World Journal of Obstetrics and Gynecology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5317/wjog.v3.i2.54

World J Obstet Gynecol 2014 May 10; 3(2): 54-60
ISSN 2218-6220 (online)

TOPIC HIGHLIGHT

Mona A El-Bahrawy, MBBCh, MSc, PhD, FRCPath, *Series Editor*

Chemotherapy for gynaecological malignancies and fertility preservation

Joseph J Sacco, Joanne Cliff, John A Green

Joseph J Sacco, Joanne Cliff, John A Green, Department of Medical Oncology, Clatterbridge Cancer Centre, Bebington, Wirral CH63 4JY, United Kingdom
Author contributions: All authors performed a literature search, wrote and reviewed the manuscript.
Correspondence to: Dr. John A Green, Department of Medical Oncology, Clatterbridge Cancer Centre, Clatterbridge Road, Bebington, Wirral CH63 4JY,
United Kingdom. j.a.green@liverpool.ac.uk
Telephone: +44-151-4827793 Fax: +44-151-4827675
Received: February 28, 2013 Revised: May 31, 2013
Accepted: August 4, 2013
Published online: May 10, 2014

Abstract

Infertility is an increasingly important issue for patients surviving cancer. Significant improvements in cancer management have led to greater numbers of patients living healthy and fulfilling lives for many years after a diagnosis of cancer, and the ability to bear children is a major component of well-being. Infertility is particularly challenging in gynaecological cancer, where multiple treatment modalities are often employed. Surgery may involve the removal of reproductive organs and subsequent chemotherapy may also lead to infertility. Mitigation of this through the use of cryopreservation of embryos, oocytes or ovarian tissue before chemotherapy may enable subsequent pregnancy in the patient or a surrogate mother. Suppression of ovarian function during chemotherapy is less well established, but promises a reduction in infertility without the risks associated with surgery. Similarly, evolving chemotherapy regimens with replacement of alkylating agents will reduce the incidence of infertility. With a combination of these techniques, an increasing proportion of patients may be able to conceive after completion of treatment, and there is no evidence of an increase in congenital abnormalities. This review discusses chemotherapy-induced infertility, interventions and success rates, and demonstrates that individualisation of management is required for optimum outcome.

Key words: Infertility; Chemotherapy; Gynaecological malignancies; Ovarian; Cryopreservation

Core tip: This paper summarises the main scenarios in which infertility presents a clinical problem in gynaecological malignancies subsequent to the use of chemotherapy. Many patients may have pre-existing infertility due to related medical conditions, and prior surgical interventions may be an important factor. Other factors to be considered include the associated prognosis and the potential need for rapid commencement of chemotherapy. The various technologies for fertility preservation are reviewed and their strengths and weaknesses discussed. The paper stresses that an individualised approach is necessary for each patient and that discussion of the issues at an early stage of management is important.

Sacco JJ, Cliff J, Green JA. Chemotherapy for gynaecological malignancies and fertility preservation. *World J Obstet Gynecol* 2014; 3(2): 54-60 Available from: URL: http://www.wjgnet.com/2218-6220/full/v3/i2/54.htm DOI: http://dx.doi.org/10.5317/wjog.v3.i2.54

INTRODUCTION

Infertility and subfertility are common sequelae of the management of gynaecological malignancies, and are a cause of psychological stress in cancer survivors. In one survey, three quarters of patients younger than 35 years who were childless at the time of diagnosis expressed

a desire to have children[1], while in a second study of adolescent females with cancer, over 80% of patients and their parents were interested in fertility preservation[2]. The ability to have children is also a determinant of well-being in cancer survivors[3,4]. Fertility issues in cancer patients have been made more prominent by an increase in survivorship across all cancers. By 2015, it has been estimated that 4% of all adults in the United Kingdom will be cancer survivors, and in some cancers, such as germ cell tumours and lymphomas, the proportion cured or surviving more than 10 years is much higher.

The management of gynaecological malignancies involves three treatment modalities which may contribute to a loss of fertility; surgery, pelvic radiotherapy and chemotherapy, resulting in fertility preservation being a particularly challenging area. A large proportion of patients will have surgery or radiotherapy that precludes a subsequent pregnancy, including the removal of both ovaries and/or uterus. However, fertility sparing surgery including unilateral oophorectomy or trachelectomy may be feasible[5,6]. While subsequent chemotherapy may cause infertility, this is by no means invariable. In addition, fertility preservation techniques such as embryo cryopreservation may be performed prior to both surgery and chemotherapy, thus allowing the option of surrogate pregnancy. In this paper we will specifically review the effects of chemotherapy on fertility, and techniques that may be employed to improve the chances of a successful pregnancy.

