
بسم الله الرحمن الرحیم

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Definition

consecutive

≥ **2** failed clinical pregnancies as documented by ultrasound / pathologic examination

nonconsecutive

- biochemical pregnancies for women undergoing IVF are acceptable

Recurrent Miscarriage is defined as the occurance of 3 or more consecutive spontaneous abortions before 20 weeks

≥ **3** consecutive losses of clinically recognized pregnancies prior to the 20th week of gestation

- ectopic, molar, biochemical pregnancies **(not included)**

≥2

≥3

< 20 WEEKS

<24 WEEKS

ESHRE , 2017 consensus statement ; RPL ≥**2** pregnancy losses, diagnosed by serum / urine hCG .
DX includes : biochemical & treated pregnancies of unknown location but , **not** included ectopic / molar pregnancies.

ASRM , 2020 ; the spontaneous loss of ≥ **2** pregnancies

RCOG 2023 recurrent miscarriage has been defined as ≥ **3** first trimester miscarriages

DEFINITION

- RPL can be divided into primary or secondary processes :

  - Primary RPL refers to pregnancy loss in women who have never carried to viability (≥24 weeks gestation)

  - secondary RPL refers to pregnancy loss in a woman who has had a previous live birth

- The prognosis for successful pregnancy is better with secondary RPL . **(controversy)**
- The greatest determinant of the incidence of RPL is **age** .
- The **number** of previous miscarriages affects the chance of a live birth across all age groups .

INCIDENCE & PREVALENCE

- **15 %** of pregnant women experience sporadic loss of **ONE** clinically recognized pregnancy .
- **1-2 %** of pregnant women experience **TWO** consecutive pregnancy losses .
- **0.4 to 1 %** have **THREE** Consecutive pregnancy losses .
- The cause of RPL can be determined in only **50 %** .
- The prevalence is higher with increasing maternal age & at very early gestational ages .

RECURRENCE RATES

- In a **1st** pregnancy, the risk of miscarriage is **11 - 13 %** .
- After **ONE MISCARRIAGE**, this rate rises slightly to **14 - 21 %** .
- After **TWO** OR **THREE** miscarriages, the rate is **24 - 29 %** & **31 - 33 %** .

RECURRENCE RATES

- **The factors influence the rates :**
- **The cause of pregnancy loss**

  - carriers of a 22:22 translocation will almost always miscarry, 13:14 translocation have a 25 % risk.

- **Interpregnancy interval (IPI)**

  - (≤ 3 m.n) (may be)

- **Gestational age at the time of pregnancy loss**

- RPL typically occurs at a similar gestational age in consecutive .

RECURRENCE RATES

- **The factors influence the rates :**
- **Advancing maternal age**

  - age is a key factor (more common in women who are > 40 years old)
  - higher rate of pregnancy loss of both normal & abnormal conceptuses
  - poor oocyte quality

- **Increasing parity**

  - the correlation between increasing maternal age & greater parity

- **Previous pregnancy outcome**

RECURRENCE RATES

- **The factors influence the rates :**
- **consanguinity**

-Observational studies have not demonstrated an association between consanguinity & RPLS

- **Smoking , alcoholic drinks , caffeine intake**
- **Obesity**
- **BMI < 19 , BMI>25**

ETIOLOGICAL FACTORS

- anatomic
- immunological
- Endocrine
- genetic
- Thrombophilic
- environmental
- Infectious

Uterine factors

- Acquired & congenital uterine abnormalities are responsible for **10 - 50 %** of RPL .

Anomalies

- impaired uterine distention
- inflammation
- decreased vascularity in a septum
- reduction in sensitivity to steroid hormones

septate uterus

bicornuate uterus

- an Increased risk of miscarriage with septate & bicornuate uteri
- Septate uterus associated with the poorest reproductive outcome & the most common abnormality associated with RPL .
- fetal survival rate in untreated septate uterus is **6 - 28 %** and the miscarriage rate is **> 60 % .**
- The longer the septum, the worse the prognosis
- The mechanism , not clearly understood, poor blood supply to septum leading to poor implantation is one possibility .

