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Ovarian reserve and response to stimulation in women undergoing fertility preservation according to malignancy type

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KEY MESSAGE
The type of cancer did not significantly affect ovarian reserve and ovarian response to ovarian stimulation in women undergoing oocyte vitrification cycle for fertility preservation.

A B S T R A C T

Research Question: Does ovarian reserve and ovarian response to ovarian stimulation in women with cancer undergoing oocyte vitrification for fertility preservation vary according to the type of malignancy?

Design: Retrospective cohort study including 105 women aged between 18 and 40 years, who were referred for fertility preservation (oocyte vitrification) between 2013 and 2016. The women were divided into three groups: breast cancer, lymphoma or other cancer. All of them had been recently diagnosed with cancer, with gonadotoxic treatment scheduled, and had oocyte vitrification after ovarian stimulation with antagonist protocol.

Results: Baseline antral follicle count and anti-Müllerian hormone were no different between women with breast cancer, lymphoma or other cancer. The number of cancelled cycles for poor ovarian response was similar between the groups. The number of FSH units per mature oocyte, the number of mature oocytes (metaphase II) retrieved, and the oocyte maturity rate were not significantly different between the three groups.

Conclusions: As the type of cancer does not seem to significantly affect ovarian reserve and ovarian response to ovarian stimulation, our results do not support the relevance of integrating this parameter when establishing ovarian stimulation protocol for oocyte vitrification cycle in women with cancer.

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Introduction

The National Cancer Institute in France reported that, in 2015, about 10,000 out of 174,000 newly diagnosed cancers occurred in women of childbearing age (Institut National du Cancer, 2017). Breast cancer, melanoma, cervical cancer and lymphoma represent the most common cancers in reproductive-aged women. Early diagnosis, intensive treatment and, more recently, oncology care, often provide a relatively good prognosis and improved survival for young patients (Institut National du Cancer, 2017). Most of these women of reproductive age with cancer look ahead to childbirth after treatment; however, many of them are faced with a significant risk of treatment-induced ovarian failure. Indeed, cancer management can affect fertility through direct gonadotoxicity of treatments, such as chemotherapy, and because of the long safety period after cancer treatment before a pregnancy can be considered (owing to risk of relapse and teratogenicity of treatments) (Bénard et al., 2016). Therefore, fertility preservation has become increasingly important for the subsequent quality of life of female (and male) cancer survivors of reproductive age.

According to the 2006 American Society of Clinical Oncology international guidelines (Loren *et al*, 2013), any patient scheduled for potential gonadotoxic treatments should be informed of the risks of infertility and the methods available for fertility preservation. Various strategies have been developed for female fertility preservation, including cryopreservation of ovarian cortex or oocyte vitrification after ovarian stimulation (Bénard et al., 2016). The choice between these options should depend on age, puberty stage, social status, ovarian reserve, type of cancer, type of treatment scheduled (molecules, doses, gonadotoxicity), available time before the onset of treatment, and, obviously, the patient's decision.

Embryo cryopreservation has recently been supplanted by oocyte vitrification with comparable success rates (Bénard et al., 2016). Oocyte vitrification allows over 90% oocyte survival rate and a comparable pregnancy rate to those obtained with fresh oocytes (Cobo et al., 2010). Data on obstetric outcomes and incidence of congenital defects among children born from vitrified oocytes are reassuring (Noyes et al., 2009) and comparable to children conceived with fresh oocytes (Cobo et al., 2014) This provides sufficient scientific proof of the efficiency and safety of this method for its use in clinical practice (Practice Committees of American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, 2013).

