CASE REPORT

Fertility-sparing surgery, with subsequent pregnancy, in persistent gestational trophoblastic neoplasia

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Gestational trophoblastic neoplasia (GTN) is primarily a disease of women of reproductive age. In most instances, it is cured by surgical evacuation of the uterus, with persistent disease being very sensitive to chemotherapy. Hysterectomy, recommended for persistent chemotherapy-resistant uterine disease, may be unacceptable to the woman who wishes to maintain her fertility. Uterine resection of localized disease, with uterine reconstruction, may be a viable alternative. A case is presented of a woman with persistent uterine GTN, treated with localized uterine resection and reconstruction, followed by two successful pregnancies and deliveries. The literature is reviewed and potential pregnancy complications of this management, particularly uterine rupture, are discussed.

Key words: fertility-sparing surgery/persistent gestational trophoblastic neoplasia/pregnancy/uterine resection/uterine rupture

Introduction

Gestational trophoblastic neoplasia (GTN) is primarily a disease of women of reproductive age. In most instances, it is cured by surgical evacuation of the uterus. Persistent disease is responsive to chemotherapy in >90% of cases (Jones and Lewis, 1988). Hysterectomy is generally recommended for the woman who has completed her childbearing, or for persistent chemotherapy-resistant uterine disease. This treatment, however, may be unacceptable to the woman who wishes to maintain her fertility. With quality of life issues becoming more important in medicine, therapies which preserve fertility, without compromising adequate treatment of the disease, should receive serious consideration. Uterine resection of localized disease, with uterine reconstruction, may be a viable alternative. Subsequent pregnancies in these patients need to be closely monitored, given the potential risk of rupture of the scarred uterus.

Case history

A 30 year old, orthodox Jewish woman, G5P3SA1M1 (gravida 5, para 3, spontaneous abortion 1, molar pregnancy 1), presented in 1997 with recurrent choriocarcinoma. In 1991 and 1992, she had two normal pregnancies and spontaneous vaginal deliveries. In 1993, she presented with a molar pregnancy, which was treated with dilatation and curettage. Pathology was consistent with complete hydatidiform mole. Surgery was followed by six cycles of methotrexate and actinomycin D due to persistent GTN, diagnosed by plateauing of her serum human chorionic gonadotrophin (HCG) concentrations. She conceived again, and had a normal pregnancy and delivery in 1995, followed by a spontaneous abortion in 1996. A curettage specimen performed at this time revealed only a placental implantation site with residual trophoblastic cells. She developed recurrent disease in 1997, diagnosed by a rising serum HCG concentration, and was treated with 10 cycles of etoposide, methotrexate and actinomycin D. While taking the oral contraceptive, serum HCG concentrations began to rise once again. Transvaginal ultrasonography and magnetic resonance imaging revealed a persistent chemoresistant focus of disease localized in her anterior uterine wall (Figure 1). She was advised to consider hysterectomy; however, since she wished to preserve her fertility, she chose to undergo uterine resection of the tumour, with uterine preservation. Preoperatively, she was counselled regarding the possible risk of bleeding necessitating hysterectomy, the potential for adhesion formation, infection, the risk of possible uterine rupture during a subsequent pregnancy, and the need for Caesarean section for delivery if a pregnancy subsequently occurred. She also donated two units of autologous blood for potential transfusion, and received peri-operative antibiotic prophylaxis.

At the time of surgery, a hysteroscopy was performed initially, and an exophytic lesion was clearly seen on the anterior aspect of the endometrial cavity. At laparotomy, however, the lesion could not be seen or palpated on the anterior uterine wall. Intra-operative ultrasound with a sterile
Figure 1. Persistent trophoblastic neoplasia – invasive mole. (A) Sagittal transvaginal image shows an echogenic endometrial mass that extends the canal at about its mid point. The margination is distinct posteriorly. The mass is not clearly demarcated from the myometrium anteriorly. (B) A colour Doppler image at the same location as image A shows the true extent of the abnormality is more extensive than the greyscale appearance would suggest. There is abnormal vascularity in the endometrial mass extending full thickness through a wedge of anterior myometrium.

