Recurrent abortion

Presnented

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Recurrent abortion evaluation and treatment

A clinical and emotional challenge for patients and providers

CANDIDATES FOR EVALUATION

Two or more failed clinical pregnancies as documented by ultrasonography or histopathologic examination.
Three consecutive pregnancy losses, which are not required to be intrauterine.

In our practice, we start investigating after two failed clinical pregnancies, including biochemical pregnancies for women undergoing in vitro fertilization.

There is a general consensus that healthy women should not undergo extensive evaluation after a single first trimester or early second trimester spontaneous miscarriage (up to 20 weeks), given these are relatively common, sporadic events.

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.

In one representative study, the overall live birth rates after normal and abnormal diagnostic evaluations for RPL were 77 and 71 percent,respectively.

management

High-quality data on management of recurrent pregnancy loss (RPL) are limited; therefore, 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 percent, respectively . Therapeutic intervention is guided by the underlying cause of RPL. In all cases, emotional support is important in caring for these often anxious couples, and may enhanc therapeutic success. .

HISTORY AND PHYSICAL EXAMINATION

Physical examination

Mental health evaluation

Most useful tests

Karyotype

Uterine assessment

Anticardiolipin antibodies and lupus anticoagulant

Thyroid function

Less useful tests

Evaluation of ovarian reserve

Medical work-up

Hypercoagulable state

Culture and serology

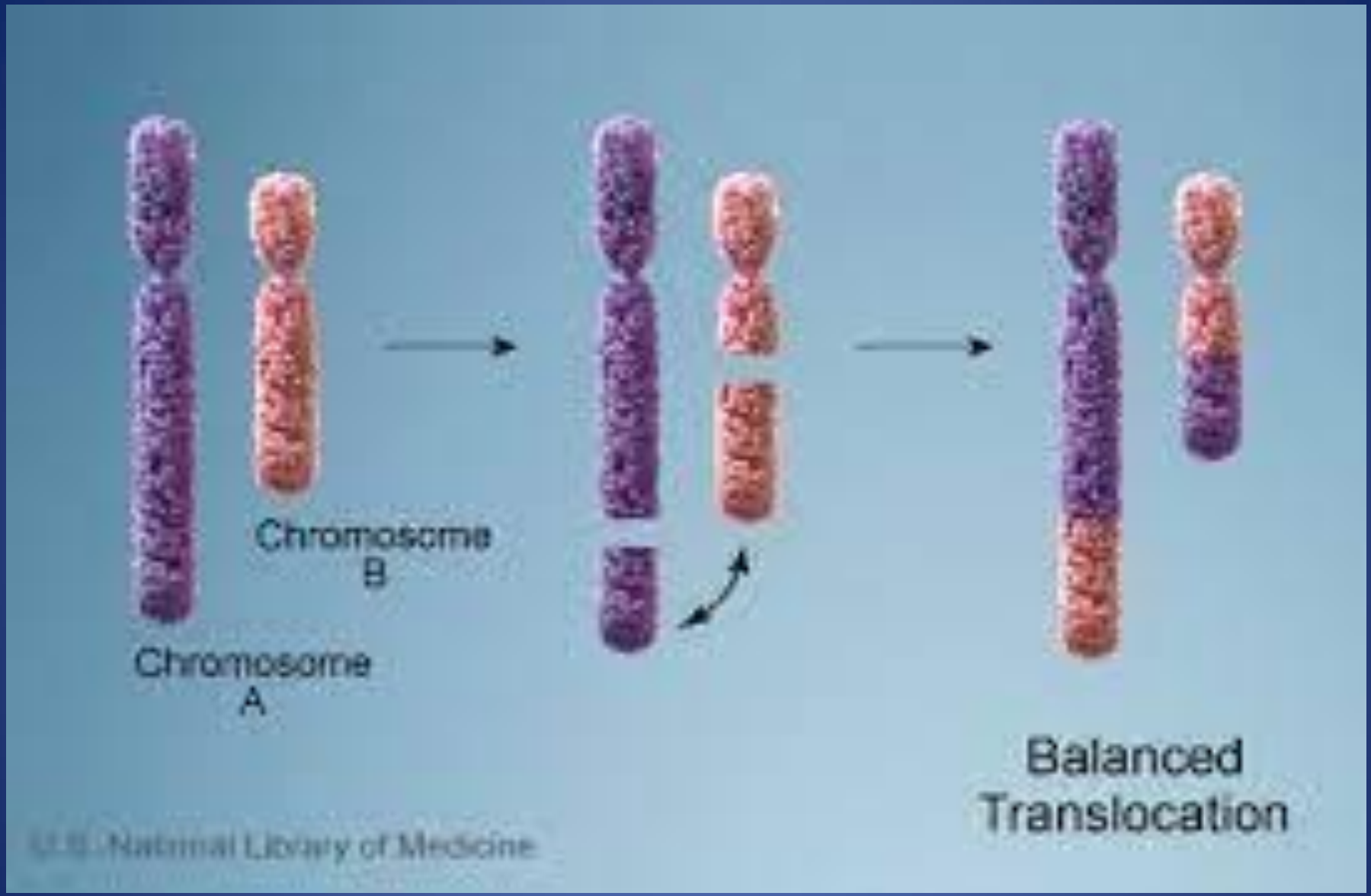
Autoantibodies and immune function

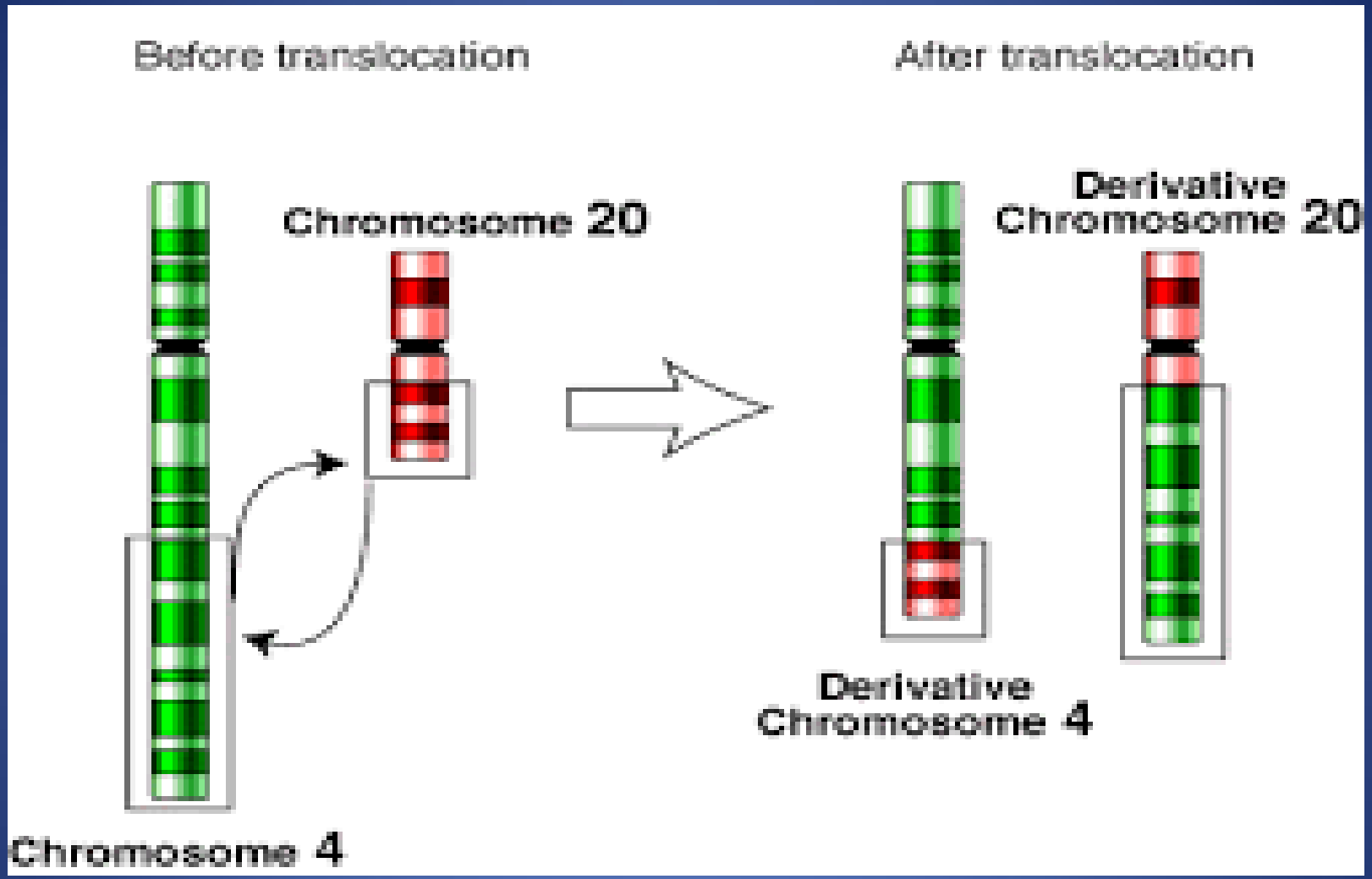
Screening for diabetes

Progesterone level

Endometrial biopsy

Sperm DNA fragmentation


Chromosome B
Chromosome A
Balanced Translocation
U.S. National Library of Medicine


Before translocation
After translocation
Chromosome 20
Derivative Chromosome 20
Derivative Chromosome 4
Chromosome 4

Couples with chromosomal abnormalities

genetic counseling

prenatal genetic studies, such as amniocentesis or CVS. Pregnancy termination is an option if the fetus is affected.

IVF with preimplantation genetic diagnosis (PGD)

PGD improves the pregnancy outcome of translocation carriers with a history of repeated pregnancy loss . On the other hand, 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

Anatomic evaluation

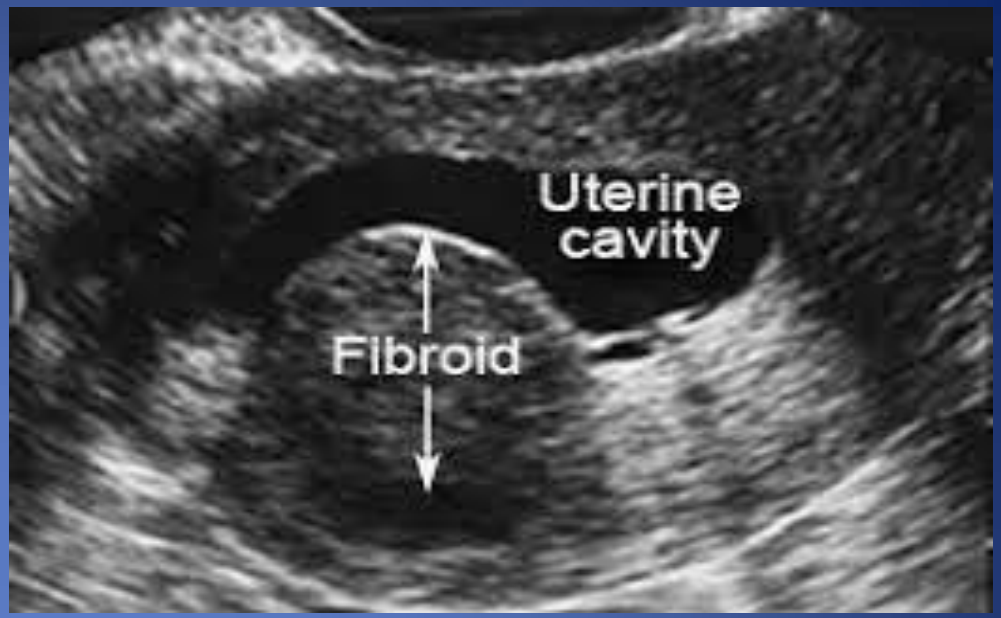
imaging of the uterus is performed to identify uterine anomalies, fibroids ,adenomyosis, and intrauterine adhesions .

