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EDITORIAL

Infertility and gynaecological oncology

Mona El-Bahrawy

Mona El-Bahrawy, Department of Histopathology, Imperial College London, Hammersmith Hospital, London W12 0NN, United Kingdom
Author contributions: El-Bahrawy M solely contributed to this paper.
Correspondence to: Dr. Mona El-Bahrawy, Department of Histopathology, Imperial College London, Hammersmith Hospital, DuCane Road, London W12 0NN, United Kingdom. m.elbahrawy@imperial.ac.uk
Telephone: +44-208-3833442 Fax: +44-208-3838141
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Abstract

Infertility and gynaecological cancer are two major problems in the field of women's health, where both have serious implications on a woman's physical, social and emotional wellbeing. There are well established links between many aspects of infertility and different types of gynaecological malignancies, including etiology, pathogenesis and disease management. In this special issue there are valuable articles that highlight different aspects of the relationship between infertility and gynaecological oncology. The issue covers conditions that represent risk factors for both infertility and gynaecological neoplasia. There is emphasis on the role of the fallopian tube being a critical organ for both conditions. There is a review on the advances in cancer diagnosis and treatment with consideration of the preservation of patient fertility. The various technologies for fertility preservation are reviewed and their strengths and weaknesses discussed. One of the important fertility preservation techniques is cryopreservation of embryo oocytes or ovarian tissue. This special issue emphasises that fertility preservation is now an important consideration in oncology clinics, and the options available to patients are routinely offered. Future developments will offer women in this difficult situation more options for fertility preservation, with an individualised approach for each patient. Equally, for infertile patients it is important to assess the risk of malignancy so as to provide optimal and timely intervention.

Key words: Infertility; Gynaecological tract; Cancer; Malignant; Tumour

Core tip: Infertility and gynaecological cancer are two major problems in the field of women's health, where both have serious implications on a woman's physical, social and emotional wellbeing. In this special issue there are valuable articles that highlight different aspects of the relationship between infertility and gynaecological oncology. This special issue emphasises that fertility preservation is now an important consideration in oncology clinics, and the options available to patients are routinely offered.

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INFERTILITY AND GYNAECOLOGICAL ONCOLOGY

Infertility and gynaecological cancer are two major problems in the field of women's health, where both have serious implications on a woman's physical, social and emotional wellbeing. There are well established links between many aspects of infertility and different types of gynaecological malignancies, including etiology, pathogenesis and disease management. In this special issue there are valuable articles that highlight different aspects of the relationship between infertility and gynaecological oncology.

Some of the conditions contributing to female factor infertility are known risk factors of gynaecological neoplasia, and infertility may itself be a risk factor for the development of several types of gynaecological neoplasms.

Factors playing a role in both infertility and gynaecological tumours include hormonal factors and endometriosis[1]. Also factors that prolong exposure to ovulation as infertility increase the risk of ovarian cancer, due to the damaging effects of the liberated reactive oxygen species on the regional epithelium[2]. The review by El Sabaa[3] addresses the different conditions that play a role in both infertility and gynaecological oncology.

Magdy and El-Bahrawy[4] specifically review the role of the fallopian tube in infertility and gynaecological oncology. Tubal factor infertility is a leading cause of female factor infertility[1]. Tubal dysfunction may due to tubal occlusion, peritubal adhesion and fimbrial damage, all of which can lead to reproductive failure. Recently several studies suggested a role for the fallopian tube in the development of ovarian carcinoma[5].

With advances in cancer diagnosis and treatment, there is notable improvement in patient survival. The ability to have children is significant for the well-being in cancer survivors. The management of gynaecological malignancies involves surgery, pelvic radiotherapy and chemotherapy, for which infertility and subfertility are common sequelae. Hence fertility preservation is a particularly challenging area in this setting. Recently fertility sparing management of gynaecological cancers has been developed.

As the trend to delay childbearing continues a greater number of women are being diagnosed with endometrial cancer at a stage in life when they wish to conceive. In his review Farthing[6] presents the studies addressing the success and limitations of conservative medical treatment with progestagens in such situation as an alternative to hysterectomy and removal of both ovaries in suitable cases.

Due to improved cure rates from radical chemo-radiotherapy many young women treated for cervical cancer will wish to attempt to preserve their fertility[7]. Evidence of the impact of pelvic radiotherapy on the female reproductive organs, the currently available fertility sparing options, and possible future strategies are reviewed by Welsh and Taylor[8].

Different fertility preservation techniques may be performed prior to both surgery and chemotherapy, to enable subsequent pregnancy in the patient or a surrogate mother. One of these techniques is cryopreservation of embryo oocytes or ovarian tissue[9]. Similarly, evolving chemotherapy regimens with replacement of alkylating agents will reduce the incidence of infertility. In their review Sacco *et al*[10] discuss different scenarios of how infertility presents a clinical problem in gynaecological malignancies as a complication to the use of chemotherapy. The various technologies for fertility preservation are reviewed and their strengths and weaknesses discussed. Wahba and Al-Inany[11] in their article provide the details of the options for ovarian stimulation for fertility preservation in women with gynecological cancer. Their review also addresses the issue of increased levels of estradiol during ovulation induction in women with estrogen sensitive cancers, such as breast and endometrial cancer.

This special issue emphasises that fertility preservation is now an important consideration in oncology clinics, and the options available to patients are routinely offered. Future developments will offer women in this difficult situation more options for fertility preservation, with an individualised approach for each patient. Equally, for infertile patients it is important to assess the risk of malignancy so as to provide optimal and timely intervention.

REFERENCES

1 **Cetin I**, Cozzi V, Antonazzo P. Infertility as a cancer risk factor - a review. *Placenta* 2008; **29** Suppl B: 169-177 [PMID: 18790330 DOI: 10.1016/j.placenta.2008.08.007]

2 **Murdoch WJ**, Martinchick JF. Oxidative damage to DNA of ovarian surface epithelial cells affected by ovulation: carcinogenic implication and chemoprevention. *Exp Biol Med (Maywood)* 2004; **229**: 546-552 [PMID: 15169974]

3 **El Sabaa BM**. Pathological conditions predisposing to infertility and gynaecological neoplasia. *World J Obstet Gynecol* 2014; **3**: 28-34 [DOI: 10.5317/wjog.v3.i2.28]

4 **Magdy N**, El-Bahrawy M. Fallopian tube: Its role in infertility and gynecological oncology. *World J Obstet Gynecol* 2014; **3**: 35-41 [DOI: 10.5317/wjog.v3.i2.35]

5 **Li J**, Fadare O, Xiang L, Kong B, Zheng W. Ovarian serous carcinoma: recent concepts on its origin and carcinogenesis. *J Hematol Oncol* 2012; **5**: 8 [PMID: 22405464 DOI: 10.1186/1756-8722-5-8]

6 **Farthing A**. Fertility sparing management of endometrial complex hyperplasia and endometrial carcinoma. *World J Obstet Gynecol* 2014; **3**: 42-44 [DOI: 10.5317/wjog.v3.i2.42]

7 **Lobo RA**. Potential options for preservation of fertility in women. *N Engl J Med* 2005; **353**: 64-73 [PMID: 16000356]

8 **Welsh LC**, Taylor A. Impact of pelvic radiotherapy on the female genital tract and fertility preservation measures. *World J Obstet Gynecol* 2014; **3**: 45-53 [DOI: 10.5317/wjog.v3.i2.45]

9 **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]

10 **Sacco JJ**, Cliff J, Green JA. Chemotherapy for gynaecological malignancies and fertility preservation. *World J Obstet Gynecol* 2014; **3**: 54-60 [DOI: 10.5317/wjog.v3.i2.54]

11 **Wahba AH**, Al-Inany H. Ovulation induction in the gynecological cancer patient. *World J Obstet Gynecol* 2014; **3**: 61-66 [DOI: 10.5317/wjog.v3.i2.61]

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TOPIC HIGHLIGHT

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

Pathological conditions predisposing to infertility and gynaecological neoplasia

Bassma Mohamed El Sabaa

Bassma Mohamed El Sabaa, Department of Pathology, Alexandria Faculty of Medicine, Alexandria University, Alexandria 21111, Egypt
Author contributions: El Sabaa BM solely wrote the paper.
Correspondence to: Bassma Mohamed El Sabaa, MD, PhD, Associate Professor, Department of Pathology, Alexandria Faculty of Medicine, Alexandria University, El Shatby, Alexandria 21111, Egypt. bassma_el_sabaa@yahoo.com
Telephone: +20-12-27574826 Fax: +20-3-4294963
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Abstract

Some of the conditions long blamed for female factor infertility are now acknowledged as well established risk factors of gynecological neoplasia. This realization has lead to the proposition that infertility might be a risk factor for the development of several types of gynecological neoplasms. This review addresses different conditions that play a role in both infertility and gynaecological neoplasia. An intricate interplay between growth factors and hormonal factors (estrogens and progestins, androgens and gonadotropins) is said to link the state of infertility to some gynecological tumors. The relation between endometriosis -as one of the well established causes of female infertility - and ovarian cancer is well known. Endometriosis has been particularly related to endometrioid and clear-cell ovarian carcinomas. Another evidence for this association is embodied in finding endometriotic lesions adjacent to ovarian cancers. The polycystic ovary syndrome (PCOS), one of the most prevalent endocrine disorders and a long studied cause of female infertility increases the risk of endometrial carcinoma. The link between PCOS and endometrial carcinoma seems to be endometrial hyperplasia. PCOS-associated endometrial carcinoma tends to present at a younger age and early stage, with lower grade and lower risk of metastasis. Turner's syndrome and other types of ovarian dysgenesis constitute a rare cause of infertility and are known to confer a definite risk of germ cell tumors. There seems to be a link between infertility and an increased risk of gynecological neoplasia. Hence, it is important to assess the risk of malignancy in each category of infertile patients so as to provide optimal and timely intervention.

Key words: Infertility-gynecological cancer; Endometriosis; Polycystic ovary syndrome; Ovarian dysgenesis; Endometrioid carcinoma; Clear cell carcinoma; Turner's syndrome; Gonadoblastoma; Hyperestrogenemia

Core tip: Female infertility is now acknowledged as a risk factor of gynecological neoplasia. In this mini-review we conduct a comprehensive literature review to verify this prospect. The principal pathogenetic mechanisms linking infertility to gynecological neoplasia are pointed out. The relationship between each of endometriosis and polycystic ovary syndrome and gynecological neoplasia is explored in depth. We discuss the relation of Turner's syndrome (the prototype of ovarian dysgenesis) to gynecological cancer. Is there a relation between increased risk of ovarian cancer and ovulation-stimulation drugs? We will attempt to answer this question.

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INTRODUCTION

In a World Health Organization 1992[1] study of 8500 infertile couples, the female factor was responsible for infertility in 37% of cases *vs* the male factor which was responsible in 8% of cases, while both factors were jointly

responsible for infertility in 35% of cases[1]. Ovulatory disorders, genetic factors, endometriosis, pelvic adhesions, tubal obstruction and hyperprolactinemia together constitute the principal causes of female factor infertility[1].

IS THERE A RELATION BETWEEN INFERTILITY AND GYNECOLOGICAL NEOPLASIA?

Some of the conditions responsible for female factor infertility are known risk factors of gynecological neoplasia. Ovarian and endometrial cancers are associated with several risk factors such as low parity, early age of menarche and late age of menopause[2].

It is a well known fact that infertile females are more at risk of endometrial cancer[2].

Compared with fertile ones, infertile women had an adjusted odds ratio for endometrial cancer of 1.7 (95%CI: 1.1-2.6). On the other hand, infertile women due to ovarian factors had an adjusted odds ratio of 4.2 (95%CI: 1.7-10.4) suggesting that much of the increased risk of endometrial carcinoma seen in some infertile women might be ascribed to anovulation[3]. In the same context, there is some evidence to suggest that infertility increases risk of ovarian cancer as well[4,5].

Numerous studies have endeavored to explain the observed increased risk of ovarian cancer in infertile females. Most have inferred that factors operative in that setting include the pathogenesis of infertility itself, the effects of ovulation inducing drugs, a "putative" shared genetic susceptibility to infertility and ovarian cancer, or an as yet unrecognized factor[6].

The etiology of ovarian cancer is poorly understood. Many hypotheses point to the cumulative insults of repeated ovulation "theory of incessant ovulation[7]" coupled with exposure of the ovary to high gonadotropin levels. These factors are believed to be the proximate players that can stimulate cell proliferation and malignant transformation of the ovarian surface epithelium. Factors interrupting ovulation and empowering progesterone stimulation or androgen reduction were found to decrease the risk of ovarian cancer. Such factors include pregnancy, breastfeeding and the use of oral contraceptives. On the other hand, factors that prolong exposure to ovulation as infertility were found to augment the risk[8-12] by as much as 36%-46%[4,5].

In fact the number of lifetime ovulatory cycles (LOC) relative to age was found to be a significant predictive factor for survival in ovarian cancer patients, where patients with higher LOC had worse overall survival (HR = 1.67; 95%CI: 1.20-2.33)[13]. Years before that research was conducted; the role of ovarian surface epithelium in ovulation had been demonstrated. Ovarian surface epithelial cells in the vicinity of the apical portion of preovulatory graafian follicles produce a urokinase which augments the production of tumour necrosis factor-α. The latter induces matrix metalloproteinase gene expression, apoptosis and inflammatory necrosis leading to follicle rupture. Afterwards, the disrupted ovarian epithelium is reconstituted by stem cell multiplication. The damaging effects of the liberated reactive oxygen species and the reparative/regenerative events that occur due to the repeated bouts of ovulation[14] have been linked to surface epithelial ovarian cancer. During the ovulatory process, DNA integrity of surface epithelial cells surrounding the rupture point is deranged. Replication of such cells will perpetuate the putative DNA error which might play a role in ovarian carcinogenesis[15].

In the same context, vitamin E and progesterone have been experimentally proven, recently, to confer protection against ovarian neoplastic transformation by abrogating ovulation associated oxidative bursts and by improving the repair capacity of surface epithelium[16].

Different phases of a woman's reproductive life display varying sensitivities of ovarian cells to hormone stimulation. Loss of ovarian function taking place during transition to menopause results in follicular depletion and hence fluctuation in estrogen and a corresponding surge in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. However, menopause is also associated with a remarkable attenuation of the negative feedback exerted by gonadal steroids on the hypothalamo-pituitary axis. Based on these facts, Tung *et al*[17] came to the conclusion that the risk reducing effects of anovulatory states as pregnancy and intake of oral contraceptives were more pronounced in pre-menopausal compared to postmenopausal women.

Evidence is now accumulating about the existence of stem cells in postnatal and adult mammalian (including human) ovaries. This has great potential for initiating major developments in understanding and managing ovarian infertility as well as ovarian carcinogenesis[18].

Pathogenetic link between infertility and gynecological "malignancy"

Abnormalities in growth factors and hormonal status seem to be the pivotal players in this link.

Growth factors: Adipose tissue and stromal cells of the ovary generate growth factors, *e.g.*, insulin-like growth factor 1 (IGF-1), transforming growth factor and tumor necrosis factor after hormonal stimulation. A complex interplay of growth factors in polycystic ovary syndrome (PCOS) patients is believed to be the main cause of subfertility/infertility in these patients[19,20]. One such example is the elevated serum IGF-I concentrations in obese PCOS patients[21-25]. On the other hand, growth factors can enhance cellular autonomy and are stimulatory to neoangiogenesis, which are key factors in tumor development and progression[26-28]. In the endometrium, estrogen exerts its trophic effect *via* driving the local expression of the *IGF-1* gene[24]. Genetic variation in strategic genes in the IGF pathway may have impact on the rate of endometrial cell proliferation/differentiation and hence on the risk of malignant transformation[25].

Steroid hormones have been implicated in the etiopathogenesis of epithelial ovarian cancer[26].

Androgens: Hyperandrogenemia during the reproductive years is known to interfere with the normal ovulatory cycle and may result in infertility[27-31]. Several lines of evidence point to a possible role for androgens in ovarian carcinogenesis. There is increased incidence of ovarian cancer after menopause when there is relative predominance of androgens over estrogens. Androgen receptor positivity is expressed in 90% of ovarian cancers with favorable outcomes and chemotherapy induced reduction in androgen elaboration by cancer cells[26].

Gonadotrophins: Pituitary gonadotrophins are considered indirect tumor promoters for ovarian cancer. Furthermore, there is increasing evidence that ovarian and uterine carcinomas express gonadotrophin receptors, indicating the possibility of a direct tumorigenic role for FSH and LH[29-32].

Estrogens: It is a well established fact since 1947, that prolonged endometrial stimulation by unopposed estrogen is a risk factor for the development of endometrial cancer[33]. Anovulatory females recorded higher serum levels of estrogen and higher incidence of endometrial carcinoma especially in PCOS[34].

ENDOMETRIOSIS AND CANCER

Multiple factors seem to be involved in the etio-pathogenesis of both endometriosis and ovarian cancer including hormonal, genetic and immunologic factors. Endometriosis confers a twofold increased risk of developing ovarian cancer rising to fourfold in high risk endometriosis patients with infertility[2].

Several studies confirm endometriosis as an independent risk factor for ovarian cancer[35]. In fact, these two conditions share common predisposing factors, comparable patterns of local invasion and distal spread, similar response to estrogen-induced growth signaling, resistance to apoptosis and genomic instability[35].

The incidence of endometriosis in epithelial ovarian cancer has been calculated to be 4.5%, 1.4%, 35.9% and 19% for serous, mucinous, clear-cell and endometrioid ovarian carcinoma, respectively[35]. It is common knowledge now that the latter two types (endometrioid[36] and clear-cell ovarian[37] carcinomas) are the types most frequently associated with endometriosis[37].

Another evidence for this association is finding endometriotic lesions adjacent to ovarian cancers. Common genetic alterations[38] as *PTEN, p53*[39-41], *HNF-1* activation[42], *K-ras*[42,43], and *bcl* gene mutations[39,44] present further evidence to a possible sequence of genetic changes resulting in transition from endometriosis to ovarian cancer[40]. Furthermore, analogous to neoplastic proliferations, endometriosis has been shown to be monoclonal with several studies documenting loss of heterozygosity[39,42,45,46].

Recently, mutation of *ARID1A*, a tumor-suppressor gene[39,47], and loss of BAF250a[48], both detected in tumor tissue and contiguous foci of atypical endometriosis (but not in distant endometriotic lesions)[48] have been considered important early events in the malignant transformation of endometriosis to endometrioid and clear cell carcinomas[39,48,49].

Another phenomenon linking endometriosis to ovarian cancer is the state of heme and iron induced oxidative stress and chronic inflammation[39,50,51] associated with endometriosis. This state entails cytokine release that through a series of complex steps can eventually culminate in unregulated mitosis, growth, apoptosis and migration; all of which represent key events in tumour development and progression[40,42].

Endometriosis-associated ovarian cancer has been shown to have a more favorable biological behavior as compared to non-endometriosis-associated ovarian cancer, with presentation at a lower stage and a better survival[35].

PCOS AND GYNECOLOGICAL NEOPLASIA

The PCOS is one of the most prevalent endocrine disorders, affecting around 5%-10%[52] of women in the reproductive age group. PCOS is characterized by signs of hyperandrogenism[53], obesity[54], hirsutism[55,56], anovulation, infertility, menstrual irregularities[57] and insulin resistance[58,59]. On sonographic examination the ovaries are usually enlarged with multiple small cysts (2-8 mm)[60,61].

PCOS patients have long-term, higher risk for endometrial hyperplasia and endometrial cancer[62-65], (three[34] to fourfold[66]) due to chronic anovulation which results in continuous estrogen stimulation of the endometrium, unopposed by progesterone[60,67].

Most of the factors known to increase the risk of developing endometrial cancer as obesity, long term unopposed hyperestrogenaemia, nulliparity, infertility and diabetes[68-70] are also known to be associated with PCOS.

The link between PCOS and endometrial carcinoma seems to be endometrial hyperplasia. Forty-eight point eight percent of PCOS cases have endometrial hyperplasia[34]. The estimated rate of progression from hyperplasia to carcinoma within 2 to 10 years seems to be 0.4% for simple hyperplasia[60] and approaches 18% for cases of atypical complex hyperplasia[60,71].

PCOS-associated endometrial carcinoma tends to present at a younger age and early stage, with lower grade and lower risk of metastasis. These factors have practically invited some authors[72,73] to advocate conservative management of carcinoma in these patients.

PCOS has also been reported to be associated with low-grade endometrial stromal sarcoma and uterine carcinosarcoma[74].

Other sex hormone dependent cancers as breast and ovarian cancers have also been linked to PCOS[61]. Recent evidence about association between PCOS and ovarian malignancy are still conflicting[71,74]. According to Danish

studies, the implied state of infertility *per se* increases the risk of borderline and malignant ovarian tumors[75]. High local steroid and growth factor concentrations - frequently observed in PCOS - are considered risk factors for ovarian carcinoma[61]. However, a large scale British study confirms that the standardized mortality rate for ovarian cancer in these patients does not exceed 0.39 (95%CI: 0.01-2.17)[76]. There is insufficient evidence to implicate PCOS in the development of vaginal, vulval and cervical cancers[34].

OVARIAN DYSGENESIS, GENETIC INFERTILITY AND CANCER

Sex chromosome abnormalities compose the largest category of chromosome aberrations and the most common genetic cause of infertility among humans[77-80]. Dysgenetic gonads are at risk for development of germ cell tumors[81-84] which may stem from genetic and/or hormonal factors[85,86].

Dysgenetic gonads are reported to progress to invasive germ cell neoplasms namely; dysgerminoma and less commonly embryonal carcinoma, teratoma, yolk sac tumor and choriocarcinoma[87]. Accordingly some authors[81,88] advocated prophylactic gonadectomy once the diagnosis of gonadal dysgenesis is established.

Turner syndrome is one of the most common conditions resulting from cytogenetic abnormalities where there is complete or partial monosomy of the X-chromosome. These patients have a significantly increased risk of ovarian gonadoblastoma[81,85], dysgerminoma[84] and cancer of the corpus uteri in addition to a constellation of somatic tumors including central nervous system, ocular and urinary bladder tumors[85,89,90]. Paradoxically, risk for breast cancer is decreased among patients with Turner syndrome[85,91,92].

FERTILITY DRUGS AND GYNECOLOGICAL CANCER

Generally, data concerning the possible association of exposure to ovulation induction medications and developing invasive ovarian cancer show no increased risk[6,93-95]. A group exploring the long-term (over 20 years) health effects of ovarian-stimulation drugs showed no relationship between ovarian cancer risk and ovulation-stimulation drugs[91]. However they stressed the importance of continuous monitoring to verify whether such risks were higher among particular user cohorts[96-98]. According to some studies, women who failed to conceive after infertility treatment were found to be at a higher risk for ovarian malignancy compared to women who responded successfully[6,91,99].

The relationship of these agents with risk of breast and endometrial cancer is still controversial[95,100].

CONCLUSION

Infertility seems to confer an increased risk of gynecological neoplasia. It is important to assess the risk of malignancy in each category of infertile patients so as to provide optimal timely intervention. To date, no solid relation has been declared between fertility drugs and causation of gynecological malignancy.

REFERENCES

1 Recent advances in medically assisted conception. Report of a WHO Scientific Group. *World Health Organ Tech Rep Ser* 1992; **820**: 1-111 [PMID: 1642014]

2 **Cetin I**, Cozzi V, Antonazzo P. Infertility as a cancer risk factor - a review. *Placenta* 2008; **29** Suppl B: 169-177 [PMID: 18790330 DOI: 10.1016/j.placenta.2008.08.007]

3 **Escobedo LG**, Lee NC, Peterson HB, Wingo PA. Infertility-associated endometrial cancer risk may be limited to specific subgroups of infertile women. *Obstet Gynecol* 1991; **77**: 124-128 [PMID: 1984211]

4 **Tworoger SS**, Fairfield KM, Colditz GA, Rosner BA, Hankinson SE. Association of oral contraceptive use, other contraceptive methods, and infertility with ovarian cancer risk. *Am J Epidemiol* 2007; **166**: 894-901 [PMID: 17656616 DOI: 10.1093/aje/kwm157]

5 **Jensen A**, Sharif H, Olsen JH, Kjaer SK. Risk of breast cancer and gynecologic cancers in a large population of nearly 50,000 infertile Danish women. *Am J Epidemiol* 2008; **168**: 49-57 [PMID: 18448441 DOI: 10.1093/aje/kwn094]

6 **Rossing MA**, Tang MT, Flagg EW, Weiss LK, Wicklund KG. A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. *Am J Epidemiol* 2004; **160**: 1070-1078 [PMID: 15561986 DOI: 10.1093/aje/kwh315]

7 **Fathalla MF**. Incessant ovulation--a factor in ovarian neoplasia? *Lancet* 1971; **2**: 163 [PMID: 4104488]

8 **Salehi F**, Dunfield L, Phillips KP, Krewski D, Vanderhyden BC. Risk factors for ovarian cancer: an overview with emphasis on hormonal factors. *J Toxicol Environ Health B Crit Rev* 2008; **11**: 301-321 [PMID: 18368558 DOI: 10.1080/10937400701876095]

9 **Hennessy BT**, Coleman RL, Markman M. Ovarian cancer. *Lancet* 2009; **374**: 1371-1382 [PMID: 19793610 DOI: 10.1016/S0140-6736(09)61338-6]

10 **Sueblinvong T**, Carney ME. Current understanding of risk factors for ovarian cancer. *Curr Treat Options Oncol* 2009; **10**: 67-81 [PMID: 19603272 DOI: 10.1007/s11864-009-0108-2]

11 **Ness RB**, Cramer DW, Goodman MT, Kjaer SK, Mallin K, Mosgaard BJ, Purdie DM, Risch HA, Vergona R, Wu AH. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. *Am J Epidemiol* 2002; **155**: 217-224 [PMID: 11821246 DOI: 10.1093/aje/155.3.217]

12 **Tung KH**, Goodman MT, Wu AH, McDuffie K, Wilkens LR, Kolonel LN, Nomura AM, Terada KY, Carney ME, Sobin LH. Reproductive factors and epithelial ovarian cancer risk by histologic type: a multiethnic case-control study. *Am J Epidemiol* 2003; **158**: 629-638 [PMID: 14507598 DOI: 10.1093/aje/kwg177]

13 **Robbins CL**, Whiteman MK, Hillis SD, Curtis KM, McDonald JA, Wingo PA, Kulkarni A, Marchbanks PA. Influence of reproductive factors on mortality after epithelial ovarian cancer diagnosis. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 2035-2041 [PMID: 19589914]

14 **Murdoch WJ**, Martinchick JF. Oxidative damage to DNA of ovarian surface epithelial cells affected by ovulation: carcinogenic implication and chemoprevention. *Exp Biol Med* (Maywood) 2004; **229**: 546-552 [PMID: 15169974]

15 **Murdoch WJ**, McDonnel AC. Roles of the ovarian surface epithelium in ovulation and carcinogenesis. *Reproduction* 2002; **123**: 743-750 [PMID: 12052228 DOI: 10.1530/rep.0.1230743]

16 **Murdoch WJ**. Carcinogenic potential of ovulatory genotox-

icity. *Biol Reprod* 2005; **73**: 586-590 [PMID: 15958727 DOI: 10.1095/biolreprod.105.042622]
17 **Tung KH**, Wilkens LR, Wu AH, McDuffie K, Nomura AM, Kolonel LN, Terada KY, Goodman MT. Effect of anovulation factors on pre- and postmenopausal ovarian cancer risk: revisiting the incessant ovulation hypothesis. *Am J Epidemiol* 2005; **161**: 321-329 [PMID: 15692075 DOI: 10.1093/aje/kwi046]
18 **Virant-Klun I**, Stimpfel M, Skutella T. Stem cells in adult human ovaries: from female fertility to ovarian cancer. *Curr Pharm Des* 2012; **18**: 283-292 [PMID: 22229565]
19 **Qiao J**, Feng HL. Extra- and intra-ovarian factors in polycystic ovary syndrome: impact on oocyte maturation and embryo developmental competence. *Hum Reprod Update* 2011; **17**: 17-33 [PMID: 20639519 DOI: 10.1093/humupd/dmq032]
20 **Kelly CJ**, Stenton SR, Lashen H. Insulin-like growth factor binding protein-1 in PCOS: a systematic review and meta-analysis. *Hum Reprod Update* 2011; **17**: 4-16 [PMID: 20634211 DOI: 10.1093/humupd/dmq027]
21 **Yee D**, Paik S, Lebovic GS, Marcus RR, Favoni RE, Cullen KJ, Lippman ME, Rosen N. Analysis of insulin-like growth factor I gene expression in malignancy: evidence for a paracrine role in human breast cancer. *Mol Endocrinol* 1989; **3**: 509-517 [PMID: 2747657]
22 **Aaronson SA**. Growth factors and cancer. *Science* 1991; **254**: 1146-1153 [PMID: 1659742]
23 **Cross M**, Dexter TM. Growth factors in development, transformation, and tumorigenesis. *Cell* 1991; **64**: 271-280 [PMID: 1988148]
24 **Murphy LJ**, Ghahary A. Uterine insulin-like growth factor-1: regulation of expression and its role in estrogen-induced uterine proliferation. *Endocr Rev* 1990; **11**: 443-453 [PMID: 2226350]
25 **McGrath M**, Lee IM, Buring J, De Vivo I. Common genetic variation within IGFI, IGFII, IGFBP-1, and IGFBP-3 and endometrial cancer risk. *Gynecol Oncol* 2011; **120**: 174-178 [PMID: 21078522 DOI: 10.1016/j.ygyno.2010.10.012]
26 **Wang PH**, Chang C. Androgens and ovarian cancers. *Eur J Gynaecol Oncol* 2004; **25**: 157-163 [PMID: 15032272]
27 **Diamanti-Kandarakis E**, Papailiou J, Palimeri S. Hyperandrogenemia: pathophysiology and its role in ovulatory dysfunction in PCOS. *Pediatr Endocrinol Rev* 2006; **3** Suppl 1: 198-204 [PMID: 16641860]
28 **Araki T**, Elias R, Rosenwaks Z, Poretsky L. Achieving a successful pregnancy in women with polycystic ovary syndrome. *Endocrinol Metab Clin North Am* 2011; **40**: 865-894 [PMID: 22108285 DOI: 10.1016/j.ecl.2011.08.003]
29 **Lukanova A**, Kaaks R. Endogenous hormones and ovarian cancer: epidemiology and current hypotheses. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 98-107 [PMID: 15668482]
30 **Huhtaniemi I**. Are gonadotrophins tumorigenic--a critical review of clinical and experimental data. *Mol Cell Endocrinol* 2010; **329**: 56-61 [PMID: 20471448 DOI: 10.1016/j.mce.2010.04.028]
31 **Grynberg M**, Even M, Berwanger da Silva AL, Gallot V, Toledano M, Frydman R, Fanchin R. [Cancer, fertility preservation and gonadotropins]. *J Gynecol Obstet Biol Reprod* (Paris) 2012; **41**: 512-518 [PMID: 22633037 DOI: 10.1016/j.jgyn.2012.04.016]
32 **Korbonits M**, Morris DG, Nanzer A, Kola B, Grossman AB. Role of regulatory factors in pituitary tumour formation. *Front Horm Res* 2004; **32**: 63-95 [PMID: 15281340]
33 **GUSBERG SB**. Precursors of corpus carcinoma estrogens and adenomatous hyperplasia. *Am J Obstet Gynecol* 1947; **54**: 905-927 [PMID: 20272298]
34 **Chittenden BG**, Fullerton G, Maheshwari A, Bhattacharya S. Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. *Reprod Biomed Online* 2009; **19**: 398-405 [PMID: 19778486]
35 **Van Gorp T**, Amant F, Neven P, Vergote I, Moerman P. Endometriosis and the development of malignant tumours of the pelvis. A review of literature. *Best Pract Res Clin Obstet Gynaecol* 2004; **18**: 349-371 [PMID: 15157647 DOI: 10.1016/j.bpobgyn.2003.03.001]
36 **Zygouris D**, Leontara V, Makris GM, Chrelias C, Trakakis E, Christodoulaki Ch, Panagopoulos P. Endometrioid ovarian cancer arising from an endometriotic cyst in a young patient. *Eur J Gynaecol Oncol* 2012; **33**: 324-325 [PMID: 22873112]
37 **Kobayashi H**, Kajiwara H, Kanayama S, Yamada Y, Furukawa N, Noguchi T, Haruta S, Yoshida S, Sakata M, Sado T, Oi H. Molecular pathogenesis of endometriosis-associated clear cell carcinoma of the ovary (review). *Oncol Rep* 2009; **22**: 233-240 [PMID: 19578761]
38 **Noack F**, Schmidt H, Buchweitz O, Malik E, Horny HP. Genomic imbalance and onco-protein expression of ovarian endometrioid adenocarcinoma arisen in an endometriotic cyst. *Anticancer Res* 2004; **24**: 151-154 [PMID: 15015590]
39 **Munksgaard PS**, Blaakaer J. The association between endometriosis and ovarian cancer: a review of histological, genetic and molecular alterations. *Gynecol Oncol* 2012; **124**: 164-169 [PMID: 22032835 DOI: 10.1016/j.ygyno.2011.10.001]
40 **Nezhat F**, Datta MS, Hanson V, Pejovic T, Nezhat C, Nezhat C. The relationship of endometriosis and ovarian malignancy: a review. *Fertil Steril* 2008; **90**: 1559-1570 [PMID: 18993168 DOI: 10.1016/j.fertnstert.2008.08.007]
41 **Govatati S**, Chakravarty B, Deenadayal M, Kodati VL, Manolla ML, Sisinthy S, Bhanoori M. p53 and risk of endometriosis in Indian women. *Genet Test Mol Biomarkers* 2012; **16**: 865-873 [PMID: 22784258 DOI: 10.1089/gtmb.2011.0295]
42 **Mandai M**, Yamaguchi K, Matsumura N, Baba T, Konishi I. Ovarian cancer in endometriosis: molecular biology, pathology, and clinical management. *Int J Clin Oncol* 2009; **14**: 383-391 [PMID: 19856044 DOI: 10.1007/s10147-009-0935-y]
43 **Xu B**, Hamada S, Kusuki I, Itoh R, Kitawaki J. Possible involvement of loss of heterozygosity in malignant transformation of ovarian endometriosis. *Gynecol Oncol* 2011; **120**: 239-246 [PMID: 21130491 DOI: 10.1016/j.ygyno.2010.10.036]
44 **Pollacco J**, Sacco K, Portelli M, Schembri-Wismayer P, Calleja-Agius J. Molecular links between endometriosis and cancer. *Gynecol Endocrinol* 2012; **28**: 577-581 [PMID: 22309646 DOI: 10.3109/09513590.2011.650761]
45 **Wang DB**, Ren FY, Ren F. Detecting and investigating the significance of high-frequency LOH chromosome regions for endometriosis-related candidate genes. *Gynecol Endocrinol* 2012; **28**: 553-558 [PMID: 22329782 DOI: 10.3109/09513590.2011.650746]
46 **Ali-Fehmi R**, Khalifeh I, Bandyopadhyay S, Lawrence WD, Silva E, Liao D, Sarkar FH, Munkarah AR. Patterns of loss of heterozygosity at 10q23.3 and microsatellite instability in endometriosis, atypical endometriosis, and ovarian carcinoma arising in association with endometriosis. *Int J Gynecol Pathol* 2006; **25**: 223-229 [PMID: 16810057]
47 **MacKenzie F**, Bullock DG, Ratcliffe JG. UK external quality assessment scheme for immunoassays in endocrinology. *Ann Ist Super Sanita* 1991; **27**: 453-457 [PMID: 1809064 DOI: 10.1007/s00292-011-1488-1]
48 **Wiegand KC**, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, Senz J, McConechy MK, Anglesio MS, Kalloger SE, Yang W, Heravi-Moussavi A, Giuliany R, Chow C, Fee J, Zayed A, Prentice L, Melnyk N, Turashvili G, Delaney AD, Madore J, Yip S, McPherson AW, Ha G, Bell L, Fereday S, Tam A, Galletta L, Tonin PN, Provencher D, Miller D, Jones SJ, Moore RA, Morin GB, Oloumi A, Boyd N, Aparicio SA, Shih IeM, Mes-Masson AM, Bowtell DD, Hirst M, Gilks B, Marra MA, Huntsman DG. ARID1A mutations in endometriosis-associated ovarian carcinomas. *N Engl J Med* 2010; **363**: 1532-1543 [PMID: 20942669 DOI: 10.1056/NEJMoa1008433]
49 **Chan A**, Gilks B, Kwon J, Tinker AV. New insights into the pathogenesis of ovarian carcinoma: time to rethink ovarian cancer screening. *Obstet Gynecol* 2012; **120**: 935-940 [PMID:

