REVIEW



Gynaecological malignancy in pregnancy

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1. Introduction

Approximately 1 in 1000 pregnancies are thought to be affected by malignancy, with the diagnosis posing challenging decision-making for health professionals [1]. Many of these difficulties arise due to the lack of evidence-based information, international consensus or guidance on the topic. Current recommendations, across Europe, state that pregnancy should be preserved alongside careful and detailed discussion with the mother by a multidisciplinary team. Clinicians should engage in open and respectful dialogue with the mother to collaboratively reach decisions that align with her wishes while also considering the medical implications [2, 3].

The most common malignancies in pregnancy are cervical, breast, melanoma and lymphoma [4, 5]. Incidence data, however, is unreliable due to many national obstetric and cancer registers not being linked. Amongst this, cervical or ovarian cancer are the most common gynaecological malignancies seen [6]. Management and treatment decisions involve a multidisciplinary team approach, with women often offered similar treatment pathways to non-pregnant patients. Pregnancy is not thought to have a negative effect on overall cancer prognosis and so termination of pregnancy is only really considered in advanced stage or aggressive tumours, diagnosed in early pregnancy [7, 8].

1.1 Epidemiology

There is an expectation that the incidence of cancer in pregnancy will rise, as already demonstrated by population-based studies [9, 10]. In many countries worldwide, women are having children later in life for economic or occupational reasons, and therefore the incidence of cancer in pregnancy is expected to increase [11]. The advent of non-invasive prenatal testing has been shown to detect preclinical cancer and is rapidly being introduced as a screening tool.

Estimations in the incidence of cancer during pregnancy, often lack information on miscarriage or termination of pregnancy, particularly in studies using combined cancer and pregnancy registers. This may result in an underestimation of the incidence. Based on data from the Annals of Oncology the relative risk of ovarian and cervical cancer is lower in pregnancy compared to non-pregnant women. In the limited data available, outcomes are similar in both populations [12]. Whilst rates of vaginal, vulval and endometrial cancer are rare in pregnancy compared to the postmenopausal population, they remain important [13].

1.2 Diagnosis

Delays in diagnosis are common as many symptoms are attributed to normal pregnancy such as breast changes, bowel habit fluctuation or bleeding. The majority (>60%) of malignant diagnoses are made in the postnatal period. There are no definitive data to suggest that cancer is more advanced when diagnosed in this period. Appropriate imaging in pregnancy provides another diagnostic challenge. Ultrasound is widely accepted as a safe method but is not adequate in cancer staging. Other forms of non-ionising radiation including magnetic resonance imaging (MRI) are deemed safe in pregnancy [14] and efficient at imaging solid or soft tissue tumours. Diffusionweighted MRI could replace positron emission tomography (PET-CT) in the detection of nodal or distant metastasis, according to studies. Data also suggests this could include solid tumours, lymphomas and distant bone metastases [15].

Ionizing imaging should be avoided as radiation can affect the development of the fetus with the threshold set at 100mGy. Fetal demise, malformations and secondary cancers are a concern, particularly at earlier gestational ages. A routine abdominal-pelvic CT radiation dose range between 8– 15 mSv. Historically PET-CT imaging was thought to confer higher doses of radiation and should be postponed until after pregnancy whenever possible, however data suggests exposure to the fetus is low when this modality is performed. As far as is possible, whilst maintaining diagnostic accuracy, radiation exposure should be minimised in the pregnant population.

1.3 Management

As with the non-pregnant population, women should be discussed at an appropriate Multidisciplinary Meeting (MDM) and referred to a tertiary unit for their on-going care. Most clinicians will be inexperienced in looking after pregnant patients and thus obstetric and gynaecology input is vital. Although prognosis can often be difficult it is important women are counselled appropriately. Clear communication regarding prognosis will inform patients' decision-making, and particularly whether the therapy will be curative or palliative [11]. Additionally, if appropriate in the context of gestation, termination of pregnancy should be discussed. Patients should be given adequate information on the impact of pregnancy on the cancer diagnosis and the impact of potential treatment on the fetus. A meta-analysis and systematic review, looking at prognosis in pregnancy, suggest that this is worse in certain hormone-dependent cancers such as melanoma, breast and vulva [16, 17].

However, confounding variables such as delays in diagnosis and differences in treatment decisions make comparison difficult. Equally, multiple studies have concluded that the prognosis is equivalent in the pregnant population, if the same treatments are offered [18].

1.4 Surgery

The recommended management depends on the tumour type, stage and patient's wishes. Surgery and/or systemic therapy are the mainstay. Surgery is safe in pregnancy and should not be delayed if it provides optimal management. It is ideally performed in the early second trimester where the balance of miscarriage, preterm birth or limited access sits most evenly. Laparoscopic procedures have been shown to be safe in pregnancy with intra-abdominal pressure recommendations of 10-12 mmHg [19, 20]. A recent study showed that laparoscopy was associated with shorter operative time and less adverse fetal effects than laparotomy [21]. Maternal physiological changes can result in more careful anaesthetic monitoring particularly hypotension which can result in placental hypoperfusion, so this is best avoided. In longer surgical procedures "lateral tilt" has not been shown to improve neonatal outcomes but is generally recommended. Overall surgery is often more technically difficult in pregnancy due to access, avoidance of the uterine body and increased vascularity.

