ICOG IGNITE

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Recurrent Pregnancy Loss

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FOGSI PRESIDENT'S DESK

Dr. Nandita Palshetkar

President FOGSI 2019

As President FOGSI 2019, it gives me immense pleasure and pride to release of the 1st ICOG newsletter on Recurrent Pregnancy Loss

ICOG is an academic wing of FOGSI which has been actively updating its members in the field of OBGY since 1984. Many stalwarts in the field of OBGY have been actively involved with ICOG. The aim of this years ICOG is the standardisation of clinical practice. ICOG has been conducting certification courses for freshly passed postgraduate students who wish to enhance they skills in the field of reproductive medicine, Endoscopy, Ultrasound, foetal medicine and two new additions vaginal surgery & critical care in obstetrics. Another important task is standardisation of these certification courses, where Standard messages should be passed on to the students.

This newsletter is to provide updates in Recurrent Pregnancy Loss. A lot of authors have contributed in order to provide the latest and up to date data on RPL. The aim of this newsletter is to ensure that the updates are put into clinical practice and help in better patient management.

I would like to thank the editor Dr. Laxmi Shrikhande , Dr. Tushar Kar (ICOG Chairperson) and Dr. Parag Biniwale (ICOG Secretary) for being so active in bringing out this wonderful newsletter. I would also like to thank everyone who has contributed towards bringing this newsletter to all our members.

"Coming together is beginning,
keeping together is Progress
and working together is Success"

CHAIRMAN MESSAGE

Prof. Tushar Kar

MD, MICOG, FICOG, FICMCH,

vChairperson, ICOG -2019-20

Dearest

Members, Fellows of ICOG & fellow FOGSIANS

At the out set I thank all members ,fellows of ICOG, past chairpersons of ICOG, office bearers of ICOG, past presidents of FOGSI & all members of all societies of FOGSI. Before I took over as chairperson ICOG, one of our vision was to publish newsletter of ICOG in various day to day clinical situation to be named as IGNITE.

The first issue of IGNITE is on Recurrent Pregnancy Loss. Most of us are coming across Recurrent Pregnancy Loss in our everyday practice for which we must update with RPL.

RPL is quite common affecting 2-3% of all women attempting to get a child, at times this may be increased. The research activity on RPL in term of literature is low compared to other clinical entity. As a result our knowledge regarding diagnosis, aetiology & management of RPL are limited. In 50% of RPL a cause can be found out & in other 50% a risk factor is found which is not the same as finding a cause. In many cases a single pathogenic factor is found today, in majority multifactorial background involving multiple genetic & environmental risk factors are seen. This complexity renders the research in RPL very difficult because of need of large no of patients & control population. Moreover there are very few dedicated RPL clinics so far in the world.

This IGNITE issue on RPL will focus mainly on diagnosis, aetiology, investigations, management & a special chapter on 'how to approach a case of a RPL'. All the contributers are of highest standard clinical expertise.

I hope readers will enjoy the recent advances including understanding molecular biology & management of RPL & carry forward this knowledge for their best clinical practice.

ICOG, being the academic wing of FOGSI always engaged in bringing out latest and best protocols & proactive guidelines, will definitely help the clinicians to understand & manage a common clinical entity like RPL in best possible way through this IGNITE Issue.

"Education is a passport to future,
For tomorrow belongs to those
Who prepares for it today"

FROM THE EDITOR'S DESK

Dr. Laxmi Shrikhande

MD, FICOG, FICMU, FICMCH

Vice Chairperson, ICOG -2019-20

Warm Greetings !!

Recurrent Pregnancy Loss is frustrating for both clinician and the couple. There are many challenges for the clinician in managing these couples right from definition to finding the cause to treatment.

Every now and then there are new developments in this field. A comprehensive ready recknor was the need of the hour for busy clinicians and Post graduate students.

ICOG being in the fore front of knowledge dissemination has come out with this IGNITE on current practices on RPL. We as editors have tried our level best to give you the comprehensive latest information on Etiology, Evaluation , Management and Recent advances of RPL..

Our gratitude to all the authors for their timely submission of crisp articles. We are also thankful to FOGSI President Dr Nandita Palshetkar and ICOG Chairperson Dr Tushar Kar for trusting us with the responsibility of this prestigious ICOG publication on RPL.

We hope that our readers will find this Ignite useful in their day to day practice.

Dr. Laxmi Shrikhande & Editorial Team

ICOG TEAM 2019

ICOG TEAM 2019

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SECRETARY MESSAGE

Dr. Parag Biniwale

Secretary ICOG

Recurrent pregnancy loss (RPL) is a common problem due to uncommon situations. As clinicians , we can't pin point a specific reason in almost 50 % women. It causes agony to everyone concerned. The patient is unclear about the outcome and the doctors also can't guarantee a 100% results. Concepts have changed over years as far as investigations and management of RPL. Gone are the times when TORCH group was blamed for recurrent miscarriage. Such couples need thorough specific investigations, lot of counselling, involvement of other specialists and tender loving care. Aspirin and low molecular weight heparin are important tools in management with expanding indications for its use.

ICOG , the academic wing of FOGSI always comes up with useful publications which aid clinicians to offer best possible care. Vice chairperson Dr Laxmi Shrikhande and her team have put best efforts in diagnosis, investigations and management of the intriguing problem of RPL. I am sure this will be a handy tool for all of us taking care of women struggling to conceive and continue pregnancy to a viable foetus.

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RECURRENT PREGNANCY LOSS-OVERVIEW

Dr. Laxmi Shrikhande, Dr. Ritu Dargan

Recurrent Pregnancy Loss is an important reproductive health issue since it affects 2%-5% of couples. The incidence of RPL varies widely between reports because of the differences in the definitions and criteria used, as well as the populations characteristics.

To differentiate RPL from early pregnancy loss, also referred to as miscarriage or spontaneous abortion, defined as the loss of a clinical pregnancy before 20 completed weeks of gestational age (18 weeks after fertilization) or, if gestational age is unknown, the loss of an embryo/fetus of < 400 g[1]

It is relatively common event, occurring in 15%-25% of pregnancies, and increasing in prevalence with maternal age[2,3]. Indeed, the risk is between 9% and 12% in women aged < 35 years, but increases to 50% in women aged > 40[3]

The definition of recurrent pregnancy loss (RPL) has long been debated and differs among international societies[4,5]

For the European Society for Human Reproduction and Embryology[4,6] and the Royal college of Obstetricians and Gynecologists7, RPL refers to three consecutive pregnancy losses, including non-visualized ones. However, according to the American Society for Reproductive Medicine[2] it is defined as two or more clinical pregnancy losses (documented by ultrasonography or histopathologic examination) but not necessarily consecutive. The WHO recommends in developing countries, where gestation is often uncertain, a birth of weight of 500 g should be used to define viability. There are 10 % to 20% of women have experience a miscarriage throughout their reproductive period. 2% of them have 2 consecutive abortions and 0.5-1% of them have 3 consecutive abortions.

Primary RPL[4,5] refers to multiple losses in a woman with no previous viable infants, whereas **secondary RPL** refers to multiple losses in a woman who has already had a pregnancy beyond 20 gestational weeks[4,5]

Tertiary RPL refers to multiple pregnancy losses between normal pregnancies[4,5]

RISK FACTORS

- **Age & timing of pregnancy loss**

When women with RPL are categorized by their ages, the probability of the next pregnancy ending in miscarriage is similar between the 30-34 years and the 35-38 years groups, and the risk rises dramatically to 70% for the 40-44 years group[13]

The increase is due to an increase in chromosomally abnormal conceptuses, probably as a result of poor oocyte quality, and a decline in uterine and ovarian function.

Advanced paternal age is also a risk factor for miscarriage. The risk of miscarriage is highest in couples where the woman is older than 35 years and the man older than 40 years.

