

Endometrial cancer during pregnancy: management strategies

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CASE PRESENTATION

A 41-year-old, G₀ woman with primary infertility was referred to our department after diagnosis of an endometrial carcinoma. Three months previously, endometrial polyps were discovered on hysteroscopy, as part of her infertility work-up. The fragmented polyps/endometrial resection revealed endometrioid adenocarcinoma, grade 1, and clear cell adenocarcinoma. Immunohistochemistry was positive for estrogen receptor, progesterone receptor, and vimentin, negative for Napsin A, mainly negative for HNF1B, with loss of PTEN (phosphatase and tensin homolog) and retained ARID1A (AT-rich interaction domain 1A) in the endometrioid component. A distinctly different component with clear cells was found, in which immunohistochemistry was partly positive for estrogen receptor, focally positive for progesterone

receptor, vimentin, and Napsin A, positive for HNF1B, with retained ARID1A and loss of PTEN. This tumor was therefore considered to be a mixed tumor with a low-grade and high-grade component (Figure 1).

The patient and her partner had unsuccessfully attempted to become pregnant for the preceding 4 years, during which time she had received hormonal stimulation once 2 years previously, and twice in the last year, in addition to having undergone a myomectomy. The last down-regulation by gonadotropin-releasing hormone analog was stopped due to the discovery of the aforementioned uterine polyps. At the time of presentation to our department, she had an unexpected positive pregnancy test, and was determined to continue her pregnancy.

DR AMANT

Based on this information, what would be the recommended further workup?

This is an extremely rare situation since virtually all cases of endometrial cancer during pregnancy were diagnosed post-partum.¹ In the absence of any data, continuation of the pregnancy is experimental. In this case the patient is very motivated and she understands the experimental nature, so a plan is needed where the risks remain as low as possible. It is remarkable that the tumor is described as a mixed entity of a

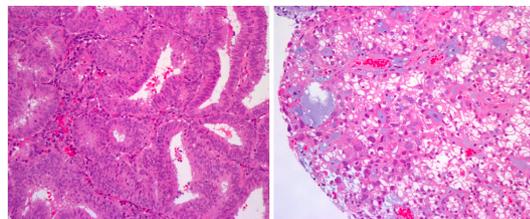


Figure 1 Endometrioid adenocarcinoma (left). Clear cell adenocarcinoma (right).

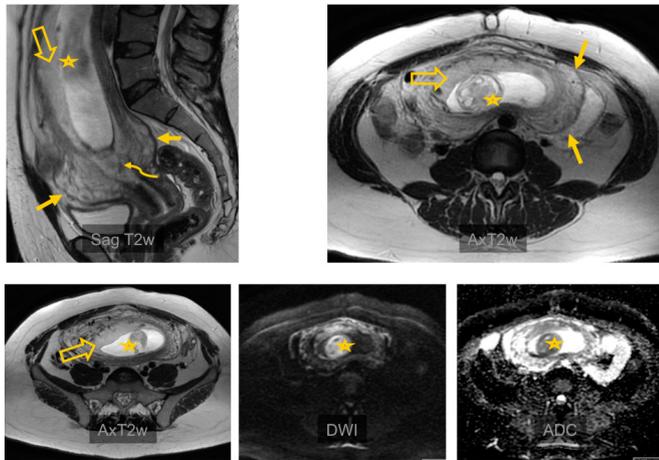


Figure 2 Magnetic resonance imaging at 15 weeks of gestation. An enlarged uterus with embryo, placenta and edematous uterine wall makes the endometrium difficult to assess. Pregnancy-related changes make diffusion weighted imaging (DWI) challenging to interpret. Contrast-enhanced sequences were not performed. No tumor is identified, but the scan's reduced sensitivity make non-bulky tumor hard to exclude. * Fetus, ⇒ placenta, → uterine wall, = endometrium.

low- and high-grade component. Basically, the idea is that pregnant patients need to be staged as non-pregnant patients.² This means that local pelvic extension needs to be documented, including pelvic lymph nodes and screening for peritoneal and organ involvement. Since a high-grade component is present, lung metastases need to be excluded. During pregnancy non-ionizing examinations like magnetic resonance imaging (MRI) and sonography are preferred. In case of extra-uterine disease, the approach needs to be individualized more in a setting where the maternal prognosis becomes more somber.