1.5 Systemic therapy

Chemotherapy should be avoided in the first trimester; however most can be safely given in the second and third trimesters. Early exposure to chemotherapy, particularly in the first trimester, risks interference with organ development. It associated with a 10%–20% risk of major malformations, fetal demise, impaired organ function and spontaneous abortion [22]. The benefit to the fetus of treatment delay until the second trimester should be balanced against maternal risk. However, in time-critical disease or advanced-staging whereby treatment initiation is a priority, termination of the pregnancy should be considered.

In the second and third trimesters, no close associations with

teratogenic effects have been discovered [23, 24], whilst some links with intrauterine growth restriction, prematurity and low birth weight have been reported [25, 26]. Given the potential benefits to the mother in cancer treatment, many cases will warrant acceptance of the risks related to chemotherapy exposure during the later trimesters. Chemotherapy is often delayed beyond 35 weeks' gestation, as a 3-week window between the last cycle of chemotherapy and delivery is important to allow both maternal and fetal bone marrow recovery. Ideally breastfeeding is best avoided initially in women receiving carboplatin, paclitaxel and cisplatin as these agents are excreted in breast milk for more than 2 weeks after administration.

1.6 Radiotherapy

Radiotherapy, particularly pelvic treatment, is avoided in pregnancy due to risks of malformation, growth restriction or fetal death. In adjuvant therapy, this should ideally be delayed until the third trimester and a decision of preterm delivery versus delayed treatment is weighed up with the advice of a clinical oncologist.

However, in cases where there is symptomatic need, such as cervical or vulval cancers, it can be given in the third trimester. Delivery should be performed at a suitable gestation to maximise viability by caesarean section and the ovaries can be transposed at the time so that they are out of the radiotherapy field. Overall, there is a limited role for radiotherapy during pregnancy unless fetal death is considered unavoidable.

1.7 Obstetric care

These complex and ethically difficult cases should be managed in a high-risk tertiary unit. The gestation at diagnosis often has a bearing on how the pregnancy is then managed. This should be carefully balanced with the patient's fertility history and wishes. A nulliparous woman with fertility difficulties is perhaps less likely to undergo a termination of pregnancy if treatment is not immediately indicated. Early multidisciplinary approaches will facilitate robust management plans, often dictated by the oncological treatments being offered.

Routine first trimester and anomaly screening should take place as planned alongside high dose folic acid. In patients with a history of previous cervical cancer treatment, length surveillance should be offered, and women counselled about vaginal progesterone if <25 mm. The European Society of Medical Oncology (ESMO) consensus panel believe cervical cerclage can be offered if there is no residual disease and limited residual cervical length [27]. Fetal assessment with doppler or ultrasound should be made post-operatively if surgical planning alongside tocolysis is required. This is more pertinent in open abdominal surgery where women experienced significantly more preterm contractions than those undergoing laparoscopy [28].

It is well documented that preterm birth carries greater neonatal morbidity. In retrospective studies, prematurity was the biggest factor in paediatric developmental problems up to 3 years of age [29]. Lu and colleagues demonstrated rates of 89% prematurity-derived neonatal mortality in patients with cancer during pregnancy (incidence rate ratio 2.7, 95% CI (confidence interval) 1.3–5.6) [30]. Data like this has resulted in a decrease of planned preterm birth delivery, a tendency to continue chemotherapy for longer during pregnancy and thus benefitting neonatal outcomes.

Chemotherapy is associated with a risk of intrauterine growth restriction, premature rupture of membranes and preterm birth [31, 32]. De Haan et al. [4] demonstrate platinum-based chemotherapy is associated with small babies whilst taxane-based therapy is associated with higher neonatal unit admissions. As a result, women should be offered regular growth scans alongside umbilical (UA) and middle cerebral artery (MCA) doppler surveillance. Delivery should be delayed until 37 weeks where possible to avoid the risks of prematurity. The role of vaginal birth in cancer treatment is much debated. Caesarean section is often advised in cervical and vulval cancers. Ovarian cancer is not a contraindication to vaginal birth. Surgical planning with the gynaecological oncology team is appropriate whereby completion surgery can be performed at the time of the delivery, if indicated. The placenta should be sent to histopathology to exclude metastasis. It is exceptionally rare for the baby to develop metastases in gynaecology cancer [30].

Pregnancy and malignancy are both significant risk factors for venous thromboembolism therefore, thromboprophylaxis with agents such as low-molecular-weight heparin should be considered both antenatally and postpartum. Appropriate thrombosis risk assessments should be made on a regular basis for these patients. Oncological treatment can be continued immediately after vaginal delivery, and 1 week after uncomplicated operative birth. It is also important to discuss non-hormonal postpartum contraception if fertility is maintained. Breastfeeding can be commenced provided chemotherapy treatment has ceased at least 3 weeks prior [33, 34].

