Recurrent Abortion

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Recurrent pregnancy loss (RPL) is a distinct disorder defined by 2 or more failed clinical pregnancies” with a ***clinical pregnancy*** that is “documented by ultrasonography or histopathological examination”.

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

The exact prevalence of RPL is difficult to estimate, but most studies report that RPL affects 1–2% of women.

In our practice, ***we start investigating after two failed clinical pregnancies, including biochemical pregnancies for women undergoing IVF***.

The rationale for including biochemical pregnancies and non-visualized pregnancies (ectopic pregnancies) in the definition of RPL comes from a retrospective cohort study of 587 women who had three or more consecutive pregnancy losses before 12 weeks gestation. Non-visualized pregnancy losses (biochemical pregnancy losses and/or pregnancies of unknown location) had the same negative impact on future live birth as an intrauterine pregnancy losses.

Prognosis for success future pregnancies should always be based on ***the number of prior losses and the maternal age .***

The incidence of RPL increases with increasing maternal age to reach 1 in 4 by age 40.

50% of the RPL cases are still unexplained.

Risk factors

Uterine factors:

Acquired and congenital uterine abnormalities are responsible for 10 to 50 percent of RPL

- **Anomalies**
- **Leiomyoma**
- **Endometrial polyps**
- **Intrauterine adhesions**
- **Cervical insufficiency**

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

The preferred technique to evaluate the uterus is ***transvaginal 3D ultrasound (3D 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 (3D US) is not available, or when tubal patency has to be investigated.

If a Müllerian uterine malformation is diagnosed, further investigation (including investigation of the kidneys and urinary tract) should be considered.

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 (3D US) is not available..

There is fair evidence that a uterine septum contributes to miscarriage and preterm birth. (Grade B)

Some evidence suggests that a uterine septum may increase the risk of other **adverse pregnancy outcomes such as malpresentation, intrauterine growth restriction, placental abruption, and perinatal mortality.** (Grade B)

Some limited studies indicate that hysteroscopic septum incision is associated with a reduction in subsequent miscarriage rates and improvement in live-birth rates in patients with a history of recurrent pregnancy loss. (Grade C)

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 American Fertility Society classification (AFS) bicornuate uterus) and RPL.

Uterine reconstruction is not recommended for hemi-uterus (former American Fertility Society classification (AFS) unicornuate uterus) and RPL .

There is insufficient evidence in favour of metroplasty in women with bicorporeal uterus and double cervix (former American Fertility Society classification (AFS) didelphic uterus) and RPL.

•Antiphospholipid Syndrome

- **Antiphospholipid syndrome :**

Five to 15 percent of patients with RPL may have APS

Clinical events that should initiate testing for aPLs are outlined by an international consensus statement.
The guidelines include recurrent pregnancy losses before the 10th week of gestation, an unexplained loss of morphologically normal fetus at or beyond 10 weeks of gestation or a history of a normal fetus delivered before 34 weeks because of severe preeclampsia/eclampsia.

For women with RPL, we recommend screening for antiphospholipid antibodies (lupus anticoagulant [LA], and anticardiolipin antibodies [ACA IgG and IgM], β2 glycoprotein I antibodies (aβ2GPI), after two pregnancy losses.

Immunological screening

HLA determination, measurement of anti-HY antibodies , Cytokine testing, Cytokine polymorphisms, Testing anti-HLA antibodies and Antinuclear antibodies (ANA) in women with RPL is not recommended 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

Endocrine factors :

Endocrine factors may account for 15 to 60 percent of RPL

- **Diabetes mellitus**
- **Polycystic ovary syndrome**
- **Thyroid antibodies and disease**
- **Hyperprolactinemia**
- **Luteal phase defect**

Uncontrolled diabetes, thyroid disorders and hyperprolactinemia are well related to an increased risk of pregnancy loss , and based on ASRM guidelines ***should be assessed and treated in the clinical setting of RPL.***

Thyroid testing including TSH (by ASRM and ESHRE) and thyroid peroxidase antibodies (TPO-Ab; by ESHRE) are recommended in patients with RPL.

Administration of levothyroxine at a dose of 25 to 50 µg/d is recommended to keep TSH levels below 2.5 mIU/mL in the first trimester.

Hyperprolactinemia has been associated with RPL through ***alterations in folliculogenesis, oocyte maturation and shorter luteal phase.***

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

Luteal phase insufficiency testing is not recommended in women with RPL

Diabetes

An increased risk of pregnancy loss is associated with abnormal glucose levels. Accordingly, it is important to correct any abnormal levels of fasting blood glucose and/or hemoglobin A1C (HgbA1c) in the preconception period to reduce the risks as recommended by ASRM .

