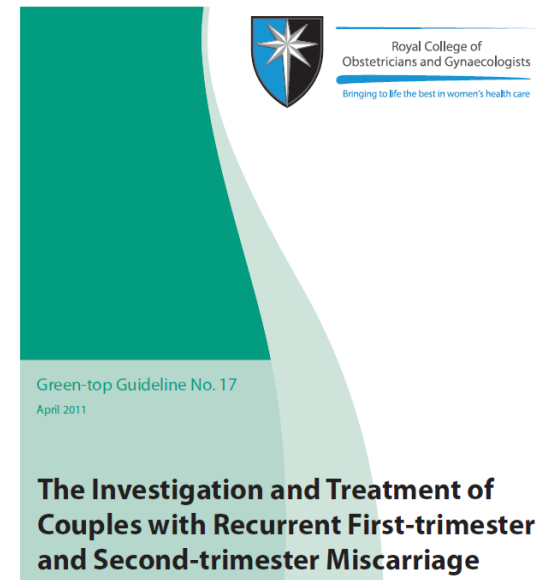


# Recurrent Miscarriage

Dr Stephen D. Quinn MSc MD MRCOG  
Consultant Obstetrician and Gynaecologist, ICHT  
Honorary Senior Clinical Lecturer  
Imperial College London

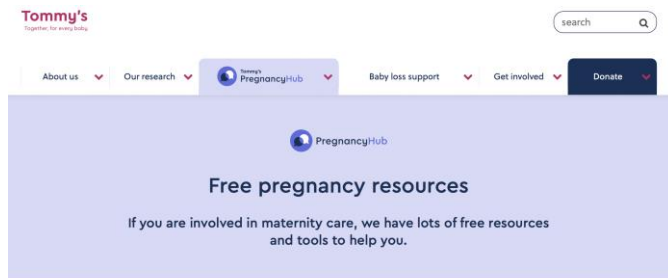
# Learning objectives

- The definition of recurrent miscarriage (RMC) and Referral Criteria and pathway
- The investigation of RMC
- The management of RMC
- The Psychological burden of RMC



# 2021 update

- 4th edition due to be published this year
- Updated by Imperial team and Tommy's RMC clinics- BWH and Coventry
- <https://www.tommys.org/pregnancy-information/health-professionals/free-pregnancy-resources>



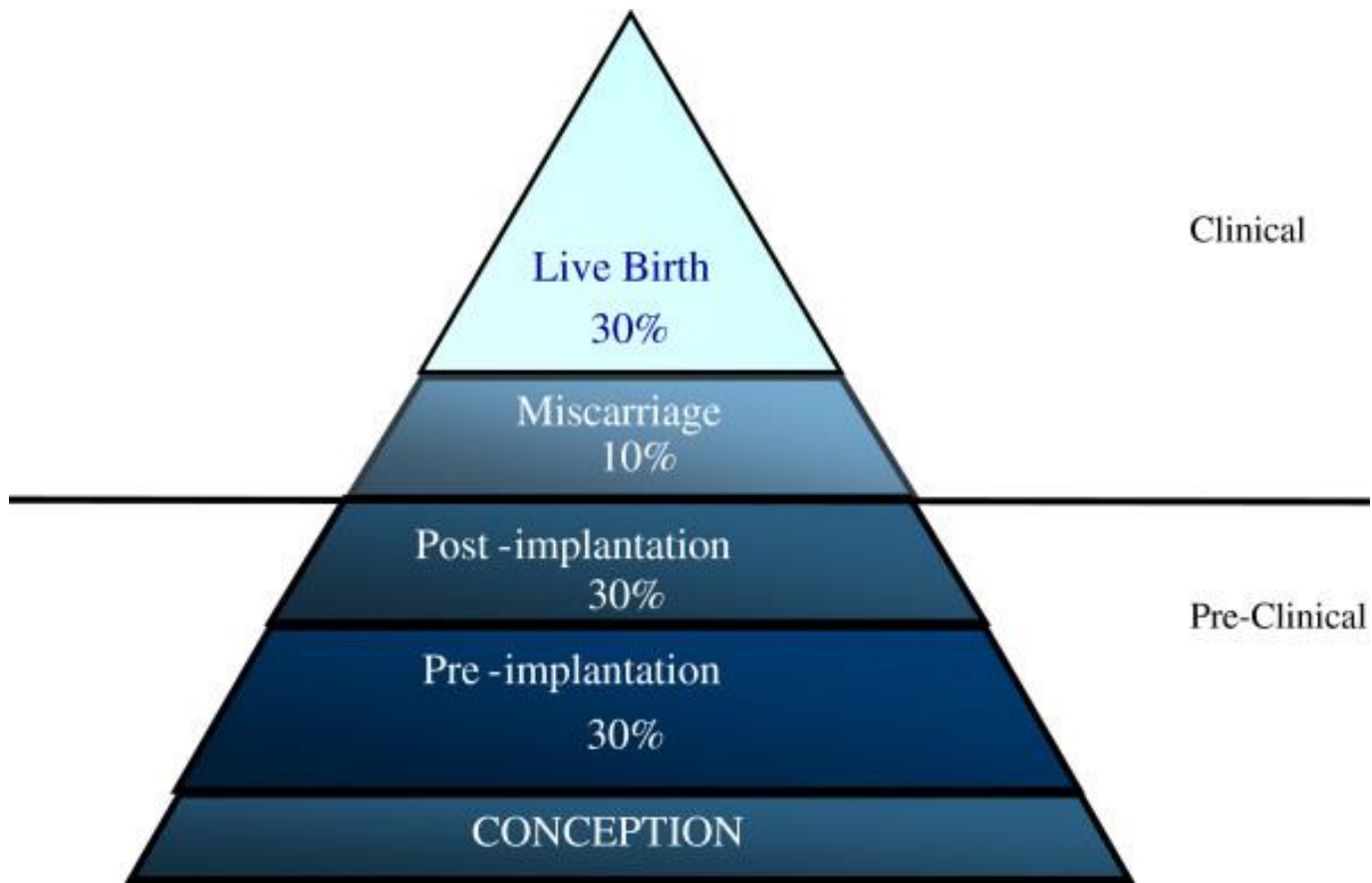
Home > PregnancyHub > For health professionals > Free pregnancy resources

## Resources to download



## Resources to download





**The pregnancy loss iceberg: an overview of the outcome of spontaneous human conceptions.** It is estimated that 70% of conceptions are lost prior to live birth. The majority of these losses occur prior to implantation or before the missed menstrual period, and since they are not revealed to the woman they are termed preclinical. In the pregnancy loss 'iceberg', they are therefore below the 'waterline'.