DR VASSMO LUND

As part of her work-up at the outside hospital before her referral, a computed tomographic (CT) scan of the chest, abdomen and pelvis had been performed, and showed no distant metastasis. An MRI of the abdomen and pelvis at 15 weeks' gestation, without contrast, showed an edematous uterine wall and endometrium, as expected during pregnancy.³ One could not delineate any distinct tumor; however, any subtle tumor could not be ruled out (Figure 2). The scan's sensitivity was reduced due to movement artifacts from the fetus, pregnancy changes, and lack of contrast. Contrast was omitted since gadolinium is contra-indicated in pregnancy.^{4,5}

DR AMANT

Based on this information, what would be the recommended treatment of endometrial carcinoma detected in the first trimester?

In case of apparent early stage endometrial cancer, one could think of surgical staging with removal of pelvic lymph nodes. This is the only situation where the cancer cannot be surgically excised since the involved organ itself is involved. One could consider administration of chemotherapy aiming to reduce or stabilize disease

and avoid further progression. But, part of the cancer is hormone receptor positive and this may be sensitive to the high gestational hormonal levels. So, one could hypothesize that the pregnancy itself helps to avoid further progression of a potentially hormone sensitive disease.⁶

Our group discussed the patient during a plenary meeting to reach a departmental consensus in regards to counseling and management. International experts were consulted. The patient and her partner were then counseled in regards to the risks involved with continuing the pregnancy, and the paucity of data to guide management. The possibility of termination of pregnancy with definitive surgical treatment of her uterine cancer consisting of a laparoscopic hysterectomy, bilateral salpingo-oophorectomy, omentectomy and sentinel lymph node biopsy was recommended as "standard of care", and it was stressed that any other management would be experimental. The patient and her partner remained adamant not to terminate the pregnancy. They were further counseled in regards to the rationale of performing nodal assessment by minimal invasive surgery during the second trimester, and the option of chemotherapy during pregnancy due to the high-risk component. Both were declined.

DR AMANT

How would you monitor this patient during pregnancy?

There is fetal and oncological monitoring. Since there is no cancer chemotherapy treatment, follow-up of fetal growth is less critical from this perspective.⁷ Most important seems the follow-up of cancer growth that may impair maternal chances though may also interfere with placental function and thus fetal growth. Therefore, I suggest to follow fetal growth by monthly sonography and tumor growth by 2-monthly pelvic MRI.

Due to high maternal age, and cancer during pregnancy, regular visits to an experienced obstetrician including trans-abdominal ultrasound to monitor fetal growth were undertaken. These visits were scheduled monthly during the second trimester, and every 2 weeks during the final months of pregnancy. Fetal growth was not compromised during pregnancy. No further MRIs were performed during pregnancy in regards to tumor growth since the patient was determined that any suspicious findings would not alter the course during pregnancy.

The patient had undergone myomectomy 2 years previously. An 8 cm intramural myoma of the anterior uterine wall was removed during laparoscopy. The endometrial cavity was not entered during the procedure, but the myoma was deeply intramural, and therefore a recommendation to deliver via cesarean section were she ever to become pregnant was made. Based on this recommendation an elective cesarean section was scheduled at 36 weeks of gestation, 2 weeks earlier than routine scheduling to minimize the risk of the patient going into spontaneous delivery without a gynecologic oncologist present. The preferred method of delivery in regards to oncologic safety was thought to be spontaneous vaginal delivery, thus not risking potential exposure of the peritoneal cavity to any cancer cells from the endometrium. However, the risk of tumor dissemination during cesarean section was considered to be smaller during an elective procedure than if an emergent cesarean section were to be required due to uterine rupture based on previous myomectomy. In addition, a potential uterine rupture

