Research Article

Mild Ovarian Stimulation Strategy versus conventional ovarian Stimulation in Poor Responder Women Undergoing ICSI

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Abstract
Introduction: One of the most frustrating problems in IVF today is the low pregnancy rate in women with poor ovarian response (Webb et al., 2016). Poor responders are estimated to comprise approximately 9-24% of IVF/ICSI patients (Papathanasiou et al., 2016). **Aim of the Work:** The aim of our study is to compare the efficacy of a mild ovarian stimulation strategy versus a conventional ovarian stimulation in women with poor ovarian response undergoing ICSI. **Patients and Methods:** This study conducted at the Nile Infertility Centre during the period between January 2018 and February 2019.The trial protocol was approved by the Ethical Committee of the department of Obstetrics & Gynecology, Minia University (approval no. MUEOB0016). **Results:** Our study was carried at Nile Infertility Center during the period between January 2018 and February 2019.The study included a total of 170 infertile women with an indication for ICSI and characterized as poor responsders according to the Bologna criteria. **In conclusion**, Mild ovarian stimulation reduce patients' burden of frequent injections, in terms of embryo quality, pregnancy rate, and cost mild ovarian stimulation is a promising alternative to conventional ovarian stimulation for poor ovarian responders.
Keywords: Mild ovarian stimulation , Mild ovarian stimulation , poor ovarian responders.

Introduction
One of the most frustrating problems in IVF today is the low pregnancy rate in women with poor ovarian response[(1)]. Poor responders are estimated to comprise approximately 9-24% of IVF/ICSI patients[(2)].

Unfortunately, there is no a universal definition of poor response but poor responders represent a heterogeneous group, the largest part consists of older patients[(3)]. The other part consists of young women who respond unexpectedly poorly, the physiological decline in the ovarian reserve is the principle factor of low pregnancy outcomes in both groups[(4)].

However several other possible aetiologies of poor ovarian response especially in young women have also been suggested[(5)]. For example a decreased number of FSH receptors available in granulosa cells, or a defective signal transduction after FSH -receptor binding, the presence of a special FSH receptor - binding inhibitor in the follicular fluid, or the presence of autoantibodies against granulosa cells[(6)].

So, poor response to gonadotrophin stimulation can be either expected or unexpected. The expected poor responders are defined as: women that are at least 35 years of age, women with a raised basal day 3 FSH level above 10 IU/ml irrespective age and/or women with a low antral follicular count of less than 5 follicles[(7)].

The unexpected poor responders are women younger than 35 years with non elevated FSH level who respond poorly during their first IVF cycle i.e. needing a total gonadotropin dose used of at least 3000 IU FSH for follicle growth or have a low follicles yield (< 3-5) despite a high daily stimulation dose or have their IVF cycle cancelled due to a low estradiol level of 300-850 pg/ml[(8)].

In the unexpected low responder women a cumulative pregnancy rate after 3 IVF cycles of 42% is found, while in the expected low responder women group the cumulative pregnancy rate is 17% (Venetis et al., 2010).

Patients and Methods
This study conducted at the Nile Infertility Centre during the period between January 2018 and February 2019. The trial protocol was

approved by the Ethical Committee of the department of Obstetrics & Gynecology, Minia University (approval no. MUEOB0016)

Planned sample size: a total of 170 patients were enrolled:-

- 85 patients underwent mild stimulation protocol
- 85 patients underwent conventional stimulation protocol**.**

Inclusion criteria:

Patients were eligible to participate in the study if they fulfilled the following criteria:

1-valid indication for IVF or ICSI.

2-Advanced maternal age(≥ 40 years).

3-And/or women who responded poorly(≤3 oocytes) during a previous IVF cycle with a conventional stimulation protocol irrespective of their age.

4-And/or women with abnormal ovarian reserve test (AFC < 5-7 follicles or AMH < 0.5-1.1ng/mL).

Exclusion criteria:

The exclusion criteria for participation in the study were:

1-Age > 43 years.

2-Polycystic ovary syndrome or any other anovulation condition.

3-History of endocrine or metabolic disorders.

4-Severe endometriosis.

5-Uterine anomalies

6-Severe male factor.

Written informed consent was obtained from each participant following consultation and before the initiation of the treatment cycle.