22996112]
50 **Rotman C**, Fischel L, Cortez G, Greiss H, Rana N, Rinehart J, Coulam CB. A search to identify genetic risk factors for endometriosis. *Am J Reprod Immunol* 2013; **69**: 92-95 [PMID: 23167810 DOI: 10.1111/aji.12034]
51 **Carvalho LF**, Samadder AN, Agarwal A, Fernandes LF, Abrão MS. Oxidative stress biomarkers in patients with endometriosis: systematic review. *Arch Gynecol Obstet* 2012; **286**: 1033-1040 [PMID: 22791380 DOI: 10.1007/s00404-012-2439-7]
52 **Fauser BC**, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, Carmina E, Chang J, Yildiz BO, Laven JS, Boivin J, Petraglia F, Wijeyeratne CN, Norman RJ, Dunaif A, Franks S, Wild RA, Dumesic D, Barnhart K. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. *Fertil Steril* 2012; **97**: 28-38.e25 [PMID: 22153789 DOI: 10.1016/j.fertnstert.2011.09.024]
53 **Al Kindi MK**, Al Essry FS, Al Essry FS, Mula-Abed WA. Validity of serum testosterone, free androgen index, and calculated free testosterone in women with suspected hyperandrogenism. *Oman Med J* 2012; **27**: 471-474 [PMID: 23226817 DOI: 10.5001/omj.2012.112]
54 **Legro RS**. Obesity and PCOS: implications for diagnosis and treatment. *Semin Reprod Med* 2012; **30**: 496-506 [PMID: 23074008 DOI: 10.1055/s-0032-1328878]
55 **Eriksen MB**, Brusgaard K, Andersen M, Tan Q, Altinok ML, Gaster M, Glintborg D. Association of polycystic ovary syndrome susceptibility single nucleotide polymorphism rs2479106 and PCOS in Caucasian patients with PCOS or hirsutism as referral diagnosis. *Eur J Obstet Gynecol Reprod Biol* 2012; **163**: 39-42 [PMID: 22504079 DOI: 10.1016/j.ejogrb.2012.03.020]
56 **Cebeci F**, Onsun N, Mert M. Insulin resistance in women with hirsutism. *Arch Med Sci* 2012; **8**: 342-346 [PMID: 22662009 DOI: 10.5114/aoms.2012.28563]
57 **Pinola P**, Lashen H, Bloigu A, Puukka K, Ulmanen M, Ruokonen A, Martikainen H, Pouta A, Franks S, Hartikainen AL, Järvelin MR, Morin-Papunen L. Menstrual disorders in adolescence: a marker for hyperandrogenaemia and increased metabolic risks in later life? Finnish general population-based birth cohort study. *Hum Reprod* 2012; **27**: 3279-3286 [PMID: 22933528 DOI: 10.1093/humrep/des309]
58 **Inoue M**, Tsugane S. Insulin resistance and cancer: epidemiological evidence. *Endocr Relat Cancer* 2012; **19**: F1-F8 [PMID: 22851686 DOI: 10.1530/ERC-12-0142]
59 **Patra SK**, Nasrat H, Goswami B, Jain A. Vitamin D as a predictor of insulin resistance in polycystic ovarian syndrome. *Diabetes Metab Syndr* 2012; **6**: 146-149 [PMID: 23158978 DOI: 10.1016/j.dsx.2012.09.006]
60 **Balen A**. Polycystic ovary syndrome and cancer. *Hum Reprod Update* 2001; **7**: 522-525 [PMID: 11727859]
61 **Spritzer PM**, Morsch DM, Wiltgen D. [Polycystic ovary syndrome associated neoplasms]. *Arq Bras Endocrinol Metabol* 2005; **49**: 805-810 [PMID: 16444364]
62 **Kilicdag EB**, Haydardedeoglu B, Cok T, Parlakgumus AH, Simsek E, Bolat FA. Polycystic ovary syndrome and increased polyp numbers as risk factors for malignant transformation of endometrial polyps in premenopausal women. *Int J Gynaecol Obstet* 2011; **112**: 200-203 [PMID: 21247566 DOI: 10.1016/j.ijgo.2010.10.014]
63 **Jakimiuk AJ**, Issat T. PCOS and cancer risk. *Folia Histochem Cytobiol* 2009; **47**: S101-S105 [PMID: 20067879 DOI: 10.2478/v10042-009-0092-1]
64 **Futterweit W**. Polycystic ovary syndrome: a common reproductive and metabolic disorder necessitating early recognition and treatment. *Prim Care* 2007; **34**: 761-789, vi [PMID: 18061817]
65 **Shang K**, Jia X, Qiao J, Kang J, Guan Y. Endometrial abnormality in women with polycystic ovary syndrome. *Reprod Sci* 2012; **19**: 674-683 [PMID: 22534323 DOI: 10.1177/19337191114 30993]
66 **Fearnley EJ**, Marquart L, Spurdle AB, Weinstein P, Webb PM. Polycystic ovary syndrome increases the risk of endometrial cancer in women aged less than 50 years: an Australian case-control study. *Cancer Causes Control* 2010; **21**: 2303-2308 [PMID: 20953904 DOI: 10.1007/s10552-010-9658-7]
67 **Navaratnarajah R**, Pillay OC, Hardiman P. Polycystic ovary syndrome and endometrial cancer. *Semin Reprod Med* 2008; **26**: 62-71 [PMID: 18181084 DOI: 10.1055/s-2007-992926]
68 **Choi Y**, Giovannucci E, Lee JE. Glycaemic index and glycaemic load in relation to risk of diabetes-related cancers: a meta-analysis. *Br J Nutr* 2012; **108**: 1934-1947 [PMID: 23167978 DOI: 10.1017/S0007114512003984]
69 **Gopal M**, Duntley S, Uhles M, Attarian H. The role of obesity in the increased prevalence of obstructive sleep apnea syndrome in patients with polycystic ovarian syndrome. *Sleep Med* 2002; **3**: 401-404 [PMID: 14592171]
70 **Wild RA**. Long-term health consequences of PCOS. *Hum Reprod Update* 2002; **8**: 231-241 [PMID: 12078834]
71 **Daniilidis A**, Dinas K. Long term health consequences of polycystic ovarian syndrome: a review analysis. *Hippokratia* 2009; **13**: 90-92 [PMID: 19561777]
72 **Farhi DC**, Nosanchuk J, Silverberg SG. Endometrial adenocarcinoma in women under 25 years of age. *Obstet Gynecol* 1986; **68**: 741-745 [PMID: 3785784]
73 **McDonald TW**, Malkasian GD, Gaffey TA. Endometrial cancer associated with feminizing ovarian tumor and polycystic ovarian disease. *Obstet Gynecol* 1977; **49**: 654-658 [PMID: 194178]
74 **Gadducci A**, Gargini A, Palla E, Fanucchi A, Genazzani AR. Polycystic ovary syndrome and gynecological cancers: is there a link? *Gynecol Endocrinol* 2005; **20**: 200-208 [PMID: 16019362]
75 **Mosgaard BJ**, Lidegaard O, Kjaer SK, Schou G, Andersen AN. Infertility, fertility drugs, and invasive ovarian cancer: a case-control study. *Fertil Steril* 1997; **67**: 1005-1012 [PMID: 9176436]
76 **Pierpoint T**, McKeigue PM, Isaacs AJ, Wild SH, Jacobs HS. Mortality of women with polycystic ovary syndrome at long-term follow-up. *J Clin Epidemiol* 1998; **51**: 581-586 [PMID: 9674665]
77 **Zhu J**, Liu X, Jin H, Lu X. Swyer syndrome, 46,XY gonadal dysgenesis, a sex reversal disorder with dysgerminoma: a case report and literature review. *Clin Exp Obstet Gynecol* 2011; **38**: 414-418 [PMID: 22268289]
78 **Heard E**, Turner J. Function of the sex chromosomes in mammalian fertility. *Cold Spring Harb Perspect Biol* 2011; **3**: a002675 [PMID: 21730045 DOI: 10.1101/cshperspect.a002675]
79 **Vaiman D**. Fertility, sex determination, and the X chromosome. *Cytogenet Genome Res* 2002; **99**: 224-228 [PMID: 12900568]
80 **Düzcan F**, Atmaca M, Cetin GO, Bagci H. Cytogenetic studies in patients with reproductive failure. *Acta Obstet Gynecol Scand* 2003; **82**: 53-56 [PMID: 12580840]
81 **Jonson AL**, Geller MA, Dickson EL. Gonadal dysgenesis and gynecologic cancer. *Obstet Gynecol* 2010; **116** Suppl 2: 550-552 [PMID: 20664451 DOI: 10.1097/AOG.0b013e3181e4bfe9]
82 **Beaulieu Bergeron M**, Lemieux N, Brochu P. Undifferentiated gonadal tissue, Y chromosome instability, and tumors in XY gonadal dysgenesis. *Pediatr Dev Pathol* 2011; **14**: 445-459 [PMID: 21692598 DOI: 10.2350/11-01-0960-OA.1]
83 **Skakkebaek NE**, Holm M, Hoei-Hansen C, Jørgensen N, Rajpert-De Meyts E. Association between testicular dysgenesis syndrome (TDS) and testicular neoplasia: evidence from 20 adult patients with signs of maldevelopment of the testis. *APMIS* 2003; **111**: 1-9; discussion 9-11 [PMID: 12752226]
84 **Kota SK**, Gayatri K, Pani JP, Kota SK, Meher LK, Modi KD. Dysgerminoma in a female with turner syndrome and Y chromosome material: A case-based review of literature. *Indian J Endocrinol Metab* 2012; **16**: 436-440 [PMID: 22629515 DOI: 10.4103/2230-8210.95706]
85 **Schoemaker MJ**, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA. Cancer incidence in women with Turner syndrome in Great Britain: a national cohort study. *Lancet Oncol* 2008; **9**:

239-246 [PMID: 18282803 DOI: 10.1016/S1470-2045(08)70033-0]
86 **Shahsiah R**, Jahanbin B, Rabiei R, Ardalan FA, Sarhadi B, Izadi-Mood N. Malignant ovarian germ cell tumours in gonadal Y chromosome mosaicism. *J Clin Pathol* 2011; **64**: 973-976 [PMID: 21752796 DOI: 10.1136/jcp.2011.090738]
87 **Pauls K**, Franke FE, Büttner R, Zhou H. Gonadoblastoma: evidence for a stepwise progression to dysgerminoma in a dysgenetic ovary. *Virchows Arch* 2005; **447**: 603-609 [PMID: 15968543]
88 **Ben Temime R**, Chachial A, Attial L, Ghodbanel I, Makhloufl T, Koubaal A, Kourda N, Ben Jilani S, Dammak T, El May A, Rahal K. 46 XY pure gonadal dysgenesis with gonadoblastoma and dysgerminoma. *Tunis Med* 2008; **86**: 710-713 [PMID: 19472738]
89 **Ben Romdhane K**, Bessrour A, Ben Amor MS, Ben Ayed M. [Pure gonadal dysgenesis with 46 XY karyotyping (Swyer's syndrome) with gonadoblastoma, dysgerminoma and embryonal carcinoma]. *Bull Cancer* 1988; **75**: 263-269 [PMID: 3370322]
90 **Changchien YC**, Haltrich I, Micsik T, Kiss E, Fónyad L, Papp G, Sápi Z. Gonadoblastoma: Case report of two young patients with isochromosome 12p found in the dysgerminoma overgrowth component in one case. *Pathol Res Pract* 2012; **208**: 628-632 [PMID: 22906432 DOI: 10.1016/j.prp.2012.07.006]
91 **Swerdlow AJ**, Hermon C, Jacobs PA, Alberman E, Beral V, Daker M, Fordyce A, Youings S. Mortality and cancer incidence in persons with numerical sex chromosome abnormalities: a cohort study. *Ann Hum Genet* 2001; **65**: 177-188 [PMID: 11427177]
92 **Bösze P**, Tóth A, Török M. Hormone replacement and the risk of breast cancer in Turner's syndrome. *N Engl J Med* 2006; **355**: 2599-2600 [PMID: 17167149]
93 **Vlahos NF**, Economopoulos KP, Creatsas G. Fertility drugs and ovarian cancer risk: a critical review of the literature. *Ann N Y Acad Sci* 2010; **1205**: 214-219 [PMID: 20840275 DOI: 10.1111/j.1749-6632.2010.05668.x]
94 **Brinton LA**, Sahasrabuddhe VV, Scoccia B. Fertility drugs and the risk of breast and gynecologic cancers. *Semin Reprod Med* 2012; **30**: 131-145 [PMID: 22549713 DOI: 10.1055/s-0032-1307421]
95 **Lerner-Geva L**, Rabinovici J, Olmer L, Blumstein T, Mashiach S, Lunenfeld B. Are infertility treatments a potential risk factor for cancer development? Perspective of 30 years of follow-up. *Gynecol Endocrinol* 2012; **28**: 809-814 [PMID: 22475084 DOI: 10.3109/09513590.2012.671391]
96 **Vlahos NF**, Economopoulos KP, Fotiou S. Endometriosis, in vitro fertilisation and the risk of gynaecological malignancies, including ovarian and breast cancer. *Best Pract Res Clin Obstet Gynaecol* 2010; **24**: 39-50 [PMID: 19733123 DOI: 10.1016/j.bpobgyn.2009.08.004]
97 **Silva Idos S**, Wark PA, McCormack VA, Mayer D, Overton C, Little V, Nieto J, Hardiman P, Davies M, MacLean AB. Ovulation-stimulation drugs and cancer risks: a long-term follow-up of a British cohort. *Br J Cancer* 2009; **100**: 1824-1831 [PMID: 19436296 DOI: 10.1038/sj.bjc.6605086]
98 **Vause TD**, Cheung AP, Sierra S, Claman P, Graham J, Guillemin JA, Lapensée L, Stewart S, Wong BC. Ovulation induction in polycystic ovary syndrome. *J Obstet Gynaecol Can* 2010; **32**: 495-502 [PMID: 20500959]
99 **Lerner-Geva L**, Rabinovici J, Lunenfeld B. Ovarian stimulation: is there a long-term risk for ovarian, breast and endometrial cancer? *Womens Health* (Lond Engl) 2010; **6**: 831-839 [PMID: 21118041 DOI: 10.2217/whe.10.67]
100 **Twombly R**. Too early to determine cancer risk from infertility treatments. *J Natl Cancer Inst* 2012; **104**: 501-502 [PMID: 22440681 DOI: 10.1093/jnci/djs197]

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TOPIC HIGHLIGHT

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

Fallopian tube: Its role in infertility and gynecological oncology

Nesreen Magdy, Mona El-Bahrawy

Nesreen Magdy, Department of Pathology, National Cancer Institute, Cairo University, Cairo 14211, Egypt
Mona El-Bahrawy, Department of Histopathology, Imperial College London, Hammersmith Hospital, London W12 0NN, United Kingdom
Mona El-Bahrawy, Department of Pathology, Faculty of Medicine, University of Alexandria, Azarita 31211, Egypt
Author contributions: Magdy N wrote the manuscript; El-Bahrawy M developed the concept and plan of the manuscript and edited and revised the manuscript.
Correspondence to: Dr. Mona El-Bahrawy, Department of Histopathology, Imperial College London, Hammersmith Hospital, DuCane Road, London W12 0NN, United Kingdom. m.elbahrawy@imperial.ac.uk
Telephone: +44-208-3833442 Fax: +44-208-3839141
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Abstract

Disorders of the fallopian tube play a very important role in both infertility and gynaecological oncology. Tubal factor infertility is considered among the leading causes of female factor infertility. Many tubal disorders are related to infertility including congenital anomalies, acute and chronic inflammatory diseases, endometriosis and other pathologies that result in partial or total fallopian tube obstruction. In the field of gynaecological oncology, ovarian surface epithelial tumors remain one of the most fatal malignancies in women worldwide carrying the worst prognosis among female genital malignancies. For decades, the cell of origin of epithelial tumors has remained controversial and was largely believed to be surface ovarian epithelium. Recently several studies suggested that there is a major role of the fallopian tube in the development of ovarian surface epithelial tumors, mainly high grade serous carcinoma and other tumour types. In this article we review the role of the fallopian tube in both infertility and gynaecological oncology.

Key words: Fallopian tube; Infertility; Endometriosis; Salpingitis; Serous carcinoma

Core tip: Disorders of the fallopian tube play a major role in infertility. These disorders include congenital anomalies, inflammation and different other causes of tubal obstruction. Recently several studies suggested a role for the fallopian tube in the development of ovarian carcinoma, mainly high grade serous carcinoma. This article reviews the role of the fallopian tube in infertility and gynaecological oncology.

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INTRODUCTION

The fallopian tube plays an important role in problems related to infertility[1] and is only recently recognized to play the leading role in the pathogenesis of pelvic (non-uterine) serous carcinomas[2].

THE FALLOPIAN TUBE AND INFERTILITY

Infertility is defined as couple's failure to conceive after 1 year of regular, unprotected intercourse[3]. Tubal factor infertility is among the leading causes of female factor infertility accounting for 7%-9.8% of all female factor infertilities. Tubal disease directly causes 36% and 85% of all cases of female factor infertility in developed and developing nations respectively[4].

The fallopian tubes must be patent with normal anatomic relation to the adjacent ovary to allow the capture

of an ovum, provide a suitable environment for fertilization, and transport the fertilized ovum to the endometrial cavity for implantation[3]. Transport of gametes and embryos is achieved by complex interaction between myosalpynx contractions, ciliary activity and the flow of tubal secretions[5]. This complex movement also aims at stirring of the tubal contents to ensure mixing of gametes and embryos with tubal secretions[6]. The fallopian tube itself acts as a sperm storage site as the endosalpinx provides a favorable environment for sperms. Sperm-endosalpingeal contact preserves the viability of sperms increasing the chance for successful fertilization[1].

Tubal factor infertility may result from complete blockage of the distal end of the fallopian tube (hydrosalpinx) as a sequelae of sexually transmitted disease (STD), surgical intervention or other intra-abdominal conditions, non-gynecological abdomino-pelvic infection, endometriosis, or a congenital anomaly. Proximal obstruction may result from salpingitis isthmica nodosa (SIN) or other inflammatory conditions, or it may be idiopathic. Peritubal adhesions or damage to the lining of the tube can impair tubal mobility, oocyte pickup, and/or sperm and embryo transport[7].

CONGENITAL ANOMALIES AND GENETIC DISORDERS

Congenital müllerian duct abnormalities are considered fairly common and have been estimated to be present in 1 in 500-700 women, yet complete absence of fallopian tube is a very rare condition that is usually unilateral and asymptomatic[8,9]. Absence or loss of patency of segments of the fallopian tube (atresia, hypoplasia, or interruption)[10], and ampullary atresia[11] were also described. These may be unilateral or bilateral, and can occur without or in conjunction with uterine anomalies, such as uni or bi-cornuate uterus[10].

The use of diethylstilbestrol (DES) during pregnancy was discontinued decades ago, but surgical specimens from patients who were born during the DES era may still be examined today, showing substantial developmental damage to the fallopian tubes. Fetal exposure to DES results in shortened, sacculated, and convoluted fallopian tubes. The fimbriae are constricted, and the os is pinpoint. The mucosa may be absent and if present, the plicae do not develop[1].

Tubal dysfunction may also be caused by the immotile cilia of Kartagener's syndrome[5], including about one half of the patients with primary ciliary dyskinesia (PCD). The latter is an autosomal recessive condition with estimated incidence of 0.5-1 in 30000 live births, causing dysfunctional motility of cilia and impaired mucociliary clearance, resulting in many clinical manifestations including recurrent sinopulmonary disease, laterality defects and infertility[12].

INFLAMMATORY DISEASES

Salpingitis causes tubal occlusion, peritubal adhesion and fimbrial damage, all of which can lead to reproductive failure[13,14]. Microorganisms and the host's immune response may result in scar tissue formation, altering the activity of tubal cilia, resulting in the partial or complete destruction of cilia with alteration of the composition and viscosity of the tubal secretions[15]. The inflammation in the tube may extend to adjacent tissues, including the ovary, forming a tubo-ovarian abscess[16].

Three major types of salpingitis are recognized: acute, chronic, and granulomatous/histiocytic[1].

Acute salpingitis (other than physiologic salpingitis, occurring at time of menses or puerperium)[1,16] is the pathologic correlate of the clinical entity, pelvic inflammatory disease (PID), which occurs in young, sexually active women in the reproductive age[1]. Acute salpingitis may be caused by an ascending infection, following invasive procedures (such as curettage or the insertion of intrauterine devices)[17], or secondary to STD by Chlamydia, N. gonorrhoeae or Mycoplasma[16]. Seminal fluid acts as a vehicle through which microbes are transferred to the upper genital tract. Some microorganisms have the ability to attach to the surface of spermatozoa, whilst others are obligate intracellular parasites within the spermatozoa[15]. Other non-sexually transmitted pathogens (*e.g.*, *E. coli*, *streptococci*, *staphylococci*, *coliform bacilli*, and *anaerobes*) may reach the tubes *via* the blood stream or lymphatics, especially after an abortion or pregnancy[16]. The response of the mucosa of the fallopian tube to microorganisms is not uniform. For example, *E. coli* cause swelling of the ciliary tips with adhesions between shortened and swollen cilia and cause shortened microvilli in non-ciliated cells. N. gonorrhoeae causes invagination in ciliated cells and loss of microvilli in non-ciliated cells[15].

Chlamydia trachomatis (a Gram-negative bacterium) is the most common organism of STDs worldwide[18], it can be isolated from a large portion of women with tubal factor infertility and elevated anti-C trachomatis antibodies can be detected in more than 70% of women with tubal occlusion. Yet, the exact pathogenesis of C trachomatis-induced tubal damage is still unknown with no available effective vaccines[19,20]. The primary site of chlamydial infections is the columnar endocervical epithelial cells[20]. It has been hypothesized that the host immune response by C trachomatis infection is responsible for the damage rather than the infection itself[21,22]. The protective host immune response is induced by production of antibodies against chlamydial major outer membrane protein (MOMP). This was supported by the recent findings that immunization with a native MOMP induces protection[22]. However, antibodies against chlamydial heat shock protein (HSP) 60 are associated with pathologies, which may provide an explanation for the observation that whole chlamydial organism-based vaccines is associated with exacerbated pathology. Chlamydial infection leads to tubal ciliated epithelial destruction with subsequent tubal infertility and ectopic pregnancy *via* production of cytokines, including interleukin (IL)-1, which has a toxic effect on ciliated tubal cells[15]. Chlamydia can enter a dormant, per-

sistent state, where, in the absence of a productive infection, there is still a low level of immune stimulation from antigen recognition. This low level stimulation is believed to cause chronic inflammatory cell infiltration[20].

In chronic salpingitis, the tubal fimbriae adhere to the ovary and adjacent tissues with subsequent obliteration of the ostium, leading to a hydrosalpinx or pyosalpinx. Hydrosalpinx is typically bilateral, but it may be unilateral. Late stages of chronic salpingitis may result in fibrous obliteration of the whole tubal lumen[16].

Granulomatous and histiocytic salpingitis may result from infection by different organisms (*e.g.*, Mycobacterium tuberculosis, Schistosoma, Oxyuris vermicularis, Actinomyces, Coccidioides immitis) or as part of a systemic granulomatous disease (*e.g.*, sarcoidosis and Crohn's disease)[17]. It may also be induced by local non-infectious causes, including foreign bodies introduced for diagnostic or therapeutic purposes (*e.g.,* lubricant jellies, mineral oil, powder or lipiodol)[1,16,17].

The commonest cause of granulomatous salpingitis is infection with Mycobacterium tuberculosis; predominantly affecting females below the age of 40 years, with peak age between 21-30 years. Tubal involvement occurs in 80%-90% of women with genital tuberculosis and is usually bilateral (90% of the cases)[23,24]. Tuberculous salpingitis is uncommon in the western world yet prevalent in developing countries[24], accounting for much less than 1% of cases in the United States, while representing nearly 40% of cases in India[1].

Female genital tuberculosis occurs secondary to primary disease elsewhere in the body. The spread is usually hematogenous or *via* the lymphatic route[24]. Sexual transmission of the disease is also documented but direct spread from other intraperitoneal foci is very rare[23]. Tuberculosis may cause minimal tubal damage and lead to ectopic pregnancy. However, extensive damage to the tubes can lead to tubal blockage in 60% of cases. Peritubal adhesions and tubo-ovarian masses have been found in 47.2% of cases[24]. As the tubercles enlarge and coalesce, they may erode through the mucosa and discharge their contents into the tubal lumen, leading to progressive scarring, with plica distortion and agglutination. Calcification can occur in areas of fibrosis[1,16,17].

Female genital schistosomiasis was described for the first time in a young Egyptian woman more than 100 years ago[25]. Tubal schistosomiasis may be one of the common causes of granulomatous salpingitis worldwide; yet it is rare in the United States[1,16]. More than 207 million people, representing 85% of those who live in Africa, are infected with schistosomiasis[26]. In Africa, the fallopian tube is involved by schistosomiasis in 22% of all infected women[1,2], with 7% presenting by infertility. The cervix, fallopian tubes and vagina are the most common gynecological sites to be affected. Blood vessel anastomoses between the pelvic organs are probably responsible for "spill-over" of eggs into the genital tract[27]. Gross findings appear to be related to fibrosis surrounding the eggs, producing a nodular or fibrotic tube[1,16].

Fungal infection rarely can cause tubo-ovarian abscesses or granulomatous salpingitis. Responsible organisms include Blastomyces dermatitidis, Coccidioides immitis, Candida, and Aspergillus reaching the fallopian tube by hematogenous spread or in the course of disseminated disease[1,16]. Pseudo-xanthomatous salpingitis (referred to as "pigmentosis tubae") is associated with endometriosis, yet it also might result from salpingitis with associated hemorrhage[1,16,17]. A granulomatous reaction may also be encountered in small to medium size arteries in patients with giant-cell arteritis[16].

ENDOMETRIOSIS

Endometriosis affects 5%-10% of the general female population of reproductive age[28], including 50%-60% of women and teenage girls with pelvic pain[29]. About 30%-50% of women with endometriosis are infertile[30]. Infertile women are 6-8 times more likely to have endometriosis than fertile women. Of infertile women 25%-50% have endometriosis[8,29]. Tubal endometriosis is identified in approximately 10% of fallopian tubes, most commonly involving the distal end[31]. Normally, endometrial tissue can be found within the mucosa of intramural and isthmic segments of the fallopian tube, referred to as endometrial colonization[1]. Endometriosis of the tube can be found within the lumen (focal replacement of tubal epithelium by uterine mucosa)[17]; or myosalpinx or on the serosa. Occasionally, tubal endometriosis may produce a mass simulating a tumor (polypoid endometriosis). Post-salpingectomy endometriosis is an apparently common form of endometriosis that occurs in the tip of the proximal stump of the fallopian tube years after tubal ligation[1].

Despite extensive research, several mechanisms have been proposed to explain endometriosis-related tubal factor infertility with no consensus reached to date[32]. The most popular hypothesis involves retrograde menstruation into the peritoneal cavity[33]. The retrograde menstruation of non-sterile menstrual blood into the peritoneal cavity provides a route for microbial transport. The menstrual debris may also promote continued survival and persistence of these microorganisms in the upper genital tract. These microorganisms may replicate causing tubal damage and the microflora stimulate chemotaxis of macrophages and the subsequent secretion of secondary inflammatory mediators identified in this condition[15].

Other mechanisms include: (1) associated pelvic inflammation causing adhesions and scar formation with subsequent impaired ovarian oocyte release or capture as well as impairment of tubal transport due to physical obstruction[15,30] in advanced stages of endometriosis[33]; (2) associated increased volume of peritoneal fluid[30], that contains increased numbers of macrophages and their secreted products (*e.g.*, growth factors, cytokines, and angiogenic factors) affecting various aspects of reproduction[33]. Also a macromolecular ovum capture inhibitor, causing formation of a membrane over the fimbrial cilia,

has been detected in the peritoneal fluid from women with endometriosis[15]; (3) Recently, endometriosis has been proposed to be an autoimmune disease because of the presence of a variety of autoantibodies against endometrium, ovary and sperm, these autoantibodies can be an important risk factor in endometriosis-associated infertility[34]; (4) Other theories are altered hormonal and cell-mediated function due to increased IgG and IgA antibodies and lymphocytes in the endometrium of women with endometriosis leading to alteration of endometrial receptivity and embryo implantation; and (5) associated endocrine and ovulatory disorders (*e.g.*, longer follicular phase with possibly lower serum estradiol levels and lower LH-dependent progesterone secretion during the luteal phase of the cycle)[30].

SIN or "adenomyosis" of the fallopian tube is a pseudo-infiltrative lesion consisting of diverticula of tubal epithelium in the isthmus. It occurs in women between the ages of 25 and 60 years (average, 30 years)[1]. The incidence of SIN in healthy, fertile women ranges from 0.6% to 11%[31]. It is bilateral in approximately 85% of cases[17]. It is accompanied by infertility in approximately one-half of patients[17] by interfering with upward sperm migration[31]. It may be difficult to distinguish SIN from tubal endometriosis in some cases[1].

ECTOPIC PREGNANCY

Ectopic pregnancy is defined as a pregnancy occurring outside the uterus or in an abnormal site within the uterus; 95%-99% arise in the fallopian tube[35]. The vast majority (80%) occur in the ampulla, with the isthmus (10%) and infundibulum (5%) being less common sites[31]. About 25% of tubal pregnancies have ruptured by the time of diagnosis[1]. This may impair/destroy tubal function with partial occlusion or luminal adhesions[36]. The usual treatment for tubal pregnancy is salpingectomy, yet segmental tubal resection may be appropriate in selected cases[17]. Retention of fertility after an ectopic pregnancy depends on how that pregnancy was managed and on the presence or absence of known risk factors[37]. Improvements in management of ectopic pregnancies have enhanced efforts towards preserving subsequent fertility; a principal goal of conservative treatment. However, conservative treatments are likely to increase the recurrence rate of ectopic pregnancy as the conserved tube is usually a damaged tube[38].

THE FALLOPIAN TUBE AND GYNECOLOGICAL ONCOLOGY

Primary fallopian tube adenocarcinoma is rare, accounting for less than 0.2% of cancer diagnoses among women annually[39]. Tubal carcinoma represents 0.7%-1.5% of gynecologic invasive malignancies[1] with an incidence of 0.41 per 100000 women in the United States[40]. In England and Wales, 40 cases of primary tubal adenocarcinoma are registered annually[41].

On the other hand, ovarian cancer is the 6th most common cancer in women worldwide and the 7th most common cause of cancer death[42] with an age-adjusted incidence rate 12.7 per 100000 women per year. This is based on cases diagnosed in 2005-2009 from 18 SEER geographic areas[43]. In Western countries, ovarian carcinoma is the 5th most common malignancy ranking 4th in cancer mortality, accounting for 4% of cancer in women and is the most frequent cause of death due to gynecological cancer. In United States women, ovarian cancer ranks 9th in incidence and 5th in mortality, accounting for 3% of cancers and 5% of cancer deaths. Serous carcinoma is the most common type of the ovarian epithelial malignancies, accounting for approximately 80% of cases[44].

Ovarian cancer has one of the highest death-to-incidence ratios[2,45] and is considered the most lethal of gynecologic malignancies[44]. The age-adjusted death rate is 8.2 per 100000 women per year in the United States[43].

A prerequisite for the success of early detection of any disease is the clear understanding of its natural history[46]. The high ovarian cancer related death rates have been attributed to the unavailability of effective screening tools, the absence of early symptoms in many patients, and the typical presentation at advanced stages when prognosis is poor[2,47]. One of the greatest obstacles to the detection of early-stage ovarian cancer was the poor understanding of its histogenesis and pathogenesis[2].

Until recently, the incessant ovulation theory has been the most accepted theory of ovarian carcinogenesis. According to this theory, constant ovulation-induced damage and repair of the ovarian surface epithelium (OSE) results in malignant transformation[48]. Ovarian carcinoma was also traditionally thought to originate from the OSE or ovarian epithelial inclusions (OEI)[2,49]. Hence, investigative efforts for early detection were centred on the ovary for decades. However, all have not been successful[2,50], as they failed to identify a convincing precursor in the ovary[49]. This was greatly reflected on the overall survival for women with ovarian cancer, which has not changed in any fundamental manner over the last 50 years[43].

Over the last several years, based on combined morphological and molecular data, a dualistic model for the pathogenesis of ovarian carcinoma has emerged[50,51]. The dualistic model divides ovarian epithelial tumors into two categories: Type Ⅰ and Type Ⅱ[1]. Type Ⅰ tumors are generally low-grade; including low grade serous carcinoma (LG-SC), low-grade endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma and malignant Brenner tumor. These tumors usually present at low stage and behave in a relatively indolent fashion[49]. In contrast, type Ⅱ tumors are high-grade, highly aggressive and present in advanced stage. They have been said to arise "*de novo*". They include high-grade serous carcinoma, high-grade endometrioid carcinoma, malignant mesodermal mixed tumour and undifferentiated carcinoma[1,49].

It is now believed that the fallopian tube may be the origin of ovarian carcinoma, rather than the ovarian surface epithelium, traditionally regarded as the origin of ovarian carcinoma[17].

ROLE OF THE FALLOPIAN TUBE IN TYPE Ⅰ OVARIAN SURFACE EPITHELIAL TUMORS

Low grade serous carcinoma is thought to evolve in a stepwise fashion from ovarian surface epithelial inclusions (OEIs)/serous cystadenomas to serous borderline tumors to invasive carcinoma[2,49,52], although they can be *de novo*[53].

The fallopian tube plays a central role in various components of this stepwise sequence[54] as it is proposed that the majority of OEIs are derived from the fallopian tube epithelial cells. These cells are capable of implanting on the ovarian surface[2] at the time of ovulation when the surface ovarian epithelium is ruptured[55].

This idea is supported by the following evidence: (1) Epithelial cells from tubal mucosa are easily shed after flushing the fallopian tube[55]; (2) Most (78%) of the OEIs and serous cystadenomas display morphological features and immunophenotype of tubal type epithelium (calretinin-/PAX8+/tubulin+)[2,50]; (3) Fallopian-derived OEIs may represent intra-ovarian endosalpingiosis; and (4) There is evidence against mesothelial origin of OEIs with müllerian metaplasia including, scarceness of hybrid or intermediate type of OEIs with both mesothelial and tubal phenotypes. In addition, studies show mesothelium-derived OEIs are not capable of growing into tumour masses with low cellular proliferative activity, compared to fallopian-derived OEIs that showed high proliferative activity and immuophenotype that are similar or almost identical to ovarian serous tumors[2,50].

ROLE OF THE FALLOPIAN TUBE IN TYPE Ⅱ OVARIAN SURFACE EPITHELIAL TUMORS

Accumulating evidence suggests that the fallopian tube epithelium, predominantly in the fimbrial region[1,49], is the source of a significant proportion of high-grade serous carcinomas[49]. This is based on identification of epithelial atypia, carcinoma *in situ*, and small high-grade serous tubal carcinomas in risk-reducing salpingo-oophorectomy (RRSO) specimens from women with BRCA mutations[1,56].

Mutation of TP53 is a hallmark of high-grade pelvic serous carcinoma[57]. The identification of TP53 mutations in Serous Tubal Intra-epithelial Carcinomas (STICs) provides support for the tubal origin of high-grade serous carcinomas[1,49]. More recently it has been found that that there are short stretches of morphologically normal tubal epithelium that are immunohistochemically positive for p53, and that have a Ki-67 proliferation index higher than normal tubal epithelium but lower than STICs. A minimum of 12 tubal secretory epithelial cells that are p53 positive has been proposed as a definition for a "p53 signature," which is a candidate for a STIC precursor. p53 signatures are also found in the general population. TP53 mutations have been found in a majority of p53 signatures[1,49].

Other molecular evidence strongly supporting the theory of fallopian tube origin of high-grade serous are: (1) lack of convincing definitive precursors of high-grade serous carcinoma in the ovary; (2) in RRSO specimens, occult carcinomas are more common in the fallopian tube than in the ovary; (3) STICs are associated, almost exclusively, with high-grade serous carcinoma, and not other histological types; (4) a high frequency of identical TP53 mutations in STICs/p53 signatures and synchronous ovarian/peritoneal high-grade serous carcinomas; (5) the finding of fallopian tube epithelial dysplasia in isolation exhibiting aneusomy for multiple chromosomes; (6) significant differences in telomere lengths between STICs and their paired concurrent ovarian/peritoneal high-grade serous carcinomas (if STICs merely represented metastases of ovarian/peritoneal carcinomas, they would be expected to have telomeres of similar lengths); (7) gene expression profiles of tubal and ovarian serous carcinomas are similar; and (8) gene expression patterns of ovarian serous carcinomas are more similar to those of normal tubal mucosa compared with normal ovarian epithelium[1].

Junctions between the different types of epithelia are often hot spots for carcinogenesis. Their role in neoplasia in certain locations, *e.g.,* cervical squamo-columnar, gastro-esophageal, and ano-rectal junctions is well recognized. Given the mounting evidence implicating the fimbria as the site of origin of ovarian serous carcinoma, the fallopian Tube-Peritoneal Junction (TPJ) is be considered a potential site of ovarian carcinogenesis. This junction is defined as the junction of the columnar epithelium of the fallopian tube and the mesothelium of the tubal serosa[1].

In are recent study TPJ was found to be highly tortuous with tongues of mesothelium extending from the infundibular peritoneal-fimbrial junction at the outer edges of the fimbriae, onto the fimbrial plicae to join the tubal epithelium at various points along and between fimbrial plicae and plica tips[58]. Transitional metaplasia occurs at the TPJ[59-61], and is reported in several studies[59,62]. It is likely that the transitional metaplasia is a normal event in the TPJ, analogous to squamous metaplasia in the cervical transformation zone[58], and may be analogously a site of tumour origin.

The origin of serous neoplasms at the TPJ could also explain the rare detection of stage I high-grade serous carcinoma. In addition, the extensive lymph-vascular system normally found at this junction with almost direct contact to the basement membrane of the tubal epithelium may explain the early spread of a minimally invasive tubal carcinoma throughout the abdominal cavity due to easy and rapid access into this system when the primary tumour is still of microscopic size[58].

Among ovarian surface epithelial tumors, the origin of intestinal-type mucinous ovarian and Brenner tumors is even more confusing than that of serous tumors as they lack a Mullerian phenotype. The recent suggestion that mucinous and Brenner tumors may arise from transitional metaplasia[61] indicates that the TPJ may be involved in carcinogenesis of a wide variety of ovarian neoplasms.

In view of the potential importance of the TPJ in ovarian, tubal, and pelvic neoplasia, a recent protocol for exami-

nation of the fallopian tubes has been proposed, designated the SEE-FIM protocol[63]. The goal of this protocol is to insure complete examination of the ovarian surface and tubal mucosa with maximum exposure of the fimbriae[63].

In summary, serous tumors develop from the fallopian tube, endometrioid, and clear cell tumors arise from fallopian tube endometriosis and mucinous, and Brenner tumors develop from transitional-type epithelium located at the TPJ[58].