Leiomyoma

- An association between **Submucous leiomyomas** & **RPL**

Impaired normal implantation

- Myoma position
- Poor endometrial receptivity of the decidua overlying the myoma
- Degeneration of decidua with increasing cytokine production

- An association between **intramural / subserous myomas & RPL** is less clear.

- It having been demonstrated in some, but not all, studies .

Adenomyosis

Endometriosis

Endometrial polyp

- Inflammatory changes in the endometrium associated with adenomyosis and/or endometriosis have been postulated as contributing to RPL .
- Whether one should perform laparoscopy to diagnose endometriosis in women with RPL is not known .
- There have been no data showing a relationship between endometrial polyps & RPL .
- All women with RPL could have 2-D ultrasound to rule out adenomyosis. (Conditional) **(ESHRE 2022)**

Intrauterine adhesions

Cervical insufficiency

- An insufficient endometrium to support fetoplacental growth.
- The main cause of intrauterine adhesions is curettage for pregnancy complications.
  (especially within the first 4 weeks postpartum)
- Cervical insufficiency is a cause of recurrent midtrimester, but not early pregnancy loss .

Cervical insufficiency

- The true incidence of cervical insufficiency remains unknown, since the DX is clinical .
- There is no satisfactory objective test that can identify insufficiency in the non-pregnant state .
- The DX is usually based on a HX of 2nd trimester miscarriage ;

(painless cervical dilatation, with intact membranes until the expulsion of the sac & a live fetus)

Defective endometrial receptivity

- Estrogen & progesterone prepare the endometrium for pregnancy .
- NI endometrial receptivity allows embryo attachment, implantation, invasion, placental development .
- These processes are disturbed when endometrial receptivity is defective, resulting in UEI & RPL .

Defective endometrial receptivity

- **Causes of defective endometrial receptivity** & **biomarkers** for evaluation of endometrial receptivity are under investigation .

- RPL is suggested to be associated with uterine stem cell deficiency & enhanced cellular senescence, which results in abnormal endometrial preparation for pregnancy & RPL.

- **Clinical tests** are not yet available.

Immunologic factors

- Each step in the establishment of normal pregnancy has been implicated as a possible site of immune-mediated reproductive failure.

- Both **autoimmune** & **alloimmune** mechanisms have been proposed.

- Since the mechanisms that allow a mother to tolerate her semi-allogeneic conceptus are not well defined, it is difficult to assess the role of aberrant immunologic factors in reproductive failure .

Antiphospholipid syndrome

- Several autoimmune diseases have been linked to poor obstetric outcome .
- antiphospholipid syndrome (APS) is the only immune condition in which pregnancy loss is a diagnostic criterion for the disease .
- **5- 15 %** of patients with RPL may have APS .

ENDOCRINE FACTORS

- Endocrine factors may account for **15 - 60 %** of RPL .

NO increased risk of miscarriage in women with well-controlled D.M

Diabetes mellitus

- poorly controlled diabetes mellitus is associated with early &late pregnancy loss .
- high hemoglobin A1C values early in pregnancy (> 8 %) to increased frequencies of miscarriage & congenital malformations .
- The increased risk in poorly controlled diabetic women is secondary to :

