A review on pregnancy complicated by ovarian epithelial and non-epithelial malignant tumors: Diagnostic and therapeutic perspectives

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Graphical abstract

Abstract

The management of gestational ovarian cancer can be challenging because of the risk of fetal wastage, and the possibility of treatment-related complications to the fetus; it is based on insufficient data from retrospective studies and case series. Here, a literature review of the diagnostic and surgical approaches to the gestational ovarian cancer has been performed; moreover, data on safety of chemotherapeutic treatments in pregnancy, including both oncologic and fetal outcomes, have also been reviewed. Up to now, 193 cases of ovarian cancers during pregnancy have been reported in the English literature. Treatment of ovarian malignancies during pregnancy depends on histology, stage, and gestational weeks. When possible, surgical excision is indicated, and fertility-sparing surgery can be offered to stage I epithelial ovarian tumours (EOC), germ cell ovarian, or sex-cord stromal ovarian tumours. Neoadjuvant and/or adjuvant chemotherapy for advanced ovarian tumours is indicated as in non-pregnant women. Administration of chemotherapy after the first trimester, can cause fetal growth restriction, while being seemingly safe. The therapeutic approach of ovarian cancer in pregnancy should be individualized and intended in specialized centers.

Introduction

Cancer diagnosed during pregnancy is likely to rise since the delay of childbearing to a later reproductive age is frequent nowadays [1]. Most common maternal malignancies are breast cancer,
cervical cancer, lymphomas and melanoma [2]. Ovarian tumours are estimated to complicate approximately 2.8–11 in 100,000 pregnancies [3]. Among these tumours, approximately 5% are malignant [4]. Many of the gestational ovarian malignancies represent a Krukenberg tumour. With this regard, any new ovarian growth should be actively managed in women with a history of gastrointestinal tract cancers [5].

Most adnexal masses during gestation are functional or benign [6]. Corpus luteum of the pregnancy and simple cysts are still frequently demonstrated in the pathological diagnosis of ovarian tumour during pregnancy, ranging from 11 to 41% [7]. The number of asymptomatic ovarian masses has increased with the use of prenatal ultrasonography. Currently surgical intervention is indicated for an ovarian mass over 6 cm in diameter or when symptomatic.

The optimal management of ovarian cancer in pregnancy takes into account both maternal and fetal risks, and is mainly based on small retrospective studies. Surgical management has been recommended in the second trimester in an effort to reduce the risk of miscarriage, torsion, rupture and delayed diagnosis of malignancy [8]. Systemic chemotherapy is not administered in the first trimester, due to the higher risk of miscarriage and congenital malformations. Overall, the combination of carboplatin and paclitaxel is suggested for invasive EOC, similarly to non-pregnant patients. Bevacizumab should be avoided, owing to insufficient evidence regarding its use during pregnancy. For non-epithelial ovarian cancer (NEOC), paclitaxel carboplatin or cisplatin-vinblastin-bleomycin (PVB) chemotherapy may be designated instead of bleomycin, etoposide, and cisplatin (BEP) regimen, which is considered more toxic [9].

The aim of the present study was to conduct a systematic review of the literature describing pregnancies and feto-maternal outcomes complicated by ovarian malignancies, including Krukenberg tumours.

Methods

The PubMed database was searched using the terms “ovarian tumours, pregnancy”, “ovarian carcinoma, pregnancy”, “surgery, pregnancy”, “chemotherapy, pregnancy”, “adnexal masses, pregnancy”, and “Krukenberg, pregnancy”. Publications between January 1986 and December 2016 in English were eligible for inclusion. Case reports or case series describing pregnant patient with ovarian malignancy coincident with pregnancy with detailed description of maternal, fetal, and tumour characteristics and outcomes were included. We finally identified 282 cases of gestational ovarian cancer that were retrieved from 45 relevant studies and reports in the literature. Among them, 193 patients were diagnosed with NEOC.