- **Lifestyle & environmental factors:**

Cigarette smoking has been suggested to have an adverse effect on trophoblastic function and is linked to an increased risk of sporadic pregnancy loss.

Obesity has also been shown to be associated with an increased risk of RPL in women. Other life style factors such as cocaine use, alcohol consumption and increased caffeine consumption have been associated with miscarriage.

The relation between sporadic and/or RPL and occupational and environmental exposure to organic

solvents, medications, ionizing radiation, and toxins have been suggested, although the studies performed are difficult to draw strong conclusions because they tend to be retrospective and confounded by alternative or additional environmental exposures.

WORKUP

For years, it was recommended to wait for three miscarriages, but several studies have now shown that the risk of a future miscarriage after two successive losses (24%-29%) is like or slightly lower than the risk after three losses (31%-33%) and the findings are comparable[8,9]. Therefore, it is now acceptable to start a workup following two consecutive losses especially in women aged > 35 years[2,10]

Evaluation starts with a complete history for both partners and information about previous pregnancies and miscarriages. A thorough gynecologic history should be obtained, as well as a family history of infertility or miscarriage. Both partners should also be questioned about the modifiable lifestyle factors, such as smoking, alcohol use, and nutritional habits[2,7,8,9]

A full workup must be ordered following the initial visit to identify treatable causes. The exact definition of a “full workup” varies between the various international societies and the different recommendations needs to be tailored according to the couple, considering factors such as the woman and her partners’ age, the personal and family medical history, the couple’s emotional and financial state.

A blood workup should include a complete blood count, fasting serum glucose and prolactin levels, serum TSH, as well as antibodies for APS (lupus anticoagulant, anticardiolipin antibodies, and anti-Beta II glycoprotein I antibodies)

Testing for thyroid autoantibodies is only recommended in case of abnormal findings suggesting thyroid disease. Testing for inherited thrombophilia's (FVL, PT G2021AA, MTHFR, PCR, PSR, AT) is not recommended unless there is a personal or a strong family history of thrombosis[2,7,8,9]

A transvaginal three-dimensional ultrasound for the assessment of the uterine cavity and the antral follicle count should be performed. The uterine cavity should be further explored with a sonohysterography, a hysterosalpingography, or a hysteroscopy. Pelvic magnetic resonance imaging can be helpful in complicated cases of anatomic defects. Finally, karyotypes for both partners should be ordered.

For years, genetic evalution of the POC was not routinely ordered because it was considered difficult and unreliable. Indeed, because it was done by routine karyotype analysis, it was associated with a risk of maternal cell contamination, a risk of false negative results, and a risk of failed cell culture because of the presence of toxic cells and substances. However , the use of new techniques , such as a single nucleotide polymorphism microarrays and comparative genomic hybridization (CGH), resolved these issues and allowed for a 23-chromosome pair analysis. The genetic evalution of the POC is nowadays considered easy and reproducible, and many referral centers for RPL currently state their evaluation of a couple with RPL with a POC Karyotype. If euploid, a full RPL workup is ordered. If an unbalanced chromosomal translocation or inversion is found, a parental karyotype is ordered and PGD offered for future attempts. Finally, an aneuploidy in the POC confirms the diagnosis and no further tests are necessary. Some studies have reported such a strategy to be more cost effective than the classic evaluation approach.. However, if a POC karyotype if not available, a full RPL workup is ordered.

* International Journal of Women’s health 2017:9 331-345

Table 2 Etiologies of recurrent pregnancy loss, recommended tests for diagnosis, and treatment options

Etiology	Tests for diagnosis	Treatment options
Uterine factor	3D ultrasonography, sonohysterography, hysterosalpingography, hysteroscopy	Hysteroscopic resection of septum
	Magnetic resonance imaging	Myomectomy, hysteroscopic removal of polyps
		Adhesiolysis
Antiphospholipid syndrome	aCL, Anti-β2GP1, lupus anticoagulant	Heparin + aspirin
Endocrine abnormality	Thyroid-stimulating hormone	Levothyroxine
	Prolactin	Bromocriptine
	Fasting glucose or HbA_{1c}	Diabetes control (weight loss, nutrition, metformin)
Genetic	Karyotype of product of conception	Genetic counseling
	Parental karyotype	Preimplantation genetic diagnosis for balanced translocation
Environmental factors	Screen for smoking, drug use, excessive alcohol and caffeine intake	Eliminate environmental toxins
Psychological		Psychological support in a specialized setting
Unexplained		Progesterone supplementation (no consensus)
		Immunomodulating treatments (no consensus)
		Preimplantation genetic screening (no consensus)
Other (no consensus)		
Luteal phase deficiency	Mid-luteal progesterone, endometrial biopsy	Progesterone supplementation
Chronic endometritis	Endometrial biopsy	Antibiotic treatment
Other infections	Cultures	Appropriate treatment
Male factor	DNA fragmentation test on sperm	Lifestyle modifications, multivitamins, donor sperm

Note: Anti-β2GP1: anti-β2 glycoprotein-I.
Abbreviations: aCL, anticardiolipin; 3D, three-dimensional.

UNEXPLAINED RPL (URPL)

Even with a comprehensive workup, an etiology for RPL is identified in less than half of the couples.

URPL is considered when a complete genetic, anatomic, endocrine, and immune evaluation was performed and are reported as normal.

URPL is associated with significant adverse psychological consequences for the couple. Besides the grief following each miscarriage, there is the anxiety and insecurity associated with each positive pregnancy test. However, couples with URPL should be informed that the chances for a future successful pregnancy could be as high as 50%- 70% and depend mostly on maternal age and the number of previous losses.

According to one study, women aged < 30 years are estimated to have a 75% chance of live birth within 2 years, compared to 40% for women aged 40 years. Moreover, for women with three miscarriages, the chance of a future live birth within 2 years is 70% compared to 45% following six miscarriages. Another study found a cumulative incidence of live birth of 50% after 24 months, and a median time to live birth of 102 weeks[11]

CONCLUSION

1. RPL is an important reproductive health issue. Various etiologies have identified over the years and successful therapeutic strategies implemented.

2. A full workup can be initiated following two consecutive losses to identify treatable causes that include uterine abnormalities, APS, endocrine diseases, and balanced translocations.

3. Lifestyle modifications should also be implemented to improve reproductive prognosis. However, almost half of the cases remain unexplained, for which various treatments are continuously being developed.

4. Regardless of the cause, a thorough follow up with an important psychological support can help most couples achieve a successful live birth

REFERENCES

1. Fertil Steril 2009;92(S) : 1520-1524

2. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril 2012; 98(5): 1103-1111

3. Incidence of early loss of pregnancy. N eng J Med 1988;319(4):189-194

4. Terminology for pregnancy loss prior to viability : a consensus statement from the ESHRE early pregnancy special interest group. Hum Reprod 2015;30(3):495-498

5. Nomenclature for pregnancy outcomes : time for a change. Obstet Gynecol 2011 ; 118(6): 1402-1408

6. Evidence based guidelines for the investigation and medical treatment of recurrent miscarriages .Hum Reprod 2006;21(9): 2216-2222

7. Royal college of Obstetricians and Gynecologists, Scientific advisory committee, Guideline No. 17. The investigation and treatment of couples with recurrent miscarriages , 2011

8. The American College of Obstetricians and Gynecologists : Practice Bulletin No. 150 Early pregnancy loss. Obstet Gyencol 2015;12(5):1258-1267

9. Recurrent Miscarriage . Lancet 1990 ; 336 (8716): 673-675

10. Novel strategies for the management of recurrent pregnancy loss. Semin Reprod Med 2015;33(3): 161-168

11. Time to conception and time to live birth in women with unexplained recurrent miscarriage. Hum Reprod 2014;29(6): 1146-1152

