

Fertility preservation in endocrine responsive breast cancer: data and prejudices

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Abstract

Even if current guidelines suggest an early referral of young breast cancer (BC) patients to fertility preservation counselling, physicians still lack knowledge about the different available strategies. Hormonal stimulation to harvest mature oocytes is considered unsafe by many oncologists and experts in reproductive medicine, particularly in the setting of oestrogen receptor-positive BC. The aim of this mini-review is to provide an overview on the available data about this topic in order to clarify potential misunderstandings and to highlight the new trends in the oncofertility field with their pros and limitations.

Keywords: *oestrogen receptor, breast cancer, fertility preservation, hormonal stimulation, ovarian stimulation*

The European Society of Medical Oncology [1], the American Society of Reproductive Medicine [2] and the American Society of Clinical Oncology [3] recommend to discuss the potential risk of iatrogenic premature ovarian failure and infertility with all young cancer patients before starting anticancer treatments [1–5]. Breast cancer (BC) represents the most frequent oncological diagnosis in women during reproductive years [4]. Unfortunately, BC survivors have a low chance of pregnancy after diagnosis compared to their normal counterpart [6], especially when adjuvant endocrine therapy is prescribed [7], even if pregnancy is considered an important goal for many young patients [4]. The potential impact of pregnancy on the risk of recurrence is another major concern [8]. To date, several studies have demonstrated that pregnancy is safe in women with a history of BC following adequate treatment and follow-up and that it does not increase the risk of recurrence, even in patients with hormone receptor-positive disease [8, 9] and/or carriers of germline BRCA mutations [10].

Controlled ovarian stimulation (COS) and subsequent oocyte/embryo freezing are the gold standard of fertility preservation (FP) in this setting [1–5]. Nonetheless, when a focused survey was administered to physicians attending two major BC conferences, 37% of the respondents (101/273) reported that they had never consulted the international guidelines about FP and 22.3% considered COS not safe in the setting of oestrogen

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receptor (ER)-positive BC [11]. Two major concerns were raised: the potential delay in the start of chemotherapy (CHT) and the possible enhancing effects of rising of oestradiol (E2) levels during OS on BC growth/recurrence.

Are these issues really clinically relevant?

Chemotherapy delay

Several studies have showed no detrimental effects on BC recurrence or survival if CHT was delayed until 12 weeks after surgery, particularly in ER-positive, early stage BC patients [12, 13]. Nowadays, thanks to an early referral to fertility specialists and the need of no more than 2 weeks for COS and oocyte retrieval, oocytes/embryos cryopreservation can be safely completed without significant CHT delay [1, 14]. The possibility of starting stimulation at any day of the menstrual cycle (random start protocol) [15] and the option of a double stimulation make this procedure feasible and effective, allowing to optimise the number of retrieved oocytes without affecting BC prognosis [1, 16, 17].

Detrimental effects of high oestrogen levels

Up to now, there is no evidence that COS promotes BC growth [18]. A systematic review by Rodgers *et al* [19] did not show any association between COS and an increased risk of BC relapse. Oktay *et al* [20–22] developed a modified OS protocol based on the concurrent use of the aromatase inhibitor letrozole and gonadotrophins, in order to maintain oestrogen levels similar to those reached in unstimulated cycle without affecting oocyte and embryo yield. The same group conducted a prospective non-randomised study which compared 79 BC patients who underwent COS with letrozole and gonadotrophins and 136 patients that did not perform FP as controls [23]. Most of the patients in the COS group (64/79; 81%) had a diagnosis of ER-positive BC. The median follow-up after adjuvant CHT was 23.4 months in the treatment group and 33.05 months in the control one. The recurrence risk was not increased compared with controls [23]. Subsequently, a prospective non-randomised study by Kim *et al* [24] confirmed this data within a longer follow-up of 5 years after diagnosis. They also reported no difference in survival among women with BRCA mutation who underwent OS [24].

More recently, Letourneau *et al* [25] compared the oncological outcome of 207 BC patients who underwent COS for FP and 122 who did not. With a median follow-up of 43 months, no impairment of DFS was reported in the FP group, even among women with ER-positive BC (DFS: HR, 0.4; 95% CI, 0.1–1.6) [25]. Authors acknowledge the retrospective nature of the study, but conclude that FP appears unlikely to affect DFS, even in the setting of neoadjuvant CHT (NACT) (in which the tumour is still present during FP). To date, NACT has gained popularity as it improves the rate of breast conserving surgery and allows *in vivo* tumour response to adapt the subsequent adjuvant treatment [26]. Kim *et al* [24] reported only one recurrence among 14 BC patients who underwent COS before surgery (7%) and 5 among 106 patients who underwent the same treatment after surgery (4%) ($p = 0.47$). The relapse-free survival rate was not statistically significantly different between pre- and post-surgery groups ($p = 0.44$) [24]. Chien *et al* [27] conducted a retrospective case–control study to evaluate the impact of COS on the time of the initiation of NACT. The mean time from diagnosis to NACT was 39.8 days versus 40.9 days ($p = 0.75$), and the median time was 41.5 days versus 35.5 days ($p = 0.50$) in the 34 patients who underwent COS versus the 48 control patients, respectively. Thus, patients who underwent COS before NACT had a delay of approximately 1 week compared to control patients, which could hardly impact prognosis [27]. Nonetheless, data about the safety of this approach focusing on ER-positive BC are still limited and long-term follow-up is needed. In case of very aggressive tumours, where CHT cannot be postponed for 2–3 weeks, ovarian tissue cryopreservation (OTC) may be considered [28].