Although the data suggesting that EOC arises in extraovarian sites and involves the ovaries secondarily is compelling, serous neoplasms (low- and high-grade) involve the ovaries and other pelvic and abdominal organs, much more extensively than the fallopian tubes. Similarly, although endometrioid and clear cell carcinomas develop from endometriosis that frequently occurs in multiple sites in the pelvis, these neoplasms are almost always confined to the ovaries. It is likely that the propensity for growth in the ovary is mulifactorial, but the precise reasons for this are unknown[58].

So the fallopian tube appears to be a strong player both in infertility and gynaecological neoplasia. This highlights the importance of thorough fallopian tube status investigation in the course of assessment of women presenting with either infertility or gynaecological tumors.

REFERENCES

1 **Vang R**, Wheeler JE. Diseases of the Fallopian Tube and Paratubal Region. In: Kurman RJ, Ellenson LH, Ronnett BM, editors. Blaustein's Pathology of the Female Genital Tract. 6th ed. New York: Springer, 2011: 529-578 [DOI: 10.1007/978-1-4419-0489-8_11]

2 **Li J**, Fadare O, Xiang L, Kong B, Zheng W. Ovarian serous carcinoma: recent concepts on its origin and carcinogenesis. *J Hematol Oncol* 2012; **5**: 8 [PMID: 22405464 DOI: 10.1186/1756-8722-5-8]

3 **Harris-Glocker M**, McLaren JF. Role of female pelvic anatomy in infertility. *Clin Anat* 2013; **26**: 89-96 [PMID: 23197390 DOI: 10.1002/ca.22188]

4 **Sharma S**, Mittal S, Aggarwal P. Management of infertility in low resource countries. *BJOG* 2009; **116** Suppl 1: 77-83 [PMID: 19740177]

5 **Lyons RA**, Saridogan E, Djahanbakhch O. The reproductive significance of human Fallopian tube cilia. *Hum Reprod Update* 2006; **12**: 363-372 [PMID: 16565155 DOI: 10.1093/humupd/dml012]

6 **Muglia U**, Motta PM. A new morpho-functional classification of the Fallopian tube based on its three-dimensional myoarchitecture. *Histol Histopathol* 2001; **16**: 227-237 [PMID: 11193199]

7 **Adamson GD**, Baker VL. Infertility, overview. In: Martini L, editor. Encyclopedia of Endocrine Diseases. Amsterdam: Elsevier Inc., Academic Press, 2004: 6-13

8 **Mahendru A**, Gajjar K, Hamed AT. Complete unilateral absence of fallopian tube. *Int J Gynaecol Obstet* 2008; **101**: 78-79 [PMID: 18048041 DOI: 10.1016/j.ijgo.2007.09.026]

9 **Yazawa H**, Yabe M, Endo S, Hayashi S. A case of congenital unilateral partial absence of fallopian tube. *Fukushima J Med Sci* 2010; **56**: 44-49 [PMID: 21485655 DOI: 10.5387/fms.56.44]

10 **Nawroth F**, Nugent W, Ludwig M. Congenital partial atresia of the Fallopian tube. *Reprod Biomed Online* 2006; **12**: 205-208 [PMID: 16478587 DOI: 10.1016/S1472-6483(10)60862-0]

11 **Johnston AC**, McComb PF. Fertility potential of women with congenital ampullary atresia of the fallopian tube. *Fertil Steril* 2003; **79**: 431-433 [PMID: 12568860 DOI: 10.1016/S0015-0282(02)04691-5]

12 **Garg A**, Wadher R, Gulati SP, Sharma N, Garg S. Primary ciliary dyskinesia--an underdiagnosed entity. *J Assoc Physicians India* 2010; **58**: 704-706 [PMID: 21510469]

13 **Kitaya K**, Yamada H. Pathophysiological roles of chemokines in human reproduction: an overview. *Am J Reprod Immunol* 2011; **65**: 449-459 [PMID: 21087337 DOI: 10.1111/j.1600-0897.2010.00928.x]

14 **Manek S**, Dhar S. Infections in the gynaecological tract. *Diagn Histopathol* 2013; **19**: 62-66 [DOI: 10.1016/j.mpdhp.2013.01.008]

15 **Hafner LM**, Pelzer ES. Tubal Damage, Infertility and Tubal Ectopic Pregnancy: Chlamydia trachomatis and Other Microbial Aetiologies. In: Kamrava M, editor. Ectopic Pregnancy - Modern Diagnosis and Management. Rijeka: InTech, 2011: 13-44 [DOI: 10.5772/21555]

16 **Young RH**, Clement PB. The Fallopian Tube and Broad Ligament. In: Mills SE, Carter D, Greenson JK, Reuter VE, Stoler MH, editors. Sternberg's Diagnostic Surgical Pathology. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2010: 2374-2391

17 **Rosai J**. Female reproductive system: Vulva, Vagina, Uterus–cervix, Uterus–corpus, Fallopian tube (including broad and round ligaments), Ovary, Placenta. In: Rosai J, editor. Rosai and Ackerman's Surgical Pathology. 10th ed. Philadelphia: Mosby, 2011: 1541-1552

18 Sexually transmitted disease surveillance 2008. Atlanta, GA: U.S. Department of Health and Human Services, 2008

19 **Rodgers AK**, Wang J, Zhang Y, Holden A, Berryhill B, Budrys NM, Schenken RS, Zhong G. Association of tubal factor infertility with elevated antibodies to Chlamydia trachomatis caseinolytic protease P. *Am J Obstet Gynecol* 2010; **203**: 494.e7-494.e14 [PMID: 20643392]

20 **Carey AJ**, Beagley KW. Chlamydia trachomatis, a hidden epidemic: effects on female reproduction and options for treatment. *Am J Reprod Immunol* 2010; **63**: 576-586 [PMID: 20192953 DOI: 10.1111/j.1600-0897.2010.00819.x]

21 **Pellati D**, Mylonakis I, Bertoloni G, Fiore C, Andrisani A, Ambrosini G, Armanini D. Genital tract infections and infertility. *Eur J Obstet Gynecol Reprod Biol* 2008; **140**: 3-11 [PMID: 18456385 DOI: 10.1016/j.ejogrb.2008.03.009]

22 **Kari L**, Whitmire WM, Crane DD, Reveneau N, Carlson JH, Goheen MM, Peterson EM, Pal S, de la Maza LM, Caldwell HD. Chlamydia trachomatis native major outer membrane protein induces partial protection in nonhuman primates: implication for a trachoma transmission-blocking vaccine. *J Immunol* 2009; **182**: 8063-8070 [PMID: 19494332 DOI: 10.4049/jimmunol.0804375]

23 **Mondal SK**, Dutta TK. A ten year clinicopathological study of female genital tuberculosis and impact on fertility. *JNMA J Nepal Med Assoc* 2009; **48**: 52-57 [PMID: 19529059]

24 **Umoh AV**, Gabriel MA. Genital tuberculosis with secondary infertility - a case report of successful treatment and subsequent live birth in Uyo, Nigeria. *J Med Med Sci* 2011; **2**: 839-842

25 **Swai B**, Poggensee G, Mtweve S, Krantz I. Female genital schistosomiasis as an evidence of a neglected cause for reproductive ill-health: a retrospective histopathological study from Tanzania. *BMC Infect Dis* 2006; **6**: 134 [PMID: 16928276 DOI: 10.1186/1471-2334-6-134]

26 **World Health Organization**. Schistosomiasis, Fact sheet N° 115; Updated March 2013. Available from: URL: http://www.who.int/mediacentre/factsheets/fs115/en/index.html

27 **Kjetland EF**, Leutscher PD, Ndhlovu PD. A review of female genital schistosomiasis. *Trends Parasitol* 2012; **28**: 58-65 [PMID: 22245065 DOI: 10.1016/j.pt.2011.10.008]

28 **Bulun SE**. Endometriosis. *N Engl J Med* 2009; **360**: 268-279 [PMID: 19144942 DOI: 10.1056/NEJMra0804690]

29 **Giudice LC**. Clinical practice. Endometriosis. *N Engl J Med* 2010; **362**: 2389-2398 [PMID: 20573927 DOI: 10.1056/NEJMcp1000274]

30 Endometriosis and infertility: a committee opinion. *Fertil Steril* 2012; **98**: 591-598 [PMID: 22704630 DOI: 10.1016/j.fertnstert.2012.05.031]

31 **Alvarado-Cabrero I**. Pathology of the Fallopian Tube and

Broad Ligament. In: Nucci MR, Oliva E, editors. Gynecologic Pathology. 1st ed. London: Elsevier, 2009: 331-366 [DOI: 10.1016/B978-044306920-8.50013-4]
32 **Bulletti C**, Coccia ME, Battistoni S, Borini A. Endometriosis and infertility. *J Assist Reprod Genet* 2010; **27**: 441-447 [PMID: 20574791 DOI: 10.1007/s10815-010-9436-1]
33 **Halis G**, Arici A. Endometriosis and inflammation in infertility. *Ann N Y Acad Sci* 2004; **1034**: 300-315 [PMID: 15731321 DOI: 10.1196/annals.1335.032]
34 **Inagaki J**, Hao L, Nakatsuka M, Yasuda T, Hiramatsu Y, Shoenfeld Y, Matsuura E. A possible mechanism of autoimmune-mediated infertility in women with endometriosis. *Am J Reprod Immunol* 2011; **66**: 90-99 [PMID: 21223425 DOI: 10.1111/j.1600-0897.2010.00956.x]
35 **Turan V**. Fertility outcomes subsequent to treatment of tubal ectopic pregnancy in younger Turkish women. *J Pediatr Adolesc Gynecol* 2011; **24**: 251-255 [PMID: 21715197 DOI: 10.1016/j.jpag.2010.12.007]
36 **García-Ulloa AC**, Arrieta O. Tubal occlusion causing infertility due to an excessive inflammatory response in patients with predisposition for keloid formation. *Med Hypotheses* 2005; **65**: 908-914 [PMID: 16005574 DOI: 10.1016/j.mehy.2005.03.031]
37 **Farquhar CM**. Ectopic pregnancy. *Lancet* 2005; **366**: 583-591 [PMID: 16099295 DOI: 10.1016/S0140-6736(05)67103-6]
38 **Bouyer J**, Job-Spira N, Pouly JL, Coste J, Germain E, Fernandez H. Fertility following radical, conservative-surgical or medical treatment for tubal pregnancy: a population-based study. *BJOG* 2000; **107**: 714-721 [PMID: 10847225 DOI: 10.1111/j.1471-0528.2000.tb13330.x]
39 **U.S. Cancer StatisticsWorking Group**. United States cancer statistics: 2003 pincidence and mortality. Centers for Disease Control and Prevention and National Cancer Institute. Atlanta: U.S. Department of Health and Human Services, 2006: 1-467
40 **Stewart SL**, Wike JM, Foster SL, Michaud F. The incidence of primary fallopian tube cancer in the United States. *Gynecol Oncol* 2007; **107**: 392-397 [PMID: 17961642 DOI: 10.1016/j.ygyno.2007.09.018]
41 **Pectasides D**, Pectasides E, Economopoulos T. Fallopian tube carcinoma: a review. *Oncologist* 2006; **11**: 902-912 [PMID: 16951394 DOI: 10.1634/theoncologist.11-8-902]
42 **Boyle P**, Levin B. World cancer report 2008. Lyon: World Health Organization, 2008
43 **Howlader N**, Noone AM, Krapcho M, Neyman N, Aminou R, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). Bethesda: National Cancer Institute. Available from: URL: http://seer.cancer.gov/csr/1975_2009_pops09/
44 **Jemal A**, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60**: 277-300 [PMID: 20610543 DOI: 10.3322/caac.20073]
45 **Delair D**, Soslow RA. Key features of extrauterine pelvic serous tumours (fallopian tube, ovary, and peritoneum). *Histopathology* 2012; **61**: 329-339 [PMID: 22372521 DOI: 10.1111/j.1365-2559.2011.04167.x]
46 **Ahmed AA**, Becker CM, Bast RC. The origin of ovarian cancer. *BJOG* 2012; **119**: 134-136 [PMID: 22168761 DOI: 10.1111/j.1471-0528.2011.03149.x]
47 **Folkins AK**, Jarboe EA, Roh MH, Crum CP. Precursors to pelvic serous carcinoma and their clinical implications. *Gynecol Oncol* 2009; **113**: 391-396 [PMID: 19237187]
48 **Fathalla MF**. Incessant ovulation--a factor in ovarian neoplasia? *Lancet* 1971; **2**: 163 [PMID: 4104488 DOI: 10.1016/S0140-6736(71)92335-X]
49 **Vang R**, Shih IeM, Kurman RJ. Fallopian tube precursors of ovarian low- and high-grade serous neoplasms. *Histopathology* 2013; **62**: 44-58 [PMID: 23240669 DOI: 10.1111/his.12046]
50 **Li J**, Abushahin N, Pang S, Xiang L, Chambers SK, Fadare O, Kong B, Zheng W. Tubal origin of 'ovarian' low-grade serous carcinoma. *Mod Pathol* 2011; **24**: 1488-1499 [PMID: 21701538 DOI: 10.1038/modpathol.2011.106]
51 **Kurman RJ**, Shih IeM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm. *Hum Pathol* 2011; **42**: 918-931 [PMID: 21683865 DOI: 10.1016/j.humpath.2011.03.003]
52 **Vang R**, Shih IeM, Kurman RJ. Ovarian low-grade and high-grade serous carcinoma: pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. *Adv Anat Pathol* 2009; **16**: 267-282 [PMID: 19700937 DOI: 10.1097/PAP.0b013e3181b4fffa]
53 **Diaz-Padilla I**, Malpica AL, Minig L, Chiva LM, Gershenson DM, Gonzalez-Martin A. Ovarian low-grade serous carcinoma: a comprehensive update. *Gynecol Oncol* 2012; **126**: 279-285 [PMID: 22555104 DOI: 10.1016/j.ygyno.2012.04.029]
54 **Laury AR**, Ning G, Quick CM, Bijron J, Parast MM, Betensky RA, Vargas SO, McKeon FD, Xian W, Nucci MR, Crum CP. Fallopian tube correlates of ovarian serous borderline tumors. *Am J Surg Pathol* 2011; **35**: 1759-1765 [PMID: 22089527 DOI: 10.1097/PAS.0b013e318233b0f7]
55 **Kurman RJ**, Shih IeM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am J Surg Pathol* 2010; **34**: 433-443 [PMID: 20154587 DOI: 10.1097/PAS.0b013e3181cf3d79]
56 **Przybycin CG**, Kurman RJ, Ronnett BM, Shih IeM, Vang R. Are all pelvic (nonuterine) serous carcinomas of tubal origin? *Am J Surg Pathol* 2010; **34**: 1407-1416 [PMID: 20861711 DOI: 10.1097/PAS.0b013e3181ef7b16]
57 **Herrington CS**, McCluggage WG. The emerging role of the distal Fallopian tube and p53 in pelvic serous carcinogenesis. *J Pathol* 2010; **220**: 5-6 [PMID: 19882674 DOI: 10.1002/path.2630]
58 **Seidman JD**, Yemelyanova A, Zaino RJ, Kurman RJ. The fallopian tube-peritoneal junction: a potential site of carcinogenesis. *Int J Gynecol Pathol* 2011; **30**: 4-11 [PMID: 21131840 DOI: 10.1097/PGP.0b013e3181f29d2a]
59 **Rabban JT**, Crawford B, Chen LM, Powell CB, Zaloudek CJ. Transitional cell metaplasia of fallopian tube fimbriae: a potential mimic of early tubal carcinoma in risk reduction salpingo-oophorectomies from women With BRCA mutations. *Am J Surg Pathol* 2009; **33**: 111-119 [PMID: 18830124 DOI: 10.1097/PAS.0b013e31817d74a7]
60 **Rabban JT**, Krasik E, Chen LM, Powell CB, Crawford B, Zaloudek CJ. Multistep level sections to detect occult fallopian tube carcinoma in risk-reducing salpingo-oophorectomies from women with BRCA mutations: implications for defining an optimal specimen dissection protocol. *Am J Surg Pathol* 2009; **33**: 1878-1885 [PMID: 19898224 DOI: 10.1097/PAS.0b013e3181bc6059]
61 **Seidman JD**, Khedmati F. Exploring the histogenesis of ovarian mucinous and transitional cell (Brenner) neoplasms and their relationship with Walthard cell nests: a study of 120 tumors. *Arch Pathol Lab Med* 2008; **132**: 1753-1760 [PMID: 18976011]
62 **Egan AJ**, Russell P. Transitional (urothelial) cell metaplasia of the fallopian tube mucosa: morphological assessment of three cases. *Int J Gynecol Pathol* 1996; **15**: 72-76 [PMID: 8852450]
63 **Medeiros F**, Muto MG, Lee Y, Elvin JA, Callahan MJ, Feltmate C, Garber JE, Cramer DW, Crum CP. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. *Am J Surg Pathol* 2006; **30**: 230-236 [PMID: 16434898 DOI: 10.1097/01.pas.0000180854.28831.77]

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TOPIC HIGHLIGHT

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

Fertility sparing management of endometrial complex hyperplasia and endometrial carcinoma

Alan Farthing

Alan Farthing, West London Gynaecological Cancer Centre, Imperial NHS Trust, London W10 0HS, United Kingdom
Author contributions: Farthing A solely contributed to this paper.
Correspondence to: Alan Farthing, MD, FRCOG, West London Gynaecological Cancer Centre, Imperial NHS Trust, Du Cane Road, London W10 0HS, United Kingdom. a.farthing@imperial.ac.uk
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Abstract

The standard treatment of endometrial cancer or atypical hyperplasia is surgical removal of the uterus and ovaries. In early stage disease this has an excellent chance of cure but results in infertility. Although the majority of patients are postmenopausal an increasing number of patients with atypical hyperplasia or endometrial cancer are presenting with a desire to retain their fertile potential. In the last 8 years a number of studies have been published involving 403 patients with endometrial cancer and 151 patients with Atypical hyperplasia treated with high dose progestagens. The response rate is 76.2% and 85.6% respectively with endometrial cancer having a recurrence rate of 40.6%. There is a 26% recurrence rate in atypical hyperplasia. Overall 26.3% of those wishing to conceive had a live baby. Although concerns exist about the risks of medical treatment, those that fail this treatment do not appear to have a significantly poorer prognosis although 20 patients (3.6%) had either ovarian cancer or metastatic disease discovered during treatment or follow up.

Key words: Endometrial cancer; Fertility sparing

Core tip: Early endometrial cancer is successfully treated with hysterectomy in most cases but an increasing number of women develop the disease whilst still hoping to conceive. We are gathering an increasing amount of data to accurately describe the risk they are taking by undergoing medical treatment with progestagens as an alternative.

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INTRODUCTION

Endometrial cancer is the commonest gynaecological malignancy in the western world and usually affects post menopausal women. However up to 14% of these cancers are now diagnosed in the premenopausal with about 4% occurring in those under the age of 40 years in the United States[1]. As the trend to delay childbearing continues a greater number of women are being diagnosed with endometrial cancer at a stage in life when they wish to conceive. Therefore the standard management of hysterectomy with removal of ovaries needs to be fully justified and the possibility of managing patients medically whilst preserving their fertility should be considered. In the last decade a significant number of studies have been published allowing us to assess the success of this medical treatment so that we can advise our patients on the risks of fertility preservation in early stage endometrial cancer. However there are pitfalls of which every gynaecological oncologist should make themselves aware.

DIAGNOSIS

Irregular menstrual bleeding at any age needs to be in-

vestigated and the diagnosis of endometrial carcinoma is made by biopsy from the endometrial cavity either at hysteroscopy or outpatient endometrial sampling. The most accurate assessment is from biopsy obtained at hysteroscopy[2] but even then it can be difficult to make the distinction between atypical hyperplasia (AH) and invasive endometrial carcinoma (EC). As EC is actually found in the hysterectomy when the preoperative diagnosis was thought to be AH in approximately 30% of cases the treatment of both AH and early stage EC should be very similar[3,4].

STAGING

A number of studies have looked at the stage of disease in younger women with endometrial cancer and although the majority are stage 1a grade 1 disease, approximately 20% are found to have disease outside the uterus[5]. In addition up to 25% of women have either synchronous or metastatic ovarian tumours[6]. With standard management of hysterectomy and bilateral salpingo-oophorectomy the extent of disease can be assessed histopathologically and this is how the FIGO staging is determined. However if medical treatment is proposed the major initial disadvantage is the lack of histological confirmation of staging and the reliance on pre treatment imaging.

Ultrasound, computed tomography (CT) and contrast enhanced magnetic resonance imaging (MRI) have been used to stage early endometrial cancers and the MRI is the most accurate being able to predict myometrial invasion with a specificity of 96% and cervical invasion in 88%[7,8].

HORMONAL TREATMENTS

The majority of grade 1 endometrial cancers have progressed from hyperplasia and are thought to have arisen because of hormonal imbalances. Obesity where there is a higher level of circulating oestrogens from fat degradation, and polycystic ovaries where infrequent, anovulatory cycles are a feature suggest that a lack of balanced progesterone is responsible. Various types and doses of progesterones have been used to reverse the hyperplasia and EC. Initially Kinkel *et al*[9] described resolution of an endometrial malignancy in 25% of patients undergoing hysterectomy after treatment with progesterones. Although small doses of progesterone may be sufficient to balance the oestrogen in hormone replacement therapy a much higher does is required in AH and EC in these premenopausal women.

The majority of studies have used Medroxyprogesterone acetate in doses of 400-800 mg daily. This can, if necessary, be taken in divided doses. The next most common is megestrol but a recent study of 148 patients showed patients treated with megestrol had a higher chance of recurrence[10]. The levonorgestrol containing intrauterine device (IUS) has not been successfully when used in isolation. It may be useful for maintenance therapy after remission has been established and a randomised study has just opened in South Korea to evaluate this[11].

A meta analysis has been published involving 403 patients with endometrial cancer and 151 patients with Atypical hyperplasia treated with high dose progestagens[12]. The response rate is 76.2% and 85.6% respectively with endometrial cancer having a recurrence rate of 40.6%. There is a 26% recurrence rate in atypical hyperplasia. Overall 26.3% of those wishing to conceive had a live baby.

In comparison removal of the uterus and ovaries would be expected to give a disease free 5 year survival of 98.2%[13]. A recent review of 148 patients in eight hospitals in South Korea obtained similar response and recurrence free response rates (77.7% and 54% respectively). Of 33 patients who failed to respond to initial treatment, and had a hysterectomy, none of them recurred implying the risk of trying and failing medical treatment is low. Risk factors that increased the risk of recurrence were obesity (body mass index > 25) and a lack of pregnancy[10]. There were no reported deaths from disease in this study but in the meta analysis by Gallos *et al*[1] there were 2 deaths and 20 patients (3.6%) had disease in the ovaries either as a concommitent ovarian tumour or metastasis.

Therefore, despite the risk that more advanced or metastatic disease can be under diagnosed and despite the risk that the EC recurs in a large number of patients there do not appear to be significant long term risks to trying medical treatment.

FOLLOW UP

The various studies have given medical therapy for variable lengths of time and there is no single protocol that has been established. Most studies have sampled the endometrium 3 monthly, and continued medical management if there is a response for up to a year[14].

Similarly long term follow can be difficult. The risk factors that led to the original carcinogenesis are usually still present and with such a high recurrence risk patients need to be encouraged to either undergo immediate fertility treatment or continue with maintenance treatment. The frequency of future endometrial samples and whether office sampling or hysteroscopy is required has not been established. Hysterectomy at some stage following child birth would seem to be sensible as a way of preventing the disease recurring in the long term but when this should be performed and whether the risk of recurrence decreases with weight loss or the menopause is not known. Once recurrence has occurred a number of patients will respond to retreatment. However there are no established guidelines for how many times a patient should be retreated or for how long.

CONCLUSION

An increasing number of patients with either AH or EC will wish to preserve their fertility in the future. These patients need an accurate diagnosis and staging with con-

trast enhanced MRI to minimise their risk of unrecognised concomitant or metastatic disease.

Medical treatment with 400 mg to 800 mg daily of medroxyprogesterone acetate appears to be the best medical management with 3 monthly endometrial sampling to establish response. Treatment can be given for 6 mo to a year and approximately 75% will have a complete initial response with just over 50% having a response without subsequent recurrence. A failed response has theoretical disadvantages of finding more advanced disease but in published studies this is so small as to not be quantifiable.

All these factors need to be taken into consideration when advising a patient about her options but in addition she needs to consider the chances of conception once if treatment is successful. Many patients will be older and have presented with infertility. If the chances of a successful pregnancy are very low at the end of a year hormonal treatment with multiple endometrial samples and uncertainty about the future risk of recurrence then after careful consideration it is possible that the patient will decide to opt for the standard curative treatment of hysterectomy and removal of ovaries.

REFERENCES

1 **Gallos ID**, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2012; **207**: 266.e1-266.12 [PMID: 23021687]

2 **Park JY**, Kim DY, Kim JH, Kim YM, Kim KR, Kim YT, Seong SJ, Kim TJ, Kim JW, Kim SM, Bae DS, Nam JH. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). *Eur J Cancer* 2013; **49**: 868-874 [PMID: 23072814 DOI: 10.1016/j.ejca.2012.09.017]

3 **Kesterson JP**, Fanning J. Fertility-sparing treatment of endometrial cancer: options, outcomes and pitfalls. *J Gynecol Oncol* 2012; **23**: 120-124 [PMID: 22523629]

4 **Leitao MM**, Kehoe S, Barakat RR, Alektiar K, Gattoc LP, Rabbitt C, Chi DS, Soslow RA, Abu-Rustum NR. Comparison of D& amp; C and office endometrial biopsy accuracy in patients with FIGO grade 1 endometrial adenocarcinoma. *Gynecol Oncol* 2009; **113**: 105-108 [PMID: 19167049 DOI: 10.1016/j.ygyno.2008.12.017]

5 **Kimura T**, Kamiura S, Komoto T, Seino H, Tenma K, Ohta Y, Yamamoto T, Saji F. Clinical over- and under-estimation in patients who underwent hysterectomy for atypical endometrial hyperplasia diagnosed by endometrial biopsy: the predictive value of clinical parameters and diagnostic imaging. *Eur J Obstet Gynecol Reprod Biol* 2003; **108**: 213-216 [PMID: 12781414 DOI: 10.1016/S0301-2115(02)00469-4]

6 **Kaku T**, Yoshikawa H, Tsuda H, Sakamoto A, Fukunaga M, Kuwabara Y, Hataeg M, Kodama S, Kuzuya K, Sato S, Nishimura T, Hiura M, Nakano H, Iwasaka T, Miyazaki K, Kamura T. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. *Cancer Lett* 2001; **167**: 39-48 [PMID: 11323097 DOI: 10.1016/S0304-3835(01)00462-1]

7 **Duska LR**, Garrett A, Rueda BR, Haas J, Chang Y, Fuller AF. Endometrial cancer in women 40 years old or younger. *Gynecol Oncol* 2001; **83**: 388-393 [PMID: 11606102 DOI: 10.1006/gyno.2001.6434]

8 **Walsh C**, Holschneider C, Hoang Y, Tieu K, Karlan B, Cass I. Coexisting ovarian malignancy in young women with endometrial cancer. *Obstet Gynecol* 2005; **106**: 693-699 [PMID: 16199623 DOI: 10.1097/01.AOG.0000172423.64995.6f]

9 **Kinkel K**, Kaji Y, Yu KK, Segal MR, Lu Y, Powell CB, Hricak H. Radiologic staging in patients with endometrial cancer: a meta-analysis. *Radiology* 1999; **212**: 711-718 [PMID: 10478237]

10 **Sironi S**, Taccagni G, Garancini P, Belloni C, DelMaschio A. Myometrial invasion by endometrial carcinoma: assessment by MR imaging. *AJR Am J Roentgenol* 1992; **158**: 565-569 [PMID: 1738995 DOI: 10.2214/ajr.158.3.1738995]

11 **Cade TJ**, Quinn MA, Rome RM, Neesham D. Can primary endeomtrial carcinoma stage 1 be cured without surgery and radiation therapy? *Gynecol Oncol* 1985; **20**: 139-155 [DOI: 10.1016/0090-8258(85)90135-0]

12 **Kim MK**, Seong SJ, Lee TS, Kim JW, Nam BH, Hong SR, Suh KS. Treatment with medroxyprogesterone acetate plus levonorgestrel-releasing intrauterine system for early-stage endometrial cancer in young women: single-arm, prospective multicenter study: Korean gynecologic oncology group study (KGOG2009). *Jpn J Clin Oncol* 2012; **42**: 1215-1218 [PMID: 23071290 DOI: 10.1093/jjco/hys171]

13 **Kato T**, Watari H, Endo D, Mitamura T, Odagiri T, Konno Y, Hosaka M, Kobayashi N, Todo Y, Sudo S, Takeda M, Dong P, Kaneuchi M, Kudo M, Sakuragi N. New revised FIGO 2008 staging system for endometrial cancer produces better discrimination in survival compared with the 1988 staging system. *J Surg Oncol* 2012; **106**: 938-941 [PMID: 22740340 DOI: 10.1002/jso.23203]

14 **Farthing A**. Conserving fertility in the management of gynaecological cancers. *BJOG* 2006; **113**: 129-134 [PMID: 16411988 DOI: 10.1111/j.1471-0528.2005.00844.x]

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TOPIC HIGHLIGHT

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

Impact of pelvic radiotherapy on the female genital tract and fertility preservation measures

Liam C Welsh, Alexandra Taylor

Liam C Welsh, Alexandra Taylor, Department of Gynaecology, Royal Marsden Hospital, London SW3 6JJ, United Kingdom
Author contributions: Welsh LC and Taylor A reviewed evidence and wrote the paper.
Correspondence to: Dr. Alexandra Taylor, MBBS, MD, Consultant in Clinical Oncology, Department of Gynaecology, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, United Kingdom. alexandra.taylor@rmh.nhs.uk
Telephone: +44-207-8082581 Fax: +44-207-8082581
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Abstract

Radiotherapy to the pelvis can have a major and deleterious impact on the female genital tract. Despite significant advances in the technical delivery of radical pelvic radiotherapy there remains no way to avoid delivering substantial radiation doses to the ovaries and uterus for patients undergoing treatment for gynaecological cancers. Due to improved cure rates from radical chemo-radiotherapy and social trends toward delayed childbirth many women treated for cervical cancer with radical chemo-radiotherapy will wish to attempt to preserve their fertility. Whilst there are now established and emerging techniques for preserving ovarian function and ovarian tissue, there remains the difficulty of the irradiated uterus which, even if pregnancy can be achieved, results in an increased risk for pregnancy-related complications. Future developments may offer women in this difficult situation more and improved options for fertility preservation.

Key words: Radiotherapy; Cervical carcinoma; Premature menopause; Infertility; Fertility preservation

Core tip: Despite significant advances in the technical delivery of radical pelvic radiotherapy there remains no way to avoid delivering substantial radiation doses to the ovaries and uterus for patients undergoing treatment for gynaecological cancers. Due to improved cure rates from radical chemo-radiotherapy many women treated for cervical cancer will wish to attempt to preserve their fertility. This article reviews emerging techniques for preserving ovarian function and ovarian tissue, as well as the impact on the uterus and the risk for pregnancy-related complications. Future developments may offer women in this difficult situation more and improved options for fertility preservation.

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INTRODUCTION

Worldwide, cervical carcinoma is the third most common cancer in women, being responsible for nearly 10% of all cancers diagnosed in women in 2008[1]. However, there is major geographical variation in the incidence of cervical cancer across the globe, with a seven fold difference in the age-standardised incidence rate between East Africa, the region with the highest rate, and Western Asia, the region with the lowest rate[1]. Two peaks occur in the age-specific incidence rates of cervical carcinoma; the first peak occurs in women aged between 30-34 years and relates to women becoming sexually active in their late teens and early 1920s, resulting in an increase in the rate of infection with human papillomavirus[1,2]. In the United Kingdom between 2007 and 2009, the proportion

of cervical carcinoma cases occurring in women less than 45 years of age was 53%[1]. A continuous trend towards delayed childbearing has been observed in developed nations, resulting in an increase in the proportion of women diagnosed with a gynaecological cancer, typically cervical carcinoma, before their first pregnancy[3]. As a result of these epidemiological and social factors, a significant and perhaps increasing number of women of reproductive age who are diagnosed with a gynaecological cancer will wish to preserve their fertility[4-6].

The treatment of early-stage cervical carcinoma (International Federation of Gynecological Oncologists, FIGO stages Ⅰ and ⅡA cervical) is radical surgery, although radical radiotherapy is equally effective[7]. However, surgery for early-stage disease has the particular advantage of sparing fertility in cases that are suitable for radical trachelectomy[3]. For more advanced cases (FIGO stages ⅡB, Ⅲ and Ⅳ), standard treatment is with radical chemo-radiotherapy which combines external beam radiotherapy with weekly cisplatin followed by intra-uterine brachytherapy[8]. Radical radiotherapy for cervical carcinoma usually includes within the treatment volume: the pelvic lymph nodes, the uterus, the cervix and upper vagina, the fallopian tubes and ovaries, and the parametrial tissues. Modern radiotherapy techniques, utilising intensity-modulated external beam radiotherapy[9,10], and image-guided brachytherapy[11] can produce high rates of local control for cervical carcinoma. The prognosis for women with cervical carcinoma treated with radical chemo-radiotherapy varies according to FIGO stage, with the 5-year overall survival ranging from about 70% for stage ⅡB, to 50% for stages ⅢA and ⅢB, and 36% for stage ⅣA[12].

Given the favourable prognosis for many women treated for cervical carcinoma with radical chemo-radiotherapy, and given the demographic considerations discussed above, fertility preservation will often be an important issue for this cohort of women[4-6]. Unfortunately pelvic radiotherapy for pre-menopausal women, at radical treatment doses, results in complete ovarian failure and premature menopause. In addition, it causes direct damage to the uterus which in itself can result in an inability to conceive or carry a pregnancy to term[13,14]. The majority of the evidence for the effects of radiotherapy on female fertility derives from long-term follow-up studies of women treated with radiotherapy for cancer during childhood or adolescence[15-19]. Whilst this information from paediatric populations is of relevance to adult women receiving radiotherapy treatment, outcomes for patients treated in childhood are superior than for adults due to lower radiotherapy doses used for paediatric cancers and to the natural decline in fertility with age[20,21].

There are no completely satisfactory options for fertility preservation for women undergoing radical pelvic radiotherapy at present, yet there are interventions which should be offered for women to consider before they embark on treatment[4,22]. Evidence of the impact of pelvic radiotherapy on the female reproductive organs, the currently available fertility sparing options, and possible future strategies will be reviewed here.

IMPACT OF PELVIC RADIOTHERAPY ON THE FEMALE GENITAL TRACT

Pelvic radiotherapy by itself has significant consequences for female fertility. The degree of fertility impairment following radiotherapy is known to be dependent on the total radiation dose, the fractionation schedule, the radiation field, and age at the time of treatment[13,14]. It is now standard practice to give concurrent cisplatin chemotherapy as a radiosensitizer with radical radiotherapy for cervical carcinoma. It is reasonable to expect that this combination therapy will increase the impact of radiotherapy on fertility, on the basis of data on the long term effects of combined chemotherapy and radiotherapy in paediatric patients[23-25]. In addition, exposure to cisplatin in the context of single agent or multi-agent chemotherapy is known to cause ovarian failure, even in the absence of concomitant pelvic radiotherapy[13].

Aside from the impact of pelvic radiotherapy on the female reproductive organs, pelvic radiotherapy can also lead to damage to the vagina resulting in tissue fibrosis and vaginal stenosis. These late normal tissue changes can be severe and have a major impact on sexual function[26,27]. It is difficult to quantify these late effects of radiotherapy on vaginal tissues, and possibly as a result of such difficulties, the incidence of vaginal stenosis after radiotherapy reported in the literature ranges from 1.2% to 88%[26-29]. It is currently standard practice to attempt to minimise vaginal stenosis following pelvic radiotherapy by asking women to use vaginal dilators after radiotherapy[30-32]. A recent systematic review of evidence for the use of vaginal dilators following pelvic radiotherapy found that whilst vaginal dilation might help treat the late effects of radiotherapy, the use of vaginal dilation during treatment can cause increased tissue damage[29]. A Cochrane review by the same authors concluded that there is no reliable evidence to show that routine regular vaginal dilation during or after radiotherapy prevents the late effects of radiotherapy or improves quality of life[33].

Ovarian failure after radiotherapy

The human ovary contains a fixed number of primordial follicles, which is maximal during foetal life at 5 mo of gestation[5,18,20]. These are steadily lost through atresia, declining to about 500000 at the time of menarche[34]. After menarche, the number of viable primordial follicles continues to fall with increasing age, declining to about 1000 at the time of menopause at an average age of 50-51 years[20,35]. The rate of loss of ovarian follicles is not constant, and accelerated atresia of the primordial follicles occurs from approximately 35 years of age[35].

