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Fertility Preservation: Exploring New Horizons in Gynaecological Malignancy

Alka B Patil, Richa Priyanka Mishra

Abstract

Fertility sparing in gynecological malignancies; what was impossible or the dream of yesterday, is the hope of today and the reality of tomorrow. Motherhood is dream of every woman. When engulfed by monster of cancer,it is saddest aspect of their life. The intuitive fertility sparing options are the sacred gifts for these shattered lives. Preservation of fertility has recently become a very important objective in gynecological oncology. Oncological advances with the paragons of objectivity, a clear decision-making process, adequate counseling about the future oncological and obstetrical risks and benefits, appropriate management, and careful follow-up within a multidisciplinary approach provides beam of hope to these women. Given the increases in 5-year cancer survival and recent advances in fertility preserving technologies, an increasing number of women with cancer are presenting for discussion of fertility preserving options [1]. This applies particularly for women who develop gynecological malignancy during their childbearing years where curative treatment also renders them infertile[2]. This study reviews the increasing role of fertility-sparing modalities in such women with cervical, endometrial and ovarian cancer. Fertility preserving methods have psychological, ethical and legal aspects that should be fully discussed.

Keywords: *Fertility sparing; Cervical Cancer; Endometrial cancer; Ovarian cancer; Ethical issue.*

Deptt of Obst and Gynaec
A.C.P.M Medical College, Dhule, Maharashtra
Alka B Patil, Prof and Head

Deptt of Obst and Gynaec
A.C.P.M Medical College, Dhule, Maharashtra
Richa Priyanka Mishra

Correspondence to:
Alka B Patil, Prof and Head, E-mail: alkabpatil@rediffmail.com

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Introduction

In recent years, fertility-sparing surgery has been arousing growing interest, with particular regard for young patients with gynaecological cancers, On the other hand, progress in improving reproductive function in patients with gynaecological malignancies has been made owing to advances;not only in surgical techniques, but also in combined fertility treatment [3]. Never before have women with newly diagnosed gynecologic malignancies had more options for preservation of fertility [4]. This current trends are based principally on our understanding of the biological behavior, histopathology, prognostic factors, epidemiology, molecular biology and natural history. Fertility preservation is a rapidly evolving field that includes medical and surgical treatments to decrease the impact of cancer treatments on future fertility ·This includes fertility preserving surgery and the use of less toxic chemotherapeutic agents for short duration. In addition, advances in assisted reproductive technology and cryotechnology provide a realistic hope for women facing premature menopause secondary to cancer treatment. Newer techniques to preserve ovarian reserve, oocytes, and embryos prior to cancer treatments have been developed to provide an opportunity to conceive in the event that cancer treatments result in permanent loss of ovarian function [1].

There are several important facts that need to be considered before offering these women with fertility sparing surgical options. Firstly, there must be a strong desire on the part of the patient or in the case of a child, of her parents to retain fertility. Secondly, fertility should be preserved without compromising the oncological safety; thereby 'optimal cancer therapy should always supersede fertility preservation as a primary objective'. Thirdly, patients should be told that data on fertility sparing procedures are limited and that many of these options are of an experimental, non-standard nature. When one considers these important facts, the number of young patients who may be candidates for the fertility preserving options get limited[5]. The extent of the patient's cancer is a major determinant of whether fertility-sparing surgery should be recommended.

The care of women with gynecological cancers is both challenging and complex, and requires a full understanding of the procedures available, if we are to improve the overall quality of life for these women. Fertility-saving surgery requires highly skilled gynecological oncologists. These women therefore need to be managed in specialist cancer centers[6] .

Learning objectives:

- To be able to identify the different fertility-saving surgical options for women diagnosed with cervical, endometrial and ovarian cancer.
- To understand the advantages and limitations of fertility-saving surgery in women with gynaecological malignancy.
- To understand that fertility-saving surgery is not appropriate in all cases.