12. International Journal of Women's health 2017:9 331-345

13. An evidence based approach to recurrent pregnancy loss SAJOG 2013;19(3):61-6

**"Don't be pushed around by the fears in your mind.
Be led by the dreams in your heart."**

ROY. T. BENNETT

AETIOLOGY OF RPL

Dr Sneha Bhuyar, Dr Basab Mukherjee

Pregnancy loss is the unexpected and unplanned loss of the foetus before it is capable of extrauterine survival. The term spontaneous miscarriage is used for pregnancy loss before 20 weeks. The miscarriage could be preclinical or clinical. Clinically recognized spontaneous miscarriage rate is between 10-15%, with the majority occurring in the first trimester of pregnancy. Recurrent spontaneous miscarriage is defined as three or more consecutive miscarriages before 20 weeks of pregnancy. About 1 to 2% of couple experience three or more consecutive pregnancy losses. Investigation of the couple may be started after two consecutive miscarriages, especially if the women is more than 35-year-old, if cardiac activity is depicted on ultrasound or when there has been difficulty in conceiving. Established causes of recurrent miscarriage include immunological (20-50%), endocrine (17-20%), anatomical (12-16%), genetic (5%), and infection (0.5-1.5%).

1. Genetic causes

2. Infective

I. Bacterial vaginosis

II. Genital Tuberculosis

3. Anatomic

I. Congenital uterine anomalies

II. Uterine fibroids

III. Cervical incompetence

4. Endocrinal

5. Haematological

I. Acquired

II. Inherited thrombophilias

6. Imunological

I. Cytokines

II. Endometrium

III. APLA

7. Miscellaneous

I. Micronutrients

II. Stress

1. GENETIC CAUSES

Chromosomal Causes

Chromosomal abnormalities account for 50% of first trimester losses. There may be abnormality in the total chromosome number (aneuploidy) or structure.

Abnormality in Chromosome Number (Aneuploidies)

These may involve autosomes or sex chromosomes. These can be trisomy's (50%). Trisomy conceptuses are commonly associated with advanced maternal age. Trisomy 16 is the commonest

aneuploidy in spontaneous miscarriages (31%) followed by trisomy 22 (11.4%) and trisomy 21 (10.5%).

Structural Abnormalities

These are observed in about 2% of cytogenetically abnormal conceptuses and include balanced chromosomal translocations, inversion and sex chromosome mosaicism. About 50% of these abnormalities are inherited. The most commonly observed rearrangement is reciprocal translocation, Robertsonian translocation and inversion.

A. Carriers of balance reciprocal translocation
B. Robertsonian translocations
C. Inversions

Sex Chromosome Mosaicism

Low level of sex chromosome mosaicism has been reported in couples with RSM. Apart from miscarriage, infertility can occasionally occur in male carriers of balanced translocation due to spermatogenetic arrest.

Single Gene Disorders

Single gene disorders associated with recurrent pregnancy loss may be X- linked dominant disorders, inherited thrombophilia's, sharing of HLA antigens, and polymorphism in HLAG and HLA E alleles.

X-linked dominant disorder - an affected mother will pass the disease to 50% of her son whereas an affected male will pass the disease to all the daughters while all the sons will be normal.

Do Abnormal Sperms Cause Recurrent Pregnancy Loss?

The concept of the role of sperm factor in cases of recurrent pregnancy loss is new and intriguing. Majority of the spontaneous miscarriages are in the first trimester & are mostly related to chromosomal abnormalities. This suggests that the chromosomal abnormalities could be derived either from the XX chromosome or XY chromosomes, which in turn lead to the belief that at least half of the proportion of cases of recurrent pregnancy loss, especially the early losses are due to sperm factor.

Androgenomes are chromosomes derived paternally. These androgenomes are created by implantation of the male pronucleus in the oocyte, where in the female pronucleus is absent. This phenomenon occurs in severely stunted embryos. There is extra embryonic trophoblastic tissue which is very well developed in these embryos. The genetic information which is necessary for the trophoblast growth is provided by the paternally transmitted genome. The development of embryo is by maternally transmitted genome. One of the classic examples is complete hydatidiform mole, which contains two sets of diploid androgenomes which are derived paternally.

Sperm DNA Damage : DNA damage in the male germ line has been associated with poor semen quality, low fertilization rate, impaired preimplantation development, increased miscarriage and an elevated incidence of disease in the offspring, including childhood cancer. The causes of this DNA damage are still uncertain but the major candidates are oxidative stress and aberrant apoptosis.

Sperm DNA Fragmentation : It has been studied that increased DNA fragmentation may be related to unexplained recurrent pregnancy loss.

2. INFECTIVE

III. Bacterial vaginosis

IV. Genital Tuberculosis : Hostile endometrium, ovarian dysfunction

3. ANATOMIC

I. Congenital uterine anomalies : 3.2 to 6.9% chance of major uterine anomalies

II. Uterine fibroids : Submucosal Variety FIGO L0 to L2

III. Cervical incompetence : Second Trimester

4. ENDOCRINAL

Thyroid Disorders LPD, PCOS, Hyperprolactinaemia, DM

5. HAEMATOLOGICAL

Thrombophilia is the increased tendency for thrombosis. It could be inherited or acquired. Acquired causes include antiphospholipid syndrome, trauma, prolonged immobility and surgery. Genetic causes of thrombophilia's are Factor V Leiden mutation, prothrombin gene mutation, polymorphism in methyltetrahydrofolate gene and hyperhomocysteinaemia.

Factor V is involved in intrinsic pathway of clotting. In normal clotting activated protein C inactivates factor V and factor VIII by cleavage at specific sites. Factor V Leiden has a G to A substitution in the gene leading to coding of arginine instead of glutamine. This substitution inhibits cleavage of factor V by activated protein C. Reduced inactivation of factor V leads to increased generation of thrombin and hence thrombosis.

The risk of thrombosis for a heterozygote is two to five-fold whereas for a homozygote the risk is 80 to 100 fold.

6. IMUNOLOGICAL

Several humoral immune effectors of RSM have been proposed over the years; these include anti-phospholipid antibodies, anti-sperm antibodies, anti-trophoblast antibodies and a deficiency of so called blocking antibodies. However, of these only anti-phospholipid antibodies have been well substantiated as etiologic agents and even then, anti-phospholipid antibodies are estimated to be the etiologic agents of RSM in only about 3% of the cases of RSM.

Antiphospholipid Syndrome

Antiphospholipid syndrome is a distinct and intriguing autoimmune syndrome and has assumed an important role as a cause of recurrent abortion. A relationship between antiphospholipid antibodies and recurrent pregnancy loss (RPL) has been recognized for the past two decades. It can cause placental thrombosis, infarction and impair trophoblastic function by mechanisms unrelated to thrombosis.

Antiphospholipid Antibodies

Antiphospholipid Antibodies (aPL) are a heterogenous group of antibodies of which the most common are the anticardiolipin (aCL) and lupus anticoagulant (LA).

Th1/Th2/Th3 Reactivity and Cytokines

The expression of Th2 cytokines at the fetomaternal interface implies that changes to cytokines balance do occur during the establishment and maintenance of pregnancy. Several researchers have proposed that there is a dynamic two-way cytokines influencing the balance of cytokines expressions within the developing placenta.

It has been proposed that the trophoblast may be vulnerable to immunological effectors; the trophoblast however is resistant to killing by cytotoxic T lymphocytes conventional natural killer (NK)

cell and conventional macrophages. Type 1 cytokines, such as TNFα and IFNγ may directly damage the conceptus by apoptosis of trophoblast cell, 26 by inhibiting the secretion of the growth stimulating factor GM-CSF from the uterine epithelium and by upregulating the procoagulant .