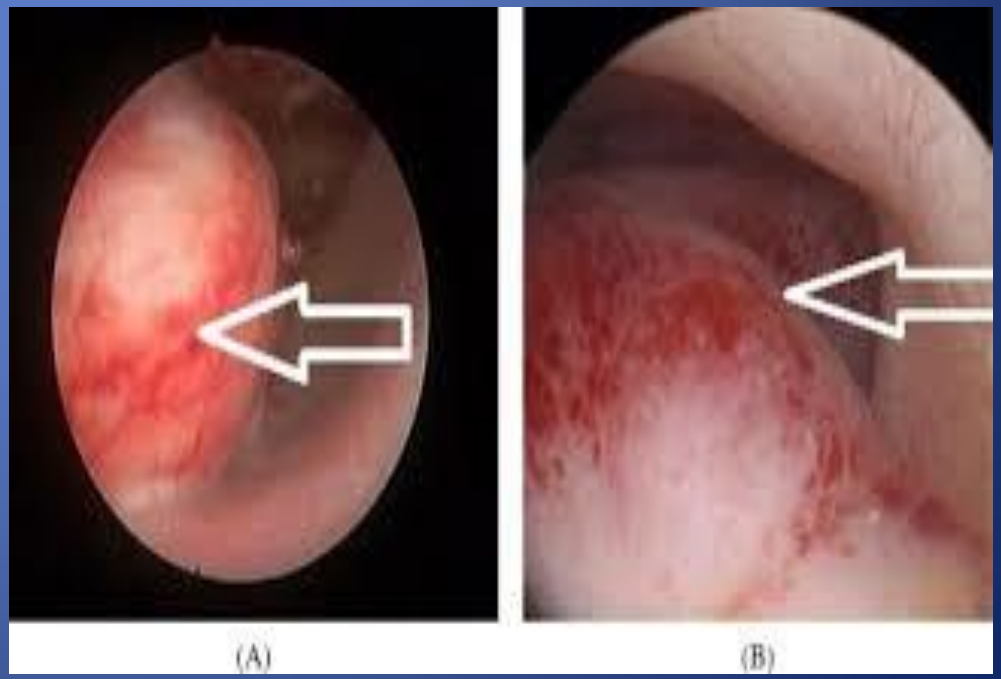
However, these anatomic abnormalities are not clearly associated with increased risk of pregnancy loss, and the impact of treatment is less well understood.

Challenges include the varied definitions of recurrent pregnancy loss and inclusion of mixed populations (general obstetric patients versus those with identified recurrent pregnancy loss.

Methods of imaging

Sonohysterography
Hysterosalpingogram
Hysteroscopy
Ultrasound(3D)
Magnetic resonance imaging





UTERINE ABNORMALITIES

uterine septum, intrauterine adhesions, or submucosal myoma can be treated hysteroscopically.

There are no randomized trials evaluating pregnancy outcome after surgical correction of uterine anomalies.

In a classic observational series, repair of bicornuate and septate uteri reduced the abortion rate from 84 percent (before surgery) to 12 percent (after surgery) .

The problem with this and similar studies is use of patients as their own controls .

However, studies using better control groups also support the efficacy of surgical correction of uterine defects, especially for uterine septum.

live birth rate After hysteroscopic resection	live birth rate before hysteroscopic resection	IN embryo transfer
15.6 %	2.7 %	large septum
18.6 %	2.8 %	small septum
21.9 %	20.9%	control group

In a prospective study, the probability of conception and live birth in women after hysteroscopic metroplasty was significantly higher than in women with unexplained infertility (live birth rate 34.1 versus 18.9 percent) .

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.

Anticardiolipin antibodies and lupus anticoagulant

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

Both tests should be done twice, six to eight weeks apart, because a low to mid positive level can be due to viral illness and revert to normal. The anticardiolipin antibody titer is considered elevated if medium or high titers of both IgG and IgM isotypes are present in blood .

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

For a patient to be diagnosed with antiphospholipid syndrome, one or more clinical and one or more laboratory criteria must be present:

Clinical

1. **One or more confirmed episode of vascular thrombosis of any type:**

   - **Venous**
   - **Arterial**
   - **Small vessel**

2. **Pregnancy complications:**

   - **Three or more consecutive spontaneous pregnancy losses at less than 10 weeks of gestation with exclusion of maternal anatomic and hormonal abnormalities and exclusion of paternal and maternal chromosomal abnormalities**
   - **One or more unexplained deaths of a morphologically normal fetus at or beyond 10 weeks of gestation (normal fetal morphology documented by ultrasound or direct examination of the fetus)**
   - **One or more premature births of a morphologically normal neonate at or before 34 weeks of gestation secondary to severe preeclampsia or placental insufficiency**

Laboratory

Testing must be positive on two or more occasions with evaluations 12 or more weeks apart:

1. Positive plasma levels of anticardiolipin antibodies of the IgG or IgM isotype at medium to high levels
2. Positive plasma levels of lupus anticoagulant
3. Anti-β2 glycoprotein-1 antibodies of the IgG or IgM isotype in titers greater than the 99th percentile

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.

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 and in euthyroid women with thyroid peroxidase (TPO) antibodies.

