Clinical practice guidelines for recurrent miscarriage

a systematic review – 2021

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BIOGRAPHY

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- She leads the multi-disciplinary Pregnancy Loss Research Group,
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- A systematic review was conducted to identify, appraise and describe clinical practice guidelines (CPG) published since 2000 to 2020 for the investigation,management, and/or follow-up of recurrent miscarriage

- 32 CPG were included, from which 373 recommendations concerning first-trimester recurrent miscarriage were identified across four subcategories:
  a. structure of care (42 recommendations, nine CPG),
  b. investigations (134 recommendations, 23 CPG),
  c. treatment (153 recommendations, 24 CPG), and
  d. counselling and supportive care (46 recommendations, nine CPG).

- They are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options .

- The aim of the present systematic review was to identify, appraise and describe published CPG for the investigation, management, and/or follow-up of first-trimester recurrent miscarriage .

INTRODUCTION

- Recurrent miscarriage affects 1–2% of women of reproductive age, depending on the definition used.

- The term used to describe the condition varies between countries and professional bodies ; for example, ESHRE uses the term ‘recurrent pregnancy loss’ *, whereas the Royal College* of Obstetricians and Gynaecologists (RCOG) in the UK uses the term ‘recurrent miscarriage’ .

- Some professional bodies or organizations, such as ESHRE and the American Society for Reproductive Medicine (ASRM) now define recurrent miscarriage as the loss of ≥ 2 consecutive pregnancies for investigations; however, the previous definition of ≥ 3 consecutive pregnancy losses remains in use by others, such as the *RCOG , the* Health Service Executive (HSE) in Ireland *and the French College* of Gynaecologists and Obstetricians

- Evidence-based, up-to-date clinical practice guidelines (CPG) are required to inform the effective management of recurrent miscarriage .

- About 70% of women who have experienced two recurrent losses will conceive a subsequent pregnancy, with a 70% success rate .

- The risk of further miscarriage increases after each successive pregnancy loss, reaching about 40% after 3 consecutive pregnancy losses .

- A previous live birth does not prevent a woman experiencing recurrent miscarriage .

- The prognosis worsens with increasing maternal age .

- The suggested causes of recurrent miscarriage include :
  - -- Uterine anomalies (fibroids, uterine septae),
  - -- Endocrine disorders (thyroid disease),
  - -- Autoimmune diseases (lupus),
  - -- Acquired thrombophilia ,
  - -- Genetic causes, in particular balanced translocations .

- Others, such as:
  - Chronic endometritis,
  - Infectious diseases,
  - Inherited thrombophilia,
  - luteal phase deficiency,
  - High sperm DNA fragmentation levels,
  - Polycystic ovary syndrome ,
  - High body mass index,

  have been proposed, but remain debated .

Investigations

- ***'Anatomical investigations'***:

- It was generally agreed that uterine anatomy should be assessed as part of the routine investigation of recurrent miscarriage.

- Opinions differed, however, on what the most appropriate investigation was, with little supporting evidence.

- Many CPG agreed that ultrasound is a suitable primary investigation for assessing pelvic anatomy .

- No consensus, however, was reached on what second-line investigations were more appropriate, with SIS , HSG , 3D TVS hysterosalpingo-contrast-sonography, and MRI all suggested.

- ***'Metabolic and endocrinologic factors' :***

✓ No clear agreement was reached, with some conflicting recommendations.

✓ TSH was recommended by three CPG .

✓ TPO antibody testing was recommended only in the event of abnormal TSH by two of the three CPG , whereas they were recommended as standard tests by three CPG .

✓ PRL level testing was recommended as standard by two CPG .

✓ Three CPG recommended a screen for diabetes .

- ***'Thrombophilia screening' :***
- Greater consensus was reached in this section with 10 CPG recommending antiphospholipid antibodies (APLA) after two or three miscarriages as standard .
- Four specified repeating APLA after 12 weeks .
- The remaining CPG requested APLA testing on meeting certain conditions, i.e. not as standard after two or three miscarriages .
- Only 1 CPG recommended an inherited thrombophilia screen as standard.
- Only 1 CPG suggested methylenetetrahydrofolate reductase (MTHFR) genetic screening and did not recommend it as standard.