# Development of home pregnancy testing

*It was not until the late 1970s that the first pregnancy kits for home use were approved by the U.S. Food & Drug Administration. While offering women the convenience of testing at home for the first time, these kits were essentially mini chemistry sets that required users to mix urine with solutions in test tubes and wait two hours for a result.*

*In addition to being somewhat complex to use, results were not always reliable; the percentage of false negatives was as high as 20 percent.*

## **TESTING BREAKTHROUGH POSSIBLE WITH LATERAL FLOW TECHNOLOGY**

*By the 1990s, testing technology had advanced to the point where home kits finally began to resemble the ones used today. The mixing chemical kits were replaced with a simple test strip with a hand-held applicator*



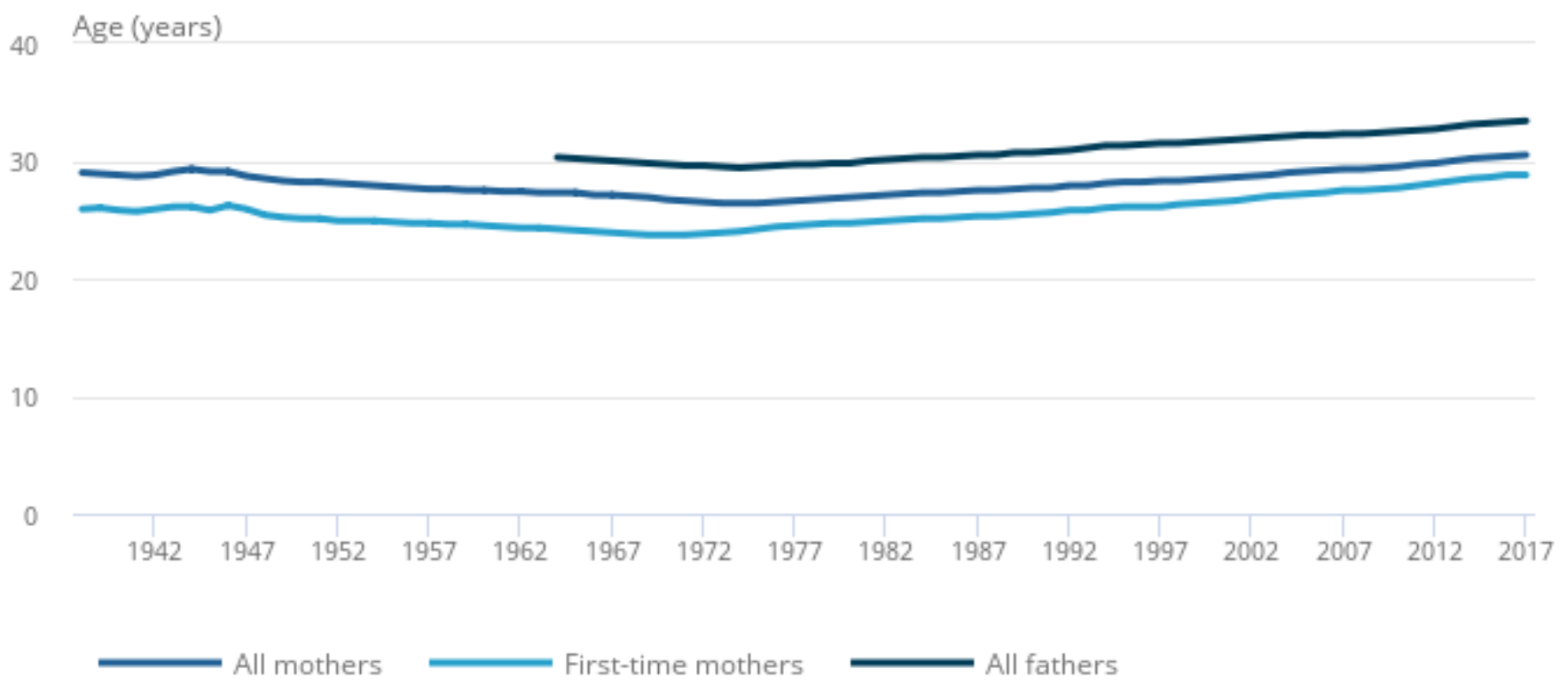
**A large prospective register linkage study reported the age-related risk of miscarriage in recognised pregnancies to be:**

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%

Nybo Anderson AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *BMJ* 2000;320:1708–12

Figure 2: Average age of mothers and fathers at the birth of their child, 1938 to 2017

England and Wales



Source: Office for National Statistics

# Recurrent miscarriage

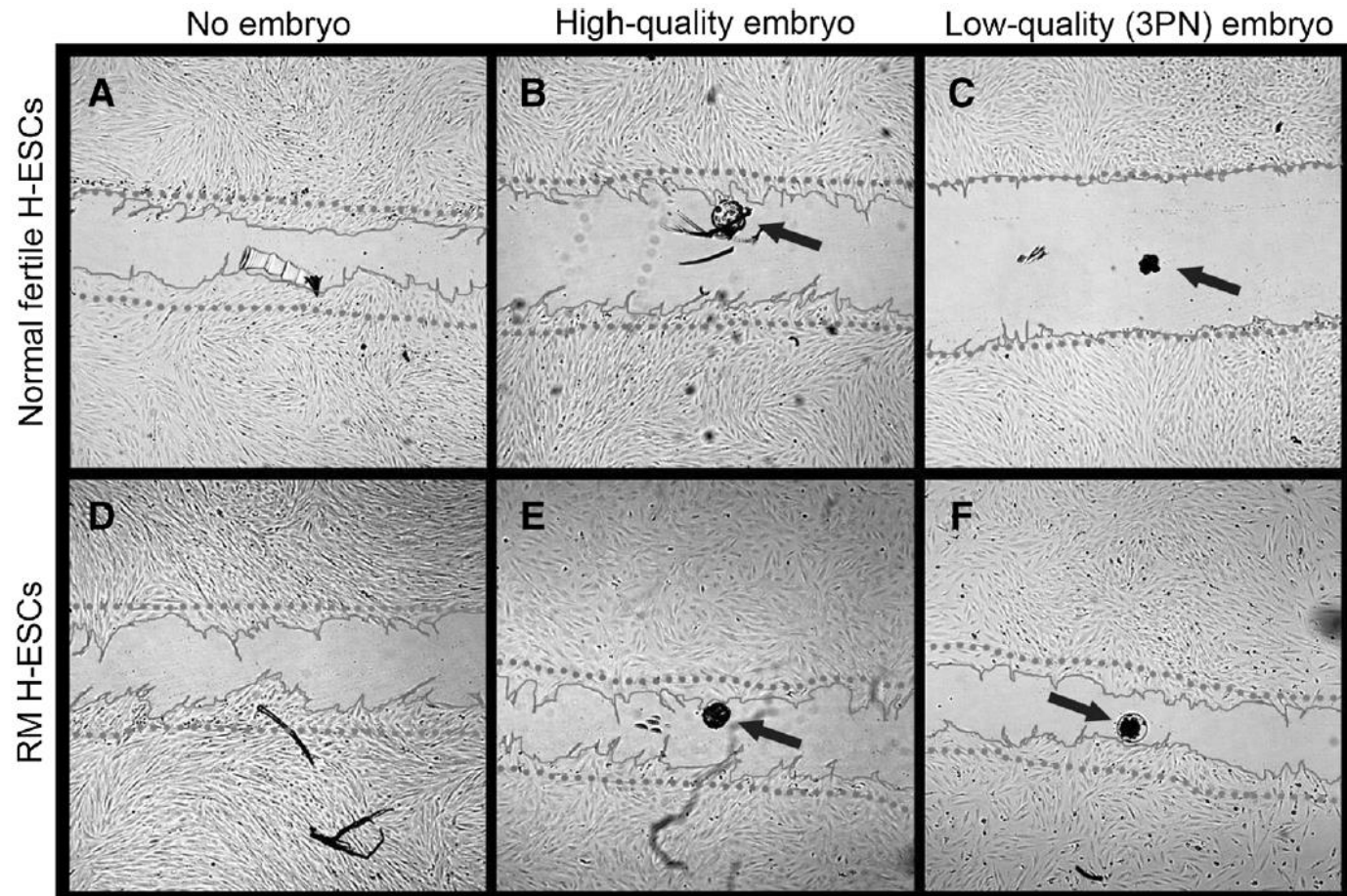
- Defined as the loss of three or more consecutive pregnancies, affects approx. 1% of couples trying to conceive.
- BG risk of first T MC is 1/4- 1/5
- 1–2% of second-trimester pregnancies miscarry before 24 weeks of gestation



