Dear Readers,

as members of Special Interest Group (SIG) of Early Pregnancy we would like to present the guidelines of Association of Early Pregnancy Units, which are obligatory in the United Kingdom.

We hope the presented material will be useful for the departments specializing in the early pregnancy. These guidelines have been made accessible to us by dr. Roy Farquharson, the co-ordinator of SIG Early Pregnancy in ESHRE with whom we cooperate.

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GUIDELINES 2007
of Association of Early Pregnancy Units

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Introduction

Early pregnancy problems form a major part of all gynaecological emergencies. In the past patients were admitted to the ward and waited for a considerable length of time before undergoing ultrasound scan and assessment. With the appearance of early pregnancy assessment units (EPU), an increasing number of women are being assessed and managed as outpatient attenders.

In recent years ultrasound diagnosis and improved understanding of problems related to early pregnancy have led to the introduction of medical and expectant management of miscarriage and selected cases of ectopic pregnancy.

It is anticipated that these guidelines will be useful for all providers of service provision within the EPU. Having undergone revision since their first introduction on the website (earlypregnancy.org.uk) in 2003. These revised guidelines were approved in 2007 and are to be reviewed in 2009.

The development of this updated version is aimed at providing the best practice guidelines drawn from evidence-based practice and standardising the care of women with early pregnancy problems.
Clinical Guidelines

General Patient Management

- A brief history is taken on the standardised proforma or locally developed triage protocol (e.g. adapted, audited and validated Manchester Triage system) (see Appendix) in accordance with RCOG guidelines including:
  1) Previous obstetric history, LMP, urine pregnancy test in this pregnancy.
  2) Pain – description.
  3) Bleeding – amount.
  4) Passage of Products of conception (POC).

- Clinical examination should be considered if appropriate.
- Transvaginal ultrasound scan (TVS) is performed if less than 7-8 weeks and also in some circumstances at more than 8 weeks, which provides the patient with the option of seeing what is visualised on the screen.
- The procedure and the reasons for the scan should be explained.
- Patient’s wishes should be respected if she strongly declines a TVS and where the gender of the professional is particularly important to the patient.
- A clear explanation should be given by the Gynaecologist/Sonographer performing the scan as to the possible or likely diagnosis/diagnoses.
- Appropriate pictures are taken for the patient’s records. Pictures are not usually given to patients in EPAU unless requested by the patient.
- All items on the proforma should be checked.
- A plan of management should be formulated based on the guidelines.
- A pregnancy test should be performed if a pregnancy is not clearly visible.
- Consideration for serum hCG assay should be given if a pregnancy test is positive.
- Support should be given where the pregnancy is non-viable or the woman is upset.
- A quiet room should be available (core standard).
- Follow up should be arranged before the woman leaves the clinic.
- Appropriate written advice and telephone numbers for contact should be given.

Standards in Early Pregnancy Care

<table>
<thead>
<tr>
<th>Standard</th>
<th>Core</th>
<th>Aspirational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Information</td>
<td>Designated Reception Area constantly staffed</td>
<td>Clear information on sensitive disposal options, pathology tests and postmortem results</td>
</tr>
<tr>
<td></td>
<td>Universal use of clear, understandable terminology</td>
<td></td>
</tr>
<tr>
<td>Patient Choice of Management</td>
<td>Education of patient relevant to diagnosis and management. Open explanation of expectant, medical and surgical options</td>
<td>Dedicated phone line for patient queries and electronic access to protocols from outside unit</td>
</tr>
<tr>
<td>Dedicated Quiet Room</td>
<td>Room for breaking bad news away from work area</td>
<td>Single-use room only with soft furnishing and absence of medical equipment</td>
</tr>
<tr>
<td>Availability of Service</td>
<td>5 day opening during office hours</td>
<td>7/24 opening and service provision with full staffing and daily scan support</td>
</tr>
<tr>
<td>Competence of Scanning</td>
<td>Recognised ultrasound training and RCOG/BMUS preceptor assessment and validation. Register of staff competent at scanning</td>
<td>Led Clinician Presence of RCOG/BMUS trainer in EPU. Annual assessment of audited activity</td>
</tr>
<tr>
<td>Blood HCG Level Measurement</td>
<td>Laboratory access to blood HCG measurement and same day result</td>
<td>Two hour result with electronic link to laboratory</td>
</tr>
<tr>
<td>Written Information Leaflets</td>
<td>Visible open access to written information leaflets in EPU</td>
<td>Online external access to PIL</td>
</tr>
<tr>
<td>Acknowledgment of Privacy and Dignity</td>
<td>To provide individualised patient support and acknowledge confidentiality</td>
<td>Place one to one care as best practise at all times with training and ongoing support facility</td>
</tr>
<tr>
<td>Bereavement Counselling</td>
<td>All staff trained in emotional aspects of early pregnancy loss. To enable access to counselling and provide immediate support</td>
<td>To provide all emotional and psychological counselling requirements within EPU and supported by dedicated staff and related agencies</td>
</tr>
<tr>
<td>Site of EPU</td>
<td>Geographically separate from all maternity areas</td>
<td>Own EPU entrance/exit</td>
</tr>
</tbody>
</table>
Chaperone

Transvaginal ultrasound scanning (TVS) is found to be extremely well tolerated as a technique by most women [1]. In the presence of a female chaperon most women feel comfortable even if the person doing the scan is male [2]. For most women the mannerism and expertise of a professional is more important than the gender. A junior member of the staff should always be supervised until he/she has attained the required level of expertise in scanning.

A chaperon can act as advocate for the women, offering reassurance and explanation of the procedure or examination. Women should be given privacy while undressing and dressing.

The woman’s age and individual preference should be taken into account. These can be related to previous experiences which sometimes the women may disclose during consultation or examination. Keep the discussion relevant and avoid unnecessary personal comments [3].

Whether a female chaperone should always be present during a transvaginal scan carried out by a male professional depends on the woman’s choice and the staff situation at the time of examination.

However the following general principles should be observed:

• Some women may prefer to undergo an examination without the presence of a chaperon. Women’s wishes should be respected and their decision should be documented in their medical record.
• If a chaperon is not available, examination may be carried out with a member of the family or friend present.
• If for some reason one can not offer a chaperon, it should be explained to the patient and, if possible, delay the examination to a later date. The discussion and its outcome should be documented.

More details may be obtained from publications of the Royal colleges of Nursing [4], Radiologists [5] and Obstetricians and Gynaecologists [6].

Guidance on Ultrasound Images

It is not necessary to seek separate permission from the patient to make the recordings of Ultrasound images. Nor is consent required to use them for any purpose, provided that, before use, the recordings are effectively anonymised by the removal of any identifying marks [7].

Record Keeping and Data Collection

Unless computer based records are available data should be maintained in handwritten registers.

Accurate record keeping is needed to ensure that pregnancy outcome is recorded with sufficient detail and that feedback is comprehensive. Audit of documentation standards should be regularly performed in the EPU.

The training of appropriate support staff to maintain high standards of record-keeping is recommended.

Guidance on Maintaining Registers

The monitoring of the management protocols in terms of acceptance and outcome can only be achieved through maintaining accurate registers. The following issues are important to establish the diagnosis and its management.

1. All first visit scans should be given a diagnosis and grouped under respective diagnostic groups, such as:
   - Visible pregnancy/threatened miscarriage – if associated with bleeding.
   - Non-visible pregnancy:
     a) Complete Miscarriage;
     b) Incomplete Miscarriage or
     c) Missed Miscarriage.
   - Ectopic pregnancy.
   - Hydatidiform mole.

2. Those scans that do not fit into any of the above categories are grouped under:
   a) Pregnancy of Unknown Location (PUL) if an intratunine or extratunine pregnancy cannot be demonstrated on scan or
   b) Intratunine Pregnancy (IUP) of Uncertain Viability if an early small sac is visible (with or without a yolk sac).
   With a positive pregnancy test, there could be three reasons for a scan result to be classified as a „Pregnancy of Unknown Location (PUL)“:
   - a very early intratunine pregnancy or
   - a complete miscarriage or
   - an early ectopic pregnancy.

Guidance on Maintaining Registers

At subsequent follow-up visits the diagnosis may become clear. However, if it is not possible to place a pregnancy into one of the diagnostic groups in section 1, and symptoms and signs of pregnancy are resolving (including serum hCG levels), this can be classified as a „resolving PUL“. 

References

3. A pregnancy in which an embryo measuring <6 mm is visible, but cardiac activity is not demonstrable on TVS, is classified as an "IUP of uncertain viability".

