Current Trends in the Management of Recurrent Pregnancy Loss and Threatened Miscarriage

Incidence of Pregnancy Loss: Global and Indian Context

1

Miscarriage is a frequent natural event occurring in approximately 20-30% of pregnancies.[1]

2

About 22% of pregnancies are lost before pregnancy is clinically recognized[1]

3

Nearly 80% of all the pregnancy loss cases occur within the first trimester.[1,2]

4

Spontaneous miscarriage rates (10% and 32%) are higher in Indian women compared to Western women.[3,4]

1. Coppola T. *Emerg Med Clin N Am*. 2003;21:667–677. 2. Macklon NS, *et al. Human Reproduction Update*. 2002;8(4):333–343. 3. Regan L, *et al. BMJ.* 1989;299:541–545. 4. Ford HB, *et al*. *MedReviews*. 2009;2(2):76–83. 5. Pallikadavath S, *et al. Fertility and Sterility*. 2005;84(2):516–518.

Threatened Miscarriage

Definition

- Vaginal bleeding in first 20 weeks of pregnancy without cervical dilatation or passage of products of conception
- May be associated with uterine contractions

Prognostic Factors for Threatened Miscarriage

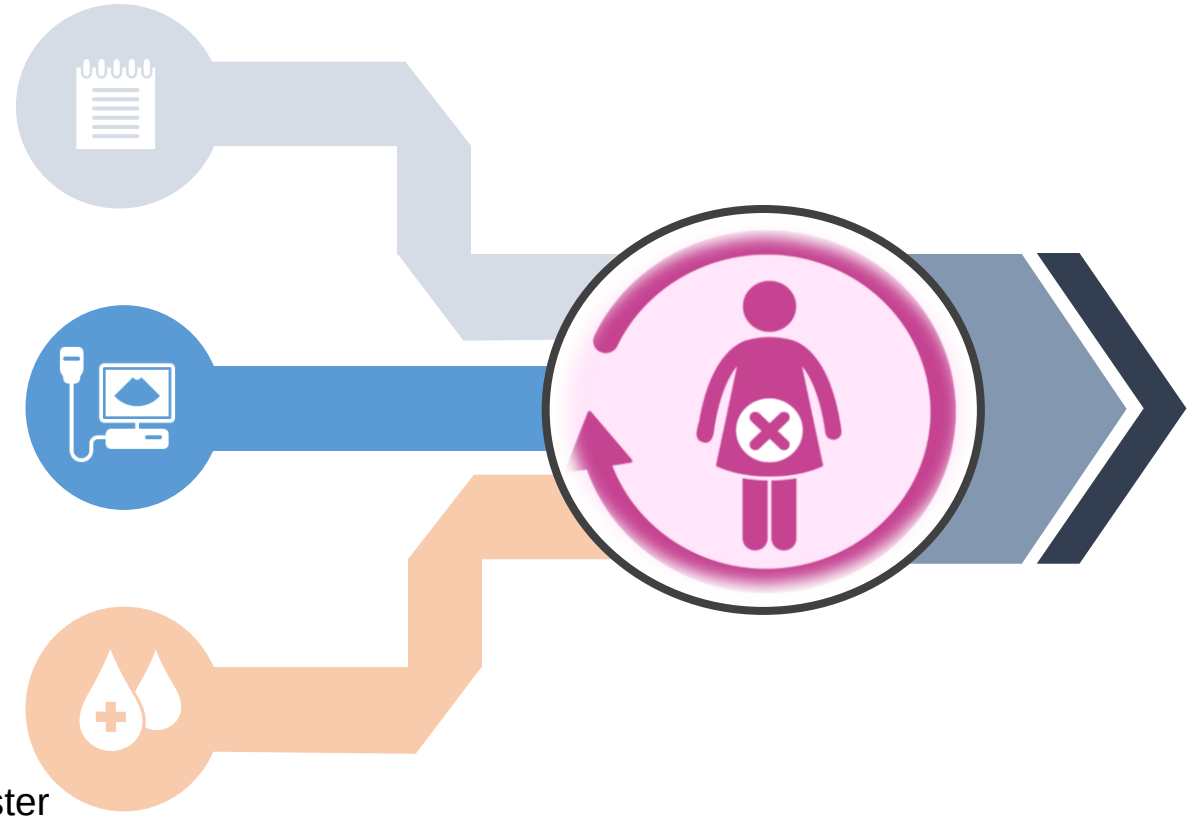
Adverse prognostic factors

History
- Maternal age >34 years
- Previous miscarriages

Sonography
- Fetal bradycardia
- Discrepancy between gestational age and crown to rump length
- Empty gestational sac >15–17 mm

Maternal serum biochemistry
- Low **β-hCG** values
- Free **β-hCG** value of 20 ng/ml
- β-hCG increase <66% in 48 hours
- Progesterone <45 nmol/L in 1st trimester
- CA125 level ≥43.1 U/mL in 1st trimester

hCG: Human chorionic gonadotropin



Fetal heart activity and lack of adverse prognostic factors convey a favourable prognosis.

Diagnostic Evaluation in Threatened Miscarriage

Endorsed by
FOGSI Family Welfare Committee (2009-12)

Checklist for Evaluation of Threatened Miscarriage

(Early pregnancy bleeding)

History

- LMP
- Pattern and amount of bleeding
- Presence of pain
- Spontaneous/ precipitating factors

Laboratory tests

- Urine pregnancy test+
- CBC
- Blood group and Rh typing (cross match if heavy bleeding)
- Urinalysis
- Ultrasonography (Preferably Transvaginal)
- Serum β hCG levels

Transvaginal ultrasound