Meta-analyses have found that the presence of TPO autoantibodies in euthyroid women is associated with an increased risk of spontaneous miscarriage that is two to three times higher than in women without these antibodies.

In addition,in meta-analysis thyroid replacement in these women was associated with a significant reduction in risk of miscarriage (relative risk 0.48)

Less useful tests

Evaluation of ovarian reserve
Medical work-up
Hypercoagulable state
Culture and serology
Autoantibodies and immune function
Screening for diabetes
Progesterone level
Endometrial biopsy
Sperm DNA fragmentation

Evaluation of ovarian reserve —

antral follicle count (AFC), basal serum FSH, AMH, or inhibin-B.
Evaluation of ovarian reserve using a day 3 FSH concentration can be considered in the evaluation of RPL in women of any age.
If measurement of FSH levels limited to women over 34 years of age, one quarter of those with elevated values would be missed.
Adequate ovarian reserve is established by:
a cycle day 3 FSH concentration less than 15 mIU/mL or
a clomiphene challenge test (An FSH level less than 15 mIU/mL on both days 3 and 10) is normal.
High day 3 serum estradiol concentrations of over 80 pg/mL are also associated with reduced oocyte numbers.
E2 elevated in 58 percent of women with unexplained RPL, vs 19 percent of controls with a known cause for their RPL.

Hypercoagulable state

There is a large and contradictory literature on the association between maternal inherited thrombophilia and recurrent spontaneous abortion occurring in the first trimester.

Evaluation for an inherited thrombophilia can be considered in rare cases of recurrent, unexplained late fetal loss (after nine 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.

Certain inherited thrombophilias

Anticoagulation of women with certain inherited thrombophilias may improve maternal outcome (eg, prevention of venous thromboembolism), but does not appear to prevent pregnancy loss. Neither the ACOG nor the ASRM recommend screening for inherited thrombophilias or MTHFR mutations for patients with recurrent pregnancy loss or any adverse pregnancy outcome unless other risk factors are present, such as a history of thrombosis in the patient or a close family member. Despite the lack of evidence and guidelines against routine screening for thrombophilia in recurrent pregnancy loss, many clinicians routinely order these tests

Culture and serology

Routine cervical cultures for Chlamydia species or Mycoplasma species, vaginal evaluation for bacterial vaginosis, and toxoplasmosis serology are not useful in the evaluation of RPL among otherwise healthy women.

Autoantibodies and immune function

Only anticardiolipin antibody and lupus anticoagulant have been clearly associated with pregnancy loss .

The pregnancy outcome of women with and without ANA is the same; available data do not support testing women with RPL for ANA.

With the exception of anticardiolipin antibody and lupus anticoagulant, we recommend not testing women with known autoimmune diseases or unexplained RPL for autoantibodies for the purpose of attempting to predict their risk of pregnancy loss.

Selection of appropriate tests for diagnosis of immune-based RPL also requires further investigation and validation. Results from HLA typing, mixed lymphocytotoxic antibody tests and mixed lymphocyte culture reactions are not predictive of pregnancy outcome .

The role of differences in the CD56+ population of cells and alterations in cytokines produced by monocytes, CD4+ cells, and endometrium remains investigational.

