# Management of early pregnancy complications

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## Abstract

Complications of early pregnancy are common, including pregnancy loss, threatened miscarriage, ectopic pregnancy, molar pregnancy and hyperemesis. There are over 30,000 ectopic pregnancies, 1600 M pregnancies and 80,000 miscarriages per year in the UK accounting for a significant proportion of healthcare resources.

This review discusses the different presentations, diagnoses and management of the common problems complicating early pregnancy.

## Introduction

Most women presenting with complications in early pregnancy are assessed, diagnosed and managed at early pregnancy assessment units (EPAUs). These units aim to provide thorough assessments, access to specialist investigations (scan, hCG), a rapid turn around of results and co-ordination of further management.

The EPAU enables continuity of care, fewer admissions and planned follow-up. It is beneficial in the provision of open access for GPs, and ideally patients particularly following a previous pregnancy loss. By streamlining investigations and treatment this system is also more cost effective.

For women who have had previous pregnancy complication a familiar setting and ongoing support in a future pregnancy is a valued service.

A downside of the EPAU system is that it is often only available at limited times, thus for complications occurring outside of these hours patients require ward contact numbers and more frequent inpatient based care.

### Hyperemesis gravidarium

Over 50% of women suffer from nausea in pregnancy. Hyperemesis gravidarium is the inability to maintain hydration resulting in dehydration and ketonuria as a result of nausea and vomiting in pregnancy. It affects between 0.1 and 1% of women. Patients become dehydrated, ketonuric, develop an electrolyte imbalance, (hyponatraemia and hypokalaemia) and in severe untreated cases a nutritional (thiamine) deficiency culminates in Wernicke's encephalopathy.

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Symptoms develop around 6–8 weeks of gestation, and are directly related to levels of hCG, peaking towards the end of the first trimester before settling in the second trimester. Women present with nausea, weakness, vomiting, and occasionally ptyalism (inability to swallow saliva). On examination there are signs of dehydration and tachycardia with or without hypotension. Those who have suffered with hyperemesis in a previous pregnancy are more likely to develop similar symptoms in subsequent pregnancies. Nausea and vomiting presenting after 12 weeks of gestation is not hyperemesis gravidarium.

The proposed pathophysiology behind hyperemesis is related to the hCG (human chorionic gonadotrophin). The hCG molecule has common alpha subunit with thyroid stimulating hormone (TSH) and is thought to exert its effect via a temporary physiological thyrotixicosis, there may be evidence of a raised free thyroxine and a low TSH. This accounts for the timing of the onset and settling of symptoms in correlation with levels of hCG. There may also be psychological and cultural factors.

In all presentations, a multiple or molar pregnancy should be excluded as these conditions also result in an increased hCG level.

Many women with mild symptoms are managed in the community; once women are ketotic and unable to maintain hydration, admission is necessary. For the majority of women intravenous rehydration with antiemetic medication, on a day case basis without admission, is sufficient to break the cycle and allow the patient to re-establish oral intake. Many units have managed to expand the role of the EPAU to incorporate this service and release capacity on the admitting wards. However, more severe cases do require an inpatient admission further rehydration, anti-emetics, thiamine supplements, daily electrolyte analysis and a gradual resumption of oral intake and monitoring of ketonuria. Intravenous rehydration with normal saline or Hartmann's with potassium supplementation and monitoring of electrolytes and ketonuria should be employed. Infusions containing dextrose should be avoided as they may precipitate Wernicke's encephalopathy. Women requiring admission are intravascularly dehydrated posing an increased thrombotic risk, thus thromboprophylaxis should be considered. Rarely, intractable cases may require treatment with steroids to relieve symptoms.

Hyperemesis is not uncommon; the majority of cases can be successfully treated as a day admission to an EPAU. The outcome for the both pregnancy and patient are excellent.

### Practice points I

*Hyperemesis*

- 50% of women suffer from nausea in pregnancy
- 0.1–1% of women suffer from hyperemesis gravidarium
- Symptoms peak at the end of the first trimester
- In severe cases there is a risk of Wernicke's encephalopathy resulting from a nutritional imbalance of reduced thiamine
- Treatment includes intravenous rehydration, electrolyte monitoring and restitution, anti-emetics, thiamine supplementation and in non-resolving cases steroid therapy
- Molar and multiple pregnancies should be excluded

## Miscarriage

15–20% of pregnancies end in miscarriage.

