Ovarian stimulation protocols for onco-fertile patients

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Abstract

Purpose To review options for ovarian stimulation before oocyte collection for fertility preservation for women with cancer or related diseases who require potentially sterilizing chemo- or radiotherapy.

Methods Narrative review of current practice.

Results Vitrification of oocytes and embryos has improved chances of pregnancy for this group of patients in recent years, increasing the uptake of fertility preservation before cancer treatment substantially. Strategies for ovarian stimulation for such patients should optimize oocyte yield whilst avoiding risk of ovarian hyperstimulation.

Conclusions Best practice in ovarian stimulation can deliver good numbers of oocytes or embryos for cryopreservation with minimal risk of ovarian hyperstimulation for women under 36 years of age. Results are less encouraging for older patients.

Keywords Superovulation · Ovarian hyperstimulation · Oncofertility · Gonadotropin · Agonist trigger

Introduction

Recent advances in the technology of vitrification of human oocytes and embryos have increased the opportunities for

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Capsule Specific patient groups have higher risk of complications of superovulation, including possibility of stimulation of tumor growth for women with ER+ breast cancers and pelvic haematoma for thrombocytopenic patients with haematological disorders.

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young women who are to undergo potentially sterilizing treatment for cancer or connective tissue disorders to consider pre-treatment storage of gametes or embryos as an ‘insurance’ for later fertility. Although it is difficult to quantify, it is clear that there has been a surge of interest in the area of ‘onco-fertility’ over the past decade, with an exponential rise in academic publications and articles in the popular press on this topic.

The treatment of this group of patients presents the fertility specialist with some unique challenges. Many will be systemically unwell with contraindications to anaesthesia or surgical oocyte collection and some will have oestrogen sensitive tumours, which may be stimulated during superovulation with gonadotropins. Issues raised during pre-treatment counseling may prove particularly confronting for these patients (and partners) since the question of the possible post-mortem utilization of their gametes or embryos must be addressed, with a written declaration of intent.

Impact of chemotherapy on fertility

The lead oncologist must be asked for a ‘best case’ prognosis for inclusion into this discussion. Many modern chemotherapy regimes, for example those used for many breast cancers, do not carry high risk of ovarian compromise, and such patients may be best counseled to avoid Controlled Ovarian Stimulation (COS) and move more quickly to cancer treatment. Each chemotherapy regime must be individually assessed but in general the most cytotoxic agents including alkylating agents and cisplatin are most likely to cause profound loss of primordial follicles (Table 1) [1].

The likelihood of ovarian failure is also influenced by patient specific factors, most importantly female age. The clinical history should include previous pregnancies and

Table 1 Risk of gonadal damage according to chemotherapy treatment used (adapted from [1])

High risk	Moderate risk	Low risk
Cyclophosphamide	Cisplatin	Vincristine
Ifosfamide	Adriamycin	Vinblastine
Chlorambucil	Actinomycin	Methotrexate
Melphalan		Bleomycin
Busulfan		Dactinomycin
Nitrogen mustard		Mercaptopurines
Procarbazine		
Nitrosureas		

their outcome, menstrual cyclicity and gynaecological history and, if time allows, an early follicular phase measurement of Follicle Stimulation Hormone (FSH), oestradiol and Anti Mullerian Hormone (AMH). A random AMH will suffice if there is need for rapid progression into treatment. Transvaginal ultrasound is also helpful, with antral follicle count and assessment of pelvic anatomy.

Success of oocyte and embryo freezing

Success rates of oocyte and embryo freezing have improved considerably since the widespread introduction of vitrification technologies a decade ago. Embryo freezing has a long history and many IVF centres are able to maintain live-birth rates of over 25 % after transfer of embryos created from eggs collected from women under 36 years of age. Success rates fall significantly as patients move beyond this age threshold. Similar statistics probably apply to embryos created from vitrified oocytes, although since this technology has been introduced more recently it is harder to derive reliable statistics. Data for survival of vitrified oocytes from cryopreservation are given in Table 2, although survival after thaw does not equate to live birth.