Negative effects of cancer treatment on fertility have been widely studied, but potential adverse effects of the cancer itself remain mostly unknown. It has been reported that malignancy itself could have deleterious effects on male fertility with qualitative and quantitative abnormalities of sperm, irrespective of treatment (Rueffer et al., 2001). On the female side, the deleterious role of cancer on ovarian function, as reflected by ovarian reserve or ovarian response to ovarian stimulation, remains unclear. Although not predictive of spontaneous fertility (Hagen et al., 2012), anti-Müllerian hormone (AMH) and antral follicle count (AFC) are currently the best ovarian reserve markers (Broekmans et al., 2006; La Marca et al., 2010). Whether cancer itself affects ovarian reserve remains controversial. Some studies have also reported lower ovarian response to ovarian stimulation in women with cancer compared with controls (Domingo et al., 2012; Friedler et al., 2012; Klock et al., 2010; Quinn et al., 2017); however, this has been refuted by others (Almog et al., 2012; Das et al., 2011; Knopman et al., 2009; Michaan et al., 2010; Noyes et al., 2010; Quintero et al., 2010; Robertson et al., 2011). Only two studies have evaluated the potential effect of the type of malignancy on ovarian response to ovarian stimulation (Alvarez and Ramanathan, 2016; Pavone et al., 2014), but with heterogenous stimulation protocols and without assessment of baseline ovarian reserve.

Our objective was to evaluate ovarian reserve, as reflected by serum AMH and AFC, and ovarian response to ovarian stimulation in women recently diagnosed with cancer, undergoing oocyte vitrification cycle, according to the type of malignancy.

Materials and methods

Population

Women aged between 18 and 40 years referred for fertility preservation by oocyte vitrification between January 2013 and December 2016 were included in this retrospective cohort study. All of them had just been diagnosed with cancer, with gonadotoxic treatment scheduled within 3–4 weeks. This study was approved by the Ethics Committee in University Hospital of Nantes (GNEDS) on 15 February 2017. Oocyte cryopreservation has always been the preferred option to embryo cryopreservation, even for married couples. Therefore, a selection bias towards young unmarried women is unlikely in our population.

Women were divided into three groups according to cancer type: breast cancer, lymphoma, and other solid cancers. Exclusion criteria were age younger than 18 years or over 40 years; history of oophorectomy or ovarian surgery; history of infertility management; history of gonadotoxic treatments and fertility preservation related to other indications (premature ovarian failure, history of oophorectomy or repeated ovarian surgery or gonadotoxic treatments, non-medical fertility preservation). Each patient underwent a clinical examination and was asked about average menstrual length (women with hormonal contraception were asked about menstrual length before taking contraception). They also underwent an endovaginal ultrasound (Siemens Acu X150) for AFC, and serum AMH measurement. Serum AMH levels were measured with the enzyme immunoassay AMH-EIA from Beckman Coulter Immunotech (Marseilles, France), from January 2013 to November 2015; then by automated electrochemiluminescence assay (Elecsys AMH assay, Roche Diagnostics, Rotkreuz, Switzerland). Each woman underwent ovarian stimulation with an antagonist protocol with conventional start in follicular phase or random-start in luteal phase. Human menopausal gonadotrophin (HMG) (Menopur®, Ferring Pharmaceuticals, Saint-Prex, Switzerland), or recombinant FSH (Gonal® F, Merk-Serono; Puregon®, MSD, New Jersey, USA) was used for ovarian stimulation. Gonadotrophin starting dose was chosen according to age, weight and ovarian reserve. All women with breast cancer had a daily co-treatment with anti-oestrogen (tamoxifen 60 mg, Astra Zeneca, Cambridge, UK), as this indication of letrozole is not permitted in France (Oktay, 2005). When ovarian response was considered optimal, ovulation was triggered by injection of either recombinant HCG (250 µg sub-cutaneous of Ovitrelle®, Merck Serono, Geneva, Switzerland) or GnRH agonist (0.2 mg of Decapeptyl®, Ipsen Pharmaceuticals, Paris, France). Oocyte retrieval was carried out 36 h after ovulation triggering. All cumulus–oocyte complexes were cultured for 2 h before denudation with hyaluronidase (Synvitro hyadase, Origio, Måløv Denmark). All mature oocytes were then vitrified with either Irvine® or Vitrolife® oocyte vitrification kit.

The outcome measures were the number of mature oocytes (MII) retrieved, the number of FSH units per mature oocyte, oocyte maturity

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