We performed a literature search using the keywords fertility preservation, cervical cancer, endometrial cancer, uterine cancer, ovarian cancer and ethical issues, in Medline, PUBMED. Each relevant identified paper was reviewed, references checked and results collated to provide an evidence-based summary of fertility-sparing treatments for gynecological malignancy.

Cervical Cancer

Worldwide, cervical cancer ranks as the third most common cancer in women, accounting for up to 13% of all female cancers [7]. Approximately 15% of all cervical cancers and 45% of surgically treated upto stage I b cancers occur in women under 40 years of age. These women represent the subset of patients who are candidates for fertility preservation, if they are identified as having a low risk of recurrence and a low risk of lymph-node involvement. Over the past decade, the treatment of cervical cancer has evolved with an increased emphasis on preservation of fertility. There has been a gradual abandonment of radical surgical procedures in favour of more conservative techniques in an effort to decrease morbidity and preserve fertility without compromising overall survival [8].

Until relatively recently, early-stage cervical cancer was surgically treated with radical hysterectomy, removing the parametrium and upper vagina along with the uterus, cervix and pelvic lymph nodes. This procedure was first performed by Ernst Wertheim in 1898. The rationale for this extensive surgery was to remove surrounding tissues according to patterns of spread. Despite morbidities such as bladder and bowel dysfunction, neuropathy, fistula, haematoma or abscess formation, five-year disease-free survival can be expected in 85–95% of women. As the median age of cervical cancer diagnosis is 40 years of age, however, for many young women these survival rates in the past have come at the cost of future fertility. In an effort to preserve fertility, Dargent proposed an alternative to radical hysterectomy. In 1994 he published information on his first series of patients treated with radical vaginal trachelectomy and laparoscopic pelvic lymphadenectomy[7].

Conisation for Stage IA1 Cervical Cancer

Cervical conization (cone biopsy) refers to the excision of a cone shaped portion of the cervix surrounding the endocervical canal and including the entire transformation zone. This can be performed using a scalpel, laser, or

electrosurgery (LEEP/LLETZ). The International Federation of Gynecology and Obstetrics (FIGO) defines stage IA1 squamous cell carcinoma (SCC) of the cervix as when the stromal invasion is <3mm in depth and the horizontal extension is <7mm. In women anxious to remain fertile, conisation of the cervix is an option, provided the surgical margins are free of dysplasia or invasive disease with no lymphovascular space involvement or positive lymph nodes.

Conization is an appropriate management for patients with FIGO stage IA1 with no lymphovascular space invasion (LVSI). Residual microinvasive cancers have been reported in 5% of patients and the risk factors identified include positive margins and positive endocervical curettings. But In the largest study done till date involving 200 patients, no patient developed any recurrence over a follow up period of (72-420) months[5,9].

Radical vaginal trachelectomy.

Radical vaginal trachelectomy (RVT) with laparoscopic pelvic lymphadenectomy is a fertility-preserving procedure that has recently gained worldwide acceptance as a method of surgically treating small invasive cancers of the cervix. RVT was first described by Daniel Dargent in 1994 and involves the removal of most, if not all, of the cervix, its contiguous parametrium, and vaginal cuff, in addition to a laparoscopic pelvic lymphadenectomy. Since RVT's original description, over 500 cases of utilization of this technique have been reported in the literature, with over 100 live births reported following this procedure. An understanding of how cervical cancer spreads is helpful so that the uterus might be spared for future childbearing. Cervical cancer tends to spread laterally from the cervix into the parametrium and inferiorly to the upper vagina. This cancer very seldom has a propensity to spread superiorly into the uterus in small stage IB cervical cancers. Consequently, in women with small stage IB tumors the removal of the cervix, contiguous parametrium and vagina (similar to removal in a radical hysterectomy) should be equally efficacious as a radical hysterectomy. This less invasive surgical approach, however, leaves the fundus of the uterus intact to allow conception and the carrying of a pregnancy to term[8].

