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ORIGINAL ARTICLE

Conversion of ICSI cycles to IUI in poor responders to controlled ovarian hyperstimulation

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Controlled ovarian hyperstimulation;
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Oocyte retrieval;
Poor response

Abstract *Aim:* Comparison between the results of the oocyte retrieval technique and the conversion to the intra-uterine insemination (IUI) technique in cases with poor ovarian response to the controlled ovarian hyperstimulation (COH) procedure.
Patients and methods: It is a retrospective observational study in women with poor ovarian response to COH which is defined as estradiol (E2) peak level < 1000 pg/mL or with $\leqslant 4$ follicles which are $\geqslant 14$ mm in diameter. Four hundred and sixteen cases were reported as poor responders in 2 IVF centers since December 2007 to July 2010. One hundred and fifty two cases of them proceeded to the oocyte retrieval procedure. These cases were assigned as group (A). Sixty eight cases converted to IUI and were assigned as group (B). One hundred and ninety six cases canceled their cycles. These cases were not included in the current study. Our data were collected from the databases of two In Vitro Fertilization (IVF) centers and analyzed retrospectively to compare the results of the different applied techniques in the studied groups. The main measured outcome parameters were the clinical pregnancy rate and the live birth rate.
Results: The group of cases proceeded to the oocyte retrieval procedure had a higher basal Follicle Stimulating Hormone (FSH) level, needed a longer duration of stimulation with higher Human Menopausal Gonadotropin (HMG) doses and had higher E2 peak levels. The clinical pregnancy

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rates and the live birth rates were higher in the group proceeded to the oocyte retrieval than the group converted to IUI but the difference was not statistically significant.

Conclusion: As the pregnancy rates difference between both groups was not statistically significant the conversion to IUI could be considered a useful substitute to the oocyte retrieval procedure in the poor responder cases. However, to adopt this conclusion, further confirmation in other prospective studies with larger sample size is a must.

1. Introduction

Nowadays, with the delayed age of conception among females, there is consequently a reduction of the so called ovarian reserve (1). The ovarian reserve can be predicted by the size of the ovaries, the number of antral follicles, the level of the basal F.S.H. and the length of the follicular phase. The Ovarian response to the controlled ovarian hyperstimualtion (COH) depends mainly on the ovarian reserve (2–4).

The poor ovarian response was first described by Garcia et al. in 1983 (5). The incidence of poor response is estimated by 5–24% of all In Vitro Fertilization (IVF) cycles (6). In another study, it was estimated by about 10% of the patients resorting to the assisted reproductive technique (7). There is not a universal definition for the poor responders (8). Most researchers agree that poor responders are those who produce less than three to four oocytes or have a low estradiol (E2) peak level [the average upper limit equals 500 pg/ml or even 1000 pg/ml on the day of administration of the Human Chorionic Gonadotropin (HCG) hormone] in a previous stimulation cycle (9). In another study, it was defined by the presence of $\leqslant$4 follicles measuring $\geqslant$ 14 mm in diameter with an E2 level < 1000 pg/mL at the time of the HCG trigger (10). The available logical solution for the poor ovarian response in the IVF/ICSI (Intra Cytoplasmic Sperm Injection) cycles is the cycle cancellation with the subsequent failure of the IVF trial. However, this solution represents a major disappointment and harbors a negative psychological impact on the patients (11).

In the current study, we conducted a comparison between the results of two different techniques, with each one having its own pros and cons, applied on a group of poor responder cases to the COH in ICSI cycles. The first technique is the ovum pick up. Despite the fact that this is the standard applied technique following the COH step in ICSI (Intra Cytoplasmic Sperm Injection) cycles, it comprises a number of disadvantages in such cases with poor ovarian response, including; high cost, the risk of anesthesia, the procedure become more difficult and risky with a small number of growing follicles and the need for a highly experienced gynecologist. The other technique is the intra-uterine insemination (IUI) technique. Although this technique is relatively simple and less expensive, there must be certain crucial inclusion criteria in the poor responder cases that choose to shift to this procedure. These inclusion criteria are; the presence of at least one patent tube by histosalpingeogram (HSG) in the female partner and the total motile sperm count must be $\geqslant$5 millions in the male partner.

