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Immature teratoma in pregnancy: A case report

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Abstract:

Ovarian cancer in pregnancy is a rare occurrence. Of all ovarian malignancies, <1% comprise immature teratomas. We present the case of a 24-year-old primigravid with an incidental finding of an ovarian new growth during a routine first-trimester ultrasound. The mass was suspicious for malignancy due to an ultrasound finding of a cystically enlarged 8.2 cm × 5.8 cm × 6.2 cm mass, with solid components and with minimal color flow on Doppler. There was an interval increase in the said mass during the second trimester, with an elevated alpha-fetoprotein (AFP) level. The patient underwent surgery at 24 weeks gestation. Histopathology revealed Immature Teratoma, FIGO Grade 3, stage IC1. She delivered to a live, term baby boy through cesarean delivery. Postpartum, she completed four cycles of chemotherapy using bleomycin, etoposide and cisplatin (BEP), and was advised surveillance with serum AFP every 3 months. Due to the limited number of cases of ovarian cancer in pregnancy reported, management is individualized. Dilemma in terms of the timing of surgery, neonatal and maternal outcomes, timing and mode of delivery, and control of tumor metastasis through chemotherapy were met, hence, a multidisciplinary team and patient decision is crucial to achieve successful and desirable outcomes for the mother and the fetus. This is the first case of immature teratoma in pregnancy reported in our institution and in a local setting.

Keywords:

Alpha-fetoprotein, antenatal chemotherapy, BEP, ovarian immature teratoma in pregnancy

Introduction

Four to eight out of every 100,000 pregnancies are complicated by a gynecologic cancer.[1] There are direct and indirect consequences of ovarian cancer on pregnancy; the former includes metastases, especially to the placenta and fetus, while the indirect consequences are the effects of surgical technique and chemotherapy.[2]

Immature teratomas, also called malignant teratoma, teratoblastoma, or embryonal teratoma, comprise <1% of ovarian teratomas and are most prevalent in the first two decades of life.[1] These contain embryonal neuroectodermal tissue component and are associated with an increase in alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH).[3] Immature teratomas are the only germ cell tumors that are histologically graded depending on the immature neural elements, and this is a prognostic factor for overall survival.[4]

The occurrence of immature teratoma in pregnancy poses a unique challenge in obstetric and oncologic management, presenting a complex interplay between maternal and fetal well-being. When encountered during pregnancy, the management of immature teratomas necessitates a careful balance between optimizing maternal oncologic outcomes while safeguarding fetal health. Through an understanding of these intricacies, healthcare providers may manage this uncommon but clinically important condition with care, ensuring the best outcomes for mother and fetus.

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Case Report

This is the case of a 24-year-old primigravid, who was referred to this institution due to an incidental finding of an ovarian mass on ultrasound. The patient has no known comorbidities, no previous surgeries, and with no family history of malignancy. She is a nonsmoker, an occasional alcohol beverage drinker, and with no history of illicit drug use. The patient had her menarche at age 13 with a regular menstrual pattern.

She had her first prenatal check-up at 12 weeks 4 days gestation where transvaginal ultrasound revealing a singleton, live, intrauterine pregnancy uterine 12 weeks 1 day age of gestation (AOG). There was an incidental finding of a right ovarian new growth, cystically enlarged, with solid component, multiloculated, thick-walled, multi-septated measuring 8.2 cm × 5.8 cm × 6.2 cm, minimal color flow on Doppler. No other diagnostics were requested. The patient was started on prenatal supplements and advised surveillance of the ovarian new growth. There was no history of exposure to teratogen, radiation, nor infections.

Baseline diagnostics done at 14 weeks 4 days gestation were unremarkable. However, at 20 weeks 1 day, the patient was lost to follow-up with a hemoglobin of 93 mg/dL. Second trimester ultrasound was done, which revealed a single, live, intrauterine pregnancy 20 weeks AOG with good cardiac and somatic activities. There was note of a 98.6% increase in the size of the right ovarian new growth, measuring 16.29 cm × 10.61 cm × 14.63 cm, Vol. 1314.87 ml. Tumor markers revealed normal LDH, Cancer antigen 125 and carcinoembryonic antigen levels, and an elevated AFP to 360 IU/mL. She was then advised to seek consultation in a tertiary institution for further evaluation and management.