2. Cervical cancer

The commonest gynaecological malignancy diagnosed in pregnancy is cervical cancer, with a reported rates of 0.1-12.0 per 10,000 pregnancies [35]. With the advent of cervical screening and more recently primary Human papillomavirus (HPV) testing, the rates of invasive cervical cancer have decreased [36]. Furthermore, in countries where HPV vaccination is available, rates of pre-malignant cervical intraepithelial neoplasia (CIN) 2/3 and invasive carcinoma have dropped dramatically. In the limited data available for prognosis of cervical cancer during pregnancy, there is no negative impact of pregnancy on the outcomes. Therefore, pregnancy-preserving management should be considered initially. Abnormal or persistent vaginal bleeding and discharge are symptoms of concern and warrant further assessment. Pregnancy is not a contraindication to cervical screening however routine screening and Test of Cure (ToC) testing can be delayed until 3 months postnatally. Follow-up cytological testing for CIN and cervical glandular intraepithelial neoplasia (CGIN) with incomplete margins should not be delayed however [37]. Hormonal cervical changes in pregnancy make for difficult assessment and so colposcopy is often reserved for concerns over invasive disease. Diagnosis, if performed should be via a punch biopsy

of an exophytic lesion or loop excision. Biopsies carry a much higher risk of bleeding. Loop diathermy carries a 25% risk of haemorrhage [28] so these procedures should be carried out in theatre by experienced professionals [21].

MRI is the best and safest diagnostic test for the staging of cervical cancer in pregnancy. CT or PET-CT should be held in reserve due to the fetal risks as discussed above. Staging is determined by local and distant spread as per The International Federation of Gynecology and Obstetrics (FIGO) 2018 guidelines [38]. In cases of advanced disease where further imaging is required, both chest x-ray to identify lung metastases and ultrasound to check for hydronephrosis can be safely used in pregnancy.

In the absence of nuclear imaging for staging, accurate nodal assessment is required in determining the prognosis and treatment planning. In early Stage I disease, laparoscopic lymph node assessment may allow treatment to be safely delayed [27]. Lympho-vascular spread would suggest urgent treatment is required and surgery is not indicated [39]. This is not recommended beyond the 22nd week due to poor node yield and there is insufficient evidence to support the use of sentinel lymph-node detection in pregnancy.

Treatment planning depends on the size of the cervical lesion and the gestation of the pregnancy. This is shown in Fig. 1.

IA1: diagnosis of early-stage cervical cancer is often made on excisional biopsy, which is unlikely to have been performed in pregnancy, however if indicated this is best performed between 14–20 weeks. 1% of stage IA1 squamous cell carcinomas are affected by lymph node metastasis, increasing to 3–6% in Stage IA2 [40].

IA1 with LVSI, IA2 and IB1: the gold-standard treatment for stage IB1 and IB2 cervical cancer is a radical hysterectomy and bilateral salpingectomy with pelvic lymphadenectomy [41]. This can be performed following termination during the first or early-second trimester or after a caesarean section delivery (during the late second/third trimester). The conservation of ovaries is dependent on the patient's age; fertility wishes and histopathology as adenocarcinomas carry a higher risk of ovarian metastases [42]. Thus, women must be fully counselled that pregnancy-preserving treatment may result in a worse oncogenic outcome [43]. For women ≤ 22 weeks, lymphadenectomy is recommended and in cases of positive pelvic lymph nodes a termination of pregnancy should be discussed. Women wishing to continue with the pregnancy, neoadjuvant chemotherapy (NACT) can be considered although only after completion of the first trimester. Trachelectomy, a surgical procedure to remove the cervix, is reserved for lymph node negative patients who wish fertilitysparing surgery. This procedure is not recommended during pregnancy due to a high risk of preterm delivery, poor obstetric outcomes and higher blood loss [44].

IB2-IB3: In cervical tumours staged beyond IB2, neoadjuvant chemotherapy should be offered to women wishing to continue with the pregnancy. NACT is given from the second trimester onwards to allow fetal maturation. A radical hysterectomy and pelvic lymphadenectomy can be performed at the time of delivery. In advanced cervical cancer (>IB2), where chemoradiotherapy is the primary recommended treatment, women may be offered a termination of pregnancy or



FIGURE 1. A diagram summarising cervical cancer management during pregnancy. AC, adjuvant chemotherapy; DTAD, delayed treatment after delivery; gw, gestational weeks; MRI, magnetic resonance imaging; NACT, neoadjuvant chemotherapy; NEG, negative; PLND, pelvic lymph node dissection; pos, positive; ST, simple trachelectomy; TOP, termination of pregnancy. *As per FIGO 2018 cervical cancer staging [27].

immediate delivery depending on gestation. If treatment is commenced in the first trimester, fetal loss will likely occur within days. Follow-up without therapy in such cases is likely to compromise the prognosis and is thus not recommended. For women requiring pelvic radiotherapy (IB3 and above) either following delivery or as an adjuvant to chemotherapy, warrant appropriate counselling. High dose pelvic radiation adversely affects the uterine cavity and endometrium with fibrotic changes meaning pregnancy is highly unlikely following treatment. Additionally, ovarian tissue can also be affected by transient or permanent loss of function. Depending on parity, fertility wishes and hormone replacement therapy (HRT) risk profile, ovarian transposition could be considered.

3. Ovarian cancer

Ovarian cancer is the second most common gynaecological cancer in pregnancy with incidence reported as 1 in 15,000–32,000 [45]. The incidence of adnexal masses in pregnancy is 0.15–5.7% which show a high rate of spontaneous rupture within the first trimester and a very rarely malignant. The distribution of histological types of ovarian cancer is much the same as the non-pregnant population with the majority being epithelial (28–30%) followed by borderline tumours of the ovary (21–35%) [46]. In younger patients, the more common ovarian malignancies are borderline ovarian tumours, non-epithelial invasive cancers (germ cell and sex cord-stromal tumours) and epithelial invasive cancers [47].

