Gynaecological malignancies in pregnancy
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Purpose of review
To review the management of gynaecological cancers occurring in association with pregnancy. To consider the impact of the cancer on the pregnancy, and the impact of the pregnancy on the cancer.

Recent findings
The management of gynaecological cancers in pregnancy remains, fortunately, a rare problem for the gynaecological oncology team. This inevitably means that many management decisions will be informed by relatively small case series and case reports. There have been interesting reports where pregnancy has been prolonged to achieve fetal viability in both cervix and ovary cancer in pregnancy, and these are discussed below.

Summary
Any cancer in pregnancy is a catastrophic event for the woman and her partner, and poses great challenges for the multidisciplinary team responsible for her care. Gynaecological cancers in pregnancy are even more stressful as the woman will naturally worry about the survival of her baby, and the implications for her future fertility. Fortunately the outcome for most women and their babies is favourable.

Keywords
endometrial neoplasm, genital neoplasm, ovarian neoplasm, pregnancy complications, uterine cervical neoplasm, vulvar neoplasm

Introduction
In the UK one woman will develop cancer in her pregnancy for every 6000 live births. This rate may increase as more women postpone childbirth into the age range when cancer becomes more common. Pregnancy will affect the management of cancer, and the cancer will affect the management of the pregnancy. The diagnosis of cancer, although uncommon, must be considered when a woman presents with symptoms during pregnancy. There are of course two patients to consider, and difficult decisions may need to be made which may advantage one and disadvantage the other. Fortunately the outcome for the woman, at least with cervical cancer, is not usually adversely affected by the pregnancy per se [1–3], but her chances of survival might be worsened by postponing treatment until fetal viability is achieved.

Clearly the diagnosis of cancer will be devastating for the woman and her partner, and will also place a particular strain on the medical staff who are looking after her. Even large gynaecological oncology centres will only have a few cases to deal with each year, and multidisciplinary management is essential. Decision-making within a specialized multidisciplinary team is obviously essential.

Cervical cancer
Cervical cancer is the most common gynaecological cancer that complicates pregnancy. In the UK there were two deaths from cervical cancer out of almost exactly 2 million live births during the triennium 2000–2002 [4] (this report is essential reading for all obstetricians and gynaecologists who want to reduce the morbidity and mortality of pregnant women; it is available online at www.cemach.org.uk). The actual current incidence of cervical cancer in pregnancy is difficult to establish and appears to be lower in the UK than historic estimates of one in 2000 [5].

Presentation
Fortunately cervical cancer tends to present at an early stage in pregnancy [1], but the diagnosis can be delayed if the woman does not appreciate that her symptoms of bleeding and/or discharge are not normal; there can also be an assumption that because the woman has had a previously normal cervical smear then she cannot have cervical cancer. There is a reluctance to perform vaginal examinations during pregnancy, and indeed the Royal College of Obstetricians and Gynaecologists states “There is no scientific evidence to support the use of ‘routine’ vaginal examination at the first antenatal visit’
Management

In general the treatment modalities for cervical cancer are the same for the pregnant and nonpregnant woman. For a microinvasive cancer of the cervix an excision can be performed; although the procedure carries risks [7,8], the outcome is usually good, the pregnancy can proceed and a vaginal delivery can be anticipated. The ‘standard’ management for stage-1b1 cervical cancer up to 20 weeks’ gestation would be a radical hysterectomy with the fetus in situ, and should be offered as a management option [9].

For more advanced disease chemoradiation will be preferred [10–14]. In early pregnancy spontaneous miscarriage will usually occur after the woman has received 34–40 Gy [15], although after 20 weeks’ gestation miscarriage can be protracted (mean 33–44 days) [16], or may not occur spontaneously in 60% [17], so that the uterus will need to be emptied.

