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Review

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

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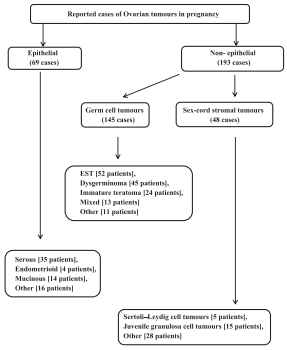
GRAPHICAL ABSTRACT



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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

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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 262 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 ultrasound features.

Computerized tomography (CT) and magnetic resonance imaging (MRI) can be useful adjuncts when screening ultrasound imaging is inconclusive. CT might clarify the extraovarian 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]. By contrast, their

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 of 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 culde-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 NEOC 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), anaemia (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], anaemia [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

Table 1
Maternal and fetal complications after treatment with certain chemotherapeutic regimens in ovarian cancer.

Ref	Regimen	Number	Reported complications/malformations	
			Mother	Fetus
[1,4,40,76–78,89]	BEP	19	Abortion (1)[a]; IUGR (1)	Respiratory failure and anaemia in parallel (1); VM and RDS in parallel (1); Anaemia (1)
[1,79,80]	EP	5	IUGR and LBW (1); Oligohydramnios and IUGR (1)	Anaemia, and thrombocytopenia in the case of oligohydramnios and IUGR (1)
[1,40,81,82]	PVB	9	Abortion (1)	Fetal death of RDS (1); VM (1)
[1,40,49,57,60,61,72,101]	Platinum alone	14	Abortion (1)	Fetal death (1); Anaemia (1)
[4,30,50,55,66,74,75]	CPac	14	IUGR (1)	Minor RDS and mild anaemia (1); RDS and TT (1)
[40,59]	CAP	6	Abortion (2)	None
[50,56,59,65,67,69]	CDDP + Taxane	6[b]	Anhydramnios (1)	Asperger syndrome (1)[b]; Neonatal deaths (2)[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.

Table 2
Epithelial ovarian tumours in pregnancy (69).[a]

Path	Serous	Endometriod	Mucinous	Other
Ref	[1,4,8,30,40,55–65]	[40,72–74]	[4,8,40,66–71]	[1,4,40,50,101,103]
Pts	(35)[a]	(4)[a]	(14)[a]	(16)[a]
%	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]	Normal [3/4]; RDS and TT [1/4]	Normal [12/14]; Polyhydramnios [1/14]; PROM [1/14]	Normal [14/16]; Ab [1/16]; IUGR [1/16]
Neonatal outcome	Healthy [27/31]; Neonatal death [2/31]; CTEV [1/31]; N/A [1/31]	Healthy [4/4]	Healthy [13/14][b]; N/A [1/14]	Healthy [15/16][c]; Asperger syndrome [1/16][c]

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 [79]. There is also potentially increased risk of secondary leukemia related to etoposide utilization. An international consensus on the treatment of gynecological malignancies during pregnancy proposed the use of alternative regimens such as PVB [9]. Indeed, PVB was used in some cases without maternal or fetal complications [1,40,81,82]. However, among nine documented cases of gestational ovarian germ cell tumours, there are reports of neonatal death due to respiratory failure, cerebral atrophy with ventriculomegaly and spontaneous abortion in three cases respectively [1,40] (Table 1). The European Society for Medical Oncology (ESMO) recommends the combination of cisplatin and weekly paclitaxel, after the first trimester, for the treatment of germ cell ovarian tumours [2], based on the safety data of non-pregnant patients with relapsed germ cell tumours [2].