Endometrial Cancer

Endometrial cancer is primarily a disease of postmenopausal women, although 25% of these cancers occur in premenopausal patients and 5% occur in patients younger than 40 years[17]. In the young women, the adenocarcinoma is usually a well differentiated, endometrioid type lesion, associated with minimal myometrial invasion, early-stage disease and good prognosis. .

These young women, particularly the infertile patients, present a therapeutic dilemma. The mainstay of therapy for endometrial cancer is the surgical removal of tumor . In the majority of cases this is achieved by total abdominal hysterectomy and bilateral salpingoophorectomy. The role of diagnostic and therapeutic lymphadenectomy is currently the subject of debate. The role of adjuvant postoperative radiation in the management of operable EC remains unresolved, though it is routinely performed in many centers. However, young, nulliparous women will lose any chance for future pregnancy by this treatment approach. Endometrial cancer is considered to be a hormone dependent tumor[18].

Young patients who develop endometrial cancer usually have risk factors that are related to unopposed estrogen stimulation. Thus, primary hormonal therapy with progesterone, as an alternative treatment for surgery, offers them the only option to preserve their fertility. There is no uniform established drug regimen or dose of progestogens. Table below summarises the results in the published literature, many successful pregnancies after subsequent fertility treatment.

Ovarian Cancer

Epithelial ovarian cancer (EOC)

Epithelial ovarian cancer (EOC) continues to represent a lethal condition which commonly affects women in a multifocal and peritoneal metastasized fashion. Attributed to a special tumor biology and large heterogeneity, clinical outcomes in EOC vary broadly and although significantly associated with an adequate systemic and operative treatment.

With the constant shifting of childbearing age towards higher ages, the increasing incidence of EOC in women with active childbearing potential constitutes a therapeutic dilemma. Both patients and treating physicians are being encountered with the abrupt loss of childbearing potential due to the malignant disease, while alternatives are being sought that try to preserve a last hope of fertility with the antitumor treatment[24].

Borderline ovarian cancer

Ovarian tumour is defined as borderline when atypical epithelial proliferation without stromal invasion is observed histopathologically. It is also called a low-malignant-potential (LMP) tumour and represents 10% of ovarian neoplasms. The highest frequency of these tumours is in the 15–29-year-old age group, and 70% of borderline tumours are diagnosed at FIGO stage I, are limited to one ovary and carry an excellent prognosis, with five-year survival of 99% [9].

Germ-cell Tumours

Germ cell tumours of the ovary are uncommon but occur primarily in young women in their late teens and early 20s[2]. They represent 70% of ovarian tumours in this age group and are highly malignant. These tumours grow rapidly and are usually symptomatic. Diagnosis can be made at an early stage and most patients present with stage IA disease. Surgery is essential for diagnosis and proper staging. Most patients can be treated by unilateral salpingo-oophorectomy. They should receive adjuvant chemotherapy except those with stage I dysgerminoma and well-differentiated stage I immature teratoma. These tumours produce tumour markers, including alpha-fetoprotein, lactate dehydrogenase and human chorionic gonadotropin, which can be used to monitor the response to chemotherapy and for subsequent follow-up[9].

Sex Cord-stromal Tumours

Sex cord-stromal tumours are low malignant potential neoplasia that develop from the cells surrounding the oocytes, and represent 5–8% of all primary ovarian neoplasms. Most of these tumours secrete oestrogen or androgen. Clinical manifestations include precocious puberty, abnormal uterine bleeding or virilisation[9].

15% of the ovarian cancers occur in young women, some of whom may want to preserve their reproductive potential. The sub-categories of patients who are appropriate for such management include those with:

a) Tumors of low malignant potential
b) Stage-Ia invasive epithelial ovarian cancer with nonclear cell histology, (grade I and II)
c) Malignant germ cell tumors
d) Malignant sex cord stromal tumor.

Fertility sparing surgical options for them include ovarian cystectomy, unilateral salpingoophorectomy, unilateral salpingo-ophorectomyplus hysterectomy (with preservation of contralateral ovary) and bilateral salpingoophorectomy (with preservation of the uterus). In the latter two procedures assisted reproductive technology (ART) is necessary to achieve pregnancy. A comprehensive surgical staging should always be performed in conjunction with these procedures[5].

