Progestin Primed Double Stimulation Protocol Versus Flexible GnRH Antagonist Protocol in Poor Responders

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AIM OF THE WORK

The primary aim of this work is to assess the difference between the progestin primed double stimulation protocol and the conventional GnRH antagonist protocol in poor responders regarding the number of M2 oocytes retrieved, the fertilization rate, the resultant embryos number, the implantation rate and the clinical pregnancy rate.

While the secondary aims are:

1. Assessing the difference in the ongoing pregnancy rate in both protocols.
2. Assessing the difference between the follicular phase and the luteal phase of the progestin primed double stimulation protocol regarding the total days of controlled ovarian hyperstimulation, the total gonadotropin dosage, the number of M2 oocytes retrieved ,the fertilization rate and the resultant embryos number.
3. Assessing the difference between the follicular phase of the progestin primed double stimulation protocol and the first round of the conventional GnRH antagonist protocol regarding the number of M2 oocytes retrieved the fertilization rate and the resultant embryos number.

PATIENTS

This study is a randomized controlled study performed at infertility and assisted reproduction unit of El-Shatby Maternity Hospital and Madinah Fertility center.

Sample size:

Sample size calculation is done by the staff members of Medical Research Institute, Alexandria University using NCSS PASS statistical software version 20.

Participants:

The study will be conducted on 80 infertile women indicated for ICSI with criteria of poor ovarian response defined by Bologna criteria (15)

All participants will be informed about the nature of the study and informed consent will be taken from all of them.

Inclusion criteria:

1. Indicated infertile women for ICSI of poor responders defined by Bologna criteria either two or more of the following:(15)

(i) advanced maternal age or any other risk factor for POR.
(ii) a previous POR ; less than 3-5 oocytes retrieved per cycle.
(iii) an abnormal ovarian reserve test (ORT): AFC less than 5-7 or AMH is less than 1.1 ng/ml.

Or two episodes of POR after maximal stimulation are sufficient to define a patient as poor responder in the absence of advanced maternal age or abnormal ORT.

Exclusion criteria:

1. Male factor infertility due to azoospermia.

2. Patients with uncorrected uterine pathology.

3. Patients with the diagnosis of severe endometriosis.

4. Patients with BMI over 35.

METHODS

Study design:

• Randomized controlled study in which 90 patients will be divided into two groups:

Group 1:45 patients will be given the progestin primed double stimulation protocol.
Group 2: 45 patients will be given the flexible GnRh antagonist follicular controlled ovarian stimulations will be done in 2 cycles.

• Written informed consents will be obtained from all participants who accept to participate in the research protocol.

Work up:

1. Complete history taking and full assessment of different infertility factors.
2. Hormonal investigations

- FSH, LH, E2, Prolactin
- AMH, TSH

3. Basal transvaginal ultrasound

Clinical and embryological procedures:

Group 1:

I. The follicular phase of the double stimulation protocol

a. luteal phase priming using combined contraceptive pills from day 21 of the previous cycle for one week (0.03 mg ethinyl estradiol, gestodene 0.075 mg, Gynera tab, Bayer Pharma AG., Berlin, Germany).

b. Controlled ovarian hyper-stimulation with 225-375 IU of gonadotropins will be started day 2-3 of menses after vaginal ultrasound confirming the absence of ovarian cysts.

c. Dydrogesterone (Duphaston, Abbott company, Illinois, United states) at 20 mg/day will be started from the first day of the ovulation induction.

d. Patient response will be monitored by**:**

1. Transvaginal follicular scanning and the dose of the gonadotropins will be modified according to the response.

2. Serum estradiol.

3. Serum progesterone and LH on the day of triggering.

e. GnRh agonist triggering (Decapeptyl, Ferring, SAINT-PREX Switzerland) in a dose of 2 ampules of 0.2 mg will be administered when leading follicle >18 mm in diameter.

f. Oocyte pickup will be done 36 hours after GnRh administration with precaution of leaving the follicles measuring 11 mm or less.

g. After the pick-up, oocytes will be denuded. The denuded oocytes are then assessed for nuclear status. Mature oocytes will be used for ICSI.

