Cryoconservation of Oocytes in a Patient with Breast Cancer and Intrauterine Early Pregnancy

Abstract

Case Report: A 38-year-old patient newly diagnosed with invasive ductal breast cancer wished to cryoconserv her unfertilised oocytes. Stimulation was started on the 26th day of her menstrual cycle with daily administration of 300 IE hMG s.c. and a GnRH antagonist (cetrorelix 0.25 mg s.c.). The patient additionally received an aromatase inhibitor during the first 5 days of stimulation (letrozole 5 mg p.o.). Induction of ovulation occurred on the 11th day of stimulation with hCG (10000 IE s.c.) and a GnRH agonist (triptorelin 0.2 mg s.c.). Seventeen oocytes were retrieved during follicle puncture and 11 were cryopreserved. Despite the administration of cetrotide (a GnRH antagonist) no luteolysis occurred during stimulation. A pregnancy test was therefore done on the 11th day of stimulation and the result was positive (β-HCG 3493 mIU/ml). Sonography showed an intrauterine pregnancy. The patient was in gestational week 5 + 0. The aspirated oocytes mostly showed a normal morphology (metaphase II) despite high progesterone levels during stimulation. The patient decided to terminate the pregnancy before starting adjuvant chemotherapy.

Conclusion: We describe the case of a patient who underwent stimulation for cryopreservation of oocytes during a spontaneous pregnancy conceived in the same cycle just before starting stimulation. Stimulation was done over a short period using a combination of a GnRH antagonist and an aromatase inhibitor to ensure the lowest possible estradiol levels. The quality of the oocytes does not appear to have been negatively affected by the high progesterone levels of early pregnancy.

Zusammenfassung


**Introduction**

As the survival rates of younger patients with oncological disease have continued to improve, there has been an increased awareness of the importance of maintaining fertility and fulfilling the wish of patients to have children. Preservation of fertility is particularly suitable for women with breast cancer, as hysterectomy is an essential part of surgical therapy to treat cervical, uterine corpus and ovarian cancer – except in younger patients with early stage disease and the wish to conceive. Around 5% of women carry a pregnancy to term after breast cancer. To what extent cytostatic therapy induces amenorrhea largely depends on patient age (< >40 years) and the cumulative dosage of cyclophosphamides [1].

There are a number of options available to protect fertility prior to starting chemotherapy: one option consists of ovarian stimulation with cryoconservation of fertilised or unfertilised oocytes. As it is highly effective and IVF and ICSI are extremely well researched technologies, this method is the option advocated by the fertility preservation network FertiPROTEKT. A number of different protocols can be used for stimulation.

Another option consists of cryoconserving ovarian tissue after laparoscopic removal. However, experience with this technique is very limited and only a few children have been born after re-transplantation [2]. The risk of metastasis after re-transplantation cannot be entirely excluded, even if there are as yet no reports of metastasis in humans after re-transplantation. In vitro maturation allows immature oocytes to be retrieved without or with only limited stimulation and the oocytes are then cultured to maturation prior to being cryopreserved. However, the reported fertility and pregnancy rates to date are distinctly lower.

GnRH analogues can have a protective effect during chemotherapy [3]. However, it is possible that GnRH analogues may reduce the impact of chemotherapy due to reduced tumour cell growth in hormone-dependent carcinomas. Outside clinical studies, the administration of a GnRH analogue for ovarian protection together with chemotherapy should only be done after discussing the option with patients with hormone receptor-negative tumours [4, 5].

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### Table 1

**Stimulation chart.**

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<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>10</th>
<th>11</th>
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### Case Report

A 38-year-old gravida II, para 0 was advised on fertility preservation after being newly diagnosed with invasive ductal breast cancer. The patient’s previous history included 1 miscarriage, 1 termination and adenitis. The patient reported that her cycles were regular (29–30/4) and that until the diagnosis of breast cancer she had used Cerazette® for contraception. The first meeting with the patient took place after mastectomy for invasive ductal breast carcinoma, stage pT2, pN2 (6/12), G2, L1, R0, M0, ER 10/12, PR 10/12, Her2neu 1+. Adjuvant chemotherapy was planned to start within two weeks.

The patient’s hormonal status on the 13th day of her menstrual cycle showed normal gonadotropin levels, and she was normoandrogenaemic and euthyreotic. Anti-Müllerian hormone levels were 4.04 ng/ml (normal range: 1.0–2.5 ng/ml), indicating a good ovarian reserve. The patient was informed in detail about all options for fertility preservation (cryoconservation of fertilised/ unfertilised oocytes, ovarian tissue banking, in vitro maturation, GnRH analogues). Because IVF/ICSI has been tested over many years and currently has the best prognosis for a successful future pregnancy, the patient opted for cryoconservation of oocytes. As the patient was not in a long-term relationship the plan was to cryoconserv unfertilised oocytes. As there was only a very short interval before starting chemotherapy, stimulation was started in the second half of the cycle on the 26th day of the patient’s cycle. The patient received 300 IE hMG s.c. daily and a GnRH antagonist (cetrorelin 0.25 mg s.c.) as well as an aromatase inhibitor (letrozole 5 mg p.o.) during the first 5 days of stimulation. Ovulation was induced on the 11th day of stimulation using hCG (10000 IE s.c.) and a GnRH agonist (triptorelin 0.2 mg s.c.) (Table 1). Surprisingly, no luteolysis occurred during stimulation despite the administration of a GnRH antagonist, and a pregnancy test was done on the 11th day of stimulation. The test was positive (β-hCG 3493 mIU/ml, E₂ 1848 pg/ml, prog 19 ng/ml). Sonography showed an intrauterine pregnancy. It was calculated that the patient was in gestational week 5 + 0. Oocyte retrieval was done on the 13th day of stimulation. Seventeen oocytes were aspirated. Most of the aspirated oocytes had a
We decided in favour of a combination of hCG (10,000 IE) and a GnRH agonist (triptorelin 0.2 mg) to induce ovulation. We considered that the standard use of hCG, which induces ovulation through binding to the LH receptor, was not appropriate as the patient was already producing hCG due to her pregnancy. As there are no reports in the literature on the induction of ovulation in pregnancy, we opted for this “safe” combination of both preparations.

There was also a risk that the oocytes would not be able to reach metaphase II or that they had already reached the stage due to endogenous production of hCG and might have become atretic. Due to the continuous high progesterone levels we initially had to assume that oocyte maturation might be impaired. Surprisingly, morphological examination of the oocytes did not confirm this.

It should be noted critically that a pregnancy test could have been done a few days earlier. Moreover, after discussing it with the patient, it would have been possible to administer the aromatase inhibitor for a longer period to ensure an optimal decrease of estradiol levels as the concerns about teratogenicity are probably speculative.

Conclusion

We report an unusual case of spontaneous pregnancy conceived shortly before the start of stimulation in the 2nd half of the menstrual cycle. Stimulation was done in the shortest possible time, starting in the 2nd half of the cycle with gonadotropins and GnRH antagonists in combination with an aromatase inhibitor to ensure relatively low estradiol levels. Surprisingly, morphological examination of the oocytes showed no impairment due to the pregnancy. We cannot draw any definitive conclusions about the future potential of the oocytes to be fertilised.

There is not sufficient data about the risk of ovarian stimulation in patients with receptor-positive breast cancer. Treatment should be done in centres integrated in the FertiPROTEKT network.

Conflict of Interest

None.

References


Deutschsprachige Zusatzinformationen online abrufbar unter: www.thieme-connect.de/ejournals/toc/gebfra.