She then sought consult at a government institution at 23 weeks and 1 day gestation. A Congenital Anomaly Scan was done, revealing no gross congenital anomalies. There was note of a 128% increase in size of the right ovarian new growth, now measuring 19.39 cm × 14.52 cm × 12.33 cm (vol. 1817.63 ml) with 2 solid components measuring 6.3 cm × 6.9 cm × 4.03 cm (vol. 94.31 ml) and 8.9 cm × 9.7 cm × 6.20 cm (vol. 284 ml), <10 locules, <4 papillarities, and strong color flow on Doppler [Appendix 1]. Repeat complete blood count revealed persistence of mild anemia (Hemoglobin 98). Hence, iron supplementation was increased to thrice daily with her other prenatal supplements.

A preoperative conference was conducted at 23 weeks 6 days gestation, which was attended by perinatology, gynecologic oncology, anesthesiology, and neonatology services. The patient was then recommended for immediate surgery following careful planning, which included the preoperative administration of corticosteroids and tocolytics, the induction of epidural anesthesia, the patient being placed in the left lateral position during surgery, performing a fertility-saving cancer surgery, and preparing the parents and child for a potential preterm delivery. At 24 weeks gestation, she underwent exploratory laparotomy, peritoneal fluid cytology, right salpingo-oophorectomy, rush frozen section of right ovary, infracolic omentectomy under continuous lumbar epidural anesthesia. Intraoperatively, there was no ascites noted. The subhepatic, subdiaphragmatic, and paracolic surfaces were smooth. There was an inadvertent rupture of the right ovarian new growth, containing approximately 200 ml of serous fluid. The mass was converted into a 13.5 cm × 15 cm complex mass containing areas of hemorrhage, sebum, hair, and teeth, with no normal ovarian tissue appreciated [Appendix 2]. The uterus was enlarged to 22-week size, the left ovary and left fallopian tube were grossly normal. Rush frozen section revealed suspicious for malignancy. Postoperative diagnosis at this point was an ovarian new growth, right, malignant, intraoperative stage 1C1. Tocolytics were continued postoperatively, and the patient tolerated the procedure well. She was eventually discharged stable on postoperative day 4.

Official Histopathology revealed Immature Teratoma, High Grade, Stage 1C1 [Appendix 3]. She was advised antenatal chemotherapy between 16 and 32 weeks gestation immediately with Cisplatin in monotherapy versus Cisplatin with Vinblastine followed by 2–3 cycles of Bleomycin, Etoposide, and Cisplatin standard chemotherapy after delivery. However, she decided to delay chemotherapy until her baby was delivered safe. A Multidisciplinary team conference was conducted, composing the services of perinatology, gynecologic oncology, neonatology, and pulmonology. The team conducted a series of plans from timing and mode of delivery, preparation in the event of a preterm delivery, timing of chemotherapy, and management of possible untoward chemotherapeutic effects. The summary of the conference was as follows: (1) Antenatal chemotherapy will not be done because the patient did not consent. Risks and complications of delaying chemotherapy such as progression of tumor and risk of metastasis on the background of a high grade malignancy, were explained to the patient and must be properly documented; (2) Timing of chemotherapy administration postpartum will be 2 weeks after a spontaneous vaginal delivery, and 3 weeks after a cesarean delivery. (3) Chemotherapy regimens to be administered postpartum are Bleomycin, Etoposide, and Cisplatin (BEP); The most problematic among the three chemotherapeutic agents is bleomycin, causing pulmonary fibrosis. Contraindications to

Bleomycin administration are reduced lung function and acute pulmonary infections. Most common symptom of bleomycin toxicity is cough and dyspnea. (4) Mode and timing of delivery: From a perinatology standpoint, it is best to await for spontaneous labor. Cesarean delivery will be done only if with obstetric indications; (5) The pulmonary service will perform Baseline pulmonary function test and diffusing capacity of the lungs for carbon monoxide or high resolution computed tomography (CT) scan of the chest before chemotherapy; (6) Metastatic work up should be done after one cycle of chemotherapy, including whole abdominal with pelvic CT scan, chest X-ray, tumor markers; (7) Since breastfeeding is contraindicated during chemotherapy, she will be referred to breastfeeding and lactation committee; (8) Patient will be referred to Malasakit Center for financial assistance.