Cytokines, hormones and other molecules are likely to play very critical roles in directing the immune reactivity towards a type 2 bias and then maintaining it that way.

Progesterone has been shown to follow another interesting route towards influencing the Th1/Th2 balance; in the presence of progesterone, lymphocytes from pregnant females produce an immune modulating factor, the progesterone- induced blocking factor (PIBF).

Prostaglandin E (PGE) may also occupy an important position in this sequence of events because of its ability to inhibit IL-2 production, to inactivate Th1 cells and to inhibit cytotoxic activity of NK cells; PGE may serve as one of the factors that skew the balance in favour of type2 responses.

Endometrium in Recurrent Miscarriage

It is the difficult position of approximately 50% of couples with recurrent miscarriage that no associated factor is found for their miscarriage despite a large number of tests on peripheral blood. It is important to look for other factors that may be associated with miscarriage. An approach to trying to answer this problem is to consider the biology of early pregnancy. The embryo has to attach to the maternal endometrial luminal epithelial cells and then the trophoblast has to invade the luminal endometrium and its glands. Any failure of this process of implantation and early pregnancy invasion will lead to miscarriage. Two possible conceptual paradigms exist to explain the current data relating to endometrium factors in recurrent miscarriage. The Endometrium is not sufficiently receptive to the early pregnancy invasion. The second is that the endometrium of women with recurrent miscarriage is exceptionally receptive allowing pregnancies that are of such poor quality that they should fail, to implant. The second paradigm is “failure of nature’s quality control”.

7. MISCELLANEOUS

i. Micronutrients : Essential minerals’ & vitamins specially folate & vitamin B12

ii. Stress : Involve complex interaction between the neuroendocrine and immune systems.

Conclusion

Etiology of RPL varies from anatomy, physiology, pathology, immunology, genetics to unexplained one.

REFERENCES

1. Practice Committee of the American Society for Reproduductive Medicine. Evaluation and Treatment of pregnancy loss: a committee opinion. Fertil Steril. 2012;98(5):1103-1111

2. Wilcox AJ. Weinberg CR, O’Connor JF, et al. Incidence of early loss of Pregnancy N Eng J Med. 1988;319(4)189-1944

3. Silver RM, Branch DW, Goldenberg R, Iams JD, Klebanoff MA. Nomenciature for pregnancy outcomes: time for a change. Obstet Gynecol. 2011:118(6):1402-1408

4. Royal College of Obstetricians and Gynaecologists, Scientific Advisory Committee, Guideline No. 17 The investigation and treatment of couples with recurrent miscarriage, 2011 Available From : http://www.rcog.org.uk/womens-health/clinical-guidance/investigation-and-treatmentcouples-recurrent-miscarriage-green-top, Accessed January 10 2017

EVALUATION

Dr Krishna Kumari, Dr Durga Shankar Das

Evaluation of Recurrent Miscarriages is initiated following two/ three consecutive miscarriages after risk stratification and based on important and independent risk factors such as maternal age / advanced paternal age and the number of previous losses. It includes taking history, physical examination and appropriate investigations which differ with the trimester though there is an overlap.1 The likelihood of finding a cause is less than 50%.[1]

HISTORY

Gestational age of the loss.

Irregular menstrual cycles or galactorrhoea suggestive of possible Endocrine dysfunction/ Hyperprolactinemia

Consanguinity/ family h/o congenital abnormalities/early losses - Genetic

Uterine instrumentation- possible intrauterine adhesions

Exposure to exogenous agents like bisphenol A and concurrent noxious agents is difficult to recall, document and to measure the toxin dose.

Radiation and Chemotherapeutic agents, chemicals.

Alcohol and caffeine intake are toxic to the embryo in a dose-dependent manner.

Use of contraceptive agents

Cigarette smoking, H/o thrombosis - APLA

PCOS

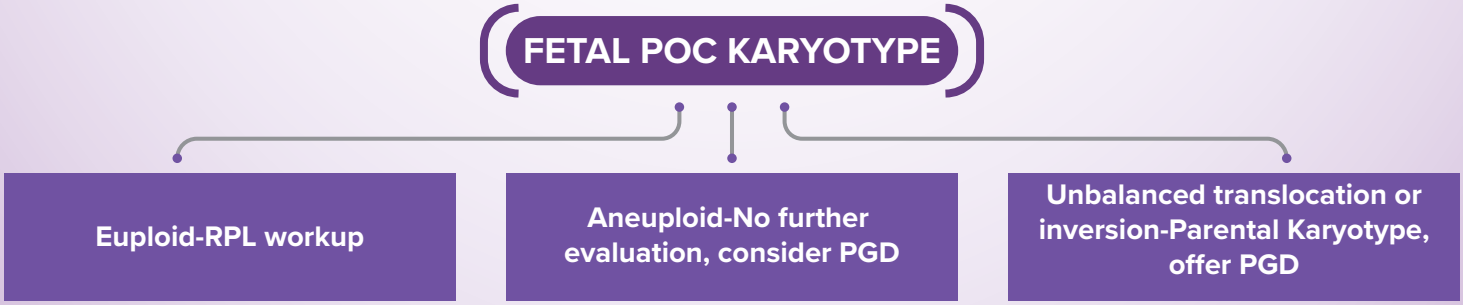
Physical examination and Mental status

EVALUATION:

Karyotyping

A fetal loss is 50% likely to be cytogenetically abnormal in first trimester and 85% normal after the first trimester.[2] Aneuploidy in abortus depends on maternal age.[3] RCOG recommends that Karyotype testing of the abortus should be the first cost effective step in the evaluation of RPL. If the products are euploid other tests should be offered. If aneuploidy is detected, evaluation of such a loss should be followed by Parental karyotyping to detect balanced reciprocal, Robertsonian translocations or mosaicism in parents. If a parental chromosomal aberration is found, it is presumed that the previous miscarriages must have been due to the balanced aberration which has been passed on to the fetus in an unbalanced manner.[5]

However, the ASRM and ACOG recommend that all RPL parents should have peripheral karyotyping independent of the POC karyotyping.



Even karyotyping of the products of conception has its limitations-Tissue specimens that have been frozen or placed in formalin may not be cultured. Tissues suitable for cytogenetic study include placental villi, chorion, amnion, skin, or internal organs. For early gestation, the entire abortus has to be submitted.[4] In cases of culture failure, FISH and molecular array study may be helpful .[5] For couples with proven euploid miscarriages, PGD is unlikely to be of benefit and they should be counselled for gamete donation[6,7]

As per ASRM committee opinion, genetic counseling plays a very important role if a karyotype abnormality is detected in parents. They should be offered pre-implantation genetic diagnosis (PGD), chorionic villus sampling or amniocentesis.[7]

Uterine assessment: All women with recurrent first-trimester miscarriage and one or more second-trimester miscarriages should have a pelvic ultrasound to assess uterine anatomy. Uterine causes could be congenital malformation or acquired causes such as adhesions or polyps. The modalities include hysterosalpingography or sonohysterography, Hysteroscopy, laparoscopy help in direct visualisation and are both diagnostic and therapeutic. MRI is an useful non invasive investigation. Ultrasound helps in the diagnosis of a septate uterus and renal abnormalities and also gives information about the presence and location of uterine myomas . (SIS)Sonohysterography delineates the internal contours of the uterine cavity and provides concomitant sonographic visualization of the outer surface and wall of the uterus ,the tubal patency and can distinguish between the septate and bicornuate uterus that are responsible for second trimester losses.8 Three-dimensional ultrasound allows visualization of both the uterine cavity and the external contour of the uterus and confirms the diagnosis of septate or bicornuate uterus suspected on USG or HSG.