CHEMOTHERAPY INDUCED INFERTILITY

At birth females are believed to have their full lifetime quota of oocytes, and these are progressively lost from the menarche. These oocytes, enclosed within granulosa cells as primordial follicles, are immature, but following activation enter a growing phase and some of these will enter the pre-ovulatory phase. Many others will undergo atresia and not reach the ovulatory phase. Once the number of remaining oocytes falls below a critical number, menopause ensues. The rate at which primordial follicles are recruited into the activated growing state is controlled by feedback mechanisms including the release of anti-mullerian hormone[7].

There are several mechanisms by which chemotherapy can result in infertility. Chemotherapeutic drugs predominantly damage growing follicles as these are the active cell population. However some drugs may also damage the granulosa cells in the resting primordial follicles, leading to death of the immature oocyte. In addition to this direct damage, the loss of growing follicles will in turn disrupt chemical feedback loops and stimulate recruitment of more primordial follicles into this phase. With repeated cycles of chemotherapy, the result is an increase in primordial follicles leaving the resting pool and entering activation leading to a reduced pool at the end of chemotherapy[8].

The risk of infertility following chemotherapy depends on ovarian reserve. Age at chemotherapy has a big impact on the risk of infertility after treatment. In breast cancer regimens, for example, the commonly used adjuvant chemotherapy combinations (triplets including cyclophosphamide, fluorouracil, methotrexate and an anthracycline) are likely to cause permanent amenorrhoea in more than 80% of women over the age of 40 years but in less than 20% of women below the age of 30 years[9]. Anti-mullerian hormone levels have been shown to be useful as a marker of ovarian reserve[10] and levels fall more dramatically with increasingly gonadotoxic regimens in pre- and post-pubescent girls undergoing chemotherapy[11]. The risk varies with the type of chemotherapy, and alkylating agents such as cyclophos- phamide are now rarely used in the first line management of gynaecological malignancies.

Chemotherapy induced infertility in ovarian cancer patients

The main areas in which fertility-sparing surgery may be considered and combined with chemotherapy are early unilateral epithelial ovarian cancer (FIGO stages I a and I c), and in the treatment of malignant ovarian germ cell tumours. The latter are usually unilateral and even in advanced disease, surgery conserving the contralateral ovary and uterus is feasible. Germ cell tumours generally affect a young population, and fertility after chemotherapy has been frequently reported in this patient population, although reports generally rely on retrospectively collected data in this rare tumour group.

Several papers have demonstrated that return of a normal menstrual cycle is common after chemotherapy and normal childbearing is possible. Many of these papers include different chemotherapy regimens including cyclophosphamide, dactinomycin and vincristine, cisplatin, vincristine and bleomycin (PVB), forerunners to the now commonly used regimen of bleomycin, etoposide and cisplatin (BEP).

The MD Anderson Cancer Centre published a retrospective series of 26 patients treated with at least 3 cycles of BEP, 16 of whom underwent unilateral salpingo-oophrectomy. Questionnaires were completed surveying menstrual function and fertility. Of the 15 patients completing the questionnaire (only one did not but was known to be pregnant at her last follow up), 10 had maintained their normal menstrual function during treatment and 3 patients who had disrupted menstruation during chemotherapy had resumption of normal menses within 6 mo of completion of treatment. Three of these patients conceived without difficulty. Only one patient remained amenorrheic and this patient was subsequently diagnosed with dysgerminoma in the remaining ovary[12].

A further study of 52 women, who all underwent BEP chemotherapy with a median follow up period of 68 mo, included 41 patients who had had fertility-sparing surgery. Of these patients, one had high dose chemotherapy and stem cell transplant and was diagnosed with intermittent biological ovarian endocrine dysfunction.

Normal menstrual cycles were observed following treatment in 39 of the 40 patients who achieved complete remission having undergone fertility-sparing surgery. Of these patients 16 patients had attempted and 12 patients (75%) had successfully achieved conception. There were a total of 15 normal term pregnancies in this patient group. There was also one ongoing pregnancy, one miscarriage and one termination[13].

Another published study included 74 patients with malignant ovarian germ cell tumours with a mean age of 20.9 years. Of these, 47 patients received chemotherapy (30 BEP, 8 PVB, 3 VAC, 4 POMB/ACE, 2 other platinum based), 62% were amenorrhoeic during chemotherapy and 92% resumed normal menses after chemotherapy. Of these, 20 patients attempted conception and 19 were successful, including one after 12 mo. Fourteen live births were recorded in this group and four patients were pregnant at the time of writing the manuscript. No birth defects were reported in the offspring[14].

