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Prospective assessment of follicular growth and the oocyte cohort after ovarian stimulation for fertility preservation in 90 cancer patients versus 180 matched controls

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KEY MESSAGE

This prospective study confirms that fewer metaphase II oocytes are retrieved after ovarian stimulation in young cancer patients compared with healthy controls, despite the same pattern of follicular growth and same number of total oocytes. Cancer disease may be involved in oocyte quality and maturation impairment.

A B S T R A C T

A lower number of metaphase II oocytes eligible for vitrification after controlled stimulation in cancer patients has recently been reported, suggesting that cancer may impair the dynamics and quality of follicular growth. In this prospective, non-interventional study, the pattern of follicular growth and oocyte cohort after ovarian stimulation in cancer patients was analysed. Ninety cancer patients, recruited before starting chemotherapy, were

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compared with 180 time- and age-matched healthy controls undergoing intracytoplasmic sperm injection. Primary outcome was total number of metaphase II oocytes and metaphase II /total oocytes rate. Basal anti-Müllerian hormone levels ($P < 0.05$) and antral follicle count ($P < 0.0001$) were significantly lower in cancer patients. Recombinant FSH total dose was significantly higher in the cancer group ($P < 0.0001$). No differences were found in duration of stimulation, mean number of mature follicles on day of ovulation induction and total oocyte number after retrieval; the number of metaphase II oocytes retrieved (6.2 ± 4.7 versus 8.8 ± 4.2; $P < 0.0001$) and number of metaphase II oocytes–total oocytes ratio were significantly lower in cancer patients (56% versus 78%, $P < 0.0001$). Fewer metaphase II oocytes were eligible for vitrification and lower maturation rate in the cancer group.

Introduction

The development of fertility-preservation techniques is becoming more challenging because cancer incidence and survival rates in young patients are continuously increasing (Torre et al., 2015). Mature oocyte cryopreservation is one of the preservation options as it is no longer considered as an experimental technique. Indeed, many improvements have been made in oocyte cryopreservation over the past decade owing to the vitrification process, with results now nearly similar to those of fresh oocytes, at least in egg donation programmes (Cobo and Diaz, 2011; Cobo et al., 2015; Rienzi et al., 2010, 2017) Furthermore, data on safety are reassuring (Cobo et al., 2014; Edgar and Gook, 2012; Noyes et al., 2009). According to The American Society for Reproductive Medicine and The American Society of Clinical Oncology, oocyte cryopreservation can be proposed as a standard technique for fertility preservation in young adults (Loren et al., 2013; Practice Committees of American Society for Reproductive Medicine and Society for Assisted Reproductive Technology, 2013), whereas ovarian tissue cryopreservation remains the best option in prepubertal girls, when no delay between cancer diagnosis and chemotherapy occurs (Donnez and Dolmans, 2013), or both.

Data on the pattern of ovarian response and oocyte quality after ovarian stimulation in this specific group of cancer patients are limited. To date, only retrospective comparative studies have been published (Almog et al., 2012; Cardozo et al., 2015; Das et al., 2011; Johnson et al., 2013; Klock et al., 2010; Knopman et al., 2009; Noyes et al., 2010; Quinn et al., 2017; Quintero et al., 2010; Robertson et al., 2011), often comparing a group of cancer patients with a historical control group and then providing conflicting results. Some of them showed lower levels of basal anti-Müllerian hormone (AMH) in cancer patients even before chemotherapy (Lawrenz et al., 2012), higher incidence of low ovarian response under ovarian stimulation for fertility preservation, or both (Klock et al., 2010; Robertson et al., 2011; Domingo et al., 2012; Friedler et al., 2012; Lawrenz et al., 2012), whereas another showed no difference (Almog et al., 2012; Das et al., 2011; Johnson et al., 2013; Knopman et al., 2009; Noyes et al., 2010; Quintero et al., 2010). More recent studies, conducted in larger series of patients, highlight a lower metaphase II–total oocytes ratio after retrieval in cancer patients, suggesting that the disease could impair the dynamics and quality of follicular growth under ovarian stimulation (Domingo et al., 2012; Friedler et al., 2012; Garcia-Velasco et al., 2013).

In a study by Rienzi et al. (2012), more than eight metaphase II oocytes were needed to provide 45% of delivery rates in patients younger than 38 years undergoing IVF and intracytoplasmic sperm injection (ICSI). These results were recently confirmed by Cobo et al. (2016) in a population of women who vitrified their oocytes for age or medical reasons other than cancer, with 41% achieving a live birth rate when eight oocytes were used in patients younger than 35 years, with a gain of 8.4% per additional oocyte. Hence, the efficiency of fertility preservation by oocyte cryopreservation is highly questionable. This is because ovarian stimulation before chemotherapy is often complicated, in some cases impossible to organize, sometimes expensive for patients and its safety remains to be confirmed.

Considering the paucity of studies on this specific topic, we aimed to design a prospective comparative study to investigate the pattern of follicular growth and to better characterize the outcome of ovarian stimulation in oocyte number and maturity. To further strengthen the statistical power of the analysis, cancer patients were compared with two concurrently treated and age-matched controls who underwent their first ICSI attempt.

Materials and methods

Study design

This was a prospective, non-interventional study carried out in the Academic IVF and Fertility Preservation Centre of Lille University Hospital, France. It was approved by the local Ethics Committee on 9 July 2011 (IORG0009553; HP16/50). Written, informed consent was obtained from cancer and control patients before inclusion and before starting ovarian stimulation.

Patients and controls

Ninety patients (mean age 29 ± 5 years [range 18–38 years]) were prospectively recruited from September 2011 to December 2014 before starting chemotherapy for breast cancer as adjuvant treatment, or for haematological malignancies or solid tumours at the Fertility Preservation Centre of Lille University Hospital (**Figure 1**). Inclusion criteria were age 38 years or younger, presence of two ovaries, absence of thrombo-embolic events and sufficient time to start ovarian stimulation on day 2 without delaying chemotherapy for more than 2 weeks. Exclusion criteria were patients with suspected uptake at positron emission tomography scan (excluding haematological malignancies) and breast cancer patients who required chemotherapy before surgery (neo-adjuvant situation).

A total of 180 healthy controls who underwent their first IVF–ICSI treatment for male infertility, and who were matched by age (+/–1 year) and by date of stimulation (within 1 month) were concomitantly recruited. They were selected to give a control-to-study patient ratio of 2:1. For both controls and patients, an ovarian reserve assessment was systematically carried out before starting ovarian stimulation by measuring the serum AMH level and determining the

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