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Estrogen/androgen priming protocol improves egg quality and the number of embryos available for transfer in poor responder patients undergoing IVF/ICSI

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Abstract

The incidence of poor response to ovarian hyperstimulation during in vitro fertilization has been shown to vary from 9% to 30 [1]As patients become older and environmental factors have an adverse effect on egg quality, a larger and larger number of patients have diminished ovarian reserve and poor response to gonadotropins. [2] These adverse effects are seen more and more frequently in our clinic. Various factors including exposure to environmental toxins, [3] aging, endometriosis, hormones, antibiotics, previous ovarian surgery, and pesticides in the food and water supply, cause premature depletion of ovarian reserve and are associated with poor ovarian reserve. Poor response to ovulation stimulation results and high cancellation rates of up to 70% and extremely low pregnancy rates of 3% to 14%. [2] [4] Various strategies for poor responders including microdose flare protocols, estrogen priming protocols, and agonist/antagonist conversion protocols as well as augmentation with various adjuncts including human growth hormone, have been tried with varying degrees of success. [5, 4] [6] However, the lack of uniform consensus on which protocol is best is a testament to the lack of stellar performance of any one of these protocols in this particular patient population. [7] The etiology of poor response to gonadotropins is partly unknown and may result from a shortened follicular phase as well as decreased sensitivity to gonadotropins. It is known that patients with decreased ovarian reserve are more susceptible to the suppressive effects of oral contraceptive pills and gonadotropin releasing hormone agonists. [8] Although these drugs are commonly used to suppress ovarian function, these drugs can adversely affect ovarian responsiveness. [8] Moreover, patients with diminished ovarian reserve appear especially susceptible to the suppressive effects of pituitary desensitizers leading to low oocyte yield and low response. It has been shown that estradiol pretreatment prior to GnRH antagonist stimulation has a beneficial effect on oocyte yield. [9] Estradiol exerts a negative feedback on the reproductive axis, which inhibits GnRH secretion and suppression of GnRH responsiveness. Previous studies have shown that utilizing the natural negative feedback of the hypothalamic pituitary ovarian axis induced by estradiol pretreatment can prevent premature increase in FSH levels as well as improve follicular synchronization and result in better coordination of the developing follicles and improved oocyte maturity. [10]

The concept of a luteal estradiol protocol was first suggested by Fanchin R. et al, based on the assumption that reducing the size and improving the homogeneity of early antral follicles would optimize ovarian response and improve cycle outcome. [10] [11] However, the gradual elevation of FSH has been shown to be counter-reproductive, thus adjuvant GnRH agonist were used to offset this effect. However, the use of GnRH in addition to oral contraceptives combined with the agonist required during the ovarian stimulation protocol, make these cycles cost prohibitive for many. A recent Meta-Analysis shows that pretreatment with transdermal estrogen improves the response to gonadotropins in poor responders. [11]. Females who receive transdermal testosterone in the prior cycle, show a two-fold increase in live birth rate, a two-fold increase in clinical pregnancy rate, and significant increase in the number of oocytes retrieved. The mechanism of action is believed to be increased FSH receptor expression in granulosa cells, promoting the initiation of primordial follicle growth and improving the number of preantral and small antral follicles. These studies indicate that androgen pretreatment amplifies the effect of FSH on the ovaries. [12] Since prior studies have shown that initial estrogen priming in poor responders is promising, and additional reports of testosterone priming have also shown in improvement in poor responder, the question we wanted to answer was whether or not combining these two stimulation adjuvants together in one protocol would cause a synergistic effect and improve ovarian responsiveness significantly. **METHODS:** A total of 25 cycles of Estrogen Androgen Priming was performed at the Palm Beach Fertility Center between September of 2014 and December of 2017. A total of 21 patients' charts were selected for inclusion into the study based on the following criteria: Inclusion Criteria: 1. At least 1 previous IVF attempt with a standard Microdose Flare or Antagonist Protocol; 2. Normal uterine Cavity; 3. Patients that are normally excluded from most studies were specifically included in this study. Some examples: previous cancelled cycle(s), advanced age, Low AMH, poor response to gonadotropins. Estrogen Androgen Priming Protocol was performed as follows: Baseline Ultrasound and Estradiol was performed on CD 2 of cycle prior to gonadotropin administration. Estradiol patches 0.1 mg was begun and changed every 3 days. On CD #15, oral micronized progesterone 200 mg p.o. bid was begun. On CD #17,

Testosterone transdermal 4 mg patch was applied every evening at 8PM and removed every morning at 8 AM. Ultrasound, E2 and P4 levels were obtained. On CD 21 estradiol, progesterone and testosterone were discontinued. Repeat baseline scan was performed 3 -5 days later and stimulation was begun with 3-4 amps of FSH and 3-4 amps of HMG. The resulting follicles were aspirated when the lead follicle was 18-20 mm in diameter. Fertilization was by ICSI in all cycles. Embryo transfer was performed on Day 5. **RESULTS:** A total of 25 cycles of estrogen and androgen priming with gonadotropin stimulation were performed at the Palm Beach Fertility Center between September 2014 and December 2017. A total of 21 cycles that met the inclusion criteria were included in the study. Four cycles did not meet the inclusion criteria for the following reasons: Three cycles had no non-priming IVF cycle. One cycle had breakthrough bleeding during the priming cycle and was disqualified.

Biography

Mark Denker is currently working as a Reproduction Endocrinologists in Palm Beach Fertility Center, USA. He has also completed 2 years of Reproductive Endocrinology and Infertility Fellowship at University of California. He is a member of American Medical Association, American Fertility Society, American Association of Gynecologic Laparoscopists, and Society of Reproductive Surgeons. He has presented in many International Professional meetings. Besides he has also published papers in reputed journals.

Speaker Publications:

1. "Nitrogen-atom incorporation at Si–SiO2 interfaces by a low-temperature (300 °C), pre-deposition, remote-plasma oxidation using N2O"; Journal of Vacuum Science & Technology A Vacuum Surfaces and Films 13(3):1671 – 1675 DOI: 10.1116/1.579749
2. The Use of Atomic Force Microscopy
3. "Stability of Ultra-Thin Gate Oxides with Boron Doped Polysilicon Gate Structures After Rapid Thermal Annealing" MRS Online Proceeding Library Archive 303' DOI: 10.1557/PROC-303-247
4. "In situ spectroscopic ellipsometry studies of hydrogen ion bombardment of crystalline silicon"; Journal of vacuum science & technology B 10(3):1111 – 1117 DOI: 10.1116/1.586086

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