Clinical practice guidelines for Recurrent miscarriage

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DEFINITION

- Recurrent pregnancy loss (RPL) is one of the most frustrating and difficult areas in reproductive medicine because the etiology is often unknown and there are few evidence-based diagnostic and treatment strategies.

- varying definitions have included:
  - ≥ 2 failed clinical pregnancies as documented by ultrasonography or histopathologic examination .
  - 3 consecutive pregnancy losses, which are not required to be intrauterine .

- we start investigating after two failed clinical pregnancies, including biochemical pregnancies for women undergoing IVF .

- Nonvisualized 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.

- The ESHRE 2017 proposing that RPL describes ≥ 2 pregnancy losses, diagnosed by either serum or urine HCG.

- ***This diagnosis includes biochemical pregnancies and treated pregnancies of unknown location but does not include confirmed ectopic or molar pregnancies .***

- 0.4 - 1 % of women have 3 consecutive pregnancy losses .

- RPL can be further divided into primary or secondary processes .

- Primary RPL refers to pregnancy loss in women who have never carried to viability (24 weeks gestation or beyond). By contrast, 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 .*

- There is no specific term for describing women who have had multiple spontaneous miscarriages interspersed with normal pregnancies (nonconsecutive pregnancy losses).

- The prevalence of miscarriage is higher with increasing maternal age , and at very early gestational ages (at less than 6 weeks of gestation the risk of miscarriage is 22 - 57 % versus 15 % at 6 _ 10 weeks and 2 _ 3 % after 10 weeks).

Percent pregnancy loss by maternal age at conception

Maternal age	Spontaneous abortions (percentage)	Ectopic pregnancies (percentage)	Stillbirths rate/1000
12-19	13.3	2.0	5.0
20-24	11.1	1.5	4.2
25-29	11.9	1.6	4.0
30-34	15.0	2.8	4.4
35-39	24.6	4.0	5.0
40-44	51.0	5.8	6.7
≥45	93.4	7.0	8.2

RISK FACTORS AND ETIOLOGY

- There are many unsolved questions regarding etiology, evaluation, and management.

- Unfortunately, *the cause of RPL can be determined in only 50 % of patients .*

- General etiological categories of RPL include :
  - ✓ Previous pregnancy loss ,
  - ✓ Anatomic ,
  - ✓ Immunological ,
  - ✓ Endocrine ,
  - ✓ Genetic ,
  - ✓ Infectious ,
  - ✓ Thrombophilic ,
  - ✓ Environmental factors .

Previous pregnancy loss

- In a first pregnancy, the risk of miscarriage is 11 - 13 % .

- After one miscarriage → rises slightly to 14 - 21 %
- After 2 miscarriages → 24 - 29 %
- After 3 miscarriages → 31 _ 33 %

- The cause of the pregnancy loss impacts the miscarriage risk. As an example, carriers of a 22:22 translocation will almost always miscarry, whereas women with 13:14 translocation have a 25 % risk.

- The gestational age of prior pregnancy loss and interpregnancy interval (IPI) may impact the risk of repeat pregnancy loss.

✓ The IPI after a first-trimester loss did not impact the live birth rate in a subsequent pregnancy .

✓ women with pregnancy loss between 14 and 19 weeks , an IPI ≤3 months was associated with an increased rate of recurrent loss compared with an IPI of >9 to 12 months.

- Advancing maternal age is associated with a higher rate of pregnancy loss of both normal and abnormal conceptuse . This probably reflects poor oocyte quality in this age group.

- Increasing parity is also associated with an increased rate of miscarriage.

- Previous pregnancy outcome can positively or negatively affect the risk in the next pregnancy.
  - ✓ The risk of miscarriage increases with each successive pregnancy loss ,
  - ✓ A pregnancy ending in live birth reduces the risk of miscarriage in the subsequent gestation .

- Gestational age at the time of pregnancy loss → etiology
  risk of recurrence

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

- The recurrence risk increases as gestational age at the time of loss increases.