1. Viable intrauterine pregnancy (check subchorionic bleed)
2. Intrauterine pregnancy of uncertain viability
   a. *MSD <25mm, **CRL <6mm – repeat TVS after 7 to 14 days)
   b. MSD >25mm, CRL >6mm- Missed miscarriage
3. Empty Uterus – rule out ectopic pregnancy by serial serum β hCG

Clinical and Pelvic examination

- Vital signs
- Source and amount of bleeding
- Passage of tissue
- Cervical tenderness (Suspect ectopic pregnancy)
- Os cosed/open
- Uterine size
- Adnexal mass (Suspect ectopic pregnancy)

Serum β hCG***

- Intrauterine pregnancy should be visible on TVS at serum β hCG titer of 1500IU or more (corresponding β hCG cut off for TAS is 6000IU)
- In viable intrauterine pregnancy, serum β hCG usually increases by over 66% in 48 hrs
- Plateauing or suboptimal rise in β hCG is suggestive of ectopic pregnancy/falling intrauterine pregnancy
- Falling β hCG titer is suggestive on non-viable pregnancy

*MSD-Mean Sac Diameter; **CRL-Crown Rump Length; *** Interpret with caution in multiple pregnancy, heterotropic pregnancy, and molar pregnancy; † Check for old bleeding/spotting/heavy clots; LMP-Last Menstrual Period; CBC-Complete Blood Count; TVS-Transvaginal Sonography; B-HCG-Beta Human Chorionic Gonadotrophin; TAS-Trans Abdominal Scan

Treatment Options for Threatened Miscarriage

It is essential to ensure that the pregnancy is viable before any treatment is considered.

Supportive

- Tender love and care
- Psychological support
- Stress itself is a risk factor for miscarriage
- Miscarriage is a stressful condition so that the vicious cycle can be broken by strong psychological support.
- Women should be reassured for a successful future pregnancy with supportive care. (Evidence level III)

Treatment Options for Threatened Miscarriage

Bed Rest

- There were no differences in the risk of miscarriage in the bed rest group versus the no bed rest group and the bed rest in hospital versus the bed rest at home.
- Although there is no definite evidence that bed rest can affect the course of pregnancy, abstinence from active environment for a couple of days may help women feel safer,[w10] thus providing emotional relief.