Diagnostic work up in gestational ovarian cancer

Most pelvic masses diagnosed during pregnancy are discovered incidentally during routine fetal ultrasound [10], excluding cases of an acute abdomen by ovarian torsion [11]. Clinical examination is extremely difficult, whereas vaginal and abdominal ultrasound are performed in the first and second/third trimester, respectively. The estimation of fluxometric parameters in pregnancy is demanding, due to the decreased blood flow impedance and the increased blood flow velocity [12]. These findings are presented both in malignant tumours and inflammatory lesions making difficult to diagnose. The reported sensitivity and specificity for malignancies are 88 and 96%, respectively [13]. Adnexal masses that persist until the second trimester, or those with septations, solid component nodules, papillary components, or an average diameter of greater than 5 cm are suggestive of malignancy and should be surgically resected [14]. Among 91 masses diagnosed as simple cysts in a study, 89 were pathologically confirmed to be benign [15]. The reported 6 malignancies were correctly identified by typical ultrasonic features.

Computerized tomography (CT) and magnetic resonance imaging (MRI) can be useful adjuncts when screening ultrasound imaging is inconclusive. CT might clarify the extraperitoneal spread of the disease but exposes the fetus to irradiation to at least 2 to 4 cGy. Contrast material can pass the placental barrier and its effects on the fetus are not clearly known; thus, it is contraindicated during pregnancy. MRI might be useful for evaluation of large masses that are difficult to visualize with ultrasound. It can also assess whether the tumour is widespread in the abdomen, discriminate acute bowel processes, and distinguish degenerating myoma from ovarian neoplasm [16]. Gadolinium has been found to cross the placenta and to stimulate malformations in animal models; hence, its use during pregnancy is contraindicated, particularly in the first trimester of pregnancy [17].

CA 125 is often physiologically elevated in benign disease processes such as menses, uterine fibroid, and endometriomas. It is also typically increased during first trimester and immediately after delivery because of chorionic invasion [18]. In second and third trimester CA 125 levels are low in maternal serum but high in the amniotic fluid [19]. If EOC is confirmed, CA 125 may be useful during later assessment or follow-up evaluation.

Surgery in gestational ovarian cancer

Preoperative considerations

Surgery in pregnant women is associated with several risks; thus, in case of low probability of malignancy, watchful waiting policy is reasonable [20]. Nevertheless, when the patient is at high risk for torsion, rupture, or infarction, acute abdomen, and most importantly malignant transformation of a mass, surgical management is indicated. In fact, the most common and serious complication of ovarian tumour during pregnancy is torsion that is usually present at gestational weeks 8–16, at which point the uterus grows intensely. The reported torsion rate of adnexal masses during pregnancy is 10–15% [21]. Rupture of the tumour is relatively rare [21].

Medically induced abortion followed by standard treatment of EOC is a potential option especially in the first trimester. If abortion is declined by the patient, surgery and chemotherapy should be avoided during the first trimester due to higher abortion rates [22]. This is based on retrospective reports from the 1970s of low-birth-weight infants as well as infants’ death within a week [23]. Safe management of complicated adnexal masses with laparoscopic surgery during the first trimester has been described [24]; albeit an increased risk of miscarriage associated with surgery in the first trimester of pregnancy. Therefore, midgestation (12–27 weeks) should be selected for ovarian surgery during pregnancy. However, the risk of premature delivery, regardless of the route of the procedure, remains quite high, reaching 22% in some series [11]. The use of corticosteroids to accelerate fetal lung maturity can be considered 48 h prior to surgery for fetuses less than 34 weeks of gestation in either patients with spontaneous preterm labor resulting from surgery or those who are intentionally delivered early [11]. Progesterone, beta 2 agonist, may be considered in patients who undergo surgery during pregnancy, regardless of their gestational age (GA) [25]. However, there is a lack of data to support a benefit of the use of tocolytic agents for pregnant women with non-obstetric surgery during pregnancy [26]. A systemic review failed to demonstrate positive effects of the routine use of prophylactic tocolytics for pregnant women who need non-obstetric surgery during pregnancy [27].
use should be reserved for circumstances in which evidence of preterm labor is apparent [27]. The patient should be placed in left lateral oblique position prior to induction of anaesthesia, with the prospect of improving uterine blood flow and preventing inferior vena cava compression and supine hypotension syndrome [11]. In addition, ovarian surgery during pregnancy may be associated with the development of changes in fetal hemodynamics. At that point, it is suggested to conduct fetal monitoring prior to and after surgery, which can be accomplished through a reassuring electronic fetal heart rate monitoring or biophysical profile [28]. On the other hand, the intraoperative fetal heart rate monitoring is more controversial, due to the limited knowledge of normal fetal physiological responses to maternal anaesthesia and surgical stress [26].

