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The management of early pregnancy complications

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Early pregnancy complications include miscarriage, ectopic pregnancies, pregnancies of unknown location, adnexal masses and hydatidiform mole. The management of women with these complications has changed with the introduction of dedicated Early Pregnancy Units, with a shift away from a surgical approach to one based on an expectant or 'watch and wait' policy.

This chapter describes the role of transvaginal sonography (TVS) in the management of these women and critically evaluates the different treatment modalities available for the management of these complications. The management of miscarriage has largely changed from a surgical to an expectant or medical approach. The treatment of ectopic pregnancy (EP) is also being managed in a similar way as the condition is increasingly detected earlier. We will argue that EP should not be diagnosed on the basis of the absence of an intrauterine pregnancy but rather by the positive visualization of an adnexal mass using TVS. If a pregnancy cannot be seen either inside or outside the uterus this should be described as a pregnancy of unknown location and managed expectantly until the outcome is confirmed.

Key words: miscarriage; ectopic pregnancy; pregnancy of unknown location; adnexal mass; hydatidiform mole; transvaginal sonography; human chorionic gonadotrophin; progesterone.

Since the introduction of Early Pregnancy Units (EPUs) the management of early pregnancy complications has rapidly evolved, facilitated by the use of transvaginal sonography (TVS) and rapid immunoassay of serum human chorionic gonadotrophin (hCG) and progesterone. Cost benefits of EPUs are well established[1], and admission can be avoided in about 40% of patients, with a further 20% requiring a shorter stay.

There has been a shift away from the more traditional surgical approach to one based on an expectant or 'watch and wait' policy.[2] Conservative management of women with first-trimester complications results in lower rates of uterine instrumentation with its sequelae and also fewer unnecessary laparoscopies. Early pregnancy complications include miscarriage, ectopic pregnancies, pregnancies of unknown location (PUL), adnexal masses and hydatidiform mole. In this chapter, we critically assess management of these conditions.

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Women with suspected complications of early pregnancy should ideally be assessed and investigated in a dedicated EPU run by specialist nurses and doctors who are competent in ultrasonography. The location, viability and gestation of the pregnancy should be established. This allows informed and individualized management decisions to be made with the patient. The effectiveness of an EPU depends not only on appropriate ultrasound training for its staff but also on knowledge of the behaviour of serum hCG and progesterone levels.

Understanding normal ultrasonographic milestones in early pregnancy is important. The gestational sac is first seen after 4 completed weeks, the yolk sac appears after 5 completed weeks, the fetal pole with a detectable heartbeat is visualized after 6 completed weeks and the fetal pole with a separate amniotic sac and coelomic cavity with yolk sac becomes visible after 7 completed weeks.[3]

Ultrasound assessment of various forms of miscarriage is complicated by the lack of consensus on the most appropriate diagnostic criteria. An example of this is the wide variation in the published literature on the optimal cut-off levels for endometrial thickness to define an incomplete miscarriage. Cut-offs between 8 and 15 mm have been used to differentiate between incomplete and complete miscarriage.[4,5] Yet these cut-offs have never been prospectively validated. In our unit, if the endometrial thickness is <15 mm and there is no evidence of retained products of conception, this is classified as a complete miscarriage. In women thought to have a complete miscarriage at their initial ultrasound, care should be taken, as it is possible that such patients in fact have an ectopic pregnancy (EP). Therefore we manage patients with a presumed complete miscarriage in the same way as those with a pregnancy of unknown location (PUL). This will be discussed in detail later in the chapter.

If the diameter of the gestational sac is >20 mm without a yolk sac or embryo, this is classified as an anembryonic pregnancy or early embryonic demise.[6]

If the crown–rump length is ≥ 6 mm and there is absence of fetal cardiac activity, or if the crown–rump length is <6 mm with no change at the time of a repeat scan 7 days later, this is classified as a missed miscarriage or early fetal demise.[6] Care must be taken when making this diagnosis—approximately one-third of embryos with a crown—rump length of less than 5 mm have no demonstrable cardiac activity at the time of the initial scan.[7]

When the gestational age of the pregnancy is uncertain, early fetal demise can be difficult to diagnose. Hately et al[8] reviewed criteria for the establishment of embryonic death following several cases of misdiagnosed fetal demise. To minimize the chances of the evacuation of a live embryo in error, they recommended that there should be a written policy as to the procedure to be adopted when the death of an embryo is suspected. Their definition of a missed miscarriage was a crown–rump length >10 mm with no evidence of heart pulsations on two separate occasions at least 7 days apart.[8] Whenever there is uncertainty about the viability of a pregnancy, a repeat scan at an interval of 1 week is necessary. Discrepancies between the crown–rump length and gestational age, small or irregular gestational sacs or an abnormal embryonic heart rate pattern are predictors of a poor pregnancy outcome.[9] All EPUs should have their own evidence-based protocols, especially when it comes to defining miscarriage.

Sub-chorionic haematomas are common and are present in up to 18% of women who present with a threatened miscarriage.[10] They are insignificant sonographic findings and there is no association between the size of haematoma and the rate of premature delivery.[10] The confirmation of fetal cardiac activity in a threatened miscarriage confers an excellent prognosis.[11]

THE ROLE OF EXPECTANT MANAGEMENT IN MISCARRIAGE

Neilsen and Hahlin[5], in a randomized prospective trial, demonstrated expectant management alone to be as effective as surgical evacuation of the uterus in women with an incomplete miscarriage. The complication rate (as measured by the development of anaemia or the number of infections) was only 3% in the expectant group compared to 11% in the surgical group. The duration of bleeding in the expectant group was 1.3 days longer ($P < 0.02$); however, there was no difference in packed cell volume or the pain experienced in each group after 14 days. Poor success rates of between 25 and 43% have been reported for expectant management of miscarriage.[12,13] When the gestational sac is intact and the cervix closed, failure is most likely. Resolution may take several weeks in such women and as many as 20% will opt out and request surgical evacuation.[13] There is no difference in psychological morbidity between expectant and surgical management.[14]