# Mechanisms and reasons for 'physiological' early pregnancy loss

- *“It is a generally accepted assumption that sporadic pregnancy losses occurring before an embryo has developed represent a **‘physiological’ phenomenon**, which prevents conceptions affected by serious structural malformations or chromosomal aberrations incompatible with life from progressing to viability.”* Larson et al.

- *“Women who experience RM may not be rejecting healthy embryos, but rather permitting embryos of low viability to implant long enough to present as a clinical pregnancy before rather than being lost as a preclinical biochemical pregnancy”* Quenby et al



**Figure 2** The migration zone after adding a high-quality, low-quality or no embryo. The migratory response of decidualized human embryonic neural stem cells (H-EnSCs) from normally fertile (A-C) and recurrent miscarriage (RM) women (D-F) was analyzed in absence of a human embryo (A,D), in presence of a high-quality embryo (B,E) or a low-quality embryo (C,F). Phase contrast pictures were taken 18 h after creating the migration zone. The dotted line represents the front of the migration zone directly after its creation. As a reference for the position of the embryo, the bottom of the plate was marked. The arrows indicate the position of the embryo. All pictures were taken with 25 × magnification. (Reproduced from Weimar *et al.* [26]).

# Biological Plausibility

1. Women with RM have been shown to express lower levels of **endometrial mucin 1**- an anti-adhesion molecule that contributes to the barrier function of the epithelium
2. ESCs of women with RM show an abnormal response to decidualization *in vitro*, manifest by attenuated prolactin production and prolonged and enhanced prokineticin 1 expression

# Biological Plausibility

## 3. Concept of 'super receptivity'

- If women with RM are less selective to embryos implanting, then it would be expected that they would report shorter intervals between pregnancies

## 4. Migration behaviour of ESCs from women with RM was similar in the presence of both low-quality and high quality embryos

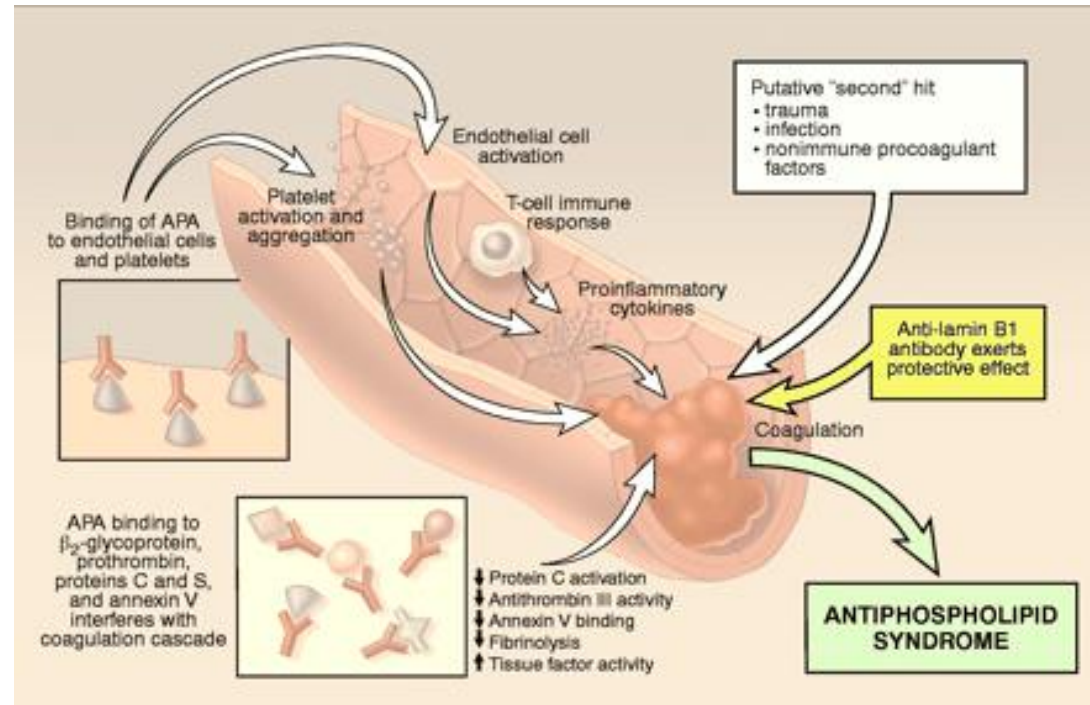
## 5.1 Epidemiological factors

<b>Risk factors</b>	<b>Evidence quality</b>	<b>Strength</b>	<b>Association</b>
<b>Advancing maternal age</b>	<b>2++</b>	<b>B</b>	Increased risk of miscarriage.
<b>Advancing paternal age</b>	<b>2++</b>	<b>B</b>	Increased risk of miscarriage, although not as markedly as with maternal age
<b>Number of previous miscarriages</b>	<b>2++</b>	<b>B</b>	Increased risk of subsequent miscarriage
<b>Previous live birth</b>	<b>2+</b>	<b>C</b>	No association with subsequent miscarriage risk

<b>Risk factors</b>	<b>Evidence quality</b>	<b>Strength</b>	<b>Association</b>
<b>Black ethnic background</b>	<b>2+</b>	<b>D</b>	Increased risk of miscarriage
<b>Consanguineous relationship</b>	<b>2-</b>	<b>D</b>	No increased risk of recurrent miscarriage
<b>Smoking</b>	<b>2+</b>	<b>D</b>	Increased risk of miscarriage
<b>Excess alcohol consumption</b>	<b>2+</b>	<b>D</b>	Increased risk of miscarriage
<b>Excess caffeine consumption</b>	<b>2++</b>	<b>B</b>	Increased risk of miscarriage
<b>Women with BMI&lt;19 or BMI&gt;25</b>	<b>2++</b>	<b>B</b>	Increased risk of recurrent miscarriage
<b>The effects of environmental chemical exposure and dietary intake need to be investigated further.</b>	<b>2-</b>	<b>D</b>	There are limited studies examining this association.