- ***'Genetic factors' :***

- Five CPG recommended karyotyping of pregnancy tissue as standard ; two did not routinely recommend, but on an individual basis as an explanatory investigation .

- A further one stated that, in cases of :
  - Congenital anomalies,
  - IUGR ,
  - In any fetal loss < 20W ,

  if quantitative fluorescent polymerase chain reaction methodologies, other-directed diagnostic inquiries, or both, did not provide a diagnosis and further cytogenetic analysis is intended, karyotype should be replaced with chromosomal microarray analysis .

- Parental karyotyping was suggested as a standard investigation by three CPG if pregnancy tissue was not available .

- Two CPG suggested it if the pregnancy tissue testing reported an abnormality .

- Two CPG mentioned other genetic tests on women and men .

- ***'Immunological screening':***

- The consensus amongst CPG in relation to immunological screening was that :
  - human leukocyte antigen analysis,
  - peripheral natural killer cell analysis,
  - uterine natural killer cell analysis ,
  - T helper 1 and 2 measurements

  were all experimental .

- The *ESHRE Early Pregnancy Guideline Development Group (2017)* cited an exception for one disorder in which women had miscarriages after one previous male child.

- ***'Male factors':***

- Four of the recommendations concerning male factors related to sperm testing: three recommended sperm testing, with sperm DNA fragmentation .

- ***'Microbiological factors' :***
- Two of these CPG recommended routinely screening for infections,
  - *one of these* recommending that endometrial biopsy may be carried out to rule out chronic endometritis *;*
  - *another* CPG recommended testing for Rubella immune status .

- Four CPG related to ***'Risk factors' :***
- alcohol, smoking, caffeine, weight status, physical activity, and the need to evaluate these .

- One CPG related to ***'Haematology'*** and stated that ;
  - full blood count ,
  - electrolytes ,
  - liver function tests

  should be standard investigations .

- Two CPG related to ***'Unexplained recurrent miscarriage'*** and how this diagnosis can be made when investigations have been conducted, and no cause of recurrent miscarriage found .

Treatment

- ***'Metabolic or endocrinologic factors':***

- Three CPG recommended that overt hypothyroidism is treated in recurrent miscarriage .

- *Two CPG stated* that subclinical hypothyroidism (TSH >4.0 mIU/l) should be treated in the presence of recurrent miscarriage .

- Three CPG recommended that treatment of subclinical hypothyroidism in recurrent miscarriage should be considered as benefits may outweigh risks .

- The recommendations were less clear on treatment if women were euthyroid and had antibodies ;
  - ✓ some recommended treatment ,
  - ✓ some recommended treatment if other autoimmune disease was present ,
  - ✓ some stated that the benefits might outweigh the risks ,
  - ✓ some *did not recommend treatment.*
- Two CPG stated that progesterone treatment had insufficient evidence demonstrating benefit , whereas three suggested it may be of help .
- Three CPG recommended bromocriptine for hyperprolactinaemia .
- According to two CPG, HCG, metformin and growth factors were not recommended .

- ***'Uterine factors' :***

- Three CPG stated that the evidence for any of the mentioned procedures in recurrent miscarriage was insufficient .

- Two CPG recommended surgical correction of any anomaly after three miscarriages : submucosal myomectomy , septal incision .

- Some stated that myomectomy makes no difference to live birth rates after ART but that it also does not reduce the miscarriage rate.

- *Some stated that some evidence* suggested that uterine surgery may be of some efficacy but with rare serious side-effects.

- ***Overall, the evidence seems insufficient to merit advising procedures on anything but an individual basis .***

- ***'Unexplained recurrent miscarriage' :***

- Two CPG recommended reassurance of excellent prognosis for future pregnancy and supportive care .

