Unilateral pelvic and para-aortic lymphadenectomy following cesarean section in a pregnant woman with endometrioid ovarian cancer. A case report

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ABSTRACT

Adnexal masses in pregnancy are not rare. The ovaries must be evaluated during routine first trimester obstetric ultrasound examination. In cases where an adnexal mass is identified and found to persist after 16 weeks of gestation, surgical evaluation is mandatory if malignancy is suspected. In the case of confirmed malignancy at surgery, re-staging after delivery is recommended and, for early-stage ovarian cancer, pelvic and para-aortic lymphadenectomy is performed. Lymph-node dissection can lead to short- and long-term complications, which could undermine the quality of life of patients. We describe the case of a 25-year-old pregnant woman with a right adnexal mass, which had not regressed after 16 weeks of gestation. The patient underwent laparoscopic right salpingo-oophorectomy, with definitive histological diagnosis of ovarian endometrioid cancer. During cesarean section, at 37 weeks of gestation and with no complication for the newborn, a re-staging was performed, involving left ovarian and peritoneal biopsies, appendectomy, omentectomy, para-aortic lymph-node dissection, and right pelvic lymphadenectomy, with every effort made to reduce long-term complications related to lymph node dissection. After 18 months the patient is disease free. To our knowledge, this is the first case of unilateral lymphadenectomy for early epithelial ovarian cancer reported in the literature.

KEYWORDS

Pregnancy, endometrioid, lymphadenectomy, ovarian cancer.

Introduction

Ovarian cancer is the fifth most common cancer affecting pregnant women and the second among all gynecological cancers, with an incidence of 1:12,000-47,000 pregnancies [1].

The estimated risk of presenting an adnexal mass during pregnancy is 0.2-2% [2]. Such masses are generally diagnosed during first trimester routine obstetric ultrasound examination and usually regress spontaneously in the second trimester of pregnancy, specifically by the 16th week, when hCG levels decrease. In 65-80% of cases, ovarian masses during pregnancy are asymptomatic, but they can cause complications in 10-30% of cases, including pelvic impaction, obstructed labor, hemorrhage, torsion, rupture, progression in cases of malignancy, and premature labor [3].

The most common are cystoadenomas, teratomas, paratubal and follicular cysts, endometriomas, corpus luteum cysts, leiomyomas, borderline ovarian tumors and finally malignant neoplasms. Ovarian hyper-stimulation syndrome is another cause of adnexal masses in pregnant women [4,5].

When evaluating, in pregnancy, adnexal masses persisting beyond 16 weeks, attention must be paid to the specific ultrasound criteria for malignancy, always keeping in mind the possible morphological changes taking place during gestation [6]. In doubtful cases, magnetic resonance imaging can be used, especially in evaluating potential peritoneal disease spread and nodal metastases [7].

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As regards the use of tumor markers for the differential diagnosis of ovarian malignancies in pregnancy, during normal pregnancy, especially in the first and last trimesters, decidua and granulosa cells produce CA 125, reducing its diagnostic value for ovarian cancer; conversely it can be used in the follow up. Inhibin B and anti-Mullerian hormone for granulosa cell tumors and human epididymis protein 4 levels are not elevated in normal pregnancy and they can be used in both diagnosis and follow up [8]. Epithelial malignant and borderline tumors are the most frequent histotypes, while germ cell and sex-cord stromal tumors are uncommon. 80% of ovarian malignancies during pregnancy are diagnosed at an early stage [9].

When an adnexal mass persists beyond 16-20 weeks of pregnancy, surgery should be indicated, while it is mandatory if malignancy is suspected. Any surgical procedure involving the ovaries should be avoided during the first trimester because of the higher miscarriage rates, most likely due to disruption of the corpus luteum. In the third trimester, the risk of preterm delivery is lower [10].

Generally, ovarian cystectomy is performed for benign pathology while a salpingo-oophorectomy should be considered when malignant pathology is suspected.

In these cases, the planning for completion staging surgery depends on the histology and stage, and completion staging may be performed during caesarean section or immediately after delivery (6–8 weeks after the initial surgery) [3].

Endometrioid carcinoma accounts for 10-15% of ovarian epithelial carcinomas, representing the second type of ovarian epithelial cancer [11]. A substantial proportion (10-50%) of ovarian endometrioid carcinomas develop from endometriosis [12]. Indeed, according to the new classification, based on histopathology and immunohistochemical and molecular genetic features, endometrioid and clear cell carcinomas originate from ovarian endometriosis. In particular, endometrioid carcinoma can develop from precursor foci of atypical endometriosis [13]. These may undergo malignant transformation in a slow stepwise fashion, showing indolent behavior and good prognosis compared to the serous histotype. Most ovarian endometrioid carcinomas are well differentiated and show low-grade nuclei. They are unilateral in 83-87% of cases [14]. They may have a chocolate-colored content with solid nodules or papillary growths, or with hemorrhagic or necrotic areas.

