European Journal of Cancer (2015) **51**, 1490–1496

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome

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Received 18 February 2015; received in revised form 25 April 2015; accepted 5 May 2015
Available online 9 June 2015

KEYWORDS
Breast cancer
Infertility
Young women
Pregnancy
Assisted reproductive technology
Recurrence

Abstract ***Introduction and aims:*** We have previously shown that pregnancy is safe following breast cancer, even in endocrine sensitive disease. Yet infertility remains common following systemic treatment. To date, no study has evaluated the safety of assisted reproductive technology (ART) after breast cancer treatment. In this study, we evaluated the impact of ART on pregnancy and long-term outcomes of young breast cancer survivors.
Methods: This is a multi-centre retrospective study in which women who were diagnosed with breast cancer between 2000 and 2009, and had a pregnancy following breast cancer diagnosis were eligible. Patients were divided into two groups according to whether ART following primary systemic therapy was performed to achieve pregnancy. We evaluated the association between ART use and clinic-pathological characteristics, pregnancy outcome and long-term breast cancer outcome.
Results: A total of 198 patients were evaluated; of whom 25 underwent ART. No significant differences in tumour characteristics were observed between both groups, except for histological grade 3 tumours, which were fewer in the ART group (36% versus 59%, $p = 0.033$). Around 90% of patients received primary adjuvant chemotherapy and more than 50% had an endocrine sensitive disease. Patients in the ART group were older at diagnosis (31.4 versus

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http://dx.doi.org/10.1016/j.ejca.2015.05.007

33.7 years, $p = 0.009$), at conception (38 versus 35 years, $p < 0.001$), and experienced more miscarriages (23.5 versus 12.6%, $p = 0.082$). Full term pregnancies were achieved in 77% and 76% of the spontaneous and ART groups, respectively. Mean follow-up between conception and last follow-up was 63 and 50 months in the spontaneous and ART groups, respectively with no difference in breast cancer outcome observed between the two groups ($p = 0.54$).

Conclusion: Pregnancy using ART in women with history of breast cancer is feasible and does not seem to be detrimental to cancer outcome. Larger studies are needed to further confirm this observation.

1. Introduction

Breast cancer is the most frequent malignancy diagnosed in women, occurring in 6–10% of patients during reproductive age [1]. Thanks to advances in adjuvant therapy, recurrence and survival rates have greatly improved over the last decades [2]. Currently around 65–70% of young breast cancer patients are alive and free of distant relapse at 10-years following diagnosis [3]. Hence, we are currently more faced with the need to address quality of life issues of young breast cancer survivors, including the wish to start or complete their family [4].

Several studies and meta-analyses have addressed the safety of pregnancy following breast cancer [5–7]. More recently, a large study by our group has demonstrated for the first time the safety of this approach in women with endocrine-sensitive disease [8]. Moreover, early termination of pregnancy does not appear to reduce the risk of relapse [5,8]. However, current systemic therapies frequently impair patients' fertility albeit a large fraction of them recover their menstrual cycles after completing primary systemic therapy [9]. This results in physicians and patients enquiring into the feasibility and safety of using assisted reproductive technology (ART) in women with history of breast cancer, in order to conceive. To date, no single study has evaluated the impact of ART to achieve pregnancy on cancer outcome.

In this study, we evaluate for the first time the effect of using ART on recurrence and death rates in patients who were previously treated for breast cancer and became subsequently pregnant.

2. Patients and methods

Five European Oncological and Fertility Centers participated in this retrospective study: Institut Jules Bordet (Brussels), Erasme Hospital (Brussels), European Institute of Oncology (Milan), Macerata Hospital (Macerata) and Hospital Val d'Hebron (Barcelona) in addition to the Danish Breast Cancer Cooperative Group (DBCCG). Some of these patients were included in a previous study in which we evaluated the safety of pregnancy following endocrine receptor positive breast cancer. Yet data on ART were not available at the time [8]. This study was approved by the Ethics committees of all participating centres including Erasme Hospital, which acted as the central ethics committee (Approval number P2013/265).

2.1. Patient population

Eligible patients were women aged 18–45 years, who were diagnosed with primary non-metastatic breast cancer between 2000 and 2009 and subsequently became pregnant (Fig. 1). The cohort was divided into two groups according to whether pregnancies occurred spontaneously (Spontaneous Group) or after ART (ART Group). ART procedures included ovulation induction (clomiphene citrate, gonadotropins) associated with intercourse or intra-uterine insemination (IUI), controlled ovarian stimulation (COS) with gonadotropins for *in vitro* fertilisation (IVF) or intra-cytoplasmic sperm injection (ICSI), and egg donation. All ART procedures were performed after completion of standard adjuvant therapy. During the study period, none of the participating centres routinely offered oocyte or embryo cryopreservation before initiating primary systemic therapy for fertility preservation of young breast cancer patients.

2.2. Data collection

The databases of all participating centres and the DBCCG were screened. The patient's oncologist, gynaecologist or family doctors were contacted in order to complete the information on the oncological and pregnancy outcomes, if needed. Data were collected on clinico-pathological characteristics, breast cancer treatment (date of diagnosis, histological type, histological grade, tumour size, nodal status, endocrine receptor status, human epidermal growth factor receptor 2 (HER2) status, type of breast surgery, chemo- and endocrine therapies), fertility treatments (ovulation induction, ovarian stimulation for IVF and oocyte donation) and pregnancy-related information (age at conception, number of pregnancies, and pregnancy outcome). Patients with less than 12 months of follow-up after pregnancy were excluded.