Assessment of polycystic ovary syndrome (PCOS), fasting insulin and fasting glucose is not recommended in women with RPL to improve next pregnancy prognosis (ESHRE)

Vitamin D testing

Pregnant women with vitamin D deficiency are at increased risk ***of adverse events such as preterm labor, gestational diabetes, small for gestational age and pre-eclampsia.*** A recent study highlighted the significant association between vitamin D deficiency and RPL.

It is suggest that all women with RPL have levels of 25-hydroxy vitamin D tested and normalized to > 30 ng/ml preconceptually to minimize pregnancy loss.

Decreased ovarian reserve

It has been demonstrated that patients with diminished ovarian reserve **have higher occurrence rate of aneuploidy , and thus higher incidence of RPL** compared to the general population.

Many clinicians advocate the use of day 3 tests of follicle stimulating hormone (FSH) and anti-müllerian hormone (AMH) to access the ovarian reserve in patients with RPL .

Ovarian reserve testing is not routinely recommended in women with RPL(ESHRE).

Genetic factors :

- Aneuploidy
- Chromosomal rearrangements
- Other

Thrombophilia and fibrinolytic factors:

ASRM and ESHRE recommend that only patients with personal or strong family history of venous thromboembolism and/or additional risk factors for thrombophilias may be tested for inherited thrombophilias in the setting of RPL.

Therefore, routine screening is for now not endorsed For women with RPL.

Environmental chemicals and stress

Personal habits

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 years.

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

Couples with RPL should be informed that smoking could have a negative impact on their chances of a live birth, and therefore cessation of smoking is recommended.

Couples with RPL should be informed that 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.

Couples with RPL should be informed that ***excessive alcohol consumption*** is a possible risk factor for pregnancy loss and a proven risk factor for foetal problems (foetal alcohol syndrome).

Couples with RPL should be advised to limit alcohol consumption.

Male factor

Both ASRM and ESHRE indicate that no evidence supports routine DNA fragmentation index screening in couples with RPL and further studies are needed on the potential benefits of antioxidant therapy.

RPL Assessment:

The ***history*** should include a description of the **gestational age** and ***characteristics*** (eg, anembryonic pregnancy, live embryo) of all previous pregnancies. Gestational age is important because RPL typically occurs at a similar gestational age in consecutive pregnancies and the most common causes of RPL vary by trimester.

Physical examination should include a general physical assessment with attention to signs of endocrinopathy (eg, hirsutism, galactorrhea) and pelvic organ abnormalities (eg, uterine malformation, cervical laceration)

We suggest the following tests for the initial evaluation of women with RPL:

•Sonohysterography for assessment of uterine abnormalities.

•Anticardiolipin antibody (IgG and IgM) titer and lupus anticoagulant performed twice, six to eight weeks apart.

•Thyroid stimulating hormone (TSH) and thyroid peroxidase antibodies.