Treatment protocol:

Following clinical evaluation along with previous medical and reproductive history, patients had an initial transvaginal ultrasound examination to measure the uterine lining and perform an antral follicle count on day 2 of the cycle.

Baseline blood levels of AMH, estradiol, FSH, LH, and progesterone were also measured. After that patients were allocated to a treatment strategy consisting of: one cycle of mild ovarian stimulation IVF (Group 1) or one cycle of conventional ovarian stimulation IVF (Group 2).

Patients were randomized to one of the two treatment groups using a computer generated randomization schedule assigned via numbered sealed envelopes.

Group 1: Patients was treated with a mild ovarian stimulation protocol consisted of: Mild dose of gonadotrophins (HMG) [150 IU Menopur (Ferring Inc., Toronto, ON, Canada)] was administered sc. daily from day 2 of the cycle.

Patient was monitored by transvaginal ultrasound, when one or more follicles reached a diameter of ≥ 14 mm on average, GnRH-antagonist Cetrorelix [0.25mg Cetrotide (Merck Serono Europe Limited, London, UK)] was initiated sc. daily to avoid a premature LH surge and continued up to the day of hCG administration.

Triggering of ovulation: Transvaginal ultrasonography was repeated every 2-4 days, when ≥ 2 follicles reached a mean diameter of 17 mm HMG was stopped and HCG [Choriomon (Ibsa Inc., Lugano, Switzerland)] was administered as a single IM bolus dose of 10,000 IU.

Oocyte retrieval: OR was performed approximately 36 h after hCG injection under transvaginal ultrasound guidance. ICSI was performed in all patients.

Embryo transfer: Depending on the embryo quality which assessed according to morphological criteria based on the overall blastomere number, appearance and the degree of fragmentation, ET was performed (under ultrasound guidance) either 2 or 3 days following OR.

Luteal-phase support: Luteal support in all patients was achieved by transvaginal administration of progesterone in the form of vaginal suppositories (Prontogest, vaginal supposetories, 400 mg daily), started from the afternoon of the day of OR.

Group 2: Patients was treated with the conventional ovarian stimulation protocol consisted of: High dose of gonadotrophins (450 IU Menopur) sc. daily started from day 2 of their cycle. Antagonist initiation, hCG administration timing, OR timing, ICSI,ET and luteal-phase support were the same as Group 1.

For both groups: Serum β-hCG levels were tested starting 2 weeks after embryo transfer, and serially, if positive, followed by a transvaginal ultrasound examination between 6 and 7 weeks of gestation.

Results

Our study was carried at Nile Infertility Center during the period between January 2018 and February 2019.The study included a total of 170 infertile women with an indication for ICSI and characterized as poor responders according to the Bologna criteria.

Of the total 170 cycles of ICSI performed on poor responders, 85 cycles were mild ovarian stimulation cycles, and 85 cycles were conventional ovarian Stimulation cycles. 19 cycles (11%) were cancelled in mild ovarian stimulation (GROUP 1), and 12 cycles (7%) were cancelled in conventional ovarian stimulation. None of these women had one ovary.

Table: Basal and demographic characteristics of mild ovarian stimulation patients (group 1) and conventional ovarian stimulation patients (group 2), in poor responders undergoing IVF/ICSI:

Characteristics	Group1 (n=85)	Group2 (n=85)	*P*- value
Age (yrs)	38.9 ± 2.6	37.3 ± 5.3	0.056
BMI (kg/m²)	28.1 ± 3.1	28.9 ± 2.1	0.23
Smoking -Active smoking -Passive smoking	 0 34(40%)	 0 39(46%)	 - 0.25
Parity	28 (33%)	30 (35%)	0.43
1ry infertility	57(67%)	55(65%)	0.37
Duration of infertility (yrs)	8.7 ± 4.5	9.1 ± 4.9	0.35
Previous ICSI cycles	38(44.7%)	41(48%)	0.66
Causes of infertility: -Diminished ovarian reserve(IOF): -IOF + poor semen quality: -IOF + tubal factor: -IOF + Endometriosis: -Multiple factors:	 44(51.7%) 22(26%) 7(8.3%) 2(2.3%) 10(11.7%)	 45(53%) 21(24.7%) 7(8.3%) 3(3.5%) 9(10.5%)	 0.86 0.84 1.000 0.67 0.83

BMI: body mass index, IOF:Incipient ovarian failure.