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 preeclampsia 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

Table 3
Non-epithelial ovarian tumours in pregnancy (193).[a]

	Germ cell Tumours (145)[a]					Ovarian sex-cord stromal tumours (48)[a]		
Path	EST	Dysgerminoma	Immature teratoma	Mixed	Other	Sertoli-Leydig tumour	Juvenile granulosa cell tumour	Other
Ref	[1,4,40,49,76,77,79,81,87,88]	[4,8,40,75,80,87]	[4,40,76,82,87,89]	[1,40,78,87]	[87]	[91]	[40,91]	[91]
Pts	(52)	(45)	(24)	(13)	(11)	(5)	(15)	(28)
%	26.9	23.3	12.4	6.7	5.7	2.6	7.7	14.5
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];							
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]					Normal [37/48]; 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][b]					Healthy [43/44]; Neonatal death [1/44];		

Path: pathology; EST: endodermal sinus tumour; Ref: reference; Pts: patients; Chemo: chemotherapy; N/A: not available; BEP: cisplatin, etoposide, bleomycin; PVB: cisplatin, vinblastine, bleomycin; EP: etoposide, cisplatin; GA: gestational age; W: week; Ab: abortion; IUGR: intrauterine growth restriction; VM: ventriculomegaly; RDS: respiratory distress syndrome.

[a] Numbers reported are shown in parentheses.

[b] One due to RDS.

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 births (77%), summarized in Table 3 [40,91]. Only 8 patients required chemotherapy during pregnancy or after delivery (16.6%). The combination of cisplatin/cyclophosphamide with or without epirubicin was the treatment of choice in most cases. Histopathologically, juvenile granulosa cell and Sertoli-Leydig tumours are the most common identified subtypes in 15 and 5 patients respectively. IUGR and fetal death occurred in 8.3 and 6.3%, respectively. Ventriculomegaly, spontaneous abortion 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

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.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