Once the diagnosis of miscarriage has been made, 56–70% of women will choose expectant management.[6,15] The rate of spontaneous completion for a miscarriage depends on the type of miscarriage. For incomplete miscarriage, 91–96% resolve spontaneously.[6,15] Expectant management is less successful for other types of miscarriage. The rate of spontaneous completion of a missed miscarriage may be as high as 84%[16]; however, in a more recent study 76% of missed miscarriages and 66% of anembryonic pregnancies resolved without intervention.[6] Other authors have reported a success rate as low as 24.7% for expectant management of missed miscarriage.[12] Miscarriage in these two groups is often more painful and less likely to become complete in the same time span as in a patient presenting with an incomplete miscarriage. In our unit, women with a missed miscarriage or anembryonic pregnancy are told that they have about a 50% chance of resolving their miscarriage without intervention within 2 weeks. After this time their chances of doing so diminish, and in such circumstances we offer surgical evacuation of the uterus. Our anecdotal experience is that while expectant management is valid for women attending with symptoms to an EPU, the situation is different when the diagnosis is made as a chance finding at the time of a nuchal scan. Our view is that such cases are more likely to experience severe pain or heavy bleeding whether they receive expectant management or medical therapy, and consequently we offer surgery.

Optimal follow-up for women who choose expectant management of miscarriage is not standardized. After 2 weeks the odds of a miscarriage becoming complete are significantly reduced. It is therefore a reasonable policy to advise women to give themselves 2 weeks to complete their miscarriage, and that intervention after this time may be sensible. Neither the endometrial thickness nor the presence of a gestational sac within the cavity is clinically useful in determining the outcome of expectant management.[17] The proportion of women completing their miscarriage in relation to time and the number of days taken to complete a miscarriage is not related to initial ultrasound findings.[17] These data suggest that follow-up for women with incomplete miscarriage need not include ultrasonography. The complication rate is so low that a single follow-up visit after 2 weeks to assess the clinical situation may be appropriate. However, women should be able to contact the clinic at any time for advice or support with the emphasis for follow-up being orientated more towards counselling rather than ultrasound-based assessment of the uterus.

The high success rate of expectant management for incomplete miscarriage means that other interventions are unlikely to alter the outcome. This was confirmed by Neilsen et al[18] who demonstrated no benefit from the use of prostaglandins for the management of incomplete miscarriage. However, for missed miscarriage

and anembryonic pregnancies medical management strategies using both prostaglandins with or without anti-progesterones may have a role.

MEDICAL MANAGEMENT OF MISCARRIAGE

The use of prostaglandin analogues (misoprostol or gemeprost) and anti-progesterone priming (mifepristone) for the medical management of miscarriage is well described.[19–25] Quoted success rates vary widely in the literature from 13 to 96%. The outcome depends not only on the type of miscarriage treated but also on the criteria used for follow-up. The total dose of prostaglandin, route of administration and its duration of use alter the outcome. Higher success rates (70–96%) are observed when the initial diagnosis is an incomplete miscarriage.[19,21] However, this is not surprising given the outcome for such miscarriages from expectant management alone. Medical intervention in this group is unlikely to improve outcome.

The efficacy of medical intervention is not certain. In a randomized clinical trial, Hinshaw[19] demonstrated no statistically significant difference in success rates between surgical and medical management of miscarriage, although patient acceptability for each method was similar. It is of interest that the number of pelvic infections in the medical management group ($P < 0.001$) was reduced. However, anecdotally, the pain and vaginal bleeding associated with medical management of miscarriage may be a limiting factor influencing its acceptability.[26] A further consideration is that these medical approaches to the management of miscarriage may have economic benefits when compared to surgical evacuation.

In a recent study, Neilsen et al[18] compared medical management of miscarriage with a combination of a prostaglandin E1 analogue and anti-progesterone and expectant management alone. There was no improvement in the rate of complete miscarriages achieved in the medical management arm. This may be explained by patient selection as we know that medical management will not improve the outcome for incomplete miscarriages.

In a randomized trial, Wood and Brain[27] compared vaginal misoprostol to placebo in the management of missed miscarriage. This demonstrated that the rate of complete miscarriage was 80% in the misoprostol group and 16% in the placebo group ($P < 0.001$).[27] Clearly, this degree of resolution combined with high levels of patient satisfaction is very encouraging, but a randomized trial examining the impact of medical therapy on the expectant management of missed miscarriage and anembryonic pregnancy is urgently required.

Infective morbidity of any non-surgical approach, whether it is expectant or medical, has been a cause for concern.[28] However, the data suggest a reduction in clinical pelvic infection using this approach.[19,29] In relation to long-term complications, it is reassuring that Blohm et al[30] showed no difference in future fertility rates between those who choose expectant management and those who have undergone surgical evacuation for their miscarriage.

SURGICAL MANAGEMENT OF MISCARRIAGE

Despite a shift towards medical and expectant management of first-trimester miscarriage, 88% of women who miscarry in the United Kingdom still undergo surgical

evacuation. Surgical evacuation of retained products of conception can be performed using sharp curettage or vacuum aspiration. There will always be a role for surgical evacuation of the uterus, especially when a woman is haemodynamically compromised or has an infective miscarriage.

In a meta-analysis of surgical procedures adopted in the management of incomplete miscarriage, vacuum aspiration was associated with statistically significantly decreased blood loss, less pain and shorter duration of procedure than sharp curettage.[31] Serious complications such as uterine perforation and other morbidity were rare; unfortunately the sample sizes of the trials were not large enough to evaluate small or moderate differences.[31] Vacuum aspiration is safe, quick to perform, and less painful than sharp curettage, and should be recommended for use in the management of incomplete miscarriage.

