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Full length article

Ovarian response and follow-up outcomes in women diagnosed with cancer having fertility preservation: Comparison of random start and early follicular phase stimulation - cohort study

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ABSTRACT

Objectives: To determine response to controlled ovarian stimulation in a random start cycle and utilisation of cryopreserved oocytes and embryos in cancer patients.
Study Design: A retrospective cohort study was carried out in an assisted reproductive treatment centre. Participants included 137 cancer patients who underwent controlled ovarian stimulation for fertility preservation between 1 Feb 2003 and 30 June 2016. The primary outcome variable was number of oocytes retrieved. Multivariable logistic regression analysis was performed, and differences compared using Chi squared test and student *t*-test as appropriate. $P < 0.05$ was considered statistically significant.
Results: Using the antagonist protocol, there was no difference in number of oocytes retrieved between the early follicular phase or at random start stimulation; 11.9 (95% CI 10.3–13.5) and 12.9 (95% CI 9.6–16.2), $P = 0.602$, respectively. Similarly, the number of embryos frozen was comparable between those starting stimulation in early follicular and random phase, 6.7 (95% CI 5.7–7.7) and 5.1 (95% CI 3.6–6.5), P= 0.1508 respectively. Among patients undergoing fertility preservation, those who returned to attempt a pregnancy had an ongoing pregnancy rate of 24.3%. Overall, 65% of oocytes and embryos were still in storage, however, 16 (11.7%) had elected to have their oocytes or embryos disposed of.
Conclusion(s): For women faced with potential gonadotoxic treatment and requiring urgent fertility preservation, ovarian stimulation with the antagonist protocol can be started at random without compromising ovarian response. Pregnancy rates following utilisation of frozen-thawed oocytes and embryos are promising, however, more research is needed to understand reasons underlying disposition of oocytes and embryos especially when survival following cancer treatment has improved significantly.

Introduction

Over the past few decades developments in cancer treatment protocols have resulted in improved long-term survival of cancer patients, however, due to their variable gonadotoxicity these treatments may leave some survivors with severely compromised ovarian function [1]. Several studies show that women of reproductive age would like the opportunity to discuss fertility implications of their cancer diagnosis and treatment [2]. Although an increasing number of oncologists discuss fertility implications with patients, the overarching urgency to treat cancer implies that not all patients have the opportunity to explore fertility preservation [3]. Uniquely for women with hormone receptor positive breast cancer there is the additional challenge of having to take the anti-oestrogen tamoxifen for several years during which pregnancy is contraindicated. Since natural fertility declines with age, any compromise in ovarian function may only become apparent when trying for a pregnancy years later after completing tamoxifen therapy [4,5].

Opportunities for fertility preservation prior to gonadotoxic treatment include: vitrification of oocytes and/ or embryos, ovarian tissue cryopreservation and concomitant administration

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of gonadotropin releasing hormone agonist (GnRH-a) with chemotherapy [6]. Offering a combination of these methods is recommended as a means of maximizing patients' chances of future fertility, rather than choosing one only. Cryopreservation of oocytes or embryos requires a woman undergoes a cycle of controlled ovarian stimulation using either of various protocols [7]. The long agonist protocol is less favoured now as it requires a longer duration of treatment due to initial pituitary down-regulation and has a higher risk of ovarian hyperstimulation syndrome (OHSS) [8]. Conversely, the antagonist protocol is devoid of initial pituitary down regulation and has a lower risk of OHSS, rendering it the preferred protocol for fertility preservation programmes [9].

Initiation of ovarian stimulation usually starts in the early follicular phase of the menstrual cycle based on the long-held view that recruitment of selectable follicles happens in this phase. However, observations made in animals as well as humans challenge this theory by demonstrating a continuous growth of antral follicles throughout the oestrous/menstrual cycles [10–12]. This was the basis of reports indicating that ovarian stimulation started in the luteal had a comparable number of mature oocytes and embryo development to early follicular start [13]. This enabled development of random start ovarian stimulation protocols for cancer patients who require urgent treatment [14]. The described random-start protocols are complex therefore there is a need for a more simplified approach.

This study aimed to establish whether response to controlled ovarian stimulation was comparable between random start, early follicular and luteal phase antagonist cycles in women needing urgent fertility preservation using a simplified protocol. Secondary outcomes included adverse events and the outcome of cryopreserved oocytes and/ or embryos.