Treatment Options for Threatened Miscarriage

HORMONES

Hcg

- Endogenous HCG which is a hormone secreted by the syncytiotrophoblast of the placenta promotes the corpus luteum to secrete progesterone and stimulates early fetoplacental endocrine functions.
- It is known to play an important physiological role in maintaining the pregnancy.
- A meta-analysis showed that there was no significant difference in the incidence of miscarriage between HCG and “no HCG”(placebo or no treatment) groups.
- Thus, more good quality researches are urgently needed to assess the impact of HCG on miscarriage

Effect of Progestogens in Threatened Miscarriages

- Production of a number of endometrial proteins such as uteroglobin, PAPP and PP14
- Regulation of cellular immunity
- Stimulation of prostaglandin E2 production, which suppresses a number of T-cell reactions
- Stimulation of lymphocyte proliferation at the fetomaternal interface
- Suppression of cellular cytotoxicity from increased interleukin 2
- Suppression of T-cell and killer-cell activity
- Shift from T-helper (Th)1 to Th2 cells
- Synthesis of progesterone-induced blocking factor
- Suppression of matrix metalloproteinases

Schindler AE. *Gynecol Endocrinol.* 2004; 18(1): 51-57.

Choosing the Right Progestogens

Injectable Progesterone

- **Intramuscular** and **Subcutaneous** injections used
- Sufficient **secretory transformation** of **endometrium**
- Adverse effects include **Injection site pain**, may cause **skin irritation**, **inflammatory reactions**, and **abscess formation**

Vaginal progesterone

- **Well tolerated** with **adequate endometrial secretory transformation**
- **does not result in high and constant blood levels**
- can cause **discharge**, **vaginal irritation** in some patients & also **discomfort** while administration

Oral progesterone

- Oral administration is the **easiest route of administration**, and generally the **most acceptable** route for the patient.
- Patients **prefer oral** administration **over injectable** or **vaginal** routes

1. FOGSI Position Statement on the Use of Progestogens. Available at https://www.fogsi.org/fogsi-gcpr/. Accessed on: 27 February 2020. 2. Griesinger G, et al. Reprod Biomed Online.2019;38(2):249–59. 3. Salehpour, S., Tamimi, M., Saharkhiz, N. Comparison of oral dydrogesterone with suppository vaginal progesterone for lutealphase support in in vitro fertilization (IVF): a randomized clinical trial. Iran J. Reprod. Med. 2013; 11: 913–918

Benefits of Oral Dydrogesterone in Threatened Miscarriage

Evidence

- Pooled data from 8 trials showed that women with TM who were randomized to the progesterone group had a lower risk of threatened miscarriage (RR = 0.64, 95% CI 0.48–0.85). Wang et al. 2019
- The use of dydrogesterone (40 mg followed by 10 mg) has been shown to reduce the incidence of pregnancy loss in threatened abortion during the first trimester in women without a history of recurrent abortion. Omar et al. 2005.
- 87.5% Successful Deliveries with Dydrogesterone (40 mg STAT) in Threatened Miscarriage: Pandian et al. 2009
- Dydrogesterone Promotes Positive Pregnancy Outcomes in Threatened Miscarriage: El-Zibdeh et al. 2009`

Evidence

- A total of five randomized controlled trials and one non-randomized trial evaluating the efficacy of dydrogesterone in the treatment of threatened miscarriage were identified.
- The number of subsequent miscarriages or continuing pregnancies per randomized woman was compared in women receiving dydrogesterone compared to standard bed rest or placebo intervention.
- There was a 13% (44/335) miscarriage rate after dydrogesterone administration compared to 24% in control women.
- Systematic Review of Dydrogesterone for the Treatment of Threatened Miscarriage: Carp et al. 2012

Global Recommendations Endorse Use of Dydrogesterone in threatened Miscarriage

Guidelines	Recommendation
2013 Australian and New Zealand Guidelines[1]	The use of oral dydrogesterone demonstrated a significant reduction in the rate of miscarriage for women presenting with a threatened miscarriage from 24% to 11%* with a favourable safety profile.
2015 European Progestin Club Guidelines for the Treatment of Threatened Miscarriage[2]	For women presenting with a clinical diagnosis of threatened miscarriage, there is a reduction in the rate of spontaneous miscarriage with the use of dydrogesterone

* (OR 0.47; 95% CI 0.31 to 0.70)

1. Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) 2013. http://www.ranzcog.edu.au/doc/progesterone-support-of-the-luteal-phase-and-early-pregnancy.html. Last accessed: 27 December 2019.
2. Schindler A, Carp H, Druckmann R et al. *Gynecol Endocrinol*. 2015;31(6):447–449.