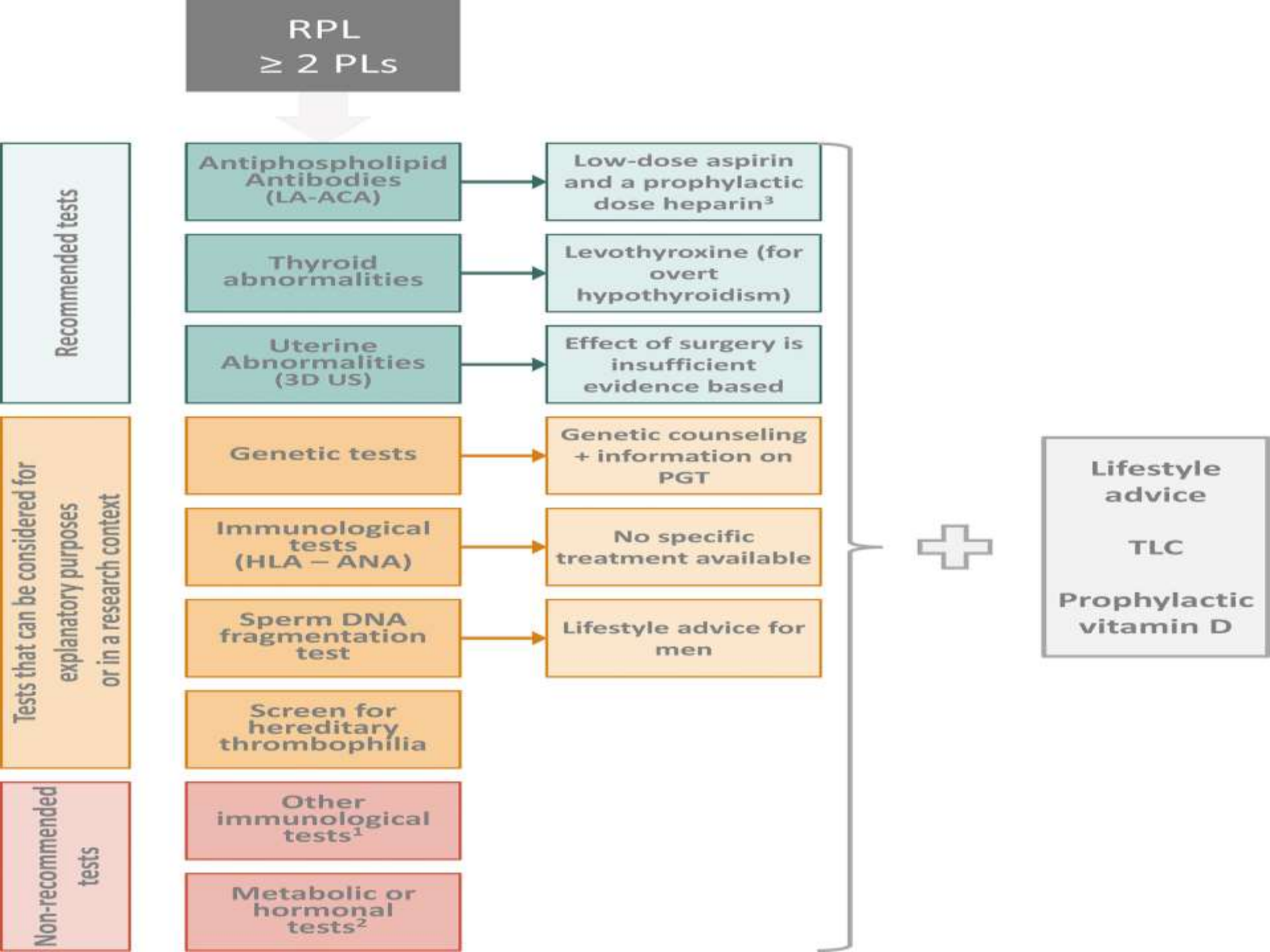
•Parental karyotype and karyotype of the abortus physical examination, and laboratory resultsif the above examinations are normal.

•Additional testing depends upon the diagnosis suggested by the history,

RPL Assessment:

On the basis of recent guidelines from the ASRM and ESHRE, there is a consensus that the assessment of RPL includes:

- ***A comprehensive history,***
- ***Certain endocrine tests,***
- ***Anatomic evaluation of the uterine cavity,***
- ***Testing for antiphospholipid antibodies***


RPL
≥ 2 PLs
Recommended tests
Antiphospholipid Antibodies (LA-ACA)
Low-dose aspirin and a prophylactic dose heparin³
Thyroid abnormalities
Levothyroxine (for overt hypothyroidism)
Uterine Abnormalities (3D US)
Effect of surgery is insufficient evidence based
Tests that can be considered for explanatory purposes or in a research context
Genetic tests
Genetic counseling + information on PGT
Immunological tests (HLA – ANA)
No specific treatment available
Sperm DNA fragmentation test
Lifestyle advice for men
Screen for hereditary thrombophilia
Non-recommended tests
Other immunological tests¹
Metabolic or hormonal tests²
Lifestyle advice
TLC
Prophylactic vitamin D

Screening for genetic factors

Cytogenetic abnormalities *(2-5% of couples):*

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(ESHRE).

Based on the review by the ASRM, karyotyping of couples may help detect parental chromosomal errors such as balanced translocations (reciprocal and Robertsonian translocations), inversions and/or deletions.

PARENTAL KARYOTYPE ABNORMALITY

Couples in whom chromosomal abnormalities are discovered in one or both partners or the abortus are generally referred for genetic counseling .

They should receive information regarding the probability of having a chromosomally normal or abnormal conception in the future. In the latter case, the ***risk of miscarriage and bearing a chromosomally abnormal offspring*** who may be phenotypically normal or abnormal and a carrier of a chromosomal defect should be discussed.

The magnitude of these risks varies according to the specific chromosomal abnormality and the sex of the carrier parent.

A number of interventions and treatments have been explored for couples with RPL due to genetic/chromosomal causes.