# Antiphospholipid syndrome

- most **important, treatable** cause of recurrent miscarriage
- Antiphospholipid antibodies:
  - **Lupus anticoagulant**
  - **Anticardiolipin antibodies**
  - **Anti-B2 glycoprotein-I antibodies**
- Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage
- By comparison, the prevalence of antiphospholipid antibodies in women with a low-risk obstetric history is less than 2%





Recommendation	Evidence quality	Strength	Rationale for the recommendation
<p><b>Aspirin and heparin (UFH or LMWH) should be recommended for women with APS. Clinicians and women should be aware that treatment with heparin, particularly unfractionated heparin, is not without some risk.</b></p>	<p><b>1+</b></p>	<p><b>B</b></p>	<p>Meta-analyses have demonstrated that treatment of APS with aspirin and heparin confers a significant benefit.</p>
<p><b>Aspirin and/or heparin should not be given to women with unexplained recurrent miscarriage (without APS)</b></p>	<p><b>1+</b></p>	<p><b>B</b></p>	<p>Meta-analyses have shown it does not improve outcomes and may be associated with side effects.</p>

# Karyotypic disorders

- A chromosomal abnormality in one partner is found in 3% to 6% of RM couples, which is x10 higher than the background population
- The most commonly encountered abnormalities include balanced translocations and inversions that do not have any consequences for the phenotype of the carrier, but in pregnancy there is a 50% risk of a fetus with an unbalanced chromosomal abnormality that can result in a miscarriage.

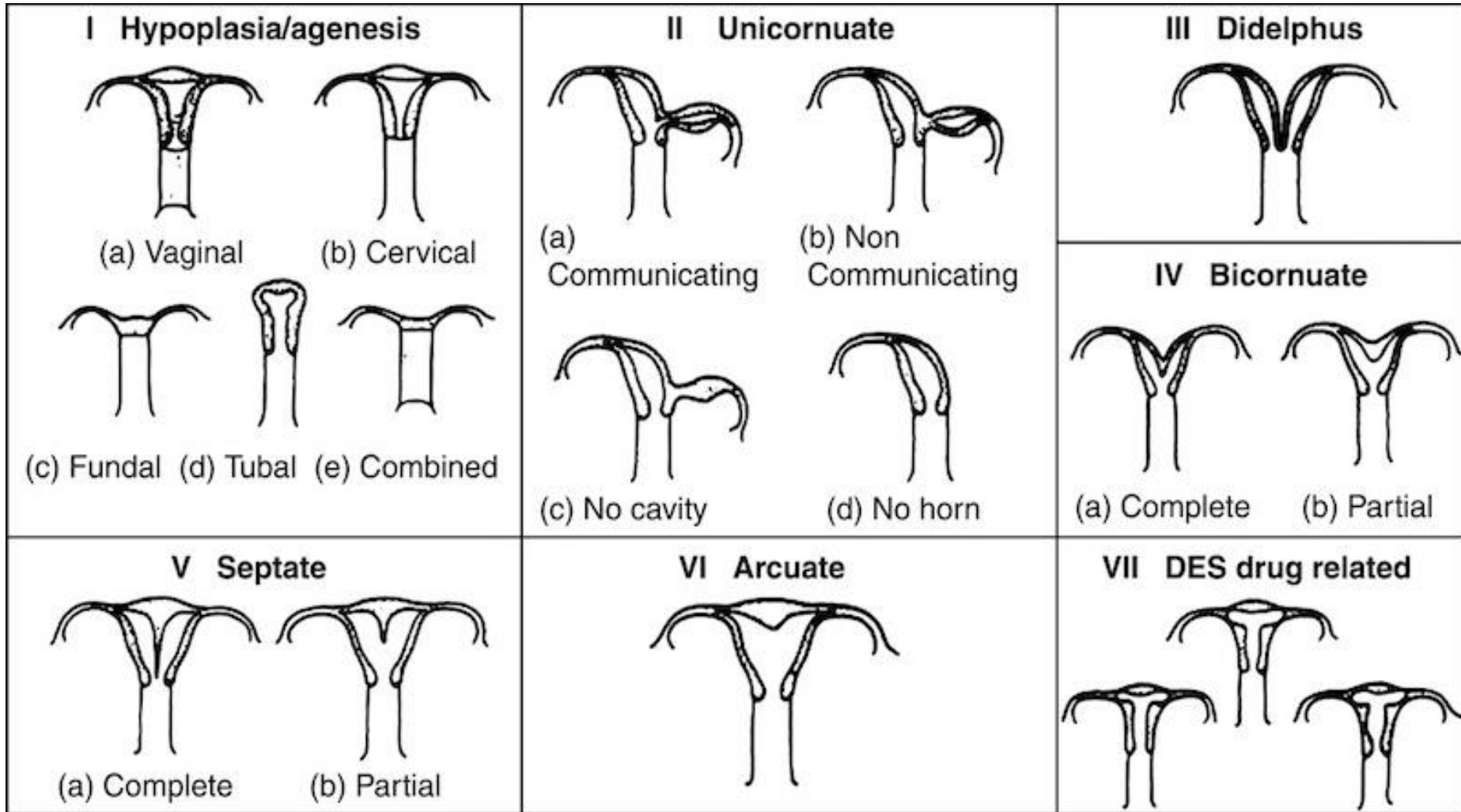
# To screen or not to screen?

- **The argument for:**
  - to optimise the counselling of RM couples with respect to any subsequent pregnancy
  - to avoid the birth of a child with congenital defects and mental handicaps due to an unbalanced karyotype by offering appropriate prenatal diagnostic screening
- **The argument against:**
  - Costly analysis
  - Large index-control study with a mean follow-up period of 5.8 years-carrier couples with at least two previous miscarriages had the same chance of having a healthy child as non-carrier couples with at least two miscarriages (83% and 84%, respectively)
  - Low risk (0.8%) of pregnancies with an unbalanced karyotype surviving into the second trimester

Recommendation	Evidence quality	Strength	Rationale for the recommendation
<p>Options for couples with chromosomal rearrangements include attempting a further natural conception, preimplantation genetic diagnosis (PGD) or gamete donation.</p>	2-	C	Live birth rates are similar following natural conception and PGD, and therefore PGD should not be routinely offered in this situation.
<p>There are currently insufficient data to support the routine use of pre-implantation genetic screening (PGS) for couples with unexplained recurrent miscarriage, while the treatment may carry a significant cost and potential risk.</p>	2-	C	Observational studies have not demonstrated improved outcomes to date, both in terms of live birth rate and time to pregnancy interval. RCTs are urgently required.

