Strategies for Fertility Preservation after chemotherapy: Awareness among Irish cancer specialists

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Abstract
The potential effect on fertility for patients undergoing cancer treatments is an important issue. The aim of this study was to assess awareness of fertility preservation strategies among cancer specialists involved in the management of young women with malignancy. A 10 question survey was sent to 94 cancer specialists in Ireland, comprising 28 medical oncologists, 32 haematologists and 34 breast surgeons, assessing awareness of: guidelines, facilities in Ireland, and potential barriers to referral. Fifty of 94 responded (53% response rate). Awareness of current success rates associated with assisted reproductive therapy was poor. Ten respondents (20%) identified the estimated delay to the delivery of chemotherapy due to fertility preservation. Three important potential barriers to referral were identified: time delays, poor prognosis disease and clinical features of the cancer. Awareness of the impact of reduced fertility is important in these patients but early consideration is vital.

Introduction
As treatments for cancers improve, physicians treating patients with cancer are becoming increasingly aware of the long-term effects of their treatment. This is a widespread issue with 22% of patients with breast cancer under 50 years of age at diagnosis. Chemotherapy treatment carries a significant risk of ovarian failure as well as premature menopause in women of childbearing years. The most important factor in this risk is the age of the patient at the time of treatment, but the type of chemotherapy agents used also has an effect. Prevention of loss of reproductive function is difficult with no good evidence for effective preventative measures. The preservation of fertility for younger patients is an important aspect of cancer survivorship. This can be achieved with relative ease in male patients through semen cryopreservation and, although more complex the cryopreservation of embryos, oocytes, or ovarian tissue in females. The largest group of these patients are those with breast cancer, but those with haematological cancers are also included in this study. The aim was to assess levels of awareness of fertility preservation among specialists involved in the diagnosis and care of patients with cancer in Ireland who are of childbearing potential.

Methods
A questionnaire was sent to 94 cancer specialists comprising 28 medical oncologists, 32 haematologists and 34 breast surgeons. All were involved in the diagnosis or treatment of cancer in pre-menopausal women potentially for treatment with chemotherapy. A list of all those actively treating these patients was available through national specialty groups. The questionnaire evaluated the respondents awareness of guidelines and current practice in fertility preservation and facilities. It examined the level of importance attached to various reported barriers to offering fertility preservation. The questionnaire comprised 10 questions in a single parts format designed to minimise the time to complete the survey and thus maximise response rates, and thus confidence in the study findings. The authors developed this survey based on a review of the literature and previous qualitative interviews and this was piloted among a small number of physicians. Just 20 who later participated in the survey. A combination of multiple-choice questions and ranking questions were used to give a forced choice, avoiding ambiguous answers.

A commercial, online survey tool (www.surveymonkey.com) was used for hosting the web-based survey and for data entry, collation and basic statistical analysis. SPSS statistical package, version 18 was used for further statistical analysis. An initial email was sent explaining the purpose of the study and a copy of the questionnaire as well as a link to a web-based version was included. This was followed up with a paper version 1 week later. A pre-addressed envelope was included in the correspondence. Non-responders received a further request for participation and a paper version 4 weeks later. Just 6 responders completed the online version, the remaining 44 replied by post. As the questionnaire was anonymous, no subset analysis could be preformed on responders within the different specialties.

Results
Of 94 questionnaires sent, 50 responses were received (a 53% response rate). Of these 31 (62%) were aware of some of the available international guidelines on the preservation of fertility in young patients undergoing chemotherapy. This included 28 aware of ASCO guidelines 10 of ESMO guidelines and 7 aware of the Royal College of Physicians and Gynaecologists guidelines. Many were aware of more than one set of recommendations. Among those replying, 41(82%) routinely referred men for sperm banking, reflecting the relative ease of preservation of male fertility. As sperm banking is available with little delay, and good subsequent success rates where sperm is used, it can often be seen as a standard element before therapy. All those who responded treat women of childbearing potential but only 42 (84%) would routinely discuss fertility with these women. International guidelines would suggest that all patients should have fertility discussed before treatment. Twenty one (46%) reported using GnRH agonists as a measure to protect ovarian function. These agents have been widely used in an attempt to suppress ovarian function and to prevent damage to the follicles at a sensitive stage in their maturation, despite a lack of evidence for their use.

Awareness of current outcomes for assisted fertility was poor, with just 42% (18) aware of conventional IVF success rates, 21% (9) for frozen embryo and 26% (11) for frozen oocyte success rates (Table 1). While 85% (41) correctly estimated costs involved (currently approximately 5000 in Ireland), just 2% were aware of the seven sites offering treatment in Ireland. While there is only one centre in receipt of state funding, six privately funded centres have indicated a willingness to treat cancer patients.

Average pregnancy rates in a woman less than 38 years

Only 20% (10) identified the estimated time delay involved, 4-6 weeks using accelerated ovarian stimulation following interruption of a cycle. The remainder over-estimated the delay involved. This is of great clinical importance when we look at the barriers to referral for consideration of ART.