In early stage epithelial ovarian cancer, fertility data is limited, largely due to the relatively small proportion of patients for whom fertility remains an issue either due to age or surgery. Epithelial ovarian cancer, in contrast to germ cell tumours tends to affect women later in life and also frequently presents at an advanced stage where fertility-sparing surgery is not possible without compromising survival. For women with early stage ovarian cancer adjuvant platinum based chemotherapy is recommended for stage I C cancer and stage I A or B cancer in high-grade tumours only. A combination of platinum with paclitaxel is the standard of care but depending on individual characteristics, some patients will receive single agent platinum.

There are some retrospective studies of fertility following a conservative approach for early stage ovarian cancer, however numbers are small and the individual treatment characteristics are not always clear for the chemotherapy patients becoming pregnant. One multicentre retrospective study looked at 52 patients with stage I epithelial ovarian cancer who were treated with fertility sparing surgery between 1965 and 2000. Forty two had stage I A disease and 10 stage I C. Twenty patients had adjuvant chemotherapy with 11 receiving cisplatin or carboplatin with paclitaxel and one single agent cisplatin. The remainder had melphalan or cisplatin and cyclophosphamide. Twenty-four patients attempted pregnancy and 17 conceived (71%), leading to 26 term pregnancies and 5 spontaneous abortions. No congenital abnormalities were reported. The estimated survival was 98% at 5 years[15].

From these studies it is clear that there is a realistic expectation of pregnancy after chemotherapy for ovarian cancer where fertility sparing surgery is possible. However the numbers in such studies are small. Studies commonly document return of menses after chemotherapy but this should not be used as a surrogate endpoint for fertility. In other tumour groups it has been shown that even those who return to normal menstruation may have problems with infertility and not infrequently early menopause. A significant proportion of these women have a history of endometriosis which in itself is associated with infertility[16]. Therefore women must be carefully counselled taking into account age at treatment, risk of a somewhat increased chance of infertility compared to the population average and narrowed fertile window even if menstruation does resume[17]. The effects of targeted therapies which are entering clinical practice on fertility are unknown.

Chemotherapy induced infertility in other gynaecological cancers

Cervical cancer continues to be a problem in young women and a proportion of early stage cancers can be treated by fertility preserving surgery. When these cancers recur cytotoxic chemotherapy is increasingly used for the treatment of advanced disease. Following the publication of two randomised controlled trials demonstrating a survival gain from the use of cisplatin based combinations compared to single agent therapy, confidence has increased in their use[18,19]. The prognosis is often poor and of the order of 1-2 years but some type 1 tumours may remain controlled for several years with the use of chemotherapy and in selected cases hormone therapy.

Chemotherapy may also be used for the treatment of advanced or recurrent endometrial cancer, which is becoming an increasing problem in younger women in view of the epidemic of obesity affecting the western world. However, these women will not have an intact uterus and gestational surrogacy may be the only available option. Vulvar cancer is also increasing in younger women, in many cases associated with HPV. However, experience with chemotherapy is limited and remissions are generally of short duration.

PRESERVING FERTILITY

Fertility preservation in women undergoing chemotherapy may involve the choice of a chemotherapy regimen less likely to induce infertility as discussed above, the cryopreservation of embryos, oocytes or ovarian tissue, or the suppression of ovarian function during chemotherapy. Each of these techniques has potential advantages and disadvantages and the appropriate approach is dependent on clinical and social circumstances.

Embryo cryopreservation

Cryopreservation of embryos relies on *in vitro* fertilisation (IVF) techniques that have been in use for over 30 years, and have led to millions of conceptions and live births. In this procedure, eggs are harvested following ovarian stimulation, IVF is performed and embryos are then frozen and stored prior to thawing and implantation at a later date. Ovarian stimulation generally involves around 2 wk of daily injections of follicle-stimulating hormone (FSH), during which oestrogen levels and follicular growth are monitored. Final maturation of the oocyte is induced through injection of human chorionic gonadotrophin

and oocytes are aspirated under ultrasound guidance. Oocyte retrieval involves an outpatient surgical procedure, using a vaginal ultrasound probe to guide transvaginal aspiration of eggs. The procedure may be performed under sedation or general anaesthesia. Eggs are fertilised *in vitro* by sperm obtained from the patient's partner or donor sperm, and the zygote is then grown *in vitro* for up to 5 d prior to cryopreservation.

The first pregnancy following embryo cryopreservation was reported in 1983, with the first live birth reported the year after. Since then it is estimated that several hundred thousand babies have been born from cryopreserved embryos. Individual success rates are relatively high, with a pregnancy rate of around 60% following transfer in two reported series[20,21]. A recent review of the literature suggests that with modern techniques, cryopreserved embryos implant at comparable rates to fresh embryos[22]. The length of storage does not impact significantly on subsequent pregnancy outcome[23], and successful pregnancy has been reported following storage for over 10 years[24]. Embryo cryopreservation does not appear to be associated with an increased risk of congenital abnormalities[25,26].

