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Live birth rates following natural cycle IVF in women with poor ovarian response according to the Bologna criteria

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STUDY QUESTION: What is the effect of natural cycle IVF in women with poor ovarian response according to the new ESHRE definition for poor ovarian responders: the Bologna criteria?

SUMMARY ANSWER: Although natural cycle IVF is a promising treatment option for normal responders, poor ovarian responders, as described by the Bologna criteria, have a very poor prognosis and do not appear to experience substantial benefits with natural cycle IVF.

WHAT IS KNOWN ALREADY: Previous trials have shown that natural cycle IVF is an effective treatment for the general infertile population and might be an option for poor ovarian responders. However, none of the trials have examined the effect of natural cycle IVF in poor responders according to the Bologna criteria, the newly introduced definition by the ESHRE Working Group on Poor Ovarian Response Definition. In this trial, we examined the effect of natural cycle IVF in poor ovarian responders fulfilling the Bologna criteria.

STUDY DESIGN, SIZE, DURATION: In this retrospective cohort trial, 164 consecutive patients, undergoing 469 natural cycle IVFs between 2008 and 2011 were included. Patients were stratified as poor and normal responders: 136 (390 cycles) were poor ovarian responders according to the Bologna criteria, whereas 28 women (79 treatment cycles) did not fulfil the criteria and were considered as normal responders.

PARTICIPANTS/MATERIALS, SETTING, METHODS: All patients were monitored with hormonal analysis and ultrasound scan every second day, from Day 7 or 8 of the cycle onwards. When a follicle of >16 mm was observed, ovulation was triggered with 5000 IU of i.m. hCG and oocyte retrieval was performed 32 h later.

MAIN RESULTS AND THE ROLE OF CHANCE: Live birth rates in poor responders according to the Bologna criteria were significantly lower compared with the control group of women; the live birth rate per cycle was 2.6 versus 8.9%, $P = 0.006$ and the live birth rate per treated patient was 7.4 versus 25%, $P = 0.005$. In poor responders according to the Bologna criteria, live birth rates were consistently low and did not differ among different age groups ($\leq$35 years, 36–39 years and $\geq$40 years), with a range from 6.8 to 7.9%.

LIMITATIONS, REASONS FOR CAUTION: A limitation of our analysis is its retrospective design; however, taking into account that we included only consecutive patients treated with exactly the same protocol, the likelihood of selection bias might be considerably limited. In addition, the control group in our study refers to women of younger age and therefore the promising results among patients who did not fulfil the Bologna criteria apply only to women of younger age.

WIDER IMPLICATIONS OF THE FINDINGS: Our trial suggests that although natural cycle IVF is a promising treatment option for younger normal responders, its potential is very limited to poor ovarian responders as described by the Bologna criteria, irrespective of patient's age. This highlights the very poor prognosis of these women and therefore the urgent need for future trials to examine the effect of ovarian stimulation protocols in women with poor ovarian response as described by the Bologna criteria.

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Key words: natural cycle IVF / Bologna criteria poor responders / live birth rates

Introduction

Poor ovarian responders constitute ∼9–24% of all women undergoing ovarian stimulation for assisted reproduction technique (Ubaldi et al., 2005). Despite the wide diversity in the definitions used to specify women with impaired response to ovarian stimulation (Polyzos and Devroey, 2011), recently a definition has been proposed by the ESHRE Working Group on Poor Ovarian Response Definition in order to homogenize this patient population, so that it is amenable for use in future clinical trials (Ferraretti et al., 2011). However, regardless of this promising initiative, it remains unclear whether poor ovarian responders experience any substantial benefit from ovarian stimulation agents.

Several randomized trials have been conducted to date, examining different down-regulation protocols (Schmidt et al., 2005; Kim et al., 2009; DiLuigi et al., 2011), different gonadotrophin doses or schedules (Raga et al., 1999; Garcia-Velasco et al., 2000), growth hormone administration (Dor et al., 1995) or even androgen pretreatment (Massin et al., 2006; Fabregues et al., 2009); yet, in spite of the available data, no clear conclusion has been drawn on which regimen may constitute the ideal therapeutic approach. Furthermore, the only randomized trial that has tested natural cycle IVF versus ovarian stimulation in poor ovarian responders suggested that natural cycles result in significantly higher implantation rates compared with a short GnRH-agonist protocol (Morgia et al., 2004).