immunologic factors

hyperglycemia

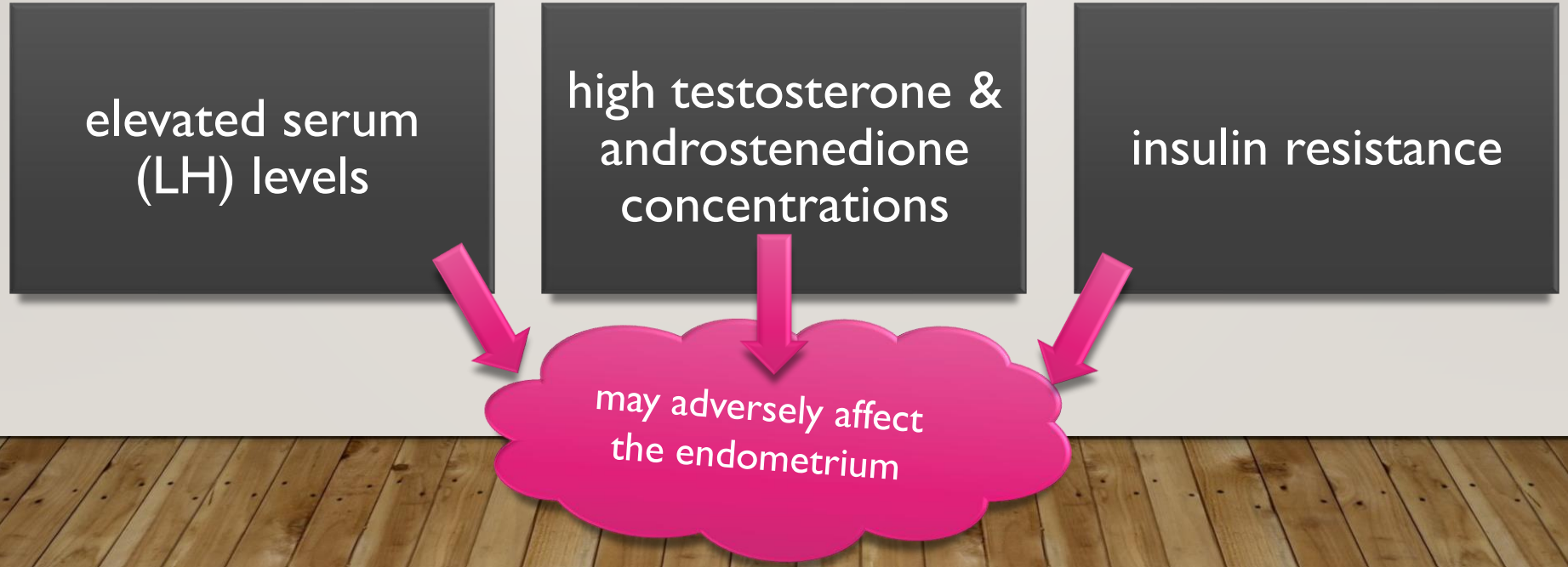
insulin resistance

maternal vascular disease

Polycystic ovary syndrome

- The miscarriage rate in (PCOS) may be as high as **20 -40 %,** the general population **(15 %)** .

- The mechanism for excess pregnancy loss in these patients is unknown, but may be related to :



Polycystic ovary syndrome

- Women with RPL have a higher prevalence of insulin resistance than fertile controls, with /without PCOS
- The benefit of **METFORMIN** in reducing the incidence of miscarriage .

Thyroid antibodies & disease

- Poorly controlled thyroid disease (hypo/ hyper- thyroidism) is associated with infertility & pregnancy loss.

- The incidence of sub clinical hypothyroid (TSH >2.5 m IU/l) reported to be raised in RPL

key point

- Excess thyroid hormone increases the risk of miscarriage independent of maternal metabolic dysfunction .

Thyroid antibodies & disease

- Thyroid autoimmunity has also been related to UEI & implantation failure .
- Some studies have reported an increased rate of fetal loss in women with high serum thyroid antibody concentrations (thyroid peroxidase or thyroglobulin), including euthyroid patients .
- In euthyroid women with recurrent pregnancy loss & positive for TPOAb, levothyroxine did not increase the live birth rate .

