

# Low-grade serous ovarian cancer in pregnancy

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## CASE PRESENTATION

A 33-year-old primigravida was referred to our gynecological oncology unit for evaluation and management of an adnexal mass during pregnancy. At a gestational age of 6 weeks, sonography revealed a multilocular solid left adnexal mass of 90×67×81 mm with a solid component of 49×50×31 mm with moderate vascularization, according to the International Ovarian Tumor Analysis (IOTA) classification<sup>1</sup> (Figure 1). Her right ovary was replaced by an irregular solid mass of 74×40×61 mm with four vascularized papillary projections with a maximum height of 24 mm protruding into an internal small cyst. No ascites was present. Blood serum demonstrated cancer antigen (CA) 125 levels of 184 U/mL; the serum markers carcinoembryonic antigen (CEA), CA 19.9 and CA 15.3 were within normal limits. Pelvic MRI without contrast confirmed the presence of a multilocular mass of her left ovary, which showed diffusion restriction and hypo-intensity at the T2-weighted sequence (Figure 2). The right ovary consisted of a solid mass with cystic components and demonstrated a weakly hyperintense signal. The absence of peritoneal carcinomatosis was confirmed.

## Dr Peters, please provide details as to discussion on management at this point

*The patient was counseled for immediate unilateral salpingo-oophorectomy to obtain a histological diagnosis. Considering the early gestational age, the risk of an iatrogenic abortion was discussed. The patient refused surgery and decided to wait until pregnancy was more advanced.*

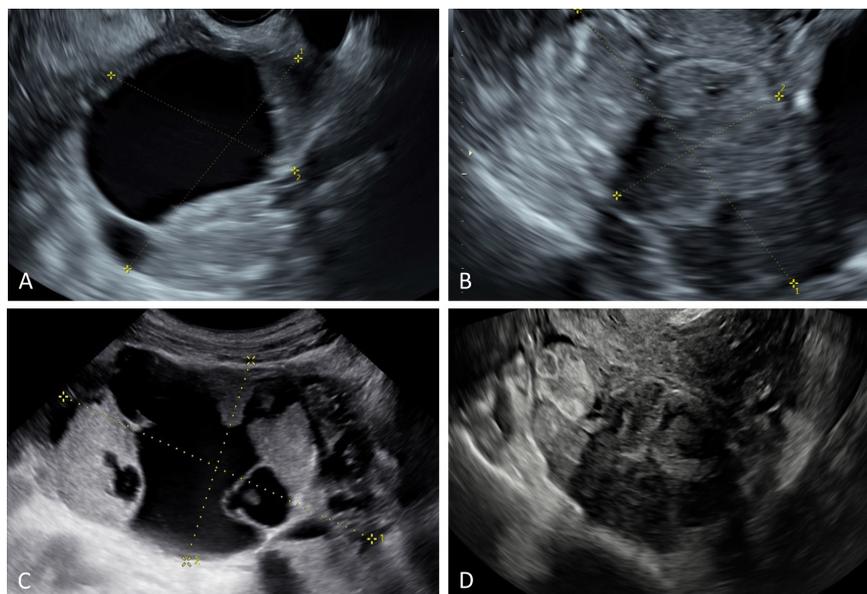
One month later, ultrasonographic follow-up showed a fetus appropriate for gestational age. Furthermore, both adnexal masses had characteristics similar to those at initial presentation (Figure 1). The patient underwent surgery at 13 weeks of gestation. At laparoscopy, tumor deposits were found on the left posterolateral wall of the uterus and the anterior surface of the rectum. In addition, miliary peritoneal disease was found on the right hemidiaphragm. The left ovary had a multilocular-solid appearance with an intact capsule, measuring approximately 10 cm, that was attached to the left posterolateral wall of the uterus. The right ovary was approximately 8 cm in diameter, had a solid appearance, and was well-vascularized. Full inspection was hampered, as it was prolapsed in the pouch of Douglas. A frozen section taken from the left ovarian capsule revealed a micropapillary borderline tumor. Considering that the right ovary that was most aberrant was difficult to access, and a definitive diagnosis was needed, the procedure was converted to a lower midline laparotomy up to the level of the umbilicus. A left ovarian cystectomy without tumor spillage and a right salpingo-oophorectomy were performed. In addition, several peritoneal biopsies were obtained. Final histopathology revealed a low-grade serous carcinoma in both ovaries (Figure 3) and in the biopsy taken from the right hemidiaphragm—International Federation of Gynecology and Obstetrics (FIGO) stage IIIC.