Surgery can be performed either by laparotomy or laparoscopy [29]. There are no available prospective studies to comparatively evaluate these strategies during pregnancy. However, multiple observational studies support that laparoscopic management of adnexal masses in pregnancy is technically feasible and associated with reduced risk of pregnancy complications [29].

General surgical considerations

The principal concept in the surgical management of adnexal masses during pregnancy is similar to that of non-pregnant women. The surgical staging of EOC typically consists of hysterectomy, bilateral salpingo-oophorectomy (BSO), omentectomy, appendectomy, peritoneal washing with cytology, systematic peritoneal biopsies in all areas of the abdomen, as well as pelvic and para-aortic lymphadenectomy [30]. The conservative treatment of EOC is strictly limited to patients with early stage disease due to frequent relapse rates [31]. A frozen section is usually required, and then actions are decided on accordingly. In advanced disease, complete removal of all macroscopic tumour lesions is essential [32]. As long as continuation of pregnancy is desired, chemotherapy should be delayed until fetal lung maturity followed by delivery and postpartum treatment [31,33]. Surgery of the pelvis is more demanding with increased GA taking into account that uterine manipulation should be avoided in order to prevent preterm contractions [16]. Similarly, systematic lymph-node dissection may be technically difficult. Therefore, in advanced tumour stages surgery could be limited to establish the diagnosis followed by a thorough clinical staging [9]. Neo-adjuvant chemotherapy until fetal maturity and delivery is then the recommended approach. In terms of mode of delivery, caesarean section at the time of fetal lung maturity is one option. Otherwise, administration of platinum-based chemotherapy, and delay surgery until a few weeks after spontaneous vaginal delivery is the management of choice [30].

If laparotomy is indicated during pregnancy a vertical midline incision provides the advantage of adequate exposure. Laparoscopic surgery should be utilized in cases of tumour size less than 6 to 8 cm, as there is no suspicion for advanced-stage ovarian cancer and complete intact removal of the mass is feasible [34]. Laparoscopic removal of ovarian tumours in early pregnancy is considered as safe as laparotomy because it reduces manipulation of the pregnant uterus during surgery [8]. Accidental rupture of the tumour at the time of surgery is considered harmful due to the potential malignant spreading. Laparoscopic surgery is generally associated with less postsurgical morbidity compared to laparotomy [35]. For technical reasons however, most of the traditional laparoscopic surgical procedures still require multiple abdominal incisions. Laparoendoscopic single-site (LESS) surgery has been introduced into clinical practice to promote the minimally invasive benefits of the laparoscopic strategy [36].

Laparoscopy and laparotomy have a similar risk profile associated with the outcome of pregnancy. Results of a retrospective study revealed an increased risk for both approaches of low-birthweight infants, preterm births, and growth restriction as compared to the general population [37].

Concerns over pneumoperitoneum induced by laparoscopy during pregnancy include reduced venous return to the heart of the pregnant patient, possible compromise of the uteroplacental perfusion, and fetal acidosis caused by carbon dioxide gas absorption [38]. On the other hand, laparoscopy is associated with fewer postoperative complications, decreased blood loss, less postoperative pain, limited use of narcotics, and shorter hospitalization. Its impact on pregnancy-related outcomes is not negative [39]. Gasless laparoscopy, if available, could be suggested due to less prominent hemodynamic and respiratory effects on mother and fetus.