Based on the latter trial, one could speculate that natural cycle IVF could be considered as the optimal treatment modality for these women, not only because it is not inferior in terms of pregnancy or implantation rates compared with ovarian stimulation, but also because it may constitute a more cost-effective and patient-friendly therapeutic option. Taking into account the above evidence, we set to review, within our centre, all the natural cycle IVF treatments performed between 2008 and 2011 and analyse the results according to the fulfilment of the Bologna criteria for poor ovarian response developed by the ESHRE Working Group on Poor Ovarian Response Definition.

Materials and Methods

Patients' selection and eligibility criteria

All consecutive patients who were treated with natural cycle IVF, between 2008 and 2011, were analysed. Patients were eligible if they had normal menstrual cycles between 25 and 35 days. The women included had undergone natural cycle IVF without any ovarian stimulation or use of GnRH antagonist and received only 5000 IU of i.m. hCG for ovulation triggering whenever a follicle of >16 mm was observed on transvaginal ultrasound scan.

Patients were stratified according to the fulfilment of the Bologna criteria for poor ovarian response. Poor responders were classified as women with at least two of the three following criteria: (i) advanced maternal age (≥40 years) or any other risk factor for poor ovarian response; (ii) a poor ovarian response (≤3 oocytes with a conventional stimulation protocol) and (iii) an abnormal ovarian reserve test result (i.e. AFC <7 follicles or AMH <1.1 ng/ml), as described by the Bologna criteria for poor ovarian response (Ferraretti et al., 2011). Patients who did not fulfil the Bologna criteria were women who underwent natural cycle IVF either due to their own choice to undergo IVF without any stimulation

or due to the failure to achieve a pregnancy after consecutive stimulated IVF/ICSI cycles.

Two independent investigators (N.P.P. and C.B.) manually scrutinized the files in order to select patients who fulfilled the Bologna criteria for poor ovarian response. Among 164 consecutive patients, undergoing 469 natural cycle between 2008 and 2011, 28 women (79 treatment cycles) did not fulfil the Bologna criteria for poor ovarian response, whereas 136 women (390 cycles) were poor ovarian responders according to the Bologna criteria.

This study was approved by our institutional review board.

Treatment schedule

Patients who underwent baseline hormonal measurement on Day 2 of the menstrual cycle and afterwards were monitored with hormonal examination [estradiol (E_2), progesterone (P), FSH and LH levels] and ultrasound scans for the assessment of follicular growth every second day, from Day 7 or 8 of the cycle onwards. When a follicle of >16 mm was observed, ovulation triggering was performed with 5000 IU of i.m. hCG. Oocyte retrieval was performed 32 h after hCG administration. Follicular flushing was performed systematically, since only one follicle was present in most of the cases.

Oocyte fertilization was performed by ICSI. In case of successful fertilization, embryo transfer was performed on Day 3 for the majority of the cycles, with only nine cycles having a Day 5 transfer due to the physician's choice. All patients received luteal phase support with 600 mg of vaginal micronized P with or without E_2.

Analysis

The oocyte retrieval rate, number of metaphase II oocytes (MIIs), embryo transfer rate, positive hCG, ongoing pregnancy and live birth rates were calculated. Results for the poor responders according to the Bologna criteria were separately reported according to patients' age and rank of treatment cycle. The age thresholds utilized were ≤35, 36–39 and ≥40 years, and separate analyses were performed for treatment cycles 1, 2, 3, 4 and ≥5. These thresholds were selected in analogy with a previous trial examining the effect of natural cycle IVF among poor responders (defined as women with at least one previous cancelled cycle due to no follicle activation or only one follicle recruited) (Schimberni et al., 2009).

Percentages were analysed by using Fisher's exact or the χ^2 test, as appropriate, with a level of significance at 0.05.

All analyses were performed in SPSS 20.0.

Results

Patients' characteristics

Patients' characteristics are presented in Table I. As shown, women fulfilling the Bologna criteria for poor responders had a significantly higher age and a longer duration of infertility, whereas the number of previous stimulated treatment cycles was comparable to that of women who did not fulfil the criteria.