References

[1] Pavlidis N. Cancer and pregnancy: what should we know about the management with systemic treatment of pregnant women with cancer? Eur J Cancer 2011;47(3):S348–52.
[2] Peccatori FA, Azim Jr HA, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, et alESMO Guidelines Working Group. Cancer, pregnancy and fertility: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(6). vi160-70.
[3] Gezginç K, Karataylı R, Yazıcı F, Acar A, Celik C, Capar M. Ovarian cancer during pregnancy. Int J Gynaecol Obstet 2011;115(2):140–3.
[4] Kwon YS, Mok JE, Lim KT, Lee IH, Kim TJ, Lee KH, et al. Ovarian cancer during pregnancy: clinical and pregnancy outcome. J Kor Med Sci 2010;25(2):230–4.
[5] Sun HD, Hsiao SM, Chen YJ, Wen KC, Li YT, Wang PH. Advanced endocervical adenocarcinoma metastatic to the ovary presenting as primary ovarian cancer. Taiwan J Obstet Gynecol 2015;54(2):201–3.
[6] Hoover K, Jenkins TR. Evaluation and management of adnexal mass in pregnancy. Am J Obstet Gynecol 2011;205(2):97–102.
[7] Katz L, Levy A, Wiznitzer A, Sheiner E. Pregnancy outcome of patients with dermoid and other benign ovarian cysts. Arch Gynecol Obstet 2010;281(5):811–5.
[8] Gasim T, Al Dakhiel SA, Al Ghamdi AA, Al Ali M, Al Jama F, Rahman J, et al. Ovarian tumors associated with pregnancy: a 20-year experience in a teaching hospital. Arch Gynecol Obstet 2010;282(5):529–33.
[9] Amant F, Halaska MJ, Fumagalli M, Dahl Steffensen K, Lok C, Van Calsteren K, et al. ESGO task force 'Cancer in Pregnancy'. Gynecologic cancers in pregnancy: guidelines of a second international consensus meeting. Int J Gynecol Cancer 2014;24(3):394–403.
[10] Yazbek J, Salim R, Woelfer B, Aslam N, Lee CT, Jurkovic D. The value of ultrasound visualization of the ovaries during the routine 11–14 weeks nuchal translucency scan. Eur J Obstet Gynecol Reprod Biol 2007;132(2):154–8.
[11] Grimm D, Woelber L, Trillsch F, Keller-v Amsberg G, Mahner S. Clinical management of epithelial ovarian cancer during pregnancy. Eur J Cancer 2014;50(5):963–71.
[12] Cavaco-Gomes J, Jorge Moreira C, Rocha A, Mota R, Paiva V, Costa A. Investigation and Management of Adnexal Masses in Pregnancy. Scientifica (Cairo) 2016;2016:3012802.
[13] Mancari R, Tomasi-Cont N, Sarno MA, Azim Jr HA, Franchi D, Carinelli S, et al. Treatment options for pregnant women with ovarian tumors. Int J Gynecol Cancer 2014;24(6):967–72.
[14] Valentin L, Hagen B, Tingulstad S, Eik-Nes S. Comparison of 'pattern recognition' and logistic regression models for discrimination between benign and malignant pelvic masses: a prospective cross validation. Ultrasound Obstet Gynecol 2001;18(4):357–65.
[15] Whitecar MP, Turner S, Higby MK. Adnexal masses in pregnancy: a review of 130 cases undergoing surgical management. Am J Obstet Gynecol 1999;181(1):19–24.
[16] Morice P, Uzan C, Gouy S, Verschraegen C, Haie-Meder C. Gynaecological cancers in pregnancy. Lancet 2012;379(9815):558–69.
[17] de Haan J, Vandecaveye V, Han SN, Van de Vijver KK, Amant F. Difficulties with diagnosis of malignancies in pregnancy. Best Pract Res Clin Obstet Gynaecol 2016;33:19–32.
[18] Aslam N, Ong C, Woelfer B, Nicolaides K, Jurkovic D. Serum CA125 at 11–14 weeks of gestation in women with morphologically normal ovaries. BJOG 2000;107(5):689–90.
[19] Sessa C, Maur M. Ovarian cancers in pregnancy. Recent Results Cancer Res 2008;178:75–8.
[20] Schmeler KM, Mayo-Smith WW, Peipert JF, Weitzen S, Manuel MD, Gordinier ME. Adnexal masses in pregnancy: surgery compared with observation. Obstet Gynecol 2005;105(5 Pt 1):1098–103.
[21] Koo FH, Wang KC, Chen CY, Chang WH, Yeh CC, Yang MJ, et al. An 11-year experience with ovarian surgery during pregnancy. J Chin Med Assoc 2013;76(8):452–7.
[22] Behtash N, Karimi Zarchi M, Modares Gilani M, Ghaemmaghami F, Mousavi A, Ghotbizadeh F. Ovarian carcinoma associated with pregnancy: a clinicopathologic analysis of 23 cases and review of the literature. BMC Preg Childbirth 2008;8:3.
[23] Mazze RI, Källén B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5405 cases. Am J Obstet Gynecol 1989;161(5):1178–85.
[24] Ko ML, Lai TH, Chen SC. Laparoscopic management of complicated adnexal masses in the first trimester of pregnancy. Fertil Steril 2009;92(1):283–7.
[25] Wang PH, Cheng MH, Lee WL. The choice of tocolytic drugs for preterm labor-comparison of COX-2 inhibitor and magnesium sulfate. J Obstet Gynaecol Res 2008;34(3):439–40.
[26] Kizer NT, Powell MA. Surgery in the pregnant patient. Clin Obstet Gynecol 2011;54(4):633–41.
[27] Chohan L, Kilpatrick CC. Laparoscopy in pregnancy: a literature review. Clin Obstet Gynecol 2009;52(4):557–69.
[28] American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol 2009;114(1):192–202.
[29] Mathevet P, Nessah K, Dargent D, Mellier G. Laparoscopic management of adnexal masses in pregnancy: a case series. Eur J Obstet Gynecol Reprod Biol 2003;108(2):217–22.
[30] Modares Gilani M, Karimi Zarchi M, Behtash N, Ghaemmaghami F, Mousavi AS, Behnamfar F. Preservation of pregnancy in a patient with advanced ovarian cancer at 20 weeks of gestation: case report and literature review. Int J Gynecol Cancer 2007;17(5):1140–3.
[31] Minig L, Otaño L, Diaz-Padilla I, Alvarez Gallego R, Patrono MG, Valero de Bernabé J. Therapeutic management of epithelial ovarian cancer during pregnancy. Clin Transl Oncol 2013;15(4):259–64.
[32] Benedet JL, Bender H, Jones 3rd H, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2000;70(2):209–62.

