RECURRENT PREGNANCY LOSS

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ESHRE Early Pregnancy Guidline Development Group
The prevalence of RPL defined as three or more consecutive miscarriages before gestation week 22,
A diagnosis of Recurrent Pregnancy Loss (RPL) could be considered after the loss of **two or more** pregnancies.

A pregnancy in the definition is confirmed at least by either serum or urine b-hCG, i.e. including non-visualized pregnancy losses (biochemical pregnancy losses and/or resolved and treated pregnancies of unknown location).

Ectopic and molar pregnancies are not included.

Pregnancy losses both after spontaneous conception and after ART treatments should be included in the definition.

Primary RPL is described as RPL without a previous ongoing pregnancy (viable pregnancy) beyond 24 weeks’ gestation, while secondary RPL is defined as an episode of RPL after one or more previous pregnancies progressing beyond 24 weeks’ gestation.

Recurrent “Early” Pregnancy Loss (REPL) is the loss of two or more pregnancies before 10 weeks of gestational age.

Prevalence of RPL is between 0.8-1.4% if only clinical miscarriages (confirmed by ultrasound and/or histology) are included; adding biochemical losses increases the prevalence to 2% to 3%.
NEW TERMINOLOGY

ASRM Practice Committee Opinion (2012)

- Recurrent Pregnancy Loss: ≥2 more failed **clinical** pregnancies, documented by ultrasound or histopathology
  - Include failed visualized ectopic?
  - Clinical pregnancy = Miscarriage?

- Based on this definition, do not include pregnancies not documented by US or histopathology:
  - Biochemical pregnancy loss
  - Spontaneously resolved pregnancy of unknown location (PUL)
  - Persisting pregnancy of unknown location (PPUL)
  - Pregnancy loss suggestive of miscarriage but US not performed and tissue not collected
NEW TERMINOLOGY

American Congress of Obstetricians and Gynecologists (2017)

- Recurrent Early Pregnancy Loss (REPL): ≥2 intrauterine pregnancy losses <10 wks
- Recurrent Pregnancy Loss (RPL): ≥2 intrauterine pregnancy losses
- Based on this definition, do not include failed visualized ectopic pregnancy

- Recurrent spontaneous abortion
- Habitual abortion
Risk factors

• Women should be sensitively informed that the risk of pregnancy loss is lowest in women aged 20 to 35 years.
• Women should be sensitively informed that the risk of pregnancy loss rapidly increases after the age of 40.
• Stress is associated with RPL, but couples should be informed that there is no evidence that stress is a direct cause of pregnancy loss.

• Couples with RPL should be informed that smoking, maternal obesity or being significantly underweight excessive alcohol consumption could have a negative impact on their chances of a live birth.
Investigations in RPL

• Medical and family history could be used to tailor diagnostic investigations in RPL

• Information on previous diagnosis of medical conditions that may be associated with RPL, including thrombophilia, PCOS, and diabetes, or a family history of hereditary thrombophilia should be collected
some diagnostic tests, although not recommended for all couples, can be relevant only in selected RPL couples, for instance:

- **prolactin** testing in women with clinical symptoms of hyperprolactinemia (oligo-amenorrhea)
- **HLA class II** determination in women with secondary RPL after the birth of a boy
- **sperm DNA fragmentation** assessment can be more relevant in males with unhealthy lifestyles (smoking, alcohol, excessive exercise, unhealthy body weight)
• parental karyotyping is less relevant in couples with female age above 39, less than 3 pregnancy losses and a negative family history, as in these couples the chance of being a carrier of a translocation is very low (below 2.2 %)

• Female age and number of previous losses are the only known factors consistently shown to impact prognosis
Screening for genetic factors

- Aneuploidies occur in comparable frequencies in both women with sporadic and recurrent pregnancy loss.
- Determining the chromosomal status of pregnancy tissue from women with recurrent pregnancy loss may provide them with a cause or reason for the particular loss being investigated, but it does not necessarily rule out other underlying conditions.
- No clear effect of genetic testing of the pregnancy tissue on prognosis (subsequent live birth) has been described so far.
- Genetic analysis of pregnancy tissue is not routinely recommended but it could be performed for explanatory purposes.
- The preferred method of genetic analysis is array-CGH, as this is not limited by tissue culture failure or false negative results due to maternal cell contamination.
Genetic and epigenetic variations associated with idiopathic recurrent pregnancy loss