- One CPG recommended that early IVF or ICSI as a potential alternative treatment .

- Three CPG recommended against IVIG for unexplained recurrent miscarriage .

- Two recommended against aspirin , LMWH , progesterone and natural micronized progesterone in the first trimester , *and the administration* of granulocyte-colony stimulating factor (GCSF).

- One CPG recommended against ASA + / - heparin *; lymphocyte immunization* therapy .

- This CPG also recommended against glucocorticoids in recurrent miscarriage with selected immunological biomarkers,

  folic acid for treatment of unexplained recurrent miscarriage,
  progesterone,
  intralipid therapy and
  endometrial scratching .

- ‘***Antiphospholipid syndrome’:***

- The CPG consistently recommended that antiphospholipid syndrome requires treatment with aspirin and heparin .

- Recommendations for dose of aspirin, and unfractionated heparin *compared with lowmolecular-* weight heparin, and whether a prophylactic or intermediate dose was required, were inconsistent.

- Some also recommended treatment with the caveat that they fulfilled clinical and laboratory criteria for antiphospholipid syndrome whereas some treatment in all cases.

- Some specified that antiphospholipid syndrome and recurrent miscarriage only warranted aspirin and heparin if there was a history of venous thromboembolism.

- ***'Immunotherapy' :***
- All CPG were in agreement that immunotherapies were not recommended outside of clinical trials or in specific autoimmune diseases , except for one which recommended IVIG for recurrent miscarriage and cellular immune abnormalities.

- ***'Thrombophilia' :***
- Most were in agreement that inherited thrombophilia and a history of recurrent miscarriage are insufficient to warrant aspirin and heparin prophylaxis in the absence of thrombotic events or risk factors.

- One suggested IVIG as an alternative if heparin, aspirin, or both, were not tolerated.

- ***'Genetic factors' :***

- Two CPG stated *that preimplantation genetic tests (PGT) should not be undertaken routinely .*

- One CPG stated that the value of PGT for aneuploidy (PGT-A) as a universal screening test for all IVF patients has yet to be determined .

- One recommended against PGT-A for recurrent miscarriage without a genetic cause.

- Some made a point of declaring that PGT and IVF do not lead to a higher live birth rate in women who experience recurrent miscarriage, whereas some clearly stated the natural live birth rate in this cohort is, in fact, higher than with PGT and IVF.

- ***'Male factors' :***

- Two CPG recommended against sperm selection .

- One recommended against antioxidants for men .

- A*nother* recommended : smoking cessation,
  normal body weight,
  limited alcohol consumption ,
  normal exercise pattern

  in couples who have experienced recurrent miscarriage .

- ***'Vitamins' :***

- One CPG recommended pre-conceptual folic acid supplementation, vitamin B6 and B9 (and during pregnancy, if occurs), in women who had experienced recurrent miscarriage and a diagnosis of :
  - ✓ B9 deficiency ,
  - ✓ hyperhomocysteinaemia, or both.

- *Two CPG* recommended advising on multi-vitamins that are safe during pregnancy, if asked .

- ***'Microbiological factors' :***
- One consensus-based CPG recommended that antibiotics may be administered to women who had experienced recurrent miscarriage and chronic endometritis *; however, another* stated that any use of antibiotics was not supported by the evidence .

- ***'Prognosis' :***
- One recommendation from one CPG including basing prognosis on the :

✓ number of preceding losses ,and

✓ female age .

- ***ART and how oocyte donation :***

- One recommendation from one CPG could be discussed as an alternative treatment in women with low ovarian reserve who have experienced recurrent miscarriage .

Counselling and/or supportive care:

- Thirteen recommendations in five CPG related to ‘risk factors’ and providing information, discussing risk factors for recurrent miscarriage with patients, or both.

- Risk factors primarily included :
  - ✓ age,
  - ✓ Anatomical factors,
  - ✓ endocrine factors ,
  - ✓ metabolic factors
  - ✓ genetic factors,
  - ✓ smoking,
  - ✓ drug ,
  - ✓ alcohol use,
  - ✓ obesity or underweight,
  - ✓ diet (caffeine consumption) ,
  - ✓ physical inactivity .