Generally, malignant ovarian germ cell tumours could be treated by conservative surgery. Surgical staging of these curable entities is crucial to determine whether adjuvant chemotherapy is required, especially in pregnant patients. The staging procedure includes washing cytology, ipsilateral salpingo-oophorectomy, peritoneal biopsies, and omentectomy. Examination of the cul-de-sac and pelvis is commonly suboptimal, because of the limited uterine manipulations in order to avoid premature uterine contractions. Lymphadenectomy during surgical staging should be performed in selected cases with enlarged nodes. Since germ-cell tumours are chemosensitive tumours, a fertility-sparing surgery is recommended even in the advanced stages providing that contralateral ovary is unaffected. Juvenile granulosa cell tumours could be adequately treated with adnexectomy offering similar surgical management as in non-pregnant women [40].

Chemotherapy in gestational ovarian cancer

General considerations

The pharmacokinetic properties of chemotherapy might be modified due to physiologic alterations during pregnancy, such as faster hepatic oxidation, increased renal clearance, and enlarged third space [41]. Small spatial configuration and high lipid solubility of the majority of chemotherapeutic agents facilitate easy transfer across the placenta. Considering that most drugs cross the placenta, their unbound concentrations are similar or higher in the fetal serum and amniotic fluid comparing to the maternal serum.

The administration of chemotherapy during the first trimester is correlated to a potentially increased risk of major malformations, spontaneous abortions, and fetal death [42]. First trimester chemotherapy exposure is associated with a 10–20% risk of fetal malformations, while administration during second and third trimester is significantly safer with a fetal malformation risk of 1.3% [43]. Hence, pregnancy termination should be considered in patients with cancer who need systemic treatment in the first trimester [2]. According to available data, chemotherapy during the second and third trimesters may lead to a relatively higher risk of premature rupture of membranes (PROM), intrauterine growth restriction (IUGR), and premature labor [43–45]. In addition, since both the mother and fetus are at risk for infections and bleeding during delivery because of hematological toxicity, chemotherapy should be discontinued 3 to 4 weeks before delivery, to prevent myelosuppression in the parturient and neonates [41].

EOC is an extremely chemosensitive disease, mainly to platinum and taxanes. Nevertheless, the available data in the literature regarding the use of chemotherapy for ovarian cancer during pregnancy is limited. Anthracyclines, doxorubicin and epirubicin, are mainly designated in FIGO and can be used after organogenesis.
in combination with platinum based chemotherapy [41,46]. However, data on long-term effects, such as learning or behavior problems that may result from the chronic prenatal exposure to chemotherapy are insufficient.

**Platinum derivatives**

Treatment with platinum derivatives during pregnancy is recommended. It is important that such a treatment is not associated with teratogenic effects, if it is provided during the second and third trimester [47]. Among 43 pregnant patients, 36 were treated with cisplatin, 6 with carboplatin, and one received both agents [47]. Several fetal adverse effects were revealed; namely, IUGR and preterm birth (each 8.3%, n = 3), oligohydramnios (5.6%, n = 2), and polyhydramnios (2.8%, n = 1). Neonatal toxicity included acute respiratory distress (8.3%, n = 3), anemia (5.6%, n = 2), microphthalmus, leukopenia, pancytopenia and creatinine elevation (each 2.8%, n = 1). Acknowledging that, sensorineural hearing loss following cisplatin use has been reported, confounding factors however such as postnatal gentamycin treatment and prematurity were also observed [41]. In contrast, carboplatin has not resulted in fetal malformations, toxicities, or adverse neonatal effects [47]. This is the rationale for the commonest utilization of carboplatin than of cisplatin. Interestingly, a meta-analysis that evaluated the use of platinum derivatives as single agents or in combination during pregnancy in women with cervical cancer did not reveal teratogenic effects in any of the 48 cases described [48].