Luis Alejandro Arias-Sosa¹ - Iván Darío Acosta¹ - Elkin Lucena-Quevedo² - Harold Moreno-Ortiz² - Clara Esteban-Pérez² - Maribel Forero-Castro¹

Fig. 3  Associated factors of RPL. The known etiology includes proven causes of RPL. The idiopathic etiology is limited to cases in which there is no scientific consensus, but recent studies have found associations with the disease.
Parental Genetic Analysis

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

- It could be carried out after individual assessment of risk: previous birth of a child with congenital abnormality, translocation in the pregnancy tissue, child with unbalanced chromosome abnormality.

- Parental karyotyping may provide couples with a possible contributing factor and prognostic information for the subsequent pregnancy.
• Regarding prognosis, couples should be informed that, even if a parental abnormality is found after karyotyping, the cumulative live birth rates are good, as are the chances of a healthy child, despite a higher risk of a subsequent pregnancy loss.

• They should be informed of the limitations of karyotyping, including that karyotyping does not predict unbalanced translocation in next pregnancy.
Recurrence of pregnancy loss (RPL) is a common, yet elusive, complication of pregnancy. Among couples at high risk of RPL, such as those carrying a structural chromosomal rearrangement, preimplantation genetic diagnosis (PGD) has been proposed as a tool to improve live birth rates and reduce the incidence of miscarriage; however, no clear consensus has been reached on its benefits in this population. This systematic review summarizes existing published research on the effect of PGD on pregnancy outcomes among carriers of chromosomal abnormalities with RPL. A comprehensive search of common databases was conducted, which yielded 20 studies. Meta-analysis was precluded owing to significant heterogeneity between studies. The primary outcome of interest was live birth rate (LBR), and a pooled total of 847 couples who conceived naturally had a LBR ranging from 25–71% compared with 26.7–87% among 562 couples who underwent IVF and PGD. Limitations of the study include lack of large comparative or randomized control studies. Patients experiencing RPL with structural chromosomal rearrangement should be counselled that good reproductive outcomes can be achieved through natural conception, and that IVF-PGD should not be offered first-line, given the unproven benefits, additional cost and potential complications associated with assisted reproductive technology.
Recurrent pregnancy loss evaluation combined with 24-chromosome microarray of miscarriage tissue provides a probable or definite cause of pregnancy loss in over 90% of patients

F. Popescu¹, C. R. Jaslow¹, and W. H. Kutteh².³.⁴.*

**WHAT IS KNOWN ALREADY:** RPL is estimated to occur in 2–4% of reproductive age couples. A probable cause can be identified in approximately 50% of patients after an ASRM recommended workup including an evaluation for parental chromosomal abnormalities, congenital and acquired uterine anomalies, endocrine imbalances and autoimmune factors including antiphospholipid syndrome.

**STUDY DESIGN, SIZE, DURATION:** Single-center, prospective cohort study that included 100 patients seen in a private RPL clinic from 2014 to 2017. All 100 women had two or more pregnancy losses, a complete evaluation for RPL as defined by the ASRM, and miscarriage tissue evaluated by 24-chromosome microarray analysis after their second or subsequent miscarriage.

**MAIN RESULTS AND THE ROLE OF CHANCE:** A definite or probable cause of pregnancy loss was identified in the vast majority (95/100; 95%) of RPL patients when a 24-chromosome pair microarray evaluation of POC testing is combined with the standard ASRM RPL workup evaluation at the time of the second or subsequent loss. The ASRM RPL workup identified an abnormality and a probable explanation for pregnancy loss in only 45/100 or 45% of all patients. A definite abnormality was identified in 67/100 patients or 67% when initial testing was performed using 24-chromosome microarray analyses on the miscarriage tissue. Only 5/100 (5%) patients, who had a euploid loss and a normal ASRM RPL workup, had a pregnancy loss without a probable or definitive cause identified. All other losses were explained by an abnormal 24-chromosome microarray analysis of the miscarriage tissue, an abnormal finding of the RPL workup, or a combination of both.

