European Journal of Obstetrics & Gynecology and Reproductive Biology 210 (2017) 76–82

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Individualised gonadotrophin ovulation induction in women with normogonadotrophic anovulatory infertility: A prospective, observational study

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ARTICLE INFO

Article history:
Received 22 July 2016
Received in revised form 30 October 2016
Accepted 8 December 2016
Available online xxx

Keywords:
Anovulatory infertility
Individualised
Gonadotrophin
Ovulation induction

ABSTRACT

Objective: The aim of this study was to evaluate an individualised gonadotrophin starting dose regimen for women with anovulatory infertility.
Study design: We included 71 normogonadotrophic anovulatory infertile women in a prospective, observational study. All underwent one ovulation induction cycle in a flexible, low-dose step-up protocol. The gonadotrophin starting dose (75–150 IU/day) was individualised according to a nomogram incorporating menstrual cycle pattern (oligo- or amenorrhoea), BMI, and mean ovarian volume. The number of women who fulfilled the criteria for human chorionic gonadotrophin (hCG) administration (one follicle ≥17 mm or 2–3 follicles ≥15 mm) was assessed.
Results: Of the 50 women (70.4%) who fulfilled the hCG criteria and underwent intrauterine insemination, 34 (47.9%) achieved monofollicular growth and 16 (22.5%) developed 2–3 mature follicles. Seventeen (23.9%) cycles were converted to *in vitro* fertilisation (IVF) due to the development of >3 mature follicles, and one (1.4%) cycle was cancelled due to risk of ovarian hyperstimulation syndrome. Baseline total antral follicle count was found to be significantly associated with fulfillment of the hCG criteria (OR 0.96, 95% CI: 0.92–0.99, $P = 0.01$).
Conclusions: The nomogram-based dose regimen was not considered suitable for ovulation induction due to a tendency to overestimate the gonadotrophin starting dose. However, the model may serve as a mild IVF regimen, especially in women prone to excessive follicle growth.

Introduction

In normogonadotrophic anovulatory infertility, the aim of treatment is to achieve monoovulation by indirect or direct stimulation of the ovaries [1,2]. The low-dose step-up protocol remains the gold standard for ovulation induction with gonadotrophins, implying a low risk of multifollicular growth [3,4]. However, the step-up approach may sometimes result in prolonged treatment periods or cancelled cycles when the starting dose of gonadotrophins is much lower than the individual FSH threshold of the most sensitive follicle [4]. Step-down protocols, mimicking more closely the natural cycle, have been introduced [5,6] but may induce hyperresponse in some women [7].

In recent years, ovulation induction treatment strategies have focused on a more patient-tailored approach [8]. In a study of 90 WHO Group II anovulatory infertile women, Imani et al. [9] developed a model to predict the individual gonadotrophin threshold dose based on baseline FSH, free IGF-1, BMI and previous response to clomiphene citrate. However, the model was considered insufficiently accurate for clinical use [10]. Nyboe Andersen et al. [11] retrospectively assessed the response to gonadotrophin treatment in 151 anovulatory infertile women. The study showed that women with amenorrhoea, increased BMI and increased

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http://dx.doi.org/10.1016/j.ejogrb.2016.12.010
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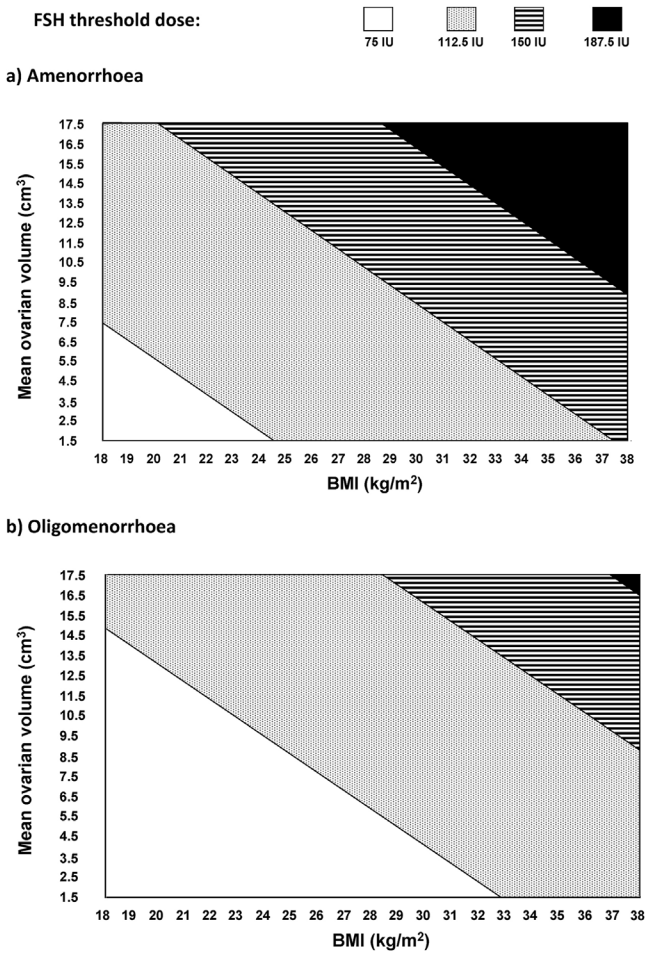