[33] Stuart GC, Kitchener H, Bacon M, duBois A, Friedlander M, Ledermann J, et al.; participants of 4th Ovarian Cancer Consensus Conference (OCCC); Gynecologic Cancer Intergroup. 2010 Gynecologic Cancer InterGroup (GCIG) consensus statement on clinical trials in ovarian cancer: report from the Fourth Ovarian Cancer Consensus Conference. Int J Gynecol Cancer 2011;21(4):750–5.
[34] Friedman JD, Ramsey PS, Ramin KD, Berry C. Pneumoamnion and pregnancy loss after second-trimester laparoscopic surgery. Obstet Gynecol 2002;99(3):512–3.
[35] Pitkin RM, Parker WH. Operative laparoscopy: a second look after 18 years. Obstet Gynecol 2010;115(5):890–1.
[36] Fader AN, Rojas-Espaillat L, Ibeanu O, Grumbine FC, Escobar PF. Laparoendoscopic single-site surgery (LESS) in gynecology: a multi-institutional evaluation. Am J Obstet Gynecol 2010;203(5):501–6.
[37] Reedy MB, Galan HL, Richards WE, Preece CK, Wetter PA, Kuehl TJ. Laparoscopy during pregnancy. A survey of laparoendoscopic surgeons. J Reprod Med 1997;42(1):33–8.
[38] Sesti F, Pietropolli A, Sesti FF, Piccione E. Gasless laparoscopic surgery during pregnancy: evaluation of its role and usefulness. Eur J Obstet Gynecol Reprod Biol 2013;170(1):8–12.
[39] Balthazar U, Steiner AZ, Boggess JF, Gehrig PA. Management of a persistent adnexal mass in pregnancy: what is the ideal surgical approach? J Minim Invasive Gynecol 2011;18(6):720–5.
[40] Zhao XY, Huang HF, Lian LJ, Lang JH. Ovarian cancer in pregnancy: a clinicopathologic analysis of 22 cases and review of the literature. Int J Gynecol Cancer 2006;16(1):8–15.
[41] Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol 2004;5(5):283–91.
[42] Leslie KK, Koil C, Rayburn WF. Chemotherapeutic drugs in pregnancy. Obstet Gynecol Clin North Am 2005;32(4):627–40.
[43] Ring AE, Smith IE, Jones A, Shannon C, Galani E, Ellis PA. Chemotherapy for breast cancer during pregnancy: an 18-year experience from five London teaching hospitals. J Clin Oncol 2005;23(18):4192–7.
[44] Azim Jr HA, Peccatori FA, Pavlidis N. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part I: Solid tumors. Cancer Treat Rev 2010;36(2):101–9.
[45] Azim Jr HA, Pavlidis N, Peccatori FA. Treatment of the pregnant mother with cancer: a systematic review on the use of cytotoxic, endocrine, targeted agents and immunotherapy during pregnancy. Part II: Hematological tumors. Cancer Treat Rev 2010;36(2):110–21.
[46] Peccatori F, Martinelli G, Gentilini O, Goldhirsch A. Chemotherapy during pregnancy: what is really safe? Lancet Oncol 2004;5(7):398.
[47] Mir O, Berveiller P, Ropert S, Goffinet F, Goldwasser F. Use of platinum derivatives during pregnancy. Cancer 2008;113(11):3069–74.
[48] Zagouri F, Sergentanis TN, Chrysikos D, Bartsch R. Platinum derivatives during pregnancy in cervical cancer: a systematic review and meta-analysis. Obstet Gynecol 2013;121(2 Pt 1):337–43.
[49] Robova H, Rob L, Hrehorcak M, Zoban P, Prusa R. Endodermal sinus tumor diagnosed in pregnancy: a case report. Int J Gynecol Cancer 2007;17(4):914–6.
[50] Cardonick E, Bhat A, Gilmandyar D, Somer R. Maternal and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy: case series and review of the literature. Ann Oncol 2012;23(12):3016–23.
[51] Cardonick E, Gilmandyar D, Somer RA. Maternal and neonatal outcomes of dose-dense chemotherapy for breast cancer in pregnancy. Obstet Gynecol 2012;120(6):1267–72.
