Recurrent Miscarriage Guideline

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Key Amendments

Date	Amendment	Approved by
26th January 2019	Documents extended for 3 years	Mr Hughes
14th December 2020	Documents approved for 3 years	Miss Blackwell
22nd July 2022	Appendix 2 added – progesterone use	Miss Blackwell
29th December 2023	Document extended for 6 months whilst under review Owner updated	Alex Blackwell
20th August 2024	Document extended for 6 months whilst under review	Alex Blackwell

Referral criteria ≥ 3 recurrent miscarriages or suspected/known Antiphospholipid Syndrome (APS).

See in specific clinic

History:
- Gestation
- Obs and Gynae risk factors
- PMH: VTE, APS
- FH: VTE
- Previous treatment

Information to patient:
- Rarely find a cause
- Not all causes have a treatment
- Lifestyle changes
- PROMISE: no benefit of Progesterone
- No benefit of clexane/aspirin unless APS
- RCOG Patient leaflet & Cedar Tree counselling

Investigations:
- Antiphospolipid antibodies: lupus anticoagulant
  - Anticardiolipin antibodies (IgM and IgG)
  - Anti-**B**2GP1 (IgM and IgG)
- Thrombophilia screen & FV Leiden (if strong FH or 2nd trimester miscarriages
- FBC, HbA1c, (Prolactin: only if symptoms)
- TSH & TPO antibodies (if abnormal check free T4)
- Pelvic USS (further imaging as needed)
- Send products for karyotyping if ≥3 miscarriage (if abnormal check parents)

APL antibodies positive:
- Repeat in 12 weeks
- Take >6 weeks after a miscarriage

Optimise diabetic & thyroid control

Abnormal karyotype:
- Parental karyotyping
- Refer to BWH genetics team

Abnormal TVUSS:
- Hysteroscopy or laparoscopy
- Renal USS
- ? Septoplasty
- ? Treat fibroids or polyps

2x Positive results = APS
- Treatment: Aspirin and Clexane
- From Positive pregnancy test to decrease the risk of miscarriage (by 54%)

Unexplained / All patients:
- Support and reassurance
- Self referral to EPAU
- USS at 6, 8 and 10 weeks
- Counselling: Cedar Tree 01905 616166 cedartreeworcs@gmail.com
- RCOG Information leaflet

Recurrent Miscarriage Guideline

- A miscarriage is the spontaneous loss of a pregnancy before the fetus reaches viability at 24 weeks. Recurrent miscarriage (RMC) or recurrent pregnancy loss (RPL) is the loss of 3 or more consecutive pregnancies. It affects 1% of couples and underlying risk factors are only found in 50% of cases. Unfortunately the prognosis is no better for those with a prior live birth. The risk of future miscarriage increases with each successive loss, and after 3 consecutive losses is 40%.

Risk factors for Miscarriage:

1. Age.

a) Maternal age: the risk of pregnancy loss is lowest in 20-35 year olds, and then rapidly increases after the age of 40 years. This is due to the decline in the number and quality of the remaining oocytes.

b) Paternal age: especially if ≥40 years and the woman is ≥35 years.

2. Lifestyle.

Age-related risk of miscarriage: (RCOG GTG 17, BMJ 2000)	
12-19 years	13%
20-24 years	11%
25-29 years	12%
30-34 years	15%
35-39 years	25%
40-44 years	51%
≥ 45 years	93%

a) Smoking and caffeine consumption: dose-dependent negative effect.

b) Excessive alcohol consumption: as little as 5 units per week can be toxic to embryos and fetus. Increased risk if >14 units per week.

c) Obesity (BMI >30): strong risk factor for both sporadic and recurrent miscarriage. There is a statistically significant increased risk of 1st trimester (odds ratio 1.2) and recurrent miscarriage (odds ratio 3.5). It is also linked to obstetric complications in the pregnancy.

d) Excessive exercise can have a negative impact.

e) There is no evidence that stress causes pregnancy loss.

