	71 (8.9)
• Tubal	36 (4.6)
• Endometriosis	272 (34.78)
• Male factor	85 (10.87)
• Low ovarian reserve	129 (16.5)
• Unexplained	189 (24.17)
• Other (implantation failure, pcos)+mixed	

Table 2 presents the overall cycle outcomes, as well as per patient cycle. Overall, oocyte retrieval was attempted in 1224 cycles (81.4 %) and was successful in retrieving an oocyte in 1090 cycles (89.1 %). Successful fertilization was achieved in 729 cycles (66.9 % per successful oocyte retrieval), and embryo transfer was performed in 628 cycles (41.8 %). Single-embryo transfer (SET) was performed in all cases. The clinical pregnancy rate per cycle started, per oocyte retrieval, and per embryo transfer was 13.7, 18.9, and 32.5 %, respectively.

Results by patients' age

There were 625 patients in the group 35 years or younger who completed 1238 cycles, and there were 125 patients in the group 36 years or older who completed 265 cycles. There was a higher cancellation rate in the group of patients over 35 years old (23.8 vs 17.4 %), but this difference did not reach statistical significance ($p=0.12$). The rate of successful oocyte retrieval per attempt was equivalent in both groups (89 vs 89.1 %). There was a slightly higher fertilization rate in the older group of patients (65.8 vs 72.2 %), which was not significant. There was an almost equivalent rate of ET per cycle in both groups (41.6 vs 43 %). In the younger group, the clinical pregnancy rates per cycle started, per oocyte retrieval, and per embryo transfer were 14.5, 19.7, and 34.5 %, respectively. These rates, which were all lower in the older group, were 10.2, 15, and 23.5 %, respectively. The differences that were significant between the two age categories were the clinical pregnancy rates per oocyte retrieval and per ET ($p=0.02$).

Results by Bologna criteria

There were a total of 704 normal responders and 78 poor responders. In each age category (≤35 years old, ≥36 years old), we stratified patients and their respective cycles by poor or normal ovarian response. In the group ≤35 years old (Table 3), 1119 cycles came from patients with normal ovarian response and 119 from patients with low ovarian response. The cancellation rates in normal responders were lower than in poor responders (16.7 vs 24.3 %); however, this difference was not significant ($p=0.152$). The remainder of patients went on to have oocyte retrieval, and the success rates in both categories were similar (89.4 vs 84.4 %), as were the rates of ETs per started cycle (41.2 vs 45.4 %). In regard to clinical pregnancies, there were 163 pregnancies among normal responders and 16 among poor responders, giving rates of 14.6 and 13.5 %, respectively, per started cycle, and 35 and 29.6 %, respectively, per ET. These differences were not significant.

In the group of patients aged ≥36 years (Table 3), there were 214 cycles from normal responders and 51 cycles from poor responders. The cancellation rate among normal

Table 2 Overall cycle outcomes according to cycle number of mnIVF

Cycle number	1	2	3	4	5	Total
Cycles started	782	436	189	75	21	1503
Cycles canceled, <i>n</i> (% per cycle)	141 (18.0)	85 (19.5)	36 (19.0)	11 (14.7)	6 (28.6)	279 (18.6)
• Premature ovulation	38 (4.8)	26 (6.0)	13 (6.9)	7 (9.4)	2 (9.5)	86 (5.7)
• No dominant follicle	52 (6.6)	31 (7.1)	8 (4.2)	3 (4.0)	–	94 (6.3)
• Cyst	20 (2.6)	10 (2.3)	6 (3.2)	–	1 (4.8)	37 (2.5)
• Other	31 (4.0)	18 (4.1)	9 (4.7)	1 (1.3)	3 (14.3)	62 (4.1)
ORs (oocyte retrieval) performed, <i>n</i> (%/cycle)	641 (90.6)	351 (80.5)	153 (81.0)	64 (85.3)	15 (71.4)	1224 (81.4)
Successful OR, <i>n</i> (% per attempt)	581 (74.3)	305 (86.9)	132 (86.3)	57 (89.1)	15 (100)	1090 (89.1)
Cycles with fertilization, <i>n</i> (% per successful OR)	390 (67.1)	200 (65.6)	87 (65.9)	41 (71.9)	11 (73.3)	729 (66.9)
Embryo transfers (ET), <i>n</i> (% per cycle)	334 (42.7)	170 (40)	80 (42.6)	37 (49.3)	7 (33.3)	628 (41.8)
Clinical pregnancies per cycle, %	15.0	13.5	10.1	10.7	14.3	13.7
Clinical pregnancies per OR, %	20.1	19.3	14.4	14.0	20.0	18.9
Clinical pregnancies per ET, %	34.5	34.7	23.5	21.6	42.9	32.5