[52] Van Calsteren K, Verbesselt R, Van Bree R, Heyns L, de Bruijn E, de Hoon J, et al. Substantial variation in transplacental transfer of chemotherapeutic agents in a mouse model. Reprod Sci 2011;18(1):57–63.
[53] Zagouri F, Sergentanis TN, Chrysikos D, Dimitrakakis C, Tsigginou A, Zografos CG, et al. Taxanes for breast cancer during pregnancy: a systematic review. Clin Breast Cancer 2013;13(1):16–23.
[54] Loibl S, Han SN, von Minckwitz G, Bontenbal M, Ring A, Giermek J, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012;13(9):887–96.
[55] Méndez LE, Mueller A, Salom E, González-Quintero VH. Paclitaxel and carboplatin chemotherapy administered during pregnancy for advanced epithelial ovarian cancer. Obstet Gynecol 2003;102(5 Pt 2):1200–2.
[56] Sood AK, Shahin MS, Sorosky JI. Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy. Gynecol Oncol 2001;83(3):599–600.
[57] Ferrandina G, Distefano M, Testa A, De Vincenzo R, Scambia G. Management of an advanced ovarian cancer at 15 weeks of gestation: case report and literature review. Gynecol Oncol 2005;97(2):693–6.
[58] Smith ER, Borowsky ME, Jain VD. Intraperitoneal chemotherapy in a pregnant woman with ovarian cancer. Obstet Gynecol 2013;122(2 Pt 2):481–3.
[59] Liu Y, Liu Y, Wang Y, Chen X, Chen H, Zhang J. Malignancies associated with pregnancy: an analysis of 21 clinical cases. Ir J Med Sci 2015;184(1):175–81.
[60] Otton G, Higgins S, Phillips KA, Quinn M. A case of early-stage epithelial ovarian cancer in pregnancy. Int J Gynecol Cancer 2001;11(5):413–7.
[61] Henderson CE, Elia G, Garfinkel D, Poirier MC, Shamkhani H, Runowicz CD. Platinum chemotherapy during pregnancy for serous cystadenocarcinoma of the ovary. Gynecol Oncol 1993;49(1):92–4.
[62] King LA, Nevin PC, Williams PP, Carson LF. Treatment of advanced epithelial ovarian carcinoma in pregnancy with cisplatin-based chemotherapy. Gynecol Oncol 1991;41(1):78–80.
[63] Malfetano JH, Goldkrand JW. Cis-platinum combination chemotherapy during pregnancy for advanced epithelial ovarian carcinoma. Obstet Gynecol 1990;75(3 Pt 2):545–7.
[64] Mantovani G, Gramignano G, Mais V, Melis GB, Parodo G, Carrucciu GM. Use of chemotherapy for ovarian cancer during human pregnancy: case report and literature review. Eur J Obstet Gynecol Reprod Biol 2007;131(2):238–9.
[65] Rouzi AA, Sahly NN, Sahly NF, Alahwal MS. Cisplatinum and docetaxel for ovarian cancer in pregnancy. Arch Gynecol Obstet 2009;280(5):823–5.
[66] Doi D, Boh Y, Konishi H, Asakura H, Takeshita T. Combined chemotherapy with paclitaxel and carboplatin for mucinous cystadenocarcinoma of the ovary during pregnancy. Arch Gynecol Obstet 2009;280(4):633–6.
[67] Serkies K, Węgrzynowicz E, Jassem J. Paclitaxel and cisplatin chemotherapy for ovarian cancer during pregnancy: case report and review of the literature. Arch Gynecol Obstet 2011;283(1):97–100.
[68] Grigoriadis C, Eleftheriades M, Panoskaltsis T, Bacanu AM, Vitoratos N, Kondi-Pafiti A, et al. Ovarian cancer diagnosed during pregnancy: clinicopathological characteristics and management. G Chir 2014;35(3–4):69–72.
[69] He SY, Shen HW, Xu L, Li XL, Yao SZ. Successful management of mucinous ovarian cancer by conservative surgery in week 6 of pregnancy: case report and literature review. Arch Gynecol Obstet 2012;286(4):989–93.
[70] Bayhan G, Aban M, Yayla M, Gül T, Yaldiz M, Erden AC. Cis-platinum combination chemotherapy during pregnancy for mucinous cystadenocarcinoma of the ovary. Case report. Eur J Gynaecol Oncol 1999;20(3):231–2.