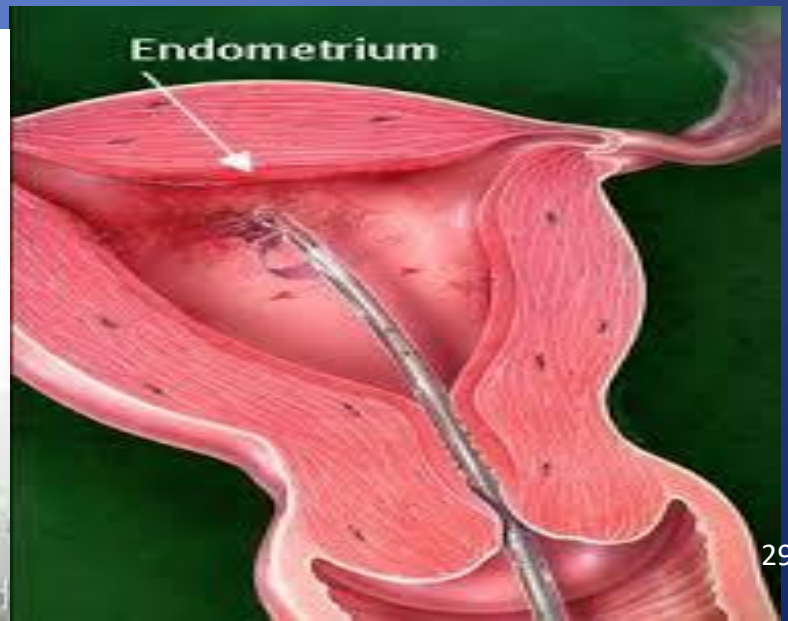
SUSPECTED IMMUNOLOGIC DYSFUNCTION

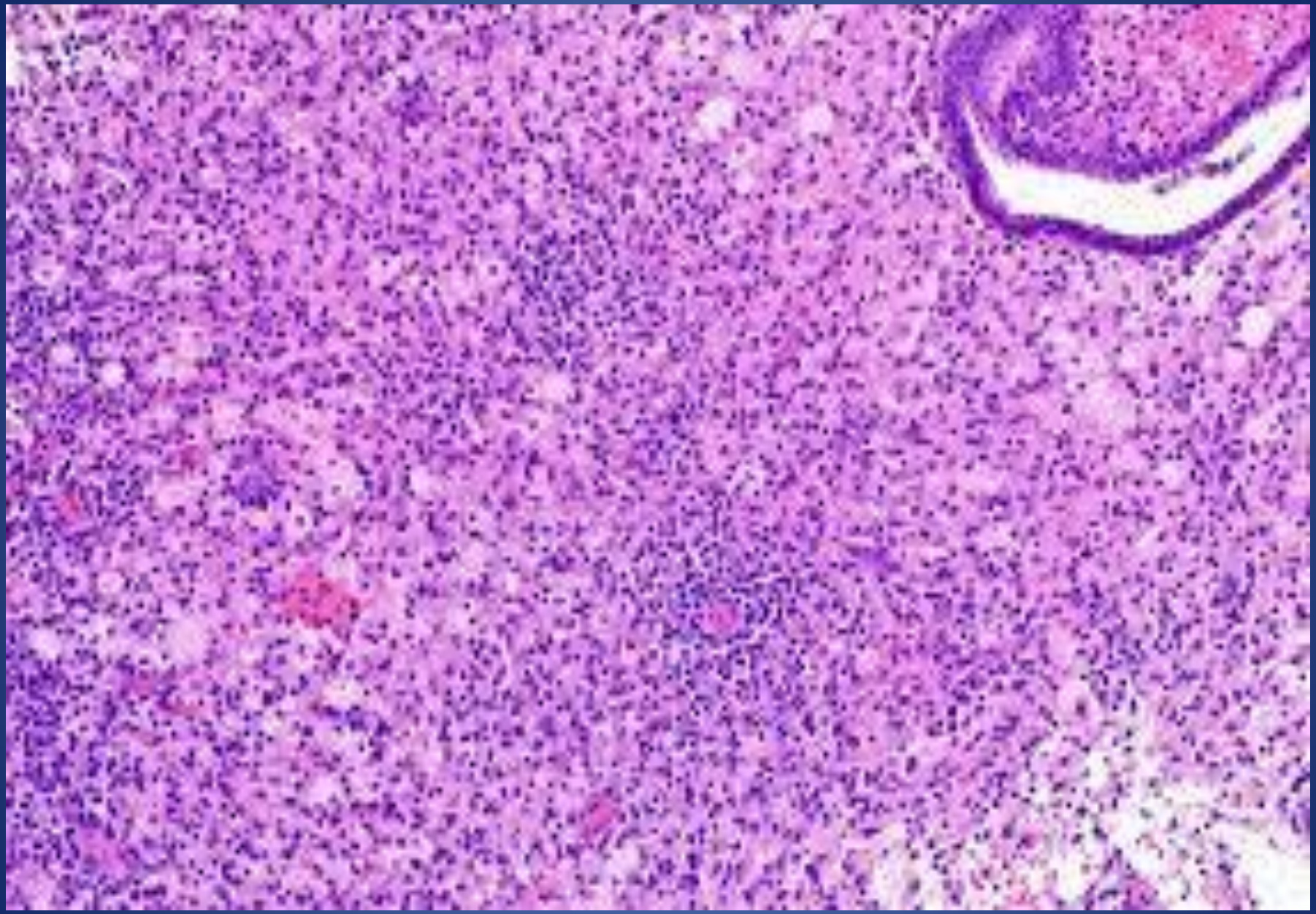
Although no alloimmune mechanism has been proven to cause RPL, several immunologic treatments have been advocated to improve the live birth rate in women with previous unexplained RPL. None are effective, and some appear to be harmful.

Screening for diabetes — Screening for diabetes mellitus should be limited to women with clinical manifestations of the disease. Only poorly controlled diabetes is associated with miscarriage.Consider local diferences

Progesterone level — Single or multiple serum progesterone levels are not predictive of future pregnancy outcome.

Endometrial biopsy — Diagnosis of a luteal phase defect 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. In the in vitro fertilization population, chronic endometritis has been associated with recurrent implantation failure in at least one study.





THYROID DYSFUNCTION AND DIABETES MELLITUS

Women with overt thyroid disease or diabetes mellitus should be treated, since these disorders can result in serious sequelae. Women with elevated serum thyroid peroxidase antibody concentrations are at high risk of developing hypothyroidism in the first trimester and autoimmune thyroiditis postpartum, and should be followed appropriately.

Euthyroid women with high serum thyroid peroxidase antibody concentrations may benefit from treatment with thyroid hormone during pregnancy to reduce the risk of miscarriage and preterm birth.

In a randomized trial, administration of levothyroxine (median dose 50 mcg daily) to early pregnant euthyroid women with positive thyroid peroxidase antibodies decreased the miscarriage rate from 13.8 to 3.5 percent .

Also lowered incidence of premature deliveries (7.0% versus 22.4%)

Further study is required to evaluate the efficacy of levothyroxine in women with RPL and positive thyroid peroxidase antibodies

HYPERPROLACTINEMIA

Normal circulating levels of prolactin may play an important role in maintaining early pregnancy. A study of 64 hyperprolactinemic women with RPL bromocriptine therapy was associated with a significantly higher rate of successful pregnancy (86 versus 52 percent) .Prolactin levels during early pregnancy were significantly greater in women who miscarried. We suggest treatment of women with hyperprolactinemia and RPL, even in the absence of overt hypogonadism.

POLYCYSTIC OVARY SYNDROME

The miscarriage rate in women with PCOS is 20 to 40 percent, higher 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.

Human menopausal gonadotropin

An observational study reported that controlled ovarian stimulation via human menopausal gonadotropin (hMG) administration appeared effective for treatment of endometrial defects in women with RPL .The mechanism may be correction of a luteal phase defect or stimulation of a thicker endometrium, thus leading to a better implantation site. Our clinical experience supports the efficacy of this treatment, although not all societies support its use.

IVF and preimplantation genetic diagnosis

Embryos of women with unexplained RPL have a higher incidence of aneuploidy for chromosomes 13,16,18, 21, 22, X, and Y than embryos obtained from healthy women

a retrospective cohort study of 300 women with RPL, the pregnancy, live birth, and miscarriage rates were similar for women who underwent IVF with preimplantation screening (PGS) and women who elected expectant management .Of the 168 retrievals performed 38 cycles (23 percent) were cancelled because of poor embryo yield or quality. Of the 130 completed PGS cycles, 103 (74 percent) yielded at least one euploid embryo.