2. Materials and methods

The data were collected from the databases of two IVF centers (IVF center, Faculty of medicine, Cairo University, Cairo, Egypt and Samir Abbas IVF Center, Jeddah, Saudi Arabia). The cycles included in this retrospective observational study were initiated during the duration from December 2007 to July 2010. During this duration, 2041 IVF cycles were initiated, four hundred and sixteen of them were reported as poor responders ($\leqslant$4 mature follicles on ultrasound examination, measuring $\geqslant$14 mm in average diameter, with an E2 level < 1000 pg/ml at the time of HCG trigger).

The recorded poor response cycles either proceeded to the oocyte retrieval and embryo transfer, or shifted to the intra-uterine insemination, or canceled the cycle. The decision was made by the patient and her partner after proper counseling with the treating physician.

Our aim was to define the best strategy suiting such poor responders, depending on the resulting outcomes of each technique. The included cases were divided into two groups; Group (A) which included 152 cases proceeded to the oocytes retrieval technique and group (B) which included 68 cases (with specific inclusion criteria) decided to convert to the IUI technique. The inclusion criteria for Group (B) cases were; the presence of at least one patent tube by HSG and the total mobile sperm count must be $\geqslant$5 millions. One hundred and nightly six cases of the poor responders canceled their cycles and so were not included in this study.

The applied standard long or short protocols used either a combination of purified or recombinant follicle stimulating hormone (FSH) and Human Menopausal Gonadotropin (HMG) with Triptorelin (Decapeptyl 0.1 mg, Ferring) or a GnRH antagonist orgalutrane 0.25 mg (Ganirelix Acetate; Scherring-Plough), as described elsewhere (12).

For the patients proceeded to the oocyte retrieval for ICSI; the oocytes were retrieved 36 h after HCG administration when at least one follicle measured a mean diameter of 18 mm using a standard transvaginal ultrasound. Embryos were cultured using a commercially available sequential culture media system. Fertilization assessment was performed 16–18 h after insemination or injection. Cleavage-stage embryos were assessed and selected based on the morphologic criteria. Embryo transfer, at the cleavage stage, was performed using Either the Labotect Embryo Catheter (Labor-Technik GŐttingen Germany) or the Wallace Embryo Replacement Catheter (Irvine Scientific, Santa Ana, CA) under direct ultrasound guidance. Vaginal progesterone suppositories (cyclogest 400 mg, Actavis UK Ltd) were used for the luteal support.

For the patients converted to IUI, the insemination occurred 36 hours after HCG administration. Sperm preparations were performed using a 90% gradient with a single wash. Inseminations were accomplished using a standard soft-tipped insemination catheter. Vaginal progesterone suppositories were used for the luteal support, provided at the same dose as for ICSI cycle.

Data were statistically described in terms of mean ± standard deviation (±SD), frequencies (number of cases) and per-

centages when appropriate. Comparison of quantitative variables between the study groups was done using Student *t*-test for independent samples. For comparing categorical data, Chi square (χ^2) test was performed. A probability value (*P*-value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 17 for Microsoft Windows.

3. Results

This retrospective observational study included 220 poor responder cases divided into two groups. Group (A) included 152 cases proceeded to the oocyte retrieval technique and group (B) included 68 cases (with specific inclusion criteria) shifted to the IUI technique.

The mean age and duration of infertility were similar in both groups (Table 1). Day 3 estradiol level and the Antral Follicle Count (AFC) were similar in both groups but the basal FSH level was higher in group A than in group B ($P = 0.033$). The demographic, clinical and the hormonal status of the cases are recorded in Table 1.

The main protocol of treatment was the antagonist protocol in both groups. The mean daily dose of HMG was higher in group A than in group B ($P = 0.01$). The number of days for the induction of ovulation was longer for group A than group B ($P = 0.018$) and the peak E2 level at the day of HCG injection was higher in group A than in group B ($P = 0.08$). The ovarian stimulation parameters are recorded in Table 2.