- If the karyotype of the miscarried pregnancy is abnormal, there is a better prognosis for the next pregnancy

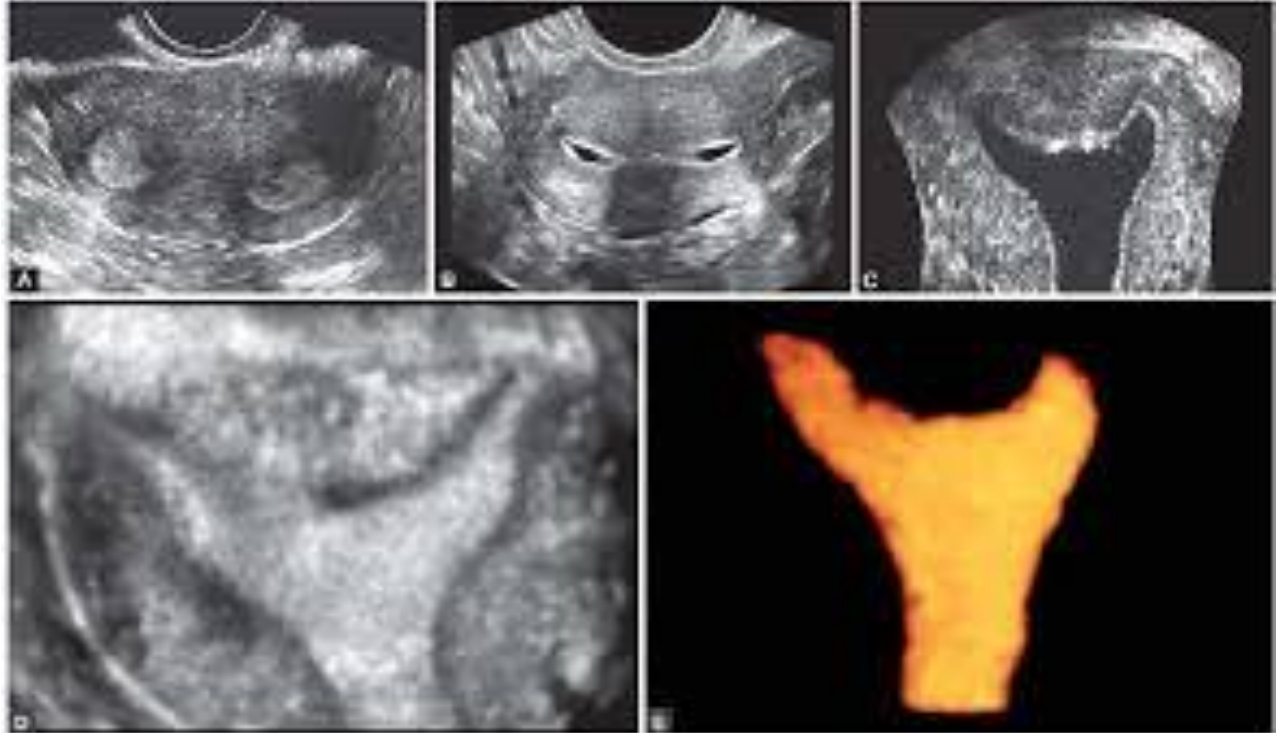
# Uterine malformations



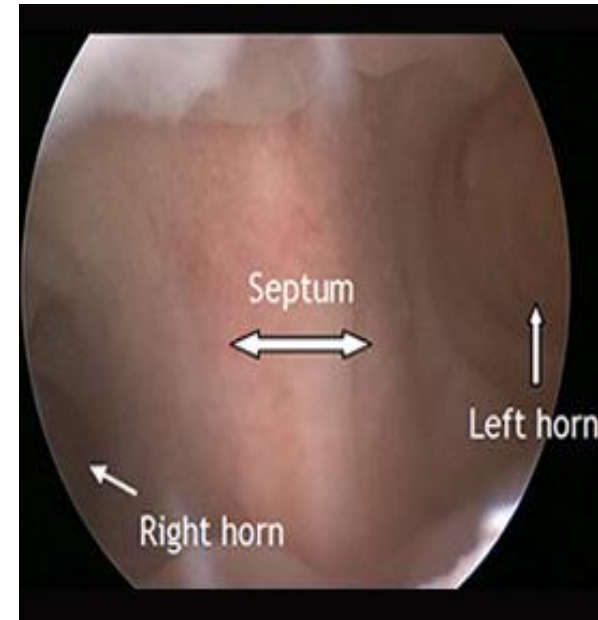
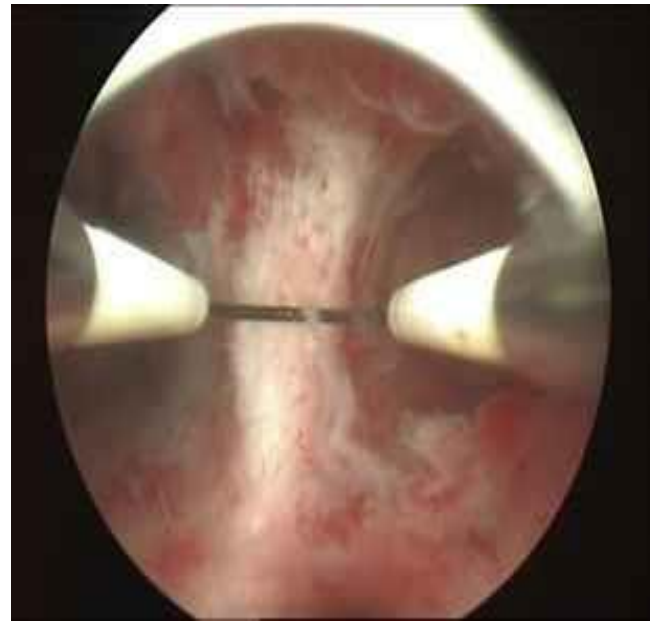
**DES: Diethylstilbestrol**

# Anatomical factors

- Ultrasound
  - 2D or 3D



# Hysteroscopy



---

<b>Recommendation</b>	<b>Evidence quality</b>	<b>Strength</b>	<b>Rationale for the recommendation</b>
<b>Resection of a uterine septum should be considered for women with recurrent first- or second- trimester miscarriage, ideally within an appropriate audit or research context.</b>	<b>2+</b>	<b>C</b>	While there is a lack of RCTs, observational and case-control studies have indicated that this treatment confers a significant benefit.



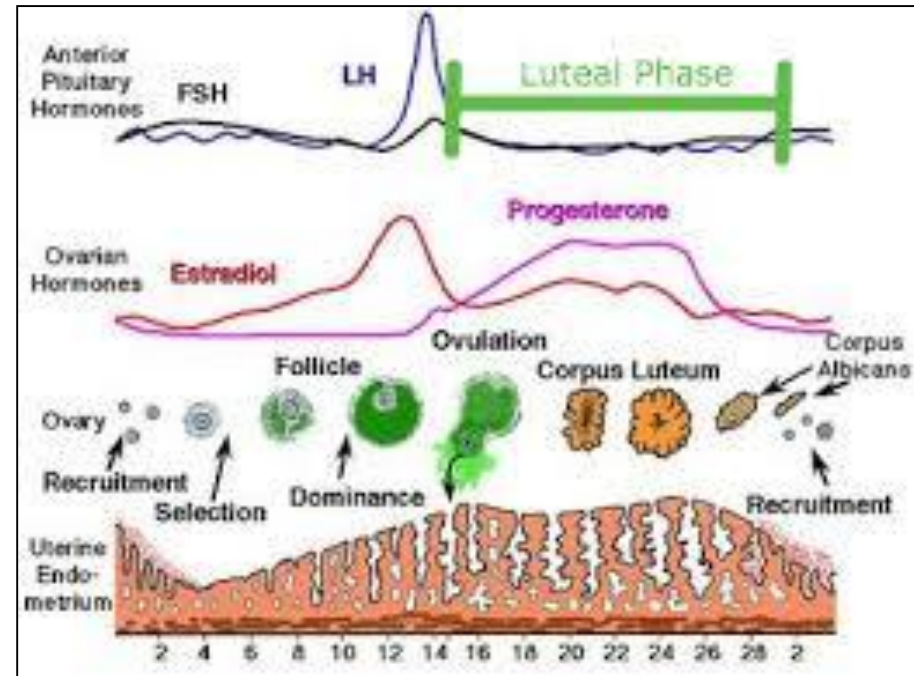
# MTHFR mutation

- MTHFR is a key enzyme in one-carbon metabolism
- Catalyzes the conversion of 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate, the predominating circulating form of folate
- **Evidence is conflicting on hyperhomocysteinaemia as a risk factor for recurrent miscarriage**

