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Timing of ovarian stimulation in patients prior to gonadotoxic therapy: an analysis of 684 stimulations☆

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ABSTRACT

Objective: Time to therapy initiation in patients requiring gonadotoxic therapy is crucial. This article evaluates the efficiency of random start ovarian stimulation in affected women.
Study design: Retrospective anonymous registry data analysis from 85 university and non-university fertility centres participating in the international network FertiPROTEKT. The study comprised 684 women undergoing ovarian stimulation for fertility preservation from 2007 to 2013. According to the time of stimulation initiation, days of ovarian stimulation, total dose of gonadotropins used, gonadotropin dose used per day, number of oocytes retrieved and incidence of ovarian hyperstimulation syndrome were analysed. Statistical analysis was performed using analysis of variance in case of continuous outcome variables and chi-square tests in case of categorical variables.
Results: Among 684 women who underwent ovarian stimulation prior to gonadotoxic therapy 472 (69.0%) started ovarian stimulation between menstrual cycle day 1–5 (group A), 109 (15.9%) between day 6–14 (group B) and 103 (15.1%) after day 14 (group C). The days of stimulation (A: 10.8 ± 2.4, B: 10.6 ± 2.7, C: 11.5 ± 2.2) and total dose of gonadotropins (A: 2496 IU ± 980, B: 2529 IU ± 940, C: 2970 IU ± 1145) were significantly increased in group C. Numbers of obtained oocytes (Group A: 11.6 ± 7.7, B: 13.9 ± 9.1, C: 13.6 ± 7.9) were significantly increased in group B and C, while the overall incidence of ovarian hyperstimulation syndrome III° was 0.15%.
Conclusion: The outcome of ovarian stimulation is similar after stimulation initiation during any phase of the menstrual cycles, supporting the concept of random-start ovarian stimulation before gonadotoxic therapy without disadvantage for the patient concerning later fertility preservation.

Introduction

Fertility preservation techniques are increasingly offered to women before gonadotoxic therapy. Besides cryopreservation of ovarian tissue and application of gonadotropin releasing hormone (GnRH) agonists, ovarian stimulation has become one of the fertility preservation standard therapies following the introduction of the vitrification technique which allows cryopreservation of unfertilised oocytes with high implantation potential [1]. In breast cancer and lymphoma patients, which contribute to around 2/3 of all counselled women (Fertiprotekt) [2], gonadotoxic therapies can be postponed in many cases to allow time-optimized single ovarian stimulations or even two consecutive ovarian stimulation cycles [3], as well as stimulations in combination with cryopreservation of ovarian tissue [4]. Such time-optimized stimulations are based on the concept that ovarian stimulations can be initiated at any time of the cycle.

Accordingly, in 2009 we introduced a new treatment protocol which allowed stimulation start in the luteal phase and thereby shortened the treatment time [5], as initiation of ovarian stimulation was cycle independent. This concept has since also been analysed by others: Case reports and studies with limited number of participants [6–8] have supported this idea as part of

☆ The study was conducted in Bern, Switzerland and Heidelberg, Germany.
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fertility preservation treatments. Furthermore, two studies involving infertility patients have further supported this treatment option [9,10].

However, a large series of cases involving many different fertility preservation centres, reflecting the realistic situation in nationwide fertility preservation programmes and stimulations in all different phases of the menstrual cycle, is still needed to prove this concept of random-start controlled ovarian stimulation.

We therefore analysed 684 stimulation cycles, registered at the international network FertiPROTEKT (www.fertiprotekt.com) from its implementation in 2007 until 2013, performed by 85 centres in Germany, Austria and Switzerland, all working according to the network's recommendations [2].

Material and methods

This study was based on a retrospective data analysis of the *Ferti*PROTEKT registry. The network was founded in 2006 to offer fertility-preserving techniques, initially in German university fertility centres but then also including private fertility centres and neighbouring German-speaking countries such as Austria and Switzerland. The aim was to scientifically evaluate and improve the techniques and make them part of oncological treatment protocols.

The network's registry includes anonymously reported details of fertility preservation treatments before gonadotoxic therapies, complications and pregnancies. 85 infertility centres provide questionnaires about basic patient information such as age, disease, type of oncological therapy, etc., and details about the fertility preservation therapy chosen. In case of ovarian stimulation, the type of ovarian stimulation protocol, gonadotropin dosage, number of collected oocytes, fertilisation technique, number of fertilised oocytes, and incidence of ovarian hyperstimulation syndrome are documented.