ECTOPIC PREGNANCY

Over the last 25 years, as the morbidity and associated mortality of EP have substantially decreased, the incidence has progressively increased. The fourth leading cause of direct maternal deaths in the UK is EP, accounting for 80% of first-trimester deaths.[32] With the advent of EPUs, the number of stable ectopic pregnancies diagnosed has significantly increased and consequently treatment modalities have become less radical. The evolution of treatment has progressed from salpingectomy at the time of laparotomy to salpingostomy with conservation of the Fallopian tube performed by laparoscopy. More recently medical management in the form of systemic methotrexate and even expectant management have been adopted in selected cases.

Clinical history and examination may not be helpful in women who present with lower abdominal pain and vaginal bleeding. With the introduction of high-resolution transvaginal ultrasound and the use of sensitive immunoassays for hCG, early visualization of an ectopic gestational sac is possible. Although spontaneous heterotopic pregnancy (Figure 1) is rare (between 1:10 000 and 1:50 000), this should be considered in women with assisted conceptions as the incidence is as high as 1%.[33] In women who have undergone assisted conception, one should always thoroughly visualize the adnexa even when an intrauterine sac has been visualized.

The diagnosis of EP should not be based on an inability to visualize an intrauterine pregnancy (IUP), but rather on the positive visualization of an adnexal mass using TVS. If a pregnancy cannot be seen, then it is a PUL—10% of which are ectopic pregnancies. If an EP is present, one should visualize between 87 and 93% using TVS prior to surgery.[34,35] Misdiagnosis should be a rare event, and the standard of care in any EPU can be judged by its false-positive and -negative rates for the diagnosis of EP. However, this is becoming more difficult to determine as fewer women with a positive diagnosis undergo laparoscopy.

The appearances of ectopic pregnancies on TVS are highly variable. Classically there is a hyperechoic ring around the gestation sac in the adnexal region (Figure 2), described as the 'bagel sign'. More often they are seen as a small inhomogeneous mass next to the ovary.[36] Brown and Doubilet[37] pooled data from 10 published studies and concluded that the most appropriate TVS criterion on which to diagnose EP is any non-cystic adnexal mass. This leads to a positive predictive value of 96.3%, negative predictive value of 94.8%, specificity of 98.9% and sensitivity of 84.4%. This performed better than the visualization of an embryo with a heartbeat in the adnexa, an adnexal

Figure 1. Heterotopic pregnancy—spontaneous conception.

cystic mass, or an adnexal mass with an echogenic or 'tubal' ring. Experienced operators will not be surprised by this as the vast majority of ectopic pregnancies that are seen using TVS appear as an inhomogeneous small mass or 'blob' next to the ovary with no evidence of a sac or embryo (Figure 3).

The dimensions of the ectopic pregnancy should be described, as should the presence of an embryo with or without a heartbeat. The amount of bleeding that has occurred should be commented upon by looking for fluid or blood in the pouch of Douglas (Figure 4). The appearances of blood and clot, as opposed to serous fluid, are quite different and should not be confused. This information is of importance to the clinician as the management options for EP are rapidly changing, and depend very much on the ultrasound appearances, the level of serum hCG and the patient's symptoms.

The corpus luteum is a useful guide when looking for an EP, as it will be on the ipsilateral side in over 85% of cases.[38]

The so-called 'pseudosac' is controversial. This is a misnomer and probably represents a fluid collection or debris in the cavity. This sign is based largely on historical data and relates to the use of transabdominal ultrasonography. Using high-resolution vaginal probes, it is possible to distinguish an early gestational sac from intra-cavity fluid, thus making misinterpretation less likely.

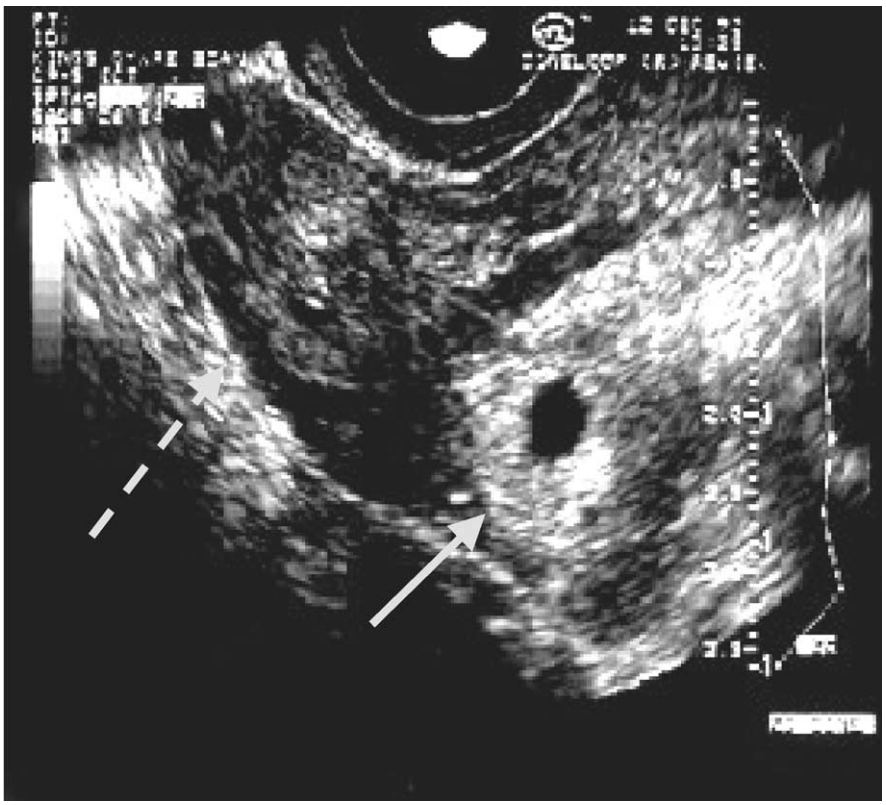

Figure 2. Ectopic pregnancy—'bagel' sign. Broken arrow depicts the right ovary and solid arrow shows ectopic pregnancy. Reproduced with permission from: Condous et al. *Ultrasound Obstet Gynecol* 2003: **22**; 420–430.