We asked responders to rank nine barriers to referral for fertility preservation in order of importance with 1 as very important and 9 as unimportant. These barriers were taken from international assessments of physicians reported barriers to referral (Table 2). There was a large degree of agreement on the barriers to referral, with the majority of responders identifying the same three most important factors, time delays to subsequent treatment, poor prognosis disease and clinical features of the cancer, such as estrogen receptor (ER) positive disease. These factors had a median score of 1, 2 and 2 respectively. Potential barriers of lack of partner, patient not requesting measures and lack of awareness, all had a median score of 5, while further potential barriers no facility to discuss this difficult topic, not locally available and cost of ART had median scores of 4, 5 and 5 respectively.
scores of 4, 4 and 3 suggesting they are less important. Thus, patient dependant factors would appear to be more important than psychosocial factors.

Discussion

Consensus guidelines increasingly recommend adjuvant chemotherapy for younger women with breast cancer, with women under 50 years deriving the greatest benefit from chemotherapy and 52% of patients are under 50 at diagnosis. 30-50% of women who receive chemotherapy for breast cancer in their 30s and 50-100% of those treated in their 40s will experience a premature menopause or ovarian failure and be rendered infertile. Ovarian reserve increases with age, particularly over 35 years but also with the use of certain chemotherapeutic drugs, in particular alkylating agents. Other reported factors include, the dose of drugs, radiotherapy (risk is associated with dose and area treated) and combined chemoradiation. 2 In some instances, this may be a temporary phenomenon with menstruation recovering months to years later; however even if menopause should return after treatment, menopause may occur 5-10 years earlier than expected. While the endocrine effects on early menopause can be treated, the reproductive effects are not amenable to manipulation. Premature menopause is an important survivorship issue particularly in those women who hope to preserve fertility following treatment. While women are offered the best available therapy to treat their cancer, it is also important that other aspects of their care, such as fertility preservation, be considered.

In our study, awareness is highlighted as being an issue, particularly in surgeons who need to discuss fertility at the time of diagnosis. Only 84% in our study reported discussing fertility with their patients. This mirrors an earlier study on awareness of male fertility services in oncology patients in 2003 and suggests that the improvements seen in male fertility preservation are now needed in females. The response rate of 53% is not unexpected though it may be a potential source of bias as those more aware of fertility issues are more likely to respond, however, the results and response rate are similar to a recent international study in this area. 4 One of the difficulties with the discussion of the risk of infertility is the lack of good quantitative data on the risks associated with specific regimens. Chemotherapy administered aromenotora (CAI) has been used as a surrogate marker for loss of fertility, but does not accurately reflect ovarian reserve. Newer markers of ovarian function such as AMH (anti-müllerian hormone) may be able to provide better data on the true effects on ovarian function.

Pregnancy rates, with assisted reproduction technology (ART) have improved greatly over recent years. These improvements may be the result of the underestimation of our cohort of reported outcomes with ART. Published data would suggest rates of 25% for frozen embryo transfer and 5-15% for frozen oocytes, the methods used most commonly in patients due to undergo chemotherapy. The most important factor is age of the patient, with highest success rates in those under 35 years. While success rates may vary in different centres, results are consistently higher than predicted by respondents.

Current options for fertility preservation include embryo, oocyte and ovarian tissue cryopreservation with later re-implantation. Embryo cryopreservation and retrieval of up to 10 embryos with improved methods of vitrification is currently available with a success rate of 30-40% per transfer. Oocyte retrieval and cryopreservation are more difficult with only success rates of 10-15% due to a decrease in egg quality and a smaller pool of eggs. Cryopreservation of ovarian tissue is promising with the first pregnancy following in-vitro maturation of cryopreserved oocytes in 2009. 5 In-vitro maturation of cryopreserved oocytes at a later stage with re-implantation does not require FSH stimulation thereby avoiding high estradiol levels. The use of ovarian tissue is reporting individual case successes and will be of greater importance in the future.

Seven live births have been reported to date, with the first in 2004. 5 Both techniques may be available in the future to women affected with cancer.

Ovarian stimulation is associated with marked increase in estradiol levels sometimes up to 20 times of the levels seen in natural cycles. 10 Because of the large body of data implicating oestrogen and oestrogen metabolites in breast cancer there is a reluctance to treat patients with ER positive tumours with hyperstimulation. However, these levels are short lived and there has been no proven association between ART and worse prognosis. Again this area was highlighted by our responders as an area of concern, but it remains underestimated and further research is needed to clarify true risks involved.

The time involved in ovarian stimulation and oocyte retrieval has improved and stimulation can take between 14 days and 6 weeks with current strategies. This was greatly underestimated in our study with only 20% of specialists aware of the time involved. This is of great importance when we consider that many see time delay to subsequent treatment as a major barrier to ART. Our study clearly suggests that patient related factors are far greater barriers to ART referral than psychosocial barriers such as cost and availability, in our country at least. These need to be examined more closely in the light of available evidence. Our study would suggest that reported barriers can be overcome, and as this is of such importance to our patients, awareness of the issues and continuing education regarding options, to physicians and patients, is vital. This is certainly an area of growing importance and further research is needed.

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References
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