Regarding the chemical pregnancy rate there was no significant difference between both groups (9.2% vs 10.3%) for groups A and B, respectively. The same goes for the clinical pregnancy rate, the abortion rate and the live birth rate (17.3% vs 5.9%, 11.2% vs 10.3% and 2.9% vs 7.4%) for groups A and B, respectively (Table 3). In group A the mean number of the retrieved oocytes was 3.4 ± 1.6, the mean of the number of the oocytes at metaphase II stage (MII) was 2.4 ± 1.4 and the number of embryos/ET (embryo transfer) was 1.9 ± 1.2.

In a multiple logistic regression model predicting the clinical pregnancy rate (model $R^2 = 0.19$; $P < 0.000$), the patient age and the peak E2 level at the day of HCG injection contributed significantly (P values = 0.002 and 0.001), respectively. The basal FSH ($P = 0.715$), the HMG dose ($P = 0.939$), the number of days of stimulation ($P = 0.196$), the number of growing follicles >14 mm ($P = 0.174$) and the AFC ($P = 0.094$) did not significantly predict the clinical pregnancy rates.

4. Discussion

As far as we know, this retrospective study is the first study conducted among the Middle East population with the aim of comparison between the conventional ICSI technique, which is the standard technique applied in most IVF centers in the Arabian countries, and the conversion to IUI in cases with poor ovarian response.

In the current study, we used mainly the antagonist protocol (61.8% and 58.8%) in group A and B, respectively. In our study we did not use a single protocol of induction, however, the main protocol of induction in both groups is the antagonist protocol. In a recent Cochrane database article by Al-Inany et al. it was concluded that the use of antagonist compared with long GnRH agonist protocols was associated with a large reduction in OHSS and there was no evidence of a difference in live-birth rates (13). In another Cochrane database by Pandian et al. (14) on the intervention on poor responders to COH it was found that the number of oocytes retrieved were significantly less in the conventional GnRHa long protocol compared to stop protocol and GnRH antagonist protocol. Total dose of gonadotrophins used was significantly higher in the GnRHa long protocol group compared to the Stop protocol and GnRH antagonist groups. Cancellation rates were significantly higher in the GnRHa flare up group compared to the GnRHa long protocol group (4). Our data showed that the Basal FSH was higher in group A than in group B ($P = 0.033$). The mean daily dose of HMG was higher in group A than in group B ($P = 0.01$), as well as the number

Table 1 Comparison of demographic data and patient characteristics between both groups.

	Group A ICSI (no = 152)	Group B IUI (no = 68)	*P*-value
Age (y)	36.3 ± 3.2	36.4 ± 2.7	0.896
Duration of infertility (y)	5.7 ± 1.9	5.9 ± 1.7	0.594
Basal FSH (IU/L)	8.2 ± 2.0	7.7 ± 1.6	0.03*
Basal LH (IU/L)	6.0 ± 1.7	5.62 ± 1.6	0.123
Basal E2 (pg/mL)	51.3 ± 16.5	53 ± 13.1	0.464
AFC (n)	8.6 ± 2.4	8.9 ± 2.4	0.402
Semen count (million/mL)	9.7 ± 3.9	9.5 ± 3.2	0.814
Ovarian factor (%)	41 (27%)	19 (27.9%)	1
Male factor (%)	37 (24.3%)	20 (29.4%)	0.531
Endometriosis (%)	18 (11.8%)	10 (14.7%)	0.711
Unexplained (%)	34 (22.4%)	12 (17.6%)	0.538
Uterine (%)	7 (4.6%)	3 (4.4%)	1
Combined (%)	15 (9.9%)	4 (5.9%)	0.476
1ry infertility (%)	100 (65.8%)	43 (63.2%)	0.83
2ry infertility (%)	52 (34.2%)	25 (36.8%)	0.83

AFC: antral follicle count.
* *P*-value < 0.05 means statistical significance.

Table 2 Ovulation stimulation characteristics in both groups.