Uterine synechiae-Two-dimensional/three-dimensional ultrasonography with sonohysterography is recommended for couples with two or more pregnancy losses.[8]

Cervical weakness- There is currently no satisfactory objective test that can identify women with cervical weakness in the non-pregnant state. Ultrasound has a limited role in diagnosing the possibility of cervical incompetency. The diagnosis is usually based on a history of second-trimester miscarriage preceded by spontaneous rupture of membranes or painless cervical dilatation.[8]

THROMBOPHILIAS

Acquired Thrombophilias:

The spectrum of antibodies found include nonspecific antinuclear antibodies as well as antibodies against individual cellular components such as phospholipids, histones, and single or double stranded DNA. Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage in comparison to <2% in women with a low-risk obstetric history .[9]

The antiphospholipid syndrome includes lupus anticoagulant antibodies, aCL antibodies, or anti β2 glycoprotein (the primary antigenic determinant) .[9] 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. There is also some evidence linking RPL to β2 glycoprotein1 (β2GP1) antibodies; thus, both the ASRM and ESHRE guidelines suggest including β2GP1 antibodies in the investigations.[9]

APS should be diagnosed based on strict laboratory and clinical criteria.[9,10]Updated Sapporo criteria (Sydney criteria) for defining pregnancy morbidity in the diagnosis of APS(relevant to recurrent miscarriages) are

- **≥1 unexplained fetal deaths ≥10 weeks of gestation** with normal anatomy by prenatal ultrasound examination or direct postnatal examination.

●**≥3 unexplained, consecutive, spontaneous pregnancy losses <10 weeks of gestation,** after exclusion of maternal anatomic and hormonal abnormalities and paternal and maternal chromosomal abnormalities.[9]

The minimum immunology work-up is measurement of anticardiolipin antibody (IgG and IgM) and lupus anticoagulant. Values should be greater than the 99th percentile of moderate or higher titres (over40 g/l or ml/l), with two positive results obtained 12 weeks apart. [9]

The detection of antiphospholipid antibodies is subject to considerable inter-laboratory variation.10 Quality control is very essential to improve the predictive value of positive aPL.The pitfalls in detection in pregnancy include-usage of non-standardized assays for aPL, failure to perform repeat confirmatory aPL testing after 12 weeks, inclusion of patients with low positive aPL levels among patients considered positive, varying definitions for case selection in series involving pregnancy loss and variable thrombogenic potential of a given patient's aPL.[10]

Inherited thrombophilias - Mostly women with second-trimester miscarriage are screened for inherited thrombophilias, factor V Leiden, factor II (prothrombin) gene mutation, activated protein-C resistance, fasting homocysteine ,aPLs and protein S. [11] They have been associated with pregnancy loss due to uteroplacental insufficiency though their causal association has not been universally proven by studies. Hence routine testing is not recommended.[12]

Infections - as a cause of repetitive losses is much less likely. Culture for U.urealyticum and M. hominis, Chlamydia trachomatis seem most plausibly related to repetitive spontaneous abortions.[9]. Endometrial biopsy is recommended if chronic endometritis including tuberculosis is suspected [13]

Thyroid (dys)function - RPL may be associated with overt hypothyroidism or hyperthyroidism. Screening asymptomatic women for subclinical thyroid dysfunction is controversial. Pregnancy losses are higher in TPO positive women with subclinical hypothyroidism and in euthyroid women with thyroid peroxidase antibodies. Hence it is recommended to test for TPO antibodies with thyroid profile in patients of recurrent pregnancy loss.[14]

PCOS - An elevated free androgen index appears to be a prognostic factor for a subsequent miscarriage in women with recurrent miscarriage[15]

Screening for diabetes - Screening for diabetes mellitus should be limited to women with clinical manifestations of the disease or at high risk. Only poorly controlled diabetes is associated with miscarriage.[9]

Ovarian reserve - elevated day 3 FSH concentration may be associated with poor quality oocytes that fail to develop after fertilization. It may be useful in cases of idiopathic recurrent miscarriages.

Medical disorders - Additional laboratory tests may be indicated in women with clinical manifestations suggestive of a medical disorder.[9]

Immune factors - excessive uterine NK cell recruitment and/or expansion, as well as elevated cytotoxic activity, are associated with implantation failure and RPL. Testing for peripheral blood NK cells as a surrogate marker of the events at the maternal–fetal interface is debatable.

Progesterone level - Diagnosis of a luteal phase defect, based upon results of endometrial biopsy, is not predictive of fertility status and not recommended. Polymorphism on the progesterone receptor gene has been associated with Recurrent Miscarriages but needs further research before testing is indicated.[16]

Male factor - ,. Some studies suggest that DNA fragmentation is increased with RPL, especially in the in vitro fertilisation setting. The ASRM guidelines state that routine sperm DNA fragmentation indexing is not indicated because of the weak evidence, but the ESHRE guidelines state that this can be done to provide an explanation for RPL.

INVESTIGATIONS RECOMMENDED FOR RECURRENT MISCARRIAGES

Investigation	Recommendation	If required
Genetic - Karyotype	Parental and fetal	
Anatomical	Two-dimensional/ three-dimensional ultrasonography and sonohysterography	Hysteroscopy, laparoscopy, or magnetic resonance imaging
Thrombophilia	Acquired APS	Inherited
Infection		Chlamydia, Endometrial biopsy and culture
Immunological		Antinuclear antibody
Endocrine	Thyroid -TSH, Antibodies	Prolactin,HbA1C
Male factor		Sperm DNA fragmentation index

KEY MESSAGES:

1. Karyotyping of the products of conception should be the first test offered to patients with recurrent miscarriages

2. RPL workup should be offered to patients with euploid miscarriages

3. Two-dimensional/three-dimensional ultrasonography with sonohysterography is recommended for couples with two or more pregnancy losses due to its non invasive nature and accuracy in predicting uterine anomalies

4. Testing for inherited thrombophilias not recommended

5. TPO antibodies testing with thyroid testing is recommended .

6. Screen only patients with pre-existing diabetes or who have high risk factors for Diabetes mellitus

7. Male factor infertility due to Sperm DNA fragmentation needs to be evaluated

REFERENCES

1) Evaluation and management of recurrent early pregnancy loss.

Stephenson M, Kutteh W.Clin Obstet Gynecol. 2007 Mar;50(1):132-45.

2)early pregnancy loss. Curr Opin Obstet Gynecol. 2010 Dec;22(6):446-51. doi:

10.1097/GCO.0b013e32833e124e.

3) Carp H, Feldman B, Oelsner G, Schiff E. Parental karyotype and subsequent live births in recurrent miscarriage. FertilSteril 2004; 81:1296.

4) Stephenson MD, Awartani KA. Cytogenetic analysis of miscarriages from couples with recurrent miscarriages: a case control study. Hum Reprod 2002;17:446-51

5) Bernardi LA, Plunkett BA, Stephenson MD. Is chromosome testing of the second miscarriage cost saving? A decision analysis of selective versus universal recurrent pregnancy loss evaluation. Fertil Steril. 2012 Jul;98(1):156-61.

6) Parental karyotype and subsequent live births in recurrent miscarriage ;May 2004Volume 81, Issue 5, Pages 1296–1301 ,Howard Carp, Baruch Feldman, M.D., Ph.D.,GabrielOelsner, M.D.,Eyal Schiff, M.D.

7) American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012;98:1103-11.

8) Evaluation of couples with recurrent pregnancy loss

Authors:Togas Tulandi, MD, MHCM;Haya M Al-Fozan, MD;Section Editor:Charles J Lockwood, MD, MHCM;Deputy Editor:Kristen Eckler, MD, FACOG;UpToDate

9) American College of Obstetricians and Gynecologists (ACOG): Practice bulletin on early pregnancy loss (2015, reaffirmed 2017)

10) UpToDate:Antiphospholipid syndrome: Pregnancy implications and management in pregnant women Charles J Lockwood, MD, MH; CM Michael D Lockshin, MD, MACR; Section Editors: Vincenzo Berghella, MD ;David S Pisetsky, MD, PhD; Deputy Editors: Vanessa A Barss, MD, FACOG, Monica Ramirez Curtis, MD, MPH

11) .ACOG Practice Bulletin No. 197: Inherited Thrombophilias in Pregnancy. Obstet Gynecol 2018; 132:e18.