The grading is established on the basis of the architectural pattern and the nuclear features, and particularly the relationship between the solid part and the glandular part.

The most common symptoms are pelvic pain and abdominal distension, but they can also be asymptomatic. CA125 is high in more than 80% of cases [15].

Case report

We present the case of a 25-year-old woman with a history of an adnexal cyst suggestive of dermoid cyst, discovered by chance before pregnancy. She denied any other significant illnesses or surgical procedures.

In July 2019, the patient became pregnant and during the first ultrasound evaluation at 8 weeks of gestation, a right adnexal neoformation was observed. The ultrasound features were suggestive of a borderline tumor of the ovary: a solid unilocular formation, measuring 35x31x33 mm, with regular margins, anechoic content, an inside papilla of 12 mm, with Color score 3 (Figure 1). Table 1 shows the IOTA ADNEX model for prediction of risk of malignancy.

Tumor marker levels were in the normal ranges

During the subsequent follow ups, the ovarian mass appeared to be slightly increased in size and therefore, as it persisted beyond the 16th week of amenorrhea, given the suspicion of malignant pathology, after detailed informed consent, we decided to remove the ovarian mass.

In November 2019, at seventeen weeks of amenorrhea, the patient underwent a laparoscopic right salpingo-oophorectomy, according to the surgical and anesthetic standards for pregnant women. The definitive histological result was FIGO G1 endometrioid adenocarcinoma of the right ovary (Figure 2, A-B). The right fallopian tube was free of disease.

After surgery, the pregnancy progressed without any complications and at the gestational age of 37 weeks, after detailed

Table 1 Prediction of malignant tumor according to the IOTA ADNEX model.

CHANCE OF BENIGN TUMOR	80.0%	1.2	68.2%
RISK OF MALIGNANCY	20.0%	0.6	31.8%
Risk of borderline	13.8%	2.2	6.3%
Risk of stage I ovarian cancer	4.0%	0.5	7.5%
Risk of stage II-IV ovarian cancer	1.3%	0.1	14.1%
Risk of metastatic cancer to the adnexa	0.9%	0.2	4.0%

Figure 1 Right solid unilocular adnexal mass, with irregular papilla with Color score 3.