4. An intrauterine gestational sac measuring less than 20 mm is also classified as an "IUP of uncertain viability" until a repeat scan confirms a viable pregnancy, a demised embryo or an empty gestational sac. The last is known as an anembryonic (empty sac) pregnancy (Farquharson et al, 2005). Blighted ovum is a term that is no longer acceptable as embryos seen on earlier scans frequently get absorbed leaving an empty gestational sac or some remnants within it. A missed miscarriage can therefore be simply classified as either fetal or anembryonic depending on the presence or absence of a measurable crown rump length within the gestational sac.

At a subsequent scan when a diagnosis becomes possible this will be recorded under the respective groups as mentioned above under section 1.

5. Scans that are performed after a diagnosis has been made are grouped under Rescans to avoid repeated counting of the same patient in a diagnostic category.

6. All non-viable pregnancies – Incomplete/Missed miscarriages should be grouped according to the method of treatment and their outcome recorded.

7. All ectopic pregnancies should be grouped according to the method of treatment and their outcome recorded.

8. Monthly statistics should be entered on a Data sheet.

The RCOG greentop guideline (Hinshaw, 2006) contains a simplified assessment algorithm which encourages a simple classification system of ultrasound appearances into the following:

1. Viable IUP;
2. Non-viable IUP (add type eg incomplete, missed etc);
3. IUP of uncertain viability;
4. Ectopic pregnancy;
5. Pregnancy of unknown location (PUL).

If the embryo has a crown rump length greater than 6mm, with no evidence of heart pulsations, this is highly suggestive of a Missed miscarriage.

When the mean gestational sac is less than 20 mm or the crown rump length is less than 6 mm a repeat examination should be performed at least one week later both to assess growth of the gestation sac and embryo and to establish whether heart activity exists.

If the gestation sac is smaller than expected for gestational age the possibility of incorrect dates should always be considered, especially in the absence of clinical features suggestive of a threatened miscarriage.

In all of the above instances a repeat scan should be undertaken in 7 days. This is necessary to confirm the diagnosis.

All scans should be performed by experienced personnel.

The following individuals are suitably trained to perform ultrasound:

1. Radiographers/midwives/Nurses with the Diploma in Medical Ultrasound (DMU)/PGDip or those who have received training by a recognised Preceptor and Trainer and who have undertaken assessment and judged to be competent by the Lead Preceptor of the local EPU.
2. Radiologists with ultrasound training and experience as recommended by the Royal College of Radiologists.
3. Obstetricians and Radiologists who have completed the joint obstetric ultrasound training scheme of the Royal College of Obstetricians and Gynaecologists and The Royal College of Radiologists, or alternatively who have appropriate experience and training in obstetric ultrasound.

Guidelines for Ultrasound Scanning

RCOG Criteria [1]

If the gestation sac has a mean diameter greater than 20 mm, with no evidence of an embryo or yolk sac, this is highly suggestive of a missed miscarriage.

References
All personnel should have appropriate peer review of their ultrasound practice. **Information should be recorded including:**

1) number of sacs and mean gestation sac diameter,
2) regularity of the outline of sac,
3) presence of haematoma,
4) presence of a yolk sac,
5) presence of a fetal pole,
6) CRL measurement (mm),
7) presence of fetal heart pulsation,
8) extra uterine observations – ovaries, adnexal mass, fluid in the P.O.D.

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**Ultrasound Features of Early Pregnancy**

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Anatomical landmarks</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks 2 days</td>
<td>Eccentrically placed gestational sac with GSD 23 mm</td>
<td>May represent pseudosac 10-20% of ectopic pregnancies have an intrauterine pseudo GS</td>
</tr>
<tr>
<td>5th week</td>
<td>DDS</td>
<td>Results from approximation of decidua capsularis and decidua vera. May be present in one third ectopics</td>
</tr>
<tr>
<td>5th week</td>
<td>GSD 5 mm</td>
<td>Confirms IUP Large YS &gt; 10 mm – poor prognosis.</td>
</tr>
<tr>
<td></td>
<td>Yolk sac (YS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Size varies from 3-8 mm (average 5 mm)</td>
<td></td>
</tr>
<tr>
<td>6th week</td>
<td>GSD 10 mm</td>
<td>Confirms IUP Confirms viability (97% of embryos with CA have a normal outcome)</td>
</tr>
<tr>
<td></td>
<td>Embryo 23 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac activity (CA)</td>
<td></td>
</tr>
<tr>
<td>7th week</td>
<td>GSD 20 mm</td>
<td>GS &gt; 20 mm, if no YS – poor prognosis</td>
</tr>
<tr>
<td></td>
<td>Head and trunk distinguishable</td>
<td></td>
</tr>
<tr>
<td>8th week</td>
<td>GSD 25 mm</td>
<td>GS &gt; 25 mm, if no embryo – poor prognosis</td>
</tr>
<tr>
<td></td>
<td>Head size ~ YS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limb buds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Midgut herniation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rhombencephalon</td>
<td></td>
</tr>
<tr>
<td>9th week</td>
<td>Choroid plexus, spine, limbs</td>
<td></td>
</tr>
<tr>
<td>10 weeks</td>
<td>Cardiac chambers,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stomach, bladder,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skeletal ossification</td>
<td></td>
</tr>
<tr>
<td>11 weeks</td>
<td>Gut returning</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Most structures identified</td>
<td></td>
</tr>
</tbody>
</table>

GSD – Gestational sac diameter
DDS – Double decidual sign
IUP – Intrauterine pregnancy
A Brief Guide to Management of Early Pregnancy Features

<table>
<thead>
<tr>
<th>Ultrasound appearance</th>
<th>Diagnosis</th>
<th>Plan of management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine gestational sac (GS), embryo and cardiac activity (CA)</td>
<td>Viable pregnancy</td>
<td>Back to GP for referral to ANC</td>
</tr>
<tr>
<td>If actively bleeding</td>
<td></td>
<td>Admit for reassurance</td>
</tr>
<tr>
<td>If a significant haematoma noted</td>
<td></td>
<td>Rescan 1 week later</td>
</tr>
<tr>
<td>If &gt; 12 weeks</td>
<td></td>
<td>Check the need for Anti-D immunoglobulin</td>
</tr>
<tr>
<td>GS &lt; 20 mm – no fetal pole</td>
<td>Early gestational sac (EGS)</td>
<td>Rescan 1 week later</td>
</tr>
<tr>
<td>GS &gt; 25 mm – no fetal pole</td>
<td>Empty sac</td>
<td>If any doubt Rescan 1 week later If no change on second scan discuss management (see under management of nonviable pregnancy)</td>
</tr>
<tr>
<td>Crown Rump Length (CRL) &lt; 6 mm CA not demonstrated</td>
<td>Pregnancy of uncertain viability (PUV)</td>
<td>Rescan 1 week later</td>
</tr>
<tr>
<td>CRL &gt; 6 mm CA not demonstrated</td>
<td>Early fetal loss</td>
<td>Rescan 1 week later if in doubt If no change on second scan discuss management (see under management of nonviable pregnancy)</td>
</tr>
<tr>
<td>Empty uterus No adnexal abnormality</td>
<td>Pregnancy of unknown location (PUL) Serum hCG negative (&lt;5); complete miscarriage or never pregnant Serum hCG positive: possible early pregnancy possible ectopic pregnancy miscarriage</td>
<td>No follow-up Repeat serum hCG 48 hours later. Rescan if necessary (see guidelines for β-hCG) Warn of the possibility of ectopic pregnancy. Give possible complete contact numbers to report if any pain.</td>
</tr>
<tr>
<td>Empty uterus Adnexal mass Fluid in Pouch of Douglas (POD) Pain</td>
<td>Ruptured ectopic pregnancy</td>
<td>Admit for assessment: Observation laparoscopy/laparotomy</td>
</tr>
<tr>
<td>Empty uterus Adnexal mass &lt; 3 cm</td>
<td>Unruptured ectopic pregnancy</td>
<td>Conservative/medical management</td>
</tr>
<tr>
<td>No other findings/symptoms</td>
<td></td>
<td>Follow up with serial hCG (see guidelines for hCG assay)</td>
</tr>
<tr>
<td>Endometrium/tissue diameter &lt; 15 mm</td>
<td>Complete miscarriage</td>
<td>Advice follow-up 2 weeks later if bleeding persists</td>
</tr>
<tr>
<td>Endometrium/tissue diameter &gt; 15 mm</td>
<td>Incomplete miscarriage</td>
<td>Discuss management (see guidelines on management of incomplete miscarriage)</td>
</tr>
<tr>
<td>Homogeneous mass within the uterus</td>
<td>Suspect trophoblastic disease Serum hCG assay</td>
<td>Surgical evacuation (see guidelines for trophoblastic disease)</td>
</tr>
<tr>
<td>Pregnancy of Unknown Location (PUL)</td>
<td>Diagnosis by exclusion</td>
<td>Follow up with serial hCG (see guidelines for ‘Inconclusive scan’)</td>
</tr>
</tbody>
</table>

Adequate time should be allowed for women to make decisions. After giving thorough explanation and answers to their queries, allow time in privacy. A quiet room would be more suitable for the woman with her partner/relative/friend. It is imperative to know that patients will vary in their response to information at the time. If not receptive rescans should be arranged for one week. On the other hand if the patient displays clear understanding and wishes to know about further management, appropriate choices are to be given. Women should also be encouraged to go home and ring later with their decision. They should be reassured that it will not be harmful to do so if they prefer to discuss this with their family and contact the unit at a later time.