Hyperprolactinemia

- Normal circulating levels of prolactin may play an important role in maintaining early pregnancy.
- Prolactin levels during early pregnancy were significantly greater in women who miscarried.
- RX with bromocriptine to lower prolactin concentration was associated with a higher rate of successful pregnancy (86 versus 52 %).

Luteal phase defect

- **ASRM 2015 Committee Opinion :**
- "no reproducible, pathophysiologically relevant, & clinically practical standard to diagnose luteal phase deficiency & distinguish fertile from infertile women" .

key point

- luteal phase deficiency as an independent cause of infertility has not been proven.
- Do not perform luteal phase testing.

Luteal phase defect

- Progesterone is required for successful implantation & maintenance of pregnancy.
- disorders related to impaired progesterone production / action are likely to affect pregnancy success.
- A defect in corpus luteum function (luteal phase defect) has been hypothesized to be a potential cause of impaired progesterone production & resultant infertility /pregnancy failure .
- it is controversial as to whether such a defect really exists & is related to miscarriage .
- no consensus on the best method of DX / RX .

Luteal phase defect

- no high-quality evidence to support the use of exogenous progesterone supplementation to prevent early miscarriage.
- Abnormal luteal-phase progesterone production may occur as results of medical conditions such as elevated prolactin or abNL thyroid function.
- women suspected to have one of these disorders are evaluated & treated for the underlying condition .

GENETIC FACTORS

- A significant proportion of RPL (**40%**) may be associated with structural rearrangement or numerical chromosomal abnormalities .

  (aneuploidy, mosaicism, translocation, inversion, deletion, fragile sites)

- **3-5 %** of couples with RPL have a major chromosomal rearrangement (0.7 % in general population).

- usually a balanced translocation (60 % reciprocal, 40 %Robertsonian) , less commonly, an inversion

Chromosomal rearrangements

- Balanced translocations are more common in the female than the male
- It is more likely to result in pregnancy loss if the translocation is of maternal origin.
- An X-linked dominant condition may not cause disease or may result in mild disease in a heterozygous female, but can be lethal in males because of the lack of a normal compensatory gene

Chromosomal rearrangements

- The likelihood that RPL is related to parental karyotypic abnormality appears to be higher when one or more of the following characteristics are present:

- young maternal age at second miscarriage
- a history of ≥ 3 miscarriages
- a history of ≥ 2 miscarriages in a sibling or the parents of either partner
- A family history of stillbirth or an abnormal liveborn (may be)

- an abnormal parental karyotype, although present, may not be the cause of the RPL,a complete evaluation of RPL is indicated

Thrombophilia & fibrinolytic factors

- Thrombosis of spiral arteries & intervillous space on maternal side of the placenta can impair adequate placental perfusion.

- **The resulting abnormalities of the uteroplacental circulation may cause:**

RPL | late fetal loss | IUFR | placental abruption | preeclampsia

inherited Thrombophilia

- Inherited thrombophilias are causes of thrombosis in pregnancy
- There is a contradictory literature on the association between maternal inherited thrombophilia & RPL occurring in **the 1ST trimester** .
- There is an association between **2nd trimester** miscarriages & inherited thrombophilias .

inherited Thrombophilia

- **Impact of common thrombophilias** :

–the following thrombophilias were associated with increased risk of developing RPL when compared with individuals attempting pregnancy who did not have thrombophilia:

- **•Factor V Leiden G1691A mutation (1st -2nd trimesters)**
- **•Prothrombin G20210A mutation**
- **•Protein S deficiency**
- **Methylenetatrahydrofolate reductase (MTHFR) mutation (heterozygous & homozygous)**

antithrombin & protein C deficiencies were not associated with increased risk of RPL.

acquired Thrombophilia

- **Antiphospholipid syndrome (APS)**
- association between **lupus anticoagulant**, **anticardiolipin antibodies** , **anti beta-2-glycoprotein-I antibodies** & adverse pregnancy outcome or vascular thrombosis.
- Adverse pregnancy outcomes include:

- ≥ 3 consecutive miscarriages before 10 weeks

- ≥ 1 morphologically normal fetal losses after the tenth week

• ≥ 1 preterm births before 34+0 weeks ,because of placental disease

acquired Thrombophilia

- **Association between Antiphospholipid antibodies & RPL :**

Lupus anticoagulant > IgG and IgM anticardiolipin > Anti-beta-2-glycoprotein-I

(not statistical significance)

Environmental chemicals stress

- no high-quality evidence showing a relationship between RPL & occupational factors, stress, low level exposure to most environmental chemicals .
- **Chemicals that have been associated with sporadic spontaneous pregnancy loss :**

- anesthetic gases (nitrous oxide)

- arsenic

- aniline dyes

- benzene

- ethylene oxide

- formaldehyde

- pesticides

- lead, mercury, cadmium

Personal habits

- The association between RPL & obesity, smoking, alcohol use, caffeine consumption is unclear .

- These factors may act in a dose-dependent fashion / synergistically to increase the rate of sporadic pregnancy loss.

- Exercise does not appear to increase the rate of sporadic pregnancy loss or RPL

Male factor

- A trend toward repeated miscarriages in women whose male partner has ab NL sperm (fewer than 4 % normal forms, sperm chromosome aneuploidy)

- An association between abnormal sperm DNA parameters (sperm DNA fragmentation, nuclear chromatin decondensation, ,sperm aneuploidy)& RPL .

- Advanced paternal age may be a risk factor for miscarriage .

Male factor

- limited data are available evaluating interventions that may affect sperm DNA fragmentation :

- **lifestyle modification (smoking cessation, weight loss/exercise, reduction in pollutant exposure)**
- **RX of infections**
- **control of diabetes**
- **RX of varicocele**
- **antioxidant therapy**
- **sperm selection**

Infection

- Some infections, such as **Listeria monocytogenes**, **Toxoplasma gondii**, **cytomegalovirus**, **primary genital herpes** are known to cause sporadic pregnancy loss, but no infectious agent has been proven to cause RPL .

- C. trachomatis ,HPV , bacterial vaginosis , chronic metritis

- **Routine TORCH screening should not be undertaken.**

Diminished ovarian reserve

- DOR appears associated with RPL but causation has not been established.

- (+VE) association between RPL & the evidence of DOR **(low AMH level & low AFC).**

- In a **1st** pregnancy, the risk of miscarriage is **11 - 13 %** .
- After **ONE MISCARRIAGE**, this rate rises slightly to **14 - 21 %** .
- After **TWO** / **THREE** miscarriages, the rate is **24 - 29 %** & **31 - 33 %** .

Most experts initiate evaluation & RX of RPL after 2 consecutive miscarriages

key point

Most women with RPL have a good prognosis for eventually having a successful pregnancy, even when a definitive diagnosis is not made & no treatment initiated .

- after **one** miscarriage women would have their health needs evaluated and would be provided with information to support future pregnancies.

- If a **second** miscarriage were to occur, they would be offered an appointment at a miscarriage clinic for initial investigations, extra support & early reassurance scans for subsequent pregnancies.

- after **three** miscarriages they would be offered a full series of evidence-based investigations

- **The minimum diagnostic work-up of couples with RPL consists of:**

medical, surgical, genetic, family HX

physical examination

Medical, Surgical, Genetic, Family HX

- GA & characteristics of previous pregnancies **(anembryonic pregnancy, live embryo)**
- HX of uterine instrumentation **(intrauterine adhesions)**
- HX of menstrual cycles , galactorrhea **(endocrine anomalies)**
- HX of congenital abnormalities / karyotypic abnormalities
- HX of exposure to environmental toxins
- HX of venous / arterial thrombosis **(antiphospholipid syndrome)**
- available information from previous laboratory, pathology, imaging studies

physical examination

- It should include a general physical assessment with attention to signs of :

  - endocrinopathy **(hirsutism, galactorrhea)**

  - pelvic organ abnormalities **(uterine malformation, cervical laceration)**

- **Mental health evaluation** including screening for depression should be part of the RPL work-up.