DISCUSSION

- The results of a recent systematic review of the current evidence on the prevalence of abnormal test results for recurrent miscarriage among patients with 2 versus ≥ 3 pregnancy losses, were *supportive of investigations after two pregnancy losses in couples who had experienced recurrent miscarriage .*

- The authors stressed the need for additional studies on the prognostic value of test results used in the recurrent miscarriage population .

- Our review illustrates that there are clear gaps in the evidence base in relation to many aspects of recurrent miscarriage and emphasizes the need for more research in the area to better inform CPG development and, ultimately, practice.

ESHRE guideline 2018 :

(European Society of Human Reproduction and Embryology)

Recurrent pregnancy loss

- This European guideline looks at how best to care for people who have experienced recurrent pregnancy loss based on the evidence currently available.

- Recurrent pregnancy loss is defined as:
  - the loss of ≥ 2 pregnancies,
  - losses from the time of conception until 24 weeks of gestation,

  it affects around 1–2% of couples.

- This definition includes pregnancy losses both after spontaneous conception and ART, but excludes ectopic and molar pregnancies .

- Information provision is one of the important aims of a RPL clinic.

- The first visit at the clinic should allow time for the clinician to review the patient's history, to answer questions and to propose a plan for investigations and, perhaps, treatment.

- The first visit is the opportunity to provide general information about RPL incidence, causes and investigations, and to link it to the patient's history.

What are the known risk factors of RPL?

- The risk of pregnancy loss is lowest in women aged 20 to 35 years and rapidly increases after the age of 40 years .

- Stress is associated with RPL, but couples should be informed that ***there is no evidence that stress is a direct cause of pregnancy loss .***

Are health behaviour modifications relevant for reducing the risk of pregnancy loss in women with a history of RPL?

- smoking could have a negative impact on their chances of a live birth, and therefore ***cessation of smoking is recommended.***

- maternal obesity or being significantly underweight is associated with obstetric complications and could have a negative impact on their chances of a live birth and on their general health .

- ***Striving for a healthy normal range BMI is recommended.***

- excessive alcohol consumption is a possible risk factor for pregnancy loss and a proven risk factor for foetal problems .

- ***Couples with RPL should be advised to limit alcohol consumption.***

- There was insufficient evidence for recommendations on other lifestyle factors, including exercise and caffeine intake .

What is the value of screening for genetic factors in the diagnosis of RPL?

- ***Genetic analysis of pregnancy tissue is not routinely recommended*** but it could be performed for explanatory purposes .

- For genetic analysis of the pregnancy tissue, array-based comparative genomic hybridization (array-CGH) is recommended based on a reduced maternal contamination effect .

- ***Parental karyotyping is not routinely recommended in couples with RPL.***

  It could be carried out after individual assessment of risk .

What is the value of thrombophilia screening in women with RPL?

- For women with RPL, we suggest not to screen for hereditary thrombophilia unless in the context of research, or in women with additional risk factors for thrombophilia .

- For women with RPL, we recommend screening for antiphospholipid antibodies (LA , and ACA IgG and IgM), after 2 pregnancy losses .

- For women with RPL, screening for β2 glycoprotein I antibodies can be considered after 2 pregnancy losses .

What is the value of immunological screening in the diagnosis of RPL?

- ***HLA determination in women with RPL is not recommended in clinical practice .***

- Measurement of anti-HY antibodies in women with RPL is not recommended in clinical practice .

- Cytokine testing should not be used in women with RPL in clinical practice .

- Cytokine polymorphisms should not be tested in women with RPL .

- There is insufficient evidence to recommend NK cell testing of either peripheral blood or endometrial tissue in women with RPL .

- Testing anti-HLA antibodies in women with RPL is not recommended .