Figure 2. Persistent trophoblastic neoplasia – invasive mole. An intra-operative transverse ultrasound image of the uterus shows the endometrial canal has been filled with saline and appears black. The intraluminal component of the tumour is of mixed echogenicity and protrudes into the canal. The myometrial component, known from the preoperative Doppler study is vague and hard to see.

Figure 3. Pathology from uterine resection. Photomicrograph from uterine resection specimen (original magnification approximately ×750) showing choriocarcinoma with the typical biphasic appearance of syncytiotrophoblast (top and centre) invading myometrium (lower).

probe, and with saline instilled into the uterine cavity, clearly delineated the lesion (Figure 2). The margins were marked out using electrocautery on the serosal surface of the uterus, using ultrasound to delineate the margins of the lesion. To minimize blood loss, a tourniquet was tied around the lower uterine segment to occlude the uterine arteries, and rubber-shod vascular clamps were placed across each infundibulopelvic ligament. A full thickness, ellipse-shaped wedge measuring
2.4×2.0×3.8 cm was then removed from the right anterior fundal region of the uterus. Intra-operative pathology consultation on the specimen identified no disease at the resection margins. The uterus was reconstructed in three layers. The repaired incision was haemostatic following removal of the tourniquet and clamps. Estimated blood loss was 350 ml. Recovery from surgery was uneventful, and serum HCG concentrations rapidly fell to normal. Final pathology revealed choriocarcinoma involving the endometrium and myometrium (Figure 3).

Postoperatively, the patient was very anxious to become pregnant, but was advised to remain on the oral contraceptive for at least 6 months. Following this, menses resumed normally, and the patient attempted to conceive, unsuccessfully, for six cycles. A hysterosalpingogram was performed which revealed free spill from the right tube, a blocked left tube, and a uterine cavity which showed some mild irregularity, but normal capacity. The patient was booked for laparoscopy and possible lysis of peritubal adhesions, but conceived spontaneously on her next cycle (14 months postoperatively). Transvaginal ultrasound at 8 weeks confirmed a healthy intrauterine pregnancy. A routine second trimester scan showed a normal fetus, a posterior placenta, and an apparently normal anterior uterine wall.

The patient was followed with biweekly ultrasound starting in the third trimester to assess thickness of the anterior uterine wall. At 26 weeks, the anterior wall had thinned to 4 mm. At 28 weeks, a repeat ultrasound showed an 8×8 cm² patch in the anterior right upper quadrant of the uterus that was now 3.3 mm thick.

Because of the concern regarding her risk for uterine rupture, she was admitted to hospital for observation. A patient care conference involving perinatology, gynaecology, radiology, gynaecological oncology, anaesthesia, paediatrics, nursing, the patient and her husband was held to discuss her management, and to review the literature on uterine rupture in an attempt to try and predict her risk for uterine rupture. It was determined that she would remain in hospital until delivery, and receive weekly celestone (betamethasone) injections for fetal lung maturation. Twice weekly ultrasounds would be performed to monitor the anterior uterine wall. At 32 weeks, or earlier if there was evidence of further uterine thinning, an elective lower segment transverse Caesarean section would be performed. The uterus would be preserved, if possible, since the patient and her husband wished to continue to preserve her fertility.

The patient was felt to be at high risk of uterine rupture; however, this was impossible to quantify based on the available literature and experience of the physicians involved. All staff was informed of this patient’s situation, and an emergency plan of action was laid out in the event of uterine rupture. I.v. access was maintained using a peripheral i.v. catheter, and she was cross-matched for two units of blood. The patient was counselled regarding signs and symptoms of uterine rupture, and the possible need for emergent delivery, blood transfusion, and hysterectomy to control uterine bleeding.

At 31 weeks gestation, ultrasound revealed that the large anterior defect now measured 2.2 mm in thickness. An elective Caesarean section was performed through the lower uterine segment, and a healthy male infant delivered, weighing 1700 g. Estimated blood loss was 400 ml. At surgery, the large defect was confirmed, although the anterior wall remained intact. The uterus appeared somewhat rotated, with the right tube and round ligament appearing to come from the anterior wall of the uterus, presumably due to the previous excision of anterior myometrium. Because of concern regarding vascularity of the pregnant uterus, no attempt was made to oversew the defect, to potentially thicken it, in anticipation of another pregnancy. Postpartum course was uneventful, and mother and infant are doing well. Pathological examination of the placenta did not reveal any evidence of disease.