[71] Huang HP, Fang CN, Kan YY. Chemotherapy for ovarian mucinous cystadenocarcinoma during pregnancy: a case report. Eur J Gynaecol Oncol 2004;25(5):635–6.
[72] Picone O, Lhommé C, Tournaire M, Pautier P, Camatte S, Vacher-Lavenue MC, et al. Preservation of pregnancy in a patient with a stage IIIB ovarian epithelial carcinoma diagnosed at 22 weeks of gestation and treated with initial chemotherapy: case report and literature review. Gynecol Oncol 2004;94(2):600–4.
[73] Atallah D, Safi J, El Kassis N, Rouzier R, Chahine G. Simultaneous early ovarian and endometrial cancer treated conservatively with spontaneous pregnancy. J Ovarian Res 2013;6:59.
[74] Gottheil S, McGee J. Endometrioid ovarian carcinoma during pregnancy presenting with acute rupture. J Obstet Gynaecol Can 2013;35(11):1020–2.
[75] Hubalek M, Smekal-Schindelwig C, Zeimet AG, Sergi C, Brezinka C, Mueller-Holzner E, et al. Chemotherapeutic treatment of a pregnant patient with ovarian dysgerminoma. Arch Gynecol Obstet 2007;276(2):179–83.
[76] Han JY, Nava-Ocampo AA, Kim TJ, Shim JU, Park CT. Pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for malignant ovarian germ cell tumors: report of 2 cases. Reprod Toxicol 2005;19(4):557–61.
[77] Elit L, Bocking A, Kenyon C, Natale R. An endodermal sinus tumor diagnosed in pregnancy: case report and review of the literature. Gynecol Oncol 1999;72(1):123–7.
[78] Horbelt D, Delmore J, Meisel R, Cho S, Roberts D, Logan D. Mixed germ cell malignancy of the ovary concurrent with pregnancy. Obstet Gynecol 1994;84(4 Pt 2):662–4.
[79] Viana LS, Tsunoda AT, Nunes JS, Fregnani JH, Vieira MA, Borges AK, et al. Preservation of pregnancy in a patient with acute abdominal pain secondary to advanced and hemorrhagic yolk sac tumor of the right ovary. J Clin Oncol 2011;29(30):e758–62.
[80] Buller RE, Darrow V, Manetta A, Porto M, DiSaia PJ. Conservative surgical management of dysgerminoma concomitant with pregnancy. Obstet Gynecol 1992;79(5 Pt 2):887–90.
[81] Malone JM, Gershenson DM, Creasy RK, Kavanagh JJ, Silva EG, Stringer CA. Endodermal sinus tumor of the ovary associated with pregnancy. Obstet Gynecol 1986;68(3). 86S-9S.
[82] Christman JE, Teng NN, Lebovic GS, Sikic BI. Delivery of a normal infant following cisplatin, vinblastine, and bleomycin (PVB) chemotherapy for malignant teratoma of the ovary during pregnancy. Gynecol Oncol 1990;37(2):292–5.
[83] Battelli C, Campo M, Buss MK, Awtrey CS, Konstantinopoulos PA. Safety and outcome of patients treated with a modified outpatient intraperitoneal regimen for epithelial ovarian, primary peritoneal or fallopian tube cancer. Chemotherapy 2013;59(4):251–9.
[84] Burgazli KM, Mericliler M, Kavukcu E, Erdogan A, Ertan AK. Discovery of asymptomatic Krukenberg tumors diagnosed during caesarean section: therapy with hyperthermic intraperitoneal chemotherapy. Postgrad Med 2013;125(4):87–90.
[85] Ortega-Deballon P, Glehen O, Levine E, Piso P, Sugarbaker PH, Hayes-Jordan A, et al. Childbearing after hyperthermic intraperitoneal chemotherapy: results from an international survey. Ann Surg Oncol 2011;18(8):2297–301.
[86] 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. Ann Oncol 2012;23(6):1481–7.
[87] Kodama M, Grubbs BH, Blake EA, Cahoon SS, Murakami R, Kimura T, et al. Feto-maternal outcomes of pregnancy complicated by ovarian malignant germ cell tumor: a systematic review of literature. Eur J Obstet Gynecol Reprod Biol 2014;181:145–56.