	Group A ICSI (no = 152)	Group B IUI (no = 68)	*P*-value
HMG dose (IU)	333.9 ± 76.0	305.9 ± 69.4	0.01*
Days of induction (d)	12.8 ± 0.95	12.5 ± 0.72	0.01*
Follicles ⩾ 14 mm (n)	3.2 ± 0.82	3.0 ± 0.84	0.116
E2 at day of HCG (pg/mL)	635.5 ± 207.8	559.9 ± 162.84	0.008*
Long protocol (%)	8 (5.3%)	4 (5.9%)	1
Short protocol (%)	50 (32.9%)	24 (35.3%)	0.846
Antagonist protocol (%)	94 (61.8%)	40 (58.8%)	0.784

* *P*-value < 0.05 means statistical significance.

Table 3 Treatment outcomes in both groups.

	Group A ICSI (no = 152)	Group B IUI (no = 68)	*P*-value
Chemical pregnancy (%)	14 (9.2%)	7 (10.3%)	0.996
Clinical pregnancy (%)	26 (17.1%)	7 (10.3%)	0.27
Abortion (%)	9 (5.9%)	2 (2.9%)	0.547
Live birth rate (%)	17 (11.2%)	5 (7.4%)	0.527

of days needed for the induction of ovulation ($P = 0.018$). The peak E2 at the day of HCG injection was also higher in group A than in group B ($P = 0.08$). However, there was no significant difference between both groups regarding the chemical pregnancy rate, clinical pregnancy rate or live birth rate.

These findings are in accordance with the study done by Wood et al. who found that the clinical pregnancy rate was higher in the IUI conversion group (12.5%) than in the ICSI group (7.7%), but the difference was not statistically significant ($P = 0.64$) (15). A similar result was reported by Shahine et al. (16) who also found that the Live birth rate was similar for the IUI conversion (6%) compared with the oocytes retrieval (7%).

Other studies supported the conversion to IUI in poor responders. Freour et al. concluded that IUI conversion is a favorable alternative to ICSI in poor responder patients (15). He studied the difference between both strategies in 44 women converted to IUI vs 41 women proceeded to ICSI (17). Also, Matorras et al. suggested that IUI conversion is an efficient alternative in poor responders, especially those who were not stimulated by doses higher than 225 IU per day of HMG, the pregnancy rate was 14% (18).

On the other hand, two recently published studies demonstrated different conclusions. Norian et al. (10) found that proceeding to oocyte retrieval carries a higher success pregnancy rate in comparison to the conversion to IUI. In addition, Nicopoullos and Abdalla conducted a retrospective analysis to determine the optimal management with one or two mature follicles after stimulation. The biochemical pregnancy rates of 13.1%, 4.9% and 9.7%, clinical pregnancy rates of 8.1%, 3.6% and 7.2%, and ongoing pregnancy rates of 6.8%, 2.0% and 5.5% were achieved in the Vaginal Egg Collection (VEC) group (1), the IUI converted group (2) and those who abandoned the cycle (3), respectively. All pregnancy outcomes were significantly higher after VEC (group 1) than for those converted to IUI (group 2), and all pregnancy outcomes were higher with borderline significance in group (3) compared to group (2). There was no significant difference in outcome between group (1) and group (3) (19). Nicopoullos and Abdalla suggested that for such poor responders, proceeding to VEC may represent their best chance of successful outcome. Conversion to IUI offers the poorest outcome and despite the potential for improvements in the cycle protocol, abandonment with a further attempt also does not improve the outcome (19).

We recommend repeated IUI cycles in such poor responders. As Farhi and Orvieto (20) found that the cumulative clinical pregnancy rates were 39% and 58% after three and six IUI cycles, respectively, and the cumulative pregnancy rate continued to increase with an increase in IUI cycle number up to the third, or fourth cycle, in patients with mechanical and combined infertility, respectively, and in up to the second cycle in patients aged 40 years or more.

Also Custers et al. (21) found that Ongoing pregnancy rate (OPR) in high-order IUI cycles are acceptable, and do not offer a rationale for cancellation before nine cycles. So, using mild COH, it may be reasonable to conduct up to nine cycles.

In conclusion, we suggest that the conversion to IUI in poor responders might be an effective alternative. As we could only include a small sample size in the present retrospective study, the obtained results need further confirmation on a larger sample size in other prospective studies. Additionally, cycle cancellation with later retrials should be considered in future studies. And lastly a good point of future studies is repeated IUI cycles result should be compared to single ICSI cycle results among a group of poor responders' women.

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