3. Antiphospholipid Syndrome (APS).

APS causes inhibition of trophoblastic function and differentiation, activation of complement pathways at the maternal–fetal interface resulting in a local inflammatory response, and thrombosis of the uteroplacental vasculature in later pregnancy.

a) Antiphospholipid antibodies: (present in 15% of women with recurrent miscarriage, verses 2% of the general population)
   - lupus anticoagulant (LA)
   - anticardiolipin antibodies (ACA IgG and IgM)
   - anti-ß$_2$ glycoprotein-I antibodies (IgG and IgM), plus:

b) Vascular thrombosis, or

c) An adverse pregnancy outcome:
   - ≥3 consecutive miscarriages at <10 weeks gestation
   - ≥1 morphologically normal fetus loss >10 weeks gestation
   - ≥1 preterm birth at <34 weeks due to placental disease

4. Inherited thrombophilia.

This causes a hypercoaguable state that leads to thrombosis of the uteroplacental circulation. ESHRE only recommends screening at part of a research trial or if a strong family history exists.

a) Factor V Leiden mutation (activated protein C deficiency): double the risk of recurrent 1st trimester loss, recurrent loss >22weeks and non-recurrent loss >19weeks.
b) Prothrombin gene mutation: double the risk of recurrent 1st trimester loss, recurrent loss <25weeks, late non-recurrent loss.
c) Protein S deficiency: recurrent and non-recurrent loss >22weeks.
d) Methylenetetrahydrofolate mutation, protein C deficiencies and antithrombin deficiencies: no associations.
e) If antithrombin low: consider confirmatory test for antithrombin deficiency (SERPINC1 gene testing at the Regional Genetics Laboratory) and if positive can consider thromboprophylaxis antenatally.

5. Genetic factors.

a) Parental chromosomal rearrangement: In 2-5% of couples with recurrent miscarriage, one partner carries a balanced structural chromosomal anomaly (balanced reciprocal or Robertsonian translocation).
    - Fetus may have an unbalanced chromosomal arrangement, resulting in a miscarriage or live birth with multiple congenital malformations or mental disability.
    - 83% chance of having a healthy child.
    - Long term prognosis is good in carriers of a structural chromosomal abnormality (71% life birth rate in 2 years)
b) Sporadic embryonic chromosomal abnormality (30-57%). A common cause of a sporadic miscarriage, increasing with maternal age, but means a better prognosis for the next pregnancy.
c) Sperm DNA fragmentation: the main cause of DNA damage is oxidative stress and this seems to be exacerbated by smoking, obesity and excessive exercise. Investigation not done on the NHS and no treatment is available other than donor sperm. Sperm selection is not recommended as no evidence of benefit.

6. Anatomical factors.

a) Congenital uterine malformations: present in 1.8-37.6% of women with recurrent miscarriage. Higher incidence of 1st trimester with septate uteri, compared to 2nd trimester miscarriages if arcuate uteri. If untreated, these factors are associated with an increased risk of miscarriage or preterm delivery with only 50% delivering at term.
b) Cervical weakness: linked to 2nd trimester miscarriage.

7. Endocrine factors.

a) Diabetes mellitus: a raised HbA1c in the 1st trimester is associated with an increased risk of miscarriage and fetal malformation.
b) Thyroid screening (TSH and TPO-antibodies) is recommended, followed by free T4 testing if abnormal. There is high prevalence of subclinical hypothyroidism and thyroid autoimmunity with recurrent miscarriage which can be treated if necessary.
    - Thyroid disease: no link if adequately treated.
    - Limited evidence regarding anti-thyroid antibodies.
    - Subclinical hypothyroidism does not increase rates of miscarriage in women with recurrent miscarriage.
c) PCOS: the exact mechanism in recurrent miscarriage is unknown; it may be due to insulin resistance, hyperinsulinaemia, hyperandrogenaemia and especially elevated free androgen levels. The prevalence of PCOS in women with recurrent miscarriage is

about 40%. More evidence is needed regarding the benefit of treatment with Metformin.

d) Hyperprolactinaemia: investigate if symptoms present as treatment may reduce the risk of recurrent miscarriage.
e) Do not test for ovarian reserve, luteal phase insufficiency, LH or androgens; as there is no evidence of link or beneficial treatment.