Women should be informed that the exact cause of a miscarriage can not be determined and in majority of cases it is due to a random or one-time genetic abnormality within the conceptus that leads to a miscarriage [2]. Women should also be told that miscarriages, in general, are not linked to parental chromosomal abnormality. A brief explanation of the outcome of the fertilised ova may be helpful in understanding that not all fertilised ova end up in full term normal pregnancies.

References
Rhesus Anti D Prophylaxis

Prophylactic Anti D is not routinely required for rhesus negative with women bleeding below 12 weeks gestation. There is minimal evidence that administering Rh immune globulin for first trimester vaginal bleeding prevents maternal sensitization or development of haemolytic disease of the newborn [2].

Threatened miscarriage

Anti-D Ig should be given to all non-sensitised RhD negative women with a threatened miscarriage after 12 weeks of pregnancy. Where bleeding continues intermittently after 12 weeks' gestation, anti-D Ig should be given at 6-weekly intervals (send EDTT to check for anti bodies prior to administering) (RCOG Grade C recommendation).

However it may be prudent to administer anti-D where bleeding is heavy or repeated or where there is associated abdominal pain particularly if these events occur as gestation approaches 12 weeks (RCOG Grade C recommendation). The period of gestation should be confirmed by ultrasound. Review on an individual basis recommended.

Spontaneous miscarriage

Anti-D Ig should be given to all non-sensitised RhD negative women who have a spontaneous complete or incomplete miscarriage after 12 weeks of pregnancy (RCOG Grade B recommendation).

The risk of immunisation by spontaneous miscarriage before 12 weeks' gestation is negligible when there has been no instrumentation to evacuate the products of conception and anti-D Ig is not required in these circumstances (RCOG Grade C recommendation).

Guidelines for Viable Intra-Uterine Pregnancy

Definition: A normally sited gestation sac with clearly identified cardiac activity.

Demonstration of fetal heart activity is generally associated with a successful pregnancy rate of 85-97% [1], depending on the period of gestation.

About 25% of all pregnancies threaten to miscarry.

A threatened miscarriage is one in which:
- the woman bleeds a little from the vagina,
- cervical os is closed,
- there is little abdominal pain and,
- pregnancy is still viable.

All women attending EPAU receive a contact number. Women will go back to GP for referral to ANC via the usual method.

Follow up appointment may be required in the following situations:
1. Significant vaginal bleeding and patient refusing to be admitted.
3. Liquor volume is reduced.
4. Fetal bradycardia.
5. For reassurance at patient's request because of previous miscarriages.
6. After IUCD removal in the EPAU.

The embryonic heart rate

Theoretically, cardiac activity should always be evident when the embryo is over 2 mm. However, in around 5-10% of embryos between 2 and 4 mm, it can not be demonstrated. Perform a follow up scan within one week.

At 6 weeks 60-150 bpm (mean 125 bpm),
6-9 weeks 175 bpm,
Thereafter gradually decreases
14 weeks 160 bpm (approximately).

Bradycardia has been found in pregnancies that subsequently miscarried. However, a single observation of slow heart rate does not necessarily indicate subsequent embryonic death, follow-up is therefore essential.

Comments

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References

Management of Non-Viable Pregnancy

Women feel sensitive about the way we refer to pregnancy loss. As their loss is not out of choice, use of language like termination/abortion can be sometimes offensive to women at this vulnerable time. Hence documentation for management of early pregnancy loss should be worded appropriately.

At all times women should be supported in making informed choices about their care and management. Adequate explanation supplemented with written information should be given. Ample time should be allowed for making a decision and if necessary another appointment arranged.

The grief reaction following first trimester miscarriage can be as profound as after stillbirth.

1. Complete Miscarriage
   Ultrasound scan – Endometrial thickness <15 mm
   It is the morphology rather than the amount of tissue that matters. There may be very little pregnancy tissue giving bright echoes or a large amount of blood showing no echogenicity at all.
   Advise to report if bleeding persists longer than 2/52.

2. Incomplete Miscarriage
   Ultrasound scan – Intrauterine tissue diameter 15-50 mm
   Conservative method should be offered as an option provided the bleeding is not heavy and a rescan arranged 2 weeks later or advice may be given to the women to report if bleeding persisted after 2 weeks.
   Alternatively, medical management may be offered if patient is not willing to wait.
   Surgical evacuation is arranged if a patient has a strong preference.

   Surgical method should be reserved for those who:
   1. make a specific request for it,
   2. change their mind during the course of conservative management,
   3. have heavy bleeding and/or severe pain,
   4. tissue diameter of > 50 mm,
   5. have infected tissue.

   Conservative management of Incomplete Miscarriage has excellent success rate and evidence suggests that it is associated with lower rates of infection than surgical management [1].

3. Missed Miscarriage (empty sac/fetal loss)
   Since the introduction of TVS, 'missed miscarriage' (previously described as 'anembryonic pregnancy', absent fetal echo, 'blighted ovum' in the past) are felt to reflect different aspects or stages of the same clinical process. The absence of a identifiable fetal pole should be referred to as an 'empty sac'.
   A previously identified fetal heart action followed by absence of heart activity should be referred to as a 'fetal loss'.
   There is an approximately 5% chance of this happening after fetal heart action is seen at 7 weeks gestation [Brigham et al. 1998 [3]] and increases with advanced maternal age.
   Following the diagnosis of early pregnancy failure by 2 qualified scanners women should be offered the choices of conservative, medical or surgical methods of miscarriage management. Patient preference is important and should be acknowledged as a determining factor in management decisions.

   Conservative management:
   · Rescan 2-3 weeks later, if necessary follow up with further resscans at 2-weekly intervals.
   · Give patient a contact number.

   Medical management may be offered if patient is not willing to wait.

   Surgical method should be reserved for those:
   • who make a specific request for it,
   • who change their mind during the course of conservative management,
   • where medical management fails.

   The incidence of gynaecological infection after surgical, expectant, and medical management of first trimester miscarriage is low (23%). There are small non-significant differences in haemorrhage rates (< 3%) and surgical evacuation carries a 1% risk of uterine perforation [2]. The RCOG has recently updated their guidelines for early pregnancy loss.

References

Conservative Management of Miscarriage

A significant number of women prefer conservative management and it may be continued as long as the patient is willing, provided there are no signs of infection such as:
   – vaginal discharge,
   – excessive bleeding,
   – pyrexia,
   – abdominal pain.

Conservative management requires:
• Motivation and preparation
• A thorough explanation on:
  o what to expect: the likely amount of blood loss and pain,
  o what analgesics to be taken,
  o what sort of sanitary protection to be used.
• Satisfactory answers to their questions and doubts.
• Reassurance that the risk of infection is negligible.
• A contact number should be available 24 hours to ring if there are any problems such as very heavy loss or severe pain. An adequately informed and reassured patient is less likely to contact for any further advice.
• A follow-up appointment for confirmation that the miscarriage is complete and to assess if she has any pain or bleeding.
• An information leaflet to support verbal explanation.
Success rates are higher with prolonged follow-up. Follow up scans may be arranged at 2 weekly intervals, until a diagnosis of complete miscarriage is made. However if patient requests a surgical or medical method at any stage it should be arranged. At Cardiff, data over a ten year interval has shown that 90% of women miscarry in three weeks time. Only a small percentage of women may go up to 6-8 weeks (AEPU annual meeting lecture, Manchester, 2006).

Medical Management of Miscarriage

The drugs used for medical management of a miscarriage include an antiprogestrone, mifepristone (200 mg) with a prostaglandin such as gemeprost or misoprostol.

The conventional prostaglandin E\textsubscript{1} analogue used for abortion procedures is gemeprost, and is effective in 95% of cases in combination with mifepristone at <63 days of amenorrhoea. The alternative E\textsubscript{1} analogue, misoprostol may be given orally or vaginally and is most effective if administered vaginally (95% versus 87% respectively) [1]. The main advantages over gemeprost are that it does not require refrigeration, it is cheaper and can be administered orally or vaginally.

The MMM has implications for patient safety as it avoids the need for an anaesthetic and surgical instrumentation.