Results from the cost analysis indicated that an initial approach of using a 24-chromosome microarray analysis on miscarriage tissue resulted in a 50% savings in cost to the health care system and to the patient.
Figure 1  The proposed testing algorithm for recurrent pregnancy loss (RPL) evaluation and treatment based on the chromosome micro-array analysis (CMA) diagnosis obtained from products of conception (POC) at the time of the second or subsequent pregnancy loss.

In conclusion, these data support the proposed new algorithm for the evaluation of RPL. The performance of a CMA of miscarriage tissue after the second or subsequent pregnancy loss, followed by the ASRM RPL workup when POC results are normal, is an effective means for determining the cause of RPL. The combination of a genetic evaluation on miscarriage tissue with an evidence-based evaluation for RPL will provide a probable or definitive cause in over 90% of all miscarriages.
HEREDITARY THROMBOPHILIA

• There is no, or at best a weak, association between RPL and hereditary thrombophilia.

• A significant association between the factor V Leiden (F5 c.1691G>A) genotype and RPL (OR 2.02; 95% CI 1.60-2.55; based on 33 case-control studies), and between the factor V Leiden mutation and the risk of a pregnancy loss in the next pregnancy (OR 1.93; 95% CI 1.21–3.09; based on 4 prospective cohort studies).

• Carriers of the Factor V Leiden mutation were more likely to have a subsequent loss as compared to non-carriers (OR 2.03; 95% CI 1.29-3.17; based on eight cohort studies).
• With regard to the clinical utility, the reviewers concluded that a positive test result was not associated with improved outcomes for the couples based on the lack of an effect of treatments on pregnancy outcome.

• In addition, there were several harms in testing, including anticoagulant-related maternal risks, costs, and unneeded treatment after a false-positive results.
ACQUIRED THROMBOPHILIA

- Testing for aPL antibodies can provide a possible cause of the PL, and treatment in the next pregnancy can prevent antiphospholipid syndrome (APS)-associated pregnancy complications.

- Based on a study showing treatment can improve LBR in women with RPL and aβ2GPI, screening can be considered
Thrombophilia Screening

• For women with RPL, it is suggested **not to** screen for **hereditary thrombophilia** except for women with additional risk factors for thrombophilia.

• For women with RPL, it **is recommended** to screen for **antiphospholipid antibodies** (Lupus Anticoagulant [LA], and Anticardiolipin antibodies [ACA IgG and IgM]), after two pregnancy losses.

• For women with RPL, screening for **β2 glycoprotein I antibodies (αβ2GPI)** can be considered after two pregnancy GPP losses.

• Measurement of **homocysteine plasma levels is not** routinely recommended in women with RPL.
Factor V Leiden mutation in women with early recurrent pregnancy loss: a meta-analysis and systematic review of the causal association

C. Sergi · T. Al Jishi · M. Walker

Results  Nine studies met the inclusion criteria and were selected for review. A total of 2,147 women were screened for the FVL mutation, 1,305 women with early RPL, and 842 women with no gestational complications. Women with early RPL had indeed a statistically significantly increased carrier frequency of FVL mutation, the common OR being 1.68 (95 % CI: 1.16–2.44).

Conclusion  FVL carrier state may increase the susceptibility for early RPL. Testing for FVL mutation should be considered in women with unexplained early RPL and thrombophylaxis has been suggested in women with unexplained RPL associated with FVL mutation.
A significant association was found between G20210A and RPL, with a combined odds ratio (OR) of 1.81 (95% confidence interval [CI]: 1.26-2.60).
### Table 5
Comparison of recommendations in the most recent German, American and British guidelines on RSA (<20th week of pregnancy) and maternal thrombophilia without prior VTE.

<table>
<thead>
<tr>
<th>RSA without VTE</th>
<th>German guideline [37]</th>
<th>American guideline [38]</th>
<th>British guideline [39]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening for APS (LA, anticoagulant antibodies IgG and IgM, anti-β2 GP1 antibodies IgG and IgM)</td>
<td>Yes</td>
<td>Yes (level of evidence 1B)</td>
<td>Yes (level of evidence D)</td>
</tr>
<tr>
<td>Screening for hereditary thrombophilia</td>
<td>AT activity, APC resistance/FVL, PGM</td>
<td>No (level of evidence 2C)</td>
<td>Only if the reason for pregnancy loss from the 2nd trimester is unclear: FVL, PGM, protein S deficiency (level of evidence D)</td>
</tr>
<tr>
<td>Prophylactic administration of medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary thrombophilia</td>
<td>No administration outside clinical studies</td>
<td>No (level of evidence 2C)</td>
<td>LMWH for pregnancy losses from the 2nd trimester (level of evidence A)</td>
</tr>
<tr>
<td>APS</td>
<td>Low-dose ASA and LMWH</td>
<td>Low-dose ASA and LMWH (level of evidence 1B)</td>
<td>Low-dose ASA and LMWH (level of evidence B)</td>
</tr>
</tbody>
</table>