The commonly used ovarian cancer tumour marker, CA125,

is not reliable during pregnancy. Concentrations have been reported as being more than 65 IU/mL in 16% of pregnant patients in the first trimester. This often returns to normal often the latter stages of pregnancy but may rise again immediately following delivery [48]. Although there is evidence to support an upper value of 112 U/mL may be normal in pregnancy, there is no international consensus [49]. If grossly elevated alongside concerning imaging findings, this would warrant referral to a Gynaecology Oncology Multi-disciplinary team (MDT) meeting.

Ultrasound may be helpful in differentiating benign from malignant ovarian cysts. MRI should be used to further characterise ovarian masses and define the extent of disease.

The risk of malignancy can be calculated by using the International Ovarian Tumour Analysis (IOTA) model which characterises components of lesions into benign and malignant categories. The features on ultrasound, used to characterise adnexal masses in non-pregnant women, are applicable in pregnant population [50].

Ultrasound features suggestive of malignancy:

 \circ solid component

papillary projections >7 mm

vascular detection within projections*

 \circ increasing size during pregnancy (incremental 20% change)

• presence of septations

o intra-abdominal free fluid

* The role of colour Doppler is debatable, as the increased vascular flow in normal pregnancy physiology can be

attributed to angiogenesis in a tumour.

Ovarian cancer diagnosis requires tissue histopathology, inspection of the abdominal cavity or fluid cytology. In the absence of symptoms or concerns over malignancy, conservative management is recommended, avoiding surgery [51]. Surgery is only indicated in asymptomatic patients if there is significant concern for malignancy or is risk of an acute event such as torsion or rupture. If possible, this should be performed between 12 and 27 weeks of gestation, and a laparoscopic approach is deemed preferrable. Laparoscopy, albeit potentially surgically challenging, is the recommended approach up to 20–22 weeks' gestation. If there is a suspicion of malignancy, laparotomy is preferrable to allow full staging, but also to reduce the risk of surgical spill and upstaging a malignant cyst.

Non-epithelial and borderline ovarian tumours are managed much the same as in the non-pregnant population (Fig. 2). These masses are often symptomatic due to size and so warrant surgical intervention. Otherwise staging and management can be delayed until delivery. Fertility-sparing surgery is recommended in these cases with a unilateral salpingooophorectomy, washings and an omental biopsy. In the management of epithelial ovarian cancer (Fig. 3), it is recommended that these patients are referred to a tertiary cancer centre for discussion at MDT. Women with localised malignant disease, ipsilateral pelvic and para-aortic lymphadenectomy should not be performed unless suspicious nodes are identified. The uterus and contralateral ovary should be preserved until the final histology results are available. If full surgical staging cannot be performed due to the space limitations of a gravid uterus, recommendation is restaging should be planned postpartum. NICE guidance recommends that women with stage IA or IB, who have had optimal surgical staging and who have low-risk disease, should not be offered adjuvant chemotherapy. Women with high-risk early-stage disease (stage IC or grade 3) should be offered adjuvant treatment with single-agent carboplatin



FIGURE 2. A diagram to demonstrate the management of non-epithelial ovarian tumours according to ESMO guidelines [27]. Staging refers to surgical staging. CT, chemotherapy; gw, gestational weeks. *According to ESMO guidelines and **CT administered according to re-staging surgery findings.



FIGURE 3. A diagram to demonstrate the management of epithelial ovarian cancer tumours according to ESMO guidelines [27]. CT, chemotherapy; gw, gestational weeks.

[52, 53]. Women who appear to have stage I disease, but who have not undergone optimal surgical staging, should discuss the individualised risks and benefits of chemotherapy.

In advanced stage epithelial ovarian cancer, termination of pregnancy should be considered when the diagnosis is made in the first half of the pregnancy. In patients wishing to continue with the pregnancy, a histological biopsy should be taken, followed by platinum-based chemotherapy. Cytoreductive surgery can be planned on a delayed primary surgery-basis after delivery. This is because intra-operative assessments for residual disease are difficult and inaccurate during pregnancy [27]. Dual agent chemotherapy of paclitaxel and carboplatin is the common first line combination for epithelial ovarian cancer. Germ cell and tumours are often treated with paclitaxel and carboplatin or with a cisplatin, etoposide, bleomycin (PEB) regimen (second-line treatment).

Paclitaxel and carboplatin are on the whole preferable firstline agents as they have the most favourable safety profile for the fetus [54]. A small percentage of patients with advanced disease will achieve pregnancy following initial treatment [46]. Pregnant women with a history of ovarian malignancy, should be carefully monitored. A CA125 and an MRI scan would be appropriate if the woman develops symptoms or there is strong clinical suspicion of recurrence. Recurrence carries a poor prognosis in ovarian cancer and the chemotherapy offered depends on the response to previous treatment (platinumsensitivity).