II. The luteal phase of the double stimulation protocol

Controlled ovarian hyper-stimulation with 225-375 IU of gonadotropins will be started the next day after the previous oocyte pickup simultaneously with Dydrogesterone (Duphaston, Abbott company, Illinois, United states) at 20 mg/day. The rest will be as the follicular phase.

III. **Fertilization and embryo quality:**

The fertilization check, which will be performed 16 to 20 hours after ICSI. The resultant embryos will be scored, and they will be vitrified for subsequent transfer.

IV. Embryo transfer

- Starting from the next menstrual cycle Day 3, patients will receive oral estradiol valerate (Cyclo-Progynova (white tablets); Bayer, Germany) daily. From Day 10 onwards, endometrium growth will be monitored by transvaginal ultrasound. When endometrial thickness ≥ 7 mm. Progesterone administration (as 800 mg/day vaginal suppositories per day and 100 mg ampule IM every other day) will be initiated and Embryo transfer will be scheduled on Day 3, 4 or 5 with maximum number of 3 class A embryos whether of cleavage or blastocyst stage.

V. Luteal support

- Progesterone administration (as 800 mg/day vaginal suppositories per day and 100 mg ampule IM every other day) will be continued until pregnancy testing 18 days after embryo transfer. The pregnant cases will continue the luteal support till the 12 weeks of gestation.

Group 2:
VI. The flexible GnRH antagonist protocol controlled ovarian stimulation

This controlled ovarian stimulation will be done twice in two different cycles
In each cycle:
a) luteal phase priming using combined contraceptive pills from day 21 of the previous cycle for one week (0.03 mg ethinyl estradiol, gestodene 0.075 mg , Gynera tab, Bayer Pharma AG., Berlin, Germany).

b) Controlled ovarian hyper-stimulation using antagonist protocol will be used. Stimulation with 225-375 IU of gonadotropins will be started day 2-3 of menses after vaginal ultrasound confirming the absence of ovarian cysts.

c) GnRH antagonist (Cetrotide , Merck Serono, Darmstadt, Germany) will be given daily as the biggest oocyte reaches size 14 mm.

d) Patient response will be monitored by**:**

1. Transvaginal follicular scanning and the dose of the gonadotropins will be modified according to the response.

2. Serum estradiol.

3. Serum progesterone on the day of triggering.

e) GnRh agonist triggering (Decapeptyl, Ferring, Saint-Prex Switzerland) in a dose of 2 ampules 0.2 mg will be administered when leading follicle >18 mm in diameter. While in the second cycle HCG triggering (Choriomon, IBSA, Lugano, Switzerland) in a dose of 10,000 IU will be administered when the leading follicle >18 mm in diameter.

f) Oocyte pickup will be done 36 hours after GnRh administration.

g) After the pick-up, oocytes will be denuded. The denuded oocytes are then assessed for nuclear status. Mature oocytes will be used for ICSI.

VII. **Fertilization and embryo quality:**

The fertilization check, which will be performed 16 to 20 hours after ICSI. The resultant embryos will be scored.
Embryos of the first cycle will be vitrified while embryos of the second cycle will be freshly transferred unless there is excess for vitrification for subsequent trials of transfer.

VIII. Embryo transfer

- Progesterone administration (as 800 mg/day vaginal suppositories per day and 100 mg ampule IM every other day) will be initiated on the day of the oocyte pick up of the second cycle. Embryo transfer will be scheduled on Day 3, 4 or 5 with maximum number of 3 class A embryos whether of cleavage or blastocyst stage that will be a mixture of the thawed embryos of the first cycle and fresh embryos of the second cycle.

IX. Luteal support

Progesterone administration (as 800 mg/day vaginal suppositories per day and 100 mg ampule IM every other day) will be continued until pregnancy testing 18 days after embryo transfer. The pregnant cases will continue the luteal support till the 12 weeks of gestation.

Statistical analysis

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0**.** **(**Armonk, NY: IBM Corp**)** Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

The used tests were

1 - Chi-square test

For categorical variables, to compare between different groups

2 - Fisher's Exact or Monte Carlo correction

Correction for chi-square when more than 20% of the cells have expected count less than 5

3 - Student t-test

For normally distributed quantitative variables, to compare between two studied groups

4 - Mann Whitney test

For abnormally distributed quantitative variables, to compare between two studied groups

5 –Wilcoxon signed ranks test

For abnormally distributed quantitative variables, to compare between two periods