Uterine factors

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

- Pregnancy loss may be related to impaired uterine distention or abnormal implantation due to :
  - ✓ decreased vascularity in a septum,
  - ✓ increased inflammation,
  - ✓ reduction in sensitivity to steroid hormones

- ***The septate uterus is the uterine anomaly associated with the poorest reproductive outcome and the most common uterine abnormality associated with RPL .***
  - ✓ The fetal survival rate is 6 - 28 % , the miscarriage rate is >60 %
  - ✓ The longer the septum, the worse the prognosis .

- Submucous leiomyomas that protrude into the endometrial cavity can impede normal implantation as a result of :
  - ✓ their position,
  - ✓ poor endometrial receptivity of the decidua overlying the myoma,
  - ✓ degeneration with increasing cytokine production

- An association between pregnancy loss and intramural or subserous myomas is less clear .

- In a meta-analysis of 15 studies evaluating the effect of adenomyosis on fertility and IVF clinical outcomes, the pregnancy loss rate was higher (due to Inflammatory changes in the endometrium) .

- There have been no data showing a relationship between endometrial polyps and RPL.

- Intrauterine adhesions lead to pregnancy loss because there is insufficient endometrium to support fetoplacental growth.

- Cervical insufficiency is a cause of recurrent mid-trimester, but not early, pregnancy loss.

Immunologic factors

- Both autoimmune (APS) and 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 .

- Several autoimmune diseases have been linked to poor obstetric outcome, but 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

Diabetes mellitus:

- *Although rare, poorly controlled diabetes mellitus is associated with early (and late) pregnancy loss.*

- Several studies have linked high hemoglobin A1C values early in pregnancy (particularly >8 %) to increased frequencies of miscarriage and congenital malformations .

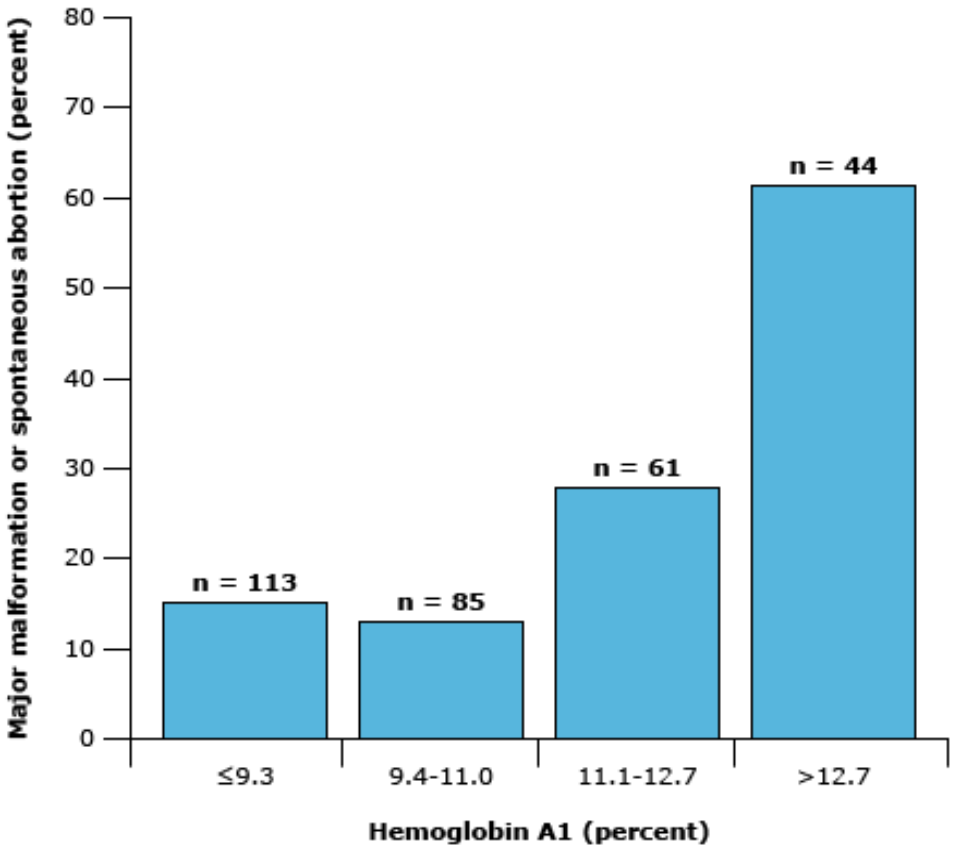
- The increased risk in poorly controlled diabetic women is believed to be secondary to :