### Table 6
Recommendation for LMWH administration during pregnancy if maternal thrombophilia is present.

<table>
<thead>
<tr>
<th></th>
<th>Recurrent early pregnancy loss/late pregnancy loss</th>
<th>Increased maternal risk for VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary thrombophilia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>APS</td>
<td>75–100 mg ASA/day, optimally initiated before conception, combined with LMWH from the time of a positive pregnancy test until 6 weeks post partum¹</td>
<td></td>
</tr>
</tbody>
</table>

LMWH: low molecular weight heparin; VTE: venous thromboembolism; APS: antiphospholipid syndrome.

¹ During pregnancy, blood pressure, proteinuria and maternal weight from the 16th–20th GW must be monitored along with monthly monitoring of fetal growth and placental perfusion.

Osteoporosis prophylaxis must be combined with monitoring thrombocyte counts during LMWH treatment in accordance with the AWMF S3 guideline [41] (between the 5th to 15th day after the start of LMWH; a drop of the thrombocyte count to less than 50% of the initial count is suspicious for heparin-induced thrombopenia type IIa, which would necessitate the immediate cessation of heparin therapy).
Immunological testing

• **Human Leukocyte Antigen (HLA)** determination in women with RPL is **not recommended** in clinical practice.

• Cytokine testing **should not be used** in women with RPL in clinical practice

• There is **insufficient evidence** to recommend **Natural Killer (NK) cell** testing of either peripheral blood or endometrial tissue in women with RPL
• **Antinuclear antibodies (ANA) testing** could be considered for explanatory purposes.

• Majority of case-control studies document an association to RPL and there is some evidence that **ANA presence affects the prognosis negatively**.

• Whether ANA positivity can identify a subset of women with RPL that responds beneficially to various forms of immunotherapy is unknown and can only be shown in randomized controlled trials.
Metabolic and endocrinologic factors

- **Prolactin** testing is not recommended in women with RPL in the absence of clinical symptoms of hyperprolactinemia (oligo/amenorrhea).
- **Androgen** testing is not recommended in women with RPL.
- **Luteal phase insufficiency** testing is not recommended in women with RPL.
- **Luteinizing Hormone** (LH) testing is not routinely recommended in women with RPL.
- **Ovarian reserve** 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.

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.
Endocrinologic Factors

• **Thyroid screening** (Thyroid stimulating hormone [TSH] and Thyroid peroxidase [TPO]-antibodies) **is recommended** in women with RPL.

• Abnormal TSH and TPO-antibody levels should be followed up by T4 testing in women with RPL.

• **No studies were found** that described or searched for an association between hyperthyroidism and recurrent pregnancy loss (RPL).
<table>
<thead>
<tr>
<th>Condition</th>
<th>Association</th>
<th>Contributing factor</th>
<th>Prognosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>Only sporadic PL</td>
<td>Only for sporadic PL</td>
<td>Yes</td>
<td>Supplementation of Levothyroxine</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>Yes</td>
<td>Yes</td>
<td>No clear effect as of yet.</td>
<td>Unknown if effective</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>No</td>
<td>No</td>
<td>No clear effect as of yet.</td>
<td>Yes: Propylthiouracil</td>
</tr>
<tr>
<td>TPO-antibodies</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Need for treatment studies</td>
</tr>
<tr>
<td>TG antibodies</td>
<td>No</td>
<td>Mostly detected combined with TPO antibodies</td>
<td>Yes</td>
<td>Need for treatment studies</td>
</tr>
</tbody>
</table>
PCOS AND DISTURBANCES OF THE INSULIN METABOLISM