For the woman at over 20 weeks’ gestation a planned delay to allow fetal viability or even maturity is also an option, and may not actually significantly affect her survival [18,19]. A delay of up to 6 weeks for stage-1b2 and 12 weeks for stage-1b1 disease is reasonable, with careful clinical and/or MRI monitoring of the woman every 2–4 weeks [3]. Steroids can be given with no apparent adverse effects on the cancer to expedite fetal lung maturity. When fetal viability or maturity is reached with stage-1b disease a Caesarean section with radical hysterectomy will usually be performed. It is possible to perform the radical hysterectomy 48–72 h after vaginal delivery, assuming labour is not obstructed; this has the advantages of reduced blood loss and a better vaginal cuff with the resected specimen [3].

Delaying intervention even further may be an option: with reassurance gained by negative histology following laparoscopic lymphadenectomy, a woman presenting with a stage-1b2 cervical cancer at 16 weeks’ gestation proceeded to elective Caesarean section and radical hysterectomy at 36 weeks, followed by chemoradiotherapy; she was alive and well at 4 years’ follow-up [20*].

Ovarian cancer

Ovarian tumours are found in about 1 in 1000 pregnancies; of these, 3–6% are malignant, so therefore ovarian cancer occurs in approximately 1 in 12 500–25 000 pregnancies [21,22]. In the UK there were no deaths from ovarian cancer in pregnancy during the triennium 2000–2002 [4].

Presentation

Most commonly ovarian cysts and tumours are detected at routine antenatal ultrasound scans. Accidents such as torsion, haemorrhage and rupture may happen to cysts and tumours, giving rise to symptoms such as pain, nausea and vomiting.

Management

Most small (<5 cm), simple cysts will resolve spontaneously; they are usually follicular or corpus-luteal in origin. Other cysts will need to be managed on an individualized basis, depending on symptoms, ultrasound features and, with caution, tumour markers. The appearances which cause concern on ultrasound are complexity (solid and cystic), bilaterality, ascites, surface excrescences and areas where metastasis is suspected [23]. MRI may add significant information and can help reduce the need for surgical intervention [24]. It is possible to use multi-variable logistic regression models to predict the likelihood of a cyst’s being malignant [25]; although this is helpful in triaging women to district-hospital or cancer-centre care, subjective assessment of an adnexal mass by an expert can be more accurate [26]. The usual tumour markers used to assess risk of malignancy have elevated levels during pregnancy (CA125, a-fetoprotein, human chorionic gonadotrophin, lactate dehydrogenase) [27], but carcinoembryonic antigen levels remain normal, which can help with monitoring in the situation where carcinoembryonic antigen is secreted by the tumour [28,29].

Surgical intervention is often necessary, for symptoms or because of concern about malignancy. Ideally this is done after 14–16 weeks’ gestation when the placenta has taken over hormonal support of the pregnancy from the corpus
luteum [30]. It may be possible to manage benign cysts laparoscopically; however, if there is a significant risk of a cyst’s being malignant then a midline laparotomy will usually be performed; rupture of a malignant cyst at surgery adversely affects prognosis, so should be avoided [31].

For all ovarian cysts in pregnancy, 23–47% are dermoids, 16–37% are cystadenoma, 7–22% are functional cysts, 12–16% are other types and 3–6% are malignant [21,22,32–34]. Of the cysts in pregnancy which are malignant, 6–40% are germ cell, 21–35% are of borderline malignancy, 28–30% are invasive epithelial, 9–16% are sex-cord stromal and 3–5% are other types [22,35,36].

Surgery
In general, at surgery, peritoneal washings are taken and then an ovarian cystectomy or salpingo-oophorectomy is performed, together with other appropriate biopsies (omental, pelvic and para-aortic nodes) depending on the clinical situation and findings. In view of the relatively young age of women who are pregnant, it is not surprising that a significant proportion of malignant cysts (6–40%) are germ cell in origin. It is important to keep this in mind when operating on ovarian tumours in this group, so that unnecessarily aggressive surgery is not performed; usually all that is required is a unilateral salpingo-oophorectomy, with appropriate peritoneal washings and omental, pelvic and para-aortic node sampling. The contralateral ovary should only be biopsied if necessary. The pregnancy can usually continue safely, and fertility can usually be preserved.