✓ hyperglycemia,
✓ maternal vascular disease,
✓ possibly immunologic factors

- *There is no increased risk of miscarriage in women with well-controlled diabetes mellitus .*

- Insulin resistance, as seen in women with PCOS , may also be a factor in pregnancy loss .

Deleterious effect of poor glycemic control on fetal outcome



- Polycystic ovary syndrome :

- The miscarriage rate in women with PCOS may be 20 - 40 % , which is higher than the baseline rate in the general obstetric population (10 - 20 %) .

- The mechanism for excess pregnancy loss in these patients is unknown, but may be related to:
  - ✓ ↑ serum LH levels,
  - ✓ high testosterone and androstenedione concentrations (which may adversely affect the endometrium),
  - ✓ insulin resistance

- *In one study, a menstrual cycle > 34 days, which is common in women with PCOS, was the most important predictor for a RPL .*

- Women with RPL have a higher prevalence of insulin resistance than fertile controls, whether or not PCOS is present .

- Thyroid antibodies and disease :

- Some studies have reported an increased rate of fetal loss in women with ↑ serum thyroid antibody concentrations (TPO or TGB), including those who are euthyroid .

- Thyroid autoimmunity has also been related to unexplained infertility and implantation failure .

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

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

- 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.

- Treatment to lower prolactin concentration was associated with a higher rate of successful pregnancy (86 versus 52 %).

- Luteal phase defect :

- A defect in corpus luteum function has been hypothesized to be a potential cause of impaired progesterone production and resultant infertility or pregnancy failure.

- Serum progesterone concentrations are not predictive of pregnancy outcome , and there is no high-quality evidence to support the use of exogenous progesterone supplementation to prevent early miscarriage.

- Several studies have shown that LPD diagnosed by endometrial biopsy is not predictive of infertility; LPD has been observed in as many as 25 % of sequential endometrial biopsies in fertile women.

- The ASRM in 2015 concluded that "there is no reproducible, pathophysiologically relevant, and clinically practical standard to diagnose LPD and distinguish fertile from infertile women" .

- *We do not perform luteal phase testing.*

Genetic factors

- Abnormalities of chromosome number or structure are the most common cause of sporadic early pregnancy loss, (at least 50 % of such losses) .
- A significant proportion of RPL may also be associated with structural or numerical chromosomal abnormalities (aneuploidy , mosaicism , translocation, inversion, deletion, fragile sites) .
- Single-gene, X-linked, or polygenic / multifactorial disorders can also result in sporadic or recurrent miscarriage.
- Aneuploiy :
- *The risk of aneuploidy increases as the number of previous miscarriages increases .*
- having one chromosomally abnormal spontaneous abortion appeared to increase the risk of a subsequent loss associated with a chromosomal abnormality .

- Chromosomal rearrangements :

- 3 - 5 % of couples with RPL have a major chromosomal rearrangement (versus 0.7 % of the general population);
  - ✓ usually a balanced translocation (60 % reciprocal, 40 % Robertsonian)
  - ✓ less commonly, an inversion .

- One or both partners may harbor lethal genes in a heterozygous or balanced combination that does not affect them, but causes pregnancy loss when inherited by the embryo in a homozygous or unbalanced state.

- Balanced translocations are more common in the female than the male and more likely to result in pregnancy loss if the translocation is of maternal origin.

- As an example, 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 .