Oocyte donation

Poor quality oocytes may be responsible for 25 percent of pregnancy losses .Ovum donation can overcome this problem and has been associated with a live birth rate of 88 percent in women with RPL .The success of ovum donation, even when the male partner's sperm is utilized for fertilization, suggests the absence of a significant paternal contribution to the etiology of RPL.

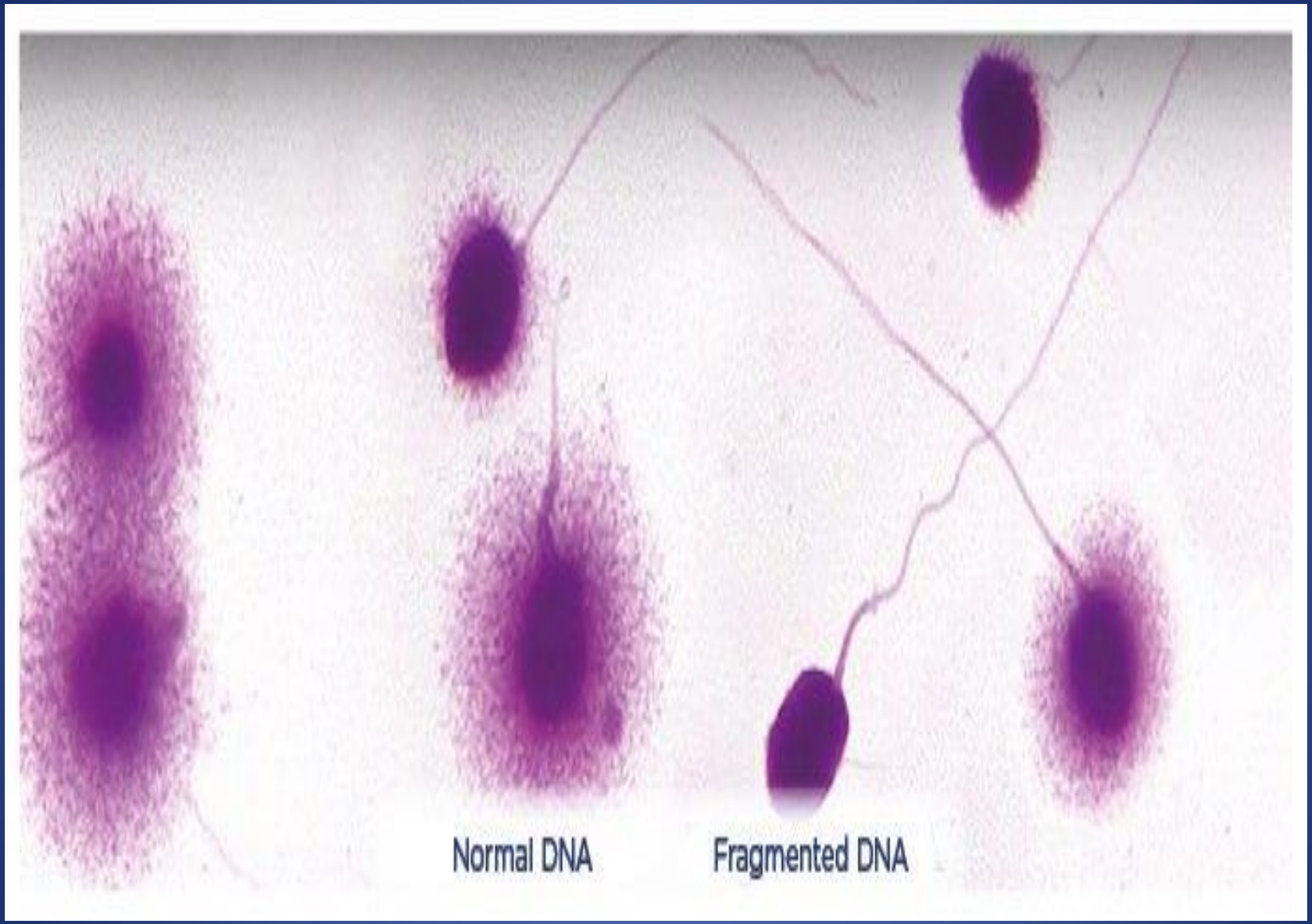
Gestational carrier

A 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 (eg, single gene defects, diminished oocyte and embryo quality). Women who decide to pursue this route should undergo a thorough evaluation as to the etiology of the RPL or failed IVF.

MALE CONTRIBUTION TO RECURRENT PREGNANCY LOSS

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.

In this experiment, in a microgel substrate under an acidic media, chromatin and sperm DNA is denatured and in the next step, by removing chromatin proteins, the DNA strands are distributed as far as possible around the sperm head which after staining are visible as halo around the sperm head. However, the breakdown of sperm DNA leads to lack of the DNA strands around head and consequently the lack of aura or very small halo around the sperm head


Normal DNA
Fragmented DNA

Timing of subsequent pregnancy — There are no high-quality data suggesting that delaying a subsequent pregnancy decreases the risk of a repeat pregnancy loss. An study of over 1000 individuals with one to two prior pregnancy losses reported that those who tried to conceive within three months of loss were more likely to achieve live birth compared with those who waited more than three months (53 versus 36 percent) .In addition, the shorter time interval for attempting conception was associated with a shorter time to pregnancy that resulted in live birth (adjusted fecundability odds ratio 1.71)

Role of low-dose aspirin to reduce risk of pregnancy loss Our approach — We suggest initiation of low-dose oral aspirin, 81 mg, prior to conception for individuals who have experienced one to two (or more) prior pregnancy losses. There is insufficient evidence to support use of preconception low-dose aspirin to prevent pregnancy loss for those who are nulliparous and/or who have not had a prior loss.