The adverse effect of advanced reproductive age may apply more strongly to cryopreserved oocytes than embryos. Data are limited but one recent study has shown that for women over 38 with fewer than eight cryopreserved oocytes, delivery rates were halved when compared with younger patients with better ovarian response (12.6 vs

27.5 % per cycle) [6]. This study [6] also reported live-birth rates of 26.3 % per cycle (95 % CI: 22.6–30.4) and 29.4 % per transfer (95 % CI: 25.3–33.8) with a total of 147 babies being born, illustrating the small size of the current literature on outcome after oocyte vitrification. Neonatal malformation rates were acceptably low, although again, data are limited. Uptake of vitrification varies considerably from centre to centre and country to country and many clinicians and embryologists remain skeptical about efficacy and safety, despite emerging studies in these areas [7].

Controlled ovarian stimulation

The goal of superovulation for this group of patients represents a compromise between obtaining a relatively large number of oocytes for vitrification, to maximize chances of later pregnancy, and the absolute need for avoidance of ovarian hyperstimulation in a patient who will shortly begin chemotherapy. Many would favour a GnRH antagonist protocol with moderately high dose of FSH, possibly determined by pre-treatment AMH. This protocol carries lower risk of OHSS and allows use of a GnRH agonist trigger as an alternative to the traditional hCG trigger, if there is a suspicion of over-response to stimulation. The GnRH agonist will displace the antagonist from the receptor leading to stimulation of the receptor and a surge of gonadotropins. The release of LH from the pituitary lasts for approximately 24–36 h as compared to the 7–10 day luteotrophic effect of hCG leading to lower pregnancy rates in GnRH agonist trigger fresh cycles. This issue is of no concern for the fertility preservation patient in whom eggs or embryos will be frozen; hence it is an ideal option for these patients. A recent Cochrane review comparing hCG to GnRH agonist trigger in Antagonist cycles confirmed a 90 % reduction in moderate to severe OHSS in the GnRH agonist group. (OR 0.10; 95 % CI 0.01–0.82 5 RCTs, 504 women) [8]. The Agonist can be given as a subcutaneous injection or using a nasal spray.

For patients planning to commence chemotherapy, timing of fertility preservation techniques can strongly influence the decision making process. For women with breast cancer, if they are referred early to a fertility specialist there is usually adequate time between breast surgery

Table 2 Outcomes of human oocyte vitrification

	Survival rate	Fertilisation rate	Implantation rate	Clinical pregnancy rate
Song et al. [2]	88 %	75 %	37 %	50 %
Cobo et al. [3]	92.5 %	58 %	39.9 %	50.2 %
Kim et al. [4]	81.0 %	73 %		80 %
Nagy et al. [5]	89.1 %	87 %	55.3 %	
Rienzi et al. [6]	84.7 %	75.2 %		34.2 %

and chemotherapy to await the onset of the woman's period and perform a standard short antagonist cycle. However, if referral is late, or for women with haematologic disorders, there may significant pressure to avoid delays in chemotherapy. In this situation it is possible to commence fertility treatment in either the pre-ovulatory or luteal phase by using a GnRH antagonist for 2–5 days to bring about a profound reduction in gonadotropins and then commence FSH stimulation [9–11].

The usual time from commencement of stimulation to starting chemotherapy is 2 weeks and chemotherapy can generally be started 48 h following egg collection. Oocyte collection should involve use of a narrow gauge needle, to reduce possibility of a post-operative pelvic haematoma with risk of infection and pelvic abscess formation during neutropaenia, and peri-operative antibiotics.