- *ANA testing could be considered for explanatory purposes .*

What is the value of screening for endocrinological abnormalities in the diagnosis of RPL?

- ***Thyroid screening (TSH and TPO) is recommended in women with RPL .***

- Abnormal TSH and TPO levels should be followed up by thyroxine (T4) testing in women with RPL .

- Assessment of PCOS , fasting insulin and fasting glucose is not recommended in women with RPL to improve next pregnancy prognosis .

- ***Prolactin testing is not recommended in women with RPL in the absence of clinical symptoms of hyperprolactinemia (oligo/ amenorrhoea) .***

- Ovarian reserve testing is not routinely recommended in women with RPL .

- Luteal phase insufficiency testing is not recommended in women with RPL .
- Androgen testing is not recommended in women with RPL .
- LH testing is not routinely recommended in women with RPL .
- Measurement of homocysteine plasma levels is not routinely recommended in women with RPL .
- Even though one study showed a significant prevalence of vitamin D deficiency in women with RPL, there are no indications that vitamin D status is a contributing factor for RPL .
- Moreover, there is no report of an association between vitamin D status and miscarriage, and hence ***testing of vitamin D status is not recommended for women with RPL***. Irrespective of RPL, vitamin D supplementation is nowadays frequently prescribed in pregnant women.

What is the value of anatomical investigations in the diagnosis of RPL?

- ***All women with RPL should have an assessment of the uterine anatomy .***

- The preferred technique to evaluate the uterus is TV - 3D ultrasound , which has a high sensitivity and specificity, and can distinguish between septate uterus and bicorporeal uterus with normal cervix .

- SHG is more accurate than HSG in diagnosing uterine malformations.
  It can be used to evaluate uterine morphology when 3D ultrasound is not available, or when tubal patency has to be investigated .

- MRI is not recommended as first line option for the assessment of uterine malformations in women with RPL, but can be used where 3D ultrasound is not available .

Does the quality of the male gametes contribute to RPL?

- In the male partner, ***it is suggested to assess life style factors :***

✓ smoking,
✓ alcohol consumption,
✓ exercise pattern, and
✓ body weight

- Assessing sperm DNA fragmentation in couples with RPL can be considered for explanatory purposes, based on indirect evidence .

*Which therapeutic interventions should be offered to couples with RPL due to **genetic/chromosomal causes** to increase live birth rate?*

- All couples with results of an abnormal foetal or parental karyotype should receive genetic counselling , and be informed about the possible treatment options available including their advantages and disadvantages.

- The limited evidence for preimplantation genetic testing (PGT) in couples with RPL shows no clear benefit of treatment.

*Which therapeutic interventions should be offered to couples with RPL and **thrombophilia** to increase the chance of a live birth?*

- For women with hereditary thrombophilia and a history of RPL, we suggest not to use antithrombotic prophylaxis unless :

✓ in the context of research, or

✓ if indicated for VTE prevention .

- For women who fulfil the laboratory criteria of APS and have a history of ≥ 3 pregnancy losses, we suggest administration with low dose aspirin (75–100 mg/day), starting before conception, and a prophylactic dose heparin starting at date of a positive pregnancy test .

- The guideline development group (GDG) suggests offering anticoagulant treatment for women with *2 pregnancy losses* and APS , only in the context of clinical research.

*Which therapeutic interventions should be offered to couples with RPL with suspicion of **immunological** background to increase live birth rate?*

- No immunological biomarker, except for high-titre antiphospholipid antibodies, can be used for selecting couples with RPL for specific immunological treatments.

*Which therapeutic interventions should be offered to couples with RPL & **metabolic or hormonal abnormalities** to increase live birth rate?*

- Overt hypothyroidism arising before conception or during early gestation should be treated with levothyroxine in women with RPL .
- There is conflicting evidence regarding treatment effect of levothyroxine for women with subclinical hypothyroidism and RPL.
- Treatment of women with subclinical hypothyroidism may reduce the risk of miscarriage, but the potential benefit of treatment should be balanced against the risks .