Genetic counselling: including a family history the outcomes following further attempts to conceive , and any relevant prenatal diagnostic tests should be offered to all couples with RPL with a known parental karyotype abnormality

KEY QUESTION:
WHICH THERAPEUTIC INTERVENTIONS SHOULD BE OFFERED TO COUPLES WITH GENETIC/CHROMOSOMAL RPL DUE TO CAUSES TO INCREASE LIVE BIRTH RATE?

Couples with karyotypic abnormalities may choose to undergo prenatal genetic studies***, such as amniocentesis or chorionic villus sampling, to determine the fetal karyotype.*** Pregnancy termination is an option if the fetus is affected.

In vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD) can be used to avoid transfer and implantation of an affected embryo.

PGD improves the pregnancy outcome of translocation carriers with a history of repeated pregnancy loss .

Gamete donation (egg or sperm), surrogacy, and adoption **are methods of preventing conception of an affected embryo. The choice depends upon the specific abnormality and parental preference.**

There are three types of preimplantation genetic testing (PGT, formerly known as PGD or preimplantation genetic diagnosis)

All require in vitro fertilization (IVF); biopsy of an embryo, or less commonly polar body/bodies (I and II), for genetic testing; and then transfer of selected fresh or frozen-thawed embryos into the uterus based on the results of genetic testing.

Preimplantation genetic testing for monogenic (single-gene) disorders (PGT-M) :

The goal of PGT-M is to establish a pregnancy that is unaffected by specific genetic characteristics, such as a known ***heritable genetic mutation carried by one or both biological parents.***

It is also used to select embryos for transfer that ***have specific characteristics, such as a particular gender or compatible human leukocyte antigen complex type***

The main reasons that couples choose PGT-M are to avoid having a pregnancy with a fetus affected by, or at risk for, a severe debilitating disease; to increase the parents' chances of having a human leukocyte antigen complex-compatible offspring; and for medically-indicated sex selection.

Preimplantation genetic testing for structural rearrangements (PGT-SR) :

The goal of PGT-SR is to establish a pregnancy that is unaffected by **a structural chromosomal abnormality (translocation) in a couple with a balanced translocation, or deletion/duplication.**

New technology may actually distinguish normal noncarrier embryos from balanced carriers

Couples with balanced translocations choose PGT-SR to reduce the risk of recurrent pregnancy loss (RPL) from unbalanced translocations

Preimplantation genetic testing for aneuploidy (PGT-A):

(formerly called preimplantation genetic screening [PGS]) :

The goal of PGT-A is to identify embryos ***with de novo aneuploidy, including subchromosomal deletions and additions (duplications), in embryo(s) of couples presumed to be chromosomally normal.***

Theoretically, avoiding transfer of these embryos will reduce the risk of miscarriage and complications related to pregnancy failure and improve the probability of conceiving a viable pregnancy.

DNA for genetic analysis is usually obtained from biopsy of trophectoderm cells from a blastocyst on day 5 or day 6 after fertilization. Biopsy of a polar body is also possible, but results are much more limited.

After biopsy, the embryo or oocyte usually must be vitrified (frozen) until results of the genetic analysis are available.

It is possible to thaw frozen unbiopsied embryos, perform PGT, and then repeat cryopreservation. Rebiopsy is also possible

Genetic analysis involves DNA amplification using a variety of strategies (eg, whole-genome amplification, polymerase chain reaction [PCR] amplification), followed by use of one of several available platforms for analysis of the amplified DNA.

Polar body biopsy (PBB) or embryo biopsy does not appear to decrease implantation and live birth rates or have any long-term harm to offspring.

Counselling should be provided to ensure that patients fully understand the benefits and limitations of PGT and other available options for prenatal diagnosis or other ways to avoid having a child with a genetic disorder.

They should understand the limitations of the technique***, the small but nonzero rate of false positive and false negative results, and the need for genetic amniocentesis (preferred) or chorionic villus biopsy to confirm PGT findings***

The data from published studies is limited by the PGS (PGT-A) technique used, as the vast majority have ***employed FISH with an embryo biopsy at Day 3, which only looks at a specific number of chromosomes at an early stage of embryo development where mosaicism is higher.***

Whole genome techniques such as array-CGH or Next Generation Sequencing (NGS) with a biopsy taken at blastocyst stage, looking at all chromosomes, are recognized to be more accurate screening techniques.

To date only one study has explored the use of the array-CGH technique, but it only included 40 women with RPL and focused on the value of morphokinetic analysis

A systematic reviews looking at PGS (PGT-A) for those couples with no known chromosomal
abnormality concluded that there is no improvement in live birth rate with PGS (PGT-A), however FISH
was used, the numbers were relatively small and the end points different.

The END