4. Endometrial cancer

Endometrial cancer is rarely diagnosed in pregnancy and is far more common in the post-menopausal population. However, the incidence of endometrial cancer is rising worldwide partly due to the epidemic of obesity and its impact on endometrial carcinoma [55]. This is resulting in an increased of number of younger women being diagnosed with 4% of cases of endometrial cancer diagnosed in women under 40 years of age [56, 57]. This poses a challenging problem, particularly in those who wish to preserve their fertility. There are a few case reports of diagnosis in much younger women following termination of pregnancy or surgical management of miscarriage [58, 59]. As a result, fertility-sparing approaches to endometrial hyperplasia and early endometrial carcinoma, have become increasingly used.

Endometrial cancers after most commonly low grade and confined to the endometrium (early stage), meaning conservative options are safe in the first instance. Treatment must be accompanied by careful monitoring in the form of imaging and biopsies. Baseline MRI imaging is important to rule out myometrial invasion but both urgent bariatric and fertilityspecialist input is required. The gold-standard treatment for atypical hyperplasia or endometrial carcinoma is total hysterectomy and bilateral salpingo-oophorectomy.

Conservative management strategies such as oral progestins have success rates of up to 76–86% [60] or alternatively the progesterone intra-uterine coil has the advantage of delivering hormonal therapy directly to the tumour with fewer side effects and ensures compliance. Success rates of 76%, a relapse rate of 26% and live birth rate of 26% have been demonstrated across pooled series [61]. There are no randomised control studies comparing the effectiveness of the non-surgical management options.

Surveillance during this period is focused on detecting progressive disease so that early recourse to surgical management can be offered. This involves hysteroscopic assessment and endometrial biopsies at 3, 6 and 12 months [62]. In defining complete pathological response, the progesterone therapy must be stopped, otherwise histological assessment can be difficult to interpret. Most guidelines suggest 3–6 monthly biopsies in the first year and annual biopsies thereafter. Maintenance progesterone therapy has been shown to reduce recurrence however prevents pregnancy. This often requires thorough patient counselling and careful coordination with fertility specialists [63].

5. Vulval and vaginal cancer

Vulvovaginal cancer in pregnancy is very rare, with less than 5% of vulval carcinomas arising in women under 40 years of age [64]. The incidence in pregnancy is reported to be between 1 in 8000 and 1 in 20,000 births, and most of the literature involves case reports [1]. Vulval carcinoma is not affected by pregnancy with 60% of women presenting with stage I disease and squamous cell carcinomas are the commonest type in pregnancy (47%).

Most women will present with abnormal bleeding, a vulval lump or pain. Diagnosis is achieved by punch biopsy however care must be taken due to an increased risk of bleeding secondary to increased gestational pelvic blood supply. Clinical findings of enlarged groin lymph nodes are concerning for advanced disease. Pelvic MRI is a reasonable and safe tool in the staging of local or distant spread.

Surgery is the cornerstone of vulval cancer treatment with a wide local incision +/- vulvectomy depending on the size and location of the lesion. Sentinel lymph node detection using Technetium-99 is safe in pregnancy and has been used for ductal breast carcinoma with negligible effect shown on the fetus [65]. Fetal exposure to locally injected technetium is small and can be further reduced by using a short treatment protocol, the lowest possible dose and performing the procedure 2 hours following injection. Single-photon emission computed tomography (SPECT-CT) is not recommended in pregnancy. In units without access to sentinel lymph node testing, inguinal lymphadenectomy should be performed following discussion with the patient in view of the significant morbidity it carries. Depending on gestation, symptoms and staging, primary surgery may be delayed until the postpartum period. Where there is a suspicion or confirmation of lymph node involvement, either termination or delivery should be discussed. Pelvic radiotherapy is contraindicated in pregnancy and is time-critical, 6-8 weeks from surgery or diagnosis [66].

Regarding mode of delivery, in the third trimester a caesarean delivery is performed to prevent vulvar wound dehiscence. In case of smaller wounds that have already healed well, vaginal delivery is an option. NACT to reduce tumour size for locally advanced disease remains experimental. Patients who have been treated with radiotherapy in the past are at an increased risk of intrauterine growth restriction because of potential impairment of the uterine vascular supply and radiation fibrosis affecting the myometrium [67]. Therefore, increased fetal surveillance is required with consideration of an early delivery at 34 weeks.

Vaginal cancer is primarily a disease of the post-menopausal woman with only 12–50 case reports in pregnancy [68]. Similarly, diagnosis is by biopsy and treatment is surgical resection depending on location. Locally advanced (>Stage 1) tumours are often deemed non-operable therefore, adiotherapy is the mainstay of treatment in these cases. Depending on gestation, women need to be counselled appropriately over the risks of pregnancy loss with the commencement of treatment versus early delivery to prevent disease progression.