Data from all 5159 documented women, who were counselled between 2007 and 2013, were screened. 809 women who underwent controlled ovarian stimulation to cryopreserve oocytes or zygotes before gonadotoxic therapies for malignant or non-malignant reasons were identified. Among those, complete data sets were available in 684 cases. These women were divided into three groups, according to the day of stimulation initiation: Proliferative phase stimulation started on day 1–5 of the menstrual cycle in group A (conventional stimulation start) day 6–14 in group B and luteal phase stimulation after day 14 in group C. Initiation of stimulation depended on the day of the menstrual cycle on which women were counselled and on the given time frame for fertility preservation therapies provided by the oncologists. All women underwent antagonist protocols to reduce the risk of ovarian hyperstimulation syndrome. Ovarian stimulation was performed with either recombinant FSH or HMG, provided by national providers such as Merck Serono (Darmstadt, Germany), MSD (Merck Sharp & Dohme GmbH, Haar, Germany), Ferring Arzneimittel GmbH (Kiel, Germany) and IBSA Institut Biochimique SA (Lugano, Switzerland). For LH-downregulation, the GnRH antagonists (GnRHant) Cetrotide® (Merck Serono) or Orgalutran® (MSD Merck Sharp & Dohme GmbH) were used.

All physicians were advised to stimulate patients according to the FertiProtekt guidelines [11].

For conventional stimulation (group A) common antagonist protocols were recommended, starting gonadotropin stimulation not later than day 5 of the menstrual cycle and GnRHant on day 6–7 of gonadotropin stimulation. For initiation of stimulation in the mid-late proliferative phase (group B), the same protocol as in group A was recommended, but women needed to be re-evaluated earlier to avoid a premature LH surge and start antagonists as soon as one follicle reached 14 mm. If the leading follicle was already 14 mm or larger, ovulation induction was recommended followed by luteal phase stimulation, as described below. For luteal phase stimulation, our previously published luteal phase stimulation protocol was recommended [5]. In brief, controlled ovarian stimulation, using both recombinant FSH and GnRHant, were initiated in parallel at any time of the luteal phase.

Data of the individual groups was analysed according to patients' characteristics, days of stimulation, total and daily gonadotropin dosage used for stimulation, incidence of ovarian hyperstimulation syndrome (OHSS) III°, number of oocytes collected and cryopreserved oocytes and zygotes.

Institution review board permission was not required due to the analysis of anonymized registry data.

Statistics

SAS 9.1 WIN (SAS Institute, Cary, NC, USA) software was used for all statistical calculations. Data were presented as mean and standard deviations in case of continuous data, and as absolute and relative frequencies in case of categorical data. Possible differences between groups were evaluated with analysis of variance in case of continuous outcome variables, with chi-square test in case of categorical variables. Level of significance alpha was set to 5%.

Results

809 women were identified who underwent controlled ovarian stimulation. 684 data sets were complete and were further analysed (Table 1). Of these, 472 (69.0%) were in group A, 109 (15.9%) in group B and 103 (15.1%) in group C.

The mean age was 29.5 ± 5.8 years. 311 (45.5%) had breast cancer, 194 (28.4%) Hodgkin's lymphoma, 151 (22.1%) other malignant diseases and 28 (4.1%) benign diseases (Table 1).

While women with benign diseases were nearly exclusively presented in group A, women with malignant diseases requiring therapy initiation without delay were more commonly presented in group B and C. In group C 50.5% of women were diagnosed breast cancer and 31.1% Hodgkin's lymphoma, in group B 48.6% and 32.1% and in group A 43.6% and 26.9%, respectively. Additional fertility preservation techniques used were co-treatment with GnRH agonists in parallel to the chemotherapy in 329 (48.1%), cryopreservation of ovarian tissue in 54 (7.9%) and transposition of the ovaries in 3 (0.4%) cases. 265 (38.7%) women cryopreserved only oocytes, 341 (49.9%) only zygotes and 56 (8.2%) both oocytes and zygotes (Table 1). Embryos were not cryopreserved, mainly due to the restrictive embryo protection law in Germany and Switzerland.

The total gonadotropin stimulation dosage was significantly higher in group C (2970 IU) versus group A (2496 IU) and B (2529 IU) (Table 2). This was firstly due to a slightly prolonged stimulation time of 11.5 days in group C, versus 10.8 days in group A, and 10.6 days in group B, and secondly due to a higher gonadotropin dosage used per day in group C (258 IU) versus group A (231 IU) and group B (239 IU). The overall cancellation rate was 0.9% and did not reach statistical significance with 0.6% in Group A, 0.91% in group B and 1.9% in group C. OHSS III° was only reported in one case (Group A). The number of oocytes obtained were significantly increased in group B and C compared to group A (13.6 ± 7.9, 13.9 ± 9.1 and 11.6 ± 7.7) (Table 2).

Discussion

Our study is the largest study to date, analysing the concept of random start stimulation as part of fertility preservation therapies. The stimulations were performed by 85 centres and the study