Laparoscopic surgery continues to be controversial in the management of ovarian cysts, in nonpregnant as well as pregnant women; its advantages are well known, and include reduced perioperative pain, shorter hospital stay and much better cosmesis (especially in pregnancy). The main disadvantages of laparoscopic surgery include the risk of uterine damage if a Veress needle technique is used instead of the preferred open (Hasson) technique; there are theoretical-only concerns about the risks to the fetus of hypercapnia; there is a risk of spillage of benign and malignant cyst contents; all laparoscopic surgery may be appropriate to consider neoadjuvant chemotherapy, just as, also controversially, it would be considered in the nonpregnant woman. Obviously a tissue diagnosis is required, from radiologically or laparoscopically guided biopsy. This management has been reported [29] and we have successfully managed a woman this way in our centre. A 38-year-old woman presented with very advanced disease at 30 weeks’ gestation, with a CA125 of 9180 units/l; she received two cycles of neoadjuvant carboplatin and then had a spontaneous vaginal delivery of a healthy baby at 35 weeks. She then had two further cycles of neoadjuvant carboplatin and paclitaxel, followed by optimal interval debulking surgery to less than 1 cm of disease; she then received a further four cycles of adjuvant carboplatin and paclitaxel. Eight months later she and the baby were well; her CA125 was 7 units/l.

Endometrial cancer
Endometrial cancer in association with pregnancy is extremely rare; it is a disease mainly of postmenopausal women, and the high levels of progesterone in pregnancy would be expected to antagonize the effect of oestrogen on the endometrium. Only 28 cases are reported in the literature; the diagnosis is usually made following curettage for persistent bleeding after a miscarriage or postpartum [50,51]. The outcome is usually good, and the treatment is the same as for the non-pregnant woman.

Chemotherapy
In the situation of invasive epithelial cancer staged at greater than FIGO 1a and 1b and of poor differentiation, adjuvant chemotherapy will be considered equally in the pregnant and nonpregnant patient. The risk of teratogenesis from chemotherapy is high in the first trimester, at about 10% [45]; after organogenesis is completed at the start of the second trimester, the risk of fetal abnormality is very low [46,47]. There is, however, a risk of intrauterine growth restriction and premature labour. Long-term outcomes are still uncertain, with little published data, but seem reassuring [48]. There are very few data on the safety of paclitaxel in pregnancy, so some centres (including our own) use single-agent carboplatin during pregnancy, with consideration of adding paclitaxel after delivery of the baby. Due to the myelosuppression caused by chemotherapy, it is important to avoid delivery within 2 weeks of administration at the white cell and platelet nadirs from the mother’s perspective, and also for the sake of the fetus, which relies on the placenta to clear chemotherapy drugs from its body [49].
It may be reasonable to treat conservatively very early-stage, well differentiated endometrial cancer in young women wishing to retain their fertility. High-dose progesterin treatment over 6–10 months with regular sampling allowed five of 10 women to have babies [52]. However, at long-term follow-up of nine of them, eight developed recurrent cancer, although all survived. In another case report, the outcome in a similar situation was death from the disease [53].

In the UK there were no deaths from endometrial cancer in pregnancy during the triennium 2000–2002 [4].

**Vulval cancer**

Vulval cancer in pregnancy is just as rare as endometrial cancer, with again only 31 cases reported in the literature [4,54–57]. Surgery should be performed as with the nonpregnant woman up until 36 weeks’ gestation [58]; if diagnosed later than this, then treatment can be postponed until early in the puerperium [59].

In the UK there was one death from vulval cancer in pregnancy during the triennium 2000–2002 [4].

**Conclusion**

Probably the most important thing with cancer in pregnancy is to think of it. It is a very rare, but very important diagnosis to make. Support and sensitivity for the frightened woman and her partner are essential, as is high-quality decision-making within the specialist gynaecological oncology multidisciplinary team at the cancer centre.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 197).