Comparison of poor responders according to the Bologna criteria and normal responders

Patients who fulfilled the Bologna criteria had 291 treatment cycles (74.6%) with an oocyte retrieval, with 247 cycles (63.3%) resulting in at least one MII oocyte. However, only 42% of the cycles resulted in an embryo transfer. Pregnancy outcomes per treatment cycle were substantially low, with a positive hCG rate of 4.6% and a live birth rate per cycle of 2.6%. Pregnancy rates per patient, irrespective of the

number of treatment cycles, were also low, with a positive hCG rate of 12.5% and a live birth rate of 7.4% (Table II). Finally, the live birth rates did not substantially change when analysing the results per oocyte retrieval (3.4%) and per embryo transfer (6.1%).

On the contrary, results in the control group of women who did not fulfil the Bologna criteria were substantially better. Although the percentage of cycles with an oocyte retrieval did not significantly differ from that of the poor responders (78 versus 75%), the percentage of cycles with an embryo transfer was significantly higher in the control group (59 versus 42%, $P = 0.011$). In addition, the pregnancy rates per treatment cycle were significantly higher compared with the poor responders according to the Bologna criteria, with a positive hCG rate of 15.2 versus 4.6% ($P = 0.0005$)] and a live birth rate of 8.9 versus 2.6% ($P = 0.006$). Pregnancy outcomes per treated patient were also significantly higher compared with the poor responders according to the Bologna criteria, with a positive hCG rate of 35.7 versus 12.5% ($P = 0.003$) and live birth rate of 25 versus 7.4% ($P = 0.005$).

Outcomes among poor responders according to the Bologna criteria

Outcomes according to patients' age

The analysis according to patients' age showed no significant difference regarding the number of cycles with oocytes and the number of cycles with MII oocytes among the three different age categories, $P = 0.516$ and $P = 0.284$, respectively (Table II). The overall transfer rate per cycle decreased with advancing patient age, although no significant differences existed between women aged ≤ 35 years and women $36-39$ years old (47.5 versus 43.5% $P = 0.490$), embryo transfer rates were significantly higher among women ≤ 35 years than those ≥ 40 years old, 47.5 versus 33% $P = 0.028$. (Table II). This difference in the overall transfer rate per cycle did not result in significant differences in terms of pregnancy rates per treatment cycle among the different age groups. Positive hCG rates were comparable $P = 0.661$ and hardly exceeded 5% per treatment cycle, while ongoing and live birth rates were also comparable $P = 0.949$ and ranged between 2.5 and 3% (Table II).

Pregnancy rates per patient also did not differ between the three age categories. Although positive hCG rates were higher in women aged ≤ 35 years and women $36-39$ years, 13.1 and 16.7%, respectively, compared with patients ≥ 40 years old, 8.8%, there was no significant difference between the groups, $P = 0.353$. Ongoing and live birth

Table I Baseline characteristics according to the fulfilment of the Bologna criteria for poor responders.

	Poor responders	Control group
Number of patients	136	28
Number of cycles	390	79
Age[a]	37.3 (3.9)[b]	30.7 (2.9)[b]
BMI[a]	23.7 (0.4)	23.7 (6.0)
Duration of infertility (years)[a]	4.7 (0.39)[b]	3.5 (1.2)[b]
Number of previous treatment cycles[a]	3.8 (2.7)	4.0 (2.0)
Type of infertility (%)		
Primary	107 (79)	25 (89)
Secondary	29 (21)	3 (11)
Cause of infertility, n (%)		
Male factor	39 (28)	11 (39)
Endometriosis	9 (7)	2 (7)
Unexplained	84 (62)	15 (54)
Tubal	3 (2)	—
Genetic	1 (1)	—

[a]Values are expressed as means and standard deviations (SD).
[b]$P < 0.05$.

Table II Outcomes according to patients' age in poor responders according to the Bologna criteria.