Oocytes are highly sensitive to radiation, and the LD50 (the radiation dose need to kill half the total number of oocytes) was estimated to be only 4 Gy[36], but more recently it has been reported to be less than 2 Gy[37]. Historically, complete ovarian failure has been known to occur after radiation doses in the region of 20 Gy in women under 40 years of age, and after only 6 Gy

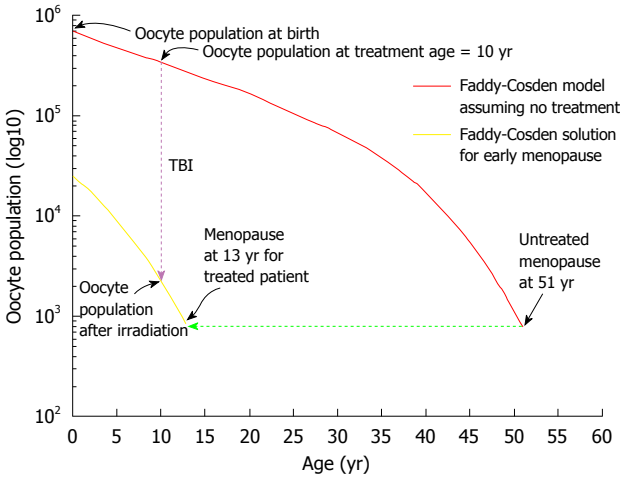

Figure 1 The effect of pelvic radiotherapy on oocyte population according to the Faddy-Gosden model. Faddy-Gosden model (Source[20], with permission) as extended by Wallace *et al*[21]. The graph illustrates the effect of total body irradiation with 14 Gy at 10 years, predicting ovarian failure at 13 years.

in older women[38]. Ovarian irradiation accelerates the natural process of follicular atresia, leading to premature menopause[20,21,37]. Due to the natural atresia of primordial follicles in the ovaries, for a given dose of radiation to the ovaries, the younger a woman is at the time of irradiation, the later will be the subsequent onset of premature menopause. This effect means that the sterilising dose of radiation falls with increasing age[20]. The Faddy-Gosden model of natural follicular atresia in healthy women has been extended by Wallace *et al*[20,21] to allow the prediction of the age of ovarian failure following treatment with a given dose of radiation (Figure 1). They have also calculated the effective sterilising radiotherapy doses (*i.e.*, the radiation dose causing ovarian failure in 97.5% of treated women) as a function of age: 20.3 Gy at birth, 18.4 Gy at 10 years, 16.5 Gy at 20 years, 14.3 Gy at 30 years and 9.5 Gy at 45 years[20].

Prediction of ovarian reserve prior to radiotherapy would be beneficial in order to avoid invasive procedures or unnecessary delays in treatment if fertility preserving measures are likely to be futile. Traditionally elevated follicle-stimulating hormone level has been used but various factors can cause a transient rise resulting in false prediction of menopause. Antimullerian hormone (AMH) is produced by growing follicles and may be a better indicator of ovarian function. The combination of serum AMH levels with ultrasound assessment of ovarian volume and total antral follicle count has been reported to more accurately predict the onset of ovarian failure[39,40].

Radiotherapy effects on the uterus

As well as the uterine dysfunction resulting from reduced ovarian hormone production, pelvic radiotherapy may also have a direct adverse effect on the uterus. Most of what is known about the long term effects of radiotherapy on the uterus comes from studies of women treated for childhood cancers[41,42]. However, these may be of limited relevance to adult women due to the significant changes that occur to the uterus during puberty[14,43,44]. Furthermore, the pre-pubertal uterus is thought to be more vulnerable to the effects of pelvic irradiation[14]. At puberty, as a result of rising ovarian oestrogen production, the uterus enlarges and changes shape from a tubular shaped organ to a pear shaped organ[43,44].

Radiotherapy doses between 14 and 30 Gy have been reported to result in adverse changes to the uterus including myometrial fibrosis, reduced uterine volume, reduced or undetectable blood supply and absent endometrium[41,42,45-47]. Critchley *et al*[41] assessed 10 women with premature ovarian failure due to whole abdominal irradiation in childhood. The uterine volume remained significantly lower in patients treated with pelvic radiotherapy compared with controls, and was correlated with age at the time of radiotherapy. Attempts to reverse these changes by means of cyclical hormone replacement therapy had limited success. Almost all treated women had loss of signal in one or both uterine arteries with Doppler ultrasound.

Holm *et al*[46] also used ultrasound to evaluate the impact of total body irradiation (TBI) with 8-14 Gy on internal genitalia and uterine blood flow. The median age was 12.7 years (range 6.1-17.6 years) at treatment and 21.5 years (range 11.6-25.6 years) at study entry. All participants had entered puberty but despite sufficient hormonal stimulus to achieve menarche in 11 out of 12 [eight with hormone replacement therapy (HRT) and 3 spontaneously], the median uterine volumes were still significantly reduced compared with normal controls. Uterine blood flow was impaired with systolic blood flow measurable in six of nine individuals, and diastolic blood flow visible in only one patient. These studies concluded that pre-pubertal irradiation may have an irreversible effect on uterine vasculature and development and that the endometrium may become unresponsive to hormonal stimuli due to a combination of effects on vasculature and to sex-steroid receptors[48].

The endometrial injury noted in the patients treated with TBI using a dose of 14.4 Gy was further studied by Bath *et al*[42] who propose this would prevent normal endometrial decidualisation (the post-ovulatory process of endometrial remodelling in preparation for pregnancy). This potentially leads to placental attachment disorders, including severe forms such as placenta accreta and placenta percreta[15,49,50]. In addition to these adverse endometrial changes it has also been suggested that pelvic radiotherapy can lead to thinning of the myometrium leading to an increased risk of uterine rupture during pregnancy[49,50].

There are few studies assessing the uterine changes after high dose pelvic radiotherapy in adults. Arrivé *et al*[51] undertook sequential magnetic resonance (MR) imaging imaging of 23 pre-menopausal women who received radiation for cervical cancer. A reduction in myometrial signal intensity on T2-weighted images was demonstrable by 1 mo after therapy and a decrease in uterine size was noted at 3 mo. A decrease in thickness and signal intensi-

ty of the endometrium was seen by 6 mo with earlier loss of uterine zonal anatomy. Four patients also had histopathological assessment which showed myometrial atrophy with fibrosis, inactive endometrium and reduction in vascular diameter. In postmenopausal women, irradiation did not significantly alter the MR imaging appearance of the uterus. The authors concluded that the early changes are due directly to radiotherapy but premature ovarian failure would have been contributory to the later atrophic changes.

Hormone replacement therapy is prescribed following radiotherapy to prevent menopausal symptoms. Combined cyclical therapy is indicated for patients previously treated for childhood cancers who still have a functional uterus. Following radiotherapy for cervical cancer, the very high doses delivered to the endometrial surface from brachytherapy is assumed to cause complete destruction of the basal layer of the endometrium. However, there have been several reports of persistent endometrial activity after treatment for cervical cancer. Habeshaw *et al*[52] reported 15 out of 63 patients treated for cervical cancer had breakthrough or cyclical vaginal bleeding when started on combined HRT several months to years after completing radiotherapy. Patients with an intact uterus following radiotherapy should therefore still be treated with oestrogen and a progestagen to avoid endometrial stimulation from unopposed oestrogen therapy.

Other than gestational surrogacy, there are no specific interventions available for uterine changes secondary to pelvic radiotherapy. Uterine dysfunction therefore represents a greater barrier to achieving viable pregnancy than does ovarian failure.

ADVERSE PREGNANCY OUTCOMES IN WOMEN TREATED WITH PELVIC RADIOTHERAPY

A number of long-term follow-up studies of pregnancy and neonatal outcomes in women treated in childhood for cancer with radiotherapy have now been published[17-19,53-57]. These studies have consistently found evidence of an increased risk of adverse pregnancy and neonatal outcomes for mothers with a prior history of irradiation in childhood, including: spontaneous miscarriages, pre-term labour, intrauterine growth retardation and low-birthweight infants[41,42,51,52]. While the risk increases with higher uterine dose, neonatal complications are noted with doses as low as 0.5 Gy.

There are no reports of a term pregnancy in patients who received more than 45 Gy to the whole uterus, which conventionally is the minimum dose delivered for gynaecological cancers. Hürmüz *et al*[58] have recently reported a patient with a full term pregnancy following pelvic chemoradiotherapy for anal cancer. Reviewing the radiotherapy fields, 30 Gy was delivered to the whole uterus while the lower segment and cervix received 50 Gy.

A fertility preserving approach using brachytherapy for cervical or vaginal clear cell adenocarcinoma was reviewed by Magné *et al*[59]. Seven of the 19 women treated for vaginal disease tried to become pregnant, with three delivering healthy term babies and one spontaneous abortion. In the 42 patients with cervical cancer, there were no successful pregnancies and two women reported spontaneous abortions.

A Canadian cohort study compared the risk of adverse pregnancy outcomes in female childhood cancer survivors who received abdominal-pelvic radiation and/or chemotherapy with alkylating agents with the risk among those who were treated by non-sterilising alkylating agents and those who were treated by non-sterilising surgery only[54]. There was no evidence of an increased risk of having a spontaneous abortion or an infant with a birth defect. Survivors receiving abdomino-pelvic radiotherapy were more likely to have a low birth weight infant (OR 3.64; 95%CI: 1.33-9.96), a premature low birth weight infant (OR 3.29; 95%CI: 0.97-11.1), or an infant who died in the perinatal period (OR 2.41; 95%CI: 0.50-11.5), compared with those receiving surgery. Risks of perinatal death and having a low birth weight infant increased with increasing dose of radiotherapy.

This association of children with low birth weight being born to mothers who had received pelvic radiotherapy has been confirmed in large studies from the United States that reviewed pregnancy outcomes among female participants in the Childhood Cancer Survivor Study (CCSS), a large multi-centre cohort of childhood cancer survivors[17,18,56]. The fertility of 5149 female survivors was compared to a cohort of 1441 randomly selected female siblings. The relative risk (RR) for survivors of ever being pregnant was 0.81 (95%CI: 0.73-0.90, $P < 0.001$) compared with siblings. In multivariate analysis, those who received an ovarian or uterine radiation dose greater than 5 Gy were less likely to have ever been pregnant with RR 0.56 for those receiving 5 to 10 Gy (95%CI: 0.37-0.85) and RR 0.18 for more than 10 Gy (95%CI: 0.13-0.26)[56].

Signorello *et al*[18] looked at singleton live births from female CCSS members from 1968 to 2002. This study included 2201 children of 1264 survivors and 1175 children of a comparison group of 601 female siblings. Survivors' children were more likely to be born pre-term than the siblings' children (21.1% *vs* 12.6%, $P < 0.001$). Compared with the children of survivors who did not receive radiotherapy, the children of survivors treated with a radiotherapy dose to the uterus of > 5 Gy had an increased risk of being born preterm (50.0% *vs* 19.6%, $P = 0.003$), low birth weight (36.2% *vs* 7.6%, $P = 0.001$), and small for gestational age (18.2% *vs* 7.8%, $P = 0.003$). Increased risks were also seen at lower uterine radiotherapy doses (starting at 0.5 Gy for preterm birth and at 2.5 Gy for low birth weight).

Similar findings were reported in a cohort review of 1688 female survivors of childhood cancer from the Danish Cancer Registry[57]. The outcomes of survivors, 2737 sisters, and 16700 comparison women in the population were identified from nationwide registries. More

than 34000 pregnancies were evaluated, 1479 of which were among cancer survivors. Survivors with any prior radiation had an increased excess risk of spontaneous abortion (OR 1.58; 95%CI: 1.2-2.2) which was greatest in those receiving higher doses to the ovaries and uterus (OR 2.8; 95%CI: 1.7-4.7).

The risk of radiotherapy induced germ line mutagenicity has also been assessed. In a United States cohort, 4214 children were born to cancer survivors with 157 (3.7%) having genetic diseases in contrast to 95 (4.1%) congenital conditions among 2339 children born to sibling controls. There was no increased risk of malformations, infant death, or altered sex ratio[55]. In the Danish series there were 82 (6.1%) birth defects among 1345 children of cancer survivors and 211 (5.0%) among 4225 children of sibling controls. These results provide reassurance that radiotherapy is very unlikely to cause inherited genetic disease in the children of cancer survivors[60].

These findings from large cohorts of women treated with abdomino-pelvic radiotherapy in childhood are all consistent with the complications of pregnancy that would be anticipated from the observations of reduced uterine volume, reduced elasticity of the myometrium and impaired uterine blood flow following pelvic radiotherapy described in section 2.2.

MEASURES TO PRESERVE FERTILITY PRIOR TO RADIOTHERAPY

Ovarian transposition

Whilst it may be practical to attempt to shield the ovaries from radiotherapy beams for some patients undergoing abdomino-pelvic radiotherapy, this will not be possible for women undergoing radical radiotherapy for gynaecological cancer due to proximity to the lymph node target volume. The ovaries are usually included in the radiation target volume for locally advanced cervical cancers due to the risk of ovarian metastases, with adenocarcinomas having a particular propensity for spread. However, for early stage disease and patients with pelvic sarcoma, lymphoma or receiving craniospinal irradiation there may be many benefits with ovarian preservation.

For these women, ovarian transposition, also known as oophoropexy, is a surgical procedure that attempts to move the ovaries outside of the radiation field. Although ovarian function can be preserved with this technique, it offers no protection to the uterus and so radiotherapy-induced uterine damage will continue to limit the chances of a successful pregnancy.

The procedure may be performed by open laparotomy and more recently with a laparoscopic technique[61-66]. The location selected for fixation of the transposed ovaries is dependent on the proposed pelvic radiotherapy field. For cervical carcinomas the transposed ovaries should be fixed well above the pelvic brim, since the standard superior border of the radiotherapy field is the L4/L5 or L3/4 vertebral space[66] (Figure 2). A high lateral position within the paracolic gutters is typically selected. Complications of ovarian transposition include benign ovarian cysts (23%), chronic pelvic pain (3%), and ovarian metastases (1%)[67]. Other reported complications include vascular injury, fallopian tube infarction, and ovarian migration[66-68].

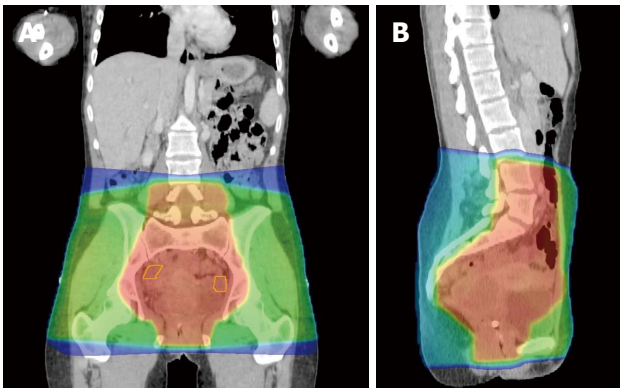

Figure 2 Typical radiotherapy dose distribution for cervical cancer. A: Coronal view; B: Sagittal view. The red area receives > 40 Gy, green > 10 Gy and blue < 10 Gy. Ovarian positions are contoured in yellow within the treated area, and transposition to the lateral para-colic region is required to be outside the low dose radiation region.

Covens *et al*[69] estimated the radiation exposure to each transposed ovary in three cervical cancer patients based on intra-uterine brachytherapy alone, and on external-beam pelvic radiotherapy (45 Gy), with and without para-aortic nodal irradiation (45 Gy). They estimated the mean radiation dose to each ovary following transposition for a course of intra-uterine brachytherapy as 1.3 Gy. The estimated doses for pelvic radiation without and with para-aortic lymph node irradiation were 1.4-1.9 Gy, and 2.3-3.1 Gy, respectively.

The reported success rates of ovarian transposition, in terms of preservation of ovarian function and fertility vary widely[15]. In a prospective study of 107 patients treated for cervical cancer, ovarian transposition to the paracolic gutters at the time of radical hysterectomy and lymphadenectomy was attempted[67]. Bilateral ovarian transposition was achieved in 104 of the 107 patients (98%). Of the 104 patients that underwent successful ovarian transposition, 59 were treated with vaginal brachytherapy alone to 60 Gy, and 25 other patients received external beam pelvic radiotherapy to 45 Gy with concurrent cisplatin, followed by vaginal brachytherapy to 15 Gy. Ovarian function was assessed by post-operative ultrasound and serial serum hormone levels. Preservation of ovarian function was achieved in 83% patients. After a median of 31 mo follow-up the rates of ovarian preservation were 100% for patients treated exclusively by surgery, 90% for patients treated by post-operative vaginal brachytherapy, and 60% for patients treated by post-operative external beam radiotherapy and vaginal brachytherapy.

Other methods of fertility preservation

The available methods for fertility preservation are summarised in Table 1. Aside from ovarian transposition, the

Table 1 Options for fertility preservation in women undergoing radical radiotherapy to the pelvis

Intervention	Procedure	Status	Time required	Pros	Cons
Ovarian transposition	Surgery to relocate ovaries within the abdomen outside of radiotherapy field	Established	Minimal (1 d)	Preserves oocytes and prevents premature menopause	Invasive surgical procedure; may require IVF; does nothing to protect uterus
Embryo cryopreservation	Mature oocyte aspiration, IVF, embryo freezing for later use	Established	2-3 wk	Established pregnancy rate of 20%-30% per transfer of 2 to 3 embryos	Requires 2 wk of ovarian stimulation; requires partner or donor sperm; requires functioning uterus or surrogacy
Donor oocytes and gestational surrogacy	IVF using donor oocytes and/or implantation of the embryo in a surrogate carrier	Established but infrequent	Not applicable	May be the only available option for some women with non-functioning uterus	Requires donor oocytes and gestational surrogate; ethical difficulties
Oocyte cryopreservation	Mature oocyte aspiration and freezing for later use	Experimental, live births reported, but only recommended as part of research	2-3 wk	Avoids need for partner or donor sperm at time of cryopreservation	Requires 2 wk of ovarian stimulation; requires functioning uterus or surrogacy
Ovarian tissue cryopreservation	Harvesting and freezing of ovarian tissue; re-implantation after radiotherapy or other gonadotoxic treatment	Experimental, but live births reported	Minimal (1 d)	Avoids need for partner or donor sperm at time of cryopreservation	Not appropriate if significant risk of ovarian involvement with malignancy

IVF: *In vitro* fertilisation.

only established method for women undergoing pelvic radiotherapy is embryo cryopreservation[5,6,70]. Mature oocytes are collected before treatment for *in-vitro* fertilisation and subsequent embryo cryopreservation. The Society for Assisted Reproductive Technology reported the live birth rate per transfer using frozen thawed embryos was 38.7% in United States women under 35 years old in 2010[71]. This technique requires a male partner or donor sperm for fertilisation. It may not suitable for many patients with cancer, because of the need for a period of ovarian stimulation that will delay the start of anti-cancer treatment.

Other fertility sparing interventions are available, but at the present time continue to be considered investigational. Oocyte cryopreservation requires ovarian stimulation and success depends on the number of mature oocytes retrieved. The oocyte survival rate (OR 2.46; 95%CI: 1.82-3.32) and high quality embryo rate (22% *vs* 8%) of oocyte cryopreservation with vitrification is significantly higher than with conventional slow freezing methods[72,73]. This improvement in technique and successful long term outcomes suggest this should now be considered an established treatment.

Ovarian tissue cryopreservation is the only option for prepubertal girls, patients who need treatment without delay or when ovarian stimulation is contraindicated due to hormone sensitive cancers[5,74-76]. Ovarian tissue is harvested laparoscopically and cryopreserved. With orthotopic transplantation, ovarian cortical fragments are reimplanted into the pelvic cavity once in remission[77,78]. However, following radiotherapy the vascular supply will be impaired and heterotopic transplantation to a remote site may be required. In 2001, Oktay *et al*[79] first reported successful transplantation to the forearm for a patient with cervical cancer, resulting in regular ovarian cycles for more than 1 year. There is the risk of introducing malignant cells preserved within the ovarian tissue. Since the first live birth was reported in 2004, orthotopic reimplantation has led to the birth of 17 healthy babies[80]. It also has the advantage of restoring endocrine function in young women after cancer treatment, with ovarian hormonal activity demonstrated within 3 to 6 mo after transplantation[81].

However, gestational surrogacy is the only option for women with preserved embryos, or preserved ovarian tissue but who have uterine compromise secondary to radiotherapy[76]. Similarly, women for whom other fertility sparing options are either inappropriate or fail have the option of oocyte donation with gestational surrogacy.

FUTURE PROSPECTS

Thankfully, fertility preservation is now an important consideration in oncology clinics, and the options available to patients are routinely offered. Despite the significant advances that have been made over the last three decades, and despite the availability of fertility sparing manoeuvres discussed above, there remain a significant number of women who will be rendered infertile as a result of life-saving cancer treatment. Techniques that do not require the preservation of embryos, or that do not require the delays associated with hormone stimulation, are the subject of ongoing intensive research efforts.

A particular problem remains for women whose uterus has been treated with radiotherapy. The first attempt at human uterus transplantation was undertaken in 2000. The transplanted uterus survived for 3 mo before failing due to thrombosis and necrosis[82]. This area has been the subject of ongoing active preclinical research efforts[83-86]. The first uterine transplant from a multi-organ donor was

undertaken in Turkey in 2011 and successfully achieved menstrual cycles after 20 d[87]. Recently two mother to daughter uterine transplants have been performed at the University of Gothenberg, Sweden and the results are awaited. Whilst there remain many technical obstacles to overcome, it may be possible to offer women who have received radiotherapy the option of uterus transplantation in the future.

CONCLUSION

Radiotherapy to the pelvis can have a major and deleterious impact on the female genital tract. Despite significant advances in the technical delivery of radical pelvic radiotherapy there remains no way to avoid delivering substantial radiation doses to the ovaries and uterus for patients undergoing treatment for gynaecological cancers. Due to improved cure rates from radical chemo-radiotherapy and social trends toward delayed childbirth many women treated for cervical cancer with radical chemo-radiotherapy will wish to attempt to preserve their fertility. Without specific interventions radical pelvic chemo-radiotherapy will always render women menopausal and infertile. Whilst there are now established and emerging techniques for preserving ovarian function and ovarian tissue, there remains the difficulty of the irradiated uterus which, even if pregnancy can be achieved, results in an increased risk for pregnancy-related complications, including spontaneous miscarriages, preterm labour, premature delivery, low birth weight, and placental abnormalities. Pre-menopausal women undergoing radical chemo-radiotherapy for gynaecological cancers need to be carefully counselled regarding the impact of this life-saving treatment on their fertility and sexual functioning, and offered support and access to such fertility sparing interventions as are currently available. Future developments may offer women in this difficult situation more and improved options for fertility preservation.

REFERENCES

1 http://www.cancerresearchuk.org/cancer-info/cancerstats/types/cervix/incidence
2 **Parkin DM**, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. *Br J Cancer* 2011; **105** Suppl 2: S77-S81 [PMID: 22158327 DOI: 10.1038/bjc.2011.489]
3 **Eskander RN**, Randall LM, Berman ML, Tewari KS, Disaia PJ, Bristow RE. Fertility preserving options in patients with gynecologic malignancies. *Am J Obstet Gynecol* 2011; **205**: 103-110 [PMID: 21411052 DOI: 10.1016/j.ajog.2011.01.025]
4 **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]
5 **Lobo RA**. Potential options for preservation of fertility in women. *N Engl J Med* 2005; **353**: 64-73 [PMID: 16000356]
6 **Simon B**, Lee SJ, Partridge AH, Runowicz CD. Preserving fertility after cancer. *CA Cancer J Clin* 2005; **55**: 211-228; quiz 263-264 [PMID: 16020423]
7 **Landoni F**, Maneo A, Colombo A, Placa F, Milani R, Perego P, Favini G, Ferri L, Mangioni C. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet* 1997; **350**: 535-540 [PMID: 9284774]
8 **Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration**. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 2008; **26**: 5802-5812 [PMID: 19001332]
9 **Lim K**, Small W, Portelance L, Creutzberg C, Jürgenliemk-Schulz IM, Mundt A, Mell LK, Mayr N, Viswanathan A, Jhingran A, Erickson B, De los Santos J, Gaffney D, Yashar C, Beriwal S, Wolfson A, Taylor A, Bosch W, El Naqa I, Fyles A. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. *Int J Radiat Oncol Biol Phys* 2011; **79**: 348-355 [PMID: 20472347 DOI: 10.1016/j.ijrobp.2009.10.075]
10 **Taylor A**, Powell ME. Conformal and intensity-modulated radiotherapy for cervical cancer. *Clin Oncol* (R Coll Radiol) 2008; **20**: 417-425 [PMID: 18558480 DOI: 10.1016/j.clon.2008.04.004]
11 **Pötter R**, Fidarova E, Kirisits C, Dimopoulos J. Image-guided adaptive brachytherapy for cervix carcinoma. *Clin Oncol* (R Coll Radiol) 2008; **20**: 426-432 [PMID: 18524555 DOI: 10.1016/j.clon.2008.04.011]
12 **Quinn MA**, Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT, Heintz AP, Ngan HY, Pecorelli S. Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet* 2006; **95** Suppl 1: S43-103 [PMID: 17161167]
13 **Meirow D**, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. *Hum Reprod Update* 2001; **7**: 535-543 [PMID: 11727861]
14 **Critchley HO**, Wallace WH. Impact of cancer treatment on uterine function. *J Natl Cancer Inst Monogr* 2005; **2005**: 64-68 [PMID: 15784827]
15 **Wo JY**, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. *Int J Radiat Oncol Biol Phys* 2009; **73**: 1304-1312 [PMID: 19306747 DOI: 10.1016/j.ijrobp.2008.12.016]
16 **Sudour H**, Chastagner P, Claude L, Desandes E, Klein M, Carrie C, Bernier V. Fertility and pregnancy outcome after abdominal irradiation that included or excluded the pelvis in childhood tumor survivors. *Int J Radiat Oncol Biol Phys* 2010; **76**: 867-873 [PMID: 19632060 DOI: 10.1016/j.ijrobp.2009.04.012]
17 **Green DM**, Whitton JA, Stovall M, Mertens AC, Donaldson SS, Ruymann FB, Pendergrass TW, Robison LL. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Am J Obstet Gynecol* 2002; **187**: 1070-1080 [PMID: 12389007]
18 **Signorello LB**, Cohen SS, Bosetti C, Stovall M, Kasper CE, Weathers RE, Whitton JA, Green DM, Donaldson SS, Mertens AC, Robison LL, Boice JD. Female survivors of childhood cancer: preterm birth and low birth weight among their children. *J Natl Cancer Inst* 2006; **98**: 1453-1461 [PMID: 17047194]
19 **Green DM**, Lange JM, Peabody EM, Grigorieva NN, Peterson SM, Kalapurakal JA, Breslow NE. Pregnancy outcome after treatment for Wilms tumor: a report from the national Wilms tumor long-term follow-up study. *J Clin Oncol* 2010; **28**: 2824-2830 [PMID: 20458053]
20 **Wallace WH**, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered? *Lancet Oncol* 2005; **6**: 209-218 [PMID: 15811616]
21 **Wallace WH**, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int J Radiat Oncol Biol Phys* 2005; **62**: 738-744 [PMID: 15936554]

22 **National Institute for Clinical Excellence**. Fertility: assessment and treatment for people with fertility problems. London: National Institute for Clinical Excellence, 2004
23 **Sklar CA**, Mertens AC, Mitby P, Whitton J, Stovall M, Kasper C, Mulder J, Green D, Nicholson HS, Yasui Y, Robison LL. Premature menopause in survivors of childhood cancer: a report from the childhood cancer survivor study. *J Natl Cancer Inst* 2006; **98**: 890-896 [PMID: 16818852]
24 **Chiarelli AM**, Marrett LD, Darlington G. Early menopause and infertility in females after treatment for childhood cancer diagnosed in 1964-1988 in Ontario, Canada. *Am J Epidemiol* 1999; **150**: 245-254 [PMID: 10430228]
25 **Byrne J**, Fears TR, Gail MH, Pee D, Connelly RR, Austin DF, Holmes GF, Holmes FF, Latourette HB, Meigs JW. Early menopause in long-term survivors of cancer during adolescence. *Am J Obstet Gynecol* 1992; **166**: 788-793 [PMID: 1550144]
26 **Lancaster L**. Preventing vaginal stenosis after brachytherapy for gynaecological cancer: an overview of Australian practices. *Eur J Oncol Nurs* 2004; **8**: 30-39 [PMID: 15003742]
27 **Hartman P**, Diddle AW. Vaginal stenosis following irradiation therapy for carcinoma of the cervix uteri. *Cancer* 1972; **30**: 426-429 [PMID: 5051667]
28 **Mahmud A**, Brydon B, Tonita J, Hanna TP, Schmidt M, Tai P. A population-based study of cervix cancer: incidence, management and outcome in the Canadian province of Saskatchewan. *Clin Oncol* (R Coll Radiol) 2011; **23**: 691-695 [PMID: 21646003]
29 **Johnson N**, Miles TP, Cornes P. Dilating the vagina to prevent damage from radiotherapy: systematic review of the literature. *BJOG* 2010; **117**: 522-531 [PMID: 20163407]
30 **White ID**, Faithfull S. Vaginal dilation associated with pelvic radiotherapy: a UK survey of current practice. *Int J Gynecol Cancer* 2006; **16**: 1140-1146 [PMID: 16803497]
31 **National Forum of Gynaecological Oncology Nurses**. Best Practice guidelines on the use of vaginal dilators in women receiving pelvic radiotherapy. Oxon: Published by Owen Mumford, 2005
32 Vaginal stenosis. In: Best Clinical Practice Gynaecological Cancer Guidelines 2009. North Sydney: NSW Department of Health, 2009: 16-17
33 **Miles T**, Johnson N. Vaginal dilator therapy for women receiving pelvic radiotherapy. *Cochrane Database Syst Rev* 2010; CD007291 [PMID: 20824858]
34 **Ogilvy-Stuart AL**, Shalet SM. Effect of radiation on the human reproductive system. *Environ Health Perspect* 1993; **101** Suppl 2: 109-116 [PMID: 8243379]
35 **Faddy MJ**, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. *Hum Reprod* 1992; **7**: 1342-1346 [PMID: 1291557]
36 **Wallace WH**, Shalet SM, Hendry JH, Morris-Jones PH, Gattamaneni HR. Ovarian failure following abdominal irradiation in childhood: the radiosensitivity of the human oocyte. *Br J Radiol* 1989; **62**: 995-998 [PMID: 2510900]
37 **Wallace WH**, Thomson AB, Kelsey TW. The radiosensitivity of the human oocyte. *Hum Reprod* 2003; **18**: 117-121 [PMID: 12525451]
38 **Lushbaugh CC**, Casarett GW. The effects of gonadal irradiation in clinical radiation therapy: a review. *Cancer* 1976; **37**: 1111-1125 [PMID: 766956]
39 **Lutchman Singh K**, Davies M, Chatterjee R. Fertility in female cancer survivors: pathophysiology, preservation and the role of ovarian reserve testing. *Hum Reprod Update* 2005; **11**: 69-89 [PMID: 15569700]
40 **Su HI**. Measuring ovarian function in young cancer survivors. *Minerva Endocrinol* 2010; **35**: 259-270 [PMID: 21178920]
41 **Critchley HO**, Wallace WH, Shalet SM, Mamtora H, Higginson J, Anderson DC. Abdominal irradiation in childhood; the potential for pregnancy. *Br J Obstet Gynaecol* 1992; **99**: 392-394 [PMID: 1622911]
42 **Bath LE**, Critchley HO, Chambers SE, Anderson RA, Kelnar CJ, Wallace WH. Ovarian and uterine characteristics after total body irradiation in childhood and adolescence: response to sex steroid replacement. *Br J Obstet Gynaecol* 1999; **106**: 1265-1272 [PMID: 10609720]
43 **Holm K**, Laursen EM, Brocks V, Müller J. Pubertal maturation of the internal genitalia: an ultrasound evaluation of 166 healthy girls. *Ultrasound Obstet Gynecol* 1995; **6**: 175-181 [PMID: 8521066]
44 **Bridges NA**, Cooke A, Healy MJ, Hindmarsh PC, Brook CG. Growth of the uterus. *Arch Dis Child* 1996; **75**: 330-331 [PMID: 8984921]
45 **Larsen EC**, Schmiegelow K, Rechnitzer C, Loft A, Müller J, Andersen AN. Radiotherapy at a young age reduces uterine volume of childhood cancer survivors. *Acta Obstet Gynecol Scand* 2004; **83**: 96-102 [PMID: 14678092]
46 **Holm K**, Nysom K, Brocks V, Hertz H, Jacobsen N, Müller J. Ultrasound B-mode changes in the uterus and ovaries and Doppler changes in the uterus after total body irradiation and allogeneic bone marrow transplantation in childhood. *Bone Marrow Transplant* 1999; **23**: 259-263 [PMID: 10084257]
47 **Laursen EM**, Holm K, Brocks V, Jarden M, Müller J. Doppler assessment of flow velocity in the uterine artery during pubertal maturation. *Ultrasound Obstet Gynecol* 1996; **8**: 341-345 [PMID: 8978010]
48 **Urbano MT**, Tait DM. Can the irradiated uterus sustain a pregnancy? A literature review. *Clin Oncol* (R Coll Radiol) 2004; **16**: 24-28 [PMID: 14768752]
49 **Pridjian G**, Rich NE, Montag AG. Pregnancy hemoperitoneum and placenta percreta in a patient with previous pelvic irradiation and ovarian failure. *Am J Obstet Gynecol* 1990; **162**: 1205-1206 [PMID: 2339720]
50 **Norwitz ER**, Stern HM, Grier H, Lee-Parritz A. Placenta percreta and uterine rupture associated with prior whole body radiation therapy. *Obstet Gynecol* 2001; **98**: 929-931 [PMID: 11704208]
51 **Arrivé L**, Chang YC, Hricak H, Brescia RJ, Auffermann W, Quivey JM. Radiation-induced uterine changes: MR imaging. *Radiology* 1989; **170**: 55-58 [PMID: 2909120]
52 **Habeshaw T**, Pinion SB. The incidence of persistent functioning endometrial tissue following successful radiotherapy for cervical carcinoma. *Int J Gynecol Cancer* 1992; **2**: 332-335 [PMID: 11576279]
53 **Green DM**, Peabody EM, Nan B, Peterson S, Kalapurakal JA, Breslow NE. Pregnancy outcome after treatment for Wilms tumor: a report from the National Wilms Tumor Study Group. *J Clin Oncol* 2002; **20**: 2506-2513 [PMID: 12011129]
54 **Chiarelli AM**, Marrett LD, Darlington GA. Pregnancy outcomes in females after treatment for childhood cancer. *Epidemiology* 2000; **11**: 161-166 [PMID: 11021613]
55 **Mueller BA**, Chow EJ, Kamineni A, Daling JR, Fraser A, Wiggins CL, Mineau GP, Hamre MR, Severson RK, Drews-Botsch C. Pregnancy outcomes in female childhood and adolescent cancer survivors: a linked cancer-birth registry analysis. *Arch Pediatr Adolesc Med* 2009; **163**: 879-886 [PMID: 19805705 DOI: 10.1001/archpediatrics.2009.112]
56 **Green DM**, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, Donaldson SS, Byrne J, Robison LL. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2009; **27**: 2677-2685 [PMID: 19364965 DOI: 10.1200/JCO.2008.20.1541]
57 **Winther JF**, Boice JD, Svendsen AL, Frederiksen K, Stovall M, Olsen JH. Spontaneous abortion in a Danish population-based cohort of childhood cancer survivors. *J Clin Oncol* 2008; **26**: 4340-4346 [PMID: 18779621 DOI: 10.1200/JCO.2007.15.2884]
58 **Hürmüz P**, Sebag-Montefiore D, Byrne P, Cooper R. Successful spontaneous pregnancy after pelvic chemoradiotherapy for anal cancer. *Clin Oncol* (R Coll Radiol) 2012; **24**: 455-457 [PMID: 22486987 DOI: 10.1016/j.clon.2012.03.006]

59 **Magné N**, Chargari C, Levy A, Rodriguez C, De Vos V, Gerbaulet A, Duvillard P, Morice P, Haie-Meder C. Clear cell adenocarcinoma of the female genital tract: long-term outcome and fertility aspects after brachytherapy aimed at a conservative treatment. *Int J Gynecol Cancer* 2012; **22**: 1378-1382 [PMID: 22932263]

60 **Winther JF**, Olsen JH, Wu H, Shyr Y, Mulvihill JJ, Stovall M, Nielsen A, Schmiegelow M, Boice JD. Genetic disease in the children of Danish survivors of childhood and adolescent cancer. *J Clin Oncol* 2012; **30**: 27-33 [PMID: 22124106 DOI: 10.1200/JCO.2011.35.0504]

61 **McCall ML**, Keaty EC, Thompson JD. Conservation of ovarian tissue in the treatment of carcinoma of the cervix with radical surgery. *Am J Obstet Gynecol* 1958; **75**: 590-600; discussion 600-605 [PMID: 13508748]

62 **Cowles RA**, Gewanter RM, Kandel JJ. Ovarian repositioning in pediatric cancer patients: Flexible techniques accommodate pelvic radiation fields. *Pediatr Blood Cancer* 2007; **49**: 339-341 [PMID: 16261563]

63 **Classe JM**, Mahé M, Moreau P, Rapp MJ, Maisonneuve H, Lemevel A, Bourdin S, Harousseau JL, Cuillière JC. Ovarian transposition by laparoscopy before radiotherapy in the treatment of Hodgkin's disease. *Cancer* 1998; **83**: 1420-1424 [PMID: 9762944]

64 **Kurt M**, Uncu G, Cetintas SK, Kucuk N, Guler S, Ozkan L. Successful spontaneous pregnancy in a patient with rectal carcinoma treated with pelvic radiotherapy and concurrent chemotherapy: the unique role of laparoscopic lateral ovary transposition. *Eur J Gynaecol Oncol* 2007; **28**: 408-410 [PMID: 17966224]

65 **Sella T**, Mironov S, Hricak H. Imaging of transposed ovaries in patients with cervical carcinoma. *AJR Am J Roentgenol* 2005; **184**: 1602-1610 [PMID: 15855125]

66 **Morice P**, Castaigne D, Haie-Meder C, Pautier P, El Hassan J, Duvillard P, Gerbaulet A, Michel G. Laparoscopic ovarian transposition for pelvic malignancies: indications and functional outcomes. *Fertil Steril* 1998; **70**: 956-960 [PMID: 9806584]

67 **Morice P**, Juncker L, Rey A, El-Hassan J, Haie-Meder C, Castaigne D. Ovarian transposition for patients with cervical carcinoma treated by radiosurgical combination. *Fertil Steril* 2000; **74**: 743-748 [PMID: 11020517]

68 **Williams RS**, Littell RD, Mendenhall NP. Laparoscopic oophoropexy and ovarian function in the treatment of Hodgkin disease. *Cancer* 1999; **86**: 2138-2142 [PMID: 10570443]

69 **Covens AL**, van der Putten HW, Fyles AW, Leung PM, O' Brien PF, Murphy KJ, DePetrillo AD. Laparoscopic ovarian transposition. *Eur J Gynaecol Oncol* 1996; **17**: 177-182 [PMID: 8780914]

70 **Jensen JR**, Morbeck DE, Coddington CC. Fertility preservation. *Mayo Clin Proc* 2011; **86**: 45-49 [PMID: 21193655 DOI: 10.4065/mcp.2010.0564]

71 Society for Assisted Reproductive Technology. Available from: URL: http://www.sart.org

72 **Cao YX**, Xing Q, Li L, Cong L, Zhang ZG, Wei ZL, Zhou P. Comparison of survival and embryonic development in human oocytes cryopreserved by slow-freezing and vitrification. *Fertil Steril* 2009; **92**: 1306-1311 [PMID: 18930218 DOI: 10.1016/j.fertnstert.2008.08.069]

73 **Cobo A**, Diaz C. Clinical application of oocyte vitrification: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril* 2011; **96**: 277-285 [PMID: 21718983 DOI: 10.1016/j.fertnstert.2011.06.030]

74 **Rodriguez-Wallberg KA**, Oktay K. Recent advances in oocyte and ovarian tissue cryopreservation and transplantation. *Best Pract Res Clin Obstet Gynaecol* 2012; **26**: 391-405 [PMID: 22301053]

75 **Silber SJ**. Ovary cryopreservation and transplantation for fertility preservation. *Mol Hum Reprod* 2012; **18**: 59-67 [PMID: 22205727]

76 **Jeruss JS**, Woodruff TK. Preservation of fertility in patients with cancer. *N Engl J Med* 2009; **360**: 902-911 [PMID: 19246362 DOI: 10.1056/NEJMra0801454]

77 **Dursun P**, Ayhan A, Yanik FB, Kuşçu E. Ovarian transposition for the preservation of ovarian function in young patients with cervical carcinoma. *Eur J Gynaecol Oncol* 2009; **30**: 13-15 [PMID: 19317249]

78 **Sonmezer M**, Oktay K. Orthotopic and heterotopic ovarian tissue transplantation. *Best Pract Res Clin Obstet Gynaecol* 2010; **24**: 113-126 [PMID: 19853515 DOI: 10.1016/j.bpobgyn.2009.09.002]

79 **Oktay K**, Economos K, Kan M, Rucinski J, Veeck L, Rosenwaks Z. Endocrine function and oocyte retrieval after autologous transplantation of ovarian cortical strips to the forearm. *JAMA* 2001; **286**: 1490-1493 [PMID: 11572742]

80 **Lee S**, Song JY, Ku SY, Kim SH, Kim T. Fertility preservation in women with cancer. *Clin Exp Reprod Med* 2012; **39**: 46-51 [PMID: 22816069 DOI: 10.5653/cerm.2012.39.2.46]

81 **Oktay K**, Karlikaya G. Ovarian function after transplantation of frozen, banked autologous ovarian tissue. *N Engl J Med* 2000; **342**: 1919 [PMID: 10877641]

82 **Fageeh W**, Raffa H, Jabbad H, Marzouki A. Transplantation of the human uterus. *Int J Gynaecol Obstet* 2002; **76**: 245-251 [PMID: 11880127]

83 **Del Priore G**, Schlatt S, Wagner R, Reynoso E, Malanowska-Stega J. Uterus transplantation: on the edge. *Semin Reprod Med* 2011; **29**: 55-60 [PMID: 21207334]

84 **Hanafy A**, Diaz-Garcia C, Olausson M, Brännström M. Uterine transplantation: one human case followed by a decade of experimental research in animal models. *Aust N Z J Obstet Gynaecol* 2011; **51**: 199-203 [PMID: 21631436]

85 **Brännström M**, Diaz-Garcia C, Hanafy A, Olausson M, Tzakis A. Uterus transplantation: animal research and human possibilities. *Fertil Steril* 2012; **97**: 1269-1276 [PMID: 22542990 DOI: 10.1016/j.fertnstert.2012.04.001]

86 **Saso S**, Ghaem-Maghami S, Chatterjee J, Brewig N, Ungar L, Smith JR, Del Priore G. Immunology of uterine transplantation: a review. *Reprod Sci* 2012; **19**: 123-134 [PMID: 22138547 DOI: 10.1177/1933719111417887]

87 **Ozkan O**, Akar ME, Ozkan O, Erdogan O, Hadimioglu N, Yilmaz M, Gunseren F, Cincik M, Pestereli E, Kocak H, Mutlu D, Dinckan A, Gecici O, Bektas G, Suleymanlar G. Preliminary results of the first human uterus transplantation from a multiorgan donor. *Fertil Steril* 2013; **99**: 470-476 [PMID: 23084266 DOI: 10.1016/j.fertnstert.2012.09.035]

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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
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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.