12) Thrombosis and Embolism during Pregnancy and the Puerperium, Reducing the Risk (Green-top 37a) http://www.rcog.org.uk/womens-health/clinical-guidance/reducing-risk-of-thrombosis-greentop37a

13) McQueen DB, Bernardi LA, Stephenson MD. Chronic endometritis in women with recurrent early pregnancy loss and/or fetal demise. FertilSteril 2014;101:1026-30.

14) Lata K, Dutta P, Sridhar S, Rohilla M, Srinivasan A, Prashad GR, Shah VN, Bhansali A. Thyroid autoimmunity and obstetric outcomes in women with recurrent miscarriage: a case-control study.Endocr Connect. 2013 Jun 22;2(2):118-24.

15) K.A. Cocksedge1,5, S.H. Saravelos1, Q. Wang1,2, E. Tuckerman3, S.M. Laird4 and T.C. Li1,3. Does free androgen index predict subsequent pregnancy outcome in women with recurrent miscarriage? Human Reproduction Vol.23, No.4 pp. 797–802, 2008

16) Schweikert A, Rau T, Berkholz A, et al. Association of progesterone receptor polymorphism with recurrent abortions. Eur J ObstetGynecolReprodBiol 2004; 113:67.

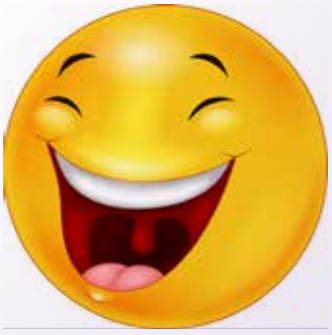
Why do we write 'ETC' at the end in the Exam??

Coz it means

E - End of

T - Thinking

C - Capacity



MANAGEMENT OF RECURRENT PREGNANCY LOSS

Dr. Fessy Louis T, Dr. Uma Pandey, Dr.Parvathy T, Dr. Shail Prasad

Recurrent pregnancy loss as defined by American Society of Reproductive Medicine as two or more pregnancy losses, which have been confirmed by either sonography or histopathological examination [1]. The European Society for Human Reproduction Special Interest Group for Early Pregnancy has defined recurrent miscarriage as three early consecutive losses or two late pregnancy losses [2].RPL can be primary or secondary. Primary RPL miscarriages have never been carried to viability, whereas in the secondary type, live birth has occurred at some time[3]. It is important to do an early evaluation in cases where fetal cardiac activity had been documented prior to the loss, in women who are older than 35 years and/or in couples with history of infertility. The timing of fetal demise provides etiologic clue, and its documentation is important in investigating the causes and treatment for RPL.

MANAGEMENT OF GENETIC CAUSES OF RPL

Genetic factors comprise approximately 3.5–5% of RPL etiologies. These include structural chromosomal abnormalities of which parental balanced and Robertsonian translocations have been reported as common causes of RPL. Monogenic disorders have also been reported as rare causes of repeated pregnancy losses. It is important to evaluate the karyotype of both partners as well as the abortus. Genetic counselling is imperative in such cases by a geneticist or a genetic counsellor, and preimplantation genetic diagnosis or donor gametes can be given as an option[4]

MANAGEMENT OF ANATOMIC CAUSES OF RPL

Anatomic abnormalities account for 12-16% cases of RPL. These include congenital uterine anomalies (incomplete mullerian fusion or septum, uterine artery anomalies, DES exposure, and cervical insufficiency) and acquired anomalies (intrauterine adhesions and uterine fibroids or polyps). Pregnancy loss occur due to defective vascularisation of endometrium leading to improper placentation. Congenital uterine anomalies are usually linked to second trimester pregnancy loss with septate uterus accounting for 70% of cases. Intrauterine adhesions result in early pregnancy losses due to its impact on placentation. It is found that RPL results if there is submucosal fibroid or intramural fibroids more than 5 cm size [(5,6).]

In case of septate uterus the treatment of choice is hysteroscopic septoplasty. Significantly better reproductive outcomes have been reported with a reduction in RPL from 83 to 33% and an increase in live birth up to 67%[7]. Post procedure, hormone therapy should be given for 2–4 months for endometrial regrowth[7]

In case of bicornuate uterus, surgery is generally not necessary until it is associated with RPL for which Strassman metroplasty is the procedure of choice.

Surgical removal of submucosal and intramural fibroids distorting the cavity results in a better pregnancy outcome and live birth rate[8]

Hysteroscopy is the mainstay in the diagnosis of intrauterine adhesions. Treatment includes hysteroscopic resection of the intrauterine adhesions and preventing regrowth of the fibrous tissue by supporting the endometrium with hormones.

Cervical insufficiency accounts for 1% cases of RPL. As per the RCOG recommendations[9], the encerclage for RPL can be – history indicated cerclage, ultrasound indicated cerclage and rescue

cerclage. In history indicated cerclage, women with three or more previous preterm births and/or second trimester losses are the candidates. Women with history of one or more spontaneous mid trimester losses or preterm birth and who are undergoing ultrasound surveillance of cervical length should be offered cerclage, if cervix is 25 mm or less at or before 24 weeks of gestation. The cerclage is usually performed around 12-14 weeks of gestation. Surgery of choice is cervical cerclage, which can be performed either by transvaginal route or by transabdominal route.

MANAGEMENT OF ENDOCRINE CAUSES OF RPL

Endocrinological causes are implicated for approximately 17–20% of RPL. These include luteal phase insufficiency, androgen disorder, thyroid disorders, and increased serum levels of prolactin. Also metabolic diseases such as polycystic ovarian syndrome (PCOS) and diabetes mellitus are included here.

Luteal phase defect, characterized by insufficient progesterone production resulting in retarded endometrial development, is thought to be associated with RPL. There is no consensus, yet supplementing the luteal phase with exogenous progesterone has remained the most common therapy in abortions. As per the Cochrane review, there was a benefit to the routine administration of progesterone in current pregnancy to all women with a history of RPL with 3 or more previous pregnancy losses10. Ideally progestogen supplementation should be started in the luteal phase, if LPD is suspected as a cause of RPL. Progesterone is started on the third day after LH surge and continued for 8–10 weeks. Treatment can be extended till 34 weeks in patients having history of preterm labor.

Systematic reviews suggest benefit from luteal phase HCG for recurrent loss11. The maximum effectiveness of hCG is when it is administered in the mid luteal phase when receptivity of corpus luteum for hCG is at its peak rather than after the establishment of pregnancy.

In women with PCOS, there may be increase in level of luteinizing hormone or androgens or both leading to premature oocytes aging and defect in endometrium maturation. Correlation between insulin resistance and resultant hyperinsulinemia in PCOS and diabetes mellitus with RPL, as there is decreased in pregnancy loss after getting treatment with the insulin sensitizing oral hypoglycemic agents .

Untreated hypothyroidism is clearly related with spontaneous miscarriage and RPL, but the association between antithyroid antibodies and RPL in euthyroid patients is not established. The Endocrine Society and ASRM recommend first trimester TSH less than 2.5 mIU/mL in patients with RPL[12]. Close monitoring and dose adjustment in first trimester is important. There are no clear recommendations in antibody-positive pregnancies with a normal TSH <2.5 mIU/L, but close follow-up during pregnancy is warranted.

Normal prolactin level is very important in maintaining early pregnancy. Normalization of prolactin levels with a dopamine agonist improved subsequent pregnancy outcomes in patients with RPL, live-birth rate being 85% in treated women compared to 52% in untreated group [13].