THE ROLE OF EXPECTANT MANAGEMENT IN ECTOPIC PREGNANCY

In a select group of women, expectant management of EP is an option. Ylostalo et al[39] managed 15% of their EPs expectantly and observed spontaneous resolution in 64.6%. Follow-up for these women involved ultrasound scans and measurements of serial serum hCG titres until they have fallen to $<$ 15 IU/l. Inclusion criteria stipulated that the patient had to be stable, compliant, and with no evidence of haemoperitoneum on TVS or other signs of tubal rupture.

In a study of 118 women selected for expectant management of EP, resolution rates were as high as 88% when initial serum hCG was less than 200 u/l.[40] In a smaller study of 67 women, similar resolution rates were seen when initial serum hCG was less than 1000 u/l.[41]

Such management requires very close follow-up and is reserved for select cases, with out-of-hours emergency back-up essential in the event of clinical deterioration. In our unit, we offer expectant management to stable women with an initial serum hCG less than 1500 u/l and an initial serum progesterone less than 20 nmol/l. This accounts for 10% of our ectopic population, with a resolution rate of 86%.

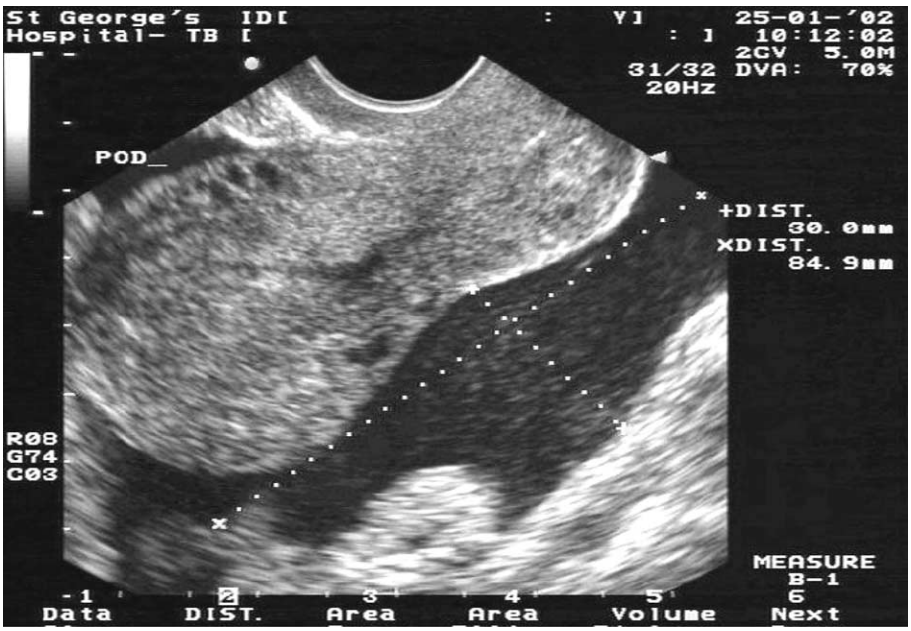

Figure 3. Blood in the pouch of Douglas. Reproduced with permission from: Condous et al. *Ultrasound Obstet Gynecol* 2003: **22**; 420–430.

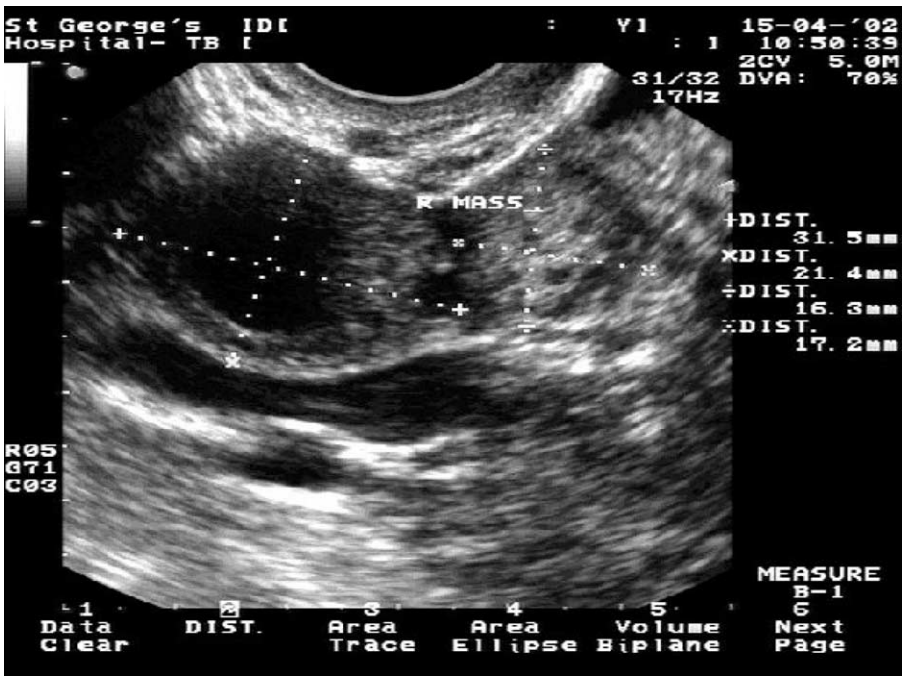

Figure 4. Inhomogeneous or inconglomerate mass adjacent to the right ovary. Reproduced with permission from: Condous et al. *Ultrasound Obstet Gynecol* 2003: **22**; 420–430.

