

## Ovarian Immature Teratoma Detected During Pregnancy

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### Abstract

**Objective:** Malignant ovarian immature teratomas should be considered in differential diagnosis of adnexal masses detected during pregnancy. This paper is reviewing the clinicopathologic and prognostic characteristics and therapeutic options for treatment of immature teratoma during pregnancy in the context of a case of pregnancy complicated with immature teratoma.

**Material and Methods:** A PubMed and Scopus search was conducted with the key words 'ovarian immature teratoma' and 'pregnancy' and all related published articles assessed. A total of 24 cases, included our case were included in the study. Age at presentation, clinical findings, histological grades and stages, treatment options and the prognosis of both mothers and fetuses was analysed.

**Results:** The median age of the patients in the published reports was 27.0± 4.2 (range 21-36) years. The main presenting symptom was adnexal mass followed by abdominal or pelvic pain. Chemotherapy was added to the surgical treatment in 68.2% of the patients; a Bleomycin, Etoposide and Cisplatin protocol was the preferred treatment option. Prognosis for both mother and foetus were good.

**Conclusion:** Immature teratoma during pregnancy should be treated immediately with surgery ± chemotherapy especially in high grade patients.

**Key words:** chemotherapy, germ cell tumors, immature teratoma, pregnancy

### Introduction

Pure immature teratoma of the ovary' term describes the germ cell tumor of the ovary by excluding patterns of endodermal sinus tumor, choriocarcinoma, and dysgerminoma (1). Pregnancy complicated by an immature teratoma is fairly rare, with a reported incidence of 0.07% (2). The consequence of a low incidence is a lack of consensus on management strategies. We described here a woman diagnosed with immature ovarian teratoma during pregnancy and review the clinicopathologic and prognostic characteristics and therapeutic options of immature teratoma cases during pregnancy. To the best of our knowledge, this is the first comprehensive review in literature which collects ovarian immature teratoma during pregnancy cases.

### Material and Methods

A PubMed and Scopus search was conducted with the key words 'ovarian immature teratoma' and 'pregnancy' and all related published articles assessed.

Totally 19 case reports and 12 review articles about the germ cell tumours of the ovary and ovarian tumours during pregnancy were determined. Cases in articles with a review of prior published cases were included if the clinicopathologic information about the cases was clearly stated. Crossing cases from the articles precluded. Cases who first diagnosed by ovarian pure immature teratoma during or related with their pregnancy were included in the study. Patients were examined by age of the patients, grade and stage of the tumour, gestational week and symptoms at diagnosis, operation type, chemotherapy, birth week-birth way, second look laparotomy, disease free survival and prognosis. Manuscripts with incomplete data (<50% of analysed criteria) and case reports published in local journals with weak data were excluded. Age, clinical findings, histologic grade and stage, treatment options and the prognosis of both mothers and fetuses were analysed by descriptive analysis with SPSS 21.0 statistical programme (SPSS package, version 21.0, SSPS Inc., Chicago, IL, USA).

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## Case

A 25-year old primiparous woman at 19 weeks gestation presented to the emergency department with a two week history of abdominal and pelvic pain of increasing severity on the day of admission. Physical examination revealed diffuse abdominal pain with rebound tenderness. Abdomino-pelvic ultrasound showed a normal 19 week pregnancy. The left ovary was in normal appearance. An 80x40x40 mm solid mass with anechoic cystic areas was seen on the right and posterior side of the uterus, with mild right-sided hydronephrosis and free fluid in the recto-uterine pouch. Serum CA125 level was slightly elevated (39.1 U/ml, range: 0-35 U/ml) and serum alpha-fetoprotein level was elevated (38.74 ng/ml, range: 0-9 ng/ml).

An emergency laparotomy was performed. A large, 150 mm diameter right adnexal mass was detected and ruptured during removal revealing white-red, jelly-like material. Frozen section could not be performed but a right salpingo-oophorectomy was done. Pathological examination revealed an immature teratoma (grade 3) of the ovary with benign peritoneal cytology. She didn't agree with chemotherapy during her pregnancy.

