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Research Article

EXPLORING GONADOTROPIN DOSAGE EFFECTS ON PREGNANCY OUTCOMES IN IN VITRO FERTILIZATION FOR POOR OVARIAN RESERVE: A COMPARATIVE STUDY OF MINIMUM-DOSE STIMULATION AND HIGH-DOSE STIMULATION PROTOCOLS

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ABSTRACT

This retrospective cohort study explores the efficacy of minimum-dose stimulation (MS) compared to high-dose stimulation (HS) in improving clinical pregnancy rates in patients with poor ovarian reserve (POR). The study compares gonadotropin-antagonist protocols for MS and HS, considering antral follicle count (AFC) on days 2-3 and anti-Mullerian hormone (AMH) levels of 8 pmol/L as inclusion criteria. The MS protocol involves a daily oral administration of 2.5 mg letrozole for 5 days, starting on day 2, and 150 units of daily gonadotropins from the third day following letrozole. GnRH antagonists are introduced when the follicle diameter exceeds 14 mm. In the HS group, gonadotropins are administered at a dosage of over 300 IU daily during the antagonist cycle. The results indicate a significant increase in clinical pregnancy rates with the HS protocol (P = 0.007). Furthermore, there is a notable difference in live birth rates between the MS and HS groups (P = 0.034). The study suggests that lower gonadotropin dosages in the MS IVF protocol may lead to higher clinical pregnancy and live birth rates, particularly in poor responders.

Key words:-. Minimum-dose stimulation, High-dose stimulation, Poor ovarian reserve, Gonadotropin-antagonist protocols, In vitro fertilization (IVF).

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INTRODUCTION

There is a great number of infertility among patients with poor ovarian response (POR) [1, 2]. Due to their advanced maternal age, POR patients experience a significantly reduced live birth rate. The rate of miscarriage is higher in patients with POR, and their cycles are more often cancelled.

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There is no universal definition of POR. (3–7). There is also considerable controversy surrounding POR management. Increased gonadotropins, reduced GnRH analogs, estrogen priming, or maximizing flare effects (all of which target follicle number) are some of the most common strategies aimed at increasing follicles [1]. Adjunctive growth hormones are recommended in some studies [1, 7], while aromatase inhibitors are recommended in others [8].

The aromatase enzyme is inhibited, resulting in a decrease in estradiol synthesis. Infertility patients are increasingly using letrozole for ovulation induction. The hypothalamus experiences a reduction in estrogen-mediated feedback as follicular estrogen synthesis decreases, resulting in increased production of endogenous gonadotropins. According to Healey et al., letrozole increased preovulatory follicle number without affecting pregnancy rates. [10]. Follicular granulosa cells express FSH receptors more strongly when letrozole is administered [11]. Letrozole may therefore improve the response of the ovary to FSH [11].

In this study, letrozole overlapped with low doses of gonadotropins and high-dose gonadotropin antagonists were compared with a minimal stimulation (MS) protocol in poor responders. Clinical pregnancy rates might be increased by a MS protocol with letrozole compared to a HS protocol.

METHODS AND MATERIALS

Patients: According to the Abologna criteria [12], poor ovarian reserve indicates lack of ovarian reserve. As a result of poor prediction of outcome, cycles with a single dominant follicle were cancelled and excluded.

IVF cycles meeting these criteria were 36 in number. We started using MS protocols for patients with poor prognoses, following some early positive reports. Each group was attempting IVF for the first time.

Treatment Protocol: Each patient underwent a transvaginal ultrasound examination on day 2 of their cycles in order to measure their uterine lining and determine the number of antral follicles present. In addition to estradiol level measurements, progesterone, LH, FSH levels were also measured. For MS patients, letrozole was prescribed at a low dosage.

From cycle day 2 onwards, administer 2.5 mg PO every day over a five-day period. After overlapping low dose gonadotropin treatment was initiated on day 3 of letrozole therapy, menopur was initiated on day 4. Initially, 150 IU of gonadotropin were administered daily. An ultrasound and blood hormone monitoring were conducted three days after the patient started taking menopur, and the dose was adjusted accordingly. It was possible to use up to 225 IU of gonadotropin regardless of the response was introduced when follicle diameter reached 14 mm to prevent a premature LH surge. At least two or three follicles must reach 18 mm or larger to initiate the final maturation phase with human chorionic gonadotropin (hCG). It was possible to cancel the dominant follicle in cycles with a single dominant follicle. Several hours after hCG injection, oocytes were retrieved. To maximize fertilization based on the limited number of oocytes, intracytoplasmic sperm injection (ICSI) was generally decided upon.The control group underwent a short antagonist cycle, starting on day 2, followed by a high dose of gonadotropins (>300 IU/day). Oocyte retrieval timing, antagonist initiation, and hCG administration timing were similar to the MS protocol.