The patient conceived again 5 months postpartum. Her pregnancy was managed in a similar fashion, and a healthy baby girl was delivered by elective Caesarean section at 33 weeks gestation.

Discussion

Gestational trophoblastic disease consists of four different neoplastic diseases, including hydatidiform mole, invasive mole, choriocarcinoma and placental site trophoblastic tumour. The incidence of GTN has considerable geographic variation, ranging from 1/100 in the Orient to 1/1500 in North America and Europe. Hydatidiform mole is a pregnancy characterized by hydropic swelling of placental villi, trophoblastic hyperplasia and, usually, absence of an intact fetus. They can be partial or complete, depending on their karyotype: 69 XXY or 46 XX or XY respectively. Trophoblastic sequelae such as invasive mole or choriocarcinoma are more common in complete moles (15–20%) versus partial moles (4–11%). After one mole, the risk of recurrence is approximately 1%, or ten times above baseline risk (Berkowitz and Goldstein, 1996).

Persistent gestational trophoblastic disease is often non-specific on ultrasound imaging, although may show as a uterine endometrial or myometrial mass. The appearance reflects tissue invasion, necrosis and haemorrhage. Doppler, however, is much more helpful, showing the hypervascularity of invasive trophoblast. Colour Doppler abnormalities are invariably more extensive than the greyscale abnormality. High velocity low resistance flow results from the arteriovenous shunting. Magnetic resonance imaging provides non-invasive confirmation of the imaging findings (Rumack et al., 1998). In this case, greyscale and Doppler ultrasound were used to map out the distribution of the tumour prior to surgery with intra-operative guidance for confirmation of the tumour margins.

Surgical evacuation of the uterus by dilatation and curettage is curative in more than 80% of women with hydatidiform mole. Persistent, and even metastatic disease, is usually exquisitely sensitive to chemotherapy, with an overall cure rate exceeding 90% (Jones and Lewis, 1988). A very small subset of patients, however, may continue to have a small focus of residual, chemotherapy-resistant disease. Successful surgical resection of extraterine chemo-resistant disease has been previously described, including thoracotomy, nephrectomy, craniotomy, and partial hepatectomy (Lehman et al., 1994). When disease is confined to the uterus, hysterectomy is generally recommended (Jones and Lewis, 1988). This may not be an acceptable
alternative for a woman who desires more children. Physicians should therefore be aware of possible treatment alternatives to maintain fertility.

There have been a few reports of localized uterine resection of a residual disease focus, followed by uterine reconstruction. These cases were similar to our case in that all were young women in whom fertility preservation was desired. The primary diagnoses included hydatidiform mole, invasive mole, and placental site trophoblastic tumour. None of the patients developed choriocarcinoma or recurrent disease postoperatively. Successful pregnancy subsequently occurred in 12/18 (66%) patients (Wilson et al., 1965; Takeuchi, 1982; Leiserowitz and Webb, 1996). Before considering this therapy, all extraterine disease must be excluded, and traditional chemotherapy should have been tried. Patients should be counselled preoperatively about the risk of bleeding, infection, and the possibility of hysterectomy due to uncontrollable bleeding, inability adequately to resect the tumour, or the intraoperative finding of multifocal uterine disease.

Because these tumours are notoriously vascular, techniques to minimize bleeding should be considered. In this case, a sterile tourniquet was tied around the lower uterine segment to occlude the ascending branches of the uterine arteries. Rubber-shod vascular clamps were also placed across the infundibulopelvic ligaments bilaterally. An additional technique to consider is intramyometrial injection of a dilute solution of vasopressin (20 units in 40 ml normal saline), as is often used in the surgical management of ectopic pregnancy, or myomectomy. It is advisable that the patient receives perioperative antibiotics, and has cross-matched blood available.