MEDICAL MANAGEMENT OF TUBAL ECTOPIC PREGNANCY

Medical treatment of EP with methotrexate is successful in 71–100% of cases.[42] Successful outcome depends on the initial serum hCG levels (the likelihood of treatment failure is greater at higher serum hCG concentrations), the size of the EP on TVS and the presence or absence of fetal heart activity. In the United Kingdom, 50 mg/m^2 methotrexate is administered intramuscularly on day 1. A second dose of methotrexate is required in up to 13% of cases if the hCG levels do not fall by 15% between days 4 and 7.[43] In the USA, 1 mg/kg methotrexate is given on days 1, 3 and 5, with folinic acid rescue on days 2, 4 and 6. Resolution rates are comparable between the two regimens.

Zilber et al[44] randomized 48 women with unruptured tubal ectopic pregnancies to either laparoscopic salpingotomy or laparoscopic local methotrexate injection. Successful resolution was seen in 80–90% and their subsequent IUP rates were 83.5 and 81%, respectively.

Hajenius et al[45] demonstrated no significant difference in homolateral tubal patency when 100 women were randomized to either systemic methotrexate or laparoscopic salpingostomy (55 versus 59%).

Methotrexate can be administered transvaginally under sonographic guidance. However, when compared to laparoscopic salpingostomy in a randomized control trial involving 100 women it was less successful.[46]

The results of another smaller study[47] demonstrated that the treatment success of methotrexate administered transvaginally under ultrasound guidance was significantly better than the 'blind' intratubal injection under laparoscopic guidance (RR 1.6, 95% CI 1.0, 2.5).

The combined results of three studies[46,48,49] involving 95 women with a small unruptured EP showed no statistically significant difference in the primary treatment success between methotrexate transvaginally under sonographic guidance and systemic methotrexate in a single-dose intramuscular regimen (RR 1.2, 95% CI 0.95, 1.5). The use of such transvaginal treatment techniques requires a high degree of training and skill, and one would not recommend their use, especially in the light of the evidence suggesting that single-dose methotrexate is just as effective.

When compared to laparoscopy, systemic methotrexate provides significant cost savings.[50,51] However, in 10% of these women persistent trophoblastic disease is seen and tubal rupture can occur even with a falling serum hCG.

It is important that there are no contraindications to the use of methotrexate. These include liver, renal or bone marrow impairment or a viable pregnancy.

In our unit we offer medical management to women with tubal ectopic pregnancies who are clinically stable with a serum hCG of $<$5000 IU/l, in whom the EP diameter is $<$30 mm with no fetal heart activity and no signs of haemoperitoneum. The success rate is 88%.

SURGICAL MANAGEMENT OF TUBAL ECTOPIC PREGNANCY

The laparoscopic approach has been conclusively shown to be better than laparotomy in the management of EP.[52–54] Laparoscopy is equally as effective as open surgery in the treatment of tubal pregnancy[55], and reduces costs considerably.[56] The laparoscopic approach results in less haemorrhage and less pain; it is associated with a shorter

hospital stay and recovery time. Nevertheless, there will always be a place for laparotomy in those women who are haemodynamically unstable.

There is no consensus about which laparoscopic treatment modality—either conservative (linear salpingostomy) or radical surgery (salpingectomy)—preserves fertility the best because no randomized control trials have been performed. The reported failure rate after conservative treatment ranges from 3 to 29%[44,52], whereas there is practically no failure after radical treatment (<0.5%). Salpingostomy is associated with higher subsequent IUP (61.4%) and recurrent EP (15.4%) rates compared with salpingectomy (subsequent IUP rate 38.1% and the recurrent EP rate 9.8%).[55]

Subsequent fertility rates are the same for laparoscopic conservative and radical treatments among women who are <30 years.[57] Those women with a history of infertility do better with conservative treatment.[57]

Conservative surgery should be performed when there is evidence of previous tubal infection at the time of laparoscopy, as this confers the best chance for future fertility. In women with no past history of tubal surgery or infertility, and whose contralateral tube is normal, the fertility results after laparoscopic salpingectomy appear comparable to those observed after conservative laparoscopic treatment.[58]

EP associated with haemoperitoneum on TVS suggests the possibility of tubal rupture, and this situation requires surgical intervention. The incidence of haemoperitoneum ranges from 18 to 34%.[59,60]

In clinical practice, the use of laparoscopy as a tool for diagnosing EP should be the exception rather than the rule, as the vast majority can be visualized using TVS.[34,35]

In our unit, of those EP treated surgically, 90% are performed by laparoscopy. If the contralateral tube is normal macroscopically we perform a salpingectomy at the time of laparoscopy.

Anecdotally, if given the choice, women are very keen to conserve their Fallopian tube at the time of surgery—although, to date, the psychological morbidity associated with conservative and radical surgery has not been prospectively evaluated.

NON-TUBAL ECTOPIC PREGNANCIES

Ectopic pregnancies are classified according to their site of implantation. Non-tubal ectopic pregnancies account for only 5% of EPs, but they contribute a disproportionate number of serious complications. Their diagnosis may be difficult and they are associated with significant haemorrhage leading to a higher morbidity and mortality than tubal EPs.

Interstitial pregnancies account for about 2% of EPs.[61] The sonographic appearance of the interstitial pregnancy is that of a bulge in the cornual region of the uterus where an extremely thin myometrial mantle surrounds the hyperechoic ring of the gestational sac.[62] The gestation sac is usually located more than 1 cm from the endometrial echo, although this is not mandatory (Figure 5). Hypoechogenic lesions situated in the cornual region may persist for 1 year, even following successful treatment and resumption of normal menstruation.

