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Do younger women with elevated basal follicular stimulating hormone levels undergoing gonadotropin-stimulated intrauterine insemination cycles represent compromised reproductive outcomes?☆

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ABSTRACT

Objective: To compare stimulation characteristics and reproductive outcomes in women representing elevated and normal day 3 FSH levels and to evaluate the prognostic significance of day 3 FSH on the reproductive outcomes of gonadotropin-stimulated IUI (GS-IUI) cycles in women < 35 years.
Study design: A cross-sectional study was designed. Unexplained infertility patients at the age ≤36 years, who underwent IUI, following gonadotropin stimulation (GS), were investigated. From 105 women with a day 3 FSH≥ 10 U/L, 170 GS/IUI cycles were assigned to Group EF; whereas a control group (Group NF, normal FSH) was constituted of 170 cycles with a day 3 FSH levels < 10 U/L. Demographic and stimulation characteristics as well as reproductive outcomes were compared. Primary outcome measure of this study was the biochemical, clinical and ongoing pregnancy rates. Secondary outcome measures were total gonadotropin dose, duration of gonadotropin stimulation, multiple pregnancy, miscarriage and cycle cancellation rates.
Results: β-hCG positivity, clinical and ongoing pregnancy rates did not differ between women with normal and elevated FSH levels ($p = 0.234$, 0.282 and 0.388, respectively). Total gonadotropin dose, multiple pregnancy and miscarriage rates were not significantly different between the groups ($p = 0{,}181$, 0.652 and 0.415, respectively). Duration of stimulation was significantly longer and cycle cancellation rate was significantly higher in Group EF than in Group NF ($p = 0.005$ and 0.021, respectively).
Conclusion: Younger women with elevated day 3 FSH represent comparable reproductive outcomes in GS-IUI cycles to those with normal FSH levels, although they may require longer periods of stimulation and are at higher risk of cycle cancellation. Thus, GS-IUI could be a possible treatment option in this patient group and should not be neglected.

Introduction

The females are born with a finite number of oocytes that gradually decreases during prepubertal development and adult life [1,2]. The ovarian functional lifespan is determined by the size of the oocyte pool provided at birth as well as by the rate at which this follicular reserve is expended [3]. Age related decrease in the follicular pool is accompanied by ovarian senescence, which finally results in the state of menopause [4]. It is well known that a period of subfertility precedes the onset of menopause and total loss of fertility [5]. In this subfertility period, the ovaries begin to signal an accelerated decline in oocyte quality as well as decline in fertility, which results in gradually elevated FSH levels, even if the menstrual cycles are regular [4]. However, the decline in ovarian function occurs, in some women, earlier.

The identification of ovarian reserve in women who are candidate for assisted reproduction is clinically relevant. Many environmental and acquired factors, such as advanced maternal age, smoking and obesity, have been identified to have deleterious

☆ This study was conducted at the Department of Obstetrics and Gynecology, Zeynep Kamil Training and Education Hospital.

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effects on women's fertility potential [6]. Even though the potential for prediction for ovarian response to controlled ovarian stimulation (COS) still remains elusive, a considerable proportion of women seeking fertility treatment have diminished ovarian reserve (DOR), defined as a decreased quantity or quality of oocytes [7–10]. Hence, DOR is associated with infertility, high cancellation rates, significant decline in pregnancy rates and poor ovarian response (POR) to COS. Also women with DOR have been reported to have high rates of pregnancy loss [7,11].

In order to determine the accurate ovarian reserve in women undergoing assisted reproduction, a set of clinical parameters, including measurements of day 3 FSH [12–14], basal inhibin-B and anti müllerian hormone (AMH) levels [15–17] and ultrasonographic assessment of antral follicle count and ovarian volume [12–14], has been introduced to clinical practice and are being used to predict outcome of IVF in terms of oocyte yield and occurrence of pregnancy. Even though both AMH and AFC are considered as the most reliable and accurate markers of ovarian reserve [18,19], FSH is more widely available and more commonly used in clinical practice to predict reproductive outcomes. It was reported that day 3 FSH levels are predictive of pregnancy outcomes and stimulation characteristics in IVF, when used either alone [20], or in combination with age [21]. Elevated day 3 FSH is a commonly encountered clinical feature in subfertile population. However, the prognostic significance of elevated day 3 FSH in younger women attempting to conceive through assisted reproduction is not well understood and still remains elusive. There is no consensus regarding how to manage younger women with elevated early follicular FSH levels, whether these women present compromised fertility outcomes and whether they should be subjected to more aggressive treatments or to prolonged conservative therapies. In this study, we aimed to compare stimulation characteristics and reproductive outcomes in women representing elevated day 3 FSH levels with those representing normal day 3 FSH levels and to evaluate the prognostic significance of day 3 FSH on the reproductive outcomes of gonadotropin-stimulated IUI (GS-IUI) cycles in women $<$ 35 years.