6. Conclusion

This paper presents an overview of the management of gynaecological malignancy in pregnancy whereby currently, the scientific basis for the is largely drawn from retrospective studies, case reports or from management in the nonpregnant population. Due to its rarity the International Network on Cancer, Infertility and Pregnancy (INCIP) was created and since inception of the registration in 2005, our knowledge on how to manage gynaecological cancers has increased. A multidisciplinary approach to management is vital to ensure the combination of clinical factors, patient wishes and ethically challenging decisions are all considered. Safe and effective treatment plans are manageable despite the complicated balance between maternal and fetal health. Women should always be well informed, feel emboldened by the information given and be aware of the available treatment options, their complications and implications to their pregnancy or to the fetus.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

AAD and AM—designed the paper. AAD—wrote the manuscript. AAD, AM, CN and AP—read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- [1] Morice P, Uzan C, Gouy S, Verschraegen C, Haie-Meder C. Gynaecological cancers in pregnancy. The Lancet. 2012; 379: 558–569.
- [2] Peccatori FA, Azim HA, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, et al. Cancer, pregnancy and fertility: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of oncology. 2013; 24: vi160–vi170.
- [3] China S, Sinha Y, Sinha D, Hillaby K. Management of gynaecological cancer in pregnancy. The Obstetrician & Gynaecologist. 2017; 19: 139– 146.
- [4] de Haan J, Verheecke M, Van Calsteren K, Van Calster B, Shmakov RG, Mhallem Gziri M, *et al.* Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. The Lancet Oncology. 2018; 19: 337–346.
- [5] Di Ciaccio PR, Campbell B, Mason KD, Shanavas M, Greenwood M, Gregory GP, *et al.* Lymphoma during pregnancy: a multicentre study by the Australasian lymphoma alliance. Blood. 2021; 138: 882.
- [6] Latimer J. Gynaecological malignancies in pregnancy. Current Opinion in Obstetrics & Gynecology. 2007; 19: 140–144.
- [7] Amant F, Van Calsteren K, Halaska MJ, Beijnen J, Lagae L, Hanssens M, et al. Gynecologic cancers in pregnancy: guidelines of an international consensus meeting. In Reed N, Green JA, Gershenson DM, Siddiqui N, Connor R (eds.) Rare and uncommon gynecological cancers (pp. 209– 227). 1st edn. Springer: Berlin. 2011.
- [8] Amant F, Van Calsteren K, Vergote I, Ottevanger N. Gynecologic oncology in pregnancy. Critical Reviews in Oncology/Hematology. 2008; 67: 187–195.
- [9] Lee Y, Roberts C, Dobbins T, Stavrou E, Black K, Morris J, et al. Incidence and outcomes of pregnancy-associated cancer in Australia, 1994–2008: a population-based linkage study. BJOG: An International Journal of Obstetrics & Gynaecology. 2012; 119: 1572–1582.
- [10] Eibye S, Kjær SK, Mellemkjær L. Incidence of pregnancy-associated cancer in Denmark, 1977–2006. Obstetrics & Gynecology. 2013; 122: 608–617.
- [11] Silverstein J, Post AL, Chien AJ, Olin R, Tsai KK, Ngo Z, et al. Multidisciplinary management of cancer during pregnancy. JCO Oncology Practice. 2020; 16: 545–557.
- [12] Halaska MJ, Uzan C, Han SN, Fruscio R, Dahl Steffensen K, Van Calster B, *et al.* Characteristics of patients with cervical cancer during pregnancy: a multicenter matched cohort study. An initiative from the international network on cancer, infertility and pregnancy. To be published in International Journal of Gynecologic Cancer. 2019. [Preprint].
- [13] Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. The Lancet. 2022; 399: 1412–1428.
- [14] Michalet M, Dejean C, Schick U, Durdux C, Fourquet A, Kirova Y. Radiotherapy and pregnancy. Radiotherapy and Pregnancy. Cancer/Radiotherapie. 2022; 26: 417–423.
- [15] Mosavi F, Ullenhag G, Ahlström H. Whole-body MRI including diffusion-weighted imaging compared to CT for staging of malignant melanoma. Upsala Journal of Medical Sciences. 2013; 118: 91–97.
- [16] Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. Breast Cancer Research and Treatment. 2016; 160: 347–360.
- [17] Kyrgidis A, Lallas A, Moscarella E, Longo C, Alfano R, Argenziano G. Does pregnancy influence melanoma prognosis? A meta-analysis. Melanoma Research. 2017; 27: 289–299.
- ^[18] Loibl S, Schmidt A, Gentilini O, Kaufman B, Kuhl C, Denkert C, *et al.* Breast cancer diagnosed during pregnancy. JAMA Oncology. 2015; 1:

1145.