Cervical ectopic pregnancies are rare (Figure 6). The cervical appearance is classically barrel shaped, and true cervical pregnancies are often relatively asymptomatic. It is important to differentiate this from an intact gestational sac passing through the cervix—which usually causes intense pain. Colour Doppler studies may assist in the diagnosis as they help to localize the uterine artery. This is a useful anatomical marker for the internal cervical os, below which the pregnancy implants. The presence of blood

Figure 5. Interstitial pregnancy with colour Doppler.

flow around the gestation sac is more suggestive of an implanted sac than one passing through the cervix. Ovarian pregnancy is also rare and has an incidence of 1:7000 deliveries and 1:34 EPs.[63] Diagnosis can be difficult, but the finding of a hyperechoic chorionic ring which moves with the ovary is highly suggestive.

Figure 6. Sagittal view of cervical pregnancy.

All non-tubal ectopic pregnancies represent a management problem. The mainstay of treatment, in general, is either systemic or local administration of methotrexate as the surgical approach is more hazardous. In our unit we rely on a single-dose systemic methotrexate regimen for the treatment of non-tubal ectopic pregnancies and have rarely had problems with this approach. Injection of 50% dextrose and methotrexate have been used to avoid major surgical intervention.[64] Similarly, systemic methotrexate and/or intratubal injection of potassium chloride has been used in unruptured interstitial pregnancies with complete resolution in 86.6–94% of cases.[65,66]

Abdominal pregnancies tend to be diagnosed later in pregnancy and are rare. The ultrasound features are well described and include the finding of an empty uterus separate from the fetus, placenta in an unusual location, no uterine mantle around the pregnancy or fetus, and extreme oligohydramnios resulting in crowding of the fetal structures.[67,68]

Caesarean section scar pregnancy has been described only recently. The diagnosis is based on the visualization of trophoblast located between the anterior uterine wall and the bladder.[69] Scar implantation should be further confirmed by applying gentle pressure on the cervix during a TVS. A gestational sac implanted outside the uterine cavity within the scar will remain in place during such a manoeuvre, while a cervical miscarriage will be easily displaced.[70]

Heterotopic pregnancies, already discussed earlier, are fortunately rare. However, with the advent of reproductive technologies their number is steadily increasing.

PREGNANCY OF UNKNOWN LOCATION

In 8–31% of women who present to an EPU, the pregnancy site will not be visualized by TVS.[71,72] These women are classified as having a 'PUL'. This is a descriptive term rather than a pathological entity. The varying prevalence may be attributable to the sonographer's ability. An inexperienced sonographer could potentially overlook some early intrauterine gestational sacs or adnexal masses, which, in turn, would result in a higher prevalence of PUL for a given EPU.

PUL is defined by TVS as there being no signs of either an intra- or extra-uterine pregnancy or retained products of conception in a woman with a positive pregnancy test (i.e. serum hCG $>$ 5 IU/l). In this clinical situation there are four possible outcomes: failing pregnancies and early immediately viable IUPs or ectopic pregnancies that are too early to visualize on TVS, and persisting PUL. The location of these failing pregnancies remains unknown and a proportion will be failing EPs that are never seen on TVS.

Women with a PUL should be managed expectantly on the basis of measurements of serum levels of hCG and progesterone. This can be on an outpatient basis. Women thought to have a complete miscarriage at the initial scan should be managed as PULs. The diagnosis of complete miscarriage based on history and scan findings alone is unreliable as up to 6% will have an EP.[73] If hCG levels do not fall, these women should be followed closely until the location of the pregnancy is confirmed.

Expectant management has been shown to be safe and to reduce the need for unnecessary surgical intervention, and it is not associated with any serious adverse outcomes.[71,74,75] Nevertheless, 9–29% of these women will require surgical intervention due to a worsening clinical condition or non-declining serum hCG.[71,74]

THE DISCRIMINATORY ZONE AND SERIAL MONITORING OF SERUM HORMONAL LEVELS

When the location of a pregnancy cannot be confirmed on the basis of an ultrasound scan, the levels of serum hCG and progesterone and their interpretation should determine the management. An understanding of the pattern of serum hCG levels in early normal pregnancy, and the correlation between low serum progesterone levels and the spontaneous resolution of a pregnancy, are important hormonal variables in the management of pregnancies of unknown location. However, laparoscopy is still performed as a first-line investigation in some units. This is no longer acceptable practice.

The concept of combining ultrasound with measurements of serum hCG using a discriminatory zone is well described.[76–78] By correlating the serum hCG values to the size of an intrauterine gestational sac, a value can be chosen that corresponds to the threshold above which an intrauterine gestation sac should be seen. If a sac cannot be seen above the discriminatory zone then steps must be taken to determine whether the pregnancy is abnormal or ectopic.

Barnhart et al[76] showed that above a discriminatory level of 1500 IU/l an intrauterine gestation sac was seen in 91.5% of cases compared with 28.6% when levels were below 1500 IU/l. In women without an ectopic mass or fluid in the pouch of Douglas, Mol et al[75] used a serum hCG cut-off of at least 2000 IU/l.

However, it should be noted that the discriminatory zone might vary among institutions due to the frequency of the probe used, different types of equipment and assay techniques. It is also dependent on the operator's experience. In early multiple pregnancies higher serum hCG titres are seen and this may lead to unnecessary concern about the location of the pregnancy.

A single measurement of hCG in practice will not be diagnostic in the majority of cases. When the serum hCG is above the discriminatory zone and an EP is present, in most cases it will be large enough to be visualized by ultrasonography. Problems arise at lower serum hCG levels or in the smaller number of cases when an ultrasound diagnosis cannot be made. In such cases it is possible to distinguish between a PUL which will develop into a normal IUP and those that subsequently become ectopic pregnancies on the basis of serum hCG increase over 48 hours. In normal IUPs there should be a 66% rise over the baseline value over 48 hours.[79] Using this well-known algorithm is not without its pitfalls, as approximately 13% of ectopic pregnancies and 15% of normal IUPs screened in this way will appear abnormal, giving contradictory results and delaying the diagnosis beyond 48 hours.[80] It is possible to have either a 'flourishing' EP or a 'sick' intrauterine, and both can give conflicting results.