8. Immune factors.

a) There may be a small association with increased T-helper-1 cytokine response (the production of pro-inflammatory cytokines interleukin 2, interferon and tumour necrosis factor alpha), rather than Th-2 response.
b) There is no evidence regarding human leucocyte antigen incompatibility.
c) Natural killer cells (NK cells): contradictory evidence, some studies suggest differences in the peripheral blood NK cell levels. NK cells are also found in the endometrium and decidua; but their role in human placentation is poorly understood. There are phenotypical and functional differences between peripheral and uterine NK cells; and uterine NK cells cannot be measured (unlike peripheral NK cells). Testing for peripheral NK cells should only be done as part of a research trial.
d) Anti-HY antibodies testing: not recommend. Can consider HLA class ii determination for prognostic purposes if secondary recurrent miscarriage after the birth of a boy, but no treatment options available. Only do as part of research trial.
e) Antinuclear antibodies (ANA): increased prevalence in recurrent miscarriage patients; can consider testing for explanatory purposes as may negatively affect prognosis, but no treatment available.

9. Infective agents.

a) Bacteraemia or viraemia: sporadic, not recurrent miscarriage, therefore TORCH screening should not be done. Bacterial vaginosis in the 1st trimester is a risk for 2nd trimester miscarriage and preterm labour and should be treated, but is not associated with recurrent miscarriage.

10. Environmental toxin exposure.

a) Ionizing radiation, organic solvents, alcohol, mercury and lead. There is a suspected association with hyperthermia.

Investigations:

1. Antiphospholipid antibodies (LA, ACA [IgG and IgM], aß2GP1 [IgG and IgM])
   a) After 2 pregnancy losses and >6 weeks following a miscarriage.
   b) If 1st test positive → repeat in 12weeks to confirm (may be transient positivity due to infection).

2. Inherited thrombophilia screen (if 2nd trimester miscarriage):
   a) Not routinely unless strong family history or as part of a research trial.
   b) Factor V Leiden, prothrombin (factor II) gene mutation, protein S & C.

3. PMH:
   a) HbA1c if Diabetic
   b) TSH and TPO-antibodies (if abnormal, test for free T4)
   c) FBC
   d) Prolactin (only if has symptoms of hyperprolactinaemia)

4. Pelvic USS: detect congenital uterine abnormalities.
    a) If unclear: [3D USS], HSG, hysteroscopy or laparoscopy. (not MRI)
    b) Sonohysterography (SHG) where available may be better than HSG at detecting uterine abnormalities.
    c) If a mullerian uterine malformation detected organise a renal USS.

5. Pregnancy tissue from the 3rd and any future consecutive miscarriages should be sent for cytogenetic analysis for karyotyping.
    a) If an unbalanced structured chromosomal abnormality is found → perform parental blood karyotyping

Management:

1. The couple should be seen together and given supportive care by a specialist with a special interest in recurrent miscarriage. This alone has been shown to result in a better prognosis for future pregnancy, with a 75% success rate, compared with 51% miscarriage rate in next pregnancy for those who do not attend the clinic. Health care professionals should recognize that for the couple this is a significant life event.
    - The aim of the first appointment should be information provision. Patients should be made aware from the start that unfortunately investigations rarely lead to treatment options, and some causes have little or no proven treatment. Give a time scale for investigation results and follow up for discussion of these.
    - They should be provided with written information; RCOG patient information leaflet:
        - https://www.rcog.org.uk/globalassets/documents/patients/patient-information-leaflets/pregnancy/pi-recurrent-and-late-miscarriage---tests-and-treatment-of-couples.pdf
        - Counselling service: Cedar Tree (cedartreeworcs@gmail.com 01905 616166)
    - Base prognosis for future pregnancies on the number of preceding pregnancy losses and female age (Brigham et al).
    - Unexplained recurrent miscarriage: No treatment found to be beneficial.
        - Direct access to the EPAU (telephone no.): USS at 6, 8 and 10 weeks.