Materials and methods

Study population

We undertook a comprehensive analysis of clinical data that is prospectively entered and stored in a database (Paradox, Borland, Scott Valley, CA, USA) at Oxford Fertility. All patients recently diagnosed with cancer and referred for fertility preservation between Feb 1, 2003 and June 30, 2016 were included in this retrospective cohort study. Approval was sought from the University of Oxford Central University Research Ethics Committee.

Treatment protocol

After a fertility specialist medical consultation, patients attend nurse treatment planning appointment as soon as possible. Treatment initiation starts immediately after this planning on the agreement of the oncologist.

The conventional antagonist protocol at Oxford Fertility during the period of the study was as follows. On day two to five of the menstrual cycle, daily ovarian stimulation with gonadotrophin (recombinant gonadotrophin alpha - Gonal F®, Serono Pharmaceuticals Ltd., Feltham, UK; Puregon®, Organon Laboratories Ltd., Hoddesdon, UK, or Menopur®, Ferring Pharmaceuticals Ltd., West Drayton, UK) was commenced. After five days of stimulation, cetrorilex acetate 250-mcg subcutaneous injection (Cetrotide®, Serono Pharmaceuticals Ltd, Feltham, UK) was introduced and continued until human chorionic gonadotrophin or buserelin for final oocyte maturation was administered. Monitoring follicle development with transvaginal ultrasound scanning and serum oestradiol started after the sixth day following the initiation of stimulation. When at least three follicles measuring ≥18 mm were seen on ultrasound scan, human chorionic gonadotropin (hCG) 6500 IU (Ovitrelle®; Serono Pharmaceuticals Ltd., Feltham, UK) or buserelin 0.5 mg was administered subcutaneously for final oocyte maturation 37 h prior to oocyte-cumulus complex retrieval. The practice was to aspirate from all follicles measuring ≥12 mm. Oocytes were then stripped clear of the cumulus cells within two hours of oocyte retrieval for women choosing oocytes vitrification, whereas those opting to freeze embryos micro-injection of oocytes with sperm was done after four hours. Fertilisation check followed 16 h from oocyte microinjection.

The random start protocol was used if stimulation started at any point after menstrual day five. It involved administration of cetrorilex acetate 250 mcg (Cetrotide®, Serono Pharmaceuticals Ltd, Feltham, UK) for three days followed by ovarian stimulation with gonadotrophin from the fourth day. The cetrorilex acetate was continued together with the gonadotrophin stimulation until ovarian response was deemed appropriate for HCG or buserelin administration as described above. Follicle growth monitoring was as for the conventional antagonist protocol starting after six days of stimulation.

Gonadotrophin dose determination

The starting dose of gonadotrophins was based on female age, body mass index (BMI), antral follicle count or anti-Mullerian hormone (AMH) concentration. Patients were stimulated on a dose ranging from 150 IU to 375 IU of Gonal-F® or Menopur®.

Outcome measures

The primary outcome measure was the number of oocytes retrieved per started cycle. We also analysed the duration from referral to oocyte retrieval; starting and total dose of gonadotrophin; duration of ovarian stimulation; number of follicles measuring ≥15 mm and peak oestradiol concentration at the time of HCG or buserelin trigger; number of fertilised oocytes and number of oocytes or embryos put in storage. For the oocytes and embryos cryopreserved, we computed those remaining in storage at the time of our analysis and determined fate of the rest. We also assessed immediate complications following oocyte retrieval.

Statistical analysis

For categorical variables, we calculated percentages and compared differences using the Chi-squared or Fisher's exact test as appropriate. For the continuous variables, we calculated their mean and compared differences using the Students *t*-test. All statistical analysis was performed in statistical software STATA® version 12 (College Station, TX, USA). *P* value <0.05 was considered significant.

Results

Baseline characteristics

We reviewed 137 records of patients who presented for fertility preservation prior to starting gonadotoxic treatment between February 1, 2003 and June 30, 2016. Nine of these had the long agonist protocol and were excluded from analysis of the main outcome variables. The remaining 127 women were on the antagonist protocol (103 in the conventional start group and 24 in the random start group). The baseline characteristics of the women on the antagonist protocol are shown in Table 1. There were no statistically significant differences in baseline characteristics of women in the two treatment groups. The mean age for women in the groups was similar, with age ranging between 18.5–