[88] Motegi M, Takakura S, Takano H, Tanaka T, Ochiai K. Adjuvant chemotherapy in a pregnant woman with endodermal sinus tumor of the ovary. Obstet Gynecol 2007;109(2 Pt2):537–40.
[89] Karimi Zarchi M, Behtash N, Modares Gilani M. Good pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for ovarian immature teratoma: a case report and literature review. Arch Gynecol Obstet 2008;277(1):75–8.
[90] Di Tucci C, Casorelli A, Morrocchi E, Palaia I, Muzii L, Panici PB. Fertility management for malignant ovarian germ cell tumors patients. Crit Rev Oncol Hematol 2017;120:34–42.
[91] Blake EA, Carter CM, Kashani BN, Kodama M, Mabuchi S, Yoshino K, et al. Feto-maternal outcomes of pregnancy complicated by ovarian sex-cord stromal tumor: a systematic review of literature. Eur J Obstet Gynecol Reprod Biol 2014;175:1–7.
[92] Kiyokawa T, Young RH, Scully RE. Krukenberg tumors of the ovary: a clinicopathologic analysis of 120 cases with emphasis on their variable pathologic manifestations. Am J Surg Pathol 2006;30(3):277–99.
[93] Dueñas-García OF, Diaz-Sotomayor M, Chanana C. Bilateral ovarian krukenberg tumor in a full-term pregnancy. ISRN Obstet Gynecol 2011;2011:620380.
[94] Co PV, Gupta A, Attar BM, Demetria M. Gastric cancer presenting as a krukenberg tumor at 22 weeks' gestation. J Gastric Cancer 2014;14(4):275–8.
[95] Stojnic J, Stefanovic A, Jeremic K, Kadija S, Jeftovic M, Jeremic J. Krukenberg tumor of gastric origin in pregnancy with dismal outcome. Eur J Gynaecol Oncol 2011;32(3):356–8.
[96] Genç M, Genç B, Solak A, Gür E, Sezgin C. Bilateral Krukenberg tumor in a 16-week pregnant woman. Eur J Gynaecol Oncol 2014;35(1):95–6.
[97] Kim SH, Abd Halim SR, Siddiqui N, Park WH. Disseminated cancer in pregnancy: krukenberg tumour. Case Rep Obstet Gynecol 2014;2014:216969.
[98] Glisić A, Atanacković J. Krukenberg tumor in pregnancy. The lethal outcome. Pathol Oncol Res 2006;12(2):108–10.
[99] Tan KL, Tan WS, Lim JF, Eu KW. Krukenberg tumors of colorectal origin: a dismal outcome–experience of a tertiary center. Int J Colorectal Dis 2010;25(2):233–8.
[100] Kodama M, Moeini A, Machida H, Blake EA, Grubbs BH, Matsuo K. Feto-maternal outcomes of pregnancy complicated by Krukenberg tumor: a systematic review of literature. Arch Gynecol Obstet 2016;294(3):589–98.
[101] Tabata T, Nishiura K, Tanida K, Kondo E, Okugawa T, Sagawa N. Carboplatin chemotherapy in a pregnant patient with undifferentiated ovarian carcinoma: case report and review of the literature. Int J Gynecol Cancer 2008;18(1):181–4.
[102] Tomlinson MW, Treadwell MC, Deppe G. Platinum based chemotherapy to treat recurrent Sertoli-Leydig cell ovarian carcinoma during pregnancy. Eur J Gynaecol Oncol 1997;18(1):44–6.
[103] Yun NR, Park JW, Hyun MK, Park JH, Choi SJ, Song E. Squamous cell carcinoma arising in an ovarian mature cystic teratoma complicating pregnancy. Obstet Gynecol Sci 2013;56(2):121–5.

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