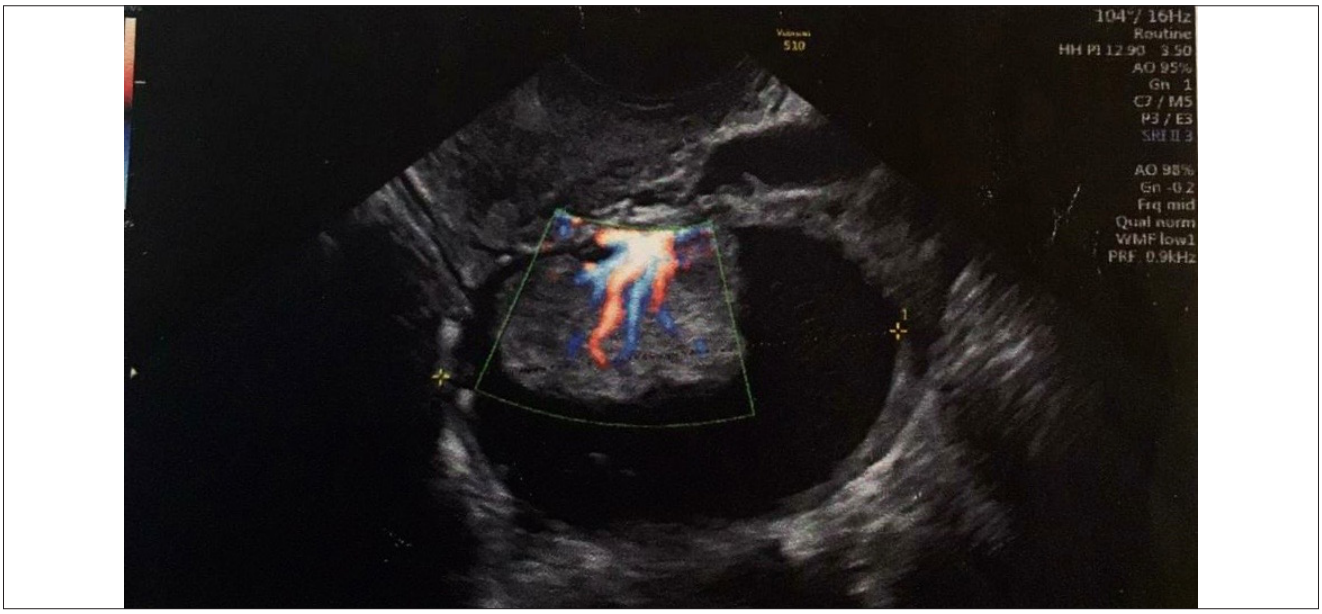
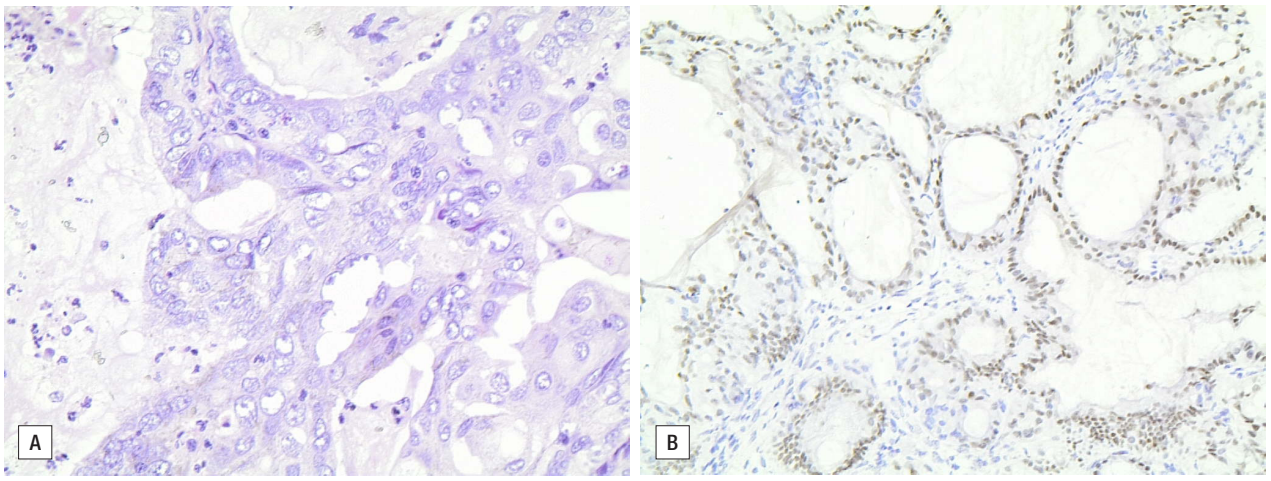


Figure 2 A-B Microscopic features of the estrogen receptor-positive endometrioid epithelial cancer.



informed consent, the patient underwent a cesarean section together with surgical staging. The patient refused to undergo an adequate surgical staging until the date of the delivery. A healthy female newborn was delivered, with normal weight and Apgar score of 9/10. The cesarean section was performed with a supraumbilical-pubic skin incision.

To ensure preservation of the patient's fertility and, at the same time, to guarantee the best surgical staging possible, during the cesarean section, unilateral right pelvic lymphadenectomy, paraaortic lymphadenectomy, appendectomy, infra-colic omentectomy, and left ovarian and multiple peritoneal biopsies were performed. The definitive histological examination showed no evidence of tumor (IA FIGO stage). Even though no family history of cancer was documented, considering that 10% of ovarian cancer cases are hereditary, the patient underwent onco-genetic counselling. Next generation sequencing testing for hereditary breast and ovarian cancer showed no variant of the ATM, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN, RAD51C, RAD51D, TP53, EPCAM, MLH1, MSH2, MSH6, PMS2 or STK11 genes. It was therefore decided to proceed with oncological follow up as per guidelines. Eighteen months later, the patient and the newborn are in excellent health and the patient is disease free.

Discussion

Ovarian masses may complicate 2.3 to 4.1% of all pregnancies [16]. Careful discrimination between benign and malignant adnexal lesions is mandatory, especially during pregnancy [17]. When the presence of a pelvic mass is suspected in a pregnant woman, ultrasonography is currently the first imaging modality for evaluation of adnexal lesions [18].

To classify adnexal masses by ultrasound, the IOTA criteria defined by Timmerman et al. in 2009 [19] are used. These criteria describe specific ultrasound features for the diagnosis of malignancy, and they have a specificity of 78% and a sensitivity of 89% when ultrasound is performed by an expert operator [6].