In patients with oestrogen sensitive tumours such as endometrial or breast cancer increasing oestrogen levels may promote tumour growth. This has led to the investigation of alternative methods of ovarian stimulation in which low dose FSH is combined with tamoxifen or letrozole[27]. While this appears to be a feasible strategy, the utility in preventing cancer recurrence or progression is unproven.

While cryopreservation of embryos is well established, several potential disadvantages exist. As discussed above, ovarian stimulation must start within the first three days of the menstrual cycle, and this technique risks delaying the commencement of chemotherapy by up to 5 wk. In addition a small percentage of patients may need more than one cycle of ovarian stimulation in order to successfully obtain oocytes. This delay in commencement of therapy may cause anxiety in patients and their families, and be unacceptable to patients, leading to a decision to forgo fertility preservation.

Oocyte cryopreservation

Embryo cryopreservation may also be inappropriate for patients who are not currently in a stable relationship, and who do not wish to use donor sperm. Cryopreservation of oocytes may be preferable in these women. The procedure for egg cryopreservation is identical to that described above except that unfertilised eggs are harvested and stored. These oocytes are later thawed and fertilised, frequently using techniques such as intracytoplasmic sperm injection (ICSI), before implantation.

Cryopreservation of oocytes is less well developed than that of embryos, as oocytes are more vulnerable to damage during the freezing process, and it was initially feared that this technique would lead to increased birth defects. While the first reports of pregnancy following oocyte cryopreservation were made in the 1980's, these did not proceed to term and low success rates deterred further investigation. However, improved techniques led to increasing success in cryopreservation in the latter half of the 1990's and a live birth following oocyte cryopreservation and ICSI was reported in 1997[28], with several other reported successes following. A recent review of the literature has identified over 900 live births following oocyte cryopreservation; reassuringly this study showed no apparent increase in congenital abnormalities[29].

Cryopreservation of ovaries remains significantly less successful than that of embryos. In a meta-analysis published in 2006, live birth rates of around 2% were reported per oocyte thawed while the overall live birth rate per embryo transfer was 21%[30]. In a different study a rate of only one live birth per 65 embryo transfer cycles was achieved[31]. Recently, an alternative technique of cryopreservation has been developed which employs vitrification instead of slow-cooling. This technique involves the use of flash cooling and a higher concentration of cryoprotectants thus preventing the formation of ice crystals, and leading to the formation of an amorphous glass-like state instead. The use of vitrification and/or other technical advances have led to significantly increased oocyte survival following freeze-thawing, with rates of between 50% and 90% now reported[32].

The advantage with this technique is that there is no requirement for a partner or donor sperm. Additionally some people have religious or ethical beliefs which are opposed to embryo freezing. However the technique is less successful than embryo cryopreservation and is only available in certain centres. In addition, most funding agencies will not currently fund the technique due to its low success rate, and thus high cost per live birth.

Cryopreservation of ovarian tissue

This is very much an experimental technique in which ovarian tissue is surgically removed, frozen and then reimplanted after cancer treatment. At laparoscopy an ovarian wedge biopsy is performed, followed by dissection of the ovarian cortex into thin strips which contain immature follicles. These are then cryopreserved and reimplanted after completion of chemotherapy. The first success with this techniques was reported in 2000, with resumption of ovarian function after transplantation[33]. The first case of a live birth following ovarian transplantation was reported in 2004[34]. Subsequent debate has suggested it is not possible to convincingly prove that the pregnancy resulted from the transplant rather than from the in situ ovary[34,35]. However, over 10 live births have now been reported[36-39], supporting the validity of the technique.

Ovarian cryopreservation requires ovarian reserve in order to be successful and is therefore less likely to be a viable option in patients over 40 years of age. A disadvantage to the technique is the risk of implantation of cancer cells[40], which must be considered and discussed

with the patient prior to the procedure. It has been proposed as an option in preadolescent children[41]. Additionally, the procedure involves the use of general anaesthesia for both the ovarian biopsy and subsequent reimplantation, with attendant risks.