She complained of intermittent pelvic pain without cervical shortening or uterine contractions during the rest of the pregnancy. A planned cesarean section birth and second look laparotomy was performed in the 32nd gestational week after antenatal steroid administration for fetal lung maturation. The 1x2 cm tumoral mass from the peritoneum of the recto-uterine pouch was removed and omentectomy, appendectomy and peritoneal biopsies were performed. Pathological examination revealed that, the mass from peritoneum of the recto-uterine pouch was immature teratoma and the rest of the biopsies and excised tissues were benign. She was started on chemotherapy with BEP protocol (bleomycin 30 mg, etoposide 100 mg/m<sup>2</sup>, cisplatin 20 mg/m<sup>2</sup>) three weeks after the operation. She completed the 6th treatment regimen with a recurrence at 1st year follow-up and died just after the operation for recurrences. The baby died right after birth because of congenital pneumonia

## Results

Clinicopathologic features and therapeutic approaches for the cases are summarized in Table 1 (1- 20). Distribution of age ranged from 21 to 36 years with a median of 27.0± 4.2 years. The main presenting symptom was adnexal mass (eight patients) followed by abdominal or pelvic pain (four cases). Four cases presented with combined abdominal pain and mass, five were diagnosed by routine ultrasonography and three by elevated serum AFP (alpha- fetoprotein) levels (some of the patients were noticed to have more than one symptom). One asymptomatic patient was diagnosed during cesarean section. The median gestational week at diagnosis was 18± 10.3 (range 8-40) weeks and the median gestational length was

38.0± 3.6 (range 28- 40) weeks of pregnancy. The grade and stages of the patients summarized in Table 2. Cesarean section was the preferred mode of delivery in 10 women (52.6%). Termination of pregnancy was administered in one case and spontaneous miscarriage occurred in another one (10.5%).

The teratoma ruptured during operation in four (17.4%) cases. Chemotherapy was added to the surgical treatment in 15 patients (68.2%); a Bleomycin, Etoposide and Cisplatin (BEP) protocol was the preferred treatment option in eight women. Four women, including our case was died because of the rapid disease progress (16.6%). Of the babies 19 were healthy. One had an intracranial immature teratoma, one had hypospadias and the fetus was died with prematurity complications. Three women had a subsequent normal pregnancy.

## Discussion

Pure immature teratomas, first characterized by Norris et al in 1976, are rare germ cell tumors which involve three germ layers with at least one of the components having an immature appearance (1, 21). Survival is determined by the size and stage of teratomas, but the grade of the primary tumor is the most important determinant of the likelihood of extra ovarian spread and for the subsequent course. Grading is based on the amount of immature neural tissue (1).

Some 36 years later to Norris et al., Zhang R. et al reported 5-year survival rate as 92.% for immature teratoma based on 63 (non-pregnant) cases with immature teratoma among 145 malign ovarian germ cell tumor cases and histology, surgical approach, chemotherapy and regimens were not predictive of five-year survival rates. Moreover they concluded that, fertility-sparing treatment should be considered for ovarian germ cell tumors without regard for the FIGO stage (22).

Young et al. showed that prognosis for ovarian malignancies was not complicated by a concurrent gestation if adequate treatment is administered timely (23). Management of ovarian tumors in pregnancy requires a multidisciplinary approach and therapeutic decision should take into account histology, grade and stage of the tumor, and the gestational week of the pregnancy (24). Clinicopathologic features and therapeutic approaches for the pregnant pure immature teratoma cases were summarized in Table 1 (1- 20). Age ranged from 21 to 36 years with a median of 27± 4.2 years. The median gestational week at diagnosis was 18± 10.3 (range 8-40) weeks and the median gestational length was 38± 3.6 (range 28- 40) weeks of pregnancy.