A prospective multicentre study conducted by Marklund *et al* [29] compared different FP strategies among 610 young BC patients who underwent CHT. Of these, 401 performed COS; after a mean follow-up of 6.3 years, no differences in terms of survival were reported between patients who underwent COS and those who did not, between those who used letrozole in the COS protocol or those who used a ‘random start’ protocol. Hence, all the available data support safety and efficacy of COS in BC patients, whenever it is possible according to their age, ovarian reserve and tumour characteristics [18–27, 29].

Alternative options

Novel strategies have been developed to avoid hormonal stimulation in BC patients: harvesting ovarian tissue with subsequent cryopreservation, harvesting immature oocytes without COS (*in vitro* maturation—IVM) or using gonadotrophin-releasing hormone analogues (GnRHa) as medical gonadoprotection.

Over 130 live births have been reported after reimplantation of ovarian tissue [2, 5, 30–41], with live birth rates exceeding 35% [5]. Nonetheless, the possible advantages of OTC should not be overemphasised, as there is a theoretical possibility of re-implanting malignant cells [42], and the procedure should not be offered to patients harbouring BRCA mutation, for the increased risk of subsequent ovarian cancer [2, 43].

Grynberg *et al* [44] reported the first live birth using IVM in a young woman with a diagnosis of ER-positive BC. Even if progresses in sustaining *in vitro* growth of human oocytes have been made, the pregnancy outcomes after IVM are still suboptimal, with lower implantation rates as compared with embryos obtained from mature oocytes [45, 46].

According to current guidelines, the ovarian suppression with GnRHa during CHT does not represent an option of FP but a strategy to reduce the detrimental impact of cytotoxic drugs on ovarian reserve [47] as data on post-treatment pregnancies remain limited [48–50]. While medical gonadoprotection should be proposed to all premenopausal patients concerned about the risk of premature ovarian insufficiency (POI), patients interested in future pregnancies should be always offered oocyte/embryo cryopreservation. Further studies are needed about GnRHa role in the setting of BRCA-mutated patients [1].

To date, evidence on long-term reproductive outcomes after BC treatment is still scarce. A recent Swedish cohort study indicates that a successful pregnancy after BC is possible both in women who underwent FP and who did not [51]. Noteworthy, the authors showed that FP is associated with significantly higher rates of post-BC live births, without any detrimental impact on survival outcomes during a mean follow-up of 5.2 years [51]. Nonetheless, FP options still have several limitations, such as a limited awareness among both the general population and also medical oncologists and the lack of ‘fast-track’ referral pathway. We have also to consider the psychological pressure added by an oncofertility counselling at the time of cancer diagnosis. Even if several countries provide FP procedures entirely with no costs for the patients, there are still realities with no coverage of costs or with a very limited refund depending on patient characteristics (disease, prognosis, age) or on the number of treatments (number of cycles, first child) [52]. Age is the most crucial factor swaying the success rate of FP: the efficacy of oocyte/embryo cryopreservation is strictly related to the number of mature oocytes retrieved, that is age-dependent, dropping precipitously after 35 years of age [53, 54]. Moreover, the effectiveness of COS may be negatively impacted by BRCA status, considering the emerging evidence of a diminished ovarian reserve and a poor response to ovarian stimulation in BRCA1/2-mutation carriers [55, 56].

Conclusion

In conclusion, a timely COS for FP remains the first choice for young BC patients interested in FP, also if they have ER-positive tumours. Modified COS protocols with letrozole combined with gonadotrophins could increase safety and it should be recommended [18, 19, 29, 57, 58]. However, the decision to adopt this strategy should be balanced and multidisciplinary. Considering the new emerging evidences, every patient should be counselled about the gonadotoxicity of the proposed treatments and the available strategies to prevent POI and preserve fertility but the possibility to access must be evaluated case by case, assessing the risk of gonadotoxicity, ovarian reserve at baseline and cost-effectiveness. It is of paramount importance to ponder for each patient the most appropriate technique for FP and discuss reproductive outcomes relying on data and not on prejudices.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Authors' contributions

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