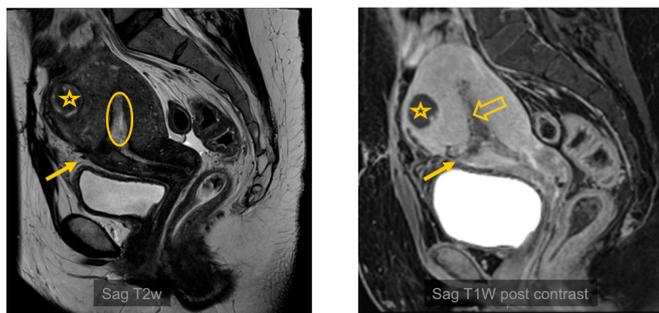


Figure 4 Magnetic resonance imaging 6 weeks after cesarean section, showing normalization of the uterus as expected 6 weeks post-partum. The cesarean scar is visible, and there is bloody content in the endometrial cavity impeding the sensitivity of tumor detection. There is no measurable tumor, and no indication of deep stromal infiltration or cervical involvement. → Cesarean scar, * intramural leiomyoma, non-perfused, ⇒ irregular endometrial lining of the uterine cavity with bloody content.

during spontaneous delivery would pose a significant threat to the unborn fetus and mother.

A healthy baby, weighing 3280 g, was delivered via elective cesarean section at 36 weeks, 3 days, by lower uterine segment incision. A gynecologic oncologist was present. After delivery the uterine cavity was inspected and gentle curettage performed. There was no macroscopic tumor detected on inspection. The peritoneal cavity was inspected for metastasis. There was no evidence of disseminated disease or grossly enlarged nodes. A hysterectomy and staging procedure was not performed at the time of cesarean section since the patient had expressed that if there were no cancer cells detected in the curettage specimen, she wished to preserve her fertility. Also, a sentinel lymph node procedure was not thought to be feasible if staging was to be performed at this time; the patient would instead have to undergo a pelvic and para-aortic lymph node dissection based on the pre-pregnancy clear-cell component.

DR NESBAKKEN

The endometrial curettage specimen revealed endometrioid adenocarcinoma, grade 2. There were fragments of atypical, partly cribriform glandular proliferation consistent with endometrioid adenocarcinoma. The tumor had areas with mucinous differentiation, foci with squamous differentiation and some areas with solid growth

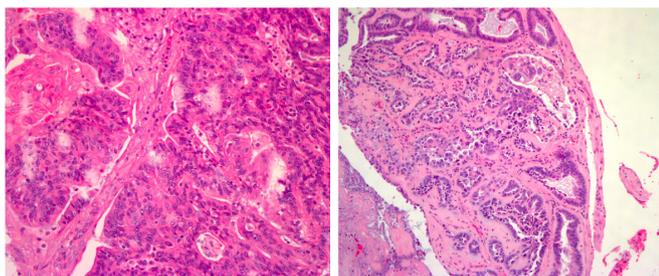


Figure 3 Endometrioid adenocarcinoma with squamous cell differentiation (left). Areas with clear cell features are shown, inconclusive in regards to the presence of a clear cell component (right).

(>5%), consistent with moderately differentiated endometrioid adenocarcinoma. In addition, there were areas with more atypia that were assessed for clear cell differentiation. Immunohistochemistry staining showed some cells positive for Napsin A, partly positive for HNF1b, and mainly negative for estrogen receptor (Figure 3). Pregnancy-related findings were present, rendering the morphological and immunohistochemical findings challenging to interpret. The overall findings were inconclusive for diagnosing a clear cell component. The morphology of this specimen differed from the initial pre-pregnant specimen; this difference may have been due to hormonal influence during pregnancy.

DR VASSMO LUND

A CT scan 6 weeks post-partum did not show any distant metastasis. MRI revealed an enlarged uterus within normal range for 6 weeks post-partum. The uterine cavity was distended >1 cm with bloody content (Figure 4). Per the available literature⁸ the distention was more than expected at this time, particularly since a post-partum ultrasound at 6 days had shown a narrow endometrium. It was challenging to differentiate between post-partum changes and viable tumor. Irregular contours of the endometrium on several sequences could represent residual tumor; however, there was no measurable tumor and no indication of deep myometrial infiltration, or cervical involvement. There was no evidence of metastatic disease.