The morbidity in those treated medically was lower than in those requiring surgery (1.7% versus 6.6%) [2].

Contraindications to Medical management

Absolute: adrenal insufficiency, long term glucocorticoid therapy, haemoglobinopathies or anticoagulant therapy, anaemia (haemoglobin < 10 g/dl), porphyria, mitral stenosis, glaucoma, non steroidal anti-inflammatory drug ingestion in previous 48 hours.

Relative: hypertension, severe asthma.

Varying rates of efficacy have been quoted with medical management in non-viable pregnancies. The efficacy is greatest for those pregnancies of less than 10 weeks or with a sac diameter of less than 24 mm (92-94%) [3].

Prostaglandin Regimens

Incomplete miscarriage
• Gemeprost 1 mg vaginally or
• Gemeprost 0.5 mg vaginally or
• Misoprostol 800 ug (4 x 200 ug tabs) vaginally.

Missed miscarriage
• Mifepristone 200 mg orally followed 36-48 hours later by cervagem 1 mg vaginally or
• Mifepristone 200 mg orally followed 36-48 hours later by misoprostol 800 ug (4 x 200 ug tabs) vaginally.

These regimens are unlicensed.

Since progesterone levels are low in non-viable pregnancy mifepristone may be avoided and prostaglandin only administered. Many units use Misoprostol (400 ug PV or PO) alone for medical management of incomplete miscarriage.

Protocol for Medical Management of Miscarriage [4]

• Ensure that the patient has read information leaflet.
• Ask if she has any questions.
• Arrange with gynaecology ward for admission to a private room with toilet facility.
• Obtain written consent for mifepristone and PG ± surgical evacuation.
• Arrange blood tests
  · measurement of haemoglobin concentration and
  · determination of ABO and Rhesus blood groups with screening for red cell antibodies.
• Anti-D immunoglobulin should be given to all non-sensitised Rh negative women undergoing medical evacuation.
• In the case of a pregnancy occurring with an IUD in situ, this devise should be removed before administration of mifepristone.
• Prescribe mifepristone 200 mg orally.
• Arrange admission 48 (36-72) hours after mifepristone administration.
• Inform the patient regarding the length of stay on the ward. Observe for three – six hours after administration of prostaglandin and discharge if clinically well.
• Women with gestation:
  · < 9 weeks on scan have only one insertion of misoprostol 800 micrograms vaginally. Misoprostol tablets are administered vaginally by the woman or clinician. If miscarriage has not occurred 4 hours after administration of misoprostol a further dose of misoprostol 400 micrograms may be administered orally or vaginally.
  · > 9 weeks on scan can have a maximum of four further doses of misoprostol 400 micrograms at 3-hourly intervals, vaginally or orally depending on the amount of bleeding and patient's preference.
• Prescribe PG (Mifepristone 800 µg tablets/Cervagem 1 mg) vaginally and Metronidazole 1 G rectally on the Drug chart.
• Prescribe Doxycycline 100 mg bd for 7 days with co-dyramol 2 tabs qds for one week to take home after the procedure.
• Inform that in case of heavy bleeding ERPC may be required and therefore she should be prepared to stay overnight if necessary.
• Women may or may not pass POC while on the ward. They should be advised of what to expect when they go home and not referred to EPAU for a scan before their follow up appointment as most of them would miscarry at a later stage after discharge from the hospital.
• Any products that are obtained should be sent for histology examination. The reasons are:
  + What sort of sanitary protection to be used.
  + What analgesics to be taken,
  + What to expect and the likely amount of blood loss,
+ Medical management of non-viable pregnancy,
  - Admission to gynaecology ward,
  - Medical management of non-viable pregnancy,
  - What to expect and the likely amount of blood loss,
+ Infection rates after expectant, medical and surgical management are not significantly different and are reassuringly lows.

Have a unit protocol for admission system with a patient pathway clearly described.
Give the patient information on admission procedure including appropriate patient information leaflet(s).
Explain the surgical procedure and obtain written consent with Doctor familiar with procedure. Mention rare anaesthetic and uncommon surgical risks involved such as uterine perforation (1%), cervical tears, intraperitoneal trauma (0.1%), intrauterine adhesions, haemorrhage and infection.
Arrange for measurement of haemoglobin concentration and determination of AB0 and Rhesus blood groups. Anti-D immunoglobulin should be given to all non-sensitised Rh negative women undergoing surgical evacuation.
All at risk women (usually women under the age of 25 years) undergoing surgical evacuation for miscarriage should be screened for Chlamydia trachomatis.
Alternatively, prescribe prophylactic doxycycline 100 mg orally twice daily for seven days and Metronidazole 1 G rectally at the time of surgical evacuation as per the local protocol.
Ensure that products of conception are seen at evacuation.
The RCOG study group [3] recommended that all tissue obtained at a surgical evacuation for miscarriage should be sent for histology examination. The reasons are:
  1. to diagnose molar pregnancy,
  2. to exclude ectopic if chorionic tissue is found on histology.
A follow-up appointment is usually not required after a surgical evacuation.
Give patient information on "What you may need to know after a miscarriage". There should be information on counselling if required in the future.

Management of Early Gestational Sac
At 4+2 weeks blastocyst measuring 1.5-2 mm is recognisable as an early gestational sac. The appearance of an early gestational sac (EGS) is the earliest reliable sign of pregnancy. The ability to demonstrate a true intrauterine gestational sac practically excludes an ectopic pregnancy since concurrent intrauterine and extratubal pregnancies are rare.
When a gestational sac-like structure is located within the uterus, its relationship to the endometrial cavity is carefully studied.

References

Surgical Evacuation of Non-Viable Pregnancy
Surgical evacuation should be preferably managed on a day case basis unless there is heavy bleeding when the patient should be admitted to Gynaecology ward.

Surgical Evacuation of Non-Viable Pregnancy
Surgical evacuation should be preferably managed on a day case basis unless there is heavy bleeding when the patient should be admitted to Gynaecology ward.

Association of Early Pregnancy Units
Ultrasound features of EGS

- It is seen as an anechoic structure with an echogenic rim.
- It is eccentrically placed i.e. it remains within a thickened decidua on one side of the uterine cavity.
- It is typically located in the fundus on the posterior wall.
- GSD is a useful indicator of GA before CRL measurement is available.

The gestational sac in such instances should be distinguished from the pseudosac that occurs in ectopic pregnancy. The pseudogestational sac may result from an ectopic as well as fluid or blood collection in the uterine cavity and it represents the endometrial cavity itself.

Management Protocol

EGSs need to be differentiated from an inconclusive scan result.

- Follow up scan is arranged in a week if confident or in 3 days to assess growth of sac if uncertain of the diagnosis.

A healthy gestational sac grows by 1.2 mm/day.

A yolk sac will usually be visible at next scan in a normal pregnancy.

Following up every early gestational sac with serial measurements of hCG leads to increased patient anxiety and wastage of resources.

There is no risk of missing a complication in this group as they are all followed up until an embryo with a heart beat is seen or a miscarriage is diagnosed.

Guidelines for hCG

Understanding hCG measurements

Urine Measurements

The urine test is simple and reliable enough to be used routinely to establish whether or not a woman is pregnant. A rapid and simple test should be available in the unit.

Serum Measurements

Measurement of hCG in Serum, permits more accurate quantification which may be useful in the following [1]:

1. Screening in women at high risk of ectopic pregnancy.
2. Determining the appropriate treatment for women with suspected ectopic pregnancy.
3. Monitoring during expectant management or medical management of women with ectopic pregnancy.

Serum hCG levels double approximately every two days in early (<8 weeks) normal intrauterine pregnancy; a lesser increase (<66% over 48 hours) is associated with ectopic pregnancy and miscarriage [2].

To find out whether or not a pregnancy is normal or pathological, the two useful clinical concepts of hCG measurement are the hCG doubling time and the discriminatory hCG level.

hCG doubling time

It refers to the time taken for the hCG level to double its original value. A hCG value of <5 IU/l is considered to be the non pregnant value.

The doubling time is particularly useful in early pregnancy i.e. before 5.5 weeks or when the serum hCG level is <5000 IU/l. As pregnancy progresses the doubling time also lengthens.

However 15% of normal pregnancies will have abnormal doubling time and 13% of ectopic pregnancies will have a normal doubling time [3].

Caution

1. In multiple pregnancies the level of hCG on D2 would be a little higher, requiring an extra two or three days for a sac to become visible.
2. The possibility of a heterotopic pregnancy should be kept in mind (1 in 3000-4000 of spontaneous conceptions and 1%-3% of assisted conceptions).

Discriminatory hCG level

It refers to a defined level of hCG above which the gestational sac of an intratuterine pregnancy should be visible on ultrasound. In women with an hCG result above the discriminatory level, but absence of an intratuterine gestational sac on ultrasound, ectopic pregnancy is a distinct possibility.