Following discussion in the multidisciplinary tumor board, the patient was counseled for immediate cytoreductive surgery, with an estimated disease-free



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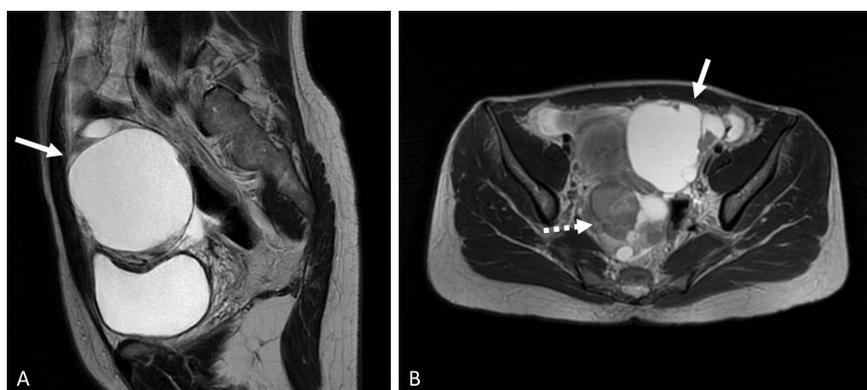
**Figure 1** Ultrasound images of low-grade serous ovarian carcinoma at 6 weeks' (upper panel) and 10 weeks' (lower panel) gestation. The left ovary is shown in panels A and C. The right ovary is shown in panels B and D. Ultrasound features did not change over time.

and overall survival of 63% and 85% at 5 years, respectively.<sup>2</sup> Yet, she expressed the strong wish to continue pregnancy. Hence, neoadjuvant chemotherapy with an expected response rate of 11% and risk of progression of 6% was discussed.<sup>3</sup> The patient accepted these risks and received carboplatin AUC4 and paclitaxel 75 mg/m<sup>2</sup> every 3 weeks. The absolute dose was recalculated for every cycle based on her actual weight during pregnancy. Serum levels of CA 125 were measured on a monthly basis and decreased to 27 U/mL.

At 35 weeks of gestation following five cycles of neoadjuvant chemotherapy, an elective cesarean section was performed via an abdominal midline incision under combined spinal epidural anesthesia. A healthy daughter was born with a weight of 2300 g (p38) and an Apgar score of 9 and 10 at 1 and 5 min following birth, respectively. This procedure was immediately followed by complete cytoreductive surgery under general anesthesia. In addition to the previously observed deposits, lesions were found at the prevesical peritoneum, the right paracolic gutter, Morrison's pouch, and the spleen. Moreover, some pelvic lymph nodes were

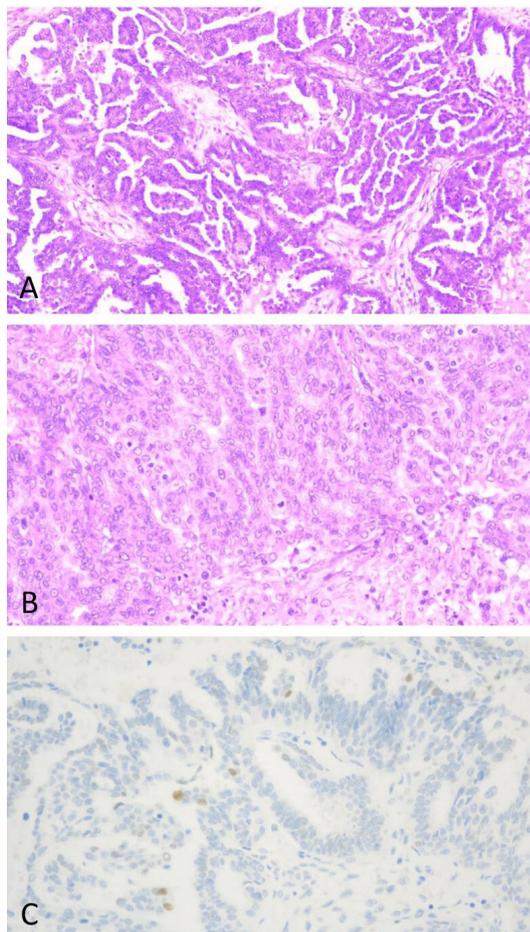
enlarged. Although we cannot rely on CA 125 serum levels during pregnancy,<sup>4</sup> the absence of an increment of CA 125 makes it more likely that these lesions were present but not detected during previous surgery due to the enlarged uterus and/or the relatively small midline incision at that time. Left salpingo-oophorectomy, infragastric omentectomy, splenectomy, resection of bulky bilateral pelvic lymph nodes, and peritoneal stripping of the right paracolic gutter, Morrison's pouch, and right hemidiaphragm were performed. A radical hysterectomy type A was needed to remove the pelvic peritoneum en bloc. No macroscopic residual tumor was evident at the end of the surgery. Histopathological findings were in line with the previous diagnosis. The placenta appeared to be devoid of tumor cells.