responders was, once again, not significantly lower than among poor responders (22.9 vs 27.5 %). The two categories had similar successful oocyte retrieval rates (89.1 vs 86.8 %). There was a trend toward a higher ET rate in normal versus poor responders (46.3 vs 31.4 %), which was on the limit of statistical significance ($p=0.05$). There were 26 clinical pregnancies among normal responders, and only 1 pregnancy among poor responders, resulting in clinical pregnancy rates of 12.2 and 1.96 %, respectively, per started cycle ($p=0.04$) and 26.3 and 6.25 %, respectively, per ET ($p=0.06$).

Discussion

To our knowledge, this is the largest series of mnIVF cycles and the first from a North American center. This is a

representative sample, as consecutive patients were included. A total of 74 cycles were excluded for diversion from the current protocol. We provide the results for all patients combined and then distinguished by indication for IVF, by age, and by ovarian response. Overall, the clinical pregnancy rate per cycle was 13.7 and 32.5 % per ET.

The cancellation rate of 18.6 % in our cohort is comparable to the 19.3 % of another large study of 1048 cycles of mnIVF which had a similar cycle protocol [21] and lower than the 28.9 % cancellation rate described in purely natural IVF cycles [4]. This further highlights the value of the short course of GnRH antagonists, gonadotrophins, and Indocid, which have been proven beneficial in lowering premature ovulation rates [6, 7, 22]. We had a fairly high number of cycles canceled due to abnormal or absent follicular recruitment (6.3 %), and

Table 3 Outcomes stratified by Bologna criteria in patients ≤ 35 and ≥ 36 years old

Ovarian response	≤ 35 years old			≥ 36 years old		
	Normal	Low	<i>p</i> value	Normal	Low	<i>p</i> value
Cycles started, <i>n</i> (%)	1119 (90.4)	119 (9.61)		214 (80.8)	51 (19.25)	
Cycles canceled, <i>n</i> (%)	188 (16.8)	29 (24.3)	0.152	49 (22.9)	14 (27.5)	0.143
OR (oocyte retrieval) performed, <i>n</i> (% per cycle)	933 (83.34)	90 (75.63)		165 (77.1)	38 (72.55)	
Successful OR, <i>n</i> (% per attempt)	834 (89.39)	76 (84.44)	0.15	147 (89.09)	33 (86.84)	0.65
Cycles with fertilization, <i>n</i> (% per successful OR)	541 (64.87)	58 (76.32)	0.044	109 (74.15)	21 (63.64)	0.22
Embryo transfers (ET), <i>n</i> (% per cycle)	461 (41.20)	54 (45.38)	0.349	99 (46.26)	16 (31.37)	0.054
Clinical pregnancies, <i>n</i>	163	16	0.404	26	1	0.040
• % per cycle started	14.57	13.45	0.014	12.15	1.96	0.035
• % per successful OR	19.57	21.05	0.373	17.69	3.13	0.064
• % per ET	35.05	29.63		26.26	6.25	

this may be influenced by the inclusion of several patients with irregular periods (i.e., anovulatory cycles).

Our pregnancy rate per started cycle of 13.7 % is higher than that of 7.9 % described by Pelinck et al. [21] ($p < 0.001$). It is interesting to note that the cycles were performed only in patients aged 18–36 years. Differences in the indication of mnIVF or in the selection of patients for mnIVF in their centers may explain this disparity.

