

## Double Trouble.

### A case of Heterotopic Pregnancy

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#### Abstract

A 29 year old in her second ongoing pregnancy was admitted via her General Practitioner at five weeks and five days gestation with abdominal pain and a positive pregnancy test. Ultrasound scan confirmed a viable intrauterine pregnancy with no adnexal pathology. The patient was reassured and discharged home with an antenatal clinic appointment. She was readmitted with the same complaint and no cause was found. At a third admission she was seen with worsening abdominal pain. A repeat ultrasound scan showed an adnexal mass and raised the suspicion of an heterotopic pregnancy. A laparoscopy confirmed a right tubal pregnancy and a salpingectomy was performed. The intrauterine pregnancy progressed uneventfully to term and delivered normally. The patient was advised regarding postnatal contraception and future pregnancy.

#### Case History

A 29 year old in her second planned pregnancy, at more than six weeks gestation, was admitted to the gynaecology ward with a 9 day history of worsening lower abdominal pain, mainly in the right iliac fossa. She described the pain as severe and constant in nature, but without radiation. It was associated with nausea but no vomiting. There was no history of any vaginal bleeding or discharge or associated urinary or other gastrointestinal symptoms. The pain was worsened by movement but there were no other aggravating or relieving factors. She had no history of pelvic inflammatory disease, intrauterine contraceptive device use, abdominal surgery, or induction of ovulation.

She had had two previous admissions with the

same complaint. She was first referred by her GP with a 40 day history of amenorrhoea and 5 days of lower abdominal pain. A urine pregnancy test was positive. Transvaginal ultrasound scan (TVS), showed a viable intrauterine pregnancy consistent with a gestation of 5 weeks 5 days. No adnexal pathology was detected. There was no evidence of free fluid in the pouch of Douglas. Her second admission was two days later when her abdominal pain had become worse. Further examination showed no change from the previous findings. A surgical review was requested and appendicitis was excluded. She was reassured again that the abdominal pain could be muscular in origin as all the investigations were unremarkable. She was discharged home with simple analgesia and open access to the ward with advice to return if her pain did not resolve or worsened. She had no relevant past medical, surgical or gynaecological history.

Previous obstetric history was of a normal vaginal delivery 3 years earlier with no antenatal, intrapartum or postnatal complication. She had been in a stable marital relationship for 4 years and had no other partners. There was no history of any sexual transmitted infections in either partner. She used to smoke 15-20 cigarettes a day and drink alcohol occasionally, but had stopped both completely when she found out that she was pregnant. On examination, she was distressed, but haemodynamically stable. The abdomen was soft but markedly tender in the right iliac fossa with some voluntary guarding but no rebound tenderness. There was no palpable abnormality and bowel sounds were normal. Pelvic examination was declined. She stated that she had had a pelvic examination on her last visit, 2 days ago and she

found it uncomfortable. Her previous vaginal examination had revealed a bulky, anteverted mobile uterus. There was cervical excitation and she was tender in the right adnexa. Swabs taken at that time were negative for infection. A repeat urgent ultrasound scan was done, which again confirmed the previous findings of a viable intrauterine pregnancy, but this time also demonstrated a small echogenic mass in the right adnexa 29mm in diameter, with some free fluid in the pouch of Douglas. These ultrasound findings raised the likelihood of a heterotopic pregnancy. Her full blood count showed a haemoglobin of 11.8g/dl and the white cell count was 8400 per mm. Urinalysis was unremarkable.

In view of her recurrent symptoms of worsening abdominal pain and ultrasound scan findings, a diagnosis of heterotopic pregnancy was possible. The differential diagnosis included ovarian cyst, ruptured corpus luteum cyst, and acute appendicitis. The size of the cyst was relatively small for torsion although not impossible. On the basis of the clinical picture and a normal white blood cell count, acute appendicitis was considered unlikely. She was counseled regarding the possible diagnoses and treatment options, but a definitive diagnosis of ectopic pregnancy could not be made without a laparoscopy. The risks of laparoscopy in this situation were explained to the patient who then agreed to have the procedure. At laparoscopy an ectopic pregnancy was confirmed in the ampullary region of the right fallopian tube. The left fallopian tube and both ovaries were normal, but a small amount of blood was noted in the pouch of Douglas. No other obvious pelvic or abdominal pathology was noted nor were perihepatic adhesions present. A right sided salpingectomy was duly performed.

She made an uneventful recovery from the procedure. Another TVUS was performed on day two post operatively which confirmed a viable intrauterine pregnancy. The histology

confirmed the diagnosis of an ectopic pregnancy due to the presence of chorionic villi and trophoblastic tissue.

## Discussion

A heterotopic pregnancy is defined as the presence of an intrauterine pregnancy coexisting with an ectopic pregnancy<sup>1</sup>. It is potentially fatal but is a rare event in natural conception cycles, where its incidence is approximately one in 7000. It is however an increasingly common complication of assisted reproduction, where the international incidence is 1%<sup>1,2</sup>. This is due to the transfer of multiple embryos in a given cycle and the increased risk of tubal damage in the sub fertile population. A recent rise in the incidence of this type of pregnancy is related to an increase in chronic pelvic inflammatory disease<sup>2</sup>.