2. **Lifestyle advice** for couple: Smoking cessation referral, dietary advice if raised BMI. (GP to refer to dietician if BMI >40). Advice not to take NSAIDs around the time of conception, as this can increase the risk of miscarriage.
    Preconception Folic acid and Vitamin D should be advised, but do not prevent recurrent miscarriage. Antioxidants for men have not been shown to improve outcome.

3. Antiphospholipid Syndrome (APS).

a) Patient to contact EPAU: serial early USS at 6, 8 and 10 weeks.
b) Review in EPAU/ recurrent miscarriage clinic to discuss commencing low dose Aspirin 75mg and LHWH from first positive pregnancy test. This should be continued throughout the pregnancy, stopping the aspirin at delivery, but continuing Clexane until 6 weeks postnatal.
c) Treatment reduces further miscarriage rate by 54% and increases live birth rate, with no adverse fetal outcomes.
d) Even with treatment, pregnancies remain high risk of complications (pre-eclampsia, fetal growth restriction and preterm birth).
e) Side effects: bone density loss associated with LMWH use in recurrent miscarriage is similar to physiological loss in pregnancy.
f) DO NOT USE: corticosteroids or IV immunoglobulin therapy as there is no benefit, and can be associated with significant maternal and fetal morbidity.

Patient weight (kg) or BMI	LMWH: Enoxaparin dose
<50 kg	20mg OD
50-90 kg	40mg OD
91-130 kg	60mg OD
131-170 kg	80mg OD
>170 kg	0.6mg/kg/day

4. Inherited thrombophilia.

a) Patient to contact EPAU: serial early USS at 6, 8 and 10 weeks
b) Do not use antithrombotic prophylaxis as there is no benefit of anticoagulant treatment, unless in the context of research.

5. Abnormal fetal or parental karyotype

- Refer to Clinical Geneticist, and counselling.

a) They will discuss the prognosis for future pregnancies, and provide the opportunity for familial chromosome studies.
b) Reproductive options include prenatal diagnostic tests with IVF, gamete donation and adoption. Preimplantation genetic screening with IVF for women with unexplained recurrent miscarriage does not improve live birth rate (30% verses 50-70% with natural conception).

6. Anatomical factors:

a) Uterine septum: discuss transcervical hysteroscopic resection. Mixed evidence from trials regarding benefit. Some studies suggest decreased pregnancy rate post resection so more evidence is needed.
b) No evidence to support: resection of submucosal fibroids, endometrial polyps or intrauterine adhesions. Although more prevalent, there is no evidence they are associated with recurrent miscarriage or that resection increases the chance of a live birth.
    a. Polyps: consider hysteroscopic resection if >1 cm
    b. Fibroids: some studies suggest benefit of myomectomy for submucous fibroids, but not for subserosal or intramural fibroids.
c) Metroplasty for bicornuate uterus or reconstruction for unicornuate uterus are not recommended as there is no evidence of benefit.

d) Cervical factors: If history of second trimester miscarriage refer to preterm-pregnancy clinic (Dr C. Hillman) for further management and surveillance with serial cervical length scans.

7. Endocrine conditions:

a) DM: Optimise control: aim for HbA1c below 48 mmol/mol (6.5%). Provided this is achievable without causing problematic hypoglycaemia, and recommend 5 mg folic acid
b) Clinical hypothyroidism: Treat with Levothyroxine to reduce maternal and fetal complications. Consider increasing dose of Levothyroxine by 30% as soon as a positive pregnancy test achieved.
c) Subclinical hypothyroidism (TSH >2.5 mIU/l with a normal free thyroxine): conflicting evidence, but treatment may reduce the risk of future miscarriage. Check TSH at 7-9 weeks and treat if hypothyroidism develops.
d) Euthyroid with thyroid antibodies (normal TSH and TPO Ab+): consider treatment with thyroxine (mixed evidence from research trials).
e) PCOS: No treatment has been shown to improve outcome. More evidence is needed regarding whether pituitary suppression before induction of ovulation reduces the risk of pregnancy loss.
f) Treat hyperprolactinaemia with bromocriptine to increase live birth rate. (See Trust Fertility guideline on Prolactin)