For women under time pressure, some clinicians continue to offer ovarian tissue cryopreservation, suggesting that there may be a possibility of pregnancy after later re-transplantation to the pelvis or other anatomic sites, or after maturation of oocytes from the tissue in vitro. Current statistics of chances of live birth from stored tissue are depressingly poor, with a handful of births worldwide. Ovarian tissue storage should only be offered as a last resort, when there is not time for a 2 week cycle of ovarian stimulation, and remains an experimental procedure. This caveat also applies to use of GnRH agonists during chemotherapy in an attempt to reduce ovarian damage by cytotoxics.

Special considerations

1) Estrogen receptor positive breast cancer

Due to the concern about the impact of raised estrogen levels on the tumour there may be a benefit to combining FSH stimulation with an aromatase inhibitor such as letrozole, or Selective Estrogen Receptor Modulator (SERM) such as tamoxifen or clomiphene [12]. Studies on the effects of letrozole on ovarian stimulation show an approximate halving of oestradiol concentrations with similar numbers of mature oocytes retrieved [13]. Limited prospective data regarding the risk of breast cancer recurrence within 2 years is so far reassuring when compared to women who chose not to undergo COS [14].

2) Haematological malignancies

Women with lymphoma and leukaemias are often unwell at the time of diagnosis and have an increased risk of bleeding, infection and thrombosis with ovarian stimulation and oocyte retrieval. The decision to proceed with COS requires multidisciplinary input and management to minimize complications, pre-operative platelet transfusion, a narrow gauge needle and peri-operative antibiotics may all be helpful in reducing

complications. Early diagnosis of pelvic haematoma and appropriate antibiotic cover is particularly important for those at risk of neutropaenia.

Ovarian stimulation immediately following chemotherapy yields low egg numbers and there is concern about the effect of the chemotherapy on egg and embryo quality hence this is generally not recommended. Ovarian tissue freezing also puts the woman at risk of surgical complications, with low success rates and the risk of transplantation of malignant cells at a later date when the ovarian tissue is replaced.

3) Non-malignant diseases (SLE, vasculitis, sickle cell disease)

Ovarian stimulation needs to be carefully considered in this group of women as they are at increased risk of thrombosis and worsening of disease. Out of a cohort of 68 women with severe SLE soon to undergo cytotoxic therapy, only 4 % chose to undergo ovarian stimulation. 91 % chose to use a GnRH analogue but the data regarding effectiveness of this option is still lacking [15].

4) PCOS or inadequate time for stimulation

Clinics experienced with In-Vitro Maturation (IVM) of immature oocytes may consider this technique, which requires lower dose of gonadotropins and shorter stimulation times. However, pregnancy rates are lower than with mature oocytes and the oocyte collection procedure is more difficult and time-consuming which may increase the risk of bleeding and infection.

Whilst survival is clearly the most important issue facing a young woman with cancer, it is clear that future fertility is also important. A rapid and efficient referral system is essential for avoidance of delay, and this can only be established in close collaboration with colleagues in medical oncology. In Sydney we run regular joint meetings and multidisciplinary teams to facilitate good communication, and have a 6 day per week, 24 h turn around for initial consultation for onco-fertility patients. Specialists planning conventional COS for patients with cancer must undertake a careful pre-treatment medical assessment of patient health in conjunction with anaesthetists and physicians. Cardiac and respiratory compromise and haematologic failure leading to thrombocytopaenia are particularly threatening complications. There is obvious need for a rapid entry into, and completion of treatment to facilitate progression into chemo- or radiotherapy.

For those women who choose not to pursue fertility preservation (up to 90 %), the consultation itself is helpful and vital to their sense of wellbeing. A study assessing clinician and patient attitudes to fertility preservation showed that oncologists were less likely to value the experience of having a discussion about fertility options in the

absence of a clear decision to proceed down this route. Whereas, women who were referred valued the opportunity and felt that it provided choice and control over the decision making process [16]. Patients also described the use of leaflets as limited and in no way a substitute for a discussion with a fertility specialist.