Fig. 1. Nomograms for prediction of individual FSH threshold dose in anovulatory patients undergoing ovulation induction with FSH preparations, according to menstrual cycle history, BMI and mean ovarian volume; a) amenorrhoea; b) oligomenorrhoea. This figure was originally published in Nyboe Andersen et al., [11]. ©The Author 2008.

ovarian volume may require higher doses of gonadotrophins to achieve follicle growth. Thus, nomograms for the prediction of the FSH threshold dose were constructed based on menstrual cycle pattern (oligo- or anovulation), BMI and mean ovarian volume (Fig. 1). In the present prospective study, we aimed to evaluate the clinical applicability of these nomograms.

Materials and methods

Study design

This prospective, observational study was carried out at the fertility units at Copenhagen University Hospital Rigshospitalet and Holbæk Hospital, Denmark, between 2010 and 2012. Women referred for treatment due to normogonadotrophic, anovulatory infertility were consecutively recruited in the study (Fig. 2). In total, 71 women with a mean (SD) age of 29.7 (±3.3) years were included. All but five women (93.0%) fulfilled the Rotterdam criteria for polycystic ovary syndrome due to the presence of polycystic ovaries and chronic anovulation [12].

The study was restricted to women with amenorrhoea (absence of bleeding for >6 months) or oligomenorrhoea (mean cycle length >35 days for >6 months), age 18–39 years, BMI 18–35 kg/m^2, early follicular phase serum FSH levels <10 IU/l, levels of prolactin and total testosterone not suggestive of hyperprolactinaemia or androgen-secreting tumours, and a male partner with a semen sample acceptable for intrauterine insemination or semen from a donor. In case of previous pelvic inflammatory disease or pelvic surgery, tubal patency was documented by either X-ray hysterosalpingography or hystero-salpingo contrast sonography.

Excluded were women with a history of >3 previous, unsuccessful gonadotrophin ovulation induction cycles at other fertility clinics or previous ovulation induction with gonadotrophin threshold doses <75 IU/day or women receiving any kind of hormonal treatment except for thyroid medication.

Power calculation

The sample size calculation was based on comparison with a fixed-dose (75 IU/day) highly purified human menopausal gonadotrophin (HP-hMG) ovulation induction study in which 50% of the women presenting with amenorrhoea or oligomenorrhoea fulfilled the hCG criteria within 14 days [13]. Assuming that the nomogram-based dose regimen could increase this proportion to 75% in a similar study population, at least 60 patients were required to achieve 80% power at a two-sided 5% significance level.

Screening procedure

Baseline clinical, sonographic and endocrine characteristics were assessed in all women after a 4 week hormonal treatment wash-out. Gynaecological and reproductive history, medication, blood pressure, body mass index (BMI), waist and hip circumference were recorded. Hirsutism was assessed according to the modified Ferryman-Gallwey score [14]. A modified Ferryman-Gallwey score ≥8 was regarded indicative of androgen excess. The endometrial thickness was measured and each ovary was scanned to count the total number of antral follicles measuring 2–9 mm [15]. The ovarian volume (0.52 × length × width × thickness) was calculated as the mean value of the left and right ovary volumes. All ultrasound examinations were performed by trained physicians using a Pro Focus ultrasound scanner with a 4–9 MHz transducer (BK Medical, Denmark).

Fasting blood samples were drawn measuring serum levels of AMH, FSH, oestradiol (E_2), luteinizing hormone (LH), progesterone, glucose, insulin, haemoglobin A1C (HbA1c), prolactin, total testosterone (T), androstenedione, sex hormone-binding globulin (SHBG), free T, dihydroepiandrosterone sulphate (DHEAS), and 17-hydroxyprogesterone (17-OHP).

Endocrine analyses

All hormone analyses except analyses of androgens were performed at the Department of Clinical Biochemistry at Rigshospitalet, Copenhagen, or at Holbæk Hospital, Denmark. Serum AMH levels were exclusively analysed at Rigshospitalet and determined in duplicate by enzyme-linked immunosorbent assay using the AMH/MIS kit (Immunotech, Beckman Coulter, Marseilles, France). E_2, insulin, progesterone, FSH and LH were determined by electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Fasting glucose was measured by enzymatic absorption photometry (Roche Diagnostics, Mannheim, Germany), HbA1c by liquid chromatography (Tosoh Medics, Inc., San Francisco, USA) and prolactin by immunofluorescent assay (BRAHMS, Hennigsdorg, Germany). Androgen levels were measured at the Department of Clinical Biochemistry and Immunology, Statens Serum Institute, Copenhagen, Denmark. Total T, androstenedione, DHEAS, and 17-OHP were determined by tandem mass spectrometry and SHBG by immunofluorimetric assays. Free T was calculated from total T and SHBG [16].