A specific challenge of pregnancy-related ovarian masses concerns decidualization of an ovarian endometrioma, caused by the hormonal changes of pregnancy, which may be mistaken for malignancy; close follow up is needed [20]. The presence of irregular papillary projections is suggestive of a malignant mass.

Endometrioid carcinoma carries the most favorable prognosis of all ovarian carcinoma histotypes with a 5-year survival rate of more than 70%. In stage I, the 5-year survival rate is approximately 95%. In particular, according to the 2019 AIOM guidelines, in patients defined as low risk (Stage IA-IB, G1) it is over 90%, and these patients do not require adjuvant therapy after surgery. Moreover, if they want to preserve their fertility, conservative surgery might be possible.

In pregnant patients with a suspected malignant adnexal mass, a careful decision must be made regarding the timing of the surgery. It is necessary to consider the risks associated with performing surgery too early (risk of miscarriage and loss of luteal function before the fourth month of pregnancy) and too late, endeavoring to avoid adverse obstetric outcomes.

Laparoscopy is a safe technique for both mother and fetus, provided it is performed according to standard criteria [21]. It is preferably scheduled between 16 and 20 weeks, in order to exploit optimal visualization of the mass in contrast to the enlarged uterus and to decrease the preterm labor rate. Other features of the surgery are first trocar positioning at least 3–4 cm above the uterine fundus, a maximal laparoscopic procedure time of 90 min, and pneumoperitoneum with a maximal intra-abdominal pressure of 10–13 mmHg. It should be performed by an experienced surgeon and the utmost attention must be paid to possible Veress needle injuries; the Hasson open entry technique can be used [21].

If oophorectomy is necessary during laparoscopy (in the event of suspected malignant mass or technical difficulty during cystectomy), the surgeon should avoid breaking the mass to avoid any pelvic contamination. Patients with epithelial ovarian carcinomas should be offered restaging surgery after delivery. In the present case, the patient was advised, in accordance with guidelines, to undergo complete surgical staging within the second trimester. However, once informed of the risks of surgery in pregnancy (preterm delivery, miscarriage and fetal distress), she

did not consent to staging until delivery. Postponing a procedure after delivery can be considered in selected cases. An adequate gynecological surgical assessment could be proposed around 22 weeks of gestation. Based on a low risk of progression to invasive cancer, surgery might be postponed until postpartum if a tumor of low malignant potential is diagnosed during the second or the third trimester [22]. For stage IA or IIA, pelvic and para-aortic lymph node dissection are recommended [21]. In women with disease confined to one ovary and with reproductive desire, a fertility-sparing approach could be considered.

For advanced-stage disease, neoadjuvant chemotherapy until fetal maturity and complete cytoreduction after delivery is considered the best approach [21].

Although correct staging for ovarian epithelial cancer involves systematic pelvic and obturator lymphadenectomy, our patient, after reading the informed consent document was very concerned about the possible adverse events, and therefore did not consent to the systematic procedure; instead, she agreed to undergo unilateral lymphadenectomy. Systematic retroperitoneal lymphadenectomy is a major surgical procedure with several important complications. In our case, although the rate of lymph node metastases for the endometrioid histotype was lower than for high-grade serous cancer, but still significant (<13% vs 19%) [22], right unilateral pelvic lymphadenectomy was performed for staging purposes and for evaluation of adjuvant post-partum chemotherapy, rather than bilateral pelvic lymph node dissection, thereby minimizing the long-term complications potentially associated with the lymph-node dissection procedure, given the patient's young age.

According to the recent recommendation published in the 2019 ESGO-ESMO consensus conference, G1 endometrioid IA stages may avoid chemotherapy, as long as they are completely staged [24].

Although she had not undergone systematic bilateral pelvic and obturator lymphadenectomy, the patient refused to receive adjuvant chemotherapy, agreeing to undergo close follow up.

To our best knowledge, this is the first report of unilateral pelvic lymphadenectomy for epithelial ovarian cancer during a cesarean section.