- RPL is related to parental karyotypic abnormality when ≥ 1 of the following characteristics are present:

✓ young maternal age at second miscarriage,

✓ a Hx of ≥ 3 miscarriages,

✓ a Hx of ≥ 2 miscarriages in a sibling or the parents of either partner ,

✓ a family Hx of stillbirth or an abnormal liveborn .

- *An abnormal parental karyotype, although present, may not be the cause of the RPL; therefore, a complete evaluation of RPL is indicated .*

Thrombophilia and fibrinolytic factors

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

- The resulting abnormalities of the uteroplacental circulation may cause :

✓ late fetal loss,
✓ IUGR ,
✓ placental abruption,
✓ preeclampsia.

- A relationship to early pregnancy loss is less clear and may be restricted to :

✓ specific thrombophilic defects that have not been completely defined,
✓ the presence of multiple defects.

- A meta-analysis reported the following thrombophilias were associated with increased risk of RPL :

✓ Factor V Leiden G1691A mutation – OR = 2.44
✓ Prothrombin G20210A mutation – OR = 2.08
✓ Protein S deficiency – OR = 3.45

- Compared with the reference population, antithrombin lll and protein C deficiencies were not associated with increased risk of RPL.

- A systematic review of the association between fibrinolytic defects and RPL found ***a significant association for factor XII deficiency .***

- There was no significant association with PAI - I 4G/5G polymorphism, increased plasminogen activator inhibitor activity, factor XII C46T polymorphism, or factor XIII polymorphisms.

- Data on other fibrinolytic defects were sparse.

Environmental chemicals and stress

- There is no high-quality evidence showing a relationship between RPL and :
- ✓ occupational factors,
- ✓ stress,
- ✓ low level exposure to most environmental chemicals .

- Chemicals that have been associated with sporadic spontaneous pregnancy loss include :
- ✓ anesthetic gases (nitrous oxide),
- ✓ arsenic,
- ✓ aniline dyes,
- ✓ benzene,
- ✓ ethylene oxide,
- ✓ formaldehyde,
- ✓ mercury,
- ✓ cadmium .

Other

- ***Personal habits*** — The association is unclear between RPL and :

✓ obesity,
✓ smoking,
✓ alcohol use,
✓ caffeine consumption

- These factors may act in a dose-dependent fashion or 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*** — There is a trend toward repeated miscarriages in women whose male partner has abnormal sperm (< 4 % normal forms, sperm chromosome aneuploidy) .

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

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

- ***Diminished ovarian reserve*** — DOR appears associated with RPL but causation has not been established .

✓ a meta-analysis reported that more individuals with RPL had evidence of DOR (low AMH level & low AFC) .

- ***Celiac disease*** — Untreated celiac disease, even when subclinical, has been associated with pregnancy loss, menstrual disorders, and infertility.
- Treatment of celiac disease appears to prevent these problems .

- ***we suggest screening women with RPL for celiac disease*** due to the effects of the disease to health in general, and the possible positive effects of treatment of the disease .

Evaluation of

Recurrent pregnancy loss

- It is important to remember that most women with RPL have a good prognosis for eventually having a successful pregnancy, even when a definitive diagnosis is not made and no treatment initiated.

- The overall live birth rates after normal and abnormal diagnostic evaluations for RPL were 77 and 71 % , respectively .

HISTORY AND PHYSICAL EXAMINATION

- The minimum diagnostic workup of couples with RPL consists of :
  - ✓ a complete medical,
  - ✓ surgical,
  - ✓ genetic,
  - ✓ family history
  - ✓ physical examination.

- 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 .

- The most common causes of RPL vary by trimester.
  - ✓ miscarriage related to chromosomal and endocrine defects tends to occur earlier in gestation than losses due to anatomic or immunological abnormalities; however, there is significant overlap.

- Additional information to consider :

✓ Has there been uterine instrumentation, which may have caused intrauterine adhesions?