Current Trends in the Management of Recurrent Pregnancy Loss

Definition

- Recurrent pregnancy loss is defined as the loss of two or more pregnancies before 24 weeks of gestation. eshre
- Recurrent miscarriage, defined as the loss of three or more consecutive pregnancies. rcog
- Recurrent pregnancy loss defined by two or more failed clinical pregnancies. asrm

Types of Recurrent Pregnancy Loss

- Primary RPL is defined as RPL without a previous ongoing pregnancy (viable pregnancy) beyond 24 weeks' gestation.

- Secondary RPL is defined as an episode of RPL after one or more previous pregnancies progressing beyond 24 weeks' gestation.

- Tertiary RPL is defined as an episode of RPL in between one or more previous pregnancies progressing beyond 24 weeks

Risk of pregnancy loss

- The risk of recurrent spontaneous miscarriage is much higher in patients with previous losses.
- The risk of miscarriage after two consecutive losses is 17% to 25% .
- The risk of miscarrying after three consecutive losses is between 25% and 46%.
- The risk gets worse with increasing maternal age.

Risk factors for recurrent pregnancy loss

AGE

- Advanced female age is a well-established risk factor for female subfertility, fetal anomalies, stillbirth, and obstetric complications (Nybo Andersen et al., 2000, Sauer, 2015)

STRESS

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

OCCUPATIONAL OR ENVIRONMENTAL EXPOSURE

- exposure to occupational and environmental factors (heavy metals, pesticide, lack of micronutrients) seems to be associated with an increased risk of pregnancy loss

Risk factors for recurrent pregnancy loss

CHRONIC ENDOMETRITIS

- Chronic endometritis is characterized by a plasma cell infiltrate in the endometrium associated with a range of pathogenic organisms. There have been a series of papers suggesting a 7-58% prevalence of chronic endometritis in women with RPL (Cicinelli et al., 2014, McQueen et al., 2014, McQueen et al., 2015)

OBESITY

- Obesity has a significant impact on female reproductive health. Increased body mass index (BMI) is associated with subfertility, poorer outcomes following fertility treatment, and pregnancy loss (Metwally et al., 2008, Pandey et al., 2010)

Management of RPL

- Obstetric history
- Medical history of thrombophilia, PCOS, and diabetes
- Family history of hereditary thrombophilia, diabetes
- Information on lifestyle of both the male and female partner.
- Medical and family history could be helpful in deciding which investigations are relevant for the individual patient.

Recurrent Pregnancy Loss: Etiology

GENETIC

- 50% to 60% of early spontaneous miscarriages are associated with a chromosomal anomaly of conceptus.
- Most common abnormality is aneuploidy.
- A strong family history of recurrent miscarriage or genetic anomaly suggests a parental karyotypic abnormality.

Recommendations for screening

- 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-CGH is recommended based on a reduced maternal contamination.
- Parental karyotyping is not routinely recommended in couples with RPL. It could be carried out after individual assessment of risk.

array–based comparative genomic hybridization [array-CGH]

Treatment for RPL with genetic background

- All couples with results of an abnormal fetal or parental karyotype should receive genetic counselling. GPP

- All couples with results of an abnormal fetal or parental karyotype may be informed about the possible treatment options available including their advantages and disadvantages. GPP

Anatomical defects

- 3.2% to 6.9% likelihood of having a major congenital uterine malformations.
- Septate uterus, bicorporeal uterus with normal cervix (AFS bicornuate uterus), bicorporeal uterus with double cervix (AFS didelphic uterus) and hemi-uterus (AFS unicornuate uterus).
- Acquired uterine malformations (submucous myomas, endometrial polyps and uterine adhesions) have been found prevalent in women who have suffered pregnancy loss, but the clinical relevance is unclear

Anatomical defects

- Endometrial polyps are found in women with RPL, but there is no clear evidence of an association with pregnancy loss
- There are no studies on the effect of treatment of fibroids on the miscarriage rate in women with RPL. In subfertile women with submucosal fibroids, myomectomy did not significantly improve live birth rate or miscarriage rate, as compared to controls with fibroids that did not have myomectomy (based on two observational studies) (Pritts et al., 2009).