DR AMANT

At this point, what treatment options would you offer the patient?

The diagnosis is now changed to grade 2 endometrioid adenocarcinoma, and some uncertainty remains in regards to the clear cell component. The patient now needs standard treatment that consists of an endoscopic assisted hysterectomy.⁹ In the absence of a clear cell component, there is no strict indication for full staging anymore. However, it may be prudent to remove only the sentinel node if this expertise is available. In addition, the peritoneal cavity may be screened for peritoneal and omental metastasis from a potential clear cell component. If staging is negative, there is no further need for external beam radiotherapy or chemotherapy.

The patient underwent robotic assisted laparoscopic hysterectomy, unilateral salpingo-oophorectomy (per patient request), omentectomy and sentinel lymph node biopsy. The peritoneal cavity was inspected with no suspicious findings. The final surgical specimen did not contain any remnants of viable tumor cells, and there were no metastasis to the sentinel lymph nodes or omentum. Based on these findings, adjuvant therapy was not administered. The patient has since been followed-up every 3 months by clinical exam, including pelvic exam and transvaginal ultrasound. She remains without evidence of disease 12 months after her final surgery.

CLOSING SUMMARY

Diagnosis of endometrial cancer during pregnancy is extremely uncommon and most cases are diagnosed after delivery. Hence, staging and treatment of endometrial cancer during pregnancy

Case studies

are rarely described. Since the uterus itself is involved, definitive treatment during pregnancy by surgery or radiotherapy with preservation of the pregnancy is impossible. In such cases, in the absence of poor prognostic markers and with adequate patient informed consent, an observational approach can be followed. In this scenario, despite the initial high-grade lesion, the patient refused standard treatment in order to save the pregnancy. Post-partum pathology demonstrated a low-grade lesion that may have been responsive to the hormonal gestational changes. Based on the surgical staging, this strategy does not seem to have jeopardized her prognosis. This case also demonstrates that pathological examination in pregnant patients can be challenging.^{10 11}

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REFERENCES

1. Ilancheran A, Low J, Ng JS. Gynaecological cancer in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2012;26:371–7.
2. Amant F, Halaska MJ, Fumagalli M, et al. Gynecologic cancers in pregnancy: guidelines of a second international consensus meeting. *Int J Gynecol Cancer* 2014;24:394–403.
3. Langer JE, Oliver ER, Lev-Toaff AS, et al. Imaging of the female pelvis through the life cycle. *Radiographics* 2012;32:1575–97.
4. Ray JG, Vermeulen MJ, Bharatha A, et al. Association between MRI exposure during pregnancy and fetal and childhood outcomes. *JAMA* 2016;316:952–61.
5. Mervak BM, Altun E, McGinty KA, et al. MRI in pregnancy: indications and practical considerations. *J Magn Reson Imaging* 2019;49:621–31.
6. Yang S, Thiel KW, Leslie KK. Progesterone: the ultimate endometrial tumor suppressor. *Trends Endocrinol Metab* 2011;22:145–52.
7. de Haan J, Verheecke M, Van Calsteren K, et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *Lancet Oncol* 2018;19:337–46.
8. Al-Muzrakchi A, Jawad N, Crofton M, et al. Imaging in the post-partum period: clinical challenges, normal findings, and common imaging pitfalls. *Abdominal Radiology* 2017;42:1543–55.
9. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. *Ann Oncol* 2016;27:16–41.
10. Hogg R, Ungár L, Hazslinszky P. Radical hysterectomy for cervical carcinoma in pregnant women – a case of decidua mimicking metastatic carcinoma in pelvic lymph nodes. *Eur J Gynecol Oncol* 2005;26:499–500.
11. Covell LM, Disciulio AJ, Knapp RC. Decidual change in pelvic lymph nodes in the presence of cervical squamous cell carcinoma during pregnancy. *Am J Obstet Gynecol* 1977;127:674–6.