OVARIAN SUPPRESSION WITH GNRH ANALOGUES

Suppression of ovarian function through the use of GnRH analogues would be hypothesised to reduce the likelihood of subsequent ovarian failure, and such protection has been shown in animals[42]. It is thought they may act in several ways. By suppressing the ovaries, recruitment of primordial follicles into the maturation phase is prevented, leading to a reduction of the number of follicles in the vulnerable actively growing phase during exposure to cytotoxic drugs. The resultant low oestrogen state is thought to reduce circulation and therefore drug delivery to the ovaries and it has also been proposed that GnRH agonists upregulate anti-apoptotic factors in the ovary[43]. While early phase studies have been promising[44,45], there remains insufficient evidence to support the safety and effectiveness of gonadotropin-releasing hormone analogues and other means of ovarian suppression on fertility preservation. A Cochrane review published in 2011 identified four randomised controlled trials in this field, the combined results of which showed an increased chance of resumption of menses with co-treatment with intramuscular or subcutaneous GnRH agonists (RR = 1.90, 95%CI: 1.30-2.79) but no difference in pregnancy rates[46]. However, more recently published randomised trials have not shown significant differences in resumption of menses[47,48].

A large Italian randomised controlled trial did show a significant difference with use of GnRH analogues with a rate of early menopause following adjuvant chemotherapy for breast cancer of 25.9% in the control group compared to 8.9% in the group that received the GnRH analogue, triptorelin[49]. A limiting factor of the data is that it is nearly all from breast cancer populations who frequently will receive tamoxifen after chemotherapy which itself may interfere with menstruation. The follow up period is generally insufficient to allow evaluation of pregnancy rates and risk of premature menopause after resumption of menses. Results of ongoing trials such as the Southwest Oncology Group study, Prevention of Early Menopause Study are awaited along with mature data from some of the already published studies to be able to more conclusively evaluate this approach.

AVAILABILITY AND FUNDING

Fertility preservation techniques are not uniformly available, with techniques such as oocyte and ovarian cryopreservation limited to specialist centres, between which reported success rates vary. Funding availability also differs widely, both between and within countries. In the United Kingdom for example, the NHS may fund up to three cycles of IVF for any woman with infertility, but there is significant regional variation in the criteria applied, and the number of cycles funded. The cost of a self-funded cycle of IVF in the United Kingdom is approximately £5000 (approximately US $8000), and storage of embryos and oocytes may additionally incur costs of several hundred pounds per year. The costs for cryopreservation techniques are likely to be higher in the United States.

CONCLUSION

Infertility is a major concern in patients undergoing treatment for gynaecological malignancies, and can be overcome by a range of techniques, which have been outlined here. While fertility preservation will not be feasible in every patient, a discussion of the issue should be entered into early in the management of each patient, taking account of the local availability of services. A multidisciplinary approach will enable complex individualised interventions, which are necessary to maximise the chances of subsequent fertility and pregnancy. Counselling of patients is essential, and support should be available in the event of the procedure being unsuccessful.

While there are clearly ethical constraints on research, further progress with oocyte and ovarian cryopreservation is required to achieve comparable success rates to embryo implantation. Standardisation of techniques and cost reduction should make it feasible for funding agencies to provide more equitable availability of fertility preservation.

REFERENCES

1 **Schover LR**, Rybicki LA, Martin BA, Bringelsen KA. Having children after cancer. A pilot survey of survivors' attitudes and experiences. *Cancer* 1999; **86**: 697-709 [PMID: 10440699 DOI: 10.1002/(SICI)1097-0142(19990815)86]

2 **Loi K**, Lau M, Loh SF, Tan YY, Hong GS, Chan MY, Tan AM. Attitudes toward fertility preservation in female cancer patients. *J Reprod Med* 2010; **55**: 411-416 [PMID: 21043367 DOI: 10.1097/00043426-200606000-00006]

3 **Dow KH**, Harris JR, Roy C. Pregnancy after breast-conserving surgery and radiation therapy for breast cancer. *J Natl Cancer Inst Monogr* 1994; (**16**): 131-137 [PMID: 7999455]

4 **Gorman JR**, Roesch SC, Parker BA, Madlensky L, Saquib N, Newman VA, Pierce JP. Physical and mental health correlates of pregnancy following breast cancer. *Psychooncology* 2010; **19**: 517-524 [PMID: 20425779 DOI: 10.1002/pon.1614]

5 **Fotopoulou C**, Braicu I, Sehouli J. Fertility-sparing surgery in early epithelial ovarian cancer: a viable option? *Obstet Gynecol Int* 2012; **2012**: 238061 [PMID: 22529854 DOI: 10.1155/2012/238061]

6 **Milliken DA**, Shepherd JH. Fertility preserving surgery for carcinoma of the cervix. *Curr Opin Oncol* 2008; **20**: 575-580 [PMID: 19106664 DOI: 10.1097/CCO.0b013e32830b0dc2]