Progesterone: The PROMISE Trial

- No evidence of benefit regarding the use of Progesterone with luteal phase insufficiency.
- The PROMISE trial clearly showed that taking progesterone supplements in the first trimester of pregnancy does not improve live birth rates overall in women with a history of unexplained recurrent miscarriage. The live birth rate for women with 3 previous miscarriages at any gestation was 67.9% in the progesterone group (65.8% if ≥3), verses 67.4% in the control group (63.3% if ≥3); a difference which was not statistically significant.
- The subgroup analysis in women with higher order miscarriages (≥4 miscarriages) found a live birth rate of 63.3% in the progesterone group (verses 58.3% in the placebo group), and if 4, 5 or ≥6 miscarriages were looked at individually, there was an increased live birth rate of between 6.4% and 7.4%. Although these figures all suggest a real benefit, again none of these differences were statistical significant; therefore no strong recommendation can be made.
- Progesterone may also be associated harm; an increased risk of hypospadia in male offspring (OR 3.7) was found in one study.
- If Progesterone is to be used the PROMISE trial recommended vaginal micronized progesterone (utrogestan) 400mg BD until 12 weeks.

Do not test for unless as part of research; as no evidence of link or benefit:

- Anti-HY antibodies, HLA, cytokines, NK cells, anti-HLA antibodies, PCOS, fasting insulin, fasting glucose
- Prolactin (unless symptoms), ovarian reserve, luteal phase insufficiency
- Androgens, LH, Homocysteine plasma level
- MRI for uterine malformations

Do not give unless as part of a RCT:

- Aspirin: evidence from the SPIN and ALIFE study showed that there is no benefit and there may even be a slight increase in future miscarriage amongst women whom do not have APS.
- LMWH: in unexplained recurrent miscarriage and inherited thrombophilia, is of no benefit.

- Human chorionic gonadotrophin for luteal phase insufficiency
- Immunotherapy (paternal cell immunization, 3rd party donor leucocytes, trophoblast membranes and IV IgG) Glucocorticoids or intralipid.
- Metformin for women with glucose metabolism defects
- Endometrial scratch: no evidence of benefit
- Lymphocyte immunization therapy: may cause harm.

Referral Criteria for the Recurrent miscarriage Clinic:

1. 3 or more consecutive pregnancies losses
2. Suspected or known APS
3. Suspected or known Inherited thrombophilia
4. Discuss any special circumstances prior to referral

References:

1. ESHRE Early Pregnancy Guideline Development Group: Recurrent Pregnancy loss. July 2017.
2. RCOG GTG No.17. The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage (April 2011, updated February 2017)
3. Clark P et al. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. Blood. 2010 May 27;115(21):4162-7.
4. www.miscarriageassociation.org.uk
5. RCOG Scientific Impact Paper No.26. The Use of Antithrombotics in the Prevention of Recurrent Pregnancy Loss. June 2011
6. https://www.rcog.org.uk/globalassets/documents/patients/patient-information-leaflets/pregnancy/pi-recurrent-and-late-miscarriage---tests-and-treatment -of-couples.pdf
7. Eric Jauniaux et al, On behalf of ESHRE Special Interest Group for Early Pregnancy (SIGEP); Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage. Hum Reprod 2006; 21
8. van Dijk MM. Is subclinical hypothyroidism associated with lower live birth rates in women who have experienced unexplained recurrent miscarriage? Reprod Biomed Online. 2016 Sep 20.
9. J Clin Endocrinol Metab, July 2006, 91(7):2587–2591
10. Coomarasamy A et al. A Randomized Trial of Progesterone in Women with Recurrent Miscarriages. New England Journal of Medicine, 2015 Nov 26, 373(22):2141-8.
11. Brigham SA et al. A Longitudinal study of pregnancy outcome following idiopathic RMC. *Hum Reprod* 1999;14:2868-71.
12. Stef P. Kaandorp et al. Aspirin plus Heparin or Aspirin Alone in Women with Recurrent Miscarriage. N Engl J Med 2010; 362:1586-1596