Fertility saving surgery for ovarian neoplasms have been traditionally adopted in early-stage malignant ovarian germ cell tumors and in ovarian sex cord-stromal tumors such as granulosa-cell tumors, Sertoli-Leydig cell tumors, ovarian dysgerminomas, as well as in

borderline tumors of the ovary, with excellent reproductive outcomes without compromising oncologic safety. Gold standard remains however hereby an adequate operative staging in order to unmask occult advanced disease with therapeutic consequences and impact on overall prognosis[24].

Assisted reproduction: The Role of the Reproductive Centres

There will be a number of women who, despite having undergone fertility-saving surgery, will have some evidence of subfertility. These women will need infertility treatment to conceive. Assisted reproduction techniques have been used to achieve this. Intracytoplasmic sperm injection, in vitro fertilisation and cryopreservation of the embryo, oocytes and ovarian tissue have all been used successfully to achieve pregnancy in women following treatment for gynaecological malignancy. However, a concern regarding assisted reproduction techniques is that women have to undergo hormonal manipulation. This may be inappropriate in endometrial cancer, where the aetiology is hormone-related, or in ovarian tumours where ovarian stimulation may increase the risk of new tumour.

Ovarian transposition

In women undergoing pelvic radiation, one can offer ovarian suspension or transposition. This procedure can be performed bylaparoscopy. The ovaries are re-located at least 3cm from the uppermargin of the radiation field. The fallopian tubes are not separate from the uterus to allow the possibility of spontaneous conception at the same setting; ovarian wedge resection is also performed for cryopreservation. In women less than 40 years of age, ovarian transposition is associated with preservation of ovarian function in 88.6% of cases[9].

Cryopreservation of Ovarian Tissue, Oocytes or Embryos

Cryopreservation of ovarian tissue or oocytes is an option for women without partners who do not opt to use donor oocytes. One can freeze the oocytes at the mature or immature stages. A promising alternative for fertility preservation is collection of immature oocytes followed by *in vitro* maturation (IVM) and vitrification of the *in vitro* matured oocytes. In any event, the best established method for fertility preservation is *in vitro* fertilisation (IVF) followed by embryo cryopreservation[9].

Table 1: Obstetric Outcome After Radical Trachelectomy for Cervical Cancer

Author	Number of Patients	Pregnancy	Miscarriage	Pre-term Delivery	Term Pregnancy	Live Births
Shepherd et al [10]	123	55	14	20	8	28
Hertel et al [11]	108	18	1	NA	NA	12
Plante et al [12]	125	106	19	8	58	66
Dargent et al [13]	47	25	12	-	13	13
Coven et al [14]	32	5	2	-	3	3
Schlareth et al [15]	12	4	2	2	NA	2
Burnett et al [16]	21	3	1	Twins	1	3

Ovarian tissue cryopreservation

Compared with oocyte or embryo cryopreservation, ovarian tissue cryopreservation has some advantages. These include the availability of thousands of oocytes in the ovarian cortex, and one can excise the ovary at the time of cancer surgery. However, it needs a surgical procedure for excision and another to transplant the frozen-thawed ovarian tissue. Furthermore, the transplant recipients should undergo ovarian stimulation with gonadotropin to produce mature oocytes. To date, there have been only a few pregnancies and live births following ovarian transplantation of frozen-thawed ovarian tissue[9].

Ethical issues: the dilemma, balancing cancer and fertility

The intersection of cancer and reproduction raises ethical issues for both cancer and fertility specialists, including issues of experimental vs. established therapies, the ability of minors to give consent, the welfare of expected children, and posthumous reproduction. In some respects cancer-related infertility is not markedly different than other kinds of infertility. A diagnosis of cancer is a life crisis for any person. Its impact varies with the type of cancer; treatment prospects; and the physical, emotional, and social resources of the patient. Younger persons face the additional potential loss of reproductive function and the opportunity to have children.