7 **Durlinger AL**, Kramer P, Karels B, de Jong FH, Uilenbroek JT, Grootegoed JA, Themmen AP. Control of primordial follicle recruitment by anti-Müllerian hormone in the mouse ovary. *Endocrinology* 1999; **140**: 5789-5796 [PMID: 10579345 DOI: 10.1210/en.140.12.5789]

8 **Meirow D**, Biederman H, Anderson RA, Wallace WH. Tox-

icity of chemotherapy and radiation on female reproduction. *Clin Obstet Gynecol* 2010; **53**: 727-739 [PMID: 21048440 DOI: 10.1097/GRF.0b013e3181f96b54]
9 **Lee SJ**, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006; **24**: 2917-2931 [PMID: 16651642 DOI: 10.1200/JCO.2006.06.5888]
10 **van Rooij IA**, Broekmans FJ, te Velde ER, Fauser BC, Bancsi LF, de Jong FH, Themmen AP. Serum anti-Müllerian hormone levels: a novel measure of ovarian reserve. *Hum Reprod* 2002; **17**: 3065-3071 [PMID: 12456604 DOI: 10.1093/humrep/17.12.3065]
11 **Brougham MF**, Crofton PM, Johnson EJ, Evans N, Anderson RA, Wallace WH. Anti-Müllerian hormone is a marker of gonadotoxicity in pre- and postpubertal girls treated for cancer: a prospective study. *J Clin Endocrinol Metab* 2012; **97**: 2059-2067 [PMID: 22472563]
12 **Brewer M**, Gershenson DM, Herzog CE, Mitchell MF, Silva EG, Wharton JT. Outcome and reproductive function after chemotherapy for ovarian dysgerminoma. *J Clin Oncol* 1999; **17**: 2670-2675 [PMID: 10561340]
13 **de La Motte Rouge T**, Pautier P, Duvillard P, Rey A, Morice P, Haie-Meder C, Kerbrat P, Culine S, Troalen F, Lhommé C. Survival and reproductive function of 52 women treated with surgery and bleomycin, etoposide, cisplatin (BEP) chemotherapy for ovarian yolk sac tumor. *Ann Oncol* 2008; **19**: 1435-1441 [PMID: 18408223 DOI: 10.1093/annonc/mdn162]
14 **Low JJ**, Perrin LC, Crandon AJ, Hacker NF. Conservative surgery to preserve ovarian function in patients with malignant ovarian germ cell tumors. A review of 74 cases. *Cancer* 2000; **89**: 391-398 [PMID: 10918171 DOI: 10.1002/1097-0142(20000715)89:]
15 **Schilder JM**, Thompson AM, DePriest PD, Ueland FR, Cibull ML, Kryscio RJ, Modesitt SC, Lu KH, Geisler JP, Higgins RV, Magtibay PM, Cohn DE, Powell MA, Chu C, Stehman FB, van Nagell J. Outcome of reproductive age women with stage IA or IC invasive epithelial ovarian cancer treated with fertility-sparing therapy. *Gynecol Oncol* 2002; **87**: 1-7 [PMID: 12468335 DOI: 10.1006/gyno.2002.6805]
16 **Macer ML**, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. *Obstet Gynecol Clin North Am* 2012; **39**: 535-549 [PMID: 23182559 DOI: 10.1016/j.ogc.2012.10.002]
17 **Letourneau JM**, Ebbel EE, Katz PP, Oktay KH, McCulloch CE, Ai WZ, Chien AJ, Melisko ME, Cedars MI, Rosen MP. Acute ovarian failure underestimates age-specific reproductive impairment for young women undergoing chemotherapy for cancer. *Cancer* 2012; **118**: 1933-1939 [PMID: 21850728 DOI: 10.1002/cncr.26403]
18 **Krishnansu ST**, Sill M, Long HJ, Ramondetta LM, Landrum LM, Oaknin A, Reid TJ, Leitao MM, Michael HE, Monk BJ. Incorporation of bevacizumab in the treatment of recurrent and metastatic cervical cancer: A Phase III randomized trial of the Gynecologic Oncology Group. *J Clin Oncol* 2013; **31** suppl: Abstr 3
19 **Long HJ**, Bundy BN, Grendys EC, Benda JA, McMeekin DS, Sorosky J, Miller DS, Eaton LA, Fiorica JV. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. *J Clin Oncol* 2005; **23**: 4626-4633 [PMID: 15911865 DOI: 10.1200/JCO.2005.10.021]
20 **Kosasa TS**, McNamee PI, Morton C, Huang TT. Pregnancy rates after transfer of cryopreserved blastocysts cultured in a sequential media. *Am J Obstet Gynecol* 2005; **192**: 2035-209; discussion 2035-209; [PMID: 15970888 DOI: 10.1016/j.ajog.2005.02.036]
21 **Veeck LL**, Bodine R, Clarke RN, Berrios R, Libraro J, Moschini RM, Zaninovic N, Rosenwaks Z. High pregnancy rates can be achieved after freezing and thawing human blastocysts. *Fertil Steril* 2004; **82**: 1418-1427 [PMID: 15533370 DOI: 10.1016/j.fertnstert.2004.03.068]