- [19] Pearl JP, Price RR, Tonkin AE, Richardson WS, Stefanidis D. SAGES guidelines for the use of laparoscopy during pregnancy. Surgical Endoscopy. 2017; 31: 3767–3782.
- [20] Rollins MD, Chan KJ, Price RR. Laparoscopy for appendicitis and cholelithiasis during pregnancy: a new standard of care. Surgical Endoscopy. 2004; 18: 237–241.
- [21] Ball E, Waters N, Cooper N, Talati C, Mallick R, Rabas S, et al. Evidencebased guideline on laparoscopy in pregnancy: commissioned by the British Society for Gynaecological Endoscopy (BSGE) endorsed by the Royal College of Obstetricians & Gynaecologists (RCOG). Facts, Views & Vision in ObGyn. 2019; 11: 5.
- ^[22] van Gerwen M, Maggen C, Cardonick E, Verwaaijen EJ, van den Heuvel-Eibrink M, Shmakov RG, *et al.* Association of chemotherapy timing in pregnancy with congenital malformation. Obstetrical & Gynecological Survey. 2021; 76: 732–733.
- ^[23] Pinnix CC, Osborne EM, Chihara D, Lai P, Zhou S, Ramirez MM, et al. Maternal and fetal outcomes after therapy for hodgkin or non-hodgkin lymphoma diagnosed during pregnancy. JAMA Oncology. 2016; 2: 1065.
- [24] Maggen C, Wolters VERA, Cardonick E, Fumagalli M, Halaska MJ, Lok CAR, et al. Pregnancy and cancer: the INCIP project. Current Oncology Reports. 2020; 22: 17.
- [25] Maggen C, Wolters VERA, Van Calsteren K, Cardonick E, Laenen A, Heimovaara JH, *et al.* Impact of chemotherapy during pregnancy on fetal growth. The Journal of Maternal-Fetal & Neonatal Medicine. 2022; 35: 10314–10323.
- ^[26] Freret TS, Exman P, Mayer EL, Little SE, Economy KE. Birthweight and chemotherapy exposure in women diagnosed with breast cancer during pregnancy. American Journal of Perinatology. 2022; 39: 554–561.
- [27] Amant F, Berveiller P, Boere IA, Cardonick E, Fruscio R, Fumagalli M, et al. Gynecologic cancers in pregnancy: guidelines based on a third international consensus meeting. Annals of Oncology. 2019; 30: 1601– 1612.
- [28] Webb KE, Sakhel K, Chauhan SP, Abuhamad AZ. Adnexal mass during pregnancy: a review. American Journal of Perinatology. 2015; 32: 1010– 1006.
- ^[29] Amant F, Vandenbroucke T, Verheecke M, Fumagalli M, Halaska MJ, Boere I, *et al.* Pediatric outcome after maternal cancer diagnosed during pregnancy. The New England Journal of Medicine. 2015; 373: 1824– 1834.
- ^[30] Lu D, Ludvigsson JF, Smedby KE, Fall K, Valdimarsdóttir U, Cnattingius S, *et al.* Maternal cancer during pregnancy and risks of stillbirth and infant mortality. Journal of Clinical Oncology. 2017; 35: 1522–1529.
- [31] Schwab R, Anic K, Hasenburg A. Cancer and pregnancy: a comprehensive review. Cancers. 2021; 13: 3048.
- [32] Sorokine A, Czuzoj-Shulman N, Abenhaim HA. Maternal and neonatal outcomes in women with a history of chemotherapy exposure: a population-based study of 8 million obstetric admissions. Archives of Gynecology and Obstetrics. 2023; 307: 747–753.
- [33] Mitchell KB, Johnson HM. Challenges in the management of breast conditions during lactation. Obstetrics and Gynecology Clinics of North America. 2022; 49: 35–55.
- [34] Damoiseaux D, Centanni D, Beijnen JH, Amant F, Huitema ADR, Dorlo TPC. Predicting chemotherapy distribution into breast milk for breastfeeding women using a population pharmacokinetic approach. Clinical Pharmacokinetics. 2023; 62: 969–980.
- [35] Castanon A, Landy R, Pesola F, Windridge P, Sasieni P. Prediction of cervical cancer incidence in England, UK, up to 2040, under four scenarios: a modelling study. The Lancet Public Health. 2018; 3: e34– e43.
- [36] Choi S, Ismail A, Pappas-Gogos G, Boussios S. HPV and cervical cancer: a review of epidemiology and screening uptake in the UK. Pathogens. 2023; 12: 298.
- [37] McGee AE, Alibegashvili T, Elfgren K, Frey B, Grigore M, Heinonen A, *et al*. European consensus statement on expert colposcopy. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2023; 290: 27–37.
- [38] Singh N, Rous B, Ganesan R. 2018 FIGO staging system for cervical cancer: summary and comparison with 2009 FIGO staging system. International Journal of Gynecology & Obstetrics. 2019; 145: 129–135.