Recommendations for screening

- All women with RPL should have an assessment of the uterine anatomy.
- The preferred technique to evaluate the uterus is transvaginal 3D US
- It can distinguish between septate uterus and bicorporeal uterus with normal cervix (former AFS bicornuate uterus)
- Sonohysterography (SHG) is more accurate than HSG in diagnosing uterine malformations
- 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 US is not available.

Recommendations for treatment

- Whether hysteroscopic septum resection has beneficial effects (improving live birth rates, and decreasing miscarriage rates, without doing harm), should be evaluated in the context of surgical trials in women with RPL and septate uterus.
- Metroplasty is not recommended for bicorporeal uterus with normal cervix (former AFS bicornuate uterus).
- Uterine reconstruction is not recommended for hemi-uterus (former AFS unicornuate uterus)
- There is insufficient evidence in favor of metroplasty in women with bicorporeal uterus and double cervix (former AFS didelphic uterus)

Recommendations for treatment

Cervical Insufficiency

- Cervical weakness is believed to be a causing factor for pregnancy loss in women experiencing recurrent second trimester pregnancy loss.

Recommendations

- Women with a history of second-trimester PLs and suspected cervical weakness should be offered serial cervical sonographic surveillance.
- In women with a singleton pregnancy and a history of recurrent second-trimester PL attributable to cervical weakness, a cerclage could be considered.

Thrombophilia

Hereditary Thrombophilia

- Factor V Leiden mutation, Prothrombin mutation, Protein C, Protein S and Antithrombin deficiency , Methylenetetrahydrofolate reductase (MTHFR) mutation

Recommendation

- Screening for hereditary thrombophilia should not be done unless in the context of research, or in women with additional risk factors for thrombophilia.
- There is no, or a weak association at best, between RPL and hereditary thrombophilia.

Thrombophilia

Acquired Thrombophilia (APS)

- only proven thrombophilia that is associated RPL
- Five to fifteen percent of women with RPL have clinically significant antiphospholipid antibody titres
- Antiphospholipid syndrome (APS) is an autoimmune disease with the presence of antiphospholipid autoantibodies (aPL) formed against the person's own tissues.
- These autoantibodies interfere with coagulation

Thrombophilia

- APS is diagnosed based on the persistent presence of antiphospholipid antibodies and vascular thrombosis and/or pregnancy complications (Miyakis et al., 2006).

- For women with RPL screening for antiphospholipid antibodies (LA and ACA , aβ2GPI [IgG and IgM]), after two pregnancy losses is recommended.

Thrombophilia

- International Consensus classification criteria for diagnosis of the antiphospholipid syndrome

Laboratory criteria

- The presence of Lupus anticoagulant (LA) or Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer Anti-β2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma on two or more occasions, at least 12 weeks apart

Clinical criteria--adverse pregnancy outcome or vascular thrombosis.

- Adverse pregnancy outcomes include:
- three or more consecutive miscarriages before 10 weeks of gestation
- one or more morphologically normal fetal losses after the 10th week of gestation
- one or more preterm births before the 34th week of gestation owing to placental disease.

Treatment for RPL and Thrombophilia

Recommendation

- For women with hereditary thrombophilia and a history of RPL, antithrombotic prophylaxis is not recommended unless in the context of research, or if indicated for VTE prevention.