A step-wise approach to the evaluation

Most useful tests

Karyotype of parents

- to detect balanced reciprocal / Robertsonian translocations / mosaicism

- the low likelihood of an abnormal karyotype in couples with RPL **(2.9 – 4.7 %)**

- it should be **the last obtained test** & only if the preceding work-up yielded negative results

.

Most useful tests

Karyotype of abortus

- many experts also recommend karyotype of abortus / products of conception.

- NL karyotype → a maternal environmental factor is the cause of pregnancy loss (but does not prove)
- abNL (aneuploidy) → usually a sufficient explanation for a nonviable pregnancy.
- Unbalanced translocation → Parental karyotyping may be offered → genetic consultation

- karyotype analysis of the abortus indicates a normal chromosomal pattern, more detailed array **CGH / FISH / NGS / SNP** demonstrate major abnormalities

Most useful tests

Uterine assessment

- **the most accurate methodologies for diagnosing congenital uterine anomalies:**

  - **3D ultrasound** (97.6%, 95% CI 94.3– 100)
  - **saline-infusion ultrasound** (96.5%, 95% CI 93.4– 99.5)
  - **HSG** (86.9%, 95% CI 79.8–94.0)
  - **2D ultrasound** (86.6%, 95% CI 81.3–91.8)

Most useful tests

Uterine assessment

- **Hysteroscopy, laparoscopy**, **(MRI)** can also be performed,

  (more expensive & (except for MRI) more invasive than other methods)

(2nd -line tests)

Most useful tests

Uterine assessment

- **•Hysteroscopy**
- considered the standard for DX of intrauterine abnormalities .
- Rx of many intrauterine lesions can be performed during the procedure .
- Because of its cost & invasiveness, hysteroscopic uterine assessment is reserved for :
  - patients who have had a nondiagnostic evaluation of RPL
  - intrauterine pathology is suspected
  - operative hysteroscopy may be necessary

Most useful tests

Uterine assessment

- **Anatomic evaluation**
- In RPL , imaging of the uterus is performed to identify :
  - **uterine anomalies**
  - **fibroids**
  - **adenomyosis**
  - **intrauterine adhesions**
- These anatomic abnormalities are not clearly associated with increased risk of pregnancy loss.
- The impact of RX is less well understood.

Antiphospholipid syndrome

Most useful tests

- Women with RPL should be offered testing for acquired thrombophilia, (**lupus anticoagulant** , **anticardiolipin antibodies** prior to pregnancy)[Grade C]**RCOG2023**

- Women with 2nd trimester RPL may be offered testing for (**Factor V Leiden**, **prothrombin gene mutation** , **protein S deficiency**). They should be made aware that there is currently limited evidence that treatment changes reproductive outcomes . [Grade C] **RCOG2023**

Antiphospholipid syndrome

Most useful tests

- The minimum immunology work-up for RPL is measurement of :
  - **anticardiolipin antibody (IgG & IgM)** (moderate / high titer levels)
  - **lupus anticoagulant** (moderate / high titer levels)

- These tests should be done twice, at least 12 weeks apart & 6 week post pregnancy termination
- **a low- to mid-positive level can be due to viral illness / temporal fluctuation in NL individuals, suboptimal sample collection and preparation, and lack of standardisation**

Antiphospholipid syndrome

Most useful tests

- **anti-beta-2-glycoprotein-I antibody** (IgG and/ or IgM class in high titer) (evidence is less conclusive)

- detection of the lupus anticoagulant is generally based upon:
  - **an activated PTT**
  - **thromboplastin time**
  - **kaolin plasma clotting time**
  - **dilute Russell viper venom test time** (more sensitive and specific test)

Thyroid function

Most useful tests

- should be assessed in women with :
  - **clinical manifestations**
  - **a personal HX of thyroid disease**

- Screening asymptomatic women for subclinical thyroid dysfunction is controversial.