Parameters	All cases	≤ 35 years	$36-39$ years	≥ 40 years
No. of patients	136	38	54	44
No. of cycles	390	122	168	100
Oocytes retrieved[a]	291 (74.6)	95 (77.9)	123 (73.2)	73 (73)
MII oocytes[a]	247 (63.3)	83 (68)	105 (62.5)	59 (59)
Embryo transfer[a]	164 (42.1)	58 (47.5)	73 (43.5)	33 (33)
Pregnancy outcomes per treatment cycle[a]				
Positive hCG	18 (4.6)	6 (4.9)	9 (5.3)	3 (3)
Ongoing pregnancy	10 (2.6)	3 (2.5)	4 (2.4)	3 (3)
Live birth rate	10 (2.6)	3 (2.5)	4 (2.4)	3 (3)
Pregnancy outcomes per patient				
Positive hCG	17 (12.5)	5 (13.1)	9 (16.7)	3 (8.8)
Ongoing pregnancy	10 (7.4)	3 (7.9)	4 (7.4)	3 (6.8)
Live birth rate	10 (7.4)	3 (7.9)	4 (7.4)	3 (6.8)

[a]Results are expressed as the number of cycles (and percentage).

Table III Outcomes according to cycle rank in poor responders according to the Bologna criteria.

Parameters	Number of consecutive cycles				
	1	2	3	4	≥5
No. of cycles	136	97	62	29	66
Oocytes retrieved	101 (74.3)	73 (75.3)	46 (74.2)	22 (75.9)	49 (74.2)
MII oocytes	86 (63.2)	57 (58.8)	40 (64.5)	21 (72.4)	43 (65.2)
Embryo transfer	52 (38.2)	38 (39.2)	30 (48.4)	16 (55.2)	28 (42.4)
Positive hCG	4 (2.9)	4 (4.1)	5 (8.1)	3 (10.3)	2 (3)
Ongoing pregnancy	0%	2 (2)	3 (4.8)	3 (10.3)	2 (3)
Live birth rate	0%	2 (2)	3 (4.8)	3 (10.3)	2 (3)

Results are expressed as the number of cycles (and percentage).

rates were low and comparable among the three groups ($P = 0.975$), ranging from 6.8 to 7.9%.

Outcomes according to the rank of treatment cycle

The proportion of cycles with oocyte retrieval remained stable across cycles 1, 2, 3, 4 or >5 and ranged from 74 to 76%. Although no difference existed between consecutive cycles regarding the number of MII oocytes and the number of cycles with an embryo transfer, cycles 3 and 4 showed better results compared with cycles 1, 2 and ≥5 (Table III). This difference was also prominent with regard to pregnancy rates. Live birth rates per treatment cycle increased with cycle rank from the first till the fourth cycle, exceeding 10% on the fourth treatment (Table III). However, the most interesting observation is that none of the 136 patients managed to achieve a live birth during their first treatment cycle.

Discussion

The current study provides evidence that poor ovarian responders, as described by the Bologna criteria, have a very poor prognosis and do not appear to experience substantial benefits with natural cycle IVF, regardless of patients' age. On the contrary, younger women who do not fulfil these criteria have a high likelihood of a live birth.

Previous reports have shown very promising pregnancy rates in infertile women undergoing natural cycle IVF, with a cumulative probability of pregnancy up to 46% (Nargund et al., 2001); nonetheless these results refer to the general population and not only to poor ovarian responders. Results from our control group, confirm the promising results of natural cycle IVF in younger women with normal ovarian response; however, when pertaining only to poor responders according to the Bologna criteria, our analysis shows that the cumulative live birth per patient does not exceed 8%.

The results of our trial contrast with a previous study examining natural cycle IVF among women with poor ovarian response (Schimberni et al., 2009). This discrepancy does not necessarily imply that our trial and the trial by Schimberni et al. are contradictory, but may reflect the diversity of the patient populations enrolled, since in that paper poor ovarian responders were defined as women who

had at least one previous cancelled cycle due to no follicle activation or only one follicle recruited (Schimberni et al., 2009). We used a more stringent criteria as developed by ESHRE Working Group on Poor Ovarian Response Definition which considered previous response to stimulation, age and ovarian reserve tests and not only previous cycle cancellations (Ferraretti et al., 2011). In this regard, it is possible that the definition used may reflect a more homogeneous group of patients, who may undeniably have a poorer prognosis without any substantial benefits from natural cycle IVF. This is further justified by the fact that the live birth rates per cycle were consistently lower than 3% in all age subgroups. In contrast, the pregnancy and live birth rates per cycle were 9.8 and 8.2%, respectively, in the Schimberni trial, with younger women (>35 years old) experiencing an even more impressive pregnancy rate of 18.1% per treatment cycle (Schimberni et al., 2009).