- Long-term follow-up data on some methods of fertility-saving surgery are limited and, therefore, women may be compromising their survival to preserve fertility.
- Treatments that save fertility may result in other morbidities such as premature delivery[25].

Psychological implications

The psychological impact of the diagnosis of cancer prior to pregnancy is expressed at several levels, requiring differentiated and specialized psychological care. The social and psychological implications of a high-risk pregnancy may be even more significant. Intensive testing, lengthy hospitalizations, prolonged bed rest at home, illness or disability superimposed on pregnancy, realistic fears for personal safety and the life of the unborn child, and a greater risk of being separated from the newborn child pose numerous additional challenges. The normal emotional changes in pregnancy may also be intensified. Emotional support and counseling are useful at the diagnosis stage to avoid the traumatic impact that diagnosis may have. Promoting the ventilation of emotions and the cessation of associated intrusive thoughts may contribute to fostering women's psychological adjustment. Revising life goals and lifestyle and activating support networks are also important[26].

Table 2: A summary of the published series reporting medical management of endometrial cancer

Author	No. of patients	Initial response	Relapse	Progestin type and dose	Live births
Kaku*et al*[19]	12	9	2	MPA: 200–800 mg daily	1
Randall and Kurman[20]	12	9	0	Megestrol acetate: 40–160 mg daily	5
Wang *et al.*[21]	9	8	4	Various	3
Sardi*et al*.[22]	4	3	0	MPA 200-500 mg / day	3
Gotlieb*et al*.[23]	13	13	6	Megestrol acetate: 160 mg daily or MPA: 200–600 mg daily	9

Pregnancy outcome

The critical threshold in the amount of tissue excised or destroyed that determines obstetric morbidity and success of treatment in terms of recurrent cancer are key questions that remain to be answered. Having a clear understanding of this relation would be useful in guiding clinical decision making. Removal or destruction of part of the cervix might compromise its function, leading to lack of mechanical support in a future pregnancy and subsequent premature rupture of membranes and preterm delivery. Gynaecologists should tailor the management of young woman to minimise possible adverse obstetric outcomes at the same time as minimising residual disease rates[27].

Discussion

Gynecologic cancers represent 12%–15% of cancers affecting women, and 21% of these are diagnosed in women of reproductive age. Current advances in our understanding of these diseases, along with improved multimodality treatment, allow for consideration of fertility options. For some women with gynecologic cancers, fertility-sparing treatment might be appropriate. Preservation of fertility has became a very important issue in gynecologic oncology[28]. It is a result of both the increasing incidence of gynecologic cancer in young patients and the increasing age at first pregnancy. Today, in a young patient with a gynecologic cancer, preservation of fertility is possible and depends primarily on the extent and type of cancer[29].

The management of early-stage cervical carcinoma in young women who desire future fertility remains a challenge to gynecologic oncologists. Tumor size, presence of positive nodes, lymphovascular space involvement, deep stromal invasion, and unfavorable histology are the most important risk factors for recurrence and should be carefully evaluated preoperatively. Nowadays, radical vaginal trachelectomy is a well-established safe procedure on early cervical cancer with large experience to date. It has good oncological and obstetrical outcomes with low morbidity and mortality, especially in tumors less than 2cm in size[30].

Endometrial cancer is the most common gynecologic malignancy, with a projected 43,470 new cases in 2010 and 7950 deaths. 1 Eight to fourteen% of affected patients will be of childbearing age, highlighting the importance of fertility preservation in this population. Fertility preserving options in endometrial cancer are currently limited to hormonal methods. Thus, successful treatment is dependent on hormone receptor expression on cancer cells. Response rates range from 26% to 89% in estrogen and progesterone receptor positive tumors, and are as low as 8-17% in those that are receptor negative. It is important to ensure that patients desiring to proceed with hormonal management are extensively counseled regarding potential risks. Clinicians should understand that there is no scientifically proven optimal progestin. Previous regimens have included megestrol acetate, medroxyprogesterone acetate, and the progesterone releasing intrauterine device. In addition, the dose to be administered and duration of therapy are unclear. Current convention is to treat with megestrol acetate 160 mg daily with repeat endometrial sampling in 3 months to determine whether there is disease regression, persistence, or progression. As endometrial cancer is linked to obesity, polycystic ovarian syndrome, and anovulation, many women with the diagnosis may have primary or secondary infertility, and require assisted reproductive technologies. Thus, concurrent referral to reproductive endocrinology may be warranted[31].