Miscarriage was traditionally classified as threatened, inevitable, complete, incomplete or missed. Most women present with pain and bleeding in early pregnancy. Alternatively, miscarriage may be diagnosed at the early dating scan with no prior warning symptoms, this is classified as a missed miscarriage.

An episode of pain or bleeding in an early pregnancy subsequently demonstrated to be a viable pregnancy is termed a threatened miscarriage.

Traditionally, classifications of complete, incomplete and inevitable miscarriage have been used. Diagnosis and management is based on clinical findings: i) examination of vaginal loss for products of conception and ii) examination of the cervical is to determine whether it is open or closed. More recently there has been a tendency to be increasingly conservative in management of miscarriage with routine use of ultrasound to aid management. Once an intra-uterine pregnancy is demonstrated by ultrasound, with uncertain viability, a follow-up scan will be arranged 10–14 days later to determine whether the pregnancy is ongoing or not. If initial symptoms are of heavy bleeding, or if they worsen between appointments, then medical intervention in terms of a surgical evacuation may be necessary at an earlier stage. Patients with a pregnancy of unknown viability who are waiting for follow-up must be informed of the risk of pain and bleeding between appointments and be given appropriate contact numbers and advised to return if their bleeding becomes heavy.

If there are symptoms (or with minimal symptoms), treatment of miscarriage is based on three alternatives: expectant, medical or surgical. Expectant management employs awaiting the natural course of events, for the products to pass spontaneously. Medical management involves combinations of oral or vaginal prostaglandins to induce the completion of miscarriage. Surgical management involves an operation, usually vacuum aspiration, to remove any remaining products of pregnancy.

There are risks and benefits associated with all approaches:

i) Expectant management requires a longer follow-up, often multiple visits, and is associated with more prolonged and heavier bleeding. Due to the unpredictable of length of follow-up and number of visits associated with expectant management many women veer away from this option. There is a higher risk of treatment failure and an increased need for later surgery. This method of treatment may be more effective for those who are symptomatic of pregnancy loss (i.e. those presenting with an incomplete miscarriage) because the process of spontaneous loss will have already begun. The timescale for completion of expectant management can extend over 2–6 weeks with the emphasis on planned follow-up at specified intervals for assessments usually with ultrasound scans to ensure all products have passed. Although figures differ depending on the length and type of follow-up that patients have (clinical versus ultrasound), around 80% complete without intervention. When counselling women, the possibility of a period of prolonged follow-up and of the risk of incomplete loss with the subsequent need for surgery – should be stressed.

ii) Medical management also aims to avoid surgery and is an accelerated method of conservative management with a more predictable timescale of completion. It can be carried out as an inpatient or outpatient procedure, provided support is available for women at home if needed. If managed in the community, follow-up is necessary once again, to ensure completion and that ongoing complications are recognized and treated.

iii) The benefit of surgical management is to limit the need for prolonged follow-up, reduce the number of symptomatic days and for early closure of treatment. Complications, although infrequent, include uterine perforation, cervical trauma, incomplete evacuation, the risk of the anaesthetic and a slightly higher infection rate when compared to expectant management.

The MIST trial (miscarriage treatment trial) and subsequent Cochrane reviews (2006, 2010) have concluded that there is no superior method of management and have recommended that the woman's preferences are taken into account when planning care; treatment should therefore be patient guided, based on an informed decisions.

Importantly, the long-term follow-up of the MIST trial concluded that there is no difference in later conception rates following the different approaches to management. It has also been suggested that empowering patients by choice in their management reduces subsequent anxiety and depression rates. Women who have been involved in the decision making process have subsequently scored more favourably on quality of life outcome questionnaires.

### Practice points II

*Miscarriage*

- Affects up to 1 in 5 pregnancies
- Treatment options are expectant, medical and surgical
- Expectant management aims to avoid surgery, may result in prolonged follow-up with a risk of heavier bleeding and failed treatment
- Medical management aims to avoid surgery, may be uncomfortable with heavier bleeding and risk of later surgery
- Surgical management allows early completion of treatment with the risk of surgical and anaesthetic complications
- There is no difference in post-treatment conception rates regardless of method of management

**Recurrent miscarriage:** recurrent miscarriage is defined as three or more consecutive miscarriages and affects 1% couples trying to conceive.