MANAGEMENT OF IMMUNOLOGICAL CAUSES OF RPL

Immunologic causes account for 20–50% of all RPL cases. Several autoimmune diseases have been linked to RPL, but the most common is Antiphospholipid antibody syndrome (APS).

Several treatments have been proposed till date, including aspirin, prednisolone, UFH aspirin, LMW heparin and immunoglobulins.

The combination of UFH with low-dose aspirin provides the highest success rate. Aspirin (75–150 mg) improves the pregnancy outcome by selective inhibition of thromboxane A2 production, thereby restoring the balance with prostaglandin. It should be started preconceptionally.[14] LMWH is emerging as the treatment of choice for RPL associated with APS[15]. Neither corticosteroids nor IVIg therapy improve the live birth rate of women with recurrent miscarriage associated with APS compared with other treatment modalities. Their use may lead to significant maternal and fetal morbidity.

MANAGEMENT OF THROMBOTIC CAUSES OF RPL

Factor V Leiden mutation and mutations in the gene encoding methylene tetrahydrofolate reductase (MTHFR) and prothrombin gene are the most common thrombotic etiology. The heritable thrombophilias associated with RPL are increased levels of serum homocysteine, prothrombin promoter mutations, protein C and protein S deficiencies, and antithrombin mutations.

As per the ACOG guidelines, the use of aspirin, heparin or both has not been shown to reduce the risk of early pregnancy loss in women with thrombophilias[16]. As per the RCOG green top guidelines[9], there is insufficient evidence to evaluate the effect of heparin in pregnancy to prevent a miscarriage in women with recurrent first-trimester miscarriage associated with inherited thrombophilia. Heparin therapy during pregnancy may improve the live birth rate of women with second-trimester miscarriage associated with inherited thrombophilia.

MANAGEMENT OF INFECTIOUS CAUSES OF RPL

The relation between infection and recurrent pregnancy losses is not established. But infections like Listeria monocytogenes, herpes simplex virus, measles, toxoplasmosis, rubella, and cytomegalovirus are associated with sporadic spontaneous abortion. The mechanism of miscarriage can be due to infection.

Testing for these infectious agents and routine antibiotic treatment is not recommended. RCOG[9] also does not recommend TORCH screening in patients with recurrent pregnancy loss.

MANAGEMENT OF OTHER CAUSES OF RPL

Environmental and occupational exposures to organic solvents, toxins, ionizing radiation, and medications can affect uterine receptivity which may have a role in causation of RPL. However, no strong co-relation has been found between RPL and occupational factors, stress, or chemicals factors as most evidence in this respect is retrospective.

Lifestyle modification by improvements in diet, exercise, abstinence from drugs, and stress reduction improve pregnancy outcomes.

The strategy of emotional support and reassurance works well in unexplained cases as even no treatment shows a good prognosis in 60–80% cases.

ROLE OF PRE IMPLANTATION GENETIC DIAGNOSIS IN RPL

PGD is being used worldwide in various centres to improve the live birth rates. PGD can decrease the chance of conceiving a child with genetic defect carried by either (dominant) or both (recessive) partners if that defect can be identified by tests on single cell or multiple trophectoderm cells. Blastocyst biopsy is better than cleavage stage biopsy and has no harmful effect on the embryo and

must be considered as the preferred method when available. Couples opting for PGD has to be counselled regarding the costs of IVF also as PGD and IVF work hand in hand.

FUTURE RESEARCH STRATEGIES AND DIRECTIONS IN RPL

• Future directions in investigating biomolecular risk factors for RM rely on integrating alternative approaches (DNA variants, gene and protein expression, epigenetic regulation) in studies of individual genes as well as whole genome analysis.

• Clinical use of markers to evaluate endometrial receptivity and serum measurements of IL-1, 8, TNF alpha has been hypothesized to improve the management of recurrent abortion.

REFERENCE :

1. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. Fertil Steril. 2008.

2. Farquharson RG, et al. ESHRE Special Interest Group for Early Pregnancy. Updated and revised nomenclature for description of early pregnancy events. Hum Reprod. 2005.

3. Ansari AH, Kirkpatrick B. Recurrent pregnancy loss: an update. J Reprod Med. 1998.

4. Fox-Lee L. et al. Recurrent pregnancy loss. Berek and Novak's gynecology. Philadelphia: Lippincott Williams & Wilkins; 2012.

5. Bajekal N, Li TC. Fibroids, infertility and pregnancy wastage. Hum Reprod Update. 2000.

6. Raga F, et al. Reproductive impact of congenital Müllerian anomalies. Hum Reprod. 1997.

7. Selvaraj P, Selvaraj K. Reproductive outcome of septate uterus following hysteroscopic septum resection. J Hum Reprod Sci. 2010.

8. Casini ML, Rossi F, Agostini R, Unfer V. Effects of the position of fibroids on fertility. Gynecol Endocrinol. 2006.

9. The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. RCOG Green-top Guideline No. 17; April 2011.

10. Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Cochrane Database Syst Rev. 2008.

11. Morley LC, et al. Human chorionic gonadotrophin (hCG) for preventing miscarriage. Cochrane Database Syst Rev. 2013.

12. De Groot L et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012.

13. Hirahara F et al. Hyperprolactinemic recurrent miscarriage and results of randomized bromocriptine treatment trials [comment]. Fertil Steril. 1998.

14. Ziakas PD et al. Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: a systematic review and meta-analysis. Obstet Gynecol. 2010.

15. Greer IA et al. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005.

16. Early pregnancy loss. Practice Bulletin No. 150. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2015.

RECENT UPDATES IN RECURRENT PREGNANCY LOSS

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INTRODUCTION

2-5% of couples have recurrent miscarriage. Recurrent pregnancy loss is classically defined as the occurrence of three or more consecutive pregnancy losses. However, the American Society of Reproductive Medicine (ASRM) has recently redefined recurrent pregnancy loss as two or more pregnancy losses. Incidence of recurrent miscarriage increases with maternal age. Primary Recurrent Pregnancy Loss (RPL) refers to no previous viable infants whereas secondary RPL refers to multiple losses in a woman who already had a pregnancy beyond 20 weeks. Tertiary RPL refers to multiple pregnancy losses in between normal pregnancies.

ETIOLOGY & WORK UP

Table 2 Etiologies of recurrent pregnancy loss, recommended tests for diagnosis, and treatment options

Etiology	Tests for diagnosis	Treatment options
Uterine factor	3D ultrasonography, sonohysterography, hysterosalpingography, hysteroscopy	Hysteroscopic resection of septum
		Myomectomy, hysteroscopic removal of polyps
	Magnetic resonance imaging	Adhesiolysis
Antiphospholipid syndrome	aCL, Anti-β2GP1, lupus anticoagulant	Heparin + aspirin
Endocrine abnormality	Thyroid-stimulating hormone	Levothyroxine
	Prolactin	Bromocriptine
	Fasting glucose or HbA_{1c}	Diabetes control (weight loss, nutrition, metformin)
Genetic	Karyotype of product of conception	Genetic counseling
	Parental karyotype	Preimplantation genetic diagnosis for balanced translocation
Environmental factors	Screen for smoking, drug use, excessive alcohol and caffeine intake	Eliminate environmental toxins
Psychological		Psychological support in a specialized setting
Unexplained		Progesterone supplementation (no consensus)
		Immunomodulating treatments (no consensus)
		Preimplantation genetic screening (no consensus)
Other (no consensus)		
Luteal phase deficiency	Mid-luteal progesterone, endometrial biopsy	Progesterone supplementation
Chronic endometritis	Endometrial biopsy	Antibiotic treatment
Other infections	Cultures	Appropriate treatment
Male factor	DNA fragmentation test on sperm	Lifestyle modifications, multivitamins, donor sperm

Note: Anti-β2GP1: anti-β2 glycoprotein-I.
Abbreviations: aCL, anticardiolipin; 3D, three-dimensional.