At 32 weeks 6 days gestation, Whole Abdominal Ultrasound was done as metastatic work-up, revealing Mild diffuse liver parenchymal disease (Mild fatty changes), Nondilated biliary tree, bilateral mild pelvocaliectasia, unremarkable sonography of the gall bladder, pancreas, and spleen. Chest X-ray revealed No demonstrable active lung infiltrates; consider small calcified granuloma, right upper lobe. The patient was seen by the pulmonology service and was advised observation of the mentioned granuloma. Patient was advised weekly Biophysical scoring with fetal biometry to which the patient was compliant. At 39 weeks age of gestation, ultrasound revealed: live, singleton, fetus in cephalic presentation with good cardiac and somatic activities. Estimated fetal weight is above the 90th percentile, consider large for gestational age (3751 g). The patient was then admitted for labor pains; however, during the trial of labor, she underwent emergency low transverse cesarean section I secondary to nonreassuring Fetal Status. The patient delivered to a live, term, male, BW 3270 g, BL 53 cm, AS 9,9, MI 40 weeks, large for gestational age. She was then discharged and scheduled for the first cycle of Bleomycin, Etoposide, and Cisplatin (BEP) at 3 weeks postpartum. During the second cycle of chemotherapy, liver enzymes were elevated, hence a 25% dose reduction for etoposide was done. She completed four cycles of chemotherapy with bleomycin, etoposide, and cisplatin. Tumor monitoring is done every 3 months with serum AFP, which is all within normal limits.

Case Discussion

In recent years, there has been an upsurge in the frequency of ovarian cancers discovered during pregnancy. One of the reasons for this increase includes the routine use of ultrasound during pregnancy.[5] The incidence of ovarian cancers discovered during pregnancy ranged from 1 in 15,000 to 1 in 32,000 pregnancies.[6] Of the adnexal masses found during pregnancy, <10% require surgery, and only 5%–10% are aggressive or borderline tumors.

Most ovarian masses are asymptomatic. The most common initial symptoms of ovarian cancer in pregnancy are pelvic or adnexal mass, abdominal pain, and abdominal distention.[6]

Most ovarian carcinomas diagnosed in pregnancy present with an incidental finding of an adnexal mass on routine ultrasound. Once detected, all women under age 40 presenting with a complex ovarian mass should be requested with LDH, AFP, and human chorionic gonadotropin (hCG). Elevation of LDH most commonly points to a diagnosis of dysgerminoma, elevated AFP to endodermal sinus tumor, yolk sac tumor, or immature teratoma, and elevated hCG to choriocarcinoma.[7]

Elevation of AFP can be a marker of open neural tube defects and is often elevated in the setting of an ovarian yolk sac tumor. Maternal AFP levels in pregnancy start to rise from about the 14th week of gestation up until about 32 weeks of gestation. Between 15 and 20 weeks, AFP levels usually range between 10 ng/ml and 150 ng/ml. The patient's AFP levels at 22 weeks were twice as high as expected, but congenital anomaly scan was also done to rule out any congenital anomalies, particularly neural tube disorders.

In addition to achieving the best possible surgical result, the safety of the mother and the fetus should be the primary goals during pregnancy. A multidisciplinary strategy combining a maternal-fetal medicine specialist, a gynecologic oncologist, and a medical oncologist experienced with gynecologic cancers must be used if malignancy is suspected.[7]

Unilateral adnexal masses with benign features on ultrasound <5 cm in diameter detected in the first trimester often represent cysts that are functional in nature, i.e. corpus luteum cyst. In the contrary, for those masses exceeding 6 cm, exhibiting complex features or ascites or persisting beyond 16 weeks AOG, surgical intervention is important to obtain a final histologic diagnosis and rule out malignancy. In addition, large cysts have a significant risk of complications such as malignancy, torsion, or labor obstruction.[7]

Timing is crucial – surgical intervention that is done too early poses a risk of miscarriage and loss of luteal function before the 4th month of pregnancy, whereas one that is done too late may lead to complications including torsion/rupture or hemorrhage, progression in case of cancer, and premature delivery. Surgery for

ovarian cancer can be scheduled ideally after 16 weeks of pregnancy, as this is when spontaneous abortions are less common, the corpus luteum becomes hormone independent throughout pregnancy, and functional cysts resolve in the majority of instances. Early second trimester is the most ideal period for laparotomy in terms of its safety for removal of persistent ovarian tumor. However, this patient was lost to follow-up at this ideal time, and her tumor was removed during her 24th week age of gestation. If diagnosed in the 3rd trimester, surgery can be delayed in favor of fetal lung maturity.[5] Premature labor is more likely, and the pregnancy outcome is poorer if surgical exploration is attempted during the third trimester. Certainly, delaying surgery is inappropriate for patients with findings suspicious for malignancy or with a clinical situation necessitating emergent laparotomy.[6]