The concerns raised regarding the reproductive potential of Bologna poor ovarian responders appear to be valid if we also consider the very good outcome in our reference group treated with a natural cycle IVF. The latter observation further highlights the very poor prognosis of the poor responders according to the Bologna criteria and therefore the urgent need for trials including these women.

In spite of the results derived from the current study, we should acknowledge that our trial focused only on the effect of natural cycle IVF. Modified natural cycle IVF (MNC), using a GnRH antagonist in combination with gonadotrophins in the late follicular phase only, has been proved to result in very high pregnancy rates among the general infertile population (Pelinck et al., 2006; Pelinck et al., 2007). Thus, it is likely that such an approach may also improve the outcome in poor ovarian responders, through a reduction in cancellation rates due to no ovulation (Rongieres-Bertrand et al., 1999). Considering that in almost 25% of the cycles among poor ovarian responders in our trial no oocyte was retrieved, it is possible that administration of an antagonist might have increased the oocyte retrieval rate and cumulative pregnancy rates. This approach needs further scrutiny in clinical trials including poor ovarian responders according to the Bologna criteria, in order to further justify whether MNC should be offered as a first approach in young poor responders. In addition, further research is needed to examine whether ovarian stimulation protocols may show a substantial benefit in poor ovarian responders according to the Bologna criteria.

An interesting finding of the current study is the increasing live birth rate per cycle with cycle rank, up to the fourth treatment cycle, among Bologna criteria poor ovarian responders. However, this should be interpreted with caution given that the analysis per cycle in our study was applied only to poor responders according to the Bologna criteria, contrary to previous trials (Pelinck et al., 2007), which included a general infertile population and reported a stable pregnancy rate per cycle. Thus, it is highly likely that in our study only women with the best prognosis have continued for further cycles and this resulted in an increasing live birth rate per cycle.

A limitation of our analysis is its retrospective design. However, based on our patients' selection process, only consecutive patients fulfilling the inclusion criteria were enrolled, which considerably decreases the likelihood of selection bias. In addition, ovulation triggering in our study was accomplished by using hCG at a dosage of 5000 IU compared with the dose of 10 000 IU used in the largest previous trial examining natural cycle IVF in poor responders (Schimberni

et al., 2009). Nevertheless, taking into account the comparable oocyte retrieval rate in our trial compared with the Schimberni trial (74.1 versus 78.1%), it is unlikely that the hCG dosage might have affected our results.

Another limitation of the current study is that our control group included patients of younger age (only 3 patients exceeded 35 years old) and this prevented us from stratifying our analysis in the control group according to age. Hence, we are unable to provide guidance for natural cycle IVF among women of advanced age who do not fulfil the Bologna criteria for poor ovarian response. However, taking into account that previous reports have shown a low pregnancy rate in women of advanced age treated with natural cycle IVF (Schimberni et al., 2009), it may be likely that, women of advanced age who do not fulfil the Bologna criteria may perform as poorly as the poor responders according to the Bologna criteria.

The clinical implication of our findings is that although natural cycle IVF is a promising treatment option for the general young infertile population, its potential is very limited for poor ovarian responders as described by the Bologna criteria. However, we should clarify that our results only represent the results obtained for poor ovarian responders according to the Bologna criteria. Other patient categories that may be considered as low ovarian responders, without incorporating the definition proposed by the working group on Poor Ovarian Response Definition (e.g. patients with abnormal ovarian reserve tests or few oocytes retrieved in a previous cycle but with threshold values higher than those proposed by the Bologna criteria), may experience benefits from natural cycle IVF, especially if they are of younger age as previously suggested. Nonetheless, it is unclear whether this benefit should be considered as an important step in the management of poor ovarian responders, since it may simply reflect the benefit among young patients who do not experience poor ovarian response to stimulation. In the meantime, future studies should test the effect of ovarian stimulation protocols in this group of patients to clarify whether they may experience any substantial benefit or whether the Bologna criteria refer to patients who are unlikely to respond to any treatment modality and may therefore be candidates for oocyte donation programmes.

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Authors' roles

N.P.P. conceived the study design and performed the analysis. All the authors participated in the manuscript drafting and the interpretation of the results.

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Conflict of interest

None declared.

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