Appendix 1

CYTOGENETICS / KARYOTYPING SPECIMEN TO GO TO B'HAM WOMEN'S HOSPITAL

(Ideally, Specimen should be at Women's the same day. Lab shuts at 5pm so latest time for Taxi to leave here is about 3.30. If likely to be after that, then phone Lab and ask them what they want us to do with the Specimen)

TELEPHONE LAB: at B'ham Women's Hospital 0121 627 2710 or 0121 627 4776 to tell them Specimen is coming.

SPECIMEN: Separated by Surgeon from ERPC specimen trap. Needs approximately 1cm cube. Goes into dry Universal container, cover with Saline

SPECIMEN FORM: Blue "Cytogenetics Referral" (Available from Midwives in Clinic if none here)

WRAP SPECIMEN IN THE FORM and place in Padded envelope to "West Midlands Regional Genetics Laboratory" (Available from Midwives in Clinic if none here)

ORGANISE TAXI.

- Alexandra Switchboard
- Cost code 182620
- Authoriser "Inese Rowbotham"
- A "Human Tissue Specimen" to go to "Genetics Reception at Birmingham Women's Hospital"

(Switchboard at Alex organise all Taxis for whole Trust so be VERY careful to tell them where you are and where it's going.)

HAND SPECIMEN TO TAXI DRIVER and make sure he knows it is to go to "Genetics Reception at Birmingham Women's Hospital" NOT the main reception desk at the Hospital!

PHONE LAB AGAIN to tell them it's on the way.

Any problems please contact: Kevin Ward (OYEZ) Charge Nurse, Theatre 4 Kidderminster Treatment Centre (Int: 55392 Ext: 01562 512384) kevin.ward5@nhs.net

Progesterone in Early Pregnancy

1. **Progesterone pessaries Cyclogest 400mg bd pv**
2. Offer to all women with early pregnancy bleeding AND previous miscarriage (the more miscarriages, the greater the benefit).[1,2,5]

2. Start progesterone when IUP seen on USS - do not need to wait for fetal heart[1]
    - USS should be arranged as soon as possible, but if it may be delayed, then progesterone should be started in the interim, and then continue/stop according to USS finding.
3. If a fetal heartbeat is then confirmed, continue progesterone until 16 completed weeks of pregnancy.[1]
4. No benefit of progesterone if early pregnancy bleeding and no previous miscarriage, so no proven benefit if give.[5]
5. If recurrent miscarriages (3x) and no bleeding - progesterone of no definite benefit
    - Can consider using progesterone with caution. [2,3]
    - Give to women with ≥4 miscarriages (ie higher order RM)[4]
    - Serial reassurance uss 6/8/10wks

References and information to help with counselling:

1. NICE NG 126 (Ectopic Pregnancy and Miscarriage)
2. RCOG New Draft GTG Recurrent Miscarriages
3. ESHRE GL
4. PROMISE Trial – summary for discussion

The subgroup analysis in women with higher order miscarriages (≥4 miscarriages) found a live birth rate of 63.3% in the progesterone group (verses 58.3% in the placebo group). If 4, 5 or ≥6 miscarriages are looked at individually, there was an increase live birth rate of between 6.4% and 7.4%. Although these figures all suggest a real benefit, none of these differences were statistically significant; therefore no strong recommendation can be made. Trial was designed to look for a 10% difference, a larger trial may detect a smaller difference [NICE].