With the use of high resolution transvaginal ultrasound the discriminatory level has been reported to be around 1000 IU/l IRP [4]. However the American Fertility Society suggested that in practice the level ought to be around 2400 IU/l.

The discriminatory level may vary in different units and depends on three factors:

1) hCG assay,
2) quality of ultrasound,
3) the experience of the person performing the ultrasound.

It usually lies between 1000-2400 IU/l.

A diagnosis of ectopic pregnancy is more likely whenever intrauterine pregnancy is not detected by ultrasound at serum hCG concentration above 2400 IU/l.

References

Association of Early Pregnancy Units

Guidelines on Management of Pregnancies of Unknown Location (PUL)

Definition
No evidence of an intrauterine or extrauterine pregnancy on transvaginal ultrasound scan (TVS) in women with a positive pregnancy test.

Initial Assessment
- Clinical history:
  - the presence of risk factors for ectopic pregnancy.
- Clinical signs.
- TVS.
- Serum hCG.

Give appropriate information to patient. Explain the need for further follow up.

Follow up
- Close surveillance with Serum hCG measurements every 2-3 days.
- See guidelines for hCG.
- Repeat TVS when serum hCG >1000 IU/l (see Discriminatory hCG level on previous page) to look for an IUP or an ectopic otherwise.
- Provide support.
- Follow up until:
  - Intrauterine pregnancy identified
  - Ectopic pregnancy diagnosed
  - Levels of serum hCG spontaneously decrease (failing PUL).

Depending on the quality of the ultrasound service provided, anything between 10 and 30% of pregnancies of unknown locations will subsequently be diagnosed as an ectopic pregnancy.

Management Protocol for Inconclusive Scan Result after the Initial Visit to EPU using Serum hCG and TVS

<table>
<thead>
<tr>
<th>hCG IU/l</th>
<th>Ultrasound</th>
<th>Pattern of change of hCG level after 48 hours</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1000</td>
<td>No intrauterine sac No Adnexal mass No fluid in POD No symptoms</td>
<td>hCG rise &gt; 66% or doubled</td>
<td>If hCG &gt; 1000 repeat ultrasound or If hCG &lt; 1000 repeat hCG</td>
</tr>
<tr>
<td>&gt; 1000</td>
<td>No intrauterine sac</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. No adnexal mass No fluid POD No symptoms

A. Falling hCG

Serial hCG levels until hCG < 20

B. Rising or plateauing hCG x 3

Diagnosis: Ectopic or PUL

Laparoscopy (if symptomatic) or Methotrexate (if asymptomatic)

2. Suspicious adnexal mass < 3 cm No fluid POD Asymptomatic

A. Falling hCG

Serial hCG levels until hCG < 20

B. Rising or plateauing hCG x 3

Diagnosis: Ectopic or PUL

Laparoscopy with D&C or Methotrexate

3. Ad. Mass > 3 cm or Fluid POD or Symptomatic

A. Falling hCG

Serial hCG levels until hCG < 20

B. Rising or plateauing hCG x 3

Laparoscopy

> 2400 No intrauterine sac Adnexal findings ± Asymptomatic

Fluctuating x3 Diagnosis: Ectopic or PUL

Laparoscopy or Methotrexate

Falling hCG: Diagnosis
- Early miscarriage or Pregnancy of Unknown Location – resolving
- With bleeding: Miscarriage
- Ectopic pregnancy PUL – Resolving
- Normal intrauterine pregnancy

Likely diagnosis:
- No bleeding: Normal intrauterine pregnancy
Possible Algorithm for Management of Pregnancies of Unknown Location

1. **Positive urinary pregnancy test**
   - **Transvaginal ultrasound scan**
     - **Pregnancy of unknown location**
       - **Haemodynamically stable**
         - **Pain free**
           - **Expectant management**
             - *Serum hCG levels at 0 and 48 hours*
               - > 66% increase in serum hCG 0-48 hours
                 - ? Intra-uterine pregnancy
                   - Rescan one week to confirm pregnancy location
                 - < 66% increase or < 15% decrease in serum hCG 0-48 hours
                   - ? Ectopic pregnancy
                     - PUL
                       - Management as clinically indicated
                         - Repeat hCG now and 48 hours later
                           - If no pregnancy seen on repeat scan and suboptimal rise in hCG consider methotrexate
       - **Pain**
         - **Serum hCG**
           - Consider laparoscopy
         - **Serum hCG**
           - Consider laparotomy
       - **Haemodynamically unstable**
         - **Pain**
           - **Serum hCG**
             - > 15% decrease in serum hCG 0-48 hours
               - ? Failing PUL
                 - Repeat serum hCG in one week to confirm failing
               - < 66% increase or < 15% decrease in serum hCG 0-48 hours
                 - ? Intra-uterine pregnancy
                   - Rescan one week to confirm pregnancy location
                 - < 66% increase or < 15% decrease in serum hCG 0-48 hours
                   - ? Ectopic pregnancy
                     - PUL
                       - Consider weekly hCG monitoring until < 15 IU/L

Algorithm

**TVS**
- Inconclusive result (no evidence of IUP or EP)
  - **Serum hCG measurements every 2-3 days**
    - **Falling**
      - Complete miscarriage
      - No further scans are necessary
      - Follow up until hCG < 20 IU/L
    - **Rising (doubling)**
      - Repeat TVS when hCG > 1000 IU/L
      - IUP
      - No further hCG assays
      - Rescan in one week
  - Suboptimal rise/plateauing/falling slowly after 2-3 measurements

Key:
- IUP Intrauterine pregnancy
- EP Ectopic pregnancy
- PUL Non-viable IUP
Guidelines for Management of Ectopic Pregnancy

Incidence: Ectopic pregnancy affects 1 in 80 pregnancies. In the EPAU population the incidence is 3%. Ectopic pregnancy can be a devastating experience.

Women have to cope with:
- the loss of a baby
- the possible loss of fertility and
- the possible loss of their life.

The psychological impact is not to be overlooked. The emotional as well as the clinical needs of individual women should be assessed and sensitively dealt with.

The fallopian tube is the most common site accounting for nearly 95% of ectopic pregnancies. Other possible sites of an ectopic pregnancy are, interstitial (2%), cervical (0.1%), ovarian (0.01%), caesarean section scar or abdominal (rare). An abdominal ectopic pregnancy may be primary or secondary resulting from a tubal miscarriage.

RISK factors are present only in 25%-50% of patients with an ectopic pregnancy. They include a history of:
- previous pelvic inflammatory disease,
- tubal surgery,
- previous ectopic pregnancy,
- infertility,
- assisted reproductive technology,
- intrauterine contraceptive device.

Smoking and a maternal age > 40 years are also associated with an increased incidence of ectopic pregnancy.

The diagnostic performance based on the combined use of transvaginal sonography (TVS) and serum hCG measurement reaches sensitivities and specificity range 95%-100%.

Patients who have had previous ectopic pregnancies or are at risk of ectopic pregnancy should be advised to present early, at 6 weeks, in subsequent pregnancies for confirmation of uterine pregnancy [2].

Symptoms
- Amenorrhoea (not universal).
- Vaginal bleeding.
- Lower abdominal pain.
- Faintness/dizziness.
- Shoulder tip pain.
- Gastrointestinal symptoms – diarrhoea or pain on defecation.

Signs
- Lower abdominal tenderness.
- Adnexal tenderness and/or mass.
- Cervical excitation.
- Shock/Collapse.

The clinical presentation and natural course of an ectopic pregnancy are unpredictable.

It is important to have a high index of suspicion for ectopic pregnancy, because the patient may not be symptomatic until rupture occurs, or on the other hand the patient may experience vague abdominal pain and/or vaginal bleeding.

Diagnosis

Ultrasound features

Like any pregnancy an ectopic pregnancy too has a natural history of evolution, hence the ultrasound findings depend on the developmental stage at the time of examination.

Almost all ectopic pregnancies occur in the fallopian tube. Ultrasound features suggestive of ectopic pregnancy are a combination of uterine and adnexal findings:

Uterine
- An empty uterus.
- Variable degree of thickening of endometrium.
- A thin endometrium may exclude the possibility of an early intrauterine pregnancy as it is not compatible with an ongoing early implantation.
- An intratubal pseudosac – mere collection of variable amount of fluid within uterine cavity, is found in approximately 5% of all ectopic pregnancies.

Adnexal
- A hyperechogenic tubal ring (‘doughnut’ or ‘bagel’ sign) is the most common finding on scan, probably due to early scanning.
- A mixed adnexal mass – either tubal miscarriage or tubal rupture.
- An ectopic sac with a yolk sac or an embryo with or without a heart beat.
- Fluid in the Pouch of Douglas.