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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]

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TOPIC HIGHLIGHT

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

Ovulation induction in the gynecological cancer patient

Amr H Wahba, Hesham Al-Inany

Amr H Wahba, Hesham Al-Inany, Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, 11562 Cairo, Egypt
Author contributions: Wahba AH searched the literature and wrote the manuscript; Al-Inany H reviewed and edited the manuscript.
Correspondence to: Dr. Amr H Wahba, Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Kasr Al Ainy St., 11562 Cairo, Egypt. dr.amrwahba@yahoo.com
Telephone: +20-2-1002642285
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Abstract

Malignancy is a serious disease that can lead to serious morbidity and mortality. However, the survival rates for women with cancers have increased significantly during the past decades, reflecting improved diagnosis and treatment. With the increased survival in young women with cancer, more attention is being paid to preservation of fertility, which is potentially jeopardized by chemotherapy and radiation therapy, aiming to limit the devastating sequelae of this serious illness by providing these young women with a hope for motherhood. *In vitro* fertilization with oocyte or embryo cryopreservation has emerged as an astounding method to preserve fertility. It entails induction of ovulation to produce oocytes, the number and quality of which are imperative factors predicting the potential efficacy of the fertility preservation procedure. The aim of this review is to discuss ovarian stimulation for fertility preservation in women with gynecological cancer.

Key words: Ovulation induction; Ovarian stimulation; Gynecological cancer

Core tip: Malignancy is a serious illness that is potentially life threatening. However, the survival rates for women with cancers have increased significantly during the past decade, reflecting improved diagnosis and treatment. The aim of this review is to discuss options for ovarian stimulation for fertility preservation in women with gynecological cancer.

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CANCERS IN REPRODUCTIVE AGE

Over the past two decades, cancer incidence rates have continued to increase[1], with approximately 10% of female cancer cases occurring under the age of 45 years[2]. Owing to the advancement in diagnosis and treatment of certain cancers at an earlier stage, improvement has been observed in the survival rates[2], raising more attention to improving the quality of life, particularly through the preservation of fertility, in these young women.

Candidates for fertility preservation are a rather heterogeneous group with a variety of underlying malignancies, the most common cancers being breast, melanoma, cervical, non Hodgkin's lymphoma and leukemia[3,4]. Gynecological cancers in this context include cancer of the breast and cancers arising from the reproductive organs (ovary, uterus, cervix and vulva). These cancers can affect patients in their reproductive years when their childbearing is not completed yet.

Approximately half of the demand for fertility preservation is from women with breast cancer[5] since it is the most common cancer in women in developed countries. In Europe, the incidence of breast cancer in premenopausal women over the past three decades was 30/100000[6]. Approximately 2% of cases occur in women aged 20-34 years and 11% in women aged 35-44 years[7]. Survival rates for breast cancer have risen in recent years, reaching 81%-87%.

Table 1 Risk of ovarian damage according to chemotherapy treatment used

High risk	Moderate risk	Low risk
Cyclophosphamide	Cisplatinum	Vincristine
Ifosfamide	Adriamycin	Vinblastine
Chlorambucil	Actinomycin	Methotrexate
Melphalan		Bleomycin
Busulfan		
Nitrogen mustard		
Procarbazine		

Endometrial cancer is considered the most common gynecological malignancy in the United States according to the American Cancer Society and the fourth most common cancer among women, behind only breast, lung and colorectal cancer[8]. However, it is rarely encountered for fertility preservation since more than 80% of cases occur in postmenopausal women and only less than 5% develop in patients younger than 40 years[9]. Ovarian cancer is primarily a disease of older women; however, it is estimated that 3% to 17% of ovarian tumors occur in women aged ≤ 40 years[10].

The oncological management of gynecological cancers used to bring the patient's fertility potential to an end due to the surgical removal of the reproductive organs harboring the malignancy. However, recently fertility sparing management of such cancers has been developed to safely remove or treat cancer without extirpating the reproductive organs. These include development of new surgical techniques, *e.g.*, radical trachelectomy for early stage cancer cervix (stage I AII)[11], unilateral adnexectomy with preservation of contralateral ovary and uterus for low malignant potential ovarian tumor[12] and early stage cancer ovary (stage I)[13], as well as novel treatment modalities, *e.g.*, high dose progestin therapy for early stage endometrial cancer (stage I A, grade 1)[14].

However, conservative surgery might entail the use of adjuvant chemotherapy or radiation therapy, both of which can still adversely affect the fertility potential. Ginsburg *et al*[15] reported decreased response in patients with cancer who had received chemotherapeutic agents before oocyte retrieval. The effect will depend on the patient's age as well as the type and dose of chemotherapeutic agent. According to their effect on ovarian reserve, chemotherapeutics are divided into three groups (high, moderate and low risk) (Table 1[16]). Alkylating agents seem to present the greatest risk of ovarian failure due to the profound loss of primordial follicles[17]. The effect of radiation therapy depends on the patient's age, site, type and dose of radiation[18].

Following fertility preserving management of gynecological cancer, the patient might conceive spontaneously. However, ovarian stimulation may be considered to cryopreserve oocytes and embryos before the adverse impact of chemotherapy/radiation therapy on ovarian reserve (as in breast cancer and cervical cancer). It might also be considered to increase the likelihood of pregnancy and decrease time interval to conception (as in endometrial cancer)[19] and in cases of associated infertility.

INDUCTION OF OVULATION IN GYNECOLOGICAL CANCER PATIENTS: THE CHALLENGES

Inducing ovulation in women with cancer should be considered cautiously and approached differently than inducing ovulation in women without cancer. Since these patients usually undergo only a single *in vitro* fertilisation (IVF) attempt before commencing chemotherapy or radiation therapy, it is crucial that as many cryopreserved embryos or oocytes as possible be obtained in this cycle for future use. Meanwhile, this should be attained with the absolute avoidance of ovarian hyperstimulation syndrome (OHSS), which can result in delay of chemotherapy and radiotherapy[20]. Unlike non-gynecological malignancies (*e.g.*, colon, hematological), gynecological cancers can be hormone responsive with resultant aggravation of the tumor due to the supraphysiological levels of estrogen released with ovarian stimulation. Thus, the fertility specialist encounters many challenges to attain this critical mission. Among these challenges are the following:

Decreased ovarian response

There are controversial reports on how cancer patients would respond to ovarian stimulation in IVF. Although some studies observed no significant change[21,22], the reproductive capacity of patients with cancers seems to be diminished and subjects with cancers are more likely to be poor responders[23]. Pal *et al*[24] reported an apparent adverse influence of malignant disease on the quality and performance of oocytes. Many explanations have been suggested. Among them, that cancer is associated with an increased catabolic state and malnutrition, resulting in weight loss which may affect the hypothalamic pituitary axis, resulting in hypothalamic dysfunction and a decrease in gonadotropin levels, thereby impairing the reproductive capacity[25]. Cancer is also associated with an increase in stress hormones which can lead to an increase in prolactin and endogenous opiate production, suppressing gonadotropin levels and further reducing fertility[26]. Moreover, recently Oktay *et al*[27] reported that women with breast and ovarian cancer, carriers of BRCA1 mutation, may respond poorly to ovarian stimulation. This may indicate a possible role of BRCA1 as an important factor responsible for the impairment in double stranded DNA break repair and a woman's infertility.

Time factor

Induction of ovulation has to be initiated before chemotherapy or radiation therapy since both therapies have deleterious effects on the ovarian reserve, resulting in premature ovarian failure and subsequent infertility[28]. Meanwhile, it is important to avoid prolonged deferral of chemotherapy or radiation therapy which can be det-

rimental to the success of cancer therapy. Typically, there is a gap of 4 to 6 wk between women undergoing breast cancer surgery and the commencement of chemotherapy, which is often sufficient to undergo ovarian stimulation. However, delayed referral of the patient to the fertility specialist results in time pressure. In this case, the best protocol that allows the quickest initiation of ovarian stimulation should be selected to shorten the deferral of chemotherapy/radiotherapy and allow early commencement of therapy. This can be ideally achieved with the use of the GnRH antagonist protocol[29]. In the conventional stimulation protocol, depending on the timing of the patient presentation, it takes up to 3 wk to reach the luteal phase when downregulation with a GnRH agonist can be started and continued for about 2 wk to prevent premature ovulation. Then, 9-14 more days are needed for ovarian stimulation with gonadotropins. On the contrary, GnRH antagonists immediately suppress the release of FSH and LH, preventing a premature LH surge. Administration is started when the size of the lead follicle reaches 12-14 mm at approximately day 6 of gonadotropin stimulation which begins on day 2, 3 of a menstrual cycle. Thus, GnRH antagonists significantly decrease the interval from patient presentation to oocyte retrieval compared to the conventional GnRH agonist protocol[30].

Instead of awaiting menses, further shortening of the interval to oocyte retrieval has been suggested by administering a GnRH antagonist during the preceding luteal phase to induce corpus luteum breakdown and synchronize the development of the next wave of follicles[31]. Menses will ensue a few days later with the ovarian stimulation initiated more quickly and the GnRH antagonist would then be restarted in the standard fashion[31]. Random-start stimulation protocol has been recently proposed as another alternative to avoid time wastage while awaiting the menses[32,33]. In this protocol, cancer patients in the luteal phase were started on GnRH antagonists to downregulate LH and initiate luteolysis. Simultaneously, follicular stimulation was initiated with recombinant FSH only to avoid exogenous LH activity which might prevent luteolysis. When this protocol was compared in a prospective multicenter trial with cancer patients stimulated during the follicular phase with either a short "flare up" protocol or an antagonist protocol, random start stimulation protocol yielded a similar number of aspirated oocytes, mature oocytes and fertilization rate[33]. However, more clinical studies are needed to assess the efficacy of this protocol, especially regarding the rates of clinical pregnancy and live-born infants originating from the use of cryopreserved embryos and oocytes[34]. It is important to stress that once a cancer diagnosis is established, early referral to a fertility specialist is highly encouraged to avoid unnecessary delay and facilitate prompt initiation of ovarian stimulation[35].

The associated increase in estradiol levels in hormonal dependent cancers

Induction of ovulation is typically associated with increased levels of estradiol. This can be serious in women with estrogen sensitive cancers, such as breast and endometrial cancer. Many strategies have been applied to minimize these estradiol peak levels. Among them are the following: (1) Tamoxifen. Tamoxifen can be used for controlled ovarian stimulation alone, starting on day 2-5 of the menstrual cycle in doses of 20-60 mg/d or in combination with gonadotropins**.** Not only does tamoxifen lower the peak estradiol levels compared to standard stimulation protocols[36], but also it has an antiestrogenic effect on breast tissue and is thus desirable to be used in estrogen receptor-positive breast cancer patients[37]; (2) Aromatase inhibitors. Aromatase inhibitors (including anastrozole and letrozole) are drugs of choice for the treatment of breast cancer in women with receptor-positive metastatic breast cancer. Their use has also been introduced as a new treatment option for ovulation induction[38]. It was reported that the peak estradiol level is lower in protocols that use aromatase inhibitors for ovarian stimulation[36]. Oktay *et al*[36] were the first to describe the use of letrozole in the GnRH-antagonist protocol in a study of 29 patients with breast cancer. The study included 33 ovarian stimulation cycles. In their study, letrozole in combination with FSH (letrozole-IVF) was compared to tamoxifen alone (Tam-IVF) and to tamoxifen in combination with FSH (TamFSH-IVF). They concluded that letrozole-IVF and TamFSH-IVF yielded more follicles, more mature oocytes and more embryos than Tam-IVF. Peak estradiol levels were lower with letrozole-IVF and Tam-IVF compared with TamFSH-IVF. Azim *et al*[39] described the use of letrozole in combination with gonadotropins in four patients with endometrial cancer. The estradiol levels in their study were lower compared with standard stimulation cycles. Data on the use of anastrozole for ovarian stimulation in anovulatory women, however, is more limited and studies so far do not support its use due to higher peak estradiol levels compared to letrozole[40]; (3) Using low doses of gonadotropins. The use of low dose gonadotropins (FSH 150 U/d) in the GnRH antagonist protocol in combination with letrozole was found to result in acceptable oocyte yield while maintaining low estradiol levels[36]. However, the use of higher doses of gonadotropins (FSH 150-375 U/d) in a GnRH antagonist protocol in combination with letrozole was recently studied by Ben-Haroush *et al*[41]. They reported a higher number of retrieved oocytes and frozen embryos than the lower dose schedule used in the study by Oktay *et al*[36], while similarly resulting in low levels of peak estradiol; (4) Using a GnRH antagonist protocol allows quick initiation of ovarian stimulation and pituitary suppression with a GnRH antagonist reduces the concentration of estradiol in patients with hormone dependent tumors[42]. Ben-Haroush *et al*[41] compared the use of high doses of FSH (150-375 U/d) in combination with letrozole in GnRH antagonist *vs* the long GnRH agonist protocol. Although the number of retrieved oocytes was higher in women in the long GnRH agonist protocol than the GnRH-antagonist protocol, the difference was not statistically significant; and (5) GnRH agonist trigger in the GnRH antagonist protocol has been shown to yield lower

estradiol concentrations compared to hCG trigger which potentiates the endogenous production of estrogen during the luteal phase owing to its longer half-life[43].

Avoidance of OHSS

OHSS is the most serious complication of ovarian stimulation since it is associated with significant morbidity which might necessitate hospitalization and intensive care. In cancer patients, the occurrence of this complication is critical since it may result in delaying or complicating planned life-saving cancer therapy. The risk of OHSS can be significantly lowered with the use of a GnRH antagonist protocol since it allows the use of a GnRH agonist trigger instead of the traditional hCG trigger if there is suspicion of overresponse to stimulation. Triggering the final oocyte maturation with hCG carries the risk of inducing OHSS[43], while using a GnRH agonist trigger in GnRH antagonist-based protocols dramatically reduces the risk of OHSS owing to the short half-life of GnRH agonist-induced endogenous LH surge which lasts for approximately 24-36 h compared to the longer half life of hCG which lasts for 7-10 d[44]. 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)[45]. Meanwhile, the use of a GnRH agonist trigger was found to result in at least similar numbers of mature oocytes and cryopreserved embryos compared with hCG[46].

Therefore, in cases of estrogen sensitive cancers, the most recommendable protocol for induction of ovulation is the use of a GnRH antagonist in combination with letrozole (5 mg/d from the second day of menstrual cycle for 5-7 d) plus low dose gonadotropins[36]. This regimen allows an acceptable oocyte yield and keeps the circulating estradiol levels rather low compared with the standard ovarian stimulation protocols[47].

SAFETY OF OVARIAN STIMULATION IN CANCER PATIENTS

Safety is a major concern when considering induction of ovulation in cancer patients for the aim of fertility preservation, which may potentially decrease the chance of successful cancer treatment, increase the risk of maternal or perinatal complications, or compromise the health of offspring.

Risk of recurrence after ovarian stimulation

The risk of recurrence and the adverse impact on survival are real concerns for gynecological cancer survivors who desire to conceive after cancer therapy. Many studies have shown that pregnancy after breast cancer treatment does not appear to adversely affect recurrence or survival[48,49]. Oktay *et al*[36] followed their patients for a mean duration of 554 ± 31 d and they found that the cancer recurrence rate was similar in the IVF and control groups (3/29 *vs* 3/31 patients, respectively; HR = 1.5, 95%CI: 0.29-7.4). They noticed that the risk was not affected by cancer stage. In a larger follow-up report by Azim *et al*[50], the rate of cancer recurrence was compared among 79 women who elected to undergo ovarian stimulation with letrozole and gonadotropins for embryo or oocyte cryopreservation and 136 control patients (whom did not undergo fertility preservation procedures). The median follow-up after chemotherapy was 23.4 mo in the study group and 33.05 mo in the control group. They concluded that the recurrence and survival rates were similar in the two groups[50]. Thus, based on the above studies, induction of ovulation does not seem to increase the risk of recurrence compared to controls; however, more studies and longer follow up are needed.

Women who had undergone fertility sparing management for endometrial cancer did not have a higher incidence of cancer recurrence with the use of fertility drugs[51].

Several rare cases of ovarian stimulation have been reported in the literature after conservative treatment for borderline or invasive ovarian tumors[52-54]. Several pregnancies were achieved but in one case a uterine recurrence was observed and, most importantly, one woman died 7 mo after ovarian stimulation following extensive recurrence of an invasive lesion[52-54].

Newborn safety

Concerns about the safety of letrozole have been raised by the American Society for Reproductive Medicine through an abstract claiming possible teratogenic effects of letrozole[55], for which the use of letrozole for the purpose of induction of ovulation was discouraged. However, this concern was not supported by a large trial published in 2006 comparing newborn safety of letrozole with that of clomiphene citrate showing that congenital malformations were less frequent in the letrozole group[56]. It has been shown that the half-life of letrozole (approximately 30-60 h) is shorter than that of clomiphene citrate (5-7 d) and, thus, should be effectively cleared from the body by the time of embryo implantation, likely preventing a teratogenic effect when used in ovulation induction[57]. Another concern of cancer patients is whether offspring exposed to cytotoxic agents have an increased risk of birth defects. Several large studies that included more than 4000 offspring of cancer survivors showed no statistically significant increase in childhood malignancies or genetic malformations[58].

CONCLUSION

Fertility preservation through IVF technology is an evolving discipline that can minimize the devastating sequelae of cancer. Induction of ovulation is the critical step that determines the success of the fertility preservation. Gynecological cancers represent a real challenge to the fertility specialist due to possible hormonal responsiveness of the cancer, making induction of ovulation potentially detrimental. The use of GnRH antagonists, aromatase

inhibitors and triggering with GnRH agonists may provide reliable methods to minimize the unfavorable rise in estradiol levels. So far, reports on the safety of ovulation induction in these patients are reassuring and young women with cancer should be counseled about the option of fertility preservation as soon as the diagnosis of cancer is established.

REFERENCES

1 **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; **63**: 11-30 [PMID: 23335087 DOI: 10.3322/caac.21166]

2 **Howlader N**, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, editors. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). Bethesda, MD: National Cancer Institute, 2012. Available from: URL: http://seer.cancer.gov/csr/1975_2009_pops09/. Accessed December 16, 2012

3 **Jemal A**, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; **59**: 225-249 [PMID: 19474385 DOI: 10.3322/caac.20006]

4 **Horner MJ**, Ries LAG, Krapcho M, Neyman N, Aminou R, Howlader N, Altekruse SF, Feuer EJ, Huang L, Mariotto A, Miller BA, Lewis DR, Eisner MP, Stinchcomb DG, Edwards BK, editors. SEER Cancer Statistics Review, 1975-2006. Bethesda, MD: National Cancer Institute, 2011. Available from: URL: http://seer.cancer.gov/csr/1975_2006/index.html. Accessed October 18, 2011

5 **Letourneau JM**, Ebbel EE, Katz PP, Katz A, Ai WZ, Chien AJ, Melisko ME, Cedars MI, Rosen MP. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. *Cancer* 2012; **118**: 1710-1717 [PMID: 21887678 DOI: 10.1002/cncr.26459]

6 **Glass AG**, Lacey JV, Carreon JD, Hoover RN. Breast cancer incidence, 1980-2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst* 2007; **99**: 1152-1161 [PMID: 17652280 DOI: 10.1093/jnci/djm059]

7 **Hickey M**, Peate M, Saunders CM, Friedlander M. Breast cancer in young women and its impact on reproductive function. *Hum Reprod Update* 2009; **15**: 323-339 [PMID: 19174449 DOI: 10.1093/humupd/dmn064]

8 **American Cancer Society**. Cancer Facts and Figures 2012. Atlanta, GA: American Cancer Society, 2012

9 **Schottenfeld D**. Epidemiology of endometrial neoplasia. *J Cell Biochem Suppl* 1995; **23**: 151-159 [PMID: 8747390 DOI: 10.1002/jcb.240590920]

10 **Duska LR**, Chang YC, Flynn CE, Chen AH, Goodman A, Fuller AF, Nikrui N. Epithelial ovarian carcinoma in the reproductive age group. *Cancer* 1999; **85**: 2623-2629 [PMID: 10375111]

11 **Burnett AF**, Roman LD, O'Meara AT, Morrow CP. Radical vaginal trachelectomy and pelvic lymphadenectomy for preservation of fertility in early cervical carcinoma. *Gynecol Oncol* 2003; **88**: 419-423 [PMID: 12648596]

12 **Zanetta G**, Rota S, Chiari S, Bonazzi C, Bratina G, Mangioni C. Behavior of borderline tumors with particular interest to persistence, recurrence, and progression to invasive carcinoma: a prospective study. *J Clin Oncol* 2001; **19**: 2658-2664 [PMID: 11352957]

13 **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]

14 **Gunderson CC**, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. *Gynecol Oncol* 2012; **125**: 477-482 [PMID: 22245711 DOI: 10.1016/j.ygyno.2012.01.003]

15 **Ginsburg ES**, Yanushpolsky EH, Jackson KV. In vitro fertilization for cancer patients and survivors. *Fertil Steril* 2001; **75**: 705-710 [PMID: 11287023 DOI: 10.1016/S0015-0282(00)01802-1]

16 **Sonmezer M**, Oktay K. Fertility preservation in female patients. *Hum Reprod Update* 2004; **10**: 251-266 [PMID: 15140872]

17 **Meirow D**, Assad G, Dor J, Rabinovici J. The GnRH antagonist cetrorelix reduces cyclophosphamide-induced ovarian follicular destruction in mice. *Hum Reprod* 2004; **19**: 1294-1299 [PMID: 15117898 DOI: 10.1093/humrep/deh257]

18 **Wallace WH**, Thomson AB, Kelsey TW. The radiosensitivity of the human oocyte. *Hum Reprod* 2003; **18**: 117-121 [PMID: 12525451]

19 **Rackow BW**, Arici A. Endometrial cancer and fertility. *Curr Opin Obstet Gynecol* 2006; **18**: 245-252 [PMID: 16735822]

20 **Koch J**, Ledger W. Ovarian stimulation protocols for oncofertilty patients. *J Assist Reprod Genet* 2013; **30**: 203-206 [PMID: 23417355]

21 **Das M**, Shehata F, Moria A, Holzer H, Son WY, Tulandi T. Ovarian reserve, response to gonadotropins, and oocyte maturity in women with malignancy. *Fertil Steril* 2011; **96**: 122-125 [PMID: 21575940 DOI: 10.1016/j.fertnstert.2011.04.070]

22 **Robertson AD**, Missmer SA, Ginsburg ES. Embryo yield after in vitro fertilization in women undergoing embryo banking for fertility preservation before chemotherapy. *Fertil Steril* 2011; **95**: 588-591 [PMID: 20542508 DOI: 10.1016/j.fertnstert.2010.04.028]

23 **Quintero RB**, Helmer A, Huang JQ, Westphal LM. Ovarian stimulation for fertility preservation in patients with cancer. *Fertil Steril* 2010; **93**: 865-868 [PMID: 19013563 DOI: 10.1016/j.fertnstert.2008.10.007]

24 **Pal L**, Leykin L, Schifren JL, Isaacson KB, Chang YC, Nikruil N, Chen Z, Toth TL. Malignancy may adversely influence the quality and behaviour of oocytes. *Hum Reprod* 1998; **13**: 1837-1840 [PMID: 9740435 DOI: 10.1093/humrep/13.7.1837]

25 **Agarwal A**, Said TM. Implications of systemic malignancies on human fertility. *Reprod Biomed Online* 2004; **9**: 673-679 [PMID: 15670419]

26 **Schenker JG**, Meirow D, Schenker E. Stress and human reproduction. *Eur J Obstet Gynecol Reprod Biol* 1992; **45**: 1-8 [PMID: 1618356 DOI: 10.1016/0028-2243(92)90186-3]

27 **Oktay K**, Kim JY, Barad D, Babayev SN. Association of BRCA1 mutations with occult primary ovarian insufficiency: a possible explanation for the link between infertility and breast/ovarian cancer risks. *J Clin Oncol* 2010; **28**: 240-244 [PMID: 19996028 DOI: 10.1200/JCO.2009.24.2057]

28 **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]

29 **Friedler S**, Koc O, Gidoni Y, Raziel A, Ron-El R. Ovarian response to stimulation for fertility preservation in women with malignant disease: a systematic review and meta-analysis. *Fertil Steril* 2012; **97**: 125-133 [PMID: 22078784 DOI: 10.1016/j.fertnstert.2011.10.014]

30 **McLaren JF**, Bates GW. Fertility preservation in women of reproductive age with cancer. *Am J Obstet Gynecol* 2012; **207**: 455-462 [PMID: 22959764 DOI: 10.1016/j.ajog.2012.08.013]

31 **Humaidan P**, Bungum L, Bungum M, Hald F, Agerholm I, Blaabjerg J, Yding Andersen C, Lindenberg S. Reproductive outcome using a GnRH antagonist (cetrorelix) for luteolysis and follicular synchronization in poor responder IVF/ICSI patients treated with a flexible GnRH antagonist protocol. *Reprod Biomed Online* 2005; **11**: 679-684 [PMID: 16417730]

32 **Cakmak H**, Fujimoto VY, Zamah AM, Rosen MP, Tran ND, Cedars MI, Rinaudo PF. Metaphase II (MII) oocytes obtained at different time points in the same in vitro fertilization cycle. *J Assist Reprod Genet* 2012; **29**: 1203-1205 [PMID: 22941385 DOI: 10.1007/s10815-012-9852-5]

33 **von Wolff M**, Thaler CJ, Frambach T, Zeeb C, Lawrenz B, Popovici RM, Strowitzki T. Ovarian stimulation to cryopreserve fertilized oocytes in cancer patients can be started in the luteal phase. *Fertil Steril* 2009; **92**: 1360-1365 [PMID: 18930226 DOI: 10.1016/j.fertnstert.2008.08.011]

34 **Cakmak H**, Rosen MP. Ovarian stimulation in cancer patients. *Fertil Steril* 2013; **99**: 1476-1484 [PMID: 23635348]

35 **Lee S**, Ozkavukcu S, Heytens E, Moy F, Oktay K. Value of early referral to fertility preservation in young women with breast cancer. *J Clin Oncol* 2010; **28**: 4683-4686 [PMID: 20876425 DOI: 10.1200/JCO.2010.30.5748]

36 **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]

37 Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1992; **339**: 71-85 [PMID: 1345869]

38 **Rodriguez-Wallberg KA**, Oktay K. Fertility preservation in women with breast cancer. *Clin Obstet Gynecol* 2010; **53**: 753-762 [PMID: 21048442 DOI: 10.1097/GRF.0b013e3181f96e00]

39 **Azim A**, Oktay K. Letrozole for ovulation induction and fertility preservation by embryo cryopreservation in young women with endometrial carcinoma. *Fertil Steril* 2007; **88**: 657-664 [PMID: 17428480 DOI: 10.1016/j.fertnstert.2006.12.068]

40 **Polyzos NP**, Tzioras S, Badawy AM, Valachis A, Dritsas C, Mauri D. Aromatase inhibitors for female infertility: a systematic review of the literature. *Reprod Biomed Online* 2009; **19**: 456-471 [PMID: 19909585]

41 **Ben-Haroush A**, Farhi J, Ben-Aharon I, Sapir O, Pinkas H, Fisch B. High yield of oocytes without an increase in circulating estradiol levels in breast cancer patients treated with follicle-stimulating hormone and aromatase inhibitor in standard gonadotropin-releasing hormone analogue protocols. *Isr Med Assoc J* 2011; **13**: 753-756 [PMID: 22332446]

42 **Al-Inany HG**, Youssef MA, Aboulghar M, Broekmans F, Sterrenburg M, Smit J, Abou-Setta AM. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *Cochrane Database Syst Rev* 2011; CD001750 [PMID: 21563131]

43 **Humaidan P**, Kol S, Papanikolaou EG. GnRH agonist for triggering of final oocyte maturation: time for a change of practice? *Hum Reprod Update* 2011; **17**: 510-524 [PMID: 21450755 DOI: 10.1093/humupd/dmr008]

44 **Engmann L**, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. *Fertil Steril* 2008; **89**: 84-91 [PMID: 17462639]

45 **Youssef MA**, Van der Veen F, Al-Inany HG, Griesinger G, Mochtar MH, Aboulfoutouh I, Khattab SM, van Wely M. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles. *Cochrane Database Syst Rev* 2011; CD008046 [PMID: 21249699 DOI: 10.1002/14651858.CD008046]

46 **Oktay K**, Türkçüoğlu I, Rodriguez-Wallberg KA. GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation. *Reprod Biomed Online* 2010; **20**: 783-788 [PMID: 20382080 DOI: 10.1016/j.rbmo.2010.03.004]

47 **Kim NY**, Ryoo U, Lee DY, Kim MJ, Yoon BK, Choi D. The efficacy and tolerability of short-term low-dose estrogen-only add-back therapy during post-operative GnRH agonist treatment for endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2011; **154**: 85-89 [PMID: 20832162 DOI: 10.1016/j.ejogrb.2010.08.008]

48 **Blakely LJ**, Buzdar AU, Lozada JA, Shullaih SA, Hoy E, Smith TL, Hortobagyi GN. Effects of pregnancy after treatment for breast carcinoma on survival and risk of recurrence. *Cancer* 2004; **100**: 465-469 [PMID: 14745861]

49 **Kroman N**, Jensen MB, Wohlfahrt J, Ejlertsen B. Pregnancy after treatment of breast cancer--a population-based study on behalf of Danish Breast Cancer Cooperative Group. *Acta Oncol* 2008; **47**: 545-549 [PMID: 18465320 DOI: 10.1080/02841860801935491]

50 **Azim AA**, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. *J Clin Oncol* 2008; **26**: 2630-2635 [PMID: 18509175 DOI: 10.1200/JCO.2007.14.8700]

51 **Park JY**, Seong SJ, Kim TJ, Kim JW, Kim SM, Bae DS, Nam JH. Pregnancy outcomes after fertility-sparing management in young women with early endometrial cancer. *Obstet Gynecol* 2013; **121**: 136-142 [PMID: 23262938 DOI: 10.1097/AOG.0b013e31827a0643]

52 **Nijman HW**, Burger CW, Baak JP, Schats R, Vermorken JB, Kenemans P. Borderline malignancy of the ovary and controlled hyperstimulation, a report of 2 cases. *Eur J Cancer* 1992; **28A**: 1971-1973 [PMID: 1419292]

53 **Mantzavinos T**, Kanakas N, Genatas C, Papadias K, Zourlas PA. Five years' follow-up in two patients with borderline tumours of the ovary hyperstimulated by gonadotrophin therapy for in-vitro fertilization. *Hum Reprod* 1994; **9**: 2032-2033 [PMID: 7868669]

54 **Bandera CA**, Cramer DW, Friedman AJ, Sheets EE. Fertility therapy in the setting of a history of invasive epithelial ovarian cancer. *Gynecol Oncol* 1995; **58**: 116-119 [PMID: 7789877]

55 **Biljan MM**, Hemmings R, Brassard N. The outcome of 150 babies following the treatment with letrozole or letrozole and gonadotropins [Abstract]. *Fertil Steril* 2005; **84** Suppl 1: S95 [DOI: 10.1016/j.fertnstert.2005.07.230]

56 **Tulandi T**, Martin J, Al-Fadhli R, Kabli N, Forman R, Hitkari J, Librach C, Greenblatt E, Casper RF. Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. *Fertil Steril* 2006; **85**: 1761-1765 [PMID: 16650422 DOI: 10.1016/j.fertnstert.2006.03.014]

57 **Casper RF**. Letrozole versus clomiphene citrate: which is better for ovulation induction? *Fertil Steril* 2009; **92**: 858-859 [PMID: 17588568 DOI: 10.1016/j.fertnstert.2007.03.094]

58 **Hawkins MM**. Pregnancy outcome and offspring after childhood cancer. *BMJ* 1994; **309**: 1034 [PMID: 7950729]

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MINIREVIEWS

Cost effective evidence-based interventions to manage obesity in pregnancy

Julie A Quinlivan

Julie A Quinlivan, Institute of Health Research, University of Notre Dame Australia, Fremantle WA 6160, Australia
Julie A Quinlivan, Institute for Women's and Children's Research, University of Adelaide, Adelaide SA 5000, Australia
Julie A Quinlivan, Department of Obstetrics and Gynaecology, Joondalup Health Campus, Joondalup WA 6027, Australia
Author contributions: Quinlivan JA designed and wrote the manuscript.
Correspondence to: Julie A Quinlivan, Professor, Institute of Health Research, University of Notre Dame Australia, Suite 106, Private Consulting Rooms, Joondalup Health Campus, Shenton Avenue, Joondalup WA 6027,
Australia. quinlivanj@ramsayhealth.com.au
Telephone: +61-8-94009631 Fax: +61-8-94009955
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Abstract

The rising tide of obesity has seen the prevalence of overweight and obese women presenting for antenatal care approach 50% in recent years. In addition, many pregnant women have gestational weight gain in excess of Institute of Medicine guidelines and develop obesity as a result of pregnancy. Both variables impact adversely upon pregnancy outcome. Individualised programs are not financially viable for cash strapped health systems. This review outlines an evidence-based, public health approach to the management of obesity in pregnancy. The interventions are affordable and in randomised and epidemiological trials, achieve benefits in pregnancy outcome.