Materials and methods

This cross-sectional study retrospectively evaluated 7263 infertility patients who underwent intrauterine insemination (IUI), following ovarian gonadotropin stimulation (GS), in the period between 2008 and 2014 after the Institutional Review Board of Zeynep Kamil Maternity and Children's Hospital approval was obtained.

Patients, who failed to conceive in spite of unprotected sexual intercourse for at least 12 month-period, were defined as infertile. These patients were subjected to a set of diagnostic tests including hormone profile (FSH, luteinizing hormone, estradiol, thyroid stimulating hormone) at 3rd day of cycle, uterine, endometrial and ovarian morphology assessment and antral follicle count (AFC) with TVS, serum progesterone measurement between 21st and 24th days of cycle, spermiogram following a 4 to 6 day sexual abstinence and hysterosalpingography (HSG) as part of the routine infertility work-up. Unexplained infertility was diagnosed if all above-mentioned diagnostic tests were normal. Male factor infertility was diagnosed if two semen analyses obtained at least 1 month apart were subnormal according to the World Health Organization criteria for normality [22]. Patients who revealed bilateral tubal obstruction were further evaluated for tubal patency with laparoscopy. Polycystic ovary syndrome (PCOS) was diagnosed according to Rotterdam 2003 criteria [23]. The diagnosis of DOR was established in the presence of risk factors such as history of ovarian surgery and radio- or chemotherapy, age $>$36 years and laboratory parameters such as total AFC $<$ 5–7, FSH $\geq$ 10–12 U/L, Estradiol $\geq$ 75 pg/ml; however, AMH was not routinely used.

Inclusion criteria were as follows; age $\leq$ 36 years, euthyroid (TSH between 0,63 and 4,82 mU/L), with at least unilateral tubal patency at HSG, unexplained infertility patients who underwent IUI following gonadotropin stimulation with recombinant or highly purified or human menopausal gonadotropins.

Patients $>$36 years of age, IUI following natural cycle or clomiphene citrate induction, PCOS and male factor infertility were excluded. However, women having only appearance of polycystic ovaries in the absence of other clinical and laboratory criteria of PCOS were included.

Gonadotropin stimulations were initiated when endometrial thickness was $<$ 5 mm in the absence of residual follicular cyst $>$14 mm at the sonographic assessment performed on the 2nd or 3rd day of spontaneous or progesterone-induced menstrual cycle. The starting gonadotropin dose was individualized according to age, body mass index (BMI), AFC and basal FSH and experience from previous cycles and was adjusted according to sonographic follicular response. Choriogonadotropin-alpha 250 μg s.c. (Ovitrelle®; Merck Serono, Turkey) was administered to induce final follicular maturation when leading follicle $\geq$ 18 mm was detected. IUI was performed 34–36 h after hCG administration. During GS-IUI processes, GnRH antagonist administration, luteal phase support with estrogen and/or progesterone or double IUI were avoided. National policy of our Ministry of Health concerning the number of follicles to be developed allows up to 2 in order to prevent multiple pregnancies. Cycles were cancelled when no follicle $\geq$ 10 mm until the 14th day of stimulation or 3 or more follicles were obtained. Biochemical pregnancy was defined as a positive pregnancy test result (β-hCG levels $>$20 mIU/ml) 14 days after embryo transfer; clinical pregnancy was defined as fetal cardiac activity observed by vaginal ultrasonography 4 or 5 weeks after oocyte retrieval and ongoing pregnancy was defined as ultrasound check of the embryo after the 9th gestational week. Oral or vaginal progesterone supplementation was administered in cases with evident vaginal bleeding after the pregnancy is observed.

From 105 women with a day 3 FSH $\geq$ 10 U/L, 170 GS/IUI cycles were assigned to Group EF (elevated FSH); whereas, a control group (Group NF; normal FSH) was constituted of those with a day 3 FSH levels $<$ 10 U/L, who had patient's file numbers subsequent to those in Group EF. As the included patients in both groups were matched with a ratio of 1:1 for induction cycle number, Group NF consisted of 170 GS/IUI cycles from 95 patients.

The included patients were compared in terms of demographic and stimulation characteristics as well as reproductive outcomes. Primary outcome measure of this study was the biochemical, clinical and ongoing pregnancy rates. Secondary outcome measures were as follows: a. total gonadotropin dose, b. duration of gonadotropin stimulation, c. multiple pregnancy rate, d. miscarriage rate and e. cycle cancellation rate.

Statistical analysis

Statistical analyses were performed using the statistical package for the social sciences for Windows 15.0 software (SPSS, Chicago, IL., USA). Descriptive statistics were given as mean, standard deviation, frequency and percentage. Parametric comparison was made by student's t test, whereas categorical data were evaluated by using the chi-square test. The assessment of parameters that significantly affect the pregnancy rates was achieved by logistic regression analysis. Values of $p < 0.05$ were considered statistically significant.