A midline laparotomy, performed through a midline vertical incision with minimal uterine manipulations, is preferred for optimal exposure.[8] This provides the best exposure to the pelvis, should surgical staging be indicated. Peritoneal washing, omentectomy, unilateral salpingo-oophorectomy, and biopsy of all suspicious locations are standard procedures. There is debate about the use of systematic pelvic and paraaortal lymphadenectomy during pregnancy due to a higher probability of problems, such as the possibility of an abortion, hemorrhage, or an early birth. Fertility sparing surgery done in this patient with the preservation of the left ovary may be considered in most malignant ovarian germ cell tumors without compromising oncologic outcome since these tumors were very sensitive to the standard combination chemotherapy (cisplatin, bleomycin, and etoposide/vinblastine).[6]

Due to the excellent chemosensitivity of immature teratomas, the aim of management in all patients is curative with preservation of fertility by performance of just unilateral salpingo-oophorectomy. Stage IA patients are suitable for surveillance.[5] The standard chemotherapy is the combination of bleomycin, etoposide, and cisplatin.[8,9] Except in cases of stage IA grade 1, antenatal chemotherapy until 32 weeks gestation or 3 weeks prior to delivery is recommended to avoid problems associated with hematopoietic suppression, i., bleeding, infection, anemia, and to avoid drug accumulation in the fetus. Despite pharmacokinetic processes being altered by pregnancy, chemotherapy should be administered between 16 and 32 weeks of pregnancy according to the same schedules and dosages as in nonpregnant women. Following each treatment round, ultrasound biometry of the fetus is advised. However, resolution of the multidisciplinary conference and family conference allowed the patient to decide on her management. The best time to induce labor is between 35 and 37 weeks of pregnancy, with a minimal interval of 3 weeks from the last cycle of chemotherapy. To induce fetal lung maturity, corticosteroids should be given if delivery is scheduled before 37 weeks of pregnancy.[5]

According to the American Cancer Society, ovarian carcinomas are the primary cause of death from genital tract malignancies. It happens once every 20,000–50,000 women. Seventy-five percent of the malignancies discovered during pregnancy are early-stage ones with a 70%–90% 5-year survival rate. Pregnancy has minimal impact on prognosis for most ovarian malignancies.[10]

The prognosis for patients with immature teratomas, whether pregnant or nonpregnant, is the same. It is related to the stage (FIGO) and grade of the tumor. The grade of the tumor is based on the degree of immaturity of the various tissues. Grade 3 tumors consist of the most immature tissues and often have a high proportion of immature neuroepithelium. In grade 3 tumors, the relapse rate is 21%.[11]

Ethical considerations

The Principle of Double Effect is invoked to explain the permissibility of an action that causes serious harm, as a side effect of promoting some good end. We weigh the benefits of adjuvant chemotherapy to the mother, on the background of an aggressive malignant tumor, and the potential risks to the fetus, i.e. prematurity, fetal growth restriction, and fetal loss.[12]

When the patient decided to delay chemotherapy, the doctor still needs to ensure that she is aware of the advantages and disadvantages of her decision, can balance it against her own values and beliefs, and can articulate her concerns and decisions in a clear and concise manner. We must respect the patient's decision after ensuring that she is aware of everything. We apply the principle of autonomy in this case [Appendix 4].[12]

Summary

Immature teratoma in pregnancy is rare. An adnexal mass persisting beyond the first trimester, and the presence of malignant sonologic features warrant immediate surgical exploration.[7] However, our main goal is to ensure the safety of both mother and fetus. Surgery may be safely done during the second trimester, after 16 weeks of gestation and before reaching the third trimester. The role of aggressive surgery is unclear due to the rarity of immature teratomas. Furthermore, peritoneal fluid cytology, unilateral salpingo-oophorectomy, infracolic omentectomy, with biopsy of suspected sites, without lymphadenectomy, may suffice due to their excellent chemosensitivity. Furthermore, adjuvant chemotherapy

may be administered between 16 and 32 weeks AOG according to the same schedule and dosages in nonpregnant women; however, the patient's and her partner's decision is crucial. To achieve successful and desirable outcomes for the mother and the fetus, management of the case with a multidisciplinary approach is recommended to discuss with the patient the timing of surgery, chemotherapeutic plans, and the time and mode of delivery of the fetus.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authorship contributions

Zia Isabella Valero Centeno, M.D. - Involved in conceptualization, methodology, resources, data curation, writing – original draft, writing – reviewing and editing, visualization.