The screening is reasonable:

there is evidence of an increased risk of miscarriage in:

- **women with subclinical hypothyroidism**
- **in euthyroid women with thyroid peroxidase (TPO) antibodies**

Most useful tests

Thyroid function

- Women with RPL should be offered ;

  - thyroid function tests

  - assessment for thyroid peroxidase (TPO) antibodies.

- RX of abnormal thyroid function may confer a benefit.

Less useful tests

- Additional laboratory tests may be indicated in women with clinical manifestations suggestive of a medical disorder.

- Testing for all of medical disorders should not be a part of the routine evaluation of asymptomatic women with RPL.

- Other endocrine assessments are not routinely indicated unless there is a clinical suspicion of pathology (diabetes ,hyperprolactinemia)

Less useful tests

Evaluation of ovarian reserve

- Ovarian reserve can be evaluated by measurement of :

  - antral follicle count (AFC)

  - basal day 3 serum (FSH)

  - (AMH)

  - inhibin-B

  - day 3 serum estradiol concentrations

Less useful tests

Screening for diabetes

- should be limited to women with clinical manifestations of the disease.
- Only poorly controlled diabetes is associated with miscarriage.

Progesterone level

- Single / multiple serum progesterone levels are not predictive of future pregnancy outcome.

Less useful tests

Endometrial biopsy

- Diagnosis of a luteal phase defect had been based upon results of endometrial biopsy.
- high quality data show that this test is not predictive of fertility status .
- In the IVF population**, chronic endometritis** has been associated with RPL .

Less useful tests

Hypercoagulable state

- There is a large & contradictory literature on the association between maternal inherited thrombophilia & RPL occurring in the 1ST trimester.

- Evaluation for an inherited thrombophilia can be considered in rare cases of recurrent, unexplained late fetal loss (>9 weeks) associated with evidence of placental ischemia , infarction , maternal vessel thrombosis.

- Women with confirmed thrombophilia can be started on an anticoagulant immediately after conception

Useless tests

Culture & serology

Routine cervical cultures for Chlamydia species or Mycoplasma species

- vaginal evaluation for bacterial vaginosis
- toxoplasmosis serology

- a higher subsequent miscarriage rate in women with recurrent miscarriage & untreated chronic endometritis **(NEED FOR FURTHER STUDIES)**

Useless tests

Autoantibodies & immune function

- Many studies have reported the presence of autoantibodies in women with RPL .
- Only **anticardiolipin antibody** & **lupus anticoagulant** have been clearly associated with RPL.
- The pregnancy outcome of women with / without **(ANA)** is the same .
- Available data do **not** support testing women with RPL for ANA.

- With the exception of anticardiolipin antibody / lupus anticoagulant, **do not** testing women with unexplained RPL for autoantibodies .

Useless tests

Autoantibodies & immune function

- not predictive of pregnancy outcome :
  - **HLA typing**
  - **mixed lymphocytotoxic antibody tests**
  - **mixed lymphocyte culture reactions**
  - **cytokine tests**
  - **NK cell tests**

The roles of

- **the differences in the CD56+ population of cells**
- **alterations in cytokines produced by monocytes, CD4+ cells, endometrium**

MALE CONTRIBUTION TO RPL

- Male contribution to RPL is still unclear.
- Sperm DNA fragmentation has been associated with miscarriage .
- there are yet to be any prospective trials demonstrating improved outcomes with intervention.
- with the exception of the karyotype analysis, no other testing is recommended for the male partner of a woman with RPL .

- Assessing sperm DNA fragmentation in couples with RPL could be considered for diagnostic purposes. (Conditional)**ESHRE2023**

Thanks for your attention