# Luteal Phase defect

- The shortened luteal phase has been associated with pregnancy loss **but the assessment and interpretation of a putative luteal phase defect is problematic**

- The use of histological and biochemical endpoints as diagnostic criteria for endometrial dating are unreliable



# Progesterone Supplementation

- Progesterone is necessary for successful implantation and the maintenance of pregnancy
- This benefit of progesterone could be explained by its immunomodulatory actions in inducing a pregnancy-protective shift from pro-inflammatory Th-1 cytokine responses to a more favourable anti-inflammatory Th-2 cytokine response

# Cochrane review October 2018

- 13 trials that enrolled a total of 2556 women with a history of recurrent miscarriages
- Progestogen with recurrent miscarriages early in their pregnancy may help lower the rates of miscarriage in that pregnancy from 27.5% to 20.1%
- Moderate quality studies

# PCO, elevated LH, and insulin resistance

- The prevalence of PCO is 40% among women with recurrent miscarriage\*
- It has been reported that hypersecretion of basal LH with or without polycystic ovaries is a risk factor for miscarriage

- Meta-analysis concluded that insulin resistance is associated with the susceptibility to recurrent miscarriages, and it may contribute to the occurrence of recurrent miscarriages

[Association between recurrent miscarriages and insulin resistance: a meta analysis.](#)

Li ZL, Xiang HF, Cheng LH, Cao YX, Wei ZL, Liu C, Hu JJ, Pan FM.

Zhonghua Fu Chan Ke Za Zhi. 2012 Dec;47(12):915-9

## 5.5 Endocrine

<b>Risk factors</b>	<b>Evidence quality</b>	<b>Strength</b>	<b>Association</b>
<b>Well controlled diabetes and thyroid disease</b>	<b>2+</b>	<b>C</b>	No increased risk of recurrent miscarriage.
<b>Subclinical hypothyroidism</b>	<b>2-</b>	<b>C</b>	Increased risk of recurrent miscarriage
<b>Thyroid autoantibodies</b>	<b>2++</b>	<b>B</b>	Increased risk of recurrent miscarriage.
<b>Polycystic ovarian syndrome</b>	<b>2-</b>	<b>D</b>	Increased risk of recurrent miscarriage.
<b>Prolactin imbalances</b>	<b>2-</b>	<b>D</b>	Increased risk of recurrent miscarriage.
<b>Luteal phase defect</b>	<b>2-</b>	<b>D</b>	Insufficient/inconclusive evidence

Recommendation	Evidence quality	Strength	Rationale for the recommendation
<b>Thyroxine supplementation is not routinely recommended for euthyroid women with TPO who have a history of miscarriage</b>	1-	A	The 'TABLET' study, in which euthyroid women with TPO and a history of miscarriage were randomised to thyroxine or placebo, found no difference in live birth outcome. There were insufficient data to perform a sub-group analysis for women with recurrent miscarriage but the ongoing 'T4-Life' study (RCT) will examine this group.
<b>Thyroxine supplementation may be considered for women with moderate SCH (TSH&gt;4) but is not routinely recommended for women with mild SCH (TSH&gt;2.5) irrespective of TPO status</b>	2+	B	Based on the review of cohort studies and conclusion reached by the RCOG SIP
<b>Regular TSH measurement from 7-9 weeks gestation is recommended in cases with TPO and/or SCH</b>	4	D	



# Immunology

- Peripheral natural killer (pNK) and uterine NK (uNK) cells
- The prognostic value of measuring pNK or uNK cell parameters is uncertain

[Seshadri S<sup>1</sup>, Sunkara SK.](#) **Natural killer cells in female infertility and recurrent miscarriage: a systematic review and meta-analysis.** [Hum Reprod Update.](#) 2014 May-Jun;20(3):429-38. 2013 Nov 27.

# Natural killer cells in female infertility and recurrent miscarriage: a systematic review and meta-analysis

Srividya Seshadri\* and Sesh Kamal Sunkara

King's College London, London, UK

\*Correspondence address. E-mail: v9dya@hotmail.com

Submitted on December 21, 2012; resubmitted on September 22, 2013; accepted on October 7, 2013

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- Abstract
  - Introduction
  - Methods
    - Identification of literature
    - Study selection and data extraction
    - Statistical analysis
  - Results
    - NK cells in infertile women versus fertile controls
    - NK cells and IVF outcome
    - NK cells in women with RM versus controls
  - Discussion
- 

**INTRODUCTION:** Embryo implantation is a complex process involving maternal hormonal changes, immune responses and maturational events in the embryo. A pregnancy could fail when these events are not synchronized. It is speculated that in women, an elevation of natural killer (NK) cells may have an effect on reproductive performance, and NK cell levels in blood are currently being used as a diagnostic test to guide the initiation of therapies in patients with infertility.

**METHODS:** We conducted a systematic review to evaluate the (i) levels of NK cells in blood and endometrium in infertile versus fertile women, (ii) association between NK cells and IVF outcome. (iii) levels of NK cells in blood and endometrium in women with recurrent miscarriage (RM)

- uNK cells may regulate angiogenesis in non-pregnant endometrium
- The mechanisms of reproductive failure associated with increased uNK cell density appear to be increased angiogenesis and peri-implantation blood flow, which may lead to early maternal circulation and hence pregnancy failure due to excessive oxidative stress

---

Risk factor	Evidence quality	Strength	Association
Uterine natural killer cells	2-	C	Insufficient/inconclusive evidence

# Male factors

- Sperm samples from recurrent pregnancy loss couples have an increase in their sperm DNA fragmentation
- DNA fragmentation is the separation or breaking of DNA strands into pieces
- Several different tests are available, but no consensus has yet been reached as to which tests are most predictive

# Sperm DNA fragmentation

- In a study comparing fertile sperm donors with couples who have unexplained RM, an assay was used that both measured DNA damage directly and also distinguished between single-stranded and double-stranded DNA damage. The study showed that 85% of the RM couples had a profile with high values of double-stranded DNA damage compared to only 33% among fertile sperm donors, suggesting a specific paternal explanation in these otherwise unexplained cases
- ?Antioxidant treatment