It is recommended that investigations into why women have miscarried should be implemented following the third consecutive miscarriage. For the majority of women the results are normal. Prognosis for the future worsens with increasing numbers of pregnancy losses, advancing maternal age, normal histopathology and a normal parental karyotype. Recurrent miscarriage is particularly devastating for couples as they may be able to conceive relatively easily but not carry an ongoing pregnancy; they may thus need increased support and counselling. EPAUs arrange specialist follow-up and offer a patient

educational role with the provision of information combined with access to support groups and counselling.

Following recurrent miscarriage, investigations may include screening for antiphospholipid syndrome, karyotyping the products of conception, diagnostic imaging for structural abnormalities and parental karyotyping looking for balanced translocations. The incidence of controlled diabetes and thyroid disease are no different in this population when compared to the general public.

As stated, for the majority of patients, investigations will be normal and no cause is identified. In a minority, there may be a treatable haematological factor such as antiphospholipid syndrome. In the case of recurrent miscarriage positive serum blood results on two separate occasions 12 weeks apart with a history of three consecutive pregnancy losses before 10 weeks are necessary to confirm antiphospholipid syndrome. (Positive bloods in association with a single pregnancy loss above 10 weeks or a poor obstetric outcome before 34 weeks secondary to placental disease are also fulfil the criteria for antiphospholipid syndrome.) For these women, treatment with aspirin and heparin will improve the chance of an ongoing pregnancy. Without treatment the likelihood of a term pregnancy may be as low as 10%, with treatment the miscarriage rate may be reduced by up to 54%.

### Practice points III

*Recurrent miscarriage*

- Defined as three or more consecutive miscarriages
- Affects 1% of couples
- For the majority of patients all investigations are normal
- A minority of patients will have antiphospholipid syndrome which can be treated with heparin and aspirin to improve the chance of an ongoing pregnancy

## Molar pregnancy

Hydatidiform gestational trophoblastic disease/neoplasia (GTN).

Molar pregnancies are rare, affecting roughly 1 in 700 conceptions. They are the result of an abnormal conception, can either be complete moles or partial moles. They are more common at the extremes of reproductive ability, and among people living in Asia. The risk of recurrence is low: 1–2%.

Complete moles are diploid, contain only paternal chromosomes and are either the result fertilization of an empty ovum with duplication of a single sperm or dispermic fertilization. They contain no fetal tissue.

Partial moles are triploid in nature, may contain fetal parts, and are the result of dispermic fertilization.

The concern with molar conceptions is the risk of progression to neoplasia if left untreated. Molar pregnancies can present as a miscarriage, or more rarely after a normal pregnancy. They are associated with characteristic appearances on an ultrasound scan (snow storm/placental vacuoles). Molar pregnancies are usually detected in the first trimester either because women present with bleeding, resulting in an early ultrasound scan, or are suspected on the dating ultrasound scan. They are also associated with a raised hCG level and the condition should be excluded in women presenting with hyperemesis.

Diagnosis is sometimes retrospective following histological examination of products of conception removed following a surgical evacuation. In cases of miscarriage, products should be screened for gestational trophoblastic disease.

Once suspected, the majority are easily treated by surgical evacuation alone, with histological confirmation. However, due to the low but potentially life threatening risk of ongoing trophoblastic tissue and neoplasia, registration and referral to specialist tertiary care is crucial.

Due to the nature of GTN with the potential for progressive disease, long-term follow-up is necessary. This involves prolonged measurement of urine hCG levels to ensure disease free status, avoidance of future pregnancy until hCG levels have been normal for 6 months and further monitoring after all future pregnancies.

Treatment with surgical evacuation and prolonged monitoring of hCG levels is usually all that is required, with repeat monitoring of levels in subsequent pregnancies. All UK cases of gestational trophoblastic disease are monitored via a national registration programme consisting of three centres based in Sheffield, Dundee and Charring Cross.

HCG is a marker of ongoing trophoblastic disease. If levels are persistently elevated further treatment is required; this is usually medical with methotrexate and in rare cases chemotherapy – a repeat evacuation is not usually helpful. GTN is extremely responsive to treatment. Chemotherapy is necessary in only 5–6% of cases with a greater than 98% cure rate and is more commonly required following complete rather than partial molar pregnancies.