Aubrey Yang Señeris - Involved in methodology, writing – reviewing and editing, visualization, supervision.

Grace Poquiz Cayabyab - Involved in methodology, writing – reviewing and editing, visualization, supervision.

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Conflicts of interest

There are no conflicts of interest.

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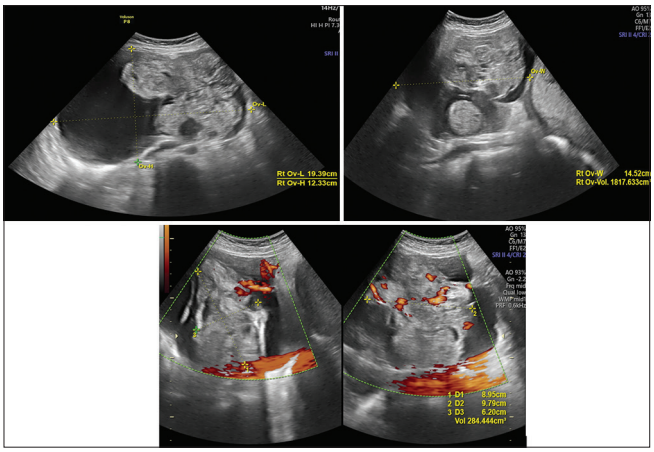
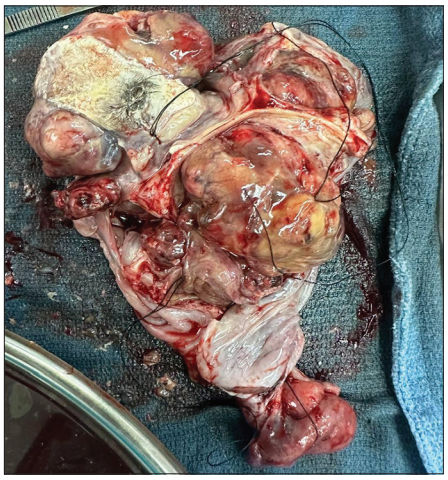
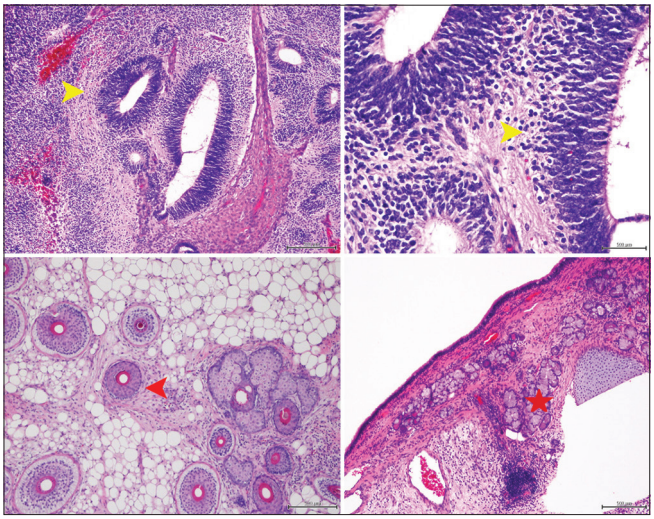


Appendix 1: Ultrasound images of right ovarian new growth at 23 weeks 1 day gestation



Appendix 2: Gross picture of the right ovary of our patient. The ovary is gray to brown, soft to firm, nodular, with clots, sebum, hair, and teeth measuring 13.5 cm × 15 cm × 5.4 cm



Appendix 3: Microscopic image of the right ovary. The ovarian tissue shows wide areas of immature neuroectodermal tissue (yellow arrows) greater than two low-power objectives. Some areas show sebaceous glands, hair follicles (red arrow), fibroadipose, fibromuscular, and fibrocollagenous (red star) tissues