- Assessment of polycystic ovary syndrome (PCOS), fasting insulin and fasting glucose is not recommended in women with RPL to improve next pregnancy prognosis.
- Insulin resistance is shown to be more prevalent in women with a history of RPL than in women without RPL.
- The mechanism of how insulin resistance can result in pregnancy loss is unknown.
- There are no studies on the prognostic potential.
<table>
<thead>
<tr>
<th></th>
<th>Association</th>
<th>Contributing factor</th>
<th>Prognosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCOS</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>Metformin for sporadic PL no studies for RPL</td>
</tr>
<tr>
<td>Insulin resistance*</td>
<td>YES (OR 3.6)</td>
<td>Unclear</td>
<td>No studies</td>
<td>No studies</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>Inconsistent (2 YES, 1 NO)</td>
<td>Unclear</td>
<td>No studies</td>
<td>No studies</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>NO</td>
<td>NO</td>
<td>No studies</td>
<td>No studies</td>
</tr>
</tbody>
</table>

*IR calculated based on fasting insulin and fasting glucose
Male Factors

• A meta-analysis showed a significant increase in miscarriage rates in men with high sperm DNA damage compared with those with low sperm DNA damage (RR 2.16; 95% CI 1.54-3.03).

• 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
Anatomy

- All women with RPL should have an assessment of the uterine anatomy.
- The preferred technique to evaluate the uterus is transvaginal 3D ultrasound (US), which has a high sensitivity and specificity, and can distinguish between septate uterus and bicorporeal uterus with normal cervix.
- Sonohysterography (SHG) is more accurate than hysterosalpingography (HSG) in diagnosing uterine malformations. It can be used to evaluate uterine morphology when 3D ultrasound (US) 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 US is not available.
- If a Müllerian uterine malformation is diagnosed, further investigation (including investigation of the kidneys and urinary tract) should be considered.
Treatment for RPL with genetic background

• All couples with results of an abnormal fetal or parental karyotype should receive genetic counselling

• All couples with results of an abnormal fetal or parental karyotype may be informed about the possible treatment options available including their advantages and disadvantages.
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 venous thromboembolism (VTE) prevention.
TREATMENT FOR WOMEN WITH RPL AND ANTIPHOSPHOLIPID SYNDROME (APS)

• For women who fulfill the laboratory criteria of APS and a history of three or more pregnancy losses, we suggest administration with low-dose aspirin (75 to 100 mg/day) starting before conception, and a prophylactic dose heparin (Unfractionated heparin [UFH] or Low molecular weight heparin [LMWH]) starting at date of a positive pregnancy test, over no treatment.

• The GDG suggests offering anticoagulant treatment for women with two pregnancy losses and APS, only in the context of clinical research.
TREATMENT FOR THYROID ABNORMALITIES ASSOCIATED WITH RPL

• **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** (SCH) and RPL.

• *Treatment of women with SCH 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, thyroid stimulating hormone (TSH) level should be checked in **early gestation** (7-9 weeks AD), 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.

• If women with **thyroid autoimmunity** and RPL are pregnant again, thyroid stimulating hormone (TSH) level should be checked in **early gestation** (7-9 weeks AD), and hypothyroidism should be treated with levothyroxine
PROGESTERONE OR HUMAN CHORIONIC GONADOTROPHIN (HCG) (FOR LUTEAL PHASE INSUFFICIENCY)

• There is **insufficient evidence** to recommend the use of **progesterone** to improve live birth rate in women with RPL and luteal phase insufficiency.

• There is **insufficient evidence** to recommend the use of **human chorionic gonadotrophin (hCG)** to improve live birth rate in women with RPL and luteal phase insufficiency.
Metformin

• Several studies on metformin found that it is effective in improving pregnancy outcomes in women with PCOS or insulin resistance

• In patients with PCOS, metformin was found to significantly reduce the rate of miscarriage

• There are no studies focusing on women with RPL and PCOS.

• There is insufficient evidence to recommend metformin supplementation in pregnancy to prevent PL in women with RPL and glucose metabolism defects
• however the evidence is too limited to support recommending controlled ovarian stimulation in women with RPL without PCOS.

• **Bromocriptine** treatment can be considered in women with RPL and hyperprolactinemia to increase live birth rate.
Vitamin D deficiency has been associated with obstetrical complications.