Following diagnosis and treatment, women are advised to delay further conception until 6 months following normalization of the hCG levels and a year after completion of chemotherapy. Barrier contraception is advised; hormonal contraception is an option once hCG levels have normalized. If contraception has been commenced before diagnosis, there may be a slight increase in the risk of gestational trophoblastic disease progressing to neoplasia with combined preparations but there is no evidence of detriment from single agent progestogens.

Thankfully, the recurrence risk is low so women who continue to have a future pregnancy can be reassured that 98 out of 100 conceptions will not be a further molar pregnancy. In the women in whom a second molar pregnancy does occur it is usually of the same histological type as the first.

### Practice points IV

*Molar pregnancy*

- Affects 1 in 700 conceptions
- The concern is the risk of progression to neoplasia if unrecognized or untreated
- All cases must be registered at a tertiary referral centre and require long-term follow-up
- The risk of recurrence is low (1–2%)
- Cases which have progressed to neoplasia are responsive to treatment; 5–6% require chemotherapy with a 98% cure rate

## Ectopic pregnancy

Ectopic pregnancy complicates approximately 1 in 50 pregnancies. Risk factors include previous ectopic pregnancy, a history of

pelvic infection or past pelvic surgery. If not recognized or managed inappropriately it can become a life threatening condition as a result of invasion and rupture of a blood vessel, resulting in massive pelvic haemorrhage; this can happen with or without rupture of the Fallopian tube.

Presentation, as with most early pregnancy complications, is with pain with or without vaginal bleeding, or as collapse with associated concerning symptoms of dizziness and fainting. Diagnosis is based on history, clinical examination and investigations including transvaginal ultrasound scan, serial hCG measurements and laparoscopy. In a normal pregnancy, the serum hCG level should rise by at least 60% in 48 h, although anything above 30% can be consistent with normal early pregnancy. The hCG levels in an ectopic pregnancy may initially rise at a normal rate but by the time of presentation the rise is usually suboptimal. Once suspected, ectopic pregnancies might be suggested by ultrasound evidence of gestational tissue outside of the body of the uterus with an empty uterine cavity. However, laparoscopy remains the gold standard for confirmation of diagnosis and allows concurrent treatment.

Although diagnosis can be suggested by pelvic ultrasound and hCG, confirmation can often takes several days due to presenting features in common with other early pregnancy complications, uncertainty on ultrasound scan and the need for serial blood levels. In the stable patient in this situation, the 48 h hCG trend and symptoms are crucial factors in determining timing and options for treatment. In cases of haemodynamic instability, secondary to a suspected bleeding ectopic pregnancy, emergency surgery is necessary either by laparotomy or laparoscopy, in order to stem the bleeding and remove the ectopic as rapidly and safely as possible.

Once diagnosed there are several options for the management of an ectopic pregnancy, depending mainly on presentation and individual circumstances. For example, in the acute emergency due to a bleeding ectopic urgent surgery is required as a lifesaving procedure. However, the majority of ectopic pregnancies are treated by scheduled laparoscopic surgery or by medical management with methotrexate. Conservative management is also an option with resolving trophoblast (the trend is for the hCG level to fall). Laparoscopic surgery may be initially diagnostic to confirm the ectopic pregnancy as the cause of pain and then therapeutic by salpingectomy or salpingotomy as definitive treatment.

Any surgery performed will have implications for future fertility potential. At the time of surgery both Fallopian tubes should be assessed. as the health of the unaffected Fallopian tube is also relevant. The surgical recommendation is for salpingectomy to be performed if the contralateral tube is deemed healthy and that salpingotomy should only be performed if there is doubt about fertility with the remaining tube. This is because preservation of the Fallopian tube following an ectopic pregnancy retains the risk of a subsequent ectopic pregnancy in the same tube, whereas a salpingectomy removes this risk. The fertility rate from a single functional tube should be sufficient to allow conception.

If there is a diseased contralateral Fallopian tube (such as a hydrosalphinx) and a salpingectomy is performed, future options for conception are likely to depend on IVF. The limitation of visual assessment of the tube should be remembered as it will give an indication of gross disease but not assess tubal patency for which a dye test is more accurate.