- [39] Alouini S, Rida K, Mathevet P. Cervical cancer complicating pregnancy: implications of laparoscopic lymphadenectomy. Gynecologic Oncology. 2008; 108: 472–477.
- [40] Smith HO, Qualls CR, Romero AA, Webb JC, Dorin MH, Padilla LA, et al. Is there a difference in survival for IA1 and IA2 adenocarcinoma of the uterine cervix? Gynecologic Oncology. 2002; 85: 229–241.
- [41] Reed N, Balega J, Barwick T, Buckley L, Burton K, Eminowicz G, et al. British Gynaecological Cancer Society (BGCS) cervical cancer guidelines: recommendations for practice. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2021; 256: 433–465.
- [42] Lyu J, Sun T, Tan X. Ovarian preservation in young patients with stage I cervical adenocarcinoma: a surveillance, epidemiology, and end results study. International Journal of Gynecologic Cancer. 2014; 24: 1513–1520.
- [43] Tirlapur A, Willmott F, Lloyd P, Brockbank E, Jeyarajah A, Rao K. The management of pregnancy after trachelectomy for early cervical cancer. The Obstetrician & Gynaecologist. 2017; 19: 299–305.
- [44] Howe T, Lankester K, Kelly T, Watkins R, Kaushik S. Cervical cancer in pregnancy: diagnosis, staging and treatment. The Obstetrician & Gynaecologist. 2022; 24: 31–39.
- [45] Franciszek Dłuski D, Mierzyński R, Poniedziałek-Czajkowska E, Leszczyńska-Gorzelak B. Ovarian cancer and pregnancy—a current problem in perinatal medicine: a comprehensive review. Cancers. 2020; 12: 3795.
- [46] Gezginç K, Karataylı R, Yazıcı F, Acar A, Celik C, Capar M. Ovarian cancer during pregnancy. International Journal of Gynecology & Obstetrics. 2011; 115: 140–143.
- [47] Oehler MK, Wain GV, Brand A. Gynaecological malignancies in pregnancy: a review. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2003; 43: 414–420.
- [48] Han SN, Lotgerink A, Gziri MM, Van Calsteren K, Hanssens M, Amant F. Physiologic variations of serum tumor markers in gynecological malignancies during pregnancy: a systematic review. BMC Medicine. 2012; 10: 86.
- [49] Bhagat N, Gajjar K. Management of ovarian cysts during pregnancy. Obstetrics, Gynaecology & Reproductive Medicine. 2022; 32: 205–210.
- ^[50] Timmerman D, Ameye L, Fischerova D, Epstein E, Melis GB, Guerriero S, *et al.* Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. The BMJ. 2010; 341: c6839.
- [51] Fauvet R, Brzakowski M, Morice P, Resch B, Marret H, Graesslin O, *et al.* Borderline ovarian tumors diagnosed during pregnancy exhibit a high incidence of aggressive features: results of a French multicenter study. Annals of Oncology. 2012; 23: 1481–1487.
- [52] Fotopoulou C, Hall M, Cruickshank D, Gabra H, Ganesan R, Hughes C, et al. British Gynaecological Cancer Society (BGCS) epithelial ovarian/fallopian tube/primary peritoneal cancer guidelines: recommendations for practice. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2017; 213: 123–139.
- [53] Davenport CF, Rai N, Sharma P, Deeks J, Berhane S, Mallett S, *et al.* Diagnostic models combining clinical information, ultrasound and biochemical markers for ovarian cancer: cochrane systematic review and meta-analysis. Cancers. 2022; 14: 3621.
- [54] Ngu S, Ngan HYS. Chemotherapy in pregnancy. Best Practice & Research Clinical Obstetrics & Gynaecology. 2016; 33: 86–101.

- [55] Smrz SA, Calo C, Fisher JL, Salani R. An ecological evaluation of the increasing incidence of endometrial cancer and the obesity epidemic. American Journal of Obstetrics and Gynecology. 2021; 224: 506.e1– 506.e8.
- ^[56] Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. The Lancet. 2022; 399: 1412–1428.
- [57] Ayhan A, Gunalp S, Karaer C, Gokoz A, Oz U. Endometrial adenocarcinoma in pregnancy. Gynecologic Oncology. 1999; 75: 298–299.
- [58] Herrera Cappelletti E, Humann J, Torrejón R, Gambadauro P. Chances of pregnancy and live birth among women undergoing conservative management of early-stage endometrial cancer: a systematic review and meta-analysis. Human Reproduction Update. 2022; 28: 282–295.
- [59] Yael HK, Lorenza P, Evelina S, Roberto P, Roberto A, Fabrizio S. Incidental endometrial adenocarcinoma in early pregnancy: a case report and review of the literature. International Journal of Gynecologic Cancer. 2009; 19: 1580–1584.
- [60] 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. American Journal of Obstetrics and Gynecology. 2012; 207: 266.e1–266.e12.
- [61] Morrison J, Balega J, Buckley L, Clamp A, Crosbie E, Drew Y, et al. British Gynaecological Cancer Society (BGCS) uterine cancer guidelines: recommendations for practice. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2022; 270: 50–89.
- [62] Morrison J, Baldwin P, Buckley L, Cogswell L, Edey K, Faruqi A, et al. British Gynaecological Cancer Society (BGCS) vulval cancer guidelines: recommendations for practice. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2020; 252: 502–525.
- [63] Cho A, Lee S, Park J, Kim D, Suh D, Kim J, et al. Continued medical treatment for persistent early endometrial cancer in young women. Gynecologic Oncology. 2021; 160: 413–417.
- [64] Morrison J, Baldwin P, Buckley L, Cogswell L, Edey K, Faruqi A, et al. British Gynaecological Cancer Society (BGCS) vulval cancer guidelines: recommendations for practice. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2020; 252: 502–525.
- [65] Pereira Arias-Bouda LM, Vidal-Sicart S, Valdés Olmos RA. Preoperative and intraoperative lymphatic mapping for radioguided sentinel lymph node biopsy in breast cancer. Atlas of Lymphoscintigraphy and Sentinel Node Mapping. 2020; 63: 185–217.
- [66] van Maaren MC, Bretveld RW, Jobsen JJ, Veenstra RK, Groothuis-Oudshoorn CG, Struikmans H, *et al.* The influence of timing of radiation therapy following breast-conserving surgery on 10-year disease-free survival. British Journal of Cancer. 2017; 117: 179–188.
- [67] Kal HB, Struikmans H. Radiotherapy during pregnancy: fact and fiction. The Lancet Oncology. 2005; 6: 328–333.
- [68] DiSaia PJ, Creasman WT, Mannel RS, McMeekin DS, Mutch DG. Clinical gynecologic oncology. 9th edn. Elsevier Health Sciences: Philadelphia. 2017.

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