In the situation where the remaining uterus is insufficient or too damaged to maintain a pregnancy, or where hysterectomy is ultimately required due to complications of hysterotomy (i.e. bleeding or infection), or due to the finding of multifocal disease, the use of a gestational carrier of an embryo, derived from IVF of the couple’s oocyte and spermatozoa, is a final option that may be considered.

Subsequent pregnancy in patients who have undergone uterine resection and reconstruction is not without risk. Achievement of pregnancy may be compromised by the presence of intrauterine and/or extraterine adhesions, resulting in infertility or recurrent pregnancy loss. Uterine rupture is a concern in the third trimester of a successful pregnancy. The risk of this is extremely difficult to predict. Most of the uterine rupture literature refers to the risk of rupture following lower transverse Caesarean section (Nielsen et al., 1989; Rozenberg et al., 1996), with occasional reference to the risk in cases of previous classical upper segment Caesarean section, myomectomy, cornual resection or uterine injury, rupture, myoma cœterization, or perforation (Dubuisson et al., 1995; Friedmann et al., 1996; Pelosi and Pelosi, 1997; Arcangeli and Pasquarette, 1997; Vilos et al., 1998). These cases differ from the situation of uterine resection and reconstruction in one very important respect: while they all involve disruption of myometrial muscle fibres, only the latter situation involves the actual removal of myometrium. Intuitively, one feels that this must confer a greater risk of rupture than the other scenarios, but it is extremely difficult to quantify.

Some authors have recommended following pregnant patients with uterine scars with ultrasound in the third trimester to monitor uterine thickness (Michaels et al., 1988; Chapman et al., 1994; Avrech et al., 1994; Rozenberg et al., 1996; Tanik et al., 1996). Only one study (Rozenberg et al., 1996) has assessed the predictive value of uterine thickness with respect to uterine rupture, in patients with previous lower transverse Caesarean section. Their results showed an inverse correlation between lower uterine segment thickness and risk of rupture, with the risks as follows: >4.5 mm: 0%, 3.6–4.5 mm: 2%, 2.6–3.5 mm: 10%, and 1.6–2.5 mm: 16%. The authors chose a threshold value of 3.5 mm as the point at which risk of rupture rises dramatically; a value that had good negative predictive value (99.3%), but poor positive predictive value (11.8%) (Rozenberg et al., 1996). It is difficult to know to what extent the results from this study can be extrapolated to the patient with a scar in the body of the uterus.

Serial ultrasound assessment of the uterine defect in the third trimester is probably worthwhile, even if the exact thickness at which action (i.e. hospitalization or delivery) should be taken is uncertain. One case report cites a patient with a previous history of lower segment transverse Caesarean section with scar rupture in a subsequent pregnancy, who was hospitalized at 25 weeks gestation for observation, at which time the lower segment thickness measured 3 mm. Serial ultrasound assessments were performed, and elective delivery by laparotomy and Caesarean section undertaken at 31 weeks, after a rapid increase in the area of the thinned segment was observed. At delivery, a very large uterine deficiency was noted, and successfully repaired. Postpartum uterine ultrasound, 2 months later, showed a 7 mm thickness in the region of the scar, compared to 15 mm elsewhere (Chapman et al., 1994).

Many questions remain. What is the ‘critical thickness’ below which the risk of rupture starts to increase? Is this critical thickness the same for the lower and upper, more contractile, segments of the uterus? Is the rise in risk of uterine rupture linear or exponential after the critical thickness is reached? Is the risk of rupture in a subsequent pregnancy even greater? At what thickness should one intervene and deliver the infant? Given the rarity of this clinical situation, and the inconceivability of performing adequate clinical studies, these questions will likely remain unanswered. Each case should therefore be considered individually, with input and advice obtained from all concerned specialities, including obstetrics, anaesthesia, paediatrics, radiology, oncology, and nursing. As we did with our patient, observation in hospital once the uterine scar thinned beyond a comfort level, frequent ultrasound surveillance of the uterus and fetus, establishment of i.v. access, implementation of an ‘action plan’ in the event of uterine rupture, and controlled delivery by lower segment transverse Caesarean section at a preterm, but viable, gestation, may be the safest way to ensure a successful outcome for both mother and baby.

References


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