Among 14 patients with gestational ovarian malignancies treated with platinum monotherapy, 13 were diagnosed with EOC, whereas one patient with endodermal sinus tumour (EST). In terms of complications and fetal outcome, spontaneous abortion [40], anemia [49], and fetal death [1] have been reported in 3 cases respectively (Table 1).

**Paclitaxel during pregnancy**

The taxane antineoplastic mode of action is unique, and the clinical experience of their use in pregnancy is limited [2]. It seems that there is no statistically significant differences in obstetric and neonatal outcomes in pregnant women treated with taxane-based regimen as compared to other cytotoxics [50]. Paclitaxel has been used during pregnancy for breast and ovarian cancers, but long-term data are scanty [51]. Due to the low molecular weight, taxanes would be expected to easily cross the placenta. However, data from animal models confirmed minimal transplacental transfer of taxanes, probably due to the high expression of P-glycoprotein in the placenta [52]. A systematic review on 50 patients with breast cancer, who had been treated with taxanes during pregnancy, revealed a completely uneventful neonatal outcome in 76.7% of cases, whereas 90% of children were healthy with a median follow-up of 16 months [53]. These results are in accordance with the data from the American and European-based registries [50,54].

**Platinum-taxane combination**

Table 2 depicts the reported patients with EOC treated with chemotherapy during pregnancy, including details of maternal and neonatal outcome. Among 69 patients, the most frequent histologic subtypes were serous [1,4,8,30,40,55–65], mucinous [4,8,40,66–71] and endometrioid [40,72–74] in 35, 14 and 4 patients, respectively. These cases have documented the use of combination of taxane and platinum for stage III gestational EOC in both adjuvant and neoadjuvant setting. The physical, neurological, psychological, hematological, and immunological functions of the infants postpartum were normal in 78.2%. Among the patients with EOC, 25 received the combination of platinum-taxane, 20 were treated with platinum based chemotherapy while platinum monotherapy was chosen in 13 (Table 2). Spontaneous abortions were experienced in 4 cases [40], IUGR in 2 [50,58], whereas ventriculomegaly [65], polyhydramnios [70], PROM [71], and respiratory distress syndrome [74] were documented in 4 cases, respectively. With regards to neonatal outcome, there were 2 reported deaths [1,65], whereas Asperger syndrome [50], and congenital talipes equinovarus [58] were diagnosed in 2 cases respectively. There is enough data available for the outcome of 14 patients treated with the combination of carboplatin/paclitaxel (Table 1). The reported complications included a case of IUGR [50] and 2 cases with RDS respectively [74,75]. Based on the overall tolerable toxicities of carboplatin and paclitaxel for both mother

| Ref | Regimen | Number | Reported complications/malformations |
|-----|---------|--------|-------------------------------------|
| [1,4,40,76–78,89] | BEP | 19 | Abortion (1)\(^a\); IUGR (1); Respiratory failure and anemia in parallel (1); VM and RDS in parallel (1); Anemia (1) |
| [1,79,80] | EP | 5 | IUGR and LBV (1); Oligohydramnios and IUGR (1) |
| [1,40,81,82] | PVB | 9 | Abortion (1); Fetal death of RDS (1); VM (1); Anemia (1) |
| [1,40,49,60,61,72,101] | Platinum alone | 14 | Abortion (1); Fetal death (1); Minor RDS and mild anemia (1); RDS and TT (1) |
| [4,30,50,55,66,74,75] | CPac | 14 | IUGR (1) |
| [40,59] | CAP | 6 | Abortion (2); None |
| [50,56,59,65,67,69] | CDDP + Taxane | 6\(^b\) | Anhydramnios (1); Asperger syndrome (1)\(^c\) |
| [40,62,63,70,71,102] | PC | 7 | Abortion (1); Polyhydramnios (1); PROM (1); RDS in the case of polyhydramnios (1) |

Ref: reference; BEP: cisplatin, etoposide, bleomycin; IUGR: intrauterine growth restriction; VM: ventriculomegaly; RDS: respiratory distress syndrome; EP: etoposide, cisplatin; LBW: low birth weight; PVB: cisplatin, vinblastine, bleomycin; CPac: carboplatin, paclitaxel; TT: testicular torsion; CAP: cisplatin, adriamycin/epirubicin, cyclophosphamide; CDDP: cisplatin; PC: cisplatin, cyclophosphamide; PROM: premature rupture of membranes.