- If women with subclinical hypothyroidism and RPL are pregnant again, TSH level should be checked in early gestation (7–9 weeks), and hypothyroidism should be treated with levothyroxine.

- There is insufficient evidence to support treatment with levothyroxine in euthyroid women with thyroid antibodies and RPL outside a clinical trial .

- There is insufficient evidence to recommend *metformin* supplementation in pregnancy to prevent pregnancy loss in women with RPL and glucose metabolism defects .

- *Bromocriptine* treatment can be considered in women with RPL and hyperprolactinemia to increase live birth rate .

- Preconception counselling in women with RPL could include the general advice to consider prophylactic *vitamin D* supplementation .

- There is insufficient evidence to recommend the use of *progesterone* or *hCG* to improve live birth rate in women with RPL and LPD .

- Controlled ovarian stimulation by *HMG* could be beneficial for decreasing the chance of a next pregnancy loss in women with RPL diagnosed with LPD .

- The evidence was too limited to support recommending controlled ovarian stimulation in women with RPL but without PCOS .

*Which therapeutic interventions should be offered to women with RPL and **uterine abnormalities** to increase live birth rates?*

- Hysteroscopic septum resection has beneficial effects (improving live birth rates, and decreasing miscarriage rates, without doing harm), and should be evaluated in the context of surgical trials in women with RPL and ***septate*** uterus .

- Metroplasty is not recommended for ***bicornuate*** uterus with normal cervix and RPL .

- Uterine reconstruction is not recommended for ***unicornuate*** uterus and RPL.

- There is insufficient evidence in favour of metroplasty in women with ***didelphic*** uterus and RPL .

- There is insufficient evidence supporting hysteroscopic removal of ***submucosal fibroids*** or endometrial ***polyps*** in women with RPL .
- Surgical removal of ***intramural fibroids*** is not recommended in women with RPL.
- There is insufficient evidence to recommend removing ***fibroids*** that ***distort*** the uterine cavity .
- There is insufficient evidence of benefit for surgical removal of intrauterine ***adhesions*** for pregnancy outcome .
- Women with a history of ***second-trimester pregnancy losses*** and suspected cervical weakness should be offered serial cervical sonographic surveillance.

*Which therapeutic interventions should be offered to couples with RPL due to **male factor** to increase live birth rate?*

- Couples with RPL should be informed that smoking, alcohol consumption, obesity and excessive exercise could have a negative impact on their chances of a live birth, and therefore :

✓ cessation of smoking,
✓ a normal body weight,
✓ limited alcohol consumption,
✓ a normal exercise pattern

is recommended.

- Sperm selection is ***not recommended*** as a treatment in couples with RPL.

- Antioxidants for men have ***not*** been shown to improve the chance of a live birth.

*Which therapeutic interventions should be offered to couples with **unexplained RPL** to increase live birth rate?*

- Lymphocyte immunization therapy should ***not*** be used as treatment for unexplained RPL as it has no significant effect and there may be serious adverse effects .

- IvIg is ***not*** recommended as a treatment of RPL .

- Glucocorticoids are ***not*** recommended as a treatment of unexplained RPL or RPL with selected immunological biomarkers .

- There is ***insufficient*** evidence to recommend intralipid therapy for improving live birth rate in women with unexplained RPL.

- There is ***insufficient*** evidence to recommended granulocyte colony stimulating factor (G-CSF) in women with unexplained RPL .

- There is ***no*** *evidence* to recommended endometrial scratching in women with unexplained RPL.