For women who fulfill the laboratory criteria of APS

- Low-dose aspirin (75 to 100 mg/day) starting before conception, and a prophylactic dose heparin (UFH or LMWH) starting at date of a positive pregnancy test is recommended

Metabolic and endocrinologic factors

Thyroid Dysfunction

- **Hyperthyroidism**, is found in 0.1-0.4% of pregnant women (Bahn et al., 2011).
- No studies were found that described or searched for an association between hyperthyroidism and recurrent pregnancy loss (RPL).

Hypothyroidism

- Recurrent miscarriages are associated with clinical and sub clinical thyroid disorders
- An association between TPOAb and RPL was found in a meta-analysis of 13 studies

Recommendations for screening

- Thyroid screening (TSH and TPO antibodies) is recommended in women with RPL.

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

Treatment for Thyroid Abnormalities

- Overt hypothyroidism arising before conception or during early gestation should be treated with levothyroxine
- Treatment of women with SCH may reduce the risk of miscarriage.
- If women with subclinical hypothyroidism and RPL are pregnant again, TSH level should be checked in early gestation (7-9 weeks AD), and hypothyroidism should be treated with levothyroxine. GPP
- If women with thyroid autoimmunity and RPL are pregnant again, TSH level should be checked in early gestation (7-9 weeks AD), and hypothyroidism should be treated with levothyroxine. GPP

Metabolic and endocrinologic factors

PCOS and Disturbances of the Insulin Metabolism

- Insulin resistance plays a significant role in recurrent pregnancy loss. Insulin resistance can be independent of polycystic ovarian status.
- Women with a history of recurrent miscarriage are at an increased risk for insulin resistance during the first trimester of a new pregnancy.
- Recent meta-analysis concluded that insulin resistance is associated with the susceptibility to recurrent miscarriages, and it may contribute to the occurrence of recurrent miscarriages.

Metabolic and endocrinologic factors

- Several studies on metformin found that it is effective in improving pregnancy outcomes in women with PCOS or insulin resistance.
- In patients with PCOS, metformin was found to significantly reduce the rate of miscarriage (Jakubowicz et al., 2002, Khattab et al., 2006, Wang et al., 2011, Al-Biate, 2015).
- Based on these results, it could be suggested that treatment with metformin increases the chance of a live birth in women with PCOS and a history of recurrent pregnancy loss.

Metabolic and endocrinologic factors

Luteal Phase defect

- The shortened luteal phase has been associated with pregnancy loss
- the assessment and interpretation of luteal phase defect is problematic.
- The use of histological and biochemical endpoints as diagnostic criteria for endometrial dating are unreliable (Evidence level III).

Diabetes Mellitus

- Evaluation for diabetes is advised with clinical suspicion.
- Glycated hemoglobin test is advised to screen diabetes (Evidence level III).

Metabolic and endocrinologic factors

Hyperprolactinemia

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

Male Factors

- Sperm samples from recurrent pregnancy loss couples have an increase in their sperm DNA fragmentation.
- Meta-analysis showed a significant increase in miscarriage in patients with high DNA damage compared with those with low DNA damage.
- Several different tests are available, but no consensus has yet been reached as to which tests are most predictive.
- Male factors abnormality is a significant cause for recurrent pregnancy loss after assisted conception.

Recommendations for Screening

- In the male partner, it is suggested to assess life style factors (smoking, alcohol consumption, exercise pattern, and body weight). GPP
- Assessing sperm DNA fragmentation in couples with RPL can be considered for explanatory purposes, based on indirect evidence.
- Routine testing for spermploidy (e.g. fluorescence *in situ* hybridization [FISH]) or DNA fragmentation is not recommended (Evidence level II).

Treatment for RPL with Male factor

- Couples with RPL should be informed that smoking, alcohol consumption, obesity and excessive exercise could have a negative impact on their chances of a live birth, and therefore cessation of smoking, a normal body weight, limited alcohol consumption and a normal exercise pattern is recommended. GPP
- Sperm selection is not recommended as a treatment in couples with RPL. GPP
- Antioxidants for men have not been shown to improve the chance of a live birth.