22 **Edgar DH**, Gook DA. A critical appraisal of cryopreservation (slow cooling versus vitrification) of human oocytes and embryos. *Hum Reprod Update* 2012; **18**: 536-554 [PMID: 22537859 DOI: 10.1093/humupd/dms016]
23 **Riggs R**, Mayer J, Dowling-Lacey D, Chi TF, Jones E, Oehninger S. Does storage time influence postthaw survival and pregnancy outcome? An analysis of 11,768 cryopreserved human embryos. *Fertil Steril* 2010; **93**: 109-115 [PMID: 19027110 DOI: 10.1016/j.fertnstert.2008.09.084]
24 **Revel A**, Safran A, Laufer N, Lewin A, Reubinov BE, Simon A. Twin delivery following 12 years of human embryo cryopreservation: case report. *Hum Reprod* 2004; **19**: 328-329 [PMID: 14747175 DOI: 10.1093/humrep/deh046]
25 **Wennerholm UB**, Hamberger L, Nilsson L, Wennergren M, Wikland M, Bergh C. Obstetric and perinatal outcome of children conceived from cryopreserved embryos. *Hum Reprod* 1997; **12**: 1819-1825 [PMID: 9308820 DOI: 10.1093/humrep/12.8.1819]
26 **Sutcliffe AG**, D'Souza SW, Cadman J, Richards B, McKinlay IA, Lieberman B. Minor congenital anomalies, major congenital malformations and development in children conceived from cryopreserved embryos. *Hum Reprod* 1995; **10**: 3332-3337 [PMID: 8822471]
27 **Oktay K**, Buyuk E, Libertella N, Akar M, Rosenwaks Z. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. *J Clin Oncol* 2005; **23**: 4347-4353 [PMID: 15824416 DOI: 10.1200/JCO.2005.05.037]
28 **Porcu E**, Fabbri R, Seracchioli R, Ciotti PM, Magrini O, Flamigni C. Birth of a healthy female after intracytoplasmic sperm injection of cryopreserved human oocytes. *Fertil Steril* 1997; **68**: 724-726 [PMID: 9341619 DOI: 10.1016/S0015-0282(97)00268-9]
29 **Noyes N**, Porcu E, Borini A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. *Reprod Biomed Online* 2009; **18**: 769-776 [PMID: 19490780 DOI: 10.1016/S1472-6483(10)60025-9]
30 **Oktay K**, Cil AP, Bang H. Efficiency of oocyte cryopreservation: a meta-analysis. *Fertil Steril* 2006; **86**: 70-80 [PMID: 16818031 DOI: 10.1016/j.fertnstert.2006.03.017]
31 **La Sala GB**, Nicoli A, Villani MT, Pescarini M, Gallinelli A, Blickstein I. Outcome of 518 salvage oocyte-cryopreservation cycles performed as a routine procedure in an in vitro fertilization program. *Fertil Steril* 2006; **86**: 1423-1427 [PMID: 17070194 DOI: 10.1016/j.fertnstert.2006.04.031]
32 **Boldt J**. Current results with slow freezing and vitrification of the human oocyte. *Reprod Biomed Online* 2011; **23**: 314-322 [PMID: 21592862 DOI: 10.1016/j.rbmo.2010.11.019]
33 **Oktay K**, Karlikaya G. Ovarian function after transplantation of frozen, banked autologous ovarian tissue. *N Engl J Med* 2000; **342**: 1919 [PMID: 10877641 DOI: 10.1056/NEJM200006223422516]
34 **Donnez J**, Dolmans MM, Demylle D, Jadoul P, Pirard C, Squifflet J, Martinez-Madrid B, van Langendonckt A. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. *Lancet* 2004; **364**: 1405-1410 [PMID: 15488215 DOI: 10.1016/S0140-6736(04)17222-X]
35 **Hubinont C**, Debieve F, Biard JM, Bernard P. Livebirth after cryopreserved ovarian tissue transplantation. *Lancet* 2012; **380**: 106; author reply 107; discussion 107-108 [PMID: 22794237 DOI: 10.1016/S0140-6736(12)61171-4]
36 **Hubinont C**, Debieve F, Biard JM, Debauche C, Bernard P. Livebirth after cryopreserved ovarian tissue autotransplantation. *Lancet* 2004; **364**: 2093 [PMID: 15589302 DOI: 10.1016/S0140-6736(04)17541-7]
37 **Meirow D**, Levron J, Eldar-Geva T, Hardan I, Fridman E, Zalel Y, Schiff E, Dor J. Pregnancy after transplantation

of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. *N Engl J Med* 2005; **353**: 318-321 [PMID: 15983020 DOI: 10.1056/NEJMc055237]