The corpus luteum may be present on the ipsilateral side in 85% of cases.

Management

In the absence of any diagnostic features on ultrasound scan (inconclusive scan result) serial hCG assay are performed.

If the patient is in significant discomfort she should be admitted to the ward. If she is clinically stable with no discomfort she may be allowed home to return for follow up. Direct contact number for the emergency ward should be given and the patient asked to attend at any time if her condition deteriorates.

Serum hCG assay

An ectopic pregnancy is more likely when the serum hCG is more than 1000 IU/l. However in the absence of any pain, hCG is to be repeated in 48 hours time.

If the hCG is falling it is suggestive of a resolving intra or extratubal pregnancy. The rate of fall of hCG tends to be slower in ectopic pregnancy than with complete miscarriages. (see guidelines on serum hCG assay).

A serum hCG level that is increasing or has plateaued may either show an ectopic pregnancy at subsequent scan or remain as a PUL.

Transvaginal ultrasound and quantitative assay of serum hCG not only play a role in the diagnosis of an ectopic preg-
nancy but also in determining the management options in a particular patient.

- Expectant management.
- Medical management.
- Surgical management.

Either hysteroscopic or open
  a. salpingotomy,
  b. salpingectomy (48 hours later, HCG should be <35% of preop level).

Both the hCG levels and the patterns of change of hCG are helpful in constructing a plan for ectopic pregnancy. The clinical picture should always be considered with hCG measurements.

A Guide to Choosing the appropriate treatment based on hCG Measurements and the expected Serial hCG patterns in the follow-up of ectopic pregnancy

<table>
<thead>
<tr>
<th>hCG level</th>
<th>Method of Treatment</th>
<th>Expected hCG pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low &lt; 1000IU/l</td>
<td>Expectant management</td>
<td>Steady downward trend</td>
</tr>
<tr>
<td>&lt; 1000 IU/l</td>
<td>Medical treatment</td>
<td>There may be an initial rise of hCG</td>
</tr>
<tr>
<td>Fluctuating 1000-3000 IU/l</td>
<td>Salpingectomy</td>
<td>Repeat after 1 week</td>
</tr>
</tbody>
</table>

**Expectant Management of Ectopic Pregnancy**

Not all ectopic pregnancies progress and pose a risk to the mother. Spontaneous resolution of tubal ectopic pregnancies has been well documented in a number of reports.

**Selection Criteria for Expectant Management**
1. absence of clinical symptoms,
2. no sign of rupture or intraperitoneal bleeding,
3. absence of haemoperitoneum,
4. a tubal mass of less than 2 cm,
5. no fetal parts,
6. serum hCG concentrations below 1,000 IU/l and declining progressively [3].

The success rate for a spontaneous resolution was 88% when the initial hCG level was <2000 IU/l [4] but only 25% at levels >2000 IU/l [5].

The risk of rupture in a woman with an ectopic exists until the hCG level has fallen to <10 IU/l. It often involves frequent hospitalisation and/or follow up. Both the physician as well as the patient must be well motivated to accept the long recovery time.

**Follow-up:** Monitor serum hCG levels every 2-3 days until less than 20IU/l, and rescan when required.

**Medical Management of Ectopic Pregnancy**

Many agents including prostaglandins, RU-486, potassium chloride and actinomycin-d have all used for the medical management of ectopic pregnancy. However the most commonly used drug is methotrexate. A single injection of methotrexate is well tolerated and is effective. Published studies have shown a success rate varying from 52 to 94% for single dose methotrexate.

**Systemic Methotrexate Treatment in Ectopic Pregnancy**

Methotrexate is a folic acid-antagonist (anti-metabolite) which prevents the growth of rapidly dividing cells by interfering with DNA synthesis. It can be administered systematically (IV, IM or orally). However, it is most commonly given according to a single-dose protocol, which involves a single intramuscular dose of 50 mg/m². Alternatively it can be given according a multiple dose regimen with alternate day administration of intramuscular methotrexate and folinic acid rescue.

**Inclusion Criteria**
1. Haemodynamically stable,
2. Indications: Unruptured tubal or other ectopic pregnancy (diagnosed with serial hCG and TVS). Persistent trophoblast after salpingotomy.
3. An ectopic pregnancy with serum hCG less than 3,000 IU.
4. An ectopic pregnancy with serum hCG value less than 1,000 IU/l should have repeat serum hCG within 48 hours if the patient remains haemodynamically stable.
   • The treatment should begin if the levels are plateauing.
   • If the levels are rising one must exclude intratuterine pregnancy before starting treatment.
5. Normal LFT's, U & E's, and FBC.

**Exclusion Criteria**
1. If there is any evidence of intraperitoneal haemorrhage i.e. haemoperitoneum on TVS.
2. Any hepatic dysfunction, thrombocytopenia (platelet count < 100 000), blood dyscrasia (WCC < 2000 cells cm³).
3. Difficulty or unwillingness of patient for prolonged follow-up (average follow-up 35 days).
4. Ectopic mass >3.5 mm.
5. The presence of cardiac activity in an ectopic pregnancy.
6. Women on concurrent corticosteroid therapy.

**Treatment Protocol**
1. Discuss options for management – expectant/surgical/medical.
2. Satisfy eligibility and exclusion criteria.
3. Counsel the patient and explain treatment protocol.
   - Give information leaflet.
4. Take height and weight.
5. Prescribe Methotrextate.
6. Organise base line blood tests, FBC, blood group, LFTs and U&Es.
7. The prescription with the height and weight documented on it is sent to Pharmacy to make up the drug.
8. Check blood results, prescribe anti-D immunoglobulin if Rhesus negative.
9. Methotrexate is given intramuscularly in buttock or lateral thigh. The empty syringe or needle should be placed in a separate Sharp Safe, labelled "Cytotoxic waste for special incineration".
10. Rest up to one hour. Check for any local reaction. If local reaction noted consider anti-histamine or steroid cream (very rare).
11. Arrange follow-up in EPAU.

Single – Dose Regimen

<table>
<thead>
<tr>
<th>Day</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Serum hCG, FBC, U&amp;Es, LFTs, G&amp;S</td>
</tr>
<tr>
<td>1</td>
<td>Serum hCG Intramuscular methotrexate 50 mg/m²</td>
</tr>
<tr>
<td>4</td>
<td>Serum hCG</td>
</tr>
</tbody>
</table>
| 7   | Serum hCG, FBC, LFT  
   2’d dose of methotrexate if hCG decrease < 15% day 4-7  
   If hCG decrease > 15% repeat hCG weekly until < 12 U/l |

Multiple – Dose Regimen

<table>
<thead>
<tr>
<th>Days</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 1, 3, 5</td>
<td>Serum hCG, FBC, U&amp;Es, LFTs, G&amp;S</td>
</tr>
<tr>
<td>2, 4, 6</td>
<td>Serum hCG Intramuscular methotrexate 1 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Serum hCG Intramuscular folic acid 0.1 mg/kg</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Continue until hCG decreased &gt; 75% in 48 hours or 4 doses of methotrexate given</td>
</tr>
</tbody>
</table>

Information for Clinician

1. Up to 75% of patients may complain of pain on days 3-7 (thought to be due to tubal miscarriage).
2. hCG levels may initially rise days 1-4 (up to 86% of patients).
3. Mean time to resolution is 35 days.
4. A second dose of Methotrexate may be given at 7 days if hCG levels fail to fall by more than 15% between day four and day seven. (327% in published literature)14% of medically treated women will require more than one dose of methotrexate).
5. Risk of tubal rupture is 7% and the risk remains while there is persistent hCG.
6. Folic acid rescue is not required for the single dose regime.
7. Avoid vaginal examination. TVS may be undertaken during first treatment week or subsequently if clinically indicated.
8. TVS should be used to monitor completeness of resolution of an ectopic pregnancy after hCG values are normalised [3].
9. Ovarian cysts may be found in the post treatment phase, which undergo spontaneous resolution.

Information for patients

1. Medical treatment for ectopic pregnancy is now well established, and approximately 90% of patients do not require further surgery. Methotrexate is used for a variety of clinical conditions, e.g. psoriasis, as well as for malignancies.
2. Prolonged follow-up is required with blood tests until serum hCG level is below 20 ii/L.
3. A further dose of methotrexate may be necessary.
4. Three quarters of women experience abdominal pain following treatment, which is due to the drug acting on tubal pregnancy. It usually occurs on days 3-7.
5. Pregnancy should be avoided for 3 months after methotrexate has been given, because of a possible teratogenic effect – advice should be to use a reliable barrier or hormonal contraception (RCOG).
6. Side effects of the drug are minimal but may include nausea, vomiting and stomatitis.
7. Maintain ample fluid intake.
8. Avoid alcohol or folic acid containing vitamins during treatment.
9. Avoid sexual intercourse until resolution of the ectopic pregnancy.
10. Avoid exposure to sunlight.