While the available data conflict, this approach is based on limited supporting data combined with the low anticipated risk of aspirin based on its use in other pregnant populations. While the 2018 American College of Obstetricians and Gynecologists practice bulletin advises against using low-dose aspirin to prevent pregnancy loss, the publication was created prior to the 2021 per-protocol analysis presented below .

Low-dose aspirin is suggested for individuals at high risk of preeclampsia or with antiphospholipid antibodies; timing of initiation varies by indication .

Risk of depression and mood disorders

many patients report psychological distress, including symptoms of depression, anxiety, and post-traumatic stress disorder (PTSD), that can last for months .Since one-quarter to one-third of individuals with pregnancy loss experience some adverse mental health outcome following pregnancy loss, and these medical conditions have available treatments, we suggest that all people diagnosed with pregnancy loss be screened for depression using a validated screening tool, such as the Edinburgh Postpartum Depression Scale. This can be done at the time of diagnosis, treatment, and/or follow-up visit to ensure this serious medical condition is not missed.

TREATMENT OPTIONS FOR UNEXPLAINED RECURRENT PREGNANCY LOSS

After evaluation, RPL remains unexplained in approximately one-half of couples. Nevertheless, the chance of a live birth is good (ie, over 50 percent with no intervention). This rate must be considered in evaluating therapies for unexplained RPL.

Although data may be lacking, treatments that may be offered to couples with unexplained RPL include the following:

Lifestyle modification —can increase fertility potential.These modifications include eliminating use of tobacco products, alcohol, and caffeine and reduction in body mass index (for obese women)

TREATMENT OPTIONS FOR UNEXPLAINED RECURRENT PREGNANCY LOSS

Lifestyle modification

Progesterone

Human menopausal gonadotropin

In vitro fertilization and preimplantation genetic diagnosis

Oocyte donation

Gestational carrier

Progesterone

supplemental vaginal progesterone therapy once a pregnancy has been established does not appear to increase the live birth rate . (no universal agreement)

data:

In the largest trial, over 800 women with RPL randomly assigned to first trimester vaginal progesterone therapy or placebo, approximately two-thirds of women in each group delivered a live infant after 24 weeks of gestation (progesterone and placebo birth rates: 66 versus 63 percent).

Furthermore, there were no differences between the groups in the rates of clinical pregnancy at 6 to 8 weeks, ongoing pregnancy at 12 weeks, ectopic pregnancy, miscarriage, or stillbirth. There were also no differences in neonatal outcomes. For this study, RPL was defined as three or more first-trimester pregnancy losses.

INEFFECTIVE OR UNPROVEN THERAPIES

Aspirin with or without heparin
Low-molecular weight heparin
Human chorionic gonadotropin
Clomiphene citrate
Immune therapy with intravenous immunoglobulin
Glucocorticoids
Other medications and/or combinations
Sitagliptin
Granulocyte colony stimulating factor (G-CSF)
Combined medical therapy

PROGNOSIS

Continued pregnancy loss

The greatest risk of recurrent loss occurs during the period up to the time of previous miscarriage. The likelihood of successful pregnancy in women with a history of RPL was evaluated in a single center cohort study of 987 women .At five years after the initial visit to a tertiary care center for RPL, 67 percent of women had a live birth. 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 another study women who conceived subsequently had a successful pregnancy beyond 24 weeks of gestation (75 percent).

Second trimester pregnancy loss

is significantly associated with recurrent second trimester loss and future spontaneous preterm birth. After a second trimester pregnancy loss, one study reported 39 percent of women had a preterm delivery in their next pregnancy, 5 percent had a stillbirth, and 6 percent had a neonatal death .In another study of 30 women with second trimester loss, the frequency of recurrent second trimester loss was 27 percent and the frequency of subsequent preterm birth was 33 percent.

Other obstetric issues

fetal growth restriction
premature delivery
cesarean delivery
perinatal death
but not for gestational hypertension or diabetes.
an increased incidence of preterm birth (8 versus 5.5 percent), very preterm birth <32 weeks gestation (2.2 versus 1.2 percent), and perinatal death (1.2 versus 0.5 percent) for the women with RPL .A different study that compared 162 women with RPL to control women additionally reported increased rates of fetal growth restriction (13 versus 2 percent) and cesarean delivery (36 versus 17 percent)

Marker of future maternal health — Studies have evaluated reproductive events as markers for future maternal illness or premature death .A study that utilized selfreported questionnaire data collected every two years from nurses reported an **association between recurrent spontaneous abortion and death before the age of 70 years** (hazard ratio 1.59, 95% CI 1.17-2.15 for three or more spontaneous pregnancy losses) .

While these findings raise interesting clinical associations, more study is required to clarify the impact of reproductive events on future maternal health.

SUMMARY AND RECOMMENDATIONS

The history should include:
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:
general physical assessment with attention to signs of endocrinopathy (eg, hirsutism, galactorrhea)
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.**
- **TSH and thyroid peroxidase 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 LAB**


Thank
you

Proposed Etiology	Proposed Incidence	Testing Supported by Evidence	Controversial Testing	Testing Not Recommended
Embryonic genetic abnormalities	60–80%			
1. Chromosomal imbalance 2. Other genetic defects		Karyotype of pregnancy tissue/ products of conception		
Parental genetic factors	2–5%			
1. Chromosomal 2. Single gene defects 3. Multifactorial		Karyotype for both female and male partners		
Anatomic factors	12–16%			
1. **Congenital** a. Incomplete müllerian fusion or septum resorption b. *Diethylstilbestrol* exposure c. Uterine artery anomalies d. Cervical incompetence 2. **Acquired** a. Cervical incompetence b. Synechiae c. Leiomyomas d. Adenomyosis		Uterine evaluation by hysterosalpingogram, 2D saline sonogram or 3D sonography (with or without saline infusion), office hysteroscopy		
Antiphospholipid syndrome	12–15%	Lupus anticoagulant Anticardiolipin IgG and IgM antibody, anti-β2-glycoprotein IgG and IgM	Testing for other phospholipid antibodies	