Postoperatively, the patient recovered well and letrozole 2.5 mg once a day was started from 6 weeks postoperatively. Pediatric follow-up demonstrated normal growth and development of the infant. The patient is free of disease at 4 months from surgery.



**Figure 2** Pelvic MRI at 6 weeks' gestation. A sagittal view of the left ovary is shown in panel A. An axial view of both the left and right ovary is shown in panel B. The solid and dashed arrows indicate the multilocular mass of the left ovary, and the irregular solid mass of the right ovary, respectively.

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**Figure 3** Histopathological images of low-grade serous ovarian carcinoma associated with high-grade morphology. Mild cytological atypia and low mitotic index characterizing low-grade serous ovarian carcinoma are shown in panel A. Areas consisting of cells with a higher degree of atypia and increased mitotic index that are arranged in a solid growth pattern are shown in panel B. Immunohistochemical analysis for p53 expression revealed a focal staining pattern indicative of p53 wild type and is shown in panel C.

### Professors Fagotti and Amant, how often is low-grade serous ovarian cancer diagnosed during pregnancy?

Overall, adnexal masses are encountered in 2.4–5.8% of all pregnancies. The majority of these masses are benign and their clinical relevance is limited. In 0.2–3.8 per 100 000 pregnancies, however, ovarian cancer is diagnosed.<sup>5</sup> Non-epithelial ovarian cancers are most prevalent, followed by tumors of low-malignant potential and epithelial ovarian cancer. This incidence may further increase in countries where the average age at the time of first pregnancy continues to rise. Moreover, novel non-invasive techniques to prenatally diagnose fetal anomalies incidentally uncover the presence of a maternal malignancy.<sup>6</sup>

Low-grade serous ovarian cancer in itself is relatively rare, as it accounts for 2% of all epithelial ovarian cancers and 4.7% of serous ovarian cancers.<sup>7</sup> The exact number of pregnant women affected by low-grade serous ovarian carcinoma is unknown, but

the relative risk might be slightly increased during pregnancy as it is predominantly diagnosed in premenopausal women. In the International Network on Cancer, Infertility and Pregnancy (INCIP) registry, eight and five out of 17 serous ovarian cancers (76%) were grade 1 and grade 2 tumors, respectively (personal communication).

### Professor Testa, how can we differentiate benign from malignant adnexal masses during pregnancy? Which ultrasonographic and radiographic characteristics are specific for low-grade serous ovarian cancer?

In non-pregnant patients, adnexal masses can be adequately diagnosed as benign, borderline or malignant using the preoperative classification system developed by the IOTA group.<sup>1</sup> Pregnancy may, however, pose an additional challenge, as increased estrogen and progesterone levels can alter the sonographic appearance of the ovarian mass. As such, benign decidualized endometriomas might be difficult to differentiate from borderline and/or invasive ovarian masses, as they all may present with papillary projections. Yet, in a large series of 113 patients in whom an adnexal mass was detected during pregnancy, the IOTA classification system resulted in an accurate diagnosis in the majority of cases.<sup>8</sup> None of the 37 patients who had a unilocular mass in this cohort was diagnosed with malignant disease. By contrast, unilocular solid masses were found to be a borderline or invasive tumor in 30% and 7% of cases, respectively. Furthermore, in 21 out of 30 patients (70%) who underwent surgery because of a multilocular-solid or solid appearance, histology confirmed the presence of malignancy.