Medical Indications and Fetal Considerations	**Patient Preferences**
Our patient was diagnosed with an ovarian new growth, probably malignant. Hence, surgical intervention must be performed. However, a surgery that is to be done during the pregnancy may pose a risk to the fetus, such as preterm labor, infection, which could ultimately result in pregnancy loss. Malignancy requires a prolonged duration of surgery, namely, peritoneal fluid cytology, unilateral salpingo-oophorectomy, infracolic omentectomy, random peritoneal sampling, bilateral pelvic node dissection, and para-aortic lymph node sampling. Here, we apply the ***Principle of Beneficence and Non-maleficence***. This necessitates assessing the potential benefits of the said surgical plan, while weighing the side effects or consequences to the mother and fetus. Our goal is to ensure both mother and fetus' safety. Performing this form of surgery would subject our patient to a longer operation time, increasing her risk for preterm labor, infections. Instead, we can consider a peritoneal fluid cytology, unilateral salpingo-oophorectomy, rush frozen section, possible infracolic omentectomy, random peritoneal sampling, and omitting lymphadenectomy, will result a shorter operation time, and a lower chance of injury to the mother and the fetus. Patient then underwent a Peritoneal Fluid Cytology, Right Salpingo-oophorectomy, Rush Frozen Section (revealing a malignant ovarian new growth), Infracolic Omentectomy, however, inadvertent rupture of the ovarian new growth occurred. Post-operatively, both mother and patient did well. Histopathology revealed Immature Teratoma, High Grade, at least St. 1C3. Adjuvant chemotherapy during pregnancy is indicated in all cases, except Stage IA Grade I. Here, we apply the ***Principle of Double Effect.*** This principle is invoked to explain the permissibility of an action that causes serious harm, as a side effect of promoting some good end. We weigh the benefits of chemotherapy to the mother, on the background of an aggressive malignant tumor, and the potential risks to the fetus, i.e. prematurity, fetal growth restriction and fetal loss. The use of standard chemotherapy BEP (bleomycin, cisplatin, etoposide) is problematic, especially etoposide. It is recommended to use only cisplatin in monotherapy or cisplatin combined with vinblastine followed by 2-3 cycles of BEP standard chemotherapy after delivery.	All the available treatment options were explained to our patient, between performing a complete cancer surgery vs a fertility-sparing surgery. We also went over the benefits and drawbacks of each technique, emphasizing that the adnexal surgery with rush frozen section would be better for the mother and the developing fetus. With all these explained, the patient agreed to the proposed plan which she eventually underwent. After surgery, the patient was informed once more that chemotherapy was necessary considering her histopathology results. As was previously indicated, the fetus may be at risk. Conversely, there is a chance that cancer will spread if chemotherapy is postponed. The patient then decided to delay chemotherapy until her baby is delivered safe. We use the ***Principle of Autonomy*** in both situations. Our patient is capable of understanding the benefits and drawbacks of the various medical options, being able to weigh those advantages and disadvantages against their own beliefs and values, and being able to express their concerns and decisions clearly and effectively in a medical setting. As her physician, we made sure the patient understands everything, then, we must respect her choice to postpone chemotherapy.
Quality of Life Quality of life is defined by the patient, not by the health care team. As her physician, we explored with her what the proposed intervention options will mean to her. She could not bear the thought of chemotherapy putting her child in danger. This would have a detrimental effect on her quality of life.	**Justice and Fetal/Child Issues** The ***Principle of Justice*** addresses what entitlements are due to individuals for their health care. The right of individuals to fair and equitable distribution of the benefits and the risks or burdens of available health care (that is, distributive justice) is particularly relevant regarding women's sexual and reproductive rights. We held a multidisciplinary team conference for our patient, which included representatives from Perinatology (due to high risk pregnancy), Gynecologic Oncology (on the background of a High Grade Immature Teratoma), Pulmonology (due to the potential side effects of chemotherapy to the mother especially Bleomycin), and Neonatology (in anticipation of a possible preterm delivery). Given that the patient would incur additional costs for the pregnancy, surgery, and chemotherapy, we made sure she received high-quality medical treatment while also offering financial support. We made sure she was directed to our hospital's Malasakit Center for financial support.

Appendix 4: Ethical analysis, four box approach