\(^a\) Numbers reported are shown in parentheses.

\(^b\) One twin pregnancy.

\(^c\) One in the case of anhydramnios.
Epithelial ovarian tumours in pregnancy (69). In three cases, fetal side effects were related to 
patients treated with BEP, the reported maternal complications with an overall good pregnancy outcome (Table 1). Among 19 
EOC during gestation.

Table 2

| Path | Serous | Endometriod | Mucinous | Other |
|------|--------|-------------|----------|-------|
| Ref  | 1,4,8,30,40,55-65 | 40,72-74 | 4,40,66-71 | 1,4,40,50,101,103 |
| Pts  | 35^a | 4^a | 14^b | 16^c |
| %    | 50.7 | 5.8 | 20.3 | 23.2 |
| Chemo [%] | Platinum/Taxane [36.2]; Platinum based [29]; Platinum alone [18.9]; None [8.7]; N/A [2.9]; Other [4.3] |
| GA at Delivery (W), [%] | >34 [68.1]; ≤34 [23.2]; N/A [8.7] |
| Obstetrical outcome | Normal [25/35]; Fetal death [1/35]; Ab [3/35]; IUGR [1/35]; VM [1/35]; N/A [4/35] |
| Neonatal outcome | Healthy [27/31]; Neonatal death [2/31]; CTEV [1/31]; N/A [1/31] |

Path: pathology; Ref: reference; Pts: patients; Chemo: chemotherapy; N/A: not available; GA: gestational age; W: week; Ab: abortion; IUGR: intrauterine growth restriction; VM: ventriculomegaly; RDS: respiratory distress syndrome; TT: testicular torsion; PROM: premature rupture of membranes; CTEV: congenital talipes equinovarus

^a Numbers reported are shown in parentheses.
^b One of the cases with RDS at birth.
^c One twin pregnancy.
^d One due to RDS

and child, this regimen is considered as the standard regimen for EOC during gestation.

The BEP regime is a reasonable therapeutic choice for NEOC with an overall good pregnancy outcome (Table 1). Among 19 patients treated with BEP, the reported maternal complications included spontaneous abortion, and IUGR, in two patients respectively [40,76]. In three cases, fetal side effects were related to respiratory failure with either anaemia or ventriculomegaly as well as myelosuppression [1,77,78]. Similarly, etoposide and cisplatin (EP) was administered in five patients with gestational ovarian malignant germ cell tumours. IUGR with either low birth weight or oligohydramnios was detected in two cases (Table 1) [1,79,80]. The second infant was delivered with anaemia and thrombocytopenia, resulting in impressive upstaging in 24%.

Hyperthermic intraperitoneal chemotherapy (HIPEC)

Intraperitoneal chemotherapy has not been widely adopted in pregnant women [58], due to significant toxicity and poor treatment completion rates [83]. However, an uneventful treated case with Krukenberg tumour managed with HIPEC after caesarian section was reported [84]. The effect of HIPEC on fertility is unknown as the available information is limited; however, seven spontaneous pregnancies following treatment with HIPEC have been described in a case series of patients diagnosed with metastatic colon cancer [85]. Another case of a pregnant woman with ovarian cancer treated with intraperitoneal carboplatin and paclitaxel developed mild pre eclampsia and thrombocytopenia at 32 weeks, as well as small for GA fetal weight, and bilateral talipes equinovarus at birth [58].