The vast majority of PULs will be at low risk of EP and, in turn, are made up of failing PULs and IUPs. A failing PUL may be extrauterine or intrauterine and generally will resolve spontaneously. A failing PUL is not necessarily a failing IUP. These pregnancies are never seen on TVS, their baseline serum progesterone at presentation will be <20 nmol/l and serial serum hCG levels fall. A baseline serum progesterone level of <20 nmol/l will identify a failing PUL with a positive predictive value of $\geq 95\%$.[74] This compares favourably with complex multiparameter diagnostic models.[74] In contrast, ongoing IUPs usually demonstrate a $>66\%$ increase in serial serum hCG levels taken at 48 hour intervals.

Hormonal results should not be taken in isolation and the clinical assessment and subsequent ultrasound findings are essential to the ongoing management. When the diagnosis of EP has been established (and this should be possible by TVS in the majority of cases), then appropriate medical or surgical management should be initiated.

The overall rate of intervention for PULs managed expectantly in our series is 12.1%, which is consistent with that of other groups.[74]

PERSISTING PREGNANCIES OF UNKNOWN LOCATION

To date there are no published data relating to persisting PUL. This small subset of women are defined as those in whom the serum hCG levels fail to decline, where there is no evidence of trophoblast disease, and the location of the pregnancy cannot be identified whether by ultrasound or laparoscopy. In general, the serum hCG levels are low ($<$500 IU/l) and have reached a plateau. We have treated nine such women successfully with methotrexate 50 mg/m^2 and their serum hCG levels subsequently resolved.

Care should be taken before giving medical treatment for a PUL before the site of the pregnancy has been identified. A positive serum hCG does not always indicate pregnancy. Germ-cell tumours may secrete hCG and should be considered, especially if a woman is adamant that she cannot be pregnant. In our unit, we have seen one malignant dysgerminoma of the ovary, one posterior cranial fossa germ-cell tumour and one placental site trophoblastic tumour present in this way.[81]

ADNEXAL MASSES IN EARLY PREGNANCY

The incidence of adnexal pathology detected in the first trimester is between 0.17 and 2.94%.[82,83] In a study of some 2245 women scanned at the end of the first trimester, 1.2% of the total persisted beyond 16 weeks and subsequently were surgically removed—there were no cases of malignancy.[82] In a study of 55 278 pregnancy terminations, there were two cases of ovarian malignancy.[83] This is in keeping with the reported frequency of ovarian cancer in pregnancy—one in 15 000 to one in 32 000.[84] Expectant management is safe and advocated[85], at least until the pregnancy is beyond 14 weeks' gestation. When symptomatic, simple ovarian cysts diagnosed during pregnancy can be successfully and safely treated with sonographically guided cyst aspiration.[86] Adnexal masses can be accurately classified according to TVS.[82,87] However, in the few cases when the nature of the cyst is in question, one must balance the risks to the pregnancy from intervention versus the risk of malignancy.

We have prospectively evaluated 3000 consecutive women who presented to the EPU. The prevalence of women with ovarian cysts was 5.3%.[88] These women were managed expectantly and followed until resolution of the ovarian cyst occurred, intervention was required or the pregnancy concluded; 72.2% resolved spontaneously, 23.6% persisted and 4.2% required intervention—there were no cases of malignancy.[88] Only 0.13% (1.3/1000) of all women in this longitudinal study required acute intervention.[88] We concluded that examining the ovaries in the first trimester is of limited value.

HYDATIDIFORM MOLE

TVS has led to the early diagnosis of molar pregnancy. Classically, the 'snow-storm' effect previously described was historically seen with transabdominal sonography.[89]

Figure 7. Complete hydatidiform mole.

In modern practice, the findings seen on TVS are described as multiple small sonolucent areas (Figure 7), which correspond to the 'grapelike' vesicles that one sees on gross pathological examination.[90]

The majority of cases of molar pregnancy (67%) seen in an EPU now present as missed or anembryonic pregnancies sonographically.[91] This highlights the importance of histological examination of products of conception to diagnose gestational trophoblastic disease. Although serum hCG levels will invariably be high, this is not specific.

Suction curettage is the method of choice of evacuation for complete molar pregnancies. Because of the lack of fetal parts, a suction catheter, up to a maximum of 12 mm, is usually sufficient to evacuate all complete molar pregnancies. Medical termination of complete molar pregnancies, including cervical preparation prior to suction evacuation, should be avoided where possible.[92] Because evacuation of a large molar pregnancy is a rare event, advice and help from an experienced colleague should be sought where appropriate. In partial molar pregnancies (Figure 8), where the size of the fetal parts deters the use of suction curettage, medical termination can be used. These women may be at increased risk for requiring treatment for persistent trophoblastic disease, although the risk for women with partial molar pregnancies needing chemotherapy is low (0.5%).[93]

The Health Departments of England, Scotland and Wales and the Royal College of Obstetricians and Gynaecologists have agreed that registration of women with a molar pregnancy to listed Screening Centres is desirable. The duration of follow-up is determined by the Screening Centre.