## Common antioxidants that improve sperm quality and quantity

Antioxidant	Mode of action	Disadvantage	Quality of evidence[46]	Clinical trials
Carnitine[53] [54] [55]	Improve posttesticular sperm motility in 2–4 months, and morphology in 3–6 months	Increase prostaglandin E <sub>2</sub> in seminal fluid[56]	High	Costa et al[57] Vitali et al[58] Lenzi et al[59] Lenzi et al[60] Cavallini et al[61]
Nonsteroidal anti-inflammatory drugs	Reduce prostaglandin in seminal plasma, improve sperm quality,[62] synergistic with carnitine[63]	High dose inhibits motility[52]	Low	Cavallini et al[64] Cavallini et al[65]
Vitamin E (α-tocopherol)	Protect spermatozoa from oxidative damage and loss of motility, improve sperm performance[66]	Not proven to be effective	Low	Giovenco et al[67] Suleiman et al[66] Kessopoulou et al[68] Moilanen and Hovatta[69]
Vitamin C (ascorbic acid)	Protect spermatozoa from endogenous oxidative DNA damage,[70] synergistic with vitamin E[71]	Not proven to be effective	Low	Rolf et al[72]
Selenium	Spermatogenesis, sperm function and motility via selenoenzyme[73] Synergistic with vitamin E[74] [75] [76]	Controversial data	Low	Bleau et al[77] Roy et al[78]
N-acetylcysteine	Reduce ROS and oxidation of sperm DNA[79] [80] Synergistic with selenium[81]		Low	Comhaire et al[82] Safarinejad and Safarinejad[81]
Zinc	Protect sperm structure via prevention of oxidative stress, apoptosis, and sperm DNA fragmentation[83]		Moderate	Omu et al[83]
Folic acid	Synergistic with Zinc[84]	Controversial data	Low	Landau et al[85] Ebisch et al[84] Wong et al[86]
Mast cell blocking agent (Tranilast)	Improvement of sperm count and motility in idiopathic oligo- and asthenozoospermia patients	Improvement not sustained if therapy discontinued[87]	Low	Yamamoto et al[88] Hibi et al[87]
Lycopene (carotenoid)	Improve sperm concentrations in testes and seminal plasma	Improvement is minimal in patients with lower baseline sperm concentration	Low	Gupta and Kumar[89]
Pentoxifylline	Preserve sperm motility and improve semen parameters[90] [91]	Low dosage has no effect High dose does not alter sperm fertilizing ability[92]	Low	Tesarik et al[90] Marrama et al[92] Okada et al[91]

## 7.7 Male factors

---

Recommendation	Evidence quality	Strength	Rationale for the recommendation
<b>There is no evidence to recommend treatments for male factors.</b>	<b>3</b>	<b>D</b>	There is a lack of studies examining relevant interventions.

## IV Immunoglobulin

- Intravenous immunoglobulin down-regulates NK-cell killing activity both in vitro and in vivo
- Meta-analysis showed that IVIG increased the rates of live birth in secondary recurrent miscarriage, but there was insufficient evidence for its use in primary recurrent miscarriage
- *Immunotherapy is expensive and has potentially serious adverse effects including transfusion reaction, anaphylactic shock and hepatitis. The use of immunotherapy should no longer be offered to women with unexplained recurrent miscarriage. RCOG*



# Intralipid

- Intravenous intralipid solution:
  - No evidence of benefit with use of intralipid
  - Well controlled, large-scale, and confirmatory studies required before it can be recommended for routine use

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Recommendation	Evidence quality	Strength	Rationale for the recommendation
<b>Immunotherapy (e.g. paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and intravenous immunoglobulin (IVIG)) is not recommended for women with recurrent miscarriage.</b>	<b>1++</b>	<b>B</b>	<b>Meta-analyses have shown no significant benefit of treatment</b>

# Intralipids Therapy Treatment

[Home](#)[About us](#)[How do the intralipids work?](#)[Intralipids In IVF](#)[Published evidence](#)[Our Research Ideas](#)[Contact](#)

Here are the summaries of some of the published articles on intralipids and their use in IVF and recurrent implantation failure.



**NHS**  
NHS advice  
on miscarriages

## Natural Killer Cell Testing



### Request A Call Back

Name

Telephone

Email

**submit**

## A practical approach to the prevention of miscarriage: Part 3-- Passive immunotherapy

Check JH (2010) Clin Exp Obstet Gynecol - 37:81-3

To evaluate the efficacy of passive immunotherapy in preventing miscarriage. Studies both pro and con concerning intravenous immunoglobulin therapy (IVIg) in preventing miscarriage were evaluated. A new therapy of i.v. intralipid infusion is also reviewed.

Intravenous immunoglobulin therapy may be effective but it is necessary to use it prior to conception and monthly thereafter. Some brands are more potent than others. The data concerning intralipid i.v. infusion involves only small case series but the results from one study were encouraging though we could not personally substantiate these findings.

Intravenous immunoglobulin (IVIg) therapy is very expensive. In the author's opinion there are no immunological studies that can determine if a woman needs immune suppression. The best way to decide is the history--the more miscarriages without any other identifiable cause the more likely passive immunotherapy may be helpful. If intralipid proves as efficacious as IVIg it will be a lot less expensive.




**Intralipids patient information leaflet**




**Recurrent implantation (IVF) failure**



**Early miscarriage patient information**



**Intralipids manufacturer's factsheet**



# Microbiome and Chronic endometritis

- Chronic endometritis (CE) appears to be associated with MC
- May be as a result of microbiome imbalance
- CE is a chronic inflammation of the endometrium, diagnosed using CD138 immunohistochemistry
- The pathophysiology of CE is poorly understood but may be due to chronic infection, secondary to dysbiosis of the endometrial microbiome
- Dysbiosis is caused by the presence of an array of microorganisms and a lack of lactobacilli in the endometrium

# Chronic Endometritis and Recurrent Miscarriage - The CERM trial

- Prospective, multi-centre, randomised, double blind adaptive designed trial. We will compare a pre-conception course of doxycycline (100mg twice daily for 14 days) to placebo in up to 1500 women with recurrent miscarriage associated with CE
- Participants will be screened for CE using an endometrial biopsy. Screen positive patients will be eligible for randomisation.
- The use of adaptive design will allow early stoppage in the case of better than expected efficacy or in the case of futility.
- Primary outcomes will be on-going pregnancy at 12 weeks and total live births. A sub-group will additionally have endometrial and biopsies swabs taken both before and after intervention to assess the effect of doxycycline on, endometritis, decidualisation and the endometrial microbiome.