The established risk factors for heterotopic pregnancy are the same as those for ectopic pregnancy which include a history of salpingitis, previous use of IUCD, previous tubal surgery, assisted reproduction and smoking. A seven fold increase in the rate of ectopic pregnancy has been cited for women with a history of chronic pelvic inflammatory disease<sup>1,2</sup>. Our patient conceived naturally and no adhesions or evidence of previous pelvic infection were seen intra-operatively. The only risk factor for this patient - although this is not a direct causative factor - was smoking, which she discontinued during pregnancy.

The clinical picture is very variable but the diagnosis of ectopic pregnancy must always be considered if there is a period of amenorrhea and abdominal pain in the reproductive age<sup>3</sup>. Our patient had presented twice with increasing abdominal pain but was reassured as an early TVUS showed a viable intrauterine pregnancy and no adnexal pathology. The possibility of heterotopic pregnancy was not considered but there are diagnostic difficulties when symptoms of ectopic pregnancy occur in the presence of

intrauterine pregnancy<sup>2</sup>.

Diagnosing a heterotopic pregnancy is not easy, and requires a high level of suspicion otherwise delayed diagnosis will continue to occur. A comparative study in 2007 found that during the period 1971-1993, definitive diagnosis of heterotopic pregnancy was made by laparoscopy or laprotomy in 59% of cases compared to 74% from 1994-2004. This shows that despite increased medical knowledge and use of improved reproductive technologies heterotopic pregnancy continues to provide a diagnostic and therapeutic challenge to modern clinicians. A high index of suspicion, repeated ultrasounds and early intervention are mandatory to salvage the viable intrauterine pregnancy and avoid maternal mortality<sup>13</sup>. In this case repeated admissions due to abdominal pain should have raised suspicion but false reassurance was given in the early scan as a viable intrauterine pregnancy with no adenexal pathology was found. The clinical findings of tenderness on abdominal examination, adenexal tenderness and cervical excitation on pelvic examination were ignored. This case report demonstrates the management of patients with heterotopic pregnancy and raises some risk management issues. A diagnostic error would have occurred, if she had not had the second scan and if suspicion had not been raised by the TVS. Delayed diagnosis could have led to complications including rupture of the ectopic pregnancy and life threatening haemorrhage. Such complications necessitate a more aggressive therapeutic approach in the form of laparotomy compared with laparoscopy, and increase the likely requirement for blood transfusion<sup>7</sup>.

The development of Transvaginal ultrasound scan, together with the availability of a highly specific radioimmunoassay technique for the detection of beta-hCG, has helped in the diagnosis of ectopic pregnancy<sup>4</sup>. A retrospective review of cases from the era

of transabdominal scan (1982-87) and from the era of Transvaginal scan (1987-95) demonstrated that the introduction of TVS has had an important effect on the evaluation of patients with ectopic pregnancy, by nearly eliminating the need for D&C and diagnostic laparoscopies permitting clinicians to take a more conservative approach to managing ectopic pregnancy<sup>11</sup>. Clinical suspicions, supported by the absence of an intrauterine gestational sac on ultrasound and a positive pregnancy test suggest possible ectopic pregnancy. In clinically stable conditions, with no evidence of intra-abdominal bleeding, serial beta-hCG estimation should be done<sup>1,3</sup>. The levels of hCG rise more slowly when pregnancy is extra uterine. The presumptive diagnosis of ectopic pregnancy is made by correlation of serum beta-hCG levels and ultrasound scan findings. If the beta- hCG is above the 'discriminatory zone', reported to be around 1500 mIU/ml, a gestational sac should be visible on transvaginal ultrasound<sup>1,3</sup>. If the intrauterine sac is not visible by the time the beta-hCG is at or above this threshold, the pregnancy has a high likelihood of being ectopic<sup>4,5</sup>. A prospective observational study conducted by Condous and Okaro found that 90.9% of ectopic pregnancies can be accurately diagnosed using TVS if based on the positive visualization of an adenexal mass<sup>12</sup>. Brown identified sensitivity, specificity and negative and positive predictive value of four sonographic criteria for ectopic pregnancy. Criteria were (a) living extrauterine pregnancy, (b) extrauterine gestational sac, (c) empty tubal ring and (d) adenexal mass. The data demonstrated that a, b and c have high specificities (99.5-100%) and high positive predictive values (97.8-100%) but low sensitivities (20.1-64.6%). Adenexal mass however, is seen in 80% of ectopic pregnancies, has specificity of 98.8%, sensitivity of 84.4% and negative predictive value of 94.8%<sup>15</sup>.

In this case, the first TVS was diagnostic of

intrauterine pregnancy and no other masses were visible. However repeat ultrasound showed an echogenic mass in the right adnexa, which raised the suspicion of heterotopic pregnancy. The other possibility could be that the adnexal mass was missed in the earlier scan. An early repeat scan during her second admission and estimation of beta-hCG may not have led to an earlier diagnosis. It was fortunate that the diagnosis was made before the fallopian tube ruptured. Women with acute or sub-acute onset of lower abdominal pain, sonographic diagnosis of intrauterine pregnancy and a pelvic mass that is either palpable or detected on ultrasound, should heighten the clinician's suspicion of heterotopic pregnancy, prompting early laparoscopy for confirmation of the diagnosis and initiation of treatment.