**Table 1.** Cases diagnosed as immature teratoma during their pregnancy.

Author, Year	Age	Grade	Stage	Week	Symptom	Operation	Chemotherapy	Birthweek-birthway	Sec.look	DFS (month)	Prognosis, other
Norris et al., 1976					All 3 were found in routine USG						3 patients (2 pregnant, 1 determined in pp USG)
Hassan et al., 1984	28	2	?	28	Anemia, abdominal pain, weakness, dyspnea	Right USO+ partial O+ C	VAC (1 course)+ external RT	28	-	-	Exitus in 3 months, healthy newborn
Matsuyama et al., 1989	27	3	1a	pp20	Lower abd pain	Right USO	VAC (7courses)	term	-	48	Good
Montz et al., 1989	N/A	N/A	1a	18	Elevated msAFP	18 w laparotomy	CVB (3 courses)	31, C	-	65	Liver recurrence 5th month (Cure with +3 courses of BEP), healthy newborn
Christman et al., 1990	N/A	3	1c		Adnexal mass (18-20 cm)	Laparotomy, rupture in operation	PVB (1 course in p+ completed pp)	term, V	Yes	?	Healthy newborn Benign in second look
Frederiksen et al., 1991	34	3	1c	17	Elevated msAFP	19 w lap. Right SOF+ omentectomy, rupture in operation	VAC (4 courses)	Term, V	Recurrence at 13th months pp, treated with surgery+ CT		Healthy newborn.
Poremba et al., 1993	27			Term	None	C+ USO	?	Term, C	?		?, Simultaneous with intracranial immature teratoma in baby
Bakri et al., 2000. Case1	33	2-3?	1a	pa10	abdominal pain, mass (14cm)	USO and staging	4 courses BEP	-	-	48	Spontaneous p after 4 years
Bakri et al., 2000. Case2	21	2	3?	8	abdominal pain, fever, sweating, weight loss	TAH+ BSO+ termination	-	termination	-	-	Rapid progress, Exitus in 2 <sup>th</sup> trimester
Kishimoto et al., 2002	28	2	3c	34	Found in routine USG, solid+ cystic mass on MRI, msAFP elevated	TAH+BSO+ PP LND+ Partial O+ C	5 courses	38	-	9	Healthy newborn, good for both
Agarwal et al., 2003	?	?	?	33	?	C+ hysterectomy+ O	yes	33, C	-	?	?, Rapid progress- patient didn't want chemotherapy in pregnancy
Han et al., 2005	27	3	1a	16	Elevated msAFP, adnexal mass (5*6cm)	Right USO	BEP (2courses in p+ 3courses pp)	38, V	L/S PPLND+ O+ LO biopsy after birth	26	Good for both, healthy newborn
Zhao et al., 2006. Case1	24	1	1	8	Pelvic mass	Right USO	-	term, V	-	18	Good for both
Zhao et al., 2006. Case2	24	1	1	17	adnexal mass	Left USO	-	term, V	-	30	Good for both



<b>Daponte et al., 2008</b>	?	1	1a	12	Adnexal mass	Right USO+surgical staging	-	34, C	C+ peritoneal biopsy	24	Healthy newborn, Frozen negative
<b>Poujade et al., 2008</b>	36	2		21	adnexal mass in USG (175mm)	Left oophorectomy	Agent? 3 courses in p, 2 courses pp	39, C	C+ left salpingectomy	After CT	remission in mother, healthy fetus
<b>Karimi-Zarchi et al., 2008</b>	26	3	3c	28	Abdominal pain	Right oophorectomy+ cytology+ partial O	BEP (in p+ 2 courses pp)	39, C	C+ O+ipsilat. LN sampling	18	Good prognose
<b>Ghaemmaghami et al., 2009</b>	25	?	?	13	adnexal mass in USG (76*45 mm)	21w-right oophorectomy+ bx from left ovary, omentum	BEP (in p)	36, C	C+ partial O+ right salpingectomy+ periton bx+ bilateral LND	12	Hipospadias and IUGR in baby
<b>Mourali et al., 2010. Case1</b>	28	1	?	Term	Determined during C, 5 cm solid+cystic	USO+O+ aortic LND+ A	-	term, C	At 2 <sup>nd</sup> C birth	36 to 2 <sup>nd</sup> birth	Healthy newborn, Radical surgery in 2nd s/c birth
<b>Mourali et al., 2010. Case2</b>	22	2	?	15	Adnexal mass (8 cm solid+cystic)	20w- USO+O+aortic LND+A	-	V	-	?	Good prognose.
<b>Helage et al., 2011.</b>	22	2	1c	37	Adnexal mass	37w C+ right USO+ peri- toneal cytology, bx, rupture in operation	BEP (after surgery)	C	-	?	Remission after chemotherapy
<b>Clinkard et al., 2011</b>	23	?	3c	18w	abd.pain+ hyperemesis, right adn mass	acute bilateral oophorectomy+ O	high dose cisplatin and etoposide	abortus	abortus	72	viable 2. pregnancy (medulloblastoma arising in immature teratoma)
<b>Mendivil et al., 2013</b>	32	3	1a	16w	Pelvic pain+ 10 cm adn mass	Robotic right USO+ inspection	-	37, V	-	?	Good prognose for mother, healthy newborn
<b>This case</b>	25	3	?	19w	Abdominal pain, 8 cm right adnexal mass	Right USO+ peritoneal cytology, rupture in operation	5 courses BEP after p	32, C	C+ O+ A+ excision of the residual mass	12	Fetus died with congenital pneumonia, mother died with recurrences.