In our study, most patients were 35 years or younger and had a normal ovarian response, leaving few patients and evidently few cycles in the groups ≥ 36 years old and poor ovarian response. The clinical pregnancy rate in women aged ≤ 35 years was 14.5 % per cycle and 34.5 % per embryo transfer. In women aged ≥ 36 years, these rates were 10.2 % per cycle and 23.5 % per ET. This observation that outcomes are better in younger patients is not surprising as follicular quality decreases with increasing age, and it confirms those of several other studies [23–25, 15].

We then further stratified the two age groups by ovarian response status according to the 2011 Bologna criteria, as clinically, this population often poses a management quandary. The results of our current analysis cannot easily be compared to most other studies involving poor responders, as the definition of poor responders is inconsistent among these. However, there are two more recent studies which use these latest Bologna criteria to evaluate natural cycle IVF treatment in poor responders [18, 19]. The earlier one by Polyzos et al. [18] concludes that poor responders do not respond well to natural cycle IVF, with ongoing pregnancy rates per cycle under 3 % in all age groups in this category. On the contrary, patients classified as normal responders gave significantly better results with a live birth rate per cycle of 8.9 % (ongoing pregnancy rates not mentioned). The results of our study differ in that the poor responders ≤ 35 years old seem to respond equally as well as the normal responders, with respective clinical pregnancy rates of 13.45 and 14.57 % ($p = 0.373$). However, we concur that poor responders ≥ 36 years old do not benefit from this treatment. These latter results we present are also in line with those of Kedem et al. [19], who studied the outcomes of a similar mnIVF protocol in poor-responder women with an average age of 39 years old and show very poor outcomes in this group. Proposed theories to support the advantage of natural IVF over stimulated IVF are that the follicle naturally selected is of better quality and the endometrium is more receptive. In older patients, as follicular quality naturally declines so does the response to any kind of assisted reproductive technique [26], which explains the negligible chance of pregnancy when combined with poor ovarian response.

We note that the selection of patients for natural cycles in our center may create a bias in the results. In other words, given that the majority of patients did not undergo stimulated IVF prior to mnIVF, their eligibility for one of the three Bologna criteria is removed. It is possible that had they undergone a stimulated IVF cycle, a certain number may have responded poorly, increasing the number of poor responders in this study, and shifting the results either more or less favorably toward the poor responders.

A weakness of our study is that due to its retrospective design, patients who decided not to undergo further treatments despite unsuccessful attempts were lost to follow-up. These dropouts may have been due to patients changing fertility centers, reaching spontaneous pregnancy, or proceeding to stimulated IVF.

We consider that including male factor infertility had no impact on our results. A previous report evaluating results of mnIVF-ICSI cycles using ejaculate or surgically retrieved sperm for male factor infertility and performed in women under 37 years of age showed similar clinical pregnancy rates per ET to those reported in our study (31.0 and 35.1 % with ejaculated and surgically retrieved sperm, respectively) [27].

A strength of this large series is that all cycles were performed according to one protocol which allows conclusions to be drawn about modified natural IVF specifically—an aspect that is especially relevant when counseling patients before treatment. Studies which combine both natural and minimal stimulation IVF cannot be interpreted in the same way in this regard [23, 25].

The attractiveness of modified natural IVF evidently comes from its easy accessibility, minimal risk of ovarian hyperstimulation, low rate of multiple pregnancies, and low cost. Also, these cycles have the advantage of being able to perform the oocyte retrieval with minimal or no sedation as it is quite a short procedure requiring only one needle passage through the vagina. However, the challenge remains selecting the right patient population. Our study shows that mnIVF is a reasonable treatment option for patients considering IVF, specifically for those ≤ 35 years old with normal or poor ovarian response, possibly for those ≥ 36 years old with normal ovarian response, and may even be considered as a first approach in these patients. As single-embryo transfer gains popularity in IVF, mnIVF may be a less aggressive but effective approach to attain this embryo in these good prognosis patients. However, in poor responders ≥ 36 years old, mnIVF is not justified, and this confirms findings of recent studies. Randomized trials are necessary to determine the optimal conditions for mnIVF, such as the timing of ovulation induction or endometrial thickness at induction, in order to maximize chance of pregnancy and to minimize chance of cancelation. Also,

further analyses by indication are necessary as current as evidence on this matter is not uniform.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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Conflict of interest The authors declare that they have no conflict of interest.

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