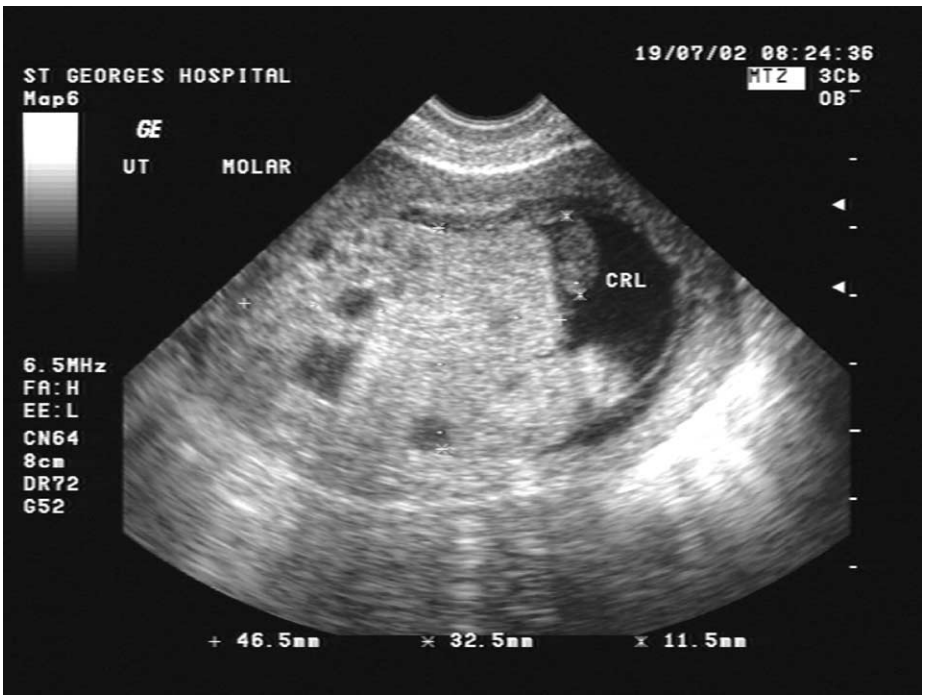

Figure 8. Partial hydatidiform mole.

SUMMARY

There has been a trend towards more conservative management of women with complications in the first trimester of pregnancy. The majority of women presenting with miscarriage can be offered expectant management with a reasonable prospect of success and with no increase in the complication rate; however, in the presence of haemodynamic compromise or infection there will always be a role for surgical evacuation of the uterus. Approximately 90% of incomplete miscarriages and 50% of missed miscarriages and anembryonic pregnancies can be expected to miscarry within 2 weeks. The odds of a woman completing her miscarriage with each subsequent week diminish with time. Most women will opt for surgical intervention if they have not completed their miscarriage within the 2-week window.

The success of expectant management for missed and anembryonic pregnancies is significantly less than for incomplete miscarriage. Medical management is more likely to play a role in these women. A trial comparing medical and expectant management in these pregnancies would be informative at this stage.

The diagnosis of EP should be based on the positive visualization of an extra-uterine pregnancy using TVS and not by the absence of an intra-uterine pregnancy. Although the vast majority of ectopic pregnancies are still managed surgically, there is great scope for the increased use of non-surgical approaches. A select group of non-ruptured tubal ectopic pregnancies should be offered medical management in the form of methotrexate as it is safe and avoids the need for surgical intervention.

Resolution is expected in up to 90% of these cases. Some will be suitable for expectant management, with successful resolution seen in up to 88% of cases. Trials comparing expectant management to current practices are needed to evaluate its benefit or otherwise.

The management of pregnancies of unknown location should be expectant and should utilize serum hCG and progesterone measurements with ancillary aids that include serial TVS. If an EP is not visualized, but there is a high index of suspicion based on symptomatology, clinical findings and sub-optimal rises of serial serum hCG levels, a laparoscopy can be performed with or without an evacuation of the uterus. In the future, we hope to not only predict viability but also locate these pregnancies.

Practice points

- early pregnancy complications should be assessed in dedicated EPUs
- the psychological morbidity associated with early pregnancy loss is well documented and all EPUs should have access to counselling services
- knowledge of normal sonographic milestones in early pregnancy development is essential
- if there is any doubt as to the viability of an early pregnancy, an interval scan in 7 days is recommended
- an understanding of various sonographic definitions of miscarriage is essential
- anembryonic pregnancy (early embryonic demise): gestational sac mean diameter of at least 20 mm with no embryonic/extra-embryonic structures present
- missed miscarriage (early fetal demise): CRL of at least 6 mm with no cardiac activity, or no change in size on weekly serial scanning
- incomplete miscarriage: disrupted endometrial echo, measuring more than 15 mm in the antero-posterior plane, with the presence of heterogenous and irregular tissues
- complete miscarriage: endometrial thickness of less than 15 mm measured in the antero-posterior plane associated with the cessation of heavy bleeding and pain
- EP should be diagnosed on the basis of positive visualization of an extra-uterine mass using TVS
- typically with TVS, an EP is visualized as an inhomogeneous mass adjacent to the ovary
- misdiagnosis should be a rare event, and the standard of care in any EPU should be determined by its false-positive and -negative rates for the diagnosis of EP
- heterotopic pregnancies occur in 1% of IVF/GIFT pregnancies
- the rate of pregnancies of unknown location is indirectly proportional to the quality of the those scanning in an EPU
- expectant management of pregnancies of unknown location is safe and the interpretation of serum hCG and progesterone levels in these cases is cornerstone to the management
- the majority of ovarian cysts diagnosed in the first trimester are physiological

- expectant management of ovarian cysts diagnosed in the first trimester is advocated
- the majority of cases of molar pregnancy seen in an EPU are described as missed or anembryonic pregnancies sonographically; therefore, histological examination of products of conception is essential for the diagnosis of gestational trophoblastic disease
- registration of women with a molar pregnancy to listed Screening Centres is desirable

Research agenda

- a randomized trial examining medical therapy versus expectant management of missed miscarriage and anembryonic pregnancy is urgently required
- a randomized trial needs to be performed to determine which laparoscopic treatment modality—either conservative (linear salpingostomy) or radical surgery (salpingectomy)—gives the best long-term outcome for fertility
- the psychological morbidity associated with conservative and radical surgery in the management of EP needs to be evaluated
- trials comparing expectant management of EP to current practices are needed
- with the improved detection of ectopic pregnancies based on the positive visualization of an adnexal mass using TVS, we need to develop new algorithms which not only predict viability of PULs but also locate the pregnancy

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