Infections

- Bacterial vaginosis is a risk factor for preterm delivery and a strong risk factor for late miscarriages.
- Vaginal swabs should be considered as screening tests during pregnancy in high risk women with previous history of late miscarriages.
- TORCH test is not recommended (Evidence level II).

Treatment for unexplained RPL

Psychological support

- Stress itself is a risk factor for miscarriage and recurrent miscarriage is a stressful condition so that the vicious cycle can be broken by strong psychological support.
- Women should be reassured for a successful future pregnancy with supportive care. (Evidence level III)

Treatment for unexplained RPL

Progesterone

- The progesterone act as immmunomodulator and it shift from proinflammatoryTh-1 cytokine responses to anti-inflammatory Th-2 cytokine response which is more favorable and pregnancy protective.
- Dihydrogesterone is a potential immunomodulator, it produces progesterone-induced blocking factors (PIBF) which is protein produced by pregnancy lymphocyte following exposure to progestorene.
- PIBF inhibits cell-mediated cytotoxicity and natural killer cell activity. Thus, it is immunoprotective for pregnancy

Treatment for unexplained RPL (Evidence)

- A Cochrane review summarized progesterone for treatment of miscarriage in all women and in women with previous miscarriage (RPL) (Haas and Ramsey, 2013). The Cochrane analysis pooled the results from four small trials.
- The miscarriage rate was lower in women with RPL receiving progesterone treatment, compared to placebo (OR 0.39; 95% CI 021-0.72).
- A more recent double blind, placebo-controlled, randomized trial of oral dydrogesterone (given from the time that a live fetus was confirmed by ultrasound until 20 weeks of gestation) among 360 women with a RPL also showed a benefit of progesterone in reducing a subsequent risk of miscarriage compared with placebo (RR 2.4; 95% CI 1.3-5.9) (Kumar et al., 2014).

Treatment for unexplained RPL (Evidence)

- 180 pregnant women (<35 years old) with at least 3 previous unexplained consecutive miscarriages oral dydrogesterone 10 mg BID,Intramuscular hCG 5000 IU every 4 days.
- Dydrogesterone group had a significantly lower miscarriage rate compared with the control group (13.4% vs. 29%; p=0.028).El-Zibdeh 2005.

Treatment for unexplained RPL (Evidence)

- Oral Dydrogesterone Treatment During Early Pregnancy to Prevent Recurrent Pregnancy Loss: Kumar et al. 2014
- Impact of administration of dydrogesterone in early pregnancy on pregnancy outcome and its correlation with Th1 and Th2 cytokine levels was studied.
- Women with either a history of RM, placed in either dydrogesterone group or placebo group, or no history of miscarriage.
- Dydrogesterone 20 mg/day from confirmation of pregnancy to 20 weeks of gestation.
- Miscarriage after 3 abortions >2.4 times in placebo vs. treatment group.
- Mean gestational age increased in the dydrogesterone group

Treatment for unexplained RPL (Evidence)

- Significant reduction of miscarriage with dydrogesterone compared to standard care: Carp et al. 2015 three studies comprising two randomised trials and one non randomised comparative trial.
- Lower Risk of Miscarriage with Oral Dydrogesterone Compared to Vaginal Progesterone: Wang et al. 2019
- Pooled data from 8 trials showed Dydrogesterone was shown to have a lower risk of miscarriage (RR = 0.49, 95% CI 0.33–0.75) than natural progesterone (RR = 0.69, 95% CI 0.40–1.19).

Global Guideline Recommendations Favor Dydrogesterone in RPL

European Progestin Club Guidelines for the Treatment of Recurrent Miscarriage 2015 [1]	Fogsi Position Statement on the Use of Progestogens (2015) [2]	ESHRE guideline on Recurrent Pregnancy Loss (2017) [3]
For women presenting with a clinical diagnosis of recurrent miscarriage, 3 or more, there is a **reduction in the rate of miscarriage with the use of dydrogesterone**.	**Dydrogesterone: 10mg BID till 20 weeks of pregnancy**	Vaginal progesterone during early pregnancy has no beneficial effect in women with unexplained RPL. There is some evidence that **oral dydrogesterone initiated when fetal heart action can be confirmed may be effective**.