**Methotrexte:** due to the risk of life-threatening bleeding from an ectopic pregnancy and the need to be absolutely certain that a viable intra-uterine pregnancy has been excluded, there are rigid criteria to be met before medical management becomes an option:

It is recommended that ultrasound findings should show a suspected ectopic mass less than 3 cm in size with minimal free fluid and no visible fetal heart. There should be minimal pain on examination and a suboptimal rise in hCG which is initially less than 3000 IU/l. (The RCOG disseminated national recommendation, from which individual units set their own treatment pathways). These criteria are employed to enable patient selection so that medical management is an option for appropriate patients who are unlikely to have spontaneous bleeding whilst undergoing treatment. Success of treatment is assessed by subsequent hCG estimations.

The main benefit of methotrexate is the avoidance of surgery. The downside includes the low risk of failure of treatment in cases in which ongoing trophoblast results in bleeding from the ectopic site and the need for surgical intervention.

Methotrexate has antifolate properties and is teratogenic, so patients must be suitably advised to delay conception following treatment and care must be taken to encourage folic acid prior to and during subsequent conceptions.

Expectant management can be employed for cases of resolving trophoblast which may either be a resolving ectopic pregnancy or an early pregnancy miscarriage. For safety, levels of hCG must be decreasing and women must be able to seek appropriate help and attend hospital easily should they need to. Follow-up needs to be rigorous to ensure that the hCG titres have returned to non-pregnant levels and complications are not missed.

For women who have experienced an ectopic pregnancy, fears for the future include the risk of a recurrent ectopic pregnancy, concerns regarding the ability to conceive again and fear relating to the health risks of a recurrent ectopic pregnancy. It may be particularly worrying for women to plan a further pregnancy if they have already experienced life-threatening emergency surgery from a ruptured ectopic or a previous pregnancy complication. If one Fallopian tube is diseased, it is likely that the other tube is also affected and spontaneous conception may be delayed or impossible. Therefore fertility may well depend on IVF which may not be an option for many women (limited NHS funding, personal finances and emotional reasons).

## Practice points V

*Ectopic pregnancy*

- Affects 1 in 50 pregnancies
- The main concern is the risk of life-threatening bleeding
- Management options depend largely on presentation and include mainly surgery or methotrexate (rarely expectant management may be employed in the case of resolving trophoblast)
- Salpingotomy is only recommended during surgical treatment if there is a concern that the contralateral tube is non-functional

## Conclusion

For the majority of women, conception, pregnancy and birth are straight forward, resulting in an uncomplicated confinement, delivery and healthy baby.

For women who do experience complications, explanation, advice follow-up and necessary investigations will help when planning for the future and deciding whether to try for a further pregnancy. Women who are informed of the long-term effects of treatment, for example, that surgical/medical management following a miscarriage does not convey differences in conception rates, and who are given an informed choice regarding their management, may find it easier to come to terms with their loss and have less anxiety and depression long-term. It must be remembered that each case is individual, all circumstances are different and women need to be informed of the risks and benefits of the all available treatment options.

The role of the EPAU with open access and support in future pregnancies in terms of regular scanning and as a point of contact for the individual, has been shown to improve the successful outcome of future pregnancies following miscarriage. Open access and choice in care options has also been advocated as helping women to feel more in control of their treatment and reducing post-treatment rates of anxiety and depression.

Besides the feeling of loss, it is normal for women to feel guilt, blame and anxiety. Women will have concern for their own health, particularly if they have required emergency treatment. Partners may also harbour feelings of guilt, responsibility and helplessness for the situation and may have conflicting emotions with concerns regarding the risk to their loved ones' health in a future pregnancy, balanced with their desire to increase their family.

It is important for patients who have had an ectopic pregnancy to understand that they require an early ultrasound in subsequent pregnancies to exclude a recurrence and to seek a medical assessment early in pregnancy.

Previously, in future conceptions, early open access and regular specialist follow-up have been available, enabling reassurance, investigations, early detection of further complications along with support throughout subsequent pregnancies. Unfortunately as healthcare services are put under ever increasing pressure to reduce costs, open access may be no longed be deemed a financially viable service.

It is important that appropriate investigations are arranged and results collated and explained. It is also necessary that patients are given appropriate counselling, information and links to support groups should they require additional care. ◆

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