Fertility sparing therapy for epithelial ovarian cancer has been suggested for well-selected patients with early stage disease. Thus, conservative approaches may be considered in young women diagnosed with FIGO stage I cancer who wish to preserve reproductive function. Subsequent use of assisted reproductive technologies (ART) may facilitate production of biologic offspring in these cancer survivors. However, each

candidate requires unique consideration by subspecialists to avoid potentially fatal management errors Fertility-sparing surgery for ovarian low malignant potential tumors is an option for motivated patients. Preservation of the contralateral adnexa increases the risk of recurrence, but surgical resection is usually curative[32].

Conclusion

Fertility preservation is often possible in people undergoing treatment for cancer. To preserve the full range of options, fertility preservation approaches should be considered as early as possible during treatment planning. The possibility of reproductive dysfunction as a consequence of cancer treatment has an established negative impact on the quality of life of cancer survivors. The merged role of the treating physician as both life-saver and protector-of-future fertility has made the field of oncofertility a substantial part of gynecologic oncology nowadays.

References

1. Michelle L. Matthews, Bradley S. Hurst, Paul B. Marshburn, Rebecca S. Usadi, Margaret A. Papadakis, and Terry Sarantou. Cancer, Fertility Preservation, and Future Pregnancy: A Comprehensive Review. *Obstetrics and Gynecology International*. 2012; 11.
2. Farthing A. Conserving fertility in the management of gynaecologicalcancers. *BJOG*. 2006; 113(2): 129-34.
3. Palomba S, Falbo A, Negro, et al. Ultra-conservative fertility-sparing strategy for bilateral borderline ovarian tumours: an 11-year follow-up. *Human Reproduction*, Vol. 100. Oxford University Press, 2010; 1–7.
4. Gershenson DM. Fertility-sparing surgery for malignancies in women. *JNatl Cancer Inst Monogr*. 2005; 34: 43-7.
5. Shweta Sardana, Balkesh Rathi. Fertility Sparing Surgery in Gynecological Malignancies. Surgical Tips. AOGD Bulletin. 2011; 11(8).
6. Ellis P, Mould T et al. Fertility-saving treatment in gynaecological oncology. *The Obstetrician &Gynaecologist.* 2009; 11(4): 239–244.
7. Lua R Eiriksson, Allan Covens et al. Fertility-sparing Surgery in Cervical Cancer. *European Obstetrics & Gynaecology.* 2011; 6(1): 52-55.
8) Beiner M E , Covens A. Surgery Insight: radical vaginal trachelectomy as a method of fertility preservation for cervical cancer. *Nature Clinical Practice Oncology.* 2007; 4: 353-361.
9. Ayman Al-Talib, Farr Nezhat, Togas Tulandi. Fertility Preservation in Women with Gynecologic Cancer. *US Obstetrics & Gynecology.* 2009; 4(1): 22-28.
10. Shepheard JH. Challenging Dogma: Radical Conservation Surgery for Early Stage Cervical Cancer in Order to Retain Fertility. *Ann R CollSurg Engl*. 2009; 91(3): 181–187.
11. Hermann H, Kohler et al. Radicaltrachelectomy combine with laproscopicpelvic lymhadenetomy: Prospective multicenter study of 100m patients with early cervical caner. *Gynecoloncology.* 2006; 103: 506-511.
12. Plante M, Gregoire J, et al. The vaginal radical trachelectomy: an update of a series of 125 cases and 106 pregnancies. *GynecolOncol*. 2011; 121(2): 290-7.
13. Dargent D, Martin x, et al. Laparoscopic Vaginal Radical Trachelectomy A Treatment to Preserve the Fertility of Cervical Carcinoma Patients. *Cancer.* 2000; 88(8): 1877-82.
14. Covens A, Shaw, P et al. Is radical trachelectomy a safe alternative to radical hysterectomy for patients with Stage IA–B carcinoma of the cervix? *Cancer.* 1999; 86: 2273–2279.
15. Schlaerth JB, Spirtos NM et al. Radical trachelectomy and pelvic lymphadenectomy with uterine preservation in the treatment of cervical cancer. *American J of Obstet& Gynecol.* 2003; 188(1): 29-34.
16. Burnett AF, Roman LD, et al. Radical vaginal trachelectomy and pelvic lymphadenectomy for preservation of fertility in early cervical carcinoma. *GynecolOncol*. 2003; 88(3):419-23.
17. Barakat R et al. Contemporary issues in the management of endometrial cancer. *CA: A Cancer J for Clinicians.* 1998; 48(5): 299–314.