Outcome

- 90% successful treatment with single dose regime.
- Recurrent ectopic pregnancy rate 10-20%.
- Tubal patency approximately 80%.

References

Surgical Management of Ectopic Pregnancy

Laparoscopy

**Advantages**
- Shorter hospital stay (1-2 days).
- Significantly less blood loss.
- Less adhesions formation.
- Lower analgesic requirements.
- Quicker post operative recovery time.
- Recurrent ectopic pregnancy rate lower (5%) than after laparotomy (16.6%).
- Subsequent intrauterine pregnancy (IUP) rate better (70%) than after laparotomy.

**Disadvantages**
- Increased risk of bowel/vascular damage.

A laparoscopic approach is superior to a laparotomy in terms of recovery from surgery.

Laparotomy is to be preferred
- in cases with haemorrhagic shock,
- where a surgeon has inadequate experience of operative laparoscopy,
- if lack of equipment and instruments,
Do what is safe in the circumstances.

Salpingectomy vs Salpinagotomy

In a meta-analysis of nine good quality comparative studies:
- There was no significant difference in the subsequent IUP between salpingotomy and salpingectomy groups (53% v 49.3%).
- The recurrent ectopic pregnancy rate was higher after salpingotomy (15%) than after salpingectomy (10%).
- Persistence of trophoblast was noted in 4.8% to 11% of salpingotomy cases, hence need to monitor hCG post-operatively.
- In contrast, almost no cases of persistence followed salpingectomy. Following salpingectomy, there is no need to measure hCG in the post-operative period.
In the presence of a healthy contralateral tube there is no clear evidence that salpingotomy should be used in preference to salpingectomy.

Laparoscopic salpingotomy should be considered as the primary treatment when managing tubal pregnancy in the presence of contralateral tubal disease and the desire for future fertility [1].

Discuss treatment with the patient and options of conserving or removing the tube.

**Recommendations arising from the 33rd RCOG Study Group [2]**

No. 26 At laparoscopy for ectopic pregnancy, precise documentation of the state of the pelvis, with particular emphasis on the affected and contralateral tube and ovaries, should be undertaken to determine prognosis of future fertility.

No. 27 The definitive procedure undertaken at surgery (removal of the ectopic; salpingotomy; unilateral salpingectomy; bilateral salpingectomy) should be determined by the reproductive aspirations of the patient, her reproductive history, the state of the pelvis and the availability of assisted conception services.

No. 28 Fimbrial evacuation (milking) of ectopic pregnancy from the fallopian tube should not be done as it predisposes to persistence of tubal pregnancy.

Follow-up regime after Salpingotomy

While trophoblast remains in the tube it has a capacity to rupture.
- Follow-up at weekly intervals until serum hCG level is <5.
- If hCG level is rising or plateauing consider further treatment with Methotrexate or surgery if hCG levels >5 000.

Suturing the salpingotomy lesion provides no benefit.

Outcome after Conservative Surgery in Women with One Tube

- Recurrent ectopic pregnancy rate 20.5%.
- IUP rate 54%.

Conservative surgery may be appropriate but only if the patient is aware of the risk involved. Salpingectomy followed by IVF is an alternative therapy in such cases.

**References**


Management of Ruptured Ectopic with Collapse

- ABC of resuscitation.
- Get help; call senior SPR on call and anaesthetist.
- Site two IV lines (at least 16 g), commence IV fluids (crystalloid), give facial oxygen and insert indwelling catheter.
- Send blood for FBC, Clotting screen and cross-match at least 4 units of blood.
- Arrange admission and laparotomy.
- Continue fluid resuscitation and ensure intensive monitoring of haemodynamic state whilst awaiting transfer to theatre.
- Do not wait for BP and pulse to normalise prior to transfer.
- Pfannensteil incision, locate tube directly and clamp.
- Salpingectomy and wash out abdomen.
• Assess bloods consider CVP/HDU discuss with anaesthetist.
• Record operative findings including the state of the remaining tube.
• Anti-D immunoglobulin to be given to Rh negative women.

Unusual Types of Ectopic Pregnancy
Ultrasound features of non-tubal pregnancies and their management have been well documented [6-9].

<table>
<thead>
<tr>
<th>Ectopic pregnancy</th>
<th>Ultrasound features</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterotopic</td>
<td>An intrauterine pregnancy and a concurrent ectopic pregnancy</td>
<td>Conservative/Methotrexate</td>
</tr>
<tr>
<td>Interstitial</td>
<td>Bright echogenic tropheoblastic tissue or gestational sac (GS) in the cornual region</td>
<td>Conservative/Methotrexate</td>
</tr>
<tr>
<td></td>
<td>GS located away from the lateral margin of the myometrium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thinning of the myometrial mantle</td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>Intra-cervical GS</td>
<td>Conservative/Methotrexate</td>
</tr>
<tr>
<td></td>
<td>Thick trophoblastic ring</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No distortion of endometrium and cavity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Closed cervical canal in continuity with the endometrial cavity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Internal os not funnelled (should be differentiated from isthmico-cervical pregnancies that are implanted low in the uterus cavity, above the cervical canal)</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>Hyperechogenic mass within the ovary</td>
<td>Conservative/Methotrexate</td>
</tr>
<tr>
<td></td>
<td>Subcapsular bleeding (must be distinguished from a haemorrhagic cyst)</td>
<td></td>
</tr>
<tr>
<td>Caesarean scar</td>
<td>Uterine cavity is empty</td>
<td>Methotrexate/dilatation and cervical packing</td>
</tr>
<tr>
<td></td>
<td>GS implanted into the scar</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative “sliding sign” [10]</td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>Empty uterus separate from the fetus</td>
<td>Methotrexate/Laparotomy</td>
</tr>
<tr>
<td></td>
<td>Fetus seen without the surrounding uterine mantle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unusual location of the placenta</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extremely low amount of liquor</td>
<td></td>
</tr>
</tbody>
</table>

References

Guidelines on the Management of Women with Recurrent Miscarriage

Definition: Recurrent miscarriage (RM) is defined as loss of three or more consecutive pregnancies although most authorities would accept two consecutive fetal losses.

Prevalence: Based on an incidence of spontaneous miscarriage of 15%, the risk of RM should be 0.4% – but it is double this at 1%. This suggests that for some couples there is an underlying cause for their RM.
Patients who have suffered consecutive pregnancy losses and have had failed pregnancy despite use of recommended treatments are best referred to designated regional centres (Miscarriage Clinic) for further assessment.

Causes of Recurrent Miscarriage

1. Unknown or Idiopathic

In 50% of cases of recurrent miscarriage no cause is found. Most women who have two or three miscarriages have nothing wrong with them that will cause them to miscarry every pregnancy. Their miscarriages are caused by random factors just as women who miscarry only once. This is the reason why tests and investigations are rarely undertaken before three consecutive miscarriages. Any drug treatment in this group would be empirical. Even at or above the age of forty, there is still a 50% chance of a successful pregnancy [4]. Couples can obtain a predicted success rate for future pregnancy by using the following table:

| Predicted probability of a successful pregnancy by age and previous miscarriage history (95% confidence interval) |
|---|---|---|---|---|---|
| Age (yrs) | Number of Previous Miscarriages | 2 | 3 | 4 | 5 |
| 20 | 92 | 90 | 88 | 85 |
| 25 | 89 | 86 | 82 | 79 |
| 30 | 84 | 80 | 76 | 71 |
| 35 | 77 | 73 | 68 | 62 |
| 40 | 69 | 64 | 58 | 52 |
| 45 | 60 | 54 | 48 | 42 |

2. Genetic and Chromosomal

A high proportion of early miscarriages would be found to have a chromosomal abnormality.

In less than 3% of cases, either the woman or her partner may possess abnormal chromosomes, which they happen to repeatedly pass on to the fetus. This can be tested by taking blood samples from both partners for chromosomal analysis. It usually takes 4-6 weeks to get the results. If a chromosomal abnormality is found in a parent, referral to the correct number are arranged differently.

3. Abnormalities of the uterus (womb) or cervix (neck of the womb)

Abnormalities in the shape of the uterus occur in probably less than 5% of women with recurrent miscarriages. Uterine abnormalities such as a bicornuate uterus (double uterus), unicornuate uterus, septate uterus or fibroid uterus may be detected on detailed ultrasound scan or hysteroscopy (telescopic examination through the vagina and neck of the womb). It is not clear whether there is any benefit in surgical correction of the abnormalities.