38 **Demeestere I**, Simon P, Emiliani S, Delbaere A, Englert Y. Fertility preservation: successful transplantation of cryopreserved ovarian tissue in a young patient previously treated for Hodgkin's disease. *Oncologist* 2007; **12**: 1437-1442 [PMID: 18165621 DOI: 10.1634/theoncologist.12-12-1437]

39 **Schmidt KT**, Rosendahl M, Ernst E, Loft A, Andersen AN, Dueholm M, Ottosen C, Andersen CY. Autotransplantation of cryopreserved ovarian tissue in 12 women with chemotherapy-induced premature ovarian failure: the Danish experience. *Fertil Steril* 2011; **95**: 695-701 [PMID: 20828687 DOI: 10.1016/j.fertnstert.2010.07.1080]

40 **Donnez J**, Silber S, Andersen CY, Demeestere I, Piver P, Meirow D, Pellicer A, Dolmans MM. Children born after autotransplantation of cryopreserved ovarian tissue. a review of 13 live births. *Ann Med* 2011; **43**: 437-450 [PMID: 21226660 DOI: 10.3109/07853890.2010.546807]

41 **Oktay K**, Buyuk E. Ovarian transplantation in humans: indications, techniques and the risk of reseeding cancer. *Eur J Obstet Gynecol Reprod Biol* 2004; **113** Suppl 1: S45-S47 [PMID: 15041130 DOI: 10.1016/j.ejogrb.2003.11.010]

42 **Ataya K**, Rao LV, Lawrence E, Kimmel R. Luteinizing hormone-releasing hormone agonist inhibits cyclophosphamide-induced ovarian follicular depletion in rhesus monkeys. *Biol Reprod* 1995; **52**: 365-372 [PMID: 7711205 DOI: 10.1095/biolreprod52.2.365]

43 **Blumenfeld Z**. How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist cotreatment in addition to cryopreservation of embrya, oocytes, or ovaries. *Oncologist* 2007; **12**: 1044-1054 [PMID: 17914074 DOI: 10.1634/theoncologist.12-9-1044]

44 **Recchia F**, Sica G, De Filippis S, Saggio G, Rosselli M, Rea S. Goserelin as ovarian protection in the adjuvant treatment of premenopausal breast cancer: a phase II pilot study. *Anticancer Drugs* 2002; **13**: 417-424 [PMID: 11984088]

45 **Urruticoechea A**, Arnedos M, Walsh G, Dowsett M, Smith IE. Ovarian protection with goserelin during adjuvant chemotherapy for pre-menopausal women with early breast cancer (EBC). *Breast Cancer Res Treat* 2008; **110**: 411-416 [PMID: 17851753 DOI: 10.1007/s10549-007-9745-y]

46 **Chen H**, Li J, Cui T, Hu L. Adjuvant gonadotropin-releasing hormone analogues for the prevention of chemotherapy induced premature ovarian failure in premenopausal women. *Cochrane Database Syst Rev* 2011; (**11**): CD008018 [PMID: 22071842 DOI: 10.1002/14651858.CD008018.pub2]

47 **Gerber B**, von Minckwitz G, Stehle H, Reimer T, Felberbaum R, Maass N, Fischer D, Sommer HL, Conrad B, Ortmann O, Fehm T, Rezai M, Mehta K, Loibl S. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. *J Clin Oncol* 2011; **29**: 2334-2341 [PMID: 21537042 DOI: 10.1200/JCO.2010.32.5704]

48 **Munster PN**, Moore AP, Ismail-Khan R, Cox CE, Lacevic M, Gross-King M, Xu P, Carter WB, Minton SE. Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2012; **30**: 533-538 [PMID: 22231041 DOI: 10.1200/JCO.2011.34.6890]

49 **Del Mastro L**, Boni L, Michelotti A, Gamucci T, Olmeo N, Gori S, Giordano M, Garrone O, Pronzato P, Bighin C, Levaggi A, Giraudi S, Cresti N, Magnolfi E, Scotto T, Vecchio C, Venturini M. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. *JAMA* 2011; **306**: 269-276 [PMID: 21771987 DOI: 10.1001/jama.2011.991]

P- Reviewers: Papatsoris AG, Tsikouras P, Zafrakas M
S- Editor: Gou SX **L- Editor**: A **E- Editor**: Zhang DN

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com