✓ Are the menstrual cycles normal? Abnormalities in cycle length may be due to endocrine dysfunction. Is there galactorrhea, which also suggests endocrine dysfunction (hyperprolactinemia)?

✓ Is there a history of congenital abnormalities or karyotypic abnormalities, which may be heritable?

- Was FHR ever detected? **RPL prior to detection of FHR suggests a chromosomal abnormality.**
- Does the family history display patterns of disease consistent with a strong genetic influence?

✓ Is there exposure to environmental toxins, which may be lethal to developing embryos?

✓ Is there a history of venous or arterial thrombosis suggestive of antiphospholipid syndrome?

✓ What information is available from previous laboratory, pathology, and imaging studies?

Physical examination

- Physical examination should include :

✓ a general physical assessment with attention to signs of endocrinopathy (hirsutism, galactorrhea)

✓ pelvic organ abnormalities (uterine malformation, cervical laceration).

Most useful tests

- ***Karyotyping of couples*** is part of the evaluation of RPL, despite the low yield of abnormality, cost, and limited prognostic value .
- The purpose is to detect balanced reciprocal or Robertsonian translocations or mosaicism that could be passed to the fetus unbalanced.
- Because of the low likelihood of an abnormal karyotype in couples with RPL, *this is the last test we obtain and only if the preceding work-up yielded negative results*.
- Many experts also recommend karyotype of the abortus or products of conception.
- A normal karyotype suggests (but does not prove) a maternal environmental factor is the cause of pregnancy loss, while an abnormal karyotype (aneuploidy) is usually a sufficient explanation for a nonviable pregnancy.
- Structural chromosomal rearrangements in the abortus may be inherited or sporadic, and are an indication for parental karyotype analysis if not already done.

Uterine assessment

- Anatomic causes of RPL are typically diagnosed using HSG or sonohysterography.

- *We prefer sonohysterography* because :

✓ it is more accurate than HSG

✓ gives more information than sonography alone .

- Hysteroscopy, laparoscopy, or MRI are used as second-line tests (more expensive and invasive) .

- Ultrasonography is particularly useful in pregnant women, in whom the other tests are relatively or absolutely contraindicated.

Anticardiolipin antibodies and lupus anticoagulan

- The minimum immunology work-up for women with RPL is measurement of *anticardiolipin antibody (IgG and IgM) and lupus anticoagulant*.

- Both tests should be done twice, 6 – 8 weeks apart, because a low to mid positive level can be due to viral illness and revert to normal.

- The detection of the lupus anticoagulant is generally based upon an activated PTT , kaolin plasma clotting time, or dilute Russell viper venom test time .

Thyroid function

- Thyroid function should be assessed in women with clinical manifestations or a personal history of thyroid disease.

- *Screening asymptomatic women for subclinical thyroid dysfunction is controversial.*

- We feel screening is reasonable since there is evidence of an increased risk of miscarriage in women with :

✓ subclinical hypothyroidism

✓ euthyroid women with TPO antibodies (2-3 times)

- Treatment is associated with a significant reduction in risk of miscarriage in euthyroid women with TPO antibodies .

Less useful tests

Evaluation of ovarian reserve — by measurement of AFC , basal serum FSH & E2 , AMH , inhibin-B

- Evaluation of ovarian reserve using a day 3 FSH concentration can be considered in women of any age.
- *If measurement of FSH levels was limited to women over 34 years of age, one quarter of those with elevated values would be missed .*
- High day 3 serum E2 concentrations of > 80 pg/mL are also associated with ↓ oocyte numbers.

Inherited thrombophilia — evaluation can be considered in rare cases of recurrent, unexplained late fetal loss (> 9 weeks of gestation) associated with evidence of placental ischemia and infarction and maternal vessel thrombosis.

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

Cervical cultures — are not useful as routine test for :

- ✓ Chlamydia
- ✓ Mycoplasma
- ✓ bacterial vaginosis
- ✓ toxoplasmosis serology

Screening for diabetes — Only poorly controlled diabetes is associated with miscarriage.