Accordingly, low-grade serous ovarian carcinomas typically present as a multilocular-solid or solid tumor. In our series consisting of 31 non-pregnant patients, these tumors were on average 73 mm (range 13–179 mm) in size and characterized by an irregular external wall and hyperechoic foci.<sup>9</sup> Acoustic shadowing was often observed and multiple papillary projections were present in up to one-third of cases. Besides, these tumors showed abundant vascularization on color Doppler. Pelvic MRI shows similar features as transvaginal/transabdominal ultrasound for the characterization of adnexal masses. Its application is mainly of value in cases where ultrasound alone is insufficient to draw a firm conclusion and to stage the disease.<sup>1</sup> Diffusion-weighted MRI is the modality of choice, as administration of gadolinium as used in conventional MRI is known to cross the placenta. Following excretion by the fetal kidney it continues to circulate in the amniotic fluid resulting in high levels of free gadolinium ions, which may have a detrimental effect on the fetus.<sup>10</sup>

### Professors Fagotti and Amant, how should women diagnosed with suspicious adnexal masses, and in particular those affected by low-grade serous ovarian cancer, be managed during pregnancy?

In pregnant patients in whom an adnexal mass is suspicious for malignancy, surgery is preferably performed between 13–20 weeks of pregnancy, as a laparoscopic approach is easier when the uterus is still within the pelvis. Open laparoscopy can be safely performed by experienced surgeons under the conditions that the abdominal cavity is accessed at least 4 cm above the uterus, intra-abdominal pressure does not exceed 13 mmHg, and the operating time is set at maximum 90 min.<sup>10</sup> We prefer not to use a Verres needle to prevent uterine perforation. Manipulation of the uterus should be minimized

as much as possible, as both uterine bleeding and contractions may lead to fetal damage and/or loss. In case of uterine manipulation, tocolytics are indicated.

Since correct histopathological diagnosis is important, representative tissue samples should be obtained by either adnexectomy and/or biopsy sampling. Although intraoperative frozen section is in most cases in line with final histopathological diagnosis, one should be aware that in up to one-third of low-grade neoplasms diagnosis is amended after full tissue processing.<sup>11</sup> Therefore, a two-step procedure based on final histological findings, treatment options, and patient's desire is preferred.

In patients with apparent FIGO I-II epithelial ovarian cancer, surgical staging during pregnancy is recommended if there is no direct indication for adjuvant chemotherapy based on histological subtype and gestational age is not beyond 22 weeks.<sup>5</sup> If administration of chemotherapeutic regimens is advised regardless of surgical staging outcome or pregnancy is beyond 22 weeks, chemotherapy should be commenced followed by surgical staging postpartum. In patients with FIGO stage III-IV disease who have a less favorable prognosis, termination of pregnancy is to be considered after which cytoreductive surgery should be performed. If the patient's preference is to preserve her pregnancy, neoadjuvant chemotherapy is indicated from the second trimester on. Cytoreductive surgery then has to be postponed until after delivery to enable adequate pelvic inspection and to ensure complete cytoreduction in case of involvement of the uterus and/or pouch of Douglas.

Low-grade serous ovarian cancer, however, is a relatively chemoresistant disease and complete cytoreductive surgery is the cornerstone of treatment. In a retrospective study examining 36 non-pregnant patients diagnosed with low-grade serous ovarian cancer who underwent neoadjuvant chemotherapy, only four patients had partial response, 30 patients had stable disease, and two showed disease progression.<sup>3</sup> This is in accordance with our findings during cytoreductive surgery. Apart from the possible effect of neoadjuvant chemotherapy, we may argue that high progesterone levels during pregnancy have stabilized the progesterone receptor (PR)-positive low-grade serous ovarian cancer, similarly to the excellent results obtained with letrozole in the adjuvant setting.<sup>12</sup> On the contrary, although data are lacking on low-grade serous ovarian cancer during pregnancy, serous borderline ovarian tumors may exhibit more aggressive features during pregnancy that might have been induced by higher progesterone levels.<sup>13</sup> Therefore, neoadjuvant chemotherapy should currently not be avoided.