# Psychological aspects

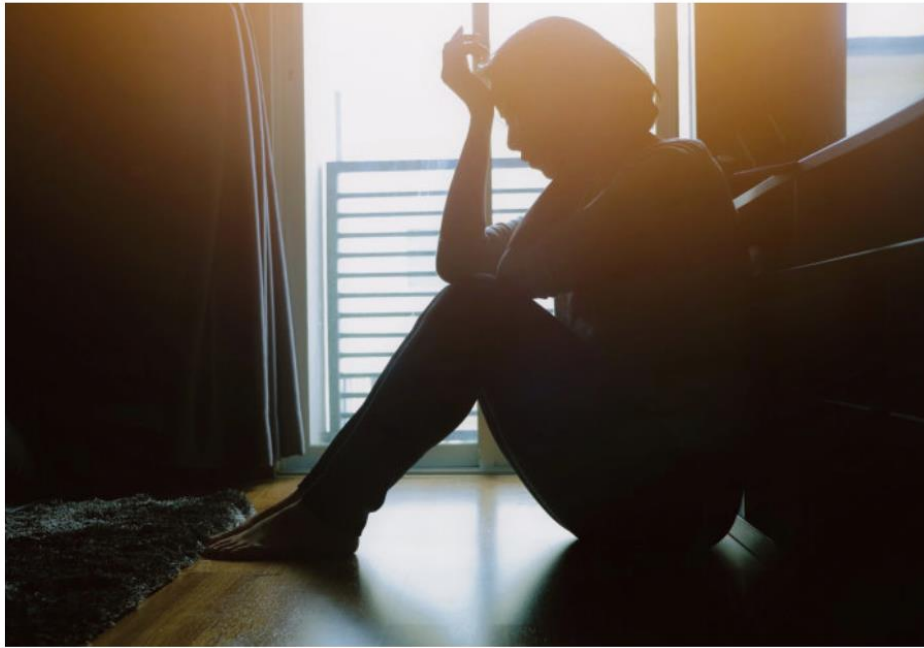


- Significant anxiety (and depression)
  - Higher suicide rates
- Risk factors for psychological morbidity
  - Childlessness
  - History of infertility or IVF

# Miscarriage and ectopic pregnancy may trigger long-term post-traumatic stress

by *Kate Wighton*

15 January 2020



**One in six women experience long-term post-traumatic stress following miscarriage or ectopic pregnancy.**

This is the finding of the [largest ever study](#) into the psychological impact of early-stage pregnancy loss, from scientists at [Imperial College London](#) and [KU Leuven](#) in Belgium.

Pregnancy loss

The research, published in the journal [American Journal of](#)



8 comments



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## RELATED STORIES



**Miscarriage and ectopic pregnancy may trigger post-traumatic stress disorder**

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**Recommendation****Evidence  
quality****Strength****Rationale for the  
recommendation**

**Women with unexplained recurrent miscarriage should be offered supportive care in the setting of a dedicated early pregnancy assessment unit.**

**2+****C**

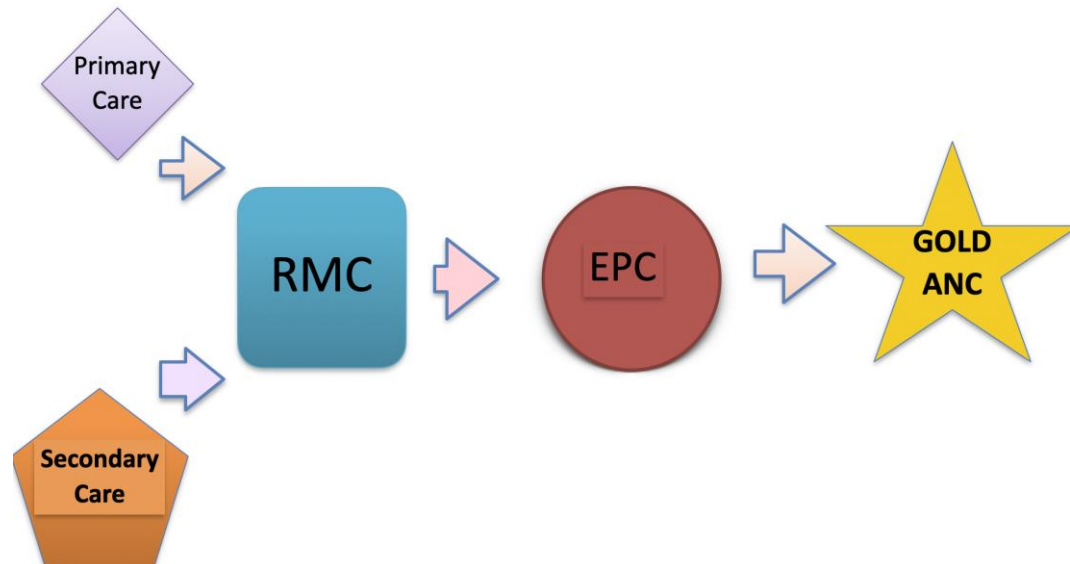
Several observational studies have suggested a beneficial effect in pregnancy outcomes.



- *“Women with unexplained recurrent miscarriage have an excellent prognosis for future pregnancy outcome without pharmacological intervention if offered supportive care alone in the setting of a dedicated early pregnancy assessment unit.” RCOG*
- Prognosis for a successful future pregnancy with supportive care alone is in the region of 75%

# Current Referral Criteria

- Three or more miscarriages of less than 12 weeks  
OR
- One or more miscarriages greater than 12 weeks gestation
- No more than one previous live birth
- Female partner less than 42 years



# The Gold Antenatal Team



- Friday mornings at St Mary's
- Couples affected by RMC, those with fertility treatments, and older women
- More frequent scans, cervical length monitoring, uterine artery dopplers at 24 weeks
- Management of LWMH and Haem. support
- Specialist midwifery support

Imperial RMC Clinic  
Ground Floor, Mint Wing,  
South Wharf Road  
London W2 1NY

Tel 02033121117/21323

E-mail: [imperial.rmc.admin@nhs.net](mailto:imperial.rmc.admin@nhs.net)  
[stephen.quinn2@nhs.net](mailto:stephen.quinn2@nhs.net)

<https://www.miscarriageassociation.org.uk/>

<https://www.tommys.org/>

## Questions



- **Zhang C. Association between Serum TNF- $\alpha$  Levels and Recurrent Spontaneous Miscarriage: A Meta-analysis.** Am J Reprod Immunol. 2015 Nov 20.
- Egerup P et al. The Effects of Intravenous Immunoglobulins in Women with Recurrent Miscarriages: A Systematic Review of Randomised Trials with Meta-Analyses and Trial Sequential Analyses Including Individual Patient Data. PLoS One. 2015 Oct 30;10(10):e0141588. doi: 10.1371/journal.pone.0141588. eCollection 2015.
- [Seshadri S<sup>1</sup>, Sunkara SK.](#) **Natural killer cells in female infertility and recurrent miscarriage: a systematic review and meta-analysis.** [Hum Reprod Update.](#) 2014 May-Jun;20(3):429-38. 2013 Nov 27.
- Li ZL, Xiang HF, Cheng LH, Cao YX, Wei ZL, Liu C, Hu JJ, Pan FM. Zhonghua Fu Chan Ke Za Zhi. [Association between recurrent miscarriages and insulin resistance: a meta analysis.](#) 2012 Dec;47(12):915-9
- **Gaskins AJ, Rich-Edwards JW, Hauser R, Williams PL, Gillman MW, Ginsburg ES, Missmer SA, Chavarro JE.** [Maternal prepregnancy folate intake and risk of spontaneous abortion and stillbirth.](#) Obstet Gynecol. 2014 Jul;124(1)
- Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database Syst Rev 2005;(2):CD002859.