Cervical weakness (formerly known as incompetence) may be acquired e.g. from previous surgery or following birth. It causes painless dilatation of the cervix and rupture of the membranes (breaking of waters) in mid pregnancy. It may be detected by transvaginal ultrasound scan in the mid-trimester starting at 14-16 weeks. If the diagnosis is made, a stitch is usually put in the cervix to prevent opening of the cervix.

4. Infection

The continuing emergence of Bacterial Vaginosis as a cause of RM is widely accepted [5]. Rubella (German Measles), Toxoplasmosis, Listeria and Parvovirus are not considered in the causation of recurrent miscarriage.

5. Hormonal

Imbalance of hormones such as progesterone and human chorionic gonadotrophin (hCG) has been suggested as a cause of miscarriage. However there is scientific evidence of benefit from hCG support but no support for injections of progesterone.

Some women with recurrent miscarriage have polycystic ovaries (PCO) in which there are multiple small cysts within the ovary causing an abnormal hormone balance and this may cause recurrent miscarriage by interfering with successful implantation of the fertilised egg. Treatment of PCO includes, metformin, diathermy to ovaries and induction of ovulation.

6. Thrombophilia or blood clotting abnormalities

Normally the blood becomes slightly thicker during pregnancy, but in some women the blood is found to clot more easily due to the presence of certain antibodies called Antiphospholipid antibodies. These blood clots in the placental blood vessels may decrease the blood flow to the baby resulting in miscarriage. Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage. The main types of antiphospholipid antibodies are Lupus Anticoagulant and Anticardiolipin antibodies (IgG & IgM). The association between phospholipid antibodies and recurrent miscarriage is referred to as Antiphospholipid Syndrome (APS). For a diagnosis of APS to be made one should have two positive tests at least six weeks apart, one positive result may be due to viral or other infection. Various treatments are available including low dose aspirin alone (75 mg) or aspirin plus low molecular weight (LMWH) or unfractionated (UFH) heparin.

Management

Individual units may have their own protocols for management of women with RM. The aim is to make all health professionals providing early pregnancy care to be aware of the current approach to this problem.
Preliminary work up

The mainstay of management of these patients is based upon emotional support supplemented by ultrasound scan in early pregnancy, which gives "success rates" of between 70-80% [7, 8].

- Patients should not be subjected to tests without a proper plan of further follow-up and management being outlined.
- It is important for both partners to be aware of what is going to happen, encourage partner's participation.
- Care should be streamlined, and tests should not be merely done to reassure the patient that something is being done.
- Reassure the couple that all known factors for RM will be explored. Give explanation of all the tests before taking blood samples.
- Routine testing for inherited clotting disorders is not recommended.
- Discuss the treatments that are available (it prepares the couple for their further consultation).
- Discuss lifestyle and preconceptual care.
- Encourage them to talk about their fears and anxieties.
- Arrange for a six-week follow-up appointment for the couple to see a specialist.
- Advise to contact their GP for referral to EPAU if they should achieve a pregnancy and arrange an ultrasound scan at six weeks gestation and thereafter fortnightly for maternal assurance until seen in the antenatal booking clinic.

Medical consultation

- In all couples with a history of Recurrent miscarriage cytogenetic analysis of the products of conception should be performed if the next pregnancy fails.
- Routine screening for thyroid and Diabetes in early pregnancy loss is uninformative.
- Give results of the tests.
- Discuss possible treatment options.

Live birth rate in Antiphospholipid syndrome:

- with 75 mg aspirin alone <70%,
- with aspirin and low molecular weight heparin >70%.

- Give detailed information about the treatment regimen that they will need in a future pregnancy:
  - aspirin ± heparin is started as soon as pregnancy is diagnosed,
  - both are continued until delivery and thereafter postnatally for 6 weeks if obese or Caesarean section or previous thrombosis history.
- hCG is recommended for women with oligomenorrhea (periods more than 35 days apart) from the time of positive serum hCG until 12 weeks gestation.

Encourage a healthy diet. Low BMI is associated with a higher rate of miscarriage, while a diet rich in fruit and vegetables has a reduced risk [11].

The Department of Health suggests that all women planning a pregnancy should have 400 pgms of folic acid before pregnancy until approximately 12 weeks gestation.

- It is advisable to avoid close contact with sheep, horses and cattle during lambing, foaling and calving.
- Avoid contact with soiled cat litter – use gloves if necessary.

Further information may be obtained from the Guidelines produced by RCOG & ESHRE [9, 10].

Guidelines for Management of Gestational Trophoblastic Disease

Incidence

Gestational Trophoblastic Neoplasia (GTN) or Disease (GTD) which incorporates Hydatidiform mole, invasive mole, choriocarcinoma, and placental site trophoblastic tumour are rare events with a calculated incidence of 1:714 live births in the UK. There is evidence of ethnic variation of GTN in the UK with Asian women having a higher incidence.
Hydatidiform moles can be subdivided in complete and partial moles based on genetic and histopathological features.

The use of ultrasound in early pregnancy has increased, however diagnosis of complete and partial molar pregnancies' pre evacuation occurs in only in 44% of cases [2]. Therefore cases that are diagnosed on histological examination only several weeks after the miscarriage require careful preparation and sensitive discussion to support and inform the woman.

Ultrasound findings may be described as

<table>
<thead>
<tr>
<th>Ultrasound features in trophoblastic disease</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine cavity filled with homogeneous central echoes and no gestational sac.</td>
<td>Complete mole</td>
</tr>
<tr>
<td>Complex mass with multiple echo free spaces in the placenta. (The ultrasound features of a complete mole are reliable but the ultrasound diagnosis of a partial molar pregnancy is more complex).</td>
<td>Partial molar pregnancy</td>
</tr>
<tr>
<td>Twin sacs, one viable fetus and the other complex mass with cystic spaces.</td>
<td>Twin pregnancy with a viable fetus and mole (complete or partial)</td>
</tr>
<tr>
<td>Ovaries: Soap bubble or spoke-wheel appearance of the ovaries in up to 50% of cases.</td>
<td>Theca lutein cysts secondary to the very high hCG levels</td>
</tr>
</tbody>
</table>

Suspicion of molar pregnancy on ultrasound scan should be explained and supported with an information leaflet from the Miscarriage Association on Hydatidiform Mole. The leaflet provides clear information on the incidence of molar pregnancies, any future risk of recurrence and clearly describes the follow up procedure and any subsequent treatments or investigations that may be required.

A twin pregnancy with a partial mole may proceed after appropriate counselling. However if complications such as preeclampsia and haemorrhage develop, termination of pregnancy may be indicated. The probability of achieving a viable baby is 40% [1].

Management of Care

Surgical evacuation of the uterus is the treatment of choice for suspected complete moles and partial moles with a CRL > 6 mm with no fetal heart movement seen and confirmed by 2 sonographers.

Suction curettage is the method of choice. Medical termination of complete molar pregnancies and cervical preparation prior to suction evacuation should be avoided where possible. The routine use of oxytocic agents remains a cause of theoretical concern due to the potential to embolise and disseminate trophoblastic tissue through the venous system. It is recommended that where possible infusions of oxytocic agents are only commenced on completion of the evacuation [1]. All products of conception obtained from surgical evacuation of the uterus must be sent for histopathological examination.

Pre-op investigations:
- Full Blood Count.
- Group and Save.
- Consider baseline measurement of BhCG.
- Chest X-Ray if symptomatic.
- Thyroid Function Tests only if symptomatic.

Arrange admission for surgical evacuation.

Follow up

Pre-arrange with the woman to provide verbal feedback of histological findings as soon as they are available with the understanding that if molar pregnancy confirmed a Gynaec Outpatient appointment will be made for the following week to answer any queries.

Discuss advice on future pregnancies and contraception:
- The only safe method of contraception is the sheath condom or cap. The use of any hormonal preparation including "the pill" is not recommended until hCG levels have returned to normal.
- Await the all clear from the Regional Screening Centre before trying to conceive. This usually means waiting until the hCG level has been normal for six months or follow up has been completed (whichever is the sooner).

If histology proves positive of molar pregnancy complete the appropriate Regional Screening Centre referral forms or online registration.

Warn the woman that the information sent by the Regional Screening Centre will be very informative but on headed paper from the oncology unit as they co-ordinate the process and provide follow up if required. Remind them that the follow up process is mainly by post and usually does not involve visiting the Specialist Centre.

In cases where there was no indication prior to diagnosis on histology the woman needs to be informed sensitively with a follow up appointment for a consultation to discuss and explain the findings.

Persistent Bleeding

If the woman continues to have persistent vaginal bleeding advice should be sought from the Regional Screening Centre before any surgical intervention.

Incidence of Chemotherapy

Women with persistent GTN should be treated by the Specialist Regional Centre with the appropriate Chemotherapy. The need for chemotherapy following a complete mole is 15% and 0.5% after a partial mole.
References