Proposed Etiology	Proposed Incidence	Testing Supported by Evidence	Controversial Testing	Testing Not Recommended
Endocrine factors	17–20%			
1. Diabetes mellitus 2. Thyroid disorders 3. Prolactin disorders 4. Luteal phase insufficiency 5. Polycystic ovarian syndrome, including insulin resistance and hyperandrogenism		HbA_{1C} TSH Prolactin	Insulin resistance screening Androgen testing	Endometrial biopsy for luteal phase defect Luteal phase progesterone levels
Infectious factors	7–56%			
1. **Acute infection** 2. **Chronic endometritis**			Cultures in lower genital track and endometrial biopsy for plasma cells	
Immunologic factors other than antiphospholipid syndrome	N/A			
1. Cellular mechanisms a. Suppressor cell or factor deficiency b. Alterations in major histocompatibility antigen expression c. Alterations in cellular immune regulation 1. TH1 immune responses to reproductive antigens (embryo or trophoblast) 2. TH2 cytokine or growth factor deficiency 3. Hormonal-progesterone, estrogen, prolactin, androgen alterations 4. *Tryptophan* metabolism 2. Other humoral mechanisms a. Antithyroid antibodies b. Antisperm antibodies c. Antitrophoblast antibodies d. Blocking antibody deficiency			Anti-thyroid antibodies Other immune cell testing and screening	Anti-sperm antibody testing Circulating natural killer cells, cytokine profiles, blocking antibodies, HLA typing, antipaternal leukocyte antibodies

Proposed Etiology	Proposed Incidence	Testing Supported by Evidence	Controversial Testing	Testing Not Recommended
Thrombotic factors	N/A			
1. Heritable thrombophilias 2. Antiphopholipid syndrome—see above				Factor V Leiden Prothrombin gene Protein C def Protein S def Antithrombin Homocysteine levels MTHFR (unless strong personal or family history of thrombotic events)
Other factors	N/A			
1. Altered uterine receptivity (integrins, adhesion molecules) 2. Environmental a. Toxins b. Illicit drugs c. Cigarettes and caffeine 3. Placental abnormalities (circumvallate, marginate) 4. Maternal medical illnesses (cardiac, renal hematologic) 5. Male factors 6. Exercise 7. Dyssynchronous fertilization 8. Psychological		Patient history regarding exposures and medical issues	Uterine receptivity testing Sperm testing including DNA fragmentation and aneuploidy	

TH, T helper; MTHFR, methylene tetrahydrofolate reductase; N/A, not applicable.

Leukocyte immunization poses a significant risk to the mother and her fetus .Several cases of graft-versus-host disease, severe intrauterine growth retardation, and autoimmune and isoimmune complications have been reported.Alloimmunization to platelets contained in the paternal leukocyte preparation is associated with cases of potentially fatal fetal thrombocytopenia. The routine use of this therapy for recurrent miscarriage is not clinically justified.

Therapy with IVIgs for recurrent pregnancy loss is expensive, invasive, and time-consuming, requiring multiple intravenous infusions over the course of pregnancy .Use of IVIgs for recurrent pregnancy loss is not supported by current evidence and may result in significant side effects such as nausea, headache, myalgias, and hypotension .More serious adverse effects include anaphylaxis (particularly in patients with IgA deficiency).

intralipid:The existing data do not support this practice and side effects can include flushing, dizziness, myalgias, nausea, anaphylactic reactions, kidney and liver dysfunction, infection, and thrombosis.

Intralipid infusions

In recurrent pregnancy loss patients is not recommended clinically and should be administered only under an institutional review board–approved protocol and in a study setting.

Inhibitors of TNF-α: although there exists only a single, small, retrospective, observational, nonrandomly assigned case series that involved treatment of recurrent pregnancy loss patients with inhibitors of TNF-α, these positive preliminary results have led a growing number of clinics to offer this therapy to patients, often at a significant cost .The safety of these compounds in pregnancy has not been appropriately studied and preliminary reports associating exposure to TNF-α inhibitors during early pregnancy to fetal VACTERL syndrome is concerning . These products are associated With rare but worrisome side effects, including liver failure, aplastic anemia, interstitial lung disease, and anaphylaxis. Other immunoregulating therapies theoretically useful in treating recurrent pregnancy loss include the use of cyclosporine, pentoxifylline, and nifedipine, although maternal and fetal risks with these agents preclude their clinical use.

Physical Examination

1. General physical examination with attention to:

    a. Obesity
    b. Hirsutism/acanthosis
    c. Thyroid examination
    d. Breast examination/galactorrhea
    e. Pelvic examination
        1. Anatomy
        2. Infection
        3. Trauma
        4. Estrogenization
        5. Masculinization

Laboratory

1. Parental peripheral blood karyotype (both partners)
2. Chromosome testing on products of conception
3. Hysterosalpingography, three-dimensional transvaginal sonography, sonohysterography, or office hysteroscopy, followed by hysteroscopy/laparoscopy, if indicated
4. Serum thyroid stimulating hormone level
5. Serum prolactin level
6. Serum HbA_{1c}
7. Antiphospholipid screening
   a. Anticardiolipin antibody levels (IgG and IgM)
   b. Lupus anticoagulant (activated partial thromboplastin time or Russell viper venom)
   c. Anti-β2-glycoprotein-1 antibodies (IgG and IgM)


Thank
You