Patients who receive antenatal chemotherapy should be closely monitored in regard to fetal growth. In case of small for gestational age, blood flow through the umbilical cord should be determined. If possible, delivery should not be induced before 37 weeks of pregnancy. Furthermore, the last cycle of neoadjuvant chemotherapy should be planned at least 3 weeks before delivery to prevent any complications from maternal and/or neonatal myelosuppression.<sup>10</sup>

#### Dr Arciuolo, please provide details on pathological findings

On gross examination the left ovary consisted of two separate parts following cystectomy with dimensions of 9.2×9×5.5 cm and 9×3.5×2 cm, respectively. The right ovary had a similar macroscopic appearance and manifested as a solid cyst measuring 9×8.5×5.8 cm. Nodular areas, cystic spaces and papillary excrescences were noticed. Microscopically, predominantly uniform nuclei with mild

to moderate atypia and low mitotic index were seen, which were arranged in a micropapillary pattern (Figure 3). Strikingly, areas with a solid pattern of growth, nuclear atypia, foci of necrosis, and increased mitotic activity (10 mitoses per 10 high-power fields) were observed. Both immunohistochemical and molecular analyses for p53 resulted wild-type. Estrogen receptor (ER) and PR were expressed by 35% and 75% of tumor cells, respectively. Based on these findings, the ovarian masses were classified as low-grade serous carcinomas.

The morphological alterations are most likely related to higher hormonal levels during pregnancy. Previously, 13 ovarian tumors were described that showed an increase in cellular size and cytoplasmic eosinophilia (pseudo-decidualized-like cells), necrosis, and atypia during pregnancy.<sup>14</sup> Nevertheless, the significantly higher mitotic activity is presumably not attributable to these hormonal changes.

#### Professors Fagotti and Amant, what would be the follow-up recommendations for the mother and her child?

Although data are scarce, ovarian cancer during pregnancy does not seem to reduce survival rates.<sup>5</sup> Hence, standard oncological follow-up postpartum seems valid. Given the diagnosis of low-grade serous carcinoma, the patient started letrozole maintenance therapy. In a retrospective study of 203 patients with low-grade serous ovarian cancer who received either letrozole 2.5 mg on a daily basis or routine surveillance following cytoreductive surgery and platinum-based chemotherapy, a significantly longer progression-free survival was observed in the hormonal treatment group (64.9 vs 24.9 months;  $p < 0.001$ ).<sup>12</sup> Results of the ongoing phase III trial examining survival rates following letrozole monotherapy/maintenance treatment versus intravenous paclitaxel/carboplatin followed by maintenance letrozole are eagerly awaited (<https://clinicaltrials.gov/ct2/show/NCT04095364>).

As the neonate has prenatally been exposed to chemotherapeutic agents, thorough examination and follow-up is recommended.<sup>5</sup> A detailed physical examination by a neonatologist is required. Blood samples should be drawn to check for hematological, hepatic, and renal functioning. In children who have been exposed to cisplatin, audiometric evaluation needs to be performed to exclude hearing impairment. Furthermore, careful periodic follow-up including neurocognitive and neuromotor development tests are recommended until adolescence. Overall, neurocognitive development is within normal limits,<sup>15</sup> but a lower verbal IQ was demonstrated in children whose mother was in a poor condition. This is most likely not a direct effect of the chemotherapy but rather indirectly attributable to a restricted mother-child interaction.

Last but not least, consideration should be given to the psychological impact all this may have on the patient, her child and her partner. Emotional support and psychological care should be offered, especially to those who use internalizing coping strategies.

#### CLOSING REMARKS

As cancer in pregnancy is uncommon, a multidisciplinary fully dedicated team is crucial. This team should include a gynecologic oncologist, ultrasonographer/radiologist, pathologist, medical oncologist, neonatologist/pediatrician, psychologist, and social worker. Moreover, data collection will help to reduce knowledge

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gaps substantially. Therefore, INCIP has launched an international registry that aims to collect and analyze data on oncological, reproductive, obstetrical, and neonatal outcomes from patients diagnosed with cancer (<https://cancerinpregnancy.org>). INCIP also launched the Advisory Board on Cancer Infertility and Pregnancy (ABCIP, [www.ab-cip.org](http://www.ab-cip.org)), where advice on individual cases can be sought. Moreover, this network aims to set up new collaborations between research groups. These efforts will further advance care for young women diagnosed with cancer during pregnancy.

**Contributors** IP: conception and design, data collection, manuscript preparation and final approval; ACT: data collection and final approval; DA: data collection, manuscript preparation and final approval; FA: manuscript preparation and final approval; AF: responsible surgeon, conception and design, manuscript preparation and final approval.

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