**C: cesarean sectio; V: vaginal birth; O: omentectomy; A:appendectomy; bx: biopsy; p: pregnancy; pp:postpartum; pa:postabortus; BEP: bleomycin+ etoposide+ cysplatin; VAC: Vincristine, Actinomycin D, Cyclophosphamide; LND: lymph node dissection; PPLND: pelvic- paraaortic LND; R: right; L: left; TAH+BSO: total abdominal hysterectomy+ bilateral salpingoophorectomy; USO: unilateral salpingoophorectomy; USG: ultrasonography; MRI: Magnetic Resonance Imaging; CVB: Cisplatin, Etoposide, Bleomycin; msAFP: maternal serum alpha-fetoprotein;**

**Table 2.** Distribution of the grade and stages of the cases.

Grade	Number of patients	Percent (%)	Stage	Number of patients	Percent(%)
1	4	16	1	2	8.7
2	6	24	1a	6	26.1
3	8	32	1c	3	13
			3	1	4.3
			3c	3	13
Missing	7	28	Missing	8	34.8

Prognosis for immature teratomas has improved due to the routine use of imaging during pregnancy and because of chemotherapy. Most ovarian cancers associated with pregnancy were detected by ultrasonography (USG) (12). For immature ovarian teratomas during pregnancy; the main presenting symptom was adnexal mass (eight cases) followed by abdominal or pelvic pain (four cases). Four cases presented with combined abdominal pain and mass, five were diagnosed by routine ultrasonography and three by elevated serum AFP (alpha-fetoprotein) levels. Some of the patients have more than one symptom and one asymptomatic patient was diagnosed during cesarean section. USG simplified the diagnosis in our case similar with most of the other ones in literature (Table 1).

Malignant ovarian germ cell tumors are usually unilateral except advanced stage cases with metastasis to the contralateral ovary (25). None of the cases reviewed was bilateral except the advanced stage cases with distant metastasis. Thus, unilateral salpingo oophorectomy with preservation of the contralateral ovary and uterus are appropriate for treatment of most cases. If metastatic disease is encountered during surgery, cytoreductive surgery is recommended. Second look laparotomy for germ cell tumors is controversial; if inadequate staging was present at the first operation, second look surgery or CT should be considered (25). Staging could not be performed at the first operation in our case, because of the lack of frozen section results. Thus, second look surgery performed during cesarean section. Cesarean section was the preferred mode of delivery for 10 women (52.6%) and second look surgery was preferred to perform during cesarean in 50% of them.

Germ cell tumors are very chemo sensitive. Patients with stage 1a, grade 1 tumors have excellent prognosis, do not require adjuvant treatment and postoperative observation is recommended. Chemotherapy recommended when extra-ovarian disease exists. The role of adjuvant chemotherapy for patients with stage 1, grade 2 or 3 tumor is controversial. BEP is the most commonly used combination (21), every 3 weeks for 3 or 4 courses (26). Chemotherapy was seen to add to the surgical treatment in 15 patients (68.2%); a Bleomycin, Etoposide and Cisplatin (BEP) protocol was the preferred treatment option in eight women.

Highly immature teratomas detected during pregnancy deserve special attention. Grade 2 or 3 immature teratomas are associated with a greater chance of potentially fatal recurrence predominantly within two years of diagnosis as occurred in our case (27). Therefore, the principle of surgery in both pregnant and non-pregnant patients is resection of as much as tumor as is feasible and safe. There is now a general consensus that a vertical midline incision with

unilateral salpingo oophorectomy, peritoneal washing and careful inspection of the abdominal cavity is appropriate, preserving the potential for later fertility (27).

The poor prognosis of malignant germ cell tumors treated by surgery alone indicates a need for adjuvant chemotherapy (2). The risk of major malformation during the first trimester of pregnancy is 10% for single agent chemotherapy and 25% for combination chemotherapy (21). Therefore, the second trimester seems safer for chemotherapy. The BEP protocol has been recommended for the treatment of immature teratomas even though there is limited experience for using this regimen during pregnancy (15, 28). The BEP treatment has been associated with ventriculomegaly, transient neonatal neutropenia and bilateral sensorineural hearing loss in two cases (11). More data are needed to determine the safety of these medications during pregnancy.

Preoperative rupture of the tumour is rare but possible due to the large size of the germ cell tumors. Intraoperative rupture worsens the prognosis and dictates a need for ancillary chemotherapy. Four of the 23 cases (17.4%) ruptured intraoperatively as occurred in our case. The patient was offered chemotherapy during her pregnancy and we discussed the risks and advantages with her, but she did not agree with chemotherapy while she was pregnant.

## Conclusion

Malignant ovarian immature teratomas should be considered in differential diagnosis of adnexal masses detected during pregnancy. Fertility-sparing surgery with or without chemotherapy during or after pregnancy are a therapeutic option. Chemotherapy improves prognosis, especially if extra ovarian spread exists. Grade 2-3 cases should be encouraged for chemotherapy during pregnancy. However, gestational age at diagnosis, stage of the disease, patient's willingness to keep the pregnancy, and fetal risks secondary to maternal treatments need to consider on a patient basis.

**Conflict of Interest:** The authors declare that there is no conflict of interest regarding the publication of this paper.

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