Compares the two groups there were no statistically significant differences in Age, body mass index, duration of infertility, parity and causes of infertility p>0.05.

Discussion

Mild ovarian stimulation in poor ovarian response groups is known to be a patient friendly method that reduces the incidence of ovarian hyperstimulation syndrome, and at the same time, reduces unnecessary discomfort to patients by using a lower dose of gonadotropin, and also reduces medical expenses[8]**.** Many studies have reported that mild ovarian stimulation, compared to conventional ovarian stimulation, improves embryo quality and implantation rates. Recently, it has been suggested that mild ovarian stimulation could reduce the proportion of mosaic embryos and aneuploidies[9]**.** While many investigators have investigated the usefulness of mild ovarian stimulation, few studies have focused on mild ovarian stimulation in poor responders.

Clinicians have a tendency to avoid mild ovarian stimulation in women with the first cycle. The reason for this is that although mild ovarian stimulation can yield results as good as conventional ovarian stimulation, many studies report higher cycle cancellation rates [10]**.**

The present study was carried at Nile Infertility Center during the period between January 2018 and February 2019.Of the total 170 cycles of ICSI performed on poor responders, 85 cycles were mild ovarian stimulation cycles, and 85 cycles were conventional ovarian Stimulation

cycles, the results showed that **t**he total number of doses of gonadotropin used during hyper-stimulation was significantly lower in the mild ovarian stimulation group than in the conventional ovarian stimulation group this is in agreement with[11], as regard this three clinical trials: The first study was RCT, entailed 695 women with expected poor ovarian response and compared a mild stimulation protocol 100 mg/day Clomiphene citrate followed by 150 IU HMG combined with a GnRH antagonist to a conventional stimulation protocol with daily 300 IU HMG combined with a GnRH agonist[12], there were no difference in ongoing pregnancy rates, but there were more oocytes and embryos in the conventional strategy. In the second RCT entailing 95 women with poor ovarian reserve, found no difference in pregnancy rates between women receiving 150 FSH/HMG combined with Letrozole in a fixed GnRH antagonist protocol and women receiving either 300 or 450 IU FSH/HMG[14]. The third trial[15] was case-control study entailed 92 women Characterized aS poor responders and compared a mild regimen consisted of 100-150 mg/day clomi-phen citrate Followed by 150 IU HMG Combined with a GnRH antagonist to a Conventional stimulation with daily 325 IU HMG and GnRH antagonist, there was no difference in the total number of embryos and clinical pregnancy rates. Despite the higher number of oocytes retrieved from patients stimulated conventionally fertilization rate was significantly lower. Again to our result : the number of mature follicles were significantly fewer in the mild ovarian stimulation group than in the conventional ovarian stimulation group this is in agreement with[16].

Conclusion

In terms of embryo quality, pregnancy rate, and cost effectiveness, mild ovarian stimulation is a promising alternative to conventional ovarian stimulation for poor ovarian responders in absence of statistic significant differences between both groups.

This study showed that Mild ovarian stimu-lation can save costs by using a smaller amount of gonadotropin, and can reduce patients' burden of undergoing frequent injections, It also gives favorable pregnancy chances in spite of the retrieval of low numbers of oocytes.

Recommendations

The most efficient approache in managing subfertile poor responders is the individuali-zation of the treatment protocol, based on (AFC) and (AMH) values prior to the IVF cycle.

Clinicians should not fear from a relatively low ovarian response to mild stimulation and that current criteria for low response or cycle cancellation do not apply under those circums-tances. Indeed, obtaining low oocyte numbers in the context of a mild stimulation protocol is not associated with poor outcomes and may aid in the selection of embryos for transfer due to the qualitative lower interference in the natural selection of good- quality oocytes.

As the mild stimulation did not show better pregnancy rates compared with a conventional stimulation protocol, the benefits of mild stimu-lation should be balanced with the potential slight decrease in pregnancy rate per cycle.

Similarly the risk of bleeding from follicular puncture is a lot less with less stimulated ovaries. Risk of multiple gestation, ovarian hyperstimulation and torsion or persistent ovarian cysts are also reduced.

As mentioned expenses can be markedly reduced using minimal stimulation protocol. For all these reasons minimal stimulation protocol will be preferred not only for women with decreased egg reserve but it may be the first choice for women with normal egg reserve undergoing their first ICSI cycle (not merely those failing to conceive from previous standard higher dose protocols).

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