- Screening for diabetes mellitus should be limited to women with clinical manifestations of the disease.

Diagnosis of a LPD — had been based upon results of endometrial biopsy.

- However, high quality data show that this test is not predictive of fertility status in the general population; therefore, ***it is no longer recommended.***

chronic endometritis — In the IVF population, has been associated with recurrent implantation failure in at least one study .

Male contribution — to RPL is still unclear.

- Sperm DNA fragmentation has been associated with miscarriage .
- However, *with the exception of the karyotype analysis, no other testing is recommended for the male partner* of a woman with RPL .

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, 6 - 8 weeks apart.
- TSH and TPO antibodies.
- Parental karyotype and karyotype of the abortus *if the above examinations are normal*.
- Additional testing depends upon the diagnosis suggested by the history, physical examination, and laboratory results.

Management of Recurrent pregnancy loss

- High-quality data on management of recurrent pregnancy loss (RPL) are limited .

- Therapeutic recommendations are largely based upon clinical experience and data from observational studies.

- Nevertheless, the prognosis for a successful future pregnancy is generally good .

- The overall live birth rates after normal and abnormal diagnostic evaluations for RPL are 77 and 71 % , respectively .

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.

- Couples with karyotypic abnormalities may choose to undergo prenatal genetic studies, such as amniocentesis or CVS , to determine the fetal karyotype.

- IVF + 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 .
- This procedure reduces the live birth rate after IVF if preimplantation testing is performed solely because of advanced maternal age .
- 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.

UTERINE ABNORMALITIES

- Are managed surgically (hysteroscopic) if the defect is a surgically correctable cause of pregnancy loss, such as a uterine septum, intrauterine adhesions, or submucosal myoma.

- In a classic observational series, repair septate uteri reduced the abortion rate from 84 % to 12 %

- The value of prophylactic cervical cerclage in women with a uterine anomaly, but no history of second trimester pregnancy loss, is controversial .

- *We do not advocate prophylactic cervical cerclage in women with no history of cervical insufficiency.*

- A gestational carrier is an option for women with irreparable uterine defects.

ANTIPHOSPHOLIPID SYNDROME

- Drugs such as aspirin and heparin appear to *improve pregnancy outcome in women with antiphospholipid syndrome who have recurrent fetal losses*.

- In contrast, such therapy is not associated with improved outcomes in women without antiphospholipid antibody syndrome.

- Although no alloimmune mechanism has been proven to cause RPL, several immunologic treatments have been advocated to improve the live birth rate in women with previous unexplained RPL.

- None are effective, and some appear to be harmful .

THYROID DYSFUNCTION AND DIABETES MELLITUS

- *Women with overt thyroid disease or diabetes mellitus should be treated*, as medically appropriate, since these disorders can result in serious sequelae.

- *Euthyroid women with ↑serum TPO antibody concentrations may benefit from treatment with thyroid hormone (median dose 50 mcg daily) during pregnancy* as may reduce the risk of:

✓ miscarriage (from 13.8 to 3.5 %)

✓ PTL (7.0 versus 22.4 %)

- Women with ↑serum TPO antibody concentrations are at high risk of developing hypothyroidism in the first trimester and autoimmune thyroiditis postpartum, and should be followed appropriately .

POLYCYSTIC OVARY SYNDROME

- The miscarriage rate in women with PCOS is 20 to 40 % , ↑ than the baseline rate in the general obstetric population .

- Metformin has been used in women with PCOS to decrease this risk, but the effectiveness of this approach is unproven.

HYPERPROLACTINEMIA

- Normal circulating levels of prolactin may play an important role in maintaining early pregnancy.

- A study of 64 hyperprolactinemic women with RPL randomly assigned to bromocriptine therapy or no bromocriptine found *treatment was associated with a significantly higher rate of successful pregnancy* (86 versus 52 %) .

- We suggest treatment of women with hyperprolactinemia and RPL, even in the absence of overt hypogonadism.