References

1. Van Calsteren K, Heyns L, De Smet F, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. J Clin Oncol. 2010;28:683-9.
2. Fruscio R, de Haan J, Van Calsteren K, Verheecke M, Mhallem M, Amant F. Ovarian cancer in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2017;41:108-17.
3. Mukhopadhyay A, Shinde A, Naik R. Ovarian cysts and cancer in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2016;33:58-72.
4. Di Carlo C, Savoia F, Gargano V, Sparice S, Bifulco G, Nappi C. Successful pregnancy complicated by spontaneous, familial, recurrent ovarian hyperstimulation syndrome: report of two cases. Gynecol Endocrinol. 2013;29:897-900.
5. Di Carlo C, Savoia F, Ferrara C, Tommaselli GA, Bifulco G, Nappi C. Case report: a most peculiar family with spontaneous, recurrent ovarian hyperstimulation syndrome. Gynecol Endocrinol. 2012;28:649-51.
6. Timmerman D, Van Calster B, Testa AC, et al. Ovarian cancer prediction in adnexal masses using ultrasound-based logistic regression models: a temporal and external validation study by the IOTA group. Ultrasound Obstet Gynecol. 2010;36:226-34.
7. Hoover K, Jenkins TR. Evaluation and management of adnexal mass in pregnancy. Am J Obstet Gynecol. 2011;205:97-102.
8. Han SN, Lotgerink A, Gziri MM, Van Calsteren K, Hanssens M, Amant F. Physiologic variations of serum tumor markers in gynecological malignancies during pregnancy: a systematic review. BMC Med. 2012;10:86.
9. Leiserowitz GS, Xing G, Cress R, Brahmbhatt B, Dalrymple JL, Smith LH. Adnexal masses in pregnancy: how often are they malignant? Gynecol Oncol. 2006;101:315-21.
10. Wolters V, Heimovaara J, Maggen C, et al. Management of pregnancy in women with cancer. Int J Gynecol Cancer. 2021;31:314-22.
11. Zhou L, Yao L, Dai L, et al. Ovarian endometrioid carcinoma and clear cell carcinoma: a 21-year retrospective study. J Ovarian Res. 2021;14:63.
12. Davis M, Rauh-Hain JA, Andrade C, et al. Comparison of clinical outcomes of patients with clear cell and endometrioid ovarian cancer associated with endometriosis to papillary serous carcinoma of the ovary. Gynecol Oncol. 2014;132:760-6.
13. Prat J, D'Angelo E, Espinosa I. Ovarian carcinomas: at least five different diseases with distinct histological features and molecular genetics. Hum Pathol. 2018;80:11-27.
14. Longacre TA, Wells M. Endometrioid tumours. In: Kurman RJ, Carcangiu ML, Herrington CS, Young RH, eds. WHO classification of tumours of female reproductive organs. Lyon: International Agency for Research on Cancer (IARC); 2014:29-32.
15. de Haan J, Verheecke M, Amant F. Management of ovarian cysts and cancer in pregnancy. Facts Views Vis Obgyn. 2015;7:25-31.
16. Giuntoli RL 2nd, Vang RS, Bristow RE. Evaluation and management of adnexal masses during pregnancy. Clin Obstet Gynecol. 2006;49:492-505.
17. Mascilini F, Savelli L, Scifo MC, et al. Ovarian masses with papillary projections diagnosed and removed during pregnancy: ultrasound features and histological diagnosis. Ultrasound Obstet Gynecol. 2017;50:116-23.
18. Czekierdowski A, Stachowicz N, Smoleń A, et al. Sonographic assessment of complex ultrasound morphology adnexal tumors in pregnant women with the use of IOTA Simple Rules Risk and ADNEX scoring systems. Diagnostics (Basel). 2021;11:414.
19. Timmerman D, Ameye L, Fischerova D, et al. Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ. 2010;341:c6839.
20. Fruscella E, Testa AC, Ferrandina G, et al. Sonographic features of decidualized ovarian endometriosis suspicious for malignancy. Ultrasound Obstet Gynecol. 2004;24:578-80.
21. Amant F, Halaska MJ, Fumagalli M, et al; ESGO task force 'Cancer in Pregnancy'. Gynecologic cancers in pregnancy: guidelines of a second international consensus meeting. Int J Gynecol Cancer. 2014;24:394-403.
22. Amant F, Berveiller P, Boere IA, et al. Gynecologic cancers in pregnancy: guidelines based on a third international consensus meeting. Ann Oncol. 2019;30:1601-12.
23. Bogani G, Tagliabue E, Ditto A, et al. Assessing the risk of pelvic and para-aortic nodal involvement in apparent early-stage ovarian cancer: a predictors- and nomogram-based analyses. Gynecol Oncol. 2017;147:61-5.
24. Colombo N, Sessa C, du Bois A, et al; ESMO-ESGO Ovarian Cancer Consensus Conference Working Group. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†. Ann Oncol. 2019;30:672-705.

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