All women of child-bearing age are at risk of having an ectopic gestation. For any women presenting with a pain in the lower abdomen, three important problems to exclude are ectopic pregnancy, ovarian cyst accidents and appendicitis<sup>1</sup>. In this patient, there was no history of any of the above-mentioned risk factors for heterotopic pregnancy, so diagnosis was initially missed. Early evaluation should be performed for abdominal pain during pregnancy<sup>1,4</sup>. Ectopic pregnancy continues to be the leading cause of first trimester maternal death. From 2003-2005, there were 10 deaths from ectopic pregnancy in the UK<sup>5</sup>. Ectopic pregnancies are associated with a high morbidity, causing tubal damage, sub-fertility and chronic pelvic pain<sup>1</sup>.

Most ectopic pregnancies can be managed quite adequately, either by a medical or a surgical approach. The role of medical management, with the use of methotrexate or local injection of potassium chloride (KCl) into the gestational sac either laparoscopically or using ultrasound guidance, is limited in heterotopic pregnancy because of concurrent intrauterine pregnancy<sup>6</sup>. A literature search found that 55% of tubal

ectopic pregnancies treated by KCl injections required subsequent salpingectomy, which raises concerns about the advisability of this treatment<sup>14</sup>. The surgical approach is either via laparoscopy or laparotomy. Laparoscopic treatment is preferred for an ectopic pregnancy in a stable patient. It is associated with less haemorrhage and analgesic requirement, shorter hospital stay and quicker postoperative recovery time<sup>6</sup>. Non-rupture of a tubal pregnancy has a positive association with future fertility. Early diagnosis and conservative surgical management are therefore important<sup>8,10</sup>. Surgical treatment is either salpingectomy or salpingostomy and both have comparable intrauterine pregnancy rates. Salpingectomy is the preferred procedure when the contralateral tube is healthy. Salpingostomy is considered to be a reasonable alternative if there is only one fallopian tube. Serial serum beta-hCG levels are measured to exclude the likelihood of persistent trophoblastic tissue after laparoscopic salpingostomy<sup>6</sup>. Salpingectomy, rather than salpingostomy, was performed in this patient because of her beta-hCG levels. In addition, the contralateral tube was apparently healthy. In haemodynamically unstable patients, a laparotomy should be performed.

Advice regarding future contraception is important. There is no absolute contraindication for any form of contraception; however a history of a previous ectopic pregnancy should influence the choice of method. There is a very small increased risk of an ectopic pregnancy in progestogen only pills (POP) users. Since a woman with a previous history of ectopic pregnancy is already at increased risk of another ectopic, the POP should normally be avoided. Injectable progestogens however inhibit ovulation and so efficacy approaches 100%. This method is therefore highly suitable for women with a previous history of ectopic pregnancy. Since the route does not depend on absorption from the gut, broad-spectrum

antibiotics have no effect on this preparation. Injectable progestogen methods are not suitable for short-term contraception due to the delay in the return of fertility. Etonogestrel 68mg (*Implanon<sup>TM</sup>*, *Organon*), the hormonal implant, inhibits complete ovulation. Efficacy is high and does not require daily compliance and it is not contraindicated in woman with previous ectopic pregnancy. The risk of ectopic pregnancy for copper intra-uterine contraceptive devices(IUCD) users is 0,03% compared to 0.02% for Lenogestril-releasing IUCD (*Mirena<sup>TM</sup>*, *Bayers HealthCare*) users, which is equivalent to 1:5 to 1:10 of all pregnancies with intrauterine device in situ. A previous ectopic pregnancy is not a contraindication to the use of IUCD. There is no evidence that IUCDs are a more effective alternative for women with a previous ectopic pregnancy<sup>9</sup>.

Women with a history of an ectopic pregnancy should have early access to ultrasound to verify a viable intrauterine pregnancy in their subsequent pregnancies as they are at an increased risk of a recurrent ectopic pregnancy<sup>5,10</sup>. This advice was given to our patient.

## Conclusion

An ectopic pregnancy is a potential fatal condition. Despite sophisticated diagnostic and therapeutic techniques, it remains the second most common cause of maternal mortality. Impairment or loss of fertility may also be an end result. Early diagnosis is important to prevent serious morbidity and to allow use of more conservative treatment modalities that may help preserve fertility. TVS is a safe, non-invasive and a powerful diagnostic tool in the investigation of first trimester problems. The increased accuracy of TVS has led to improved accuracy. The use of TVS in combination

with serial serum beta-hCG measurements has facilitated rapid diagnosis and management of ectopic pregnancies<sup>4</sup>.

Ectopic pregnancy should be included in the differential diagnosis of women who present with abdominal pain and/or vaginal bleeding by all health care professionals responsible for the care of women in their reproductive years.

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