Key words: Obesity; Pregnancy; Randomised trial; Evidence-based

Core tip: Public health approaches are feasible and effective to manage obesity in pregnancy. In primary care settings, women planning pregnancy should have their body mass index monitored in their medical record and receive nutrition advice, have comorbidities of depression and smoking addressed, receive influenza vaccination and education on gestational weight gain targets. Once pregnant, hospital management should focus on monitoring gestational weight gain to Institute of Medicine targets according to the patient's booking body mass index, combined with screening for diabetes, hypertensive and growth disorders. Following birth, care should handed back to primary care for ongoing weight interventions.

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INTRODUCTION

The rising tide of obesity has seen the prevalence of overweight and obese women presenting for antenatal care approach 50% in recent years[1]. Obesity at conception and gestational weight gain (GWG) in excess of Institute of Medicine guidelines both result in postnatal obesity, and each has an independent detrimental impact upon pregnancy outcome.

Obesity is a major risk factor for maternal and fetal complications, including maternal and fetal mortality, miscarriages, gestational diabetes mellitus (GDM), pregnancy-induced hypertensive disorders, infection, thromboembolic disease, obstructive sleep apnoea, fetal growth abnormalities, a need for induction of labour, difficulties with fetal monitoring and anaesthesia, birth trauma, caesarean section, post-partum haemorrhage, stillbirth and postpartum depression[1-17].

A pregnant woman of "normal" body mass index at

her booking antenatal visit who subsequently gains 20 kg in pregnancy will face similar complications to the mother who presents for antenatal care already obese but subsequently achieves an ideal GWG. Women who are obese at conception and then have excessive GWG experience the highest rate of complications.

In 2009, the Institute of Medicine revised its recommendations for GWG advising that overweight and obese women should restrict gains to 6.8-11.3 kg and 4.9-9.0 kg respectively[2]. Women of normal body mass index should restrict GWG to 11.5-16.0 kg. Whilst these levels remain subject to debate, and may be further refined as new studies are published, they remain the current goalposts for care.

The high prevalence of women who are overweight or obese at conception, and of women who have excessive GWG throughout pregnancy, means that every women presenting for antenatal care is at risk of obesity related complications. Expensive strategies to manage obesity in pregnancy are not logistically or financially feasible given the volume of caseload to manage. Instead, a public health approach is warranted. Universally applied cheaper interventions directed at the entire patient population are likely to have a greater clinical impact than expensive interventions directed at a motivated minority of extremely obese women.

How then, do we manage the obesity in pregnancy, and how do we assist all our antenatal patients achieve ideal GWG without sending our clinical services broke?

PREGNANCY PLANNING IN PRIMARY CARE

The start to this answer lies in primary care

All women attending primary care facilities should have their height, weight and body mass index recorded in their patient record. They should received feedback on their body mass index at every visit if it is greater than 25, and be informed of the increased pregnancy risks. The primary care provider should encourage each woman to engage with local opportunities for exercise and reinforce good dietary habits.

If a woman is specifically planning pregnancy, then folic acid and iodine supplements should be recommended. Obese women have an increased risk of neural tube defects that cannot be explain by non-use of a supplement alone, resulting in current recommendations that they take a higher dose 5 mg supplement rather than the lower 0.5 mg dose for prophylaxis[18]. Obese pregnant women also have lower levels of iodine and are at increased risk of iodine deficiency related complications[19]. Recommendation for supplementation conforms to a public health approach to obesity management in the women planning pregnancy.

An increasing number of reproductive age women have undergone bariatric surgery to manage their weight. Some of these women may still be overweight or obese, but others may have lost weight and be of normal body mass index. It is important to try and avoid pregnancy within 18 mo of bariatric surgery if possible as several studies have reported an increased risk of fetal growth and nutritional complications[20,21].

Depression is more common in obese women and is the major risk factor for postnatal depression. Addressing depression prior to conception can help influence the postnatal course and may lead to improved mother to child attachment[22,23].

Smoking cessation advice should be provided to women who smoke. Alcohol and other drug use should also be addressed. Although benefits are seen if women stop smoking at any stage of pregnancy, the earlier they stop, the greater the benefit.

Finally, influenza vaccination should be recommended. Influenza is more severe in obese pregnant women, but is a significant concern in all pregnancies[24]. Many women decide against vaccination as they have concerns over safety, and primary care providers need to address these concerns and reassure their patients[25].

The cost of these primary care interventions is minimal. Women will meet the cost of their recommended supplements and vaccination programs for influenza are already often nationally funded. Other measures should not add more than a few minutes to an existing scheduled consultation.

ANTENATAL CARE AND THE HOSPITAL RESPONSIBILITY

The first component of care is planning at the hospital-booking visit. Women who are excessively obese will need to be referred to centres able to manage their weight. However, the majority of antenatal care may be able to be safety provided closer to home.

It is important that the body mass index is recorded in the notes at booking. This enables maternity care staff to advise women of their Institute of Medicine recommended GWG for their body mass index (BMI) category and set a target for weight gain or restriction.

In reviewing the various meta analyses of randomised trials for interventions in pregnancy for overweight and obese pregnant women, dietary interventions are effective whereas physical exercise and mixed interventions are less so[26-29]. Furthermore, dietary interventions are cheaper and have greater acceptability to pregnant women.

For example, in the LIP trial, half the eligible women approached to enter the trial declined (n = 317). Of the 360 women randomised, a further 56 dropped out. Therefore, one could assume that the group of women completing the trial were a subgroup of motivated obese pregnant women. It was therefore disappointing that so few of this apparently motivated subgroup took advantage of the free exercise interventions offered. Dietary interventions were associated with excellent compliance with 92% of intervention women completing all sessions. In contrast, only 56% of intervention women attended the aerobic classes for at least half of the lessons[28].

If motivated pregnant obese women will not attend aerobic classes despite free gym membership, physical testing and personal coaching, and given the cost of the intervention to the public health budget, then meaningful changes in health status at a population level are unlikely to be achieved. Of course, this doesn't preclude staff from recommending women seek their own strategies to increase their levels of exercise through walking and making healthy choices in their daily life (*e.g.*, walking up the stairs and not taking a lift).

This swings the public health focus back to dietary interventions. In a recent meta-analysis, four dietary interventions were reviewed[26,30-33]. Three were effective. The common elements to the effective interventions were that they measured BMI at booking, weighed at each visit, and provided repeated feedback on GWG. The interventions had varying costs. One was expensive and involved ten sessions with qualified dieticians. Whilst effective as an intervention, it is not feasible to implement broadly as a public health strategy. The second effective dietary intervention provided brief feedback at each routinely scheduled antenatal visit on GWG and diet. It also included a session with a clinical psychologist to address psychological factors involved in weight management. However, the most effective strategy was also the cheapest. This involved the simple use of a diary with patient feedback at each visit on GWG.

This strategy can be easily implemented into routine obstetric practice. By placing scales in the clinic and recording weight at each visit into a hand held maternity card, and offering feedback during routinely scheduled consultations, we can imitate the strategy of the effective randomised trial for the minimal cost of some staff education and a set of scales.

The other public health interventions to be implemented in antenatal care are to advise all women to take Folic Acid and Iodine supplements. The role of Vitamin D supplements is less clear although Vitamin D deficiency is more common in obese pregnant women and their offspring and some authorities are now recommending routine supplementation[17,34].

The increased risk of gestational diabetes warrants routine screening with a full 75 g glucose tolerance test at 28 wk. Some centres also advocate an early test at 20 wk but the cost benefit of such a policy has not yet been fully evaluated[17]. In accordance with local hospital policies, consideration should also be made for formal anaesthetic review, and for surveillance of fetal growth and hypertensive complications given these risks are increased in obese pregnant women.

POSTNATAL CARE AND LINKING BACK INTO THE COMMUNITY

Following childbirth, overweight and obese women have an increased risk for thromboembolism. If delivery has been by caesarean section, then discussion about thromboprophylaxis is warranted. Some agencies recommend that all obese women should be offered thromboprophylaxis[1,17].

Overweight and obese pregnant women face increased difficulties with breastfeeding. This is often due to their large nipple and breast size. Midwifery staff may need to assist mothers with early feeding sessions to ensure correct attachment to avoid nipple trauma.

The final step in management is to ensure adequate transmission of information from the maternity hospital to the primary care provider. This is vital to continue monitoring and encouragement of any dietary strategies adopted in the antenatal period, to promote exercise and monitor for depression and breastfeeding difficulties. It is important that hospitals acknowledge obesity or excessive GWG are complications that impacted upon the pregnancy and note them in the discharge summary to draw attention to their ongoing management in primary care.

CONCLUSION

It is likely that increasing novel and effective strategies to manage obesity in pregnancy will emerge in the next few years. However, it will be important that these new strategies are compared to the current gold standard outlined in this review.

Healthcare is consuming increasing proportions of national expenditure and this situation cannot continue forever. We have to become more effective with the resources we have and implement those strategies with an evidence base we can afford.

Pregnancy is a time of idealization over reality; a time when interventions are accepted and women look to establish life changes. We cannot afford to miss this opportunity for intervention.

REFERENCES

1 **National Health and Medical Research Council of Australia**. Clinical Practice Guidelines for the management of overweight and obesity in adults, adolescents and children in Australia. Australian Government, NHMRC, Department of Health. Canberra, 2013. Accessed Nov 10, 2013. Available from: URL: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/n57_obesity_guidelines_131204_0.pdf

2 **Institute of Medicine**. Weight gain during pregnancy: Reexamining the guidelines. Report Brief. Institute of Medicine of the National Academies, May 2009. Accessed Nov 10, 2013. Available from: URL: http://iom.edu/~/media/Files/ReportFiles/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines/Report Brief - Weight Gain During Pregnancy.pdf

3 **National Institute for Health and Clinical Excellence**. Weight management before, during and after pregnancy. NICE Public Health Guideline 27. NICE, NICE Evidence. 2010. Accessed Nov 10, 2013. Available from: URL: http://www.nice.org.uk/nicemedia/live/13056/49926/49926.pdf

4 **de Jersey SJ**, Nicholson JM, Callaway LK, Daniels LA. A prospective study of pregnancy weight gain in Australian women. *Aust N Z J Obstet Gynaecol* 2012; **52**: 545-551 [PMID: 23113826 DOI: 10.1111/ajo.12013]

5 **Robker RL**. Evidence that obesity alters the quality of oocytes and embryos. *Pathophysiology* 2008; **15**: 115-121 [PMID:

18599275 DOI: 10.1016/j.pathophys.2008.04.004]
6 **Wu LL**, Norman RJ, Robker RL. The impact of obesity on oocytes: evidence for lipotoxicity mechanisms. *Reprod Fertil Dev* 2011; **24**: 29-34 [PMID: 22394715 DOI: 10.1071/RD11904]
7 **The American College of Obstetricians and Gynecologists**. Obesity in Pregnancy: Committee Opinion Number 549. 2013. Accesssed Nov 10, 2013. Available from: URL: http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Obstetric_Practice/Obesity_in_Pregnancy
8 **Crane JM**, Murphy P, Burrage L, Hutchens D. Maternal and perinatal outcomes of extreme obesity in pregnancy. *J Obstet Gynaecol Can* 2013; **35**: 606-611 [PMID: 23876637]
9 **Salihu HM**. Maternal obesity and stillbirth. *Semin Perinatol* 2011; **35**: 340-344 [PMID: 22108084 DOI: 10.1053/j.semperi.2011.05.019]
10 **Maasilta P**, Bachour A, Teramo K, Polo O, Laitinen LA. Sleep-related disordered breathing during pregnancy in obese women. *Chest* 2001; **120**: 1448-1454 [PMID: 11713118]
11 **Leddy MA**, Power ML, Schulkin J. The impact of maternal obesity on maternal and fetal health. *Rev Obstet Gynecol* 2008; **1**: 170-178 [PMID: 19173021]
12 **Yu CK**, Teoh TG, Robinson S. Obesity in pregnancy. *BJOG* 2006; **113**: 1117-1125 [PMID: 16903839]
13 **Chu SY**, Kim SY, Schmid CH, Dietz PM, Callaghan WM, Lau J, Curtis KM. Maternal obesity and risk of cesarean delivery: a meta-analysis. *Obes Rev* 2007; **8**: 385-394 [PMID: 17716296]
14 **McIntyre HD**, Gibbons KS, Flenady VJ, Callaway LK. Overweight and obesity in Australian mothers: epidemic or endemic? *Med J Aust* 2012; **196**: 184-188 [PMID: 22339524]
15 **Gherman RB**. Shoulder dystocia: an evidence-based evaluation of the obstetric nightmare. *Clin Obstet Gynecol* 2002; **45**: 345-362 [PMID: 12048394]
16 **Fraser R**. Chan KL. Problems of obesity in obstetric care. *Curr Obstet Gynaecol* 2003; **13**: 239-243 [DOI: 10.1016/S0957-5847(03)00036-2]
17 **Royal Australian and New Zealand College of Obstetricians and Gynaecologists**. Management of obesity in pregnancy C-obs 49. RANZCOG Endorsed March 2013. Accessed Nov 10, 2013. Available from: URL: http://www.ranzcog.edu.au/doc/management-of-obesity-in-pregnancy.html
18 **Shaw GM**, Velie EM, Schaffer D. Risk of neural tube defect-affected pregnancies among obese women. *JAMA* 1996; **275**: 1093-1096 [PMID: 8601928]
19 **Gowachirapant S**, Melse-Boonstra A, Winichagoon P, Zimmermann MB. Overweight increases risk of first trimester hypothyroxinaemia in iodine-deficient pregnant women. *Matern Child Nutr* 2014; **10**: 61-71 [PMID: 23937433 DOI: 10.1111/mcn.12040]
20 **Hezelgrave NL**, Oteng-Ntim E. Pregnancy after bariatric surgery: a review. *J Obes* 2011; **2011**: 501939 [PMID: 21785717 DOI: 10.1155/2011/501939]
21 **Maggard MA**, Yermilov I, Li Z, Maglione M, Newberry S, Suttorp M, Hilton L, Santry HP, Morton JM, Livingston EH, Shekelle PG. Pregnancy and fertility following bariatric surgery: a systematic review. *JAMA* 2008; **300**: 2286-2296 [PMID: 19017915 DOI: 10.1001/jama.2008.641]
22 **Stunkard AJ**, Faith MS, Allison KC. Depression and obesity. *Biol Psychiatry* 2003; **54**: 330-337 [PMID: 12893108]
23 **Sundaram S**, Harman JS, Peoples-Sheps MD, Hall AG, Simpson SH. Obesity and postpartum depression: does prenatal care utilization make a difference? *Matern Child Health J* 2012; **16**: 656-667 [PMID: 21533884 DOI: 10.1007/s10995-011-0808-7]
24 **Karlsson EA**, Marcelin G, Webby RJ, Schultz-Cherry S. Review on the impact of pregnancy and obesity on influenza virus infection. *Influenza Other Respir Viruses* 2012; **6**: 449-460 [PMID: 22335790 DOI: 10.1111/j.1750-2659.2012.00342.x]
25 **White SW**, Petersen RW, Quinlivan JA. Pandemic (H1N1) 2009 influenza vaccine uptake in pregnant women entering the 2010 influenza season in Western Australia. *Med J Aust* 2010; **193**: 405-407 [PMID: 20919972]
26 **Quinlivan JA**, Julania S, Lam L. Antenatal dietary interventions in obese pregnant women to restrict gestational weight gain to Institute of Medicine recommendations: a meta-analysis. *Obstet Gynecol* 2011; **118**: 1395-1401 [PMID: 22105270 DOI: 10.1097/AOG.0b013e3182396bc6]
27 **Streuling I**, Beyerlein A, Rosenfeld E, Hofmann H, Schulz T, von Kries R. Physical activity and gestational weight gain: a meta-analysis of intervention trials. *BJOG* 2011; **118**: 278-284 [PMID: 21134106 DOI: 10.1111/j.1471-0528.2010.02801.x]
28 **Vinter CA**, Jensen DM, Ovesen P, Beck-Nielsen H, Jørgensen JS. The LiP (Lifestyle in Pregnancy) study: a randomized controlled trial of lifestyle intervention in 360 obese pregnant women. *Diabetes Care* 2011; **34**: 2502-2507 [PMID: 21972411 DOI: 10.2337/dc11-1150]
29 **Quinlivan JA**. Dietary component of lifestyle interventions helps obese pregnant women. *Evid Based Med* 2013; **18**: e4 [PMID: 22740359 DOI: 10.1136/eb-2012-100794]
30 **Wolff S**, Legarth J, Vangsgaard K, Toubro S, Astrup A. A randomized trial of the effects of dietary counseling on gestational weight gain and glucose metabolism in obese pregnant women. *Int J Obes (Lond)* 2008; **32**: 495-501 [PMID: 18227847 DOI: 10.1038/sj.ijo.0803710]
31 **Thornton YS**, Smarkola C, Kopacz SM, Ishoof SB. Perinatal outcomes in nutritionally monitored obese pregnant women: a randomized clinical trial. *J Natl Med Assoc* 2009; **101**: 569-577 [PMID: 19585925]
32 **Quinlivan JA**, Lam LT, Fisher J. A randomised trial of a four-step multidisciplinary approach to the antenatal care of obese pregnant women. *Aust N Z J Obstet Gynaecol* 2011; **51**: 141-146 [PMID: 21466516 DOI: 10.1111/j.1479-828X.2010.01268.x]
33 **Guelinckx I**, Devlieger R, Mullie P, Vansant G. Effect of lifestyle intervention on dietary habits, physical activity, and gestational weight gain in obese pregnant women: a randomized controlled trial. *Am J Clin Nutr* 2010; **91**: 373-380 [PMID: 19955397 DOI: 10.3945/ajcn.2009.28166]
34 **Bodnar LM**, Catov JM, Roberts JM, Simhan HN. Prepregnancy obesity predicts poor vitamin D status in mothers and their neonates. *J Nutr* 2007; **137**: 2437-2442 [PMID: 17951482]

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RESEARCH REPORT

Effect of gynecologic oncologist availability on ovarian cancer mortality

Sherri L Stewart, Darryl Cooney, Shawn Hirsch, Lauren Westervelt, Thomas B Richards, Sun Hee Rim, Cheryll C Thomas

Sherri L Stewart, Thomas B Richards, Sun Hee Rim, Cheryll C Thomas, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, Atlanta, GA 30341, United States
Darryl Cooney, Shawn Hirsch, Lauren Westervelt, SciMetrika, LLC, Research Triangle Park, North Carolina, NC 27703, United States
Author contributions: Stewart SL, Cooney D, Richards TB and Rim SH designed the research; Thomas CC provided data access and technical assistance for cancer data; Cooney D, Hirsch S and Westervelt L analyzed the data; Stewart SL, Cooney D, Hirsch S and Westervelt L wrote the paper; all authors provided critical comments and revisions on the paper.
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Correspondence to: Sherri L Stewart, PhD, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, 4770 Buford Highway, F-76, Atlanta, GA 30341, United States. sstewart2@cdc.gov
Telephone: +1-770-4884616 Fax: +1-770-4884335
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Abstract

AIM: To determine the association between the distribution of gynecologic oncologist (GO) and population-based ovarian cancer death rates.

METHODS: Data on ovarian cancer incidence and mortality in the United States was supplemented with United States census data, and analyzed in relation to practicing GOs. GO locations were geocoded to link association between county variables and GO availability. Logistic regression was used to measure areas of high and low ovarian cancer mortality, adjusting for contextual variables.

RESULTS: Practicing GOs were unevenly distributed in the United States, with the greatest numbers in metropolitan areas. Ovarian cancer incidence and death rates increased as distance to a practicing GO increased. A relatively small number (153) of counties within 24 miles of a GO had high ovarian cancer death rates compared to 577 counties located 50 or more miles away with high ovarian cancer death rates. Counties located 50 or more miles away from a GO practice had an almost 60% greater odds of high ovarian cancer mortality compared to those with closer practicing GOs (OR = 1.59, 95%CI: 1.18-2.15).

CONCLUSION: The distribution of GOs across the United States appears to be significantly associated with ovarian cancer mortality. Efforts that facilitate outreach of GOs to certain populations may increase geographic access.

Key words: Ovarian cancer; Gynecologic oncologists; Mortality; Access to care

Core tip: Ovarian cancer death rates increase with increasing distance to practicing gynecologic oncologists in the United States. Lower ovarian cancer mortality is significantly associated with geographic proximity to gynecologic oncologists. A more even geographic distribution of gynecologic oncologists may help in decreasing some barriers to appropriate, guidelines-based ovarian cancer care, which could result in reduced ovarian cancer deaths in the United States.

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INTRODUCTION

Ovarian cancer (OC) is the deadliest gynecologic malignancy and the fifth leading cause of cancer death among women in the United States[1]. Each year, more than 22000 women are diagnosed with and almost 16000 women die from the disease[1]. The majority of diagnoses (61%) are at late stages, when the disease is present in both ovaries and has spread throughout the peritoneal cavity[2]. Treatment for late-stage OC requires both surgery and chemotherapy, the costs of which confer a substantial burden on the United States healthcare system. The annual cost of managing OC patients in the United States is estimated to be approximately $612 million[3].

While treatment protocols for epithelial OC (accounting for 90% of all malignant cases) have improved, five-year survival for late-stage OC is just 27%[2]. The poor survival rate associated with OC is often attributed to the absence of gynecologic-specific signs and symptoms, and the lack of an effective screening test that can detect the disease at early stages. Currently, optimal surgery and delivery of chemotherapy are the only methods available to reduce OC mortality[4]. Several studies have suggested that optimal treatment (from staging through receipt of chemotherapy) resulting in better outcomes is more often achieved through subspecialist gynecologic oncologist (GO) care[5-9], leading several organizations to recommend OC patients receive treatment from GOs[4].

Despite the evidence and recommendations, many OC patients (about 30%-60%) are not treated by a GO[7,8]. Several barriers exist to receipt of guidelines-based care, including socioeconomic factors such as insurance status. In this study, we examined a potential geographic barrier to receipt of GO care. Our objective was to examine the geographic relationship between GO providers and OC mortality, in order to determine the effect that geographic availability of specialized care has on mortality, and add further evidence to the association between receipt of GO care and OC outcomes.

MATERIALS AND METHODS

Data sources and inclusion criteria

County level OC mortality data (2002-2006) were obtained from the Centers for Disease Control and Prevention (CDC) National Vital Statistics System (NVSS) through a public-use data file http://www.cdc.gov/nchs/ accessed on 2/17/2011. County-level contextual data were from several additional sources including: (1) Area Resource File (ARF 2008); (2) 2000 United States Census Summary File; and (3) United States Census Bureau's 2005 Small Area Health Insurance Estimates (SAHIE). OC incidence data (2002-2006) were obtained from CDC' s National Program of Cancer Registries (NPCR) and the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) for registries that met data high-quality criteria for publication[1]. Mortality data and incidence data covered 100% and 97% of the United States population, respectively. A list of practicing GOs in 2009, along with their practice address was obtained from the Foundation for Women's Cancer website (http://www.foundationforwomenscancer.org/find-a-gynecologic-oncologist. This list is populated by the Society of Gynecologic Oncologists and is estimated to cover 95% of practicing GOs (personal communication-SGO).

This study only includes data from the 48 contiguous United States states and the District of Columbia as the geography of Hawaii and Alaska results in transportation networks that are substantially different from other parts of the country. Of the 3141 counties that compose the United States, 32 counties and boroughs in Hawaii (5) and Alaska (27) were excluded from all analyses. Data from the remaining 3109 counties were used to examine the distribution of GOs (Figure 1). Data from 731 counties were suppressed due to less than four OC incident or death cases and patient confidentiality concerns; data from 198 counties were suppressed due to a death rate of zero and female population of 10000 or less; data from 112 counties in Kansas (45) and Minnesota (65) were excluded due to county-level incidence data release restrictions for these states. Data from the remaining 2068 counties were used to analyze the association between GO availability and county-level death rates (Tables 1-3, Figure 2).

Coding and variable definitions

County of residence (the geographic unit of analysis for this study) for each OC death was determined by using county Federal Information Processing Standards (FIPS) codes. FIPS codes were used to aggregate data at the county level, and to calculate five-year average OC incidence and death rates. FIPS codes were also used to categorize counties as metropolitan, non-metropolitan or rural based on 2003 USDA rural urban continuum (RUCA) codes. The following variables were included as measures of county socioeconomic status: (1) county household income inequality ratio; (2) the percent of county population living below the federal poverty line; and (3) the percent of county population without health insurance. The county household income inequality ratio is defined as the ratio of the number of households with incomes above the population's top 22% household income to the number of houses with incomes below the population's bottom 22% household income. To assess availability of physicians other than GOs for OC treatment, the average number of general surgeons, primary care physicians (PCPs) and obstetrician/gynecologists (OB/GYNs) per 100000 women in the county were derived using female population estimates from 2002-2006. Primary care physicians were defined as general practitioners, family medicine and internal medicine practitioners. Socioeconomic status and physician variables were categorized into equal tertiles (high, moderate and low) based on all counties included in the analysis. The 2002-2006 female population estimates were also used to calculate the county composition percentages for age, race, and ethnicity. Age was modeled as the percent of county population in the following age categories: 0 to 44 years, 45 to 54 years, 55 to

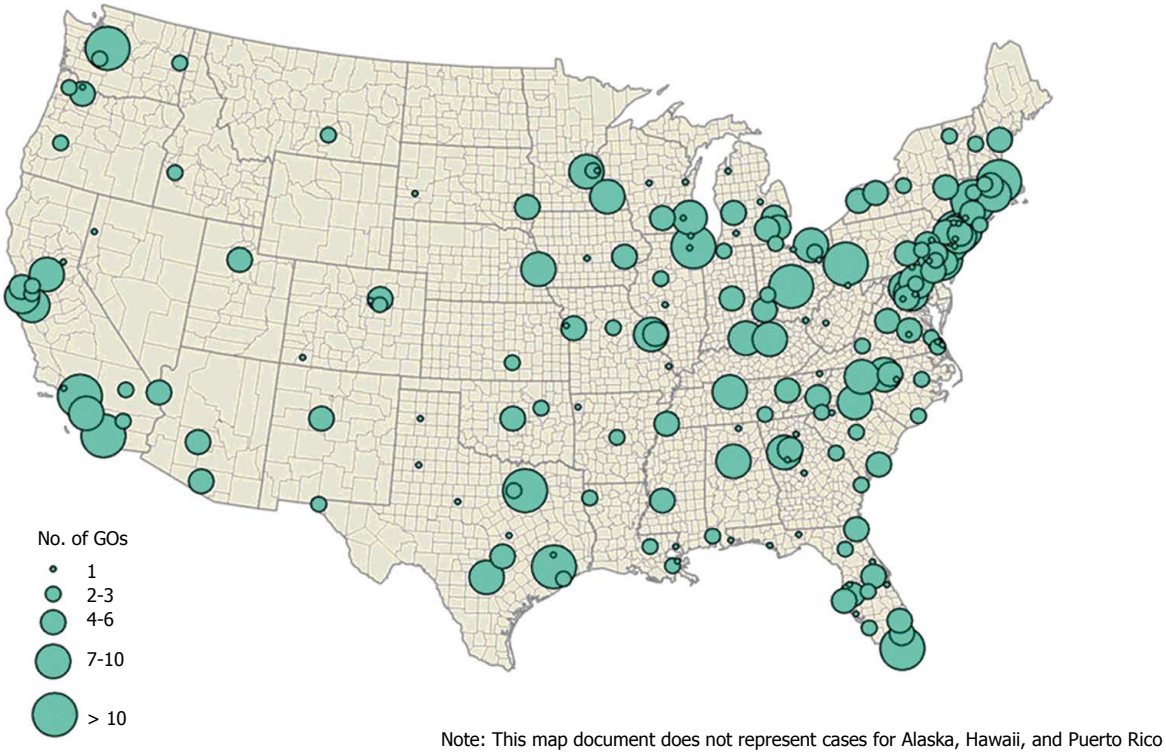

Figure 1 Location and number of gynecologic oncologist practices in the United States. GO: Gynecologic oncologist.

64 years, 65 to 74 years, and 75 years or older. Race/ethnicity was defined as the percent of county population in the following groups: non-Hispanic white, non-Hispanic black, non-Hispanic Asian-Pacific Islander, non-Hispanic other (which including non-Hispanic American Indian/Alaska Native), and Hispanic.

Statistical analysis

Mapping and statistical analyses were used to assess the relationship between the county-level death rate and distance to the nearest GO. County centroids were defined as the geographic center for a county and GOs were geocoded to latitude-longitude coordinate locations within the continental United States using ArcGIS (version 9, ESRI). Geographic access to specialized care was measured as the linear distance, ignoring roads, from county geographic centroid to nearest GO. This distance was then split into tertiles of 0-24 miles, 25-49 miles, and greater than 50 miles. Geographic availability to other less specialized care (PCPs, general surgeons and OB/GYN) was defined as the average number of each of these physicians per average female population (per 100000) for a county from 2002-2006 (data are from the Area Resource file). Death rates were dichotomized as low or high [less than or greater than the median death rate (11.6 per 100100)]. A logistic regression model was fit to the data to determine the association between distance to a GO and high county death rate, after adjusting for other county-level variables. Both forward and backward selection were examined, built with the criteria of a $P < 0.05$ value for model entry or inclusion, and both methods led to the same conclusions. The inclusion of OB/GYNs in the model caused a lack of stability due to collinearity with other variables; therefore even though it was found initially to be significant, this covariate was removed to improve the model stability. All statistical analyses were performed using SAS (version 9.2; Cary, North Carolina).

RESULTS

GO practice characteristics in the United States

The location and number of practicing GOs in the United States are shown in Figure 1. Of the 3109 United States counties, 2906 do not have a practicing GO and only 143 counties have more than one practicing GO. GO density is highest in the Northeast region of the United States. Within individual states, practicing GO locations are unevenly distributed, and practices tend to cluster in particular counties or regions. Florida appears to have a relatively even distribution of GOs across the state, while North Dakota and Wyoming have no practicing GOs within the state.

Table 1 shows GO practice location in relation to United States county characteristics. A total of 536 United States counties were within 24 miles of a practicing GO, 890 counties were located between 25 and 49 miles of a GO, and 1683 counties were located over 50 miles from a GO. The vast majority of counties within 24 miles of a GO practice (90.7%) were classified as metropolitan, whereas only 38.8% and 15.2% of counties within 25 to 49 miles and over 50 miles from a GO were classified as metropolitan, respectively. Most counties within 24 miles of a GO (81.9%) had a large difference in income among the highest and lowest earning households, while

Table 1 United States county characteristics by distance to gynecologic oncologist practice location

	Distance to closest gynecologic oncologist		
	0 to < 25 miles	> 25 to < 50 miles	> 50 miles
No. of US counties	**536**	**890**	**1683**
County designation	*n* (%)	*n* (%)	*n* (%)
Metropolitan	486 (90.7)	345 (38.8)	255 (15.2)
Non-metropolitan	42 (7.8)	424 (47.6)	901 (53.5)
Rural	8 (1.5)	121 (13.6)	527 (31.3)
Socioeconomic characteristics	***n* (%)**	***n* (%)**	***n* (%)**
Income inequality ratio[1]			
Low (< 3.84)	26 (4.9)	226 (25.4)	773 (45.9)
Moderate (> 3.84 to < 6.71)	71 (13.3)	323 (36.3)	664 (39.4)
High (> 6.71)	438 (81.9)	341 (38.3)	246 (14.6)
Percent of county below poverty level			
Low (< 11%)	295 (55.0)	292 (32.8)	452 (26.9)
Moderate (> 11% to < 15.2%)	163 (30.4)	307 (34.5)	577 (34.4)
High (> 15.2%)	78 (14.6)	291 (32.7)	654 (38.9)
Percent of county uninsured			
Low (< 13.3%)	257 (47.9)	333 (37.4)	437 (26.0)
Moderate (> 13.3% to < 18.5%)	181 (33.8)	321 (36.1)	563 (33.4)
High (> 18.5%)	98 (18.3)	236 (25.5)	683 (40.6)
Physician characteristics (per 100000 women)	***n* (%)**	***n* (%)**	***n* (%)**
Primary care physicians			
0	1 (0.2)	15 (1.7)	115 (6.8)
Low (< 105.79)	120 (22.4)	347 (39.0)	515 (30.6)
Moderate (> 105.79 to 169.97)	182 (34.0)	327 (36.7)	505 (30.0)
High (> 169.97)	233 (43.5)	201 (22.6)	548 (32.6)
General surgeons			
0	51 (9.5)	223 (25.1)	666 (39.6)
Low (< 11.72)	135 (25.2)	273 (30.7)	307 (18.2)
Moderate (> 11.72 to < 20.47)	138 (25.7)	249 (28.0)	352 (20.9)
High (> 20.47)	212 (39.6)	145 (16.3)	358 (21.3)
OB/GYNs			
0	65 (12.1)	327 (37.7)	936 (55.6)
Low (< 11.27)	94 (17.5)	235 (26.4)	259 (15.4)
Moderate (> 11.27 to < 20.53)	139 (25.9)	199 (22.4)	268 (15.9)
High (> 20.53)	238 (44.4)	129 (14.5)	220 (13.1)
Population Characteristics	**% (SE)**	**% (SE)**	**% (SE)**
Non-Hispanic white	77.6 (17.7)	82.5 (16.9)	81.4 (20.1)
Non-Hispanic black	12.1 (14.1)	10.0 (14.8)	7.0 (14.6)
Non-Hispanic Asian/Pacific Islander	2.4 (3.5)	0.8 (1.3)	0.6 (0.8)
Non-Hispanic other[2]	1.6 (1.2)	2.0 (4.8)	3.2 (8.1)
Hispanic	6.3 (8.8)	4.7 (8.7)	7.7 (14.6)
Ages 0 to 44	60.8 (5.2)	58.0 (5.3)	55.7 (6.6)
Ages 45 to 54	14.7 (1.3)	14.4 (1.5)	14.4 (1.6)
Ages 55 to 64	10.5 (1.6)	11.3 (1.8)	11.5 (2.0)
Ages 65 to 74	6.8 (1.7)	7.9 (1.6)	8.7 (1.9)
Ages 75+	7.3 (2.2)	8.4 (2.3)	9.8 (3.1)

[1]Defined as the ratio of the number of households with incomes above the population's top 22% household income to the number of houses with incomes below the population's bottom 22% household income; [2]Includes Non-Hispanic American Indian/Alaska Native.

Table 2 Ovarian cancer incidence and mortality by distance to gynecologic oncologist practice location

	Distance to closest gynecologic oncologist		
	0 to < 25 miles	⩾ 25 to < 50 miles	⩾ 50 miles
Mortality			
N	499	707	974
Rate (SE)	10.09 (3.14)	12.02 (4.73)	13.57 (6.43)
Incidence			
N	519	855	1418
Rate (SE)	14.21 (4.23)	15.11 (6.54)	16.31 (8.51)

Table 3 Adjusted odds of high ovarian cancer mortality by gynecologic oncologist practice location

County level variable	Odds ratio	Odds ratio 95%CI	*P*-value
Distance to GO			
⩾ 25 to < 50 miles *vs* < 25 miles	1.40	(1.04, 1.89)	0.029
⩾ 50 miles *vs* < 25 miles	1.59	(1.18, 2.15)	0.003
General surgeon per avg. pop.			
1st Tertile: (< 11.72) *vs* 0	0.35	(0.24, 0.50)	< 0.001
2nd Tertile: (> 11.72 to < 20.47) *vs* 0	0.35	(0.24, 0.51)	< 0.001
3rd Tertile: (> 20.47) *vs* 0	0.32	(0.22, 0.48)	< 0.001
Incidence Rate	1.15	(1.12, 1.18)	< 0.001
% Population Age 45 to 54	1.25	(1.15, 1.37)	< 0.001
% Population Age 75+	1.39	(1.31, 1.48)	< 0.001
% Population non-Hispanic Asian/Pacific Islander	0.88	(0.80, 0.96)	0.004
% Population Hispanic	0.99	(0.97, 1.00)	0.027

The model is adjusted for all the covariates shown in the county level variable column. GO: Gynecologic oncologist.

relatively few counties over 50 miles from a GO (14.6%) had a large difference in income among high and low earning households. Poverty levels were relatively low in counties within 24 miles of a GO (55.0% of counties had less than 11% of the population in poverty), and were higher in counties greater than 50 miles from a GO (38.9% of counties had 15.2% or more of population in poverty). Counties within 24 miles of a GO also had high densities of PCPs (43.5% had greater than 169 per 100000 women), general surgeons (39.6% had greater than 20 per 100000 women), and OB/GYNs (44.4% had greater than 20 per 100000 women). These physicians were less prevalent in counties 50 miles or greater from a GO practice compared to those within 24 miles of a GO practice. A substantial proportion of counties 50 miles or greater from a GO practice did not have any general surgeons (39.6%), and most did not have any OB/GYNs (55.6%). The majority of women in each distance category were non-Hispanic white, although the percentage was slightly lower in counties within 24 miles of a GO (range 77.6%-82.5%). Overall, higher percentages of women aged 65 and older were found in counties farther away from GO practice locations compared to those within 24 miles of a GO practice location.