Non-epithelial ovarian cancer in pregnancy

The majority of patients with NEOC present with bulky masses that may be measured up to 30 cm [13]; nevertheless more than 90% of them are diagnosed with early stage disease. Taking into account the favorable prognosis of stage I NEOC, the fertility-sparing surgical approach with optimal staging is recommended. This is based on a retrospective review of borderline ovarian tumours during pregnancy, which revealed a high incidence of aggressive features [86]. Restaging was performed in 52% of cases, resulting in impressive upstaging in 24%.

Table 3 summarizes the reported 193 patients diagnosed with NEOC, and treated with chemotherapy during pregnancy. Among 145 documented cases of germ cell tumours, histopathology was compatible with EST in 52 patients [1,4,40,49,76,77,79,81,87,88], dysgerminoma in 45 [4,8,40,75,80,87], immature teratoma in 24 [4,40,76,82,87,89], whereas mixed elements were revealed in 13 patients [1,40,78,87], respectively. Platinum-bleomycin based chemotherapy was administered in 68 patients. As far as recognized fetal growth abnormalities is concerned, IUGR was relatively common (14.5%) [76,79,80,87]. Spontaneous abortion was experienced in five cases (3.4%) [40,87], whereas ventriculomegaly [1,77,88] and respiratory distress syndrome [1,39,1,40] were identified in three and two cases, respectively.

The abortion rate of women with a history of germ cell tumours is in line with the general population (11.5%), whereas the malformation rate is rather increased (7.27% versus 3%). This elevation is associated with the tumour biology and the mutations in the
karyotype, more commonly in bilateral tumours. Interestingly enough, it has been demonstrated that up to 5% of dysgerminoma patients are phenotypic females with 46, XY karyotype [90]. As such, the performance of karyotype examination is indicated in patients who want to conceive, in order to be excluded genetic disorders, especially in those previously diagnosed with dysgerminoma.

In terms of sex-cord stromal tumours, among 46 patients who mainly underwent unilateral salpingo-oophorectomy (USO) or node removal in the second and third trimesters, 69.4% achieved preservation of the fetus [91]. Furthermore, 71 and 26.1% of cases required one or multiple surgical debulking procedures respectively. Infants were born at term at 60.9% of cases. Overall, treatment was delayed for retention of pregnancy in 95.2% of patients; nevertheless, serious adverse events occurred in a total of 40% of cases. These included maternal shock/hemoperitoneum, recurrence during pregnancy, maternal and/or neonatal death, and fetal loss after surgery. It is of importance to clarify that adverse outcomes presented entirely in patients with risk factors such as higher stage and older age. There is a total of 48 reported cases of sex cord stromal tumours that resulted mostly in live birth (81.8%) via the abdominal route (75.8%), and neonatal deaths were each experienced in one case.

**Pregnancy complicated by Krukenberg tumour**

Krukenberg tumour is a rare type of ovarian tumour initially described as a malignancy derived from the ovarian stroma, with mucoid degeneration and signet ring cells, which was also named ‘carcinoma microcellular’. This entity has been expanded to include all glandular carcinomas metastasizing to the ovaries from different sites [92].

Krukenberg tumours’ incidence accounts for approximately 1–2% of ovarian cancers. They are associated with a dismal prognosis, the optimal management remains unclear [93–95], and the outcome is often considered to be lethal [96]. The persistent gastrointestinal symptoms, as well as the physiologic and hormonal changes during pregnancy, usually mask the presentation of Krukenberg tumours [4,97]. Thus, early diagnosis may be delayed. Fetal asphyxia and virilization may be associated with advanced malignant disease and ovarian Krukenberg tumour. The mechanism of androgen overproduction is still poorly understood [98]. Stillbirth and prematurity represent the leading causes of fetal and neonatal mortality.

Identification of the primary site of Krukenberg ovarian tumours is rather challenging. Gastric cancer has been demonstrated as the most common primary source, where 76% of Krukenberg tumours originate from the stomach, followed by the intestine (11%), breast (4%), and appendix (3%) [99]. Sex hormones during pregnancy, promote the development and diffusion of gastric cancer by stimulating the underlying precancerous lesions. Placental growth factor levels have been determined to be much higher than vascular endothelial growth factor levels in gastric cancer tissue, and were also associated with serosal invasion, lymph node metastasis, cancer stage, and survival rates [84].