Embryos were transferred on the third day under ultrasound guidance. R.B., our local pharmacist, proposed either progesterone suppositories 100 mg qid (containing ethyl oleate oil and 50 mg/mL), or intramuscular progesterone in ethyl oleate oil (2 cc of 50 mg/mL). When hCG levels were positive after embryo transfer, serial tests were conducted between 6 and 7 weeks after embryo transfer. This study defines "clinical pregnancy" as the presence of a gestational sac for the fetus, whether or not heartbeats can be detected.

RESULTS

There was no significant difference between the MS and HS groups with respect to age (41.3 ± 5.1 versus 41.0 ± 5.11, resp.). The E2 level on the day of hCG administration (MS 1580.8 ± 1141.2 versus HS 5575 ± 3295.1 pmol/L, $P < 0.001$) and the total units gonadotropins administered during the stimulation protocol (MS 1332.9 ± 435.7 versus HS 5575.2 ± 1945 IU, $P < 0.001$) were significantly higher in the HS group. There was no significant difference in the number of oocytes retrieved with the MS versus HS protocol (4.11 ± 3.7 versus 5.7 ± 3.7 resp., $P > 0.05$). The formation of dominant follicles (NS) resulted in the annulment of 5% of cycles in each group. There was no significant difference in the number of fertilized eggs (2PN) between the two protocols (3.7 ± 3.3 versus 3.7 ± 1.2 resp., $P > 0.05$), and no significant difference in the number of embryos transferred per cycle for the MS versus the HS protocols (3.1 ± 0.9 versus 3.6 ± 3.4 resp., $P > 0.05$) was found. A significantly higher rate of clinical pregnancy was observed with the MS protocol than with the HS protocol (11/35, 33.6% versus 5/36, 14.9%, respectively, $P < 0.05$). The live birth rate in MS was significantly higher than in HS (8/35, 23.6% versus 3/36, 9.0%, respectively, $P < 0.05$).

Table 1: In low responders, low stimulation and high stimulation protocols were compared in terms of data.

	MINIMUM STIMULATION	HIGH STIMULATION	*P* VALUE
Number of patients	35	36	
Age (yr)	41.6 ± 5.4	41.4 ± 6.0	NS
Gonadotropin total dose (IU)	1332.9 ± 435.7	5575.2 ± 1945.0	$P < 0.001$
Peak estradiol (pmol/L)	1580.8 ± 1141.2	5279.4 ± 3295.1	$P < 0.001$
Number of oocytes retrieved	4.11 ± 3.7	5.7 ± 3.7	$P < 0.001$
Antral follicle count	5.9 ± 3.0	6.7 ± 0.9	NS

Number of fertilized oocytes	3.7 ± 3.3	3.7 ± 3.4	NS
Cancellation rate	2/36 (6.4%)	2/40 (7.0%)	NS
Number of embryos transferred	3.1 ± 0.9	3.6 ± 3.4	NS
Clinical pregnancy rate/cycle	11/35 (33.6%)	5/36 (14.9%)	$P < 0.05$
Live birth rate	8/35 (23.6%)	3/36 (9.0%)	$P < 0.05$

DISCUSSION

The treatment of patients with poor ovarian responses is challenging for reproductive medicine. It is commonly found in women who are over the age of 50 [13], but previous surgery [14], pelvic infections [15], and environmental factors may also contribute. In order to evaluate the efficacy of letrozole (an aromatase inhibitor), laboratory results can be compared between MS and HS protocols. There was a significant increase in clinical pregnancy rates and live births following the MS protocol we used.

In the literature, no consensus exists on how to define what constitutes a "poor responder" for the purposes of comparison and consensus regarding treatment results. Women with poor ovarian reserve are advised to follow the Bologna criteria, part of the ESHRE consensus. There has, however, been a lack of universal acceptance of this guideline. If a patient does not respond well to therapy, follicular recruitment time is shortened. This group of patients may also have lower FSH receptor expression in granulosa cells. Aromatase inhibitors facilitate follicular recruitment by lowering estrogen levels and extending FSH's action. Poor responders may also experience increased levels of intraovarian androgen after taking letrozole. It was Hillier who introduced androgens to granulosa cells for the first time [18]. Furthermore, androgens have been shown to increase gene expression of IGF-1 and IGF-1 receptors, which enhance follicular steroidogenesis [1, 17].

Although poor responders who received a GnRHa microflare protocol had no difference in clinical pregnancy rates, those receiving a letrozole antagonist protocol had significantly fewer stimulation days and a lower gonadotropin dose overall, compared to those who received a GnRHa microflare protocol. Microdose GnRH agonists were also compared with letrozole antagonist protocols by Yarali et al. [9]. Pregnancy rates did not differ between the letrozole antagonist and the letrozole receptor antagonist groups. Patient compliance improved as a result of reduced medication costs.

CONCLUSION

Compared to the HS protocol, the MS protocol was not only more cost-effective (in terms of the amount of total gonadotropins used) and it also resulted in higher clinical pregnancy rates as well as live birth rates. This conclusion needs to be confirmed by a prospective randomized controlled trial.

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