OC burden in relation to GO practice

Table 2 displays OC incidence and mortality in relation to GO practice locations. Both OC incidence and death

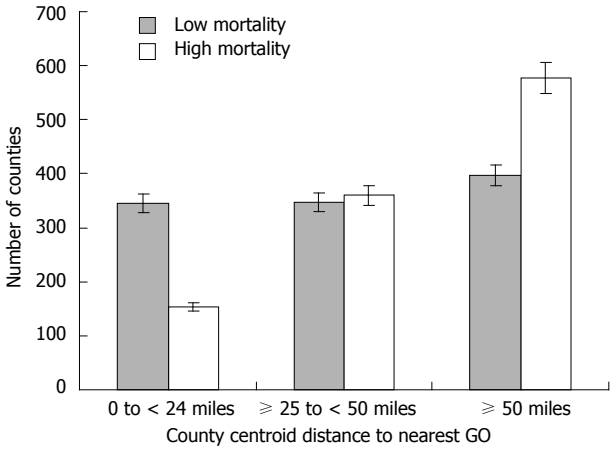

Figure 2 Dichotomized ovarian cancer mortality (high/low) by distance to gynecologic oncologist practice location. GO: Gynecologic oncologist.

rates increase as distance to GO practice increases. Counties within 24 miles of a GO practice location had the lowest incidence (14.21) and death (10.09) rates. Counties located 50 miles or greater from a GO practice had the highest OC incidence (16.31) and death (13.57) rates.

Figure 2 shows dichotomized county-level OC death rates in relation to GO practice location. The number of counties with a high death rate increased as distance from practicing GOs increased. A total of 153 counties within 24 miles of a GO had high death rates compared to 577 counties 50 miles or greater from a GO.

The adjusted results of the association between high OC mortality and GO practice location are shown in Table 3. High OC mortality was significantly associated with increased distance from GOs. Counties with GO practices 25-49 miles from the county centroid had a 40% greater odds of high OC mortality compared to those counties with practices within 24 miles (OR = 1.40, 95%CI: 1.04-1.89). Counties with practices greater than 50 miles to a GO had an almost 60% greater odds of high OC mortality (OR = 1.59, 95%CI: 1.18-2.15). The presence of a general surgeon was associated with a decreased chance of high OC mortality compared to counties without a general surgeon; however, this effect was relatively constant and the OR did not vary substantially in relation to increasing density of general surgeons per average population of women (ORs: 0.32-0.35). Other factors associated with an increased odds of high OC mortality include counties with high OC incidence rates (OR = 1.15, 95%CI: 1.12-1.18), counties with higher proportions of women aged 45-54 years (OR = 1.25, 95%CI: 1.15-1.37), and higher proportions of women 75 years or older (OR = 1.39, 95%CI: 1.31-1.48). Conversely, counties with higher proportions of non-Hispanic Asian/Pacific Islander and Hispanic women had a reduced odds of high OC mortality (OR = 0.88, 95%CI: 0.80-0.96, OR=0.99, 95%CI: 0.97-1.00, respectively).

DISCUSSION

Our findings indicate that there is an uneven distribution of GOs in the United States, with higher concentrations of GOs in metropolitan counties. While there are lower numbers of GOs overall compared to other potential OC practitioners, GO availability tends to be geographically similar to the availability of these other practitioners. Importantly, we have established that increasing distance from a GO has a significant association with increased likelihood of higher OC death rates.

Previous studies with other cancers have demonstrated similar results. In addition to uneven distribution of specialists, Odisho *et al*[10] noted significant prostate, bladder and kidney cancer mortality reductions in counties with urologists compared to those without. Similar results have been reported with regard to dermatologists and melanoma[11]. A lung cancer study also reported uneven distribution of specialist providers, but found no difference in mortality based on the density of thoracic surgeons or oncology services[12]. Further, this study reported that a higher proportion of PCPs (as opposed to specialists) was associated with a lung cancer mortality reduction in some populations[12]. This PCP finding is somewhat consistent with our study in that we also observed decreased OC mortality in relation to the density of general surgeons; however, the mortality reduction in our study was similar regardless of increasing density of PCPs.

Current and projected shortages in the availability of cancer care providers have been well-documented. In a recent workshop sponsored by the United States Institute of Medicine, it was noted that almost all oncology professions are experiencing workforce shortages, including physicians, nurses, allied health care professionals, public health workers, social workers, and pharmacists[13]. A 2007 study commissioned by the American Society of Clinical Oncology found that the demand for oncologists is likely to increase dramatically by the year 2020, driven by the aging and growth of the population as well as improvements in cancer survival rates[14]. The supply of oncologists is only projected to increase 14% during the same timeframe, creating a shortage of 2500 to 4080 oncologists[14]. A similar situation exists for gynecologic oncologists. A 2010 study projected that at constant training rates, the annual number of new cancer cases per practicing GOs will rise 19%, with an expected increased caseload of almost 20% over the next 40 years[15]. In New Zealand, which also has an uneven distribution of GOs, a reorganization of gynecologic cancer care has been suggested in order to ensure that all patients have access to subspecialists in the face of GO shortages[16]. This model is based on one adopted in the United Kingdom, and establishes a connection between major comprehensive cancer centers that have GOs and smaller satellite hospitals without GOs. This connection may help to facilitate multidisciplinary care for patients in the smaller centers. Additionally, a national gynecologic cancer steering group with representation from the comprehensive cancer centers, and key medical and nursing disciplines would oversee care coordination, including development of a standardized protocol for treatment

and referral guidelines[16]. A similar coordinated approach may assist with alleviating the negative outcomes (higher OC mortality) that geographic barriers to GO care has in the United States. However, it should be noted that several other factors in addition to geographic availability may impact receipt of quality care for OC in the United States. These factors are numerous and include lack of insurance or other socioeconomic limitations, language and cultural differences, psychosocial, lifestyle and behavioral factors[17-19].

Given the lack of geographic availability of GOs in many areas in the United States, an emphasis on OC prevention may be suggested. However, OC is difficult to prevent and no evidence-based early detection methods are currently available[4]. Several studies investigating serum CA-125 levels in combination with transvaginal ultrasound as a potential early detection method resulted in more harms than benefits to patients[20,21], and did not reduce overall OC mortality[20]. A comprehensive evidence review assessing oral contraceptive use for OC prevention also found the potential for more harms than benefits, particularly with regard to effects on quality of life from increases in breast cancer and vascular events caused by oral contraceptive use[22]. The identification of patients who are at an increased risk for OC due to genetic mutations in the *BRCA* gene currently offers the greatest potential for prevention of OC[23]. Stressing the importance of family history knowledge, and appropriate genetic counseling and testing to determine BRCA status among women may ultimately reduce ovarian cancer risk and mortality in some women[24].

This study has several strengths. To our knowledge, it is the first to relate geographic proximity to GOs with lower OC mortality in the United States. Additionally, the use of population-based OC data from a large portion of the United States likely improved the accuracy of the results. Limitations to this study include the ecologic study design which impedes the ability to apply the results at the individual level. Also while our data sources were current at the beginning of the study, they are now slightly dated and the years of OC incidence and mortality vary from that of the practicing GOs. However, since OC incidence and death rates changed little over the last decade, and any changes in GO numbers and distribution by state are relatively minor, this likely has little impact on the results. Finally, although our data sources are comprehensive in coverage, a small percentage of GO providers and OC incident cases remain missing from our analysis. It is unlikely that the results would be different based on these small percentages; however, we are unable to make any conclusions with regard to the areas where data are missing.

The uneven distribution of GOs across the United States appears to be significantly associated with OC mortality, with death rates increasing as distance to GO increases. These findings may have important implications for the oncology workforce and cancer control planning. Appropriate genetic counseling and testing for the prevention of OC, as well as facilitated outreach to GOs in order to provide a coordinated approach to quality OC care, may be promoted through the efforts of cancer control planners in the United States National Comprehensive Cancer Control Program. Future studies examining the effects of GO distribution on OC mortality at the individual level may assist with further defining barriers to quality OC care in the United States.

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COMMENTS

Background

Ovarian cancer (OC) is the deadliest gynecologic malignancy and the fifth leading cause of cancer death among women in the United States. Several studies have suggested that optimal treatment and better outcomes for OC are more often achieved through subspecialist gynecologic oncologist (GO) care. Despite this evidence many patients (about 30%-60%) are not treated by a GO.

Research frontiers

OC is a deadly disease, with no known effective prevention. Studies in areas that improve treatment and outcomes from the disease, such as receipt of care from a GO, is a research hotspot in OC mortality reduction.

Related publications

http://www.ncbi.nlm.nih.gov/pubmed/17540806; http://www.ncbi.nlm.nih.gov/pubmed/21256581; http://www.ncbi.nlm.nih.gov/pubmed/16449677

Innovations and breakthroughs

Research into factors related to limited access to GO (such as patient socioeconomic factors) is an important and timely topic. This study examines whether geography may be a potential barrier to GO access.

Applications

OC mortality increases significantly as distance to GO increases. These findings have important implications for the oncology workforce and cancer control planning. Facilitated outreach to GO and a more coordinated and quality approach to OC care is suggested.

Terminology

Gynecologic oncologist: A physician who has completed an obstetrics and gynecology residency and then pursued subspecialty training through a gynecologic oncology fellowship (which includes intensive surgical, chemotherapeutic, radiation, and research training). Geographic Information System: integrates data for analyzing and displaying all forms of geographically referenced information which allows for viewing, understanding, and interpreting data to reveal relationships, patterns, and trends.

Peer review

In this study, the authors examined a potential geographic barrier to receipt of GO care. The objective of the study was to examine the geographic relationship between GO providers and OC patient mortality, in order to determine the effect that geographic availability of specialized care has on mortality. The experimental design is appropriate, and the data seem high quality. This is an interesting article.

REFERENCES

1 **United States Cancer Statistics Working Group**. United States Cancer Statistics: 1999–2009 Incidence and Mortality Web-based Report. Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute, 2013

2 **Howlader N**, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA, editors. SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD: National Cancer Institute, 2013

3 **Dizon D**, Meyers J. The Economic Burden of Ovarian Cancer in a United States Managed Care Database. SGO 41st Annual Meeting on Women's Cancer, 2010

4 **Stewart SL**, Rim SH, Richards TB. Gynecologic oncologists and ovarian cancer treatment: avenues for improved survival. *J Womens Health (Larchmt)* 2011; **20**: 1257-1260 [PMID: 21819252 DOI: 10.1089/jwh.2011.3053]

5 **Chan JK**, Kapp DS, Shin JY, Husain A, Teng NN, Berek JS, Osann K, Leiserowitz GS, Cress RD, O'Malley C. Influence of the gynecologic oncologist on the survival of ovarian cancer patients. *Obstet Gynecol* 2007; **109**: 1342-1350 [PMID: 17540806 DOI: 10.1097/01.aog.0000265207.27755.28]

6 **Chan JK**, Kapp DS, Shin JY, Osann K, Leiserowitz GS, Cress RD, O'Malley C. Factors associated with the suboptimal treatment of women less than 55 years of age with early-stage ovarian cancer. *Gynecol Oncol* 2008; **108**: 95-99 [PMID: 17949796 DOI: 10.1016/j.ygyno.2007.08.087]

7 **Cress RD**, Bauer K, O'Malley CD, Kahn AR, Schymura MJ, Wike JM, Stewart SL, Leiserowitz GS. Surgical staging of early stage epithelial ovarian cancer: results from the CDC-NPCR ovarian patterns of care study. *Gynecol Oncol* 2011; **121**: 94-99 [PMID: 21256581 DOI: 10.1016/j.ygyno.2010.12.359]

8 **Earle CC**, Schrag D, Neville BA, Yabroff KR, Topor M, Fahey A, Trimble EL, Bodurka DC, Bristow RE, Carney M, Warren JL. Effect of surgeon specialty on processes of care and outcomes for ovarian cancer patients. *J Natl Cancer Inst* 2006; **98**: 172-180 [PMID: 16449677 DOI: 10.1093/jnci/djj019]

9 **Goff BA**, Matthews BJ, Larson EH, Andrilla CH, Wynn M, Lishner DM, Baldwin LM. Predictors of comprehensive surgical treatment in patients with ovarian cancer. *Cancer* 2007; **109**: 2031-2042 [PMID: 17420977 DOI: 10.1002/cncr.22604]

10 **Odisho AY**, Cooperberg MR, Fradet V, Ahmad AE, Carroll PR. Urologist density and county-level urologic cancer mortality. *J Clin Oncol* 2010; **28**: 2499-2504 [PMID: 20406931 DOI: 10.1200/jco.2009.26.9597]

11 **Aneja S**, Aneja S, Bordeaux JS. Association of increased dermatologist density with lower melanoma mortality. *Arch Dermatol* 2012; **148**: 174-178 [PMID: 22351816 DOI: 10.1001/archdermatol.2011.345]

12 **Backhus LM**, Hayanga AJ, Au D, Zeliadt SB. The effect of provider density on lung cancer survival among blacks and whites in the United States. *J Thorac Oncol* 2013; **8**: 549-553 [PMID: 23446202 DOI: 10.1097/JTO.0b013e318287c24c]

13 **Levit L**, Smith AP, Benz EJ, Ferrell B. Ensuring quality cancer care through the oncology workforce. *J Oncol Pract* 2010; **6**: 7-11 [PMID: 20539724 DOI: 10.1200/jop.091067]

14 **Erikson C**, Salsberg E, Forte G, Bruinooge S, Goldstein M. Future supply and demand for oncologists: challenges to assuring access to oncology services. *J Oncol Pract* 2007; **3**: 79-86 [PMID: 20859376 DOI: 10.1200/jop.0723601]

15 **Wallace AH**, Havrilesky LJ, Valea FA, Barnett JC, Berchuck A, Myers ER. Projecting the need for gynecologic oncologists for the next 40 years. *Obstet Gynecol* 2010; **116**: 1366-1372 [PMID: 21099604 DOI: 10.1097/AOG.0b013e3181fc3a22]

16 **Sykes P**, Vaughan M, Chrystal K, Ehrenberg N, Hefford M, Hutchings S, Tan AL, Simcock B, Kee DN. Providing care for women with gynaecological malignancy: the need for a coordinated national approach. *N Z Med J* 2012; **125**: 57-65 [PMID: 22932655]

17 **Brown JP**, Tracy JK. Lesbians and cancer: an overlooked health disparity. *Cancer Causes Control* 2008; **19**: 1009-1020 [PMID: 18551371 DOI: 10.1007/s10552-008-9176-z]

18 **Doll KM**, Puliaev R, Chor J, Roston A, Patel UA, Patel A. Detection of gynecologic cancers in indigent women in an urban inner-city hospital. *Int J Gynecol Cancer* 2012; **22**: 1113-1117 [PMID: 22810968 DOI: 10.1097/IGC.0b013e31825f7fa0]

19 **Forman AD**, Hall MJ. Influence of race/ethnicity on genetic counseling and testing for hereditary breast and ovarian cancer. *Breast J* 2009; **15** Suppl 1: S56-S62 [PMID: 19775331 DOI: 10.1111/j.1524-4741.2009.00798.x]

20 **Buys SS**, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, Reding DJ, Greenlee RT, Yokochi LA, Kessel B, Crawford ED, Church TR, Andriole GL, Weissfeld JL, Fouad MN, Chia D, O'Brien B, Ragard LR, Clapp JD, Rathmell JM, Riley TL, Hartge P, Pinsky PF, Zhu CS, Izmirlian G, Kramer BS, Miller AB, Xu JL, Prorok PC, Gohagan JK, Berg CD. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA* 2011; **305**: 2295-2303 [PMID: 21642681 DOI: 10.1001/jama.2011.766]

21 **Partridge E**, Kreimer AR, Greenlee RT, Williams C, Xu JL, Church TR, Kessel B, Johnson CC, Weissfeld JL, Isaacs C, Andriole GL, Ogden S, Ragard LR, Buys SS. Results from four rounds of ovarian cancer screening in a randomized trial. *Obstet Gynecol* 2009; **113**: 775-782 [PMID: 19305319 DOI: 10.1097/AOG.0b013e31819cda77]

22 **Havrilesky LJ**, Gierisch JM, Moorman PG, Coeytaux RR, Urrutia RP, Lowery WJ, Dinan M, McBroom AJ, Wing L, Musty MD, Lallinger KR, Hasselblad V, Sanders GD, Myers ER. Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer. Evidence Report/Technology Assessment No. 212. AHRQ Publication No 13-E002-EF. Rockville, MD: Agency for Healthcare Research and Quality, June 2013

23 **Vaughan S**, Coward JI, Bast RC, Berchuck A, Berek JS, Brenton JD, Coukos G, Crum CC, Drapkin R, Etemadmoghadam D, Friedlander M, Gabra H, Kaye SB, Lord CJ, Lengyel E, Levine DA, McNeish IA, Menon U, Mills GB, Nephew KP, Oza AM, Sood AK, Stronach EA, Walczak H, Bowtell DD, Balkwill FR. Rethinking ovarian cancer: recommendations for improving outcomes. *Nat Rev Cancer* 2011; **11**: 719-725 [PMID: 21941283 DOI: 10.1038/nrc3144]

24 **Domchek SM**, Friebel TM, Singer CF, Evans DG, Lynch HT, Isaacs C, Garber JE, Neuhausen SL, Matloff E, Eeles R, Pichert G, Van t'veer L, Tung N, Weitzel JN, Couch FJ, Rubinstein WS, Ganz PA, Daly MB, Olopade OI, Tomlinson G, Schildkraut J, Blum JL, Rebbeck TR. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA* 2010; **304**: 967-975 [PMID: 20810374 DOI: 10.1001/jama.2010.1237]

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RESEARCH REPORT

Fetal lung surfactant and development alterations in intrahepatic cholestasis of pregnancy

Yi-Ling Ding, Li-Juan Zhang, Xin Wang, Qi-Chang Zhou, Na Li, Chang-Xiu Wang, Xiu-Quan Zhang

Yi-Ling Ding, Li-Juan Zhang, Xin Wang, Na Li, Chang-Xiu Wang, Department of Obstetrics and Gynecology, Xiangya Second Hospital, Central South University, Changsha 410011, Hunan Province, China
Qi-Chang Zhou, Ultrasonography, Department of Radiology, Xiangya Second Hospital, Central South University, Changsha 410011, Hunan Province, China
Xiu-Quan Zhang, Department of Obstetrics and Gynecology and Reproductive Genetics, University of Utah School of Medicine, Salt Lake City, UT 84132, United States
Author contributions: Ding YL and Zhang LJ contributed equally to this work; Zhang LJ and Ding YL developed the conception and designed the study; Wang X, Li N and Wang CX collected and analyzed the data; Zhou QC conducted the ultrasonography; Zhang LJ and Zhang XQ drafted the manuscript and interpreted the data; Zhang XQ revised and final approved the manuscript.
Correspondence to: Xiu-Quan Zhang, MD, Department of Obstetrics and Gynecology and Reproductive Genetics, University of Utah School of Medicine, 50 North Medical. Drive, Salt Lake City, UT 84132,
United States. xiuquan.zhang@hsc.utah.edu
Telephone: +1-801-5853117 Fax: +1-801-5813552
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Abstract

AIM: To investigate the association between total bile acid (TBA) level during intrahepatic cholestasis of pregnancy (ICP) and fetal lung surfactant alteration.

METHODS: We recruited 42 ICP and 32 normal pregnancy women in this study. The maternal blood, fetal blood and amniotic fluid TBA level were detected using a circulating enzymatic method. Umbilical blood pulmonary surfactant protein A (SP-A) was evaluated with enzyme-linked immunosorbent assay. High performance liquid chromatography was used for the determination of phosphatidyl choline (PC), phosphatidyl inositol (PI), lysolecithin (LPC) and sphingomyelin (SM). Amniotic fluid lamellar body was counted with a fully automatic blood cell counter. Fetal lung area and fetal body weight were calculated from data obtained with an iu22 color supersonic diagnostic set. Clinical information of a nonstress test, amniotic fluid properties and neonatal Apgar score, and birth weight were recorded for review.

RESULTS: The TBA level in maternal blood, fetal blood and amniotic fluid in the ICP group were significantly higher than that in the control group (maternal blood: 34.11 ± 6.75 mmol/L *vs* 4.55 ± 1.72 mmol/L, $P < 0.05$; fetal blood: 11.9 ± 2.23 mmol/L *vs* 3.52 ± 1.56 mmol/L, $P < 0.05$; amniotic fluid: 3.89 ± 1.99 mmol/L *vs* 1.43 ± 1.14 mmol/L, $P < 0.05$). Amniotic fluid PC and PI in the ICP group were significantly lower than that in the control group (PC: 65.71 ± 7.23 μg/mL *vs* 69.70 ± 6.68 μg/mL, $P < 0.05$; PI: 3.87 ± 0.65 μg/mL *vs* 4.28 ± 0.74 μg/mL, $P < 0.05$). PC/LPC ratio of the ICP group was lower than that of the control group (14.40 ± 3.14 *vs* 16.90 ± 2.52, $P < 0.05$). Amniotic LB in the ICP group was significantly lower than that of the control group ((74.13 ± 4.37) × 10^9/L *vs* (103.0 ± 26.82) × 10^9/L, $P < 0.05$). Fetal umbilical blood SP-A level in the ICP group was significantly higher than that of the control group (30.26 ± 7.01 ng/mL *vs* 22.63 ± 7.42 ng/mL, $P < 0.05$). Fetal lung area/body weight ratio of the ICP group was significantly lower than that of the control group (5.76 ± 0.63 cm^2/kg *vs* 6.89 ± 0.48 cm^2/kg, $P < 0.05$). In the ICP group, umbilical cord blood TBA concentration was positively correlated to the maternal blood TBA concentration ($r = 0.746$, $P < 0.05$) and umbilical blood SP-A ($r = 0.422$, $P < 0.05$), but it was negatively correlated to the amniotic fluid lamellar corpuscle ($r = 0.810$, $P < 0.05$) and fetal lung area/body weight ratio ($r = 0.769$, $P < 0.05$). Furthermore, umbilical blood TBA showed a negative correlation to PC, SM and PI ($r_{pc} = 0.536$, $r_{sm} = 0.438$, $r_{pi} = 0.387$ respectively, $P < 0.05$). The neonatal asphyxia, neonatal respiratory distress syndrome, fetal distress and perinatal death rates in the ICP group are higher than that of the

control group.

CONCLUSION: ICP has higher TBA in maternal and fetal blood and amniotic fluid. The high concentration of TBA may affect fetal pulmonary surfactant production and fetal lung maturation.

Key words: Intrahepatic cholestasis of pregnancy; Total bile acid; Pulmonary surfactant; Surfactant protein; Phospholipids; Amniotic fluid lamellar body

Core tip: We studied total bile acid (TBA) concentration in maternal, fetal and amniotic fluid and its relationship with fetal surfactant, surfactant protein A, amniotic lamellar body and fetal lung development. Results demonstrated that intrahepatic cholestasis of pregnancy (ICP) has higher TBA in maternal and fetal blood and amniotic fluid. The high concentration of TBA may affect fetal pulmonary surfactant production and fetal lung maturation. It calls attention to delayed maturation of fetal lungs in ICP patients and to take steps to carefully check and improve fetal pulmonary maturity.

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INTRODUCTION

Intrahepatic cholestasis of pregnancy is a maternal metabolic disease affecting up to 5% of pregnancies[1]. It is characterized by rising maternal serum bile acids and can be complicated by fetal distress, neonatal asphyxia and neonatal respiratory distress syndrome[2-4]. The etiology of intrahepatic cholestasis of pregnancy (ICP) is poorly understood but the perinatal complications are closely correlated with maternal total bile acid (TBA) level[5,6]. Savonius found that high TBA can cause neonatal lung injury but its mechanism is not clear[7]. In order to explore fetal lung alteration during ICP and its possible mechanisms, we investigated maternal and fetal TBA, fetal surfactant production and fetal lung development.

MATERIALS AND METHODS

Protocols were approved by Central South University Xiangya Second Hospital Scientific Research Department. Informed consents were obtained from all patients involved in this study.

Clinical information

A total of 72 cases were recruited in this study during 2010 and 2011. It includes 40 ICP patients and 32 normal pregnant women with singleton pregnancy delivered using cesarean section. In the ICP group, the patients' ages were from 18 to 40 years old and the average age was 27.7 ± 1.37 years. The gestational ages were from 33 wk to 41 wk + 5 d and the average gestational age was 37.25 ± 2.34 wk. In the normal pregnancy group, the patients' ages were from 19 to 36 years old and the average age was 27.2 ± 4.67. The gestational ages were from 33 ± 2 to 40 ± 6 wk and the average gestational age was 37.5 ± 2.67 wk. There were no statistical differences between the ICP group and control group for maternal age, gestational age or pregnancy times. ICP was diagnosed with the diagnostic criteria referenced in the eighth edition of the national text book of obstetrics and gynecology[8]. Patients with liver disease, gall bladder disease, chronic vascular disease, gestational hypertension, gestational diabetes, anemia, kidney disease, heart disease or other pregnancy complications were excluded.

Sample collections

Maternal blood was collected at a fasting state before cesarean section. Fetal blood was collected through the umbilical artery immediately after delivery of the fetus during cesarean section. Amniotic fluid was collected with a syringe through the amniotic membrane just after cutting and separating the myometrium during cesarean section, with careful attention to avoid blood pollution.

Blood specimens were injected into a test tube dedicated with heparin immediately after being collected. After centrifuge (3000 r/min, 15 min), the supernatant was collected and stored at -20 ℃ for future experiments. For amniotic fluid, the upper solution was collected after centrifuge (3000 r/min, 15 min), then mixed 1:1 volume with methanol/chloroform. After centrifuge again (2500 r/min, 10 min), the lower liquid was extracted and mixed with a methanol-water extractor (1:1, v/v). The supernatant and interface impurities were discarded after centrifuge (2500 r/min, 10 min), 10 mL lower fluid was taken and sealed into a test tube, then stored for future tests at -20 ℃. Before testing, a mobile phase containing chloroform was used to dissolve the samples.

Amniotic fluid assay for TBA, SPA, phospholipids

TBA was detected using the automatic biochemical analyzer (Hitachi 7060, Japan) with the TBA detection kit (Sigma, Shanghai Trading Co. Ltd.), following the instruction of the assay kit. The calibration was made each time using the standard calibrator. Surfactant protein A (SP-A) was detected with the SP-A detection kit using an enzyme-linked immunosorbent assay (Wuhan technology co., China and United States)[9]. Phospholipids phosphatidylcholine (PC), phosphatidylinositol (PI), lysolecithin (LPC) and sphingomyelin (SM) were detected with high-performance liquid chromatography (HPLC, Shanghai National Medicine Chemical Reagent Co. Ltd.) with the standard phospholipids (Sigma, Shanghai Trading Co. Ltd.). uPrasil column (300 mm × 4 mm, 5 μm)

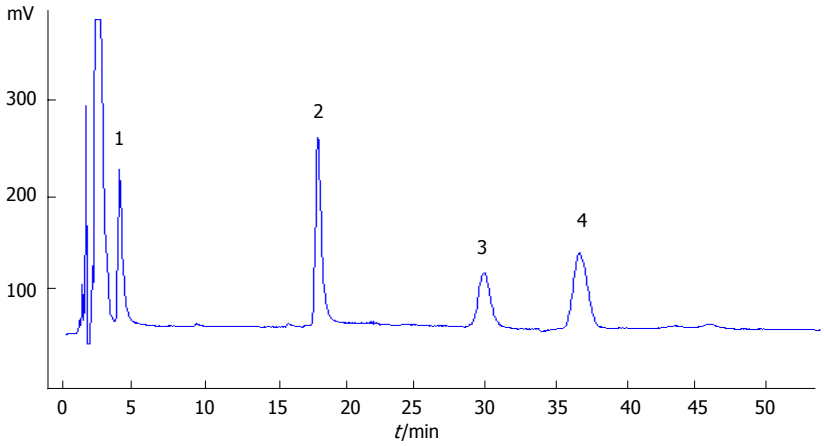

Figure 1 Chromatogram of phospholipids. High-performance liquid chromatography was used for phospholipids measurement. Peaks represent the phospholipids extracted from amniotic fluids. Peaks refer to the following components: 1: Phosphatidylinositol; 2: Phosphatidylcholine; 3: Lysolecithin; 4: Sphingomyelin.

was used with a HW2000 chromatographic data station for data analysis. The procedures and steps were carried out accurately following the instructions of the agent kit and instrument. The phospholipid concentration results are shown in Figure 1. Amniotic fluid lamellar body was counted using a hematology analyzer (ABX-Pentra120, Diamond Diagnostics, United States).

Ultrasonography

Color ultrasonic diagnostic system (Philips iu22, United States, probe frequency 2.5-6.0 OMHZ) was used for fetal lung area and fetal body weight within 3 days of delivery. Fetal body weights were assessed and calculated by checking the fetal biparietal diameter, head circumference, abdominal circumference and femoral length. Fetal lung areas were calculated by measuring the fetal left and right lung area by freezing an image shot when the fetal heart was at the diastolic phase while the probe was parallel to the longitudinal line of the fetus. The area was digitally analyzed by the computerized system automatically. Data was taken by one professional individual using a mean of 3 measurements. Total lung area and lung area/body weight were digitally calculated[10].

Fetal heart rate patterns, amniotic fluid characteristics and neonatal Apgar score were recorded for evaluation. The situation of the neonates was also recorded for three days to evaluate the fetus and neonates.

Statistical analysis

Software SPSS13.0 was used for statistics. Student *t*-test was used for measurement data and χ^2 test was used for numerous data. Correlation was analyzed using Pearson and Spearman correlation analysis.

RESULTS

Total bile acid level

The TBA concentration in maternal peripheral vein blood, fetal umbilical artery blood and amniotic fluid in the ICP group was 34.11 ± 6.76, 11.9 ± 2.23, and 3.89 ± 1.99 mmol/L respectively. They were significantly higher than that of the control group which were maternal: 4.55 ± 1.72 mmol/L, fetal: 3.52 ± 1.56 mmol/L, and amniotic fluid: 1.43 ± 1.14 mmol/L ($P < 0.05$ respectively). In addition, the TBA level in maternal serum was higher than that in fetal serum or amniotic fluid in both the ICP group and control group (Table 1).

Amniotic phospholipid components and lamellar body

The PC and PI concentrations in amniotic fluid in ICP group were 65.71 ± 7.23 μg/mL and 3.87 ± 0.65 μg/mL respectively. They were evidently lower than that in the normal control group (69.70 ± 3.68, 4.28 ± 0.74 μg/mL respectively, $P < 0.05$). In the ICP group, LPC content in amniotic fluid was 4.72 ± 0.86 μg/mL, which was much higher than that in control group (4.21 ± 0.64 μg/mL, $P < 0.05$); the SM content in both groups had no statistical difference. The ratio of PC/LPC in the ICP group (14.40 ± 3.14) was much lower than that of the control group (16.90 ± 2.52, $P < 0.05$). The lamellar body in the ICP group was evidently lower than that of the control group ($P < 0.05$) (Table 1).

Fetal SP-A and fetal lung area/body weight

In the ICP group, fetal SP-A concentration was 30.26 ± 7.01 ng/mL, which is significantly higher than that of the control group, 22.63 ± 7.42 ng/mL ($P < 0.05$). The fetal lung area/body weight ratio of the ICP group was 5.76 ± 0.63 cm^2/kg, while the control group was 6.89 ± 0.48 cm^2/kg, which is a significant difference ($P < 0.05$) (Figure 2).

Correlation analysis

The maternal TBA concentration and fetal TBA level are positively correlated ($r = 0.746$, $P < 0.05$). Fetal TBA is positively correlated with fetal SP-A concentrations ($r = 0.422$, $P < 0.05$), but negatively correlated with amniotic fluid lamellar small mass ($r = 0.810$, $P < 0.05$) or fetal lung area/body weight ratio ($r = 0.769$, $P < 0.05$). Furthermore, fetal TBA is negatively correlated with am-

Table 1 Variable characteristics between intrahepatic cholestasis of pregnancy and the control group

	Control (n = 32)	Intrahepatic cholestasis of pregnancy (n = 40)
Total bile acid (mmol/L)		
Maternal serum	4.55 ± 1.72	34.11 ± 6.75[a]
Umbilical artery serum	3.52 ± 1.56	11.9 ± 2.23[a]
Amniotic fluid	1.43 ± 1.14	3.89 ± 1.99[a]
Amniotic fluid phospholipids		
PC (μg/mL)	69.70 ± 6.68	65.71 ± 7.23[a]
PI (μg/mL)	4.28 ± 0.74	3.87 ± 0.65[a]
LPC (μg/mL)	4.21 ± 0.64	4.72 ± 0.86[a]
SM (μg/mL)	3.95 ± 0.53	3.63 ± 0.66
PC/LPC (μg/mL)	6.90 ± 2.52	14.40 ± 3.14[a]
Lamellar body (× 10^9/L)	103.0 ± 26.82	74.13 ± 4.37[a]
Perinatal outcomes		
Fetal distress	4 (12.4)	13 (32.5)
Neonatal asphyxia	1 (3.13)	2 (5)
NRDS	2 (6.25)	6 (15)
Perinatal death	0	1 (2.5)

Data are expressed as absolute mean ± SD or numbers (percentage). PC: Phosphatidylcholine; PI: Phosphatidylinositol; LPC: Lysolecithin; SM: Sphingomyelin; NRDS: Neonatal respiratory distress syndrome. [a]P < 0.05 *vs* control group.

niotic fluid PC, SM and PI (r_{pc} = 0.536, r_{sm} = 0.438, r_{pi} = 0.387, P < 0.05). In addition, amniotic fluid lamellar body are positively correlated with fetal lung area/body weight ratio (r = 0.929, P < 0.05).

Perinatal outcomes

The fetal distress, neonatal asphyxia, neonatal respiratory distress syndrome and perinatal death rates in the ICP and control group are shown in Table 1.

DISCUSSION

Intrahepatic cholestasis of pregnancy is a peculiar disease in middle-late pregnancy, with the pathological characteristics of hepatic capillary bile duct silts, causing increasing clinical bile components in peripheral blood and liver function damage[11,12]. High TBA has toxic cellular effects to many organs and mainly affects the fetus[13], leading to perinatal complications such as fetal distress, meconium inhaled syndrome and neonatal asphyxia[3,4]. The mechanism of ICP causing poor perinatal outcome has not yet been elucidated. Current studies suggest that maternal TBA level is the most sensitive index to diagnose ICP and predict the perinatal outcomes[4,14,15].

Fetal serum bile acid is synthesized from fetal liver, which increases with the gestational weeks. During late normal pregnancy, fetal blood bile acid concentration is higher than the maternal level[16,17]. Bile acid as fat soluble small molecules, diffuses through the placenta, then to maternal blood circulation and the normal liver system removes them from the body. During ICP, under the action of various factors, maternal bile acid levels increase, which damages the placenta, causing insufficiency of placental transferring, leading to fetal bile acid deposition in the body, and finally the fetal blood and the amniotic

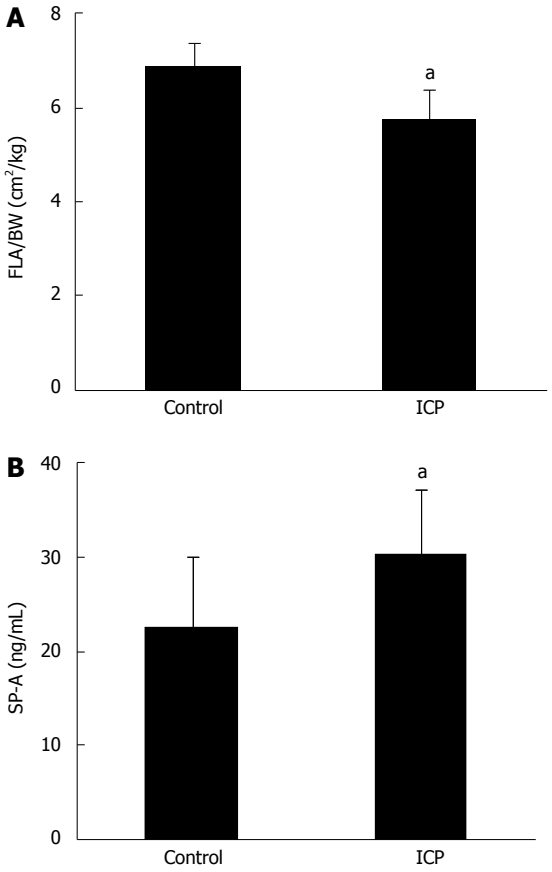

Figure 2 Fetal lung area/body weight ratio and fetal surfactant protein A. A: Ratio between fetal lung area (FLA) and fetal body weight (BW). [a]P < 0.05 *vs* control; B: Fetal surfactant protein A (SP-A) concentration. Intrahepatic cholestasis of pregnancy (ICP) has a higher SP-A than that in the control group, [a]P < 0.05 *vs* control.

fluid bile acid levels become higher[18]. With the rise of maternal bile acid concentration, fetal blood bile acid increases and causes delay of fetal lung development[15].

Animal experiments and clinical studies have demonstrated that ICP leads to fetal and neonatal acute lung injury and causes bile acid pneumonia[19]. The cause of poor perinatal outcomes due to ICP is not very clear. Injection of cholic acids into the rabbit trachea induces dyspnea and respiratory failure[20]. The morphological changes are consistent with neonatal pulmonary hyaline membrane disease, decreasing of light transmittance, swelling, atelectasis and pulmonary hyaline membrane disease[6,14,21]. After giving pulmonary surfactant treatment, the symptoms and pathological changes reduce or disappear[22,23]. In a bronchoalveolar fluid study (BALF), it was found that the more bile acid content in BALF, the less production of the pulmonary surfactant A and D. It was demonstrated that the lung injury induced by bile acid is associated with pulmonary surfactant insufficiency[6]. Zecca *et al*[19] found that bile acids exist in all newborns in the BALF study on ICP.

Cholic acid can cause a dysfunction of surface active substances synthesis in the lung and induces an inflammatory reaction and chemical pneumonia. With bronchoalveolar lavage, Hills *et al*[24] found that the pulmonary

phospholipid content is lower in sudden infant death syndrome than in normal cases, and bile acid content increased. It prompted the idea that bile acid may achieve the role of pulmonary surfactant to the lungs through acting on phospholipase[24]. In this study, umbilical cord blood SP-A in the ICP group is higher than that of the normal group and the umbilical cord blood total bile acid concentration is also higher. SP-A is the lung protein component of pulmonary surfactant, which is a hydrophilic multifunctional glycoprotein. Under normal circumstances, the alveolar capillary barrier is intact, which can prevent SP-A serum from entering the blood circulation. When the lungs are injured, the alveolar capillary permeability increases, then SP-A leaks from the alveolar cavity to the alveolar capillaries, which induces an increasing blood SP-A concentration[25]. We speculated that high amniotic bile acid concentrations can destroy the continuity of the pulmonary vascular endothelium, causing the fetus alveolar capillary damage and increasing alveolar capillary permeability. SP-A can damage the alveolar capillary membrane barrier, then get into the blood circulation, leading a SP-A rise in serum[26,27].