18. Emons G, G Fleckenstein, et al. Hormonal interactions in endometrial cancer. *Endocrine-Related Cancer.* 2000; 7: 227–242.
19. Kaku T,Yoshikawa H et al. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. *Cancer Letters.* 2001; 167(1): 39-48.
20. Randall TC, Kumaran RJ. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under age 40. *jObstet Gynecol*. 1997; 90(3): 434-40.
21. Wang, CB, Wang, CJ, Huang, HJ, Hsueh, S, Chou, HH, Soong, YK. and Lai, CH. Fertility-preserving treatment in young patients with endometrial adenocarcinoma. *Cancer*. 2002; 94: 2192–2198. doi: 10.1002/cncr.10435.
22. Sardi J, Anhezer Henry JP et al. Primary hormonal treatment for early endometrial carcinoma. *Eur J GynaecolOncol.* 1998; 19(6): 565-8.
23. Gotlieb, Walter H, Beiner, Mario E et al. Outcome of Fertility-Sparing Treatment With Progestins in Young Patients With Endometrial Cancer. *Obstetrics & Gynecology.* 2003; 102(4): 718-725.
24. Fotopoulou C, Braicu I et al. Fertility-Sparing Surgery in Early Epithelial Ovarian Cancer: A Viable Option. *Obstetrics and Gynecology International.* 2011; 2012(2012). doi:10.1155/2012/238061.
25. The Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in cancer patients. *Fertil Steril*. 2005; 83(6): 1622-8.
26. Canavarro MC Pires, RSA. The Impact of Gynecological Cancer on Reproductive Issues and Pregnancy: *Psychological Implications. Current Women's Health Reviews.* 7(4); 367-378.
27. Arbyn M, Kyrgiou M et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. *BMJ.* 2008; 337: a1284.
28. Liou WS, Yap OW, et al. Innovations in fertility preservation for patients withgynecologic cancers. *FertilSteril*. 2005; 84(6): 1561-73.
29. Vesna K, Alexandros M. Fertility Preserving Management in Gynecologic Cancer Patients: The Need for Centralization. *Intl J of Gynecol Cancer.* 2010; 20(9): 1613-1619.
30. Cubal AF, Carvalho J, et al. Fertility-Sparing Surgery for Early-Stage Cervical Cancer. *International Journal of Surgical Oncology.* Volume 2012 (2012), Article ID 936534, 11 pages.
31. Eskander RN, Randall LM, et al. Fertility preserving options in patients with gynecologic malignancies. *American Journal of Obstetrics & Gynecology.* 2011; 103-110.
32. Douglas NC, Fan L, et al. Fertility sparing therapy for ovarian cancer has inherent risks and benefits. *Arch Gynecol Obstet.* 2005; 272(4): 304-8. Epub 2005 Oct 13.