Conclusions

The Royal College of Obstetricians and Gynaecologists, National Institute for Health and Clinical Excellence, British Fertility Society and American Society for Reproductive Medicine all recommend that young people with a cancer diagnosis should be advised by specialists on the reproductive implications of their treatment and their options for future fertility. It is imperative that research continues in this area and that a continued dialogue exists between oncologists and fertility specialists to enhance the outcomes for patients.

References

1. Sonmezer M, Oktay K. Fertility preservation in female patients. *Hum Reprod Update*. 2004;10:251–66.
2. Song WY, Sun YP, Jin HX, Xin ZM, Su YC, Chian RC. Clinical outcome of emergency egg vitrification for women when sperm extraction from the testicular tissues of the male partner is not successful. *Syst Biol Reprod Med*. 2011;57:210–3. doi:10.3109/19396368.2011.566666.
3. Cobo A, Meseguer M, Remohí J, Pellicer A. Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. *Hum Reprod*. 2010;25:2239–46. doi:10.1093/humrep/deq146.
4. Kim TJ, Laufer LR, Hong SW. Vitrification of oocytes produces high pregnancy rates when carried out in fertile women. *Fertil Steril*. 2010;93:467–74. doi:10.1016/j.fertnstert.2008.12.094.
5. Nagy ZP, Chang CC, Shapiro DB, Bernal DP, Kort HI, Vajta G. The efficacy and safety of human oocyte vitrification. *Semin Reprod Med*. 2009;27:450–5. doi:10.1055/s-0029-1241054.
6. Rienzi L, Cobo A, Paffoni A, Scarduelli C, Capalbo A, Vajta G, et al. Consistent and predictable delivery rates after oocyte vitrification: an observational longitudinal cohort multicentre study. *Hum Reprod*. 2012;27:1606–12.
7. Vajta G, Nagy ZP, Cobo A, Conceicao J, Yovich J. Vitrification in assisted reproduction: myths, mistakes, disbeliefs and confusion. *Reprod Biomed Online*. 2009;19(Suppl3):1–7.
8. Youssef MAFM, Van der Veen F, Al-Inany HG, Griesinger G, Mochtar MH, Aboulfoutouh I, et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles. *Cochrane Database Syst Rev*. 2011, Issue 1. Art. No.: CD008046. doi:10.1002/14651858.CD008046.
9. Stowitzki T. Ovarian stimulation in cancer patients. European Society of Human Reproduction and Embryology Campus Workshop: Cancer and Fertility. Heidelberg Nov14–15th 2008.
10. Ozkaya E, San Roman G, Oktay K. Luteal phase GnRHa trigger in random start fertility preservation cycles. *J Assist Reprod Gen*. 2012;29:503–5.
11. Friedman BE, Pao S, Westphal LM, Lathi RB. Oocyte retrieval following continued stimulation five days beyond ovulations yields live birth after frozen embryo transfer. *J Assist Reprod Gen*. 2012;29:433–5.
12. Kim SS, Donnez J, Barri P, et al. Recommendations for fertility preservation in patients with lymphoma, leukaemia and breast cancer. ISFP Practice Committee. *J Assist Reprod Gen*. 2012;29:465–8.
13. Checa Vizcaino MA, Chorchado AR, Cuadari ME, et al. The effects of letrozole on ovarian stimulation for fertility preservation in cancer-affected women. *Reprod Biomed Online*. 2012;24:606–10.
14. Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer. *J Clin Oncol*. 2008;26:2630–5.
15. Henes M, Henes JC, Neunhoeffer E, et al. Fertility preservation methods in young women with SLE prior to cytotoxic therapy: experiences from the FertiPROTEKT network. *Lupus*. 2012;21:953–8.
16. Peddie VL, Porter MA, Barbour R, et al. Factors affecting decision making about fertility preservation after cancer diagnosis: a qualitative study. *BJOG Obs Gyn*. 2012;119:1049–57.