5. PRISM Trial – summary for discussion

Women with early pregnancy bleeding and one or two miscarriages, when given progesterone until 16 weeks showed a 4% increase in number of babies born (verses placebo). Even greater benefit of 15% if bleeding and a history of recurrent miscarriages (≥3). https://www.youtube.com/watch?v=Khke7zMLmMg

6. Tommy's information leaflet to be given to patients

EARLY PREGNANCY BLEEDING & PROGESTERONE

Progesterone is an effective treatment for women who have early pregnancy bleeding AND 1 or more previous miscarriages

20% OF WOMEN

Bleeding before 12 weeks can happen for about **20% of pregnant women.**

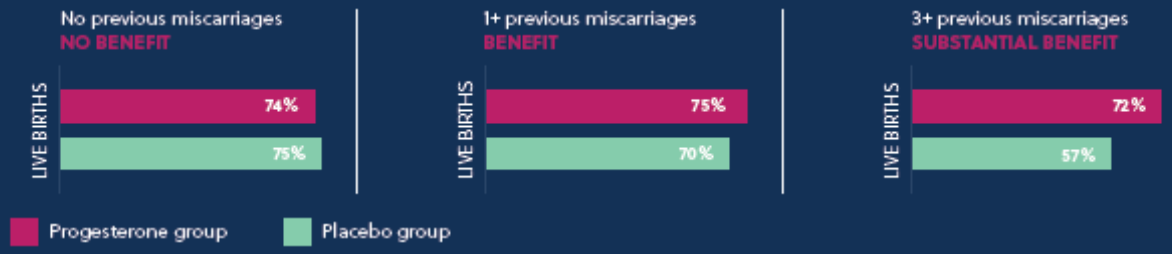
Although women are often worried at the sight of blood, **it is not always a sign of a problem.**

However, bleeding in early pregnancy does increase the risk of miscarriage.

What is progesterone? Progesterone is a natural hormone that is important during pregnancy; it helps to grow the lining of the womb and helps the mother's body to accept the growing baby.

A large UK-wide medical research trial* has now shown that **progesterone can prevent miscarriage** if you are bleeding in early pregnancy AND have a history of previous miscarriage.

Who was shown to benefit from progesterone treatment?



What is the treatment?

Progesterone (the drug used in the trial was called Utrogestan®) is taken as vaginal pessaries, 400mg twice daily, from the time you see a doctor with bleeding up to 16 weeks of pregnancy.

400mg 2xDAILY

Progesterone treatment is safe to use in pregnancy.

WHERE CAN I GET THIS TREATMENT?

If you are bleeding in early pregnancy:

- please call your Early Pregnancy Unit (EPU) at your local hospital and ask to be seen
- If your EPU is closed, visit your hospital Accident and Emergency unit
- bring this guidance with you or refer to www.tommys.org/PRISM.

This information was produced by Tommy's with the guidance of Professor Arri Coomarasamy and his team at the Tommy's National Centre for Miscarriage Research. The trial took place from May 2015 - 2017. Follow-up of patients was completed by June 2018. To find out more visit www.tommys.org/PRISM.

*PRISM Trial: Multi-centre randomised placebo-controlled trial of effects of vaginal progesterone in women with early pregnancy bleeding. Coomarasamy et al. (2019). A Randomized Trial of Progesterone in Women with Early Pregnancy Bleeding. N Engl J Med, May 2019.

This study was funded by the National Institute for Health Research (NIHR) HTA programme (project reference 12/167/26). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Tommy's

Clinic Date: **Consultant:** **Couple seen together: Y/N**

Female name *ID Sticker*		**Occupation**
Hospital/ NHS Number		**Age**
DOB		

Partner name *ID Sticker*		**Occupation**
Hospital/NHS Number		**Age**
DOB		

Married		**Related to partner**	
Duration of relationship			

Fertility complaint		
Duration of subfertility: **LMP:**	**P + **	**Age at Menarche:**
Regular cycle: _____ / _____	**Irregular cycle:**	**IMB/HMB/Dysmen**
Previous Contraception:		**Stopped:**
History:		
Intercourse frequency: **/wk**	**Advice on frequency:**	**Problems:** *PCB/Dyspareunia/male factor*

Obstetric History				
Date:	Outcome:	Gestation:	Management, treatment, histology:	Current partner:

Medical History			
PMH:			
Known APS:			
Known thrombophilia:			
Surgical History:			
Previous VTE	Date:	Treatment:	
DH:		Illicit drugs:	
Allergies:		Reaction:	
Folic Acid	400microg/d	5mg/day (BMI>29 or PMH)	Advice to start: Yes
Smear:	Date:	Result:	Previous treatment:
FH: VTE			
Other: Symptoms of hyperprolactinaemia			
Previous Fertility Investigation/treatments:			

Lifestyle							
Female patient				**Partner**			
BMI (spreadsheet if <19 or >29):			_____	**BMI (spreadsheet if <19 or >29):**			_____
Ht cm		**Wt** kg		**Ht** cm		**Wt** kg	
Smoker	**Y/N** **Ex:**	**Number:** **/day** **Smoking cessation Ref**		**Smoker**	**Y/N** **Ex:**	**Number:** **/day** **Smoking cessation Ref**	
Caffeine consumption:							
Exercise:							

Exposure to toxins:	
Alcohol consumption /wk **Advice given:**	**Alcohol consumption /wk** **Advice given**

Partner History		
Medical conditions:		
Testicular problems/surgery:		
Vasectomy/reversal:		
Previous Infections/STIs:		
Children from previous relationships?	**Difficulty in conceiving?**	
Previous Fertility Investigations / Treatment:		
DH:	**Illicit drugs:**	**Allergies:** Reaction:

Examination: Female	**Partner**

Initial Plan and Advice given			
Investigation:	**Date:**	**Result:**	**Requested Today:** √
FSH			
LH			
Testosterone			
Prolactin			
TSH			
AMH			
Progesterone | Day:			
Rubella Immunity			
Chlamydia			
TVUSS (Natural or OI)			
HSG or Lap&Dye			*Leaflet given [ ]*
Semen Analysis:			*Leaflet given [ ]*
Total count: >39M 1)	Motility: Total >40% Progressive >32%		Morph >4%
Andrology			*Leaflet given [ ]*
Recurrent Miscarriage Investigations:			
APL antibodies			
Thrombophilia screen			

FBC			
HbA1c			
TSH & TPO antibodies			
TVUSS			
Karyotyping			
Medications commenced:			
Clomiphene	50/100/150mg OD day 2-6 for _____ months		*Leaflet given [ ]*
Letrazole	2.5/5/7.5mg OD day 2-6 for _____months		*Leaflet given [ ]*
OI with FSH Menopur			*Leaflet given [ ]*
MPA	10mg tds for 7days (after neg PT on day 35)		*Leaflet given [ ]*
Folic Acid	400microg or 5mg (BMI>29 or PMH)		
Metformin			
Other:			
Other leaflets given:	*Clinic visit sheet*	*Lifestyle advice sheet*	*Weight loss sheet*
	IVF/ICSI	*RCOG RMC leaflet*	*Cedartree contact details*
Follow-Up and Further Care:			
Initial Plan:			
Fertility clinic follow-up			
Referral to:	ART: NHS / Private	Pre-pregnancy counselling:	
Plan for next pregnancy for Recurrent Miscarriage patients:			
[ ] General Advice	BMI, smoking, alcohol, NSAIDs RCOG information leaflet and Cedar Tree Counselling service details		
[ ] Unexplained	1. Reassurance and supportive care in EPAU, no evidence that any specific medical treatment improves outcome. 2. Self-referral to EPAU for serial early USS: at 6, 8 and 10 weeks		
[ ] Progesterone	Consider progesterone: vaginal micronized Utrogestan 400mg bd until 12wks/cyclogest. Limited evidence, but may be beneficial if >4 miscarriages		
[ ] APS confirmed	1. Self-referral to EPAU for serial early USS: at 6, 8 and 10 weeks. 2. Review to commence Aspirin and LMWH from 12 weeks. Stop aspirin at delivery, continue clexane until 6 weeks postnatally.		
[ ] Inherited thrombophilia:	Limited evidence of benefit from treatment with LMWH & Aspirin.		
[ ] NK cells	Potential treatments in early stages of research. • Offer information: Professor. S Quenby runs a private clinic at Coventry and Warwick Hospital; costing in the region of £600.		

Other:	
Sign, print, GMC number, date:	