THROMBOPHILIA

- Anticoagulation of women with certain inherited thrombophilias may improve maternal outcome (prevention of VTE), but does not appear to prevent pregnancy loss.

TREATMENT OPTIONS FOR UNEXPLAINED RECURRENT PREGNANCY LOSS

- After evaluation, RPL remains unexplained in approximately 50% of couples.
- The chance of a live birth is good (> 50 % with no intervention).

- Treatments that may be offered to couples with unexplained RPL include the following:

✓ Lifestyle modification (↓use of tobacco products, alcohol, and caffeine , ↓ BMI)

✓ Progesterone (a 2017 meta-analysis reported a ↓ risk of miscarriage and ↑ live birth rate with first-trimester progestogen supplementation compared with placebo or no treatment, the effects were modest)

✓ HMG (COH appeared effective for treatment of endometrial defects by correction of a LPD or stimulation of a thicker endometrium)

✓ IVF and PGD

✓ Oocyte donation (Poor quality oocytes may be responsible for 25 % of pregnancy losses - live birth rate of 88 %)

✓ Gestational carrier (may be considered by women with RPL or recurrent IVF implantation failures not associated with recurrent embryonic aneuploidy or obvious intrinsic gamete factors)

- The following therapies are not supported by data, and we do not recommend them:

✓ Aspirin + / - heparin

✓ LMWH (trials show no benefit to LMWH treatment in women without an inherited thrombophilia)

✓ HCG (there is insufficient evidence to recommend the use of hCG to prevent pregnancy loss)

✓ Clomiphene citrate (due to anti-estrogen effect on the endometrium, do not use in women with RPL)

✓ Immune therapy with IVIG (have no beneficial effect of immunotherapy for treatment of RPL)

✓ Glucocorticoids (have several anti-inflammatory effects, suppression of NKC activity, but do not appear to be effective for preventing RPL * ↑ PPROM , GDM , HTN)

✓ Other medications and/or combinations

- Combined treatment with prednisone, progesterone, aspirin, and folate does not appear to be beneficial.
- G-CSF (the pilot study for G-CSF was small and did not assess the clinically important outcomes)
- combination of prednisone (20 mg/day), progesterone (20 mg/day), aspirin (100 mg/day), and folate (5 mg every second day) it is unclear which of the treatments was beneficial.

PROGNOSIS

- The greatest risk of recurrent loss occurs during the period up to the time of previous miscarriage.
- Increasing maternal age and a higher number of miscarriages at time of initial visit were associated with a significant decrease in the likelihood of having a live birth.
- In women with recurrent early first trimester pregnancy loss, the presence of fetal cardiac activity is reassuring of subsequent viable delivery, although the pregnancy loss rate remains above that of the general population.
- Second trimester pregnancy loss is significantly associated with recurrent second trimester loss and future spontaneous PTL .
- Women with a Hx of RPL who become pregnant may be at higher risk for developing IUGR and PTL , but not for HTN or DM .

SUMMARY AND RECOMMENDATIONS

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

- Uterine abnormalities are managed surgically if the defect is a surgically correctable cause of pregnancy loss, (uterine septum, intrauterine adhesions, or submucosal myoma).

- For women with unexplained RPL, we recommend **not** using supplemental vaginal progesterone , (has been established does not improve live birth rates). It is not known if IM progesterone or other progestin therapies provide a benefit.

- We recommend **not** using immunotherapy or glucocorticoids for treatment of RPL. These drugs are not effective and may be harmful.

- We suggest treatment of women with hyperprolactinemia and RPL .

- A variety of treatments have been offered to couples with unexplained RPL. We start with low risk, simple, and less expensive interventions and, if unsuccessful, move on to higher risk, more complex and expensive options.

- Women with a history of RPL who become pregnant may be at higher risk for developing IUGR and PTL . Detection of fetal cardiac activity in early pregnancy is reassuring of subsequent viable delivery, although the pregnancy loss rate remains above that of the general population.


Thanks all with best wishes