Pulmonary surfactant is synthesized in alveolar type Ⅱ epithelial cells. When lung injury happens, the AT Ⅱ cell synthesis ability decreases, which leads to the alveolar capillary permeability increasing and pulmonary surfactant decreasing[28,29]. Cholic acid can promote the secretion of phospholipase A2 and restrain and reduce the secretion of pulmonary surface active substance[20]. So, even although the amniotic fluid lecithin/sphingomyelin ratio (L/S) indicates mature lung, unusually high levels of cholic acid can still reverse the activity of phospholipase A2, causing a relative lack of lung surface. When using pulmonary surfactant to treat newborns diagnosed with bile acid pneumonia, Zecca found that clinical symptoms and signs obviously improved[19]. In our study, PC and PI levels in ICP amniotic fluid are lower than that in normal pregnancy. We speculate that there may be high concentrations of bile acids in the amniotic fluid and fetal circulation which work together in the respiratory tract and lungs of the fetus. A high level of bile acid has a cytotoxic effect in the lungs, destroying the AT-Ⅱ cells and decreasing PS, PC and PI synthesis. Our results showed that the ICP's LPC in amniotic fluid levels are higher than that of the normal group, which might be caused by the degradation in the amniotic fluid. As to what causes the degradation of the PC, further studies are needed. LPC has a direct toxic effect which may damage AT Ⅱ cells, then affect the synthesis of PS. It can increase the damaging effect to the alveolar capillary system caused by TBA in fetal blood and amniotic fluid. This change may result in increasing cell membrane permeability and alveolar infiltrates.

The lamellar body is the special structure of lung surface active material stored in alveolar type Ⅱ cellular cytoplasm which has a typical structure like an onion[30]. LB can be found in normal middle pregnancy and increases obviously at 34 to 36 gestational weeks. It is discharged by alveolar type Ⅱ cells and attached to the alveolar surface, then contacts with amniotic fluid. Amniotic fluid LB increases gradually with the progress of pregnancy and fetal maturity. So, the LB measurement can predict fetal lung maturity[31]. Reports shows high bile acid can induce fetal rat alveolar type Ⅱ epithelial cells to degenerate through necrosis, the cell surface microvilli structure disappears, the nucleus and mitochondria swells, the balloon sample changes and ridge cavitations disappear[25]. It can also result in the decrease of lamellar corpuscle numbers and the disappearing of the board layer structure.

In conclusion, our study demonstrated that maternal bile acid concentration is associated with fetal and amniotic fluid bile acid level. A maternal high blood bile acid level results in an increased fetal and amniotic bile acid level, which leads to a reduced synthesis of fetal pulmonary surfactant and delayed fetal lung development. High bile acid concentration has an increased perinatal morbidity and mortality. This study may help us to predict perinatal outcomes, to develop strategies improving the prenatal outcome, and to further study the mechanism of how fetal pulmonary AT-Ⅱ cells are affected. It calls attention to delayed maturation of fetal lungs in ICP patients and to take steps to carefully check and improve fetal pulmonary maturity.

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COMMENTS

Background

Intrahepatic cholestasis of pregnancy (ICP) can be complicated by fetal distress, neonatal asphyxia and neonatal respiratory distress syndrome. The etiology of ICP is poorly understood but the perinatal complications are closely correlated with maternal total bile acid (TBA) level. It is necessary to explore fetal lung alteration and development during ICP and its possible mechanisms affecting fetal pulmonary maturation.

Research frontiers

Lung development in ICP is a research hotspot since neonatal respiratory distress syndrome is a serious complication which is usually related to the immaturity of fetal lungs. Finding out the relationship of TBA concentration in maternal, fetal and amniotic fluid and its association with fetal surfactant, surfactant protein A, amniotic lamellar body and fetal lung development will help us to predict and improve perinatal outcomes. It calls clinical attention to delayed maturation of fetal lungs in ICP and to improve fetal pulmonary maturity.

Innovations and breakthroughs

Previous studies have found that high TBA can cause neonatal lung injury but its mechanism is not clear. In order to explore fetal lung alteration during ICP and its possible mechanisms, the authors investigated maternal and fetal TBA, fetal surfactant production, fetal surfactant protein level and fetal lung development. The study demonstrated that a maternal high blood bile acid level results in an increased fetal and amniotic bile acid level, which leads to a reduced synthesis of fetal pulmonary surfactant and delayed fetal lung development.

Applications

This study may help to predict perinatal outcomes, to develop strategies im-

proving the perinatal outcome, and to further study the mechanism of how fetal pulmonary AT-Ⅱ cells are affected. It calls attention to delayed maturation of fetal lungs in ICP patients and to take steps to carefully check and improve fetal pulmonary maturity.

Terminology

ICP: It is also called obstetric cholestasis, jaundice of pregnancy, or pruritus of pregnancy. It is a medical condition during pregnancy in which hepatic capillary bile duct silt. It typically presents with itching and can lead to complications for both mother and fetus. Pulmonary surfactant: It is a surface-active lipoprotein complex formed by type Ⅱ alveolar cells which reduces surface tension. Mature surfactant in the fetus is very important for neonates to start normal breathing after birth.

Peer review

The manuscript has new information on lung volume and levels of surfactant phospholipid and surfactant protein A in ICP. This information advances to understanding fetal lung injury in ICP.

REFERENCES

1 **Abedin P**, Weaver JB, Egginton E. Intrahepatic cholestasis of pregnancy: prevalence and ethnic distribution. *Ethn Health* 1999; **4**: 35-37 [PMID: 10887460 DOI: 10.1080/13557859998173]

2 **Zecca E**, De Luca D, Baroni S, Vento G, Tiberi E, Romagnoli C. Bile acid-induced lung injury in newborn infants: a bronchoalveolar lavage fluid study. *Pediatrics* 2008; **121**: e146-e149 [PMID: 18166532 DOI: 10.1542/peds.2007-1220]

3 **Pan C**, Perumalswami PV. Pregnancy-related liver diseases. *Clin Liver Dis* 2011; **15**: 199-208 [PMID: 21112001 DOI: 10.1016/j.cld.2010.09.007]

4 **Pathak B**, Sheibani L, Lee RH. Cholestasis of pregnancy. *Obstet Gynecol Clin North Am* 2010; **37**: 269-282 [PMID: 20685553 DOI: 10.1016/j.ogc.2010.02.011]

5 **Zecca E**, De Luca D, Marras M, Caruso A, Bernardini T, Romagnoli C. Intrahepatic cholestasis of pregnancy and neonatal respiratory distress syndrome. *Pediatrics* 2006; **117**: 1669-1672 [PMID: 16651322 DOI: 10.1542/peds.2005-1801]

6 **Rioseco AJ**, Ivankovic MB, Manzur A, Hamed F, Kato SR, Parer JT, Germain AM. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. *Am J Obstet Gynecol* 1994; **170**: 890-895 [PMID: 8141222 DOI: 10.1016/S0002-9378(94)70304-3]

7 **Savonius H**, Riikonen S, Gylling H, Haukkamaa M. Pregnancy outcome with intrahepatic cholestasis. *Acta Obstet Gynecol Scand* 2000; **79**: 323-325 [PMID: 10746851 DOI: 10.1080/j.1600-0412.2000.079004323.x]

8 **Feng YJ**, Shen J. Obstetrics and Gynecology. Beijing: People Health Press, 2011: 137-139

9 **Chaiworapongsa T**, Hong JS, Hull WM, Romero R, Whitsett JA. Amniotic fluid concentration of surfactant proteins in intra-amniotic infection. *J Matern Fetal Neonatal Med* 2008; **21**: 663-670 [PMID: 18828060 DOI: 10.1080/14767050802215664]

10 **Liang Q**, Zhou QC, Peng QH, Zhang M, Sun W, Cao DM, Ding YL. [Comparison of five different ultrasonographic parameters for diagnosis of lethal fetal pulmonary hypoplasia]. *Zhonghua Fu Chan Ke Zazhi* 2008; **43**: 332-335 [PMID: 18953864]

11 **Li MK**, Crawford JM. The pathology of cholestasis. *Semin Liver Dis* 2004; **24**: 21-42 [PMID: 15085484 DOI: 10.1055/s-2004-823099]

12 **Favre N**, Bourdel N, Sapin V, Abergel A, Gallot D. [Importance of bile acids for intra-hepatic cholestasis of pregnancy]. *Gynecol Obstet Fertil* 2010; **38**: 293-295 [PMID: 20363659 DOI: 10.1016/j.gyobfe.2010.02.011]

13 **Zhang XQ**, Ding YL, Zhang LJ. Why more attentions to fetus in cases of intrahepatic cholestasis of pregnancy? *World J Obstet Gynecol* 2013; **2**: 62-64 [DOI: 10.5317/wjog.v2.i4.62]

14 **Zhou L**, Qi HB, Luo X. [Analysis of clinical characteristics and perinatal outcome of early-onset intrahepatic cholestasis of pregnancy]. *Zhonghua Fu Chan Ke Zazhi* 2013; **48**: 20-24 [PMID: 23531246]

15 **Smolarczyk R**, Grymowicz M, Sienko J, Czajkowski K. Successful perinatal outcome in an early onset intrahepatic cholestasis of pregnancy with extremely high serum hepatic function tests. *Gynecol Endocrinol* 2009; **25**: 475-476 [PMID: 19499412 DOI: 10.1080/09513590902945147]

16 **Serrano MA**, Brites D, Larena MG, Monte MJ, Bravo MP, Oliveira N, Marin JJ. Beneficial effect of ursodeoxycholic acid on alterations induced by cholestasis of pregnancy in bile acid transport across the human placenta. *J Hepatol* 1998; **28**: 829-839 [PMID: 9625319 DOI: 10.1016/S0168-8278(98)80234-1]

17 **Howard PJ**, Murphy GM. Bile acid stress in the mother and baby unit. *Eur J Gastroenterol Hepatol* 2003; **15**: 317-321 [PMID: 12610328 DOI: 10.1097/00042737-200303000-00016]

18 **Ding YL**, Tang LL. [Stereological study on syncytial cell of human placenta and determinations of total bile acid in cord blood of intrahepatic cholestasis of pregnancy]. *Zhonghua Fu Chan Ke Zazhi* 2005; **40**: 453-456 [PMID: 16080870]

19 **Zecca E**, Costa S, Lauriola V, Vento G, Papacci P, Romagnoli C. Bile acid pneumonia: a "new" form of neonatal respiratory distress syndrome? *Pediatrics* 2004; **114**: 269-272 [PMID: 15231944]

20 **Henderson RD**, Fung K, Cullen JB, Milne EN, Marryatt G. Bile aspiration: an experimental study in rabbits. *Can J Surg* 1975; **18**: 64-69 [PMID: 235362]

21 **Grabowski M**, Kasran A, Seys S, Pauwels A, Medrala W, Dupont L, Panaszek B, Bullens D. Pepsin and bile acids in induced sputum of chronic cough patients. *Respir Med* 2011; **105**: 1257-1261 [PMID: 21592756 DOI: 10.1016/j.rmed.2011.04.015]

22 **Zecca E**, De Luca D, Barbato G, Marras M, Tiberi E, Romagnoli C. Predicting respiratory distress syndrome in neonates from mothers with intrahepatic cholestasis of pregnancy. *Early Hum Dev* 2008; **84**: 337-341 [PMID: 17928172 DOI: 10.1016/j.earlhumdev.2007.09.012]

23 **Gilson SD**, Stone EA. Sinus mucocele secondary to craniofacial trauma in a dog. *J Am Vet Med Assoc* 1991; **198**: 2100-2102 [PMID: 1885313 DOI: 10.1007/s00134-008-1321-3]

24 **Hills BA**, Chen Y, Masters IB, Hills YC. Raised bile acid concentrations in SIDS lungs at necropsy. *Arch Dis Child* 1997; **77**: 120-123 [PMID: 9301349 DOI: 10.1136/adc.77.2.120]

25 **Bersten AD**, Hunt T, Nicholas TE, Doyle IR. Elevated plasma surfactant protein-B predicts development of acute respiratory distress syndrome in patients with acute respiratory failure. *Am J Respir Crit Care Med* 2001; **164**: 648-652 [PMID: 11520731 DOI: 10.1164/ajrccm.164.4.2010111]

26 **Gnadt M**, Kardziev B, Schmidt M, Högger P. Surfactant protein A (SP-A) and angiotensin converting enzyme (ACE) as early biomarkers for pulmonary edema formation in ventilated human lung lobes. *Lung* 2012; **190**: 431-440 [PMID: 22466057 DOI: 10.1007/s00408-012-9386-8]

27 **Sone K**, Akiyoshi H, Shimizu J, Cao Z, Li Y, Tanaka T, Hayashi A, Sugii S, Ohashi F. Surfactant protein-A concentration in sera from dogs with pulmonary parenchymal diseases. *J Vet Med Sci* 2013; **75**: 685-691 [PMID: 23328605 DOI: 10.1292/jvms.12-0255]

28 **Mura M**, Binnie M, Han B, Li C, Andrade CF, Shiozaki A, Zhang Y, Ferrara N, Hwang D, Waddell TK, Keshavjee S, Liu M. Functions of type II pneumocyte-derived vascular endothelial growth factor in alveolar structure, acute inflammation, and vascular permeability. *Am J Pathol* 2010; **176**: 1725-1734 [PMID: 20167862 DOI: 10.2353/ajpath.2010.090209]

29 **Lucas R**, Verin AD, Black SM, Catravas JD. Regulators of endothelial and epithelial barrier integrity and function in acute lung injury. *Biochem Pharmacol* 2009; **77**: 1763-1772 [PMID: 19428331 DOI: 10.1016/j.bcp.2009.01.014]

30 **Zhang L**, Yu K, Robert KW, DeBolt KM, Hong N, Tao JQ,

Fukuda M, Fisher AB, Huang S. Rab38 targets to lamellar bodies and normalizes their sizes in lung alveolar type II epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2011; **301**: L461-L477 [PMID: 21764986 DOI: 10.1152/ajplung.00056.2011]

31 **Lockwood CM**, Crompton JC, Riley JK, Landeros K, Dietzen DJ, Grenache DG, Gronowski AM. Validation of lamellar body counts using three hematology analyzers. *Am J Clin Pathol* 2010; **134**: 420-428 [PMID: 20716798 DOI: 10.1309/AJCPWEUIM2CWUOV8]

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OBSERVATIONAL STUDY

Simulation training in contemporary obstetrics education

Pooja Doehrman, Laurie Erickson, Kylie Galfione, Briggs Geier, Kanav Kahol, Aaron Ashby

Pooja Doehrman, Laurie Erickson, Kylie Galfione, Briggs Geier, OB/GYN, Residency Banner Good Samaritan Medical Center, Phoenix, AZ 85006, United States
Kanav Kahol, Aaron Ashby, Department of Simulation Educational and Training Center, Banner Good Samaritan Medical Center, Phoenix, AZ 85006, United States
Author contributions: Erickson L, Galfione K and Geier B designed the simulation course, and design of the study; Kahol K and Ashby A assisted with running the experiment, management of the simulation equipment and collection of the audio visual data; Doehrman P performed the statistical analysis, drafted and edited the manuscript with the assistance of the above authors.
Correspondence to: Pooja Doehrman, MD, MPH, OB/GYN, Residency Banner Good Samaritan Medical Center, 1111 E. McDowell Road, Phoenix, AZ 85006,
United States. poojadeb@gmail.com
Telephone: +1-602-8392687 Fax: +1-602-8392359
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Abstract

AIM: To investigate the use of the Gaumard's Noelle S550.100 Maternal and Neonatal Simulators for teaching forceps delivery.

METHODS: Twenty two (n = 22) resident physicians were enrolled in a simulation course on operative forceps deliveries. The physicians enrolled in the course were all part of an accredited Obstetrics and Gynecology residency program and ranged in their training from post graduate year (PGY) 1-4. Each participant received simulation based teaching on the indications, contraindications, proper application, delivery and removal of forceps by a single teacher. The Gaumard's simulator and Simpson forceps were used for this course. Statistical analysis using SPSS statistical software was performed after the completion of the simulation training program. A paired student t-test was performed to compare the cohort's mean pretest and post simulation training scores. Follow up skills assessment scores at one month, 3 mo and 6 mo were compared to the baseline pretest score using a paired student t-test.

RESULTS: There was statistically significant improvement in the post simulation training performance evaluations compared to the pretest, 13.7 (SD = 3.14) *vs* 7.9 (SD = 4.92), $P < 0.05$. Scores at 1 mo, 3 mo, and 6 mo were compared to the pretest score and showed retention of skills: 4.6 (SD = 5.5, 95%CI: 2.21-7.07), 4.4 (SD = 5.2, 95%CI: 2.13-6.70), and 5.6 (SD = 4.8, 95%CI: 3.53-7.75) points, respectively. There were statistically significant differences between residents by post graduate training year on pretest scores, however these differences were not present after simulation training. Pretest scores for PGY 1, 2, 3, 4 were 3.5 (SD = 2.27, 95%CI: 2.13-5.00), 7.25 (SD = 6.70, 95%CI: 1.50-13.00), 10.75 (SD = 1.5, 95%CI: 9.50-12.00), 12.17 (SD = 2.57, 95%CI: 10.33-14.00). After simulation training PGY 1 residents did as well as well as the upper level residents. Posttest mean test scores for PGY 1, 2, 3, 4 were 13.75 (SD = 1.49, 95%CI: 12.75-14.63), 10.25 (SD = 0.24, 95%CI: 4.25-14.00), 15.00 (SD = 1.16, 95%CI: 14.00-16.00), 15.17 (SD = 0.75, 95%CI: 14.67-15.67).

CONCLUSION: Our simulation based training program not only produced short term gains, but participants were able to retain the skills learned and demonstrate their knowledge months later.

Key words: Simulation; Education; Forceps; Delivery; Labor

Core tip: In this article the authors investigated the use of the Gaumard's Noelle S550.100 Maternal and Neonatal Simulators for teaching forceps delivery. They describe the process of developing a simulation program, application, and evaluation at Banner Good Samaritan Medical Center. The intervention was successful in teaching resident physicians the steps of application, delivery and removal in forceps operative delivery. The authors hope is that their method may be applied in

development of a variety of simulation based programs to improved education in obstetrics.

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INTRODUCTION

As rapid technologic growth expands the skills set of graduating residents in obstetrics and gynecology (ob/gyn) in the areas of minimally invasive surgery, there is a profound loss of basic skills in operative delivery. The current average number forceps deliveries for graduating ob/gyn residents are below what is necessary to be proficient in this invaluable skill. The average ob/gyn resident has performed 6 forceps assisted operative vaginal deliveries, compared to 120 laparoscopic surgeries[1]. As the use of forceps decline, cesarean sections and the associated complications are more prevalent than ever. Cesarean sections account for over one third of deliveries performed each year and outnumber operative vaginal deliveries by three to one. In 2007, cesarean sections were at an all-time high at 32%[2,3]. Cesarean delivery involves major abdominal surgery, and is associated with higher rates of maternal and neonatal complications compared with vaginal birth[4,5]. The rates of cesarean sections vary widely depending on geographic region, and some authors argue this is due to a regional lack of skilled providers in operative vaginal delivery[6].

The residency program at Banner Good Samaritan Medical Center was keenly aware of this trend as their own residents experienced decreasing numbers of real life forceps deliveries. Simulation training was presented as a viable solution to providing graduate medical training in forceps delivery without effecting patient safety.

Other surgical specialties have harnessed the power of simulation to provide residents with a foundation of skills prior to performing procedures on live patients[7]. This is particularly important for emergency situations and high stress surgical scenarios[7,8]. General surgeons have developed simulation courses based on proven techniques for teaching fundamental laparoscopic skills. The strength of these courses is in providing residents experience performing skills in the safety of the simulation lab where failures of efficiency can be overcome without effecting patient care. Furthermore, simulation training provides equality in resident training as it is not dependent on the chance of exposure to surgical emergencies.

The existence of the Simulation Education and Training Center at Banner Good Samaritan Medical Center was a critical factor in the creation of this program. Opened in 2006, this 6000 square foot, two million dollar facility has trained 5000 health care professional. The aim of this program was to evaluate the use of the Gaumard's Noelle S550.100 Maternal and Neonatal Simulators in the development of a forceps simulation program for training residents in obstetrics and gynecology.

MATERIALS AND METHODS

Study design

Resident physicians in obstetrics and gynecology from a single center participated in simulation training as part of their education in operative delivery techniques. Their performance before and after training was recorded to evaluate and improve forceps training for resident physicians. Initially, 25 residents chose to participate, with only 3 unable to complete the course. The residents were divided into five groups. Participants were first able to perform a simulated forceps delivery and given a pretest score on their performance based on a specific checklist (Figure 1). Each group then received simulation based teaching on the indications, contraindications, proper application, delivery and removal of forceps by a single teacher. A posttest was then administered using the same assessment checklist to evaluate their forceps delivery skills. Video recordings of the 22 residents were obtained at their 1 mo, 3 mo, and 6 mo follow up assessments.

Sixteen steps were identified as critical aspects for forceps application and delivery based on Dennen's Forceps Deliveries, 3rd Ed[9]. The steps were reviewed by six independent board certified physicians in obstetrics and gynecology from the Department of Obstetrics and Gynecology at Banner Good Samaritan Medical Center. The steps were rated in terms of importance and weighted averages calculated to gauge if any steps should be excluded from the assessment or tutorial.

The same checklist was used for each of the evaluations. A blinded scorer was used to grade each anonymous video recording. The physician scoring each video was unaware of the resident's identity, as well as their year of post graduate training to limit bias. Residents were gowned and gloved in the video to hide their identity. A second evaluator reviewed all of the follow up videos to establish reliability of the score assessment tool. Both evaluators were board certified in obstetrics and gynecology for over 10 years and routinely performed forceps deliveries at a large tertiary care center. Both evaluators had performed over 100 forceps deliveries and had experience evaluating resident performance in operative deliveries for over 10 years.

Simulation training

The decision was made to teach the following steps for placement of the first blade: identifying fetal position, orientation of the forceps, choice of first blade, application of the first blade in the vertical position, use of the vaginal hand to guide placement of the first blade, advancement of the blade into the horizontal position along the opposite thigh.

Steps for placing the second blade included: starting

Name_____
Date _____
Date _____
Date _____

	Pre	Post	1 mo	3 mo	6 mo
Chose appropriate type of forceps					
Correctly identified position of vtx					
Chose correct first blade for placement					
Started vertically					
Proper vaginal hand placement					
Proper upper hand placement					
Brought forcep out along thigh					
Started vertically with second blade					
Proper vaginal hand placement-second					
Proper upper hand placement					
Brought forcep out along thigh-second					
Verified correct placement-post fontanelle					
Verified correct placement-sagital suture					
Verified correct placement-blades					
Correct hand positioning for traction					
Appropriate traction direction					
Appropriate removal of forceps					

Figure 1 Checklist for pretest and posttest.

in the vertical position, placement of vaginal hand to guide blade, and advancing blade from vertical to horizontal along the opposite thigh.

Additional steps included, checking the placement of the forceps on the neonatal head by feeling for the posterior fontanel and sagittal suture. Finally, steps for delivery included correct hand position for traction and appropriate removal.

Examples of the steps in forceps application and desired hand positions are illustrated in Figure 2.

Statistical analysis

Statistical analysis using SPSS statistical software was performed after the completion of the simulation training program. A paired student *t*-test was performed to compare the cohort's mean pretest and post simulation scores. Follow up skills assessment scores at 1 mo, 3 mo and 6 mo were compared to the baseline pretest score using a paired student *t*-test.

RESULTS

Inter-rater reliability was investigated by calculating the Pearson correlation coefficient. This provided evidence on the reliability of the testing instrument itself. Pearson correlation between evaluator one and two was 0.7 ($P < 0.001$).

The pretests were compared to posttest scores for the 22 participants who complete the simulation curriculum. There was statistically significant improvement in the post simulation training performance evaluations compared to the pretest, 13.7 (SD = 3.14) *vs* 7.9 (SD = 4.92), $P < 0.05$. Scores at one month, three months, and six months were compared to the pretest score and showed retention of skills (Figure 3). The difference between pretest and follow up scores at one month, three month and six month were: 4.6 (SD = 5.5, 95%CI: 2.21-7.07), 4.4 (SD = 5.2, 95%CI: 2.13-6.70), and 5.6 (SD = 4.8, 95%CI: 3.53-7.75) points, respectively (Table 1).

There were statistically significant differences between residents by post graduate training year on pretest scores, however these differences were not present after simulation training. Pretest scores for PGY 1, 2, 3, 4 were 3.5 (SD = 2.27, 95%CI: 2.13-5.00), 7.25 (SD = 6.70, 95%CI: 1.50-13.00), 10.75 (SD = 1.5, 95%CI: 9.50-12.00), 12.17 (SD = 2.57, 95%CI: 10.33-14.00). PGY 1 residents as a group scored lower compared with PGY 2, 3, and 4. After simulation training PGY 1 residents did as well as well as the upper level residents. Posttest mean test scores for PGY 1, 2, 3, 4 were 13.75 (SD = 1.49, 95%CI: 12.75-14.63), 10.25 (SD = 0.24, 95%CI: 4.25-14.00), 15.00 (SD = 1.16, 95%CI: 14.00-16.00), 15.17 (SD = 0.75, 95%CI: 14.67-15.67).

Increased year of resident training had a statistically significant association with higher pretest skills assessment scores, (Pearson correlation = 0.637, $P = 0.001$). However, after simulation training there was no difference in skills assessment scores among resident based on year of training with forceps delivery.

DISCUSSION

Simulation training offers a solution to the problem of declining resident exposure to forceps operative deliveries nationally. Our simulation based training program not only produced short term gains, but residents were able to retain the skills learned and demonstrate their knowledge months later. Analysis of pretest scores showed an association between forceps skills and year of training, with improved scores with increased year of post graduate year. However, after simulation training this association no longer exists. Considering, clinical experience

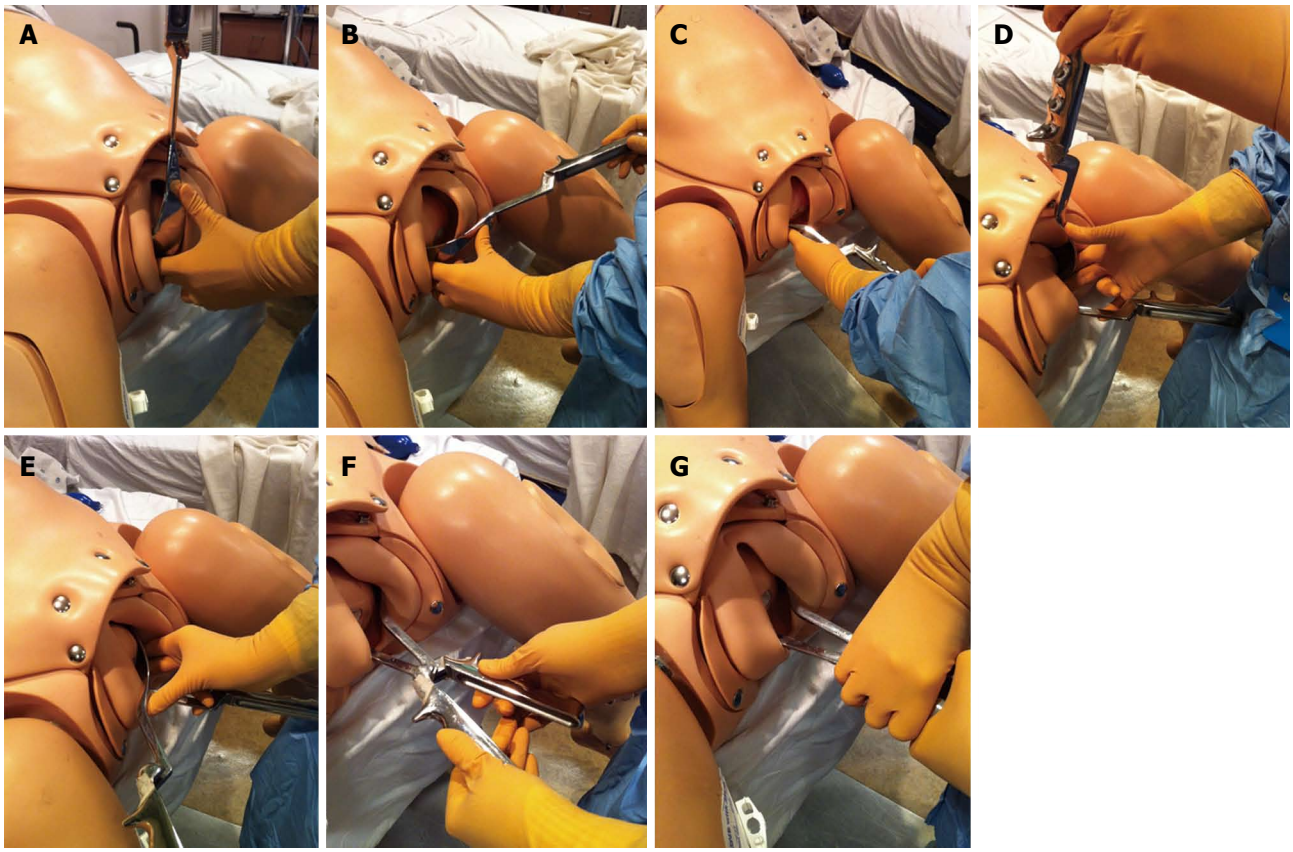

Figure 2 Examples of the steps in forceps application and desired. A: The vertical application of the first blade of closed Simpson forceps; B: Position of the vaginal hand used to guide the first blade; C: Rotation of the handle of the blade to the horizontal position along the opposite thigh; D: Application of the second blade starting in the vertical position; E: Position of the vaginal hand in order to direct the placement of the second blade; F: Lock forceps in the correct orientation; G: Placement of hands and direction of traction.

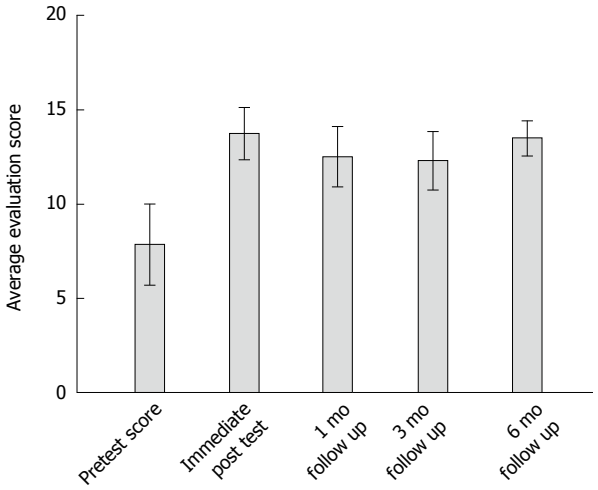

Figure 3 Average residency scores on forceps application skills before and after simulation training. Error bars: 95%CI.

with forceps generally increases by year of training, our study suggests that these differences in real life experience may be overcome by simulation training. Simulation training has the potential for providing the necessary experience resident physicians need in adjunct with real life experience to produce qualified obstetricians with the necessary skills to perform operative deliveries independently.

The Gaumard's Noelle S550.100 Maternal and Neonatal Simulators was limited in its ability to replicate a forceps delivery. The anatomy of a real fetal skull, specifically the contours if the maxillary bone, provide the points of articulation for the forceps instrument. The Noelle S550.100 Neonatal Simulator did not have the same cranial bone structure and thus the forceps frequently slipped or became misplaced during the delivery. Therefore, the trainees in this study were only expected to apply the forceps correctly and demonstrate the correct plane of traction. The residents were not expected to complete the delivery due to the limitations of the simulator. The maternal simulator in contrast had very realistic anatomy; fetal station could correctly be identified by palpation of the ischial spines just as in a live patient.

Another limitation of this program is the lack of data collected on the effect of simulation training on resident performance in real life settings. An opportunity for further program evaluation includes follow up surveys to assess if simulation training increased resident confidence and likeliness to perform forceps deliveries when in practice. Twenty percent of the residents who took part in this program are now in practice and their feedback on whether or not they routinely perform forceps deliveries would provide important follow up data to support con-

Table 1 Comparison of the difference between pretest, posttest and follow up assessments

	Paired differences					*t*	*df*	Sig. (2-tailed)
	Mean	SD	SEM	95%CI of the difference				
				Lower	Upper			
Pretest-immediate posttest	-5.864	4.357	0.929	-7.795	-3.932	-6.313	21	0.000
Pretest-one month follow up	-4.636	5.482	1.169	-7.067	-2.206	-3.967	21	0.001
Pretest-post 3 mo	-4.409	5.152	1.098	-6.693	-2.125	-4.014	21	0.001
Pretest-post 6 mo	-5.636	4.756	1.014	-7.745	-3.527	-5.558	21	0.000

tinued simulation education.

Additionally, research opportunities to further investigate the effect of simulation training on resident performance in real life settings would include a prospective study with assessment of real life operative delivery skills assessments before and after simulation training.

COMMENTS

Background

The current average number forceps deliveries for graduating ob/gyn residents are below what is necessary to be proficient in this invaluable skill. Cesarean sections account for over one third of deliveries performed each year. Cesarean delivery involves major abdominal surgery, and is associated with higher rates of maternal and neonatal complications compared with vaginal birth. The rates of cesarean sections vary widely depending on geographic region, and some authors argue this is due to a regional lack of skilled providers in operative vaginal delivery. Simulation training is a viable solution to providing graduate medical training in forceps delivery without effecting patient safety.

Research frontiers

There are increasing demands on the health care system to adhere to the highest standards of safety and cost efficiency. Additionally, new changes to the Accreditation Council for Graduate Medical Education restrictions on resident work hours creates further challenges to garnering the necessary skills in operative delivery. The power of simulation has been harnessed by varies surgical specialties to provide residents with a foundation of skills prior to performing procedures on live patients.

Innovations and breakthroughs

Simulation training is particularly important for emergency situations and high stress surgical scenarios. General surgeons have developed simulation courses based on proven techniques for teaching fundamental laparoscopic skills. The strength of these courses is in providing residents experience performing skills in the safety of the simulation lab where failures of efficiency can be overcome without effecting patient care. Furthermore, simulation training provides equality in resident training as it is not dependent on the chance of exposure to surgical emergencies.

Applications

This study suggests that simulation training may provide the needed training in forceps deliveries that are required for residents in obstetrics and gynecology to be proficient in these skills.

Terminology

Forceps are tools used to assist in the second stage of labor for a variety of indications, such as: arrest of descent, prolonged second stage, maternal exhaustion, pr concerning fetal heart tracings. The second stage of labor is defined as the periods of labor after complete cervical dilation during which time the fetus passes through the pelvis, but prior to expulsion.

Peer review

This is a well-designed observational study in which resident physicians participated in a simulation course on operative forceps deliveries, before and after assessment were performed. The findings demonstrate the potential utility of simulation training to provide experience and technical skills that are not readily available in real life settings. These methods may be beneficial for teaching a variety of obstetrical skills that may in the future improve the health of mothers and children.

REFERENCES

1 Accreditation Council for Graduate Medical Education. Obstetrics and Gynecology Case Logs National Data Report. Department of Applications and Data Analysis, 2010

2 **American College of Obstetricians and Gynecologists**. Operative vaginal delivery. ACOG Practice Bulletin number 17, Washington, DC: American College of Obstetricians and Gynecologists, 2000

3 **Hamilton BE**, Martin JA, Ventura SJ. Births: Prelimimary data for 2007. National vital statistics reports. Hyattsville, MD: National Center for Health Statistics, 2009: 12

4 **Yang Q**, Wen SW, Oppenheimer L, Chen XK, Black D, Gao J, Walker MC. Association of caesarean delivery for first birth with placenta praevia and placental abruption in second pregnancy. *BJOG* 2007; **114**: 609-613 [PMID: 17355267 DOI: 10.1111/j.1471-0528.2007.01295.x]

5 **Liston FA**, Allen VM, O'Connell CM, Jangaard KA. Neonatal outcomes with caesarean delivery at term. *Arch Dis Child Fetal Neonatal Ed* 2008; **93**: F176-F182 [PMID: 17942582 DOI: 10.1136/adc.2006.112565]

6 **Sinha P**, Langford K. Forceps delivery in 21st century obstetrics. *J Gynecol Obstet* 2009; **11**: 2

7 **Brindley PG**, Jones DB, Grantcharov T, de Gara C. Canadian Association of University Surgeons' Annual Symposium. Surgical simulation: the solution to safe training or a promise unfulfilled? *Can J Surg* 2012; **55**: S200-S206 [PMID: 22854147 DOI: 10.1503/cjs.027910]

8 **Maschuw K**, Schlosser K, Kupietz E, Slater EP, Weyers P, Hassan I. Do soft skills predict surgical performance?: a single-center randomized controlled trial evaluating predictors of skill acquisition in virtual reality laparoscopy. *World J Surg* 2011; **35**: 480-486 [PMID: 21190109 DOI: 10.1007/s00268-010-0933-2]

9 **Hale RW**, Dennen EH. Dennen's Forceps Deliveries. Washington: American College of Obstetricians and Gynecologists, 2001. Available from: URL: http://vufind.carli.illinois.edu/vf-uic/Record/uic_1600186

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In press

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Organization as author

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Volume with supplement

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Books

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Chapter in a book (list all authors)

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Author(s) and editor(s)

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Conference proceedings

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Conference paper

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Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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