A systematic review identified pregnancies complicated by Krukenberg tumour [100]. The vast proportion of pregnancies ended in live birth (81.8%) via the abdominal route (75.8%), and more than half of the cases underwent cytoreductive surgery in the 3rd trimester (54.5%). Intraoperative findings are composed mostly of ascites (45.7%), followed by carcinomatosis (25.7%) and non-ovarian distal metastases (14.3%). Optimal tumour debulking for both the primary cancer and ovarian tumour was achieved in 12 cases (60.0%). More than half of the cases received chemotherapy (57.1%), almost entirely in the postpartum period. Provided

**Table 3**

| Path | Germ cell Tumours (145)\(^{a}\) | Ovarian sex-cord stromal tumours (48)\(^{a}\) |
|------|-----------------------------|----------------------------------|
| Ref  | Pt(s) [1,40,49,76,77,79,81,87,88] | Pt(s) [40,91] |
| %   | 26.9 | 8 | 26.9 | 3 | 23.3 | 67 |
| Chemo [%] | Platinum/bleomycin-based [BEP and PVB] [35.2]; EP [2.6]; None [26.9]; Other [10.3] | Platinum based [Platinum, cyclophosphamide ± epirubicin] [1.5]; None [20.7]; N/A [3];
| GA at Delivery (W), [\(\%\)] | \(>34 [71.5]\); \(<34 [20.7]\); N/A [7.7]; | Normal [37/48];
| Obstetrical outcome | Normal [109/145]; IUGR [21/145]; Ab [5/145]; N/A [4/145]; VM [3/145]; RDS [2/145]; Fetal death [1/145] | IUGR [4/48]; Fetal death [3/48]; N/A [2/48]; Ab [1/48]; VM [1/48]
| Neonatal outcome | Healthy [131/139]; N/A [4/139]; Neonatal death [4/139] | Healthy [43/44]; Neonatal death [1/44];

\(\) Numbers reported are shown in parentheses.

\(^{a}\) One due to RDS.
that the primary cancers were already diagnosed and treated before pregnancy in 20% of cases, the development of ovarian metastases during gestation has been estimated at a median of 11 months following diagnosis of the primary cancer. This highlights the importance of close follow-up in such cases for prompt diagnosis and treatment that would positively affect the outcome. The prognosis was overall dismal and the reported median survival time was 6 months.

Conclusions

Centralization of treatment of gestational ovarian cancer may help to develop a plan for a prospective study. Overall, the therapeutic approach mirrors that outside pregnancy, taking into account that surgery and neoadjuvant and/or adjuvant chemotherapy are feasible in most cases. Surgical procedures including adnexal cystectomy or salpingo-oophorectomy can be performed by either laparotomy or laparoscopy during pregnancy. Optimal timing of surgery is at midgestation, whereas chemotherapy can be administered during the second and third trimesters. Carboplatin- and paclitaxel-based regimens are recommended for EOC, whereas BEP, PVB, and carboplatin-paclitaxel can be considered for non-epithelial counterparts. The existing studies on the surgical and chemotherapeutic treatment demonstrate overall favorable fetal outcomes; nevertheless, long-term data on children exposed to intrauterine chemotherapy is required in order to understand the downstream effects of the treatments. Women with Krukenberg tumour complicated pregnancies have a poor prognosis which may be improved provided that radical surgery is utilized for both primary and metastatic tumours.

Future perspectives in gestational ovarian cancer

There is a lack of consensus regarding the treatment of ovarian malignancies. Most of the available literature comprises case reports or retrospective studies with a small number of patients. Collaboration between cancer centers and registries is essential in an effort to record survival data of patients and the long-term effects of the drugs on the developing children. Indeed, patients should be referred to centers with specific experience and registered through www.cancerinpregnancy.org. A multidisciplinary approach is encouraged.

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