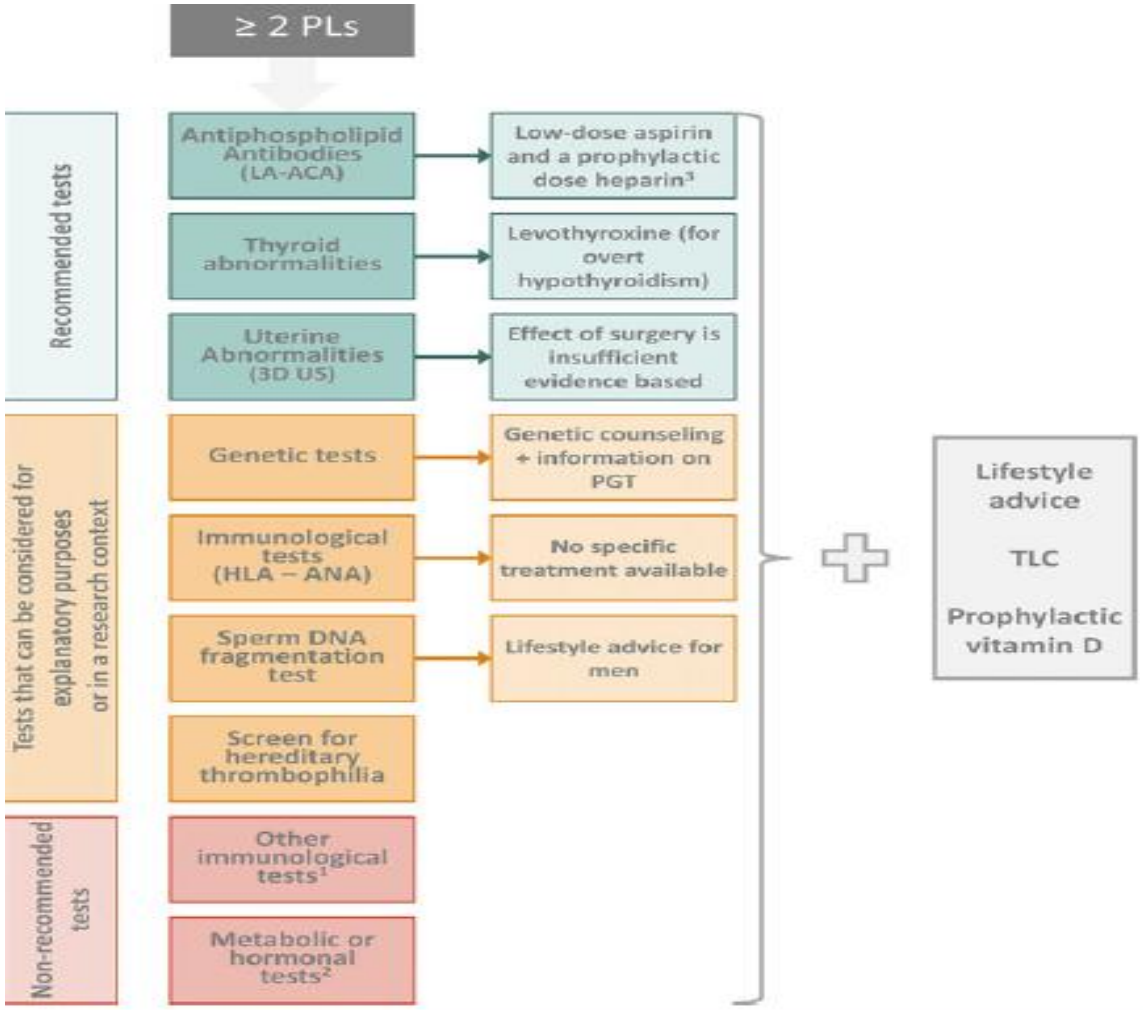
- Heparin or low dose aspirin are ***not*** recommended, as there is evidence that they do not improve live birth rate in women with unexplained RPL

- Low dose folic acid is routinely started preconceptionally to prevent neural tube defects, but it has ***not*** *been shown* to prevent pregnancy loss in women with unexplained RPL.

- Vaginal progesterone does ***not*** *improve* live birth rates in women with unexplained RPL .

- If women with RPL ask about using multivitamin supplements, they should be advised on multivitamin supplements that are safe in pregnancy.

summary of the recommendations for investigations and treatments of couples with recurrent pregnancy loss




Thanks all with best wishes