BID, twice daily; DYD, dydrogesterone

1. Schindler AE et al. *Gynecol Endocrinol.* 2015;31(6):447–449
2. Fogsi Position Statement on the Use of Progestogens. https://www.fogsi.org/fogsi-gcpr/. Accessed on 30th December, 2019.

Conclusion

- The majority of miscarriages are sporadic and are thought to result from genetic causes that are greatly influenced by maternal age.
- Recurrent pregnancy loss is defined by two or more failed clinical pregnancies.
- Up to 50% of cases of RPL will not have a clearly defined etiology.
- Evaluation of RPL can proceed after two consecutive clinical pregnancy losses.
- Assessment of RPL focuses on screening for genetic factors and antiphospholipid syndrome, assessment of uterine anatomy, hormonal and metabolic factors, and lifestyle variables.
- Psychological counseling and support should be offered to couples with RPL

Thank You!

IND2141805 17 June 2020

There is, I am convinced, no picture that conveys in all its dreadfulness, a vision of sorrow, despairing, remediless, supreme. If I could paint such a picture, the canvas would show only a woman looking down at her empty arms.

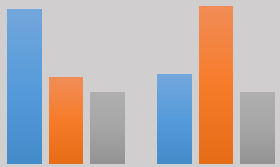
Charlotte Brontë

Lower Risk of Miscarriage with Oral Dydrogesterone Compared to Vaginal Progesterone: Wang *et al.* 2019

Conclusive findings from clinical evidence

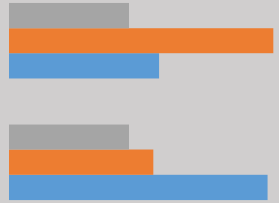
Pooled data from 8 trials showed that women with TM who were randomized to the **progesterone** group had a **lower risk of threatened** miscarriage (RR = 0.64, 95% CI 0.48–0.85).

Dydrogesterone was shown to have a lower risk of miscarriage (RR = 0.49, 95% CI 0.33–0.75) than natural progesterone (RR = 0.69, 95% CI 0.40–1.19).



Oral progestogen has a lower risk of miscarriage (RR = 0.55, 95% CI 0.38–0.79) vs. vaginal administration (RR = 0.58, 95% CI 0.28–1.21).

Dydrogesterone, but not natural progesterone, was associated with a **lower risk of miscarriage**.



RR: risk ratio; CI, confidence interval

Wang XX. *J Obstet Gynaecol Res*. 2019;45(4):794–802.

13 Progesterone compared to no treatment/placebo for unexplained RPL

Patient or population: Unexplained RPL
Intervention: Progesterone
Comparison: No treatment/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment/placebo	Risk with Progesterone				
Miscarriage rate (Haas and Ramsey, 2013)	376 per 1.000	191 per 1.000 (112 to 303)	OR 0.39 (0.21 to 0.72)	225 (4 RCTs)	⨁◯◯◯ VERY LOW [a,b]	*(women with previous miscarriage only)*
Miscarriage rate *(Coomarasamy et al., 2015)*	334 per 1.000	321 per 1.000 (264 to 391)	RR 0.96 (0.79 to 1.17)	826 (1 RCT)	⨁⨁◯◯ LOW [b,c]	*Single RCT*
Live birth rate *(Coomarasamy et al., 2015)*	633 per 1.000	659 per 1.000 (595 to 728)	RR 1.04 (0.94 to 1.15)	826 (1 RCT)	⨁⨁⨁◯ MODERATE [b,c]	*Single RCT*
Miscarriage rate *(Saccone et al., 2017)*	282 per 1.000	203 per 1.000 (149 to 273)	RR 0.72 (0.53 to 0.97)	1586 (10 RCTs)	⨁⨁⨁◯ MODERATE [d]	*Review including (Coomarasamy et al., 2015)*

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. 4 RCTs of very poor quality (as assessed by reviewers)
b. Optimal information size not met
c. Single RCT
d. differences in direction of effect