There are no studies evaluating the effect of vitamin D supplementation on the chance of a live birth in the next pregnancy in women with RPL.

Preconception counseling in women with RPL could include the general advice to consider prophylactic vitamin D supplementation (up to 4000IU/d).
In the absence of consistent evidence for an association between HHcy and RPL, assessing Hcy levels is **not routinely** recommended.

However, if HHcy is detected in women with RPL, treatments are available that can lower Hcy levels and possibly improve the chance of a live birth rate in the next pregnancy.
Treatment for uterine abnormalities in RPL

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

• Metroplasty is not recommended for bicorporeal uterus with normal cervix (former AFS bicornuate uterus) and RPL.

• Uterine reconstruction is not recommended for hemi-uterus (former AFS unicornuate uterus) and RPL.

• There is insufficient evidence in favor of metroplasty in women with bicorporeal uterus and double cervix (former AFS didelphic uterus) and RPL.
ACQUIRED INTRAUTERINE MALFORMATIONS

• 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. After hysteroscopic removal of intrauterine adhesions in women with RPL, precautions have to be taken to prevent recurrence of adhesions.
CERVICAL INSUFFICIENCY

• Women with a history of second-trimester PLs and suspected cervical weakness should be offered serial cervical sonographic surveillance.

• In women with a singleton pregnancy and a history of recurrent second-trimester pregnancy loss attributable to cervical weakness, a cerclage could be considered.

• There is no evidence that this treatment increases perinatal survival.
• **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.

• 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 and a normal exercise pattern is recommended.
Treatment for 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.
- **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.
- **Intravenous immunoglobulin** (IvIg) is not recommended as a treatment of RPL.
- **Glucocorticoids** are not recommended as a treatment of unexplained RPL or RPL with selected immunological biomarker.
- There is no evidence to recommended **endometrial scratching** in women with unexplained RPL.
- There is insufficient evidence to recommended **G-CSF** 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.

• There is insufficient evidence to recommend intralipid therapy for improving live birth rate 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.
Treatment efficacy for idiopathic recurrent pregnancy loss – a systematic review and meta-analyses

Emma Rasmek Roepke1, Margareta Hellgren2, Ragnhild Hjertberg3, Lennart Blomqvist4, Leif Matthiesen5, Emir Henic6, Sujata Lalitkumar7 & Annika Strandell2

Introduction: Medical treatment of women with idiopathic recurrent pregnancy loss is controversial. The objective was to assess the effects of different treatments on live birth rates and complications in women with unexplained recurrent pregnancy loss. Material and methods: We searched Medline, Embase, the Cochrane Library and identified 1415 publications. This systematic review included 21 randomized controlled trials regarding acetylsalicylic acid, low-molecular-weight heparin, progesterone, intravenous immunoglobulin or leukocyte immune therapy in women with ≥3 consecutive miscarriages of unknown cause. The study quality was assessed and data was extracted independently by at least two authors. Results: No significant difference in live birth rate was found, neither when acetylsalicylic acid was compared with low-molecular-weight heparin nor with placebo. Meta-analyses of low-molecular-weight heparin vs. control found no significant differences in live birth rate; risk ratio (RR) 1.47 (95% CI 0.83-2.61). Treatment with progesterone starting in the luteal phase seemed effective in increasing live birth rate; RR 1.18 (95% CI 1.09-1.27) but not when started after conception. Intravenous immunoglobulin showed no effect on live birth rate compared with placebo; RR 1.07 (95% CI 0.91-1.26). Paternal immunization compared with autologous immunization showed a significant difference in outcome; RR 1.8 (95% CI 1.34-2.41), although the studies were small and at high risk of bias. Conclusion: The literature does not allow advice on any specific treatment for idiopathic recurrent pregnancy loss, with the exception of progesterone from ovulation. We suggest that any treatment for recurrent pregnancy loss should be used within the context of a randomized controlled trial.
Invited Editorial

Pregnancy loss: French clinical practice guidelines

Fig. 3. Algorithm for evaluation and management of recurrent pregnancy loss.
Figure 2 Frequency of American Society of Reproductive Medicine—recurrent pregnancy loss (ASRM RPL) workup abnormalities among all 100 RPL patients evaluated and the recommended treatment for each abnormality result. See ‘Materials and Methods’ for details of evaluation.