This table shows the routine management of RPL. Ideally it should be started after two consecutive losses rather than three, especially in women beyond 35yrs. Complete history and gynecological examination are mandatory [1,2]. The work up must be tailored according to the couple's age, family history and so on.

Now let us see some of the current newer concepts in the management of RPL.

RECENT ADVANCES IN THE MANAGEMENT OF RPL

Over the years correction of uterine anomalies, aspirin and heparin for APLA syndrome and acquired and inherited thrombophilias have improved outcome in RPL. Still half of the cases remain unexplained and are empirically treated with progesterone supplementation, anti-coagulation and/or immuno-modulatory treatment. Regardless of the cause, long term prognosis with couples with RPL is good and most of them eventually achieve healthy live birth.

IMMUNE DYSREGULATION AND RPL

Abnormal Th-1 / Th-2 profile, CD-4 T-helper cells and uterine natural killer (NK) activity can lead to Recurrent Pregnancy Loss. Hence immuno-modulatory treatment has been proposed. Aspirin and LMWH in combination did not improve LBR in these situations and hence not recommended. (ESHRE guidelines and recurrent pregnancy loss 2017) Aspirin and LMWH may be of use in known cases of APLA syndrome. Addition of prednisolone decreases the number of uterine NK cells and may be used to increase LBR [3 ,4]. Whereas some studies showed no effect of steroids. Use of steroids in the first trimester is still controversial. They are known to increase the risk of prematurity, GDM and hypertension. Over all, steroid administration in the absence of auto-immunity is not recommended. ESHRE also does not recommend steroids for treatment of RPL.

INTRA VENOUS IMMUNO GLOBULIN (IVIG)

IVIg is a fractionated blood product used in treatment of RPL during the recent years. 8 trials involving 442 women with RPL did not show significant increase in LBR when compared to placebo. IVIg used in RPL failed to show positive impact [6, 7]. Recent meta-analysis of 11 RCTs showed no differences in LBR between IVIg and placebo groups (RR: 0.92, 95% confidence interval [CI]: 0.75–1.12, P=0.42). [8] Therefore, it is not recommended. Therapeutic effect of IVIg in RPL is controversial and positive results were obtained from trials where women had cellular immune abnormalities such as increased NK cell levels and / or cytotoxicity and T cell abnormalities. However significant increase in LBR with secondary miscarriage rather than primary miscarriage has been demonstrated [5]. In one study IVIg was used at the time of positive pregnancy.400mg/kg followed by repeat dose every 4 weeks up to 31 weeks had a favourable outcome in RPL. [5] According to ESHRE guidelines, IVIg is not recommended for treatment for RPL.

IMMUNIZATION USING WHITE BLOOD CELLS

Immunization using purified lymphocytes from the partner or third party or products from early embryos failed to show any positive impact and hence should not be used. [9] (ESHRE guidelines on RPL).

TNF–A AND RPL

Several studies have shown the association of TNF–α gene polymorphism at position 308G/A with RPL. It is a potent cytokine produced by phagocytes, NK cells and antigen stimulated T cells and are associated with increased adverse pregnancy outcomes. TNF-α induces apoptosis of cytotrophoblast and hence placental development, which is the basic cause for RPL. Hence, its antagonist Adalimumab has been used. Retrospective study of 75 patients with this drug and IVIg when added to anti-coagulants showed improved LBR. [10] Still there are concerns over the safety of the drug. No prospective studies are available.

INTRA LIPIDS FOR RECURRENT MISCARRIAGE

Intra lipids are fat emulsions known to have immuno-modulatory property and act by inhibiting uterine NK cell activity. [11] This is useful for both recurrent miscarriage and recurrent implantation failure in ART. It is given as soon as the UPT is positive and continued up to the end of first trimester once in a month. Some people continue even up to 34 weeks. Only small studies are available. Some of the studies show that intra lipid infusion does not improve the LBR (Braverman IVF & Reproductive Immunology, 19th Jan 2017).

GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSF) AND RPL

Granulocyte colony-stimulating factor (G-CSF) is a cytokine which is produced by decidual cells and it is found to have a positive impact on trophoblast and has anti-abortive action. Recent studies indicate possible effects of TNF-α blocker and G-CSF in improving the live birth rate in recurrent miscarriage. According to the study by Santjohanser et al, there is a promising role for use of G-CSF as a treatment option for recurrent miscarriage patients.[12] Further larger trials are needed to confirm the benefit of G-CSF. One RCT is found to increase LBR in RPL compared to placebo without major side effects (p value = 0.006) [13]. Large multi centric trials are needed before recommending this into clinical practice.

ROLE OF GLYCODELIN AND NUCLEAR HORMONE RECEPTORS (PPARS)

There is down regulation of glycodelin expression and up regulation of PPAR expression in recurrent miscarriage. Reduced glycodelin is associated with miscarriage and up regulated PPARs appears to compensate for either active immune response or disturbed cytotrophoblast differentiation. There is also evidence that circulating placental micro particles are increased in a sub group of RPL patients. Micro particles exposed phosphatidylserine and induce coagulation. This indicates acquired pro-coagulant state outside pregnancy. Hence, LMWH and aspirin may be used and few placebo control trials have proven their benefit. [12]

SPERM DNA FRAGMENTATION (SDF) AND RPL

Sperm DNA Fragmentation Index (SDF) is found to be higher in couple with RPL. Results of study on 102 cases of RPL couple compared with a control of 114 fertile men showed there is correlation between increased SDF and impaired reproductive capacity in terms of fertilization and pregnancy to term. [14] Therefore it seems reasonable to offer SDF in couples with RPL. Besides advanced paternal age, many environmental factors like smoking, obesity, exposure to heat and toxins increases SDF. Lifestyle modification, nutrition, dietary supplementation may alleviate the damage and avert further pregnancy loss. (Tremellen et al, 2007; Showell et al 2014, Datillo et al, 2016). A multi centric study by Camille et al, 2018 showed sperm aneuploidy, SDF was associated with unexplained RPL. Though assay of SDF is not recommended by many societies, it could be useful in selected cases.

PROGESTERONE SUPPLEMENTATION FOR RPL

Multiple RCTs give variable outcome regarding progesterone supplementation. Multi centric RCT among 836 women did not show any difference in LBR between progesterone supplementation and placebo [15]. More recently 10 RCTs including 1586 women with RPL showed reduced miscarriage rate and higher chance of live birth following progesterone supplementation [15]. In some studies, synthetic progestins are found to be more beneficial than natural and micronized progesterone. Micronized progesterone is given 400mg per day vaginally till 20 weeks. Dydrogesterone, which is retro progesterone, is known to have immuno-modulatory properties such as decreasing pro-inflammatory and increasing anti- inflammatory cytokines in early pregnancy. In cases of RPL, dydrogesterone is given at the dose of 10 mg BD till 20 weeks. As on current data available it is difficult to recommend the time of initiation of treatment, route, dose and type of preparation. PROMISE trial for supplementation of progesterone in RPL shows there is no evidence for first trimester progesterone therapy improving outcome in women with history of RPL.

PGS FOR RPL

It was introduced in 1993 to select euploid embryos in couple undergoing IVF and thus improving the implantation rate and reducing miscarriage [16]. The analysis of the chromosome was done by Flouresent in situ Hybridization (FISH) analysis, Chromosomal Microarray Analysis (CMA), Comparative Genomic Hybridization (CGH) array, Chromosomal Microarray Analysis (aCGH), Single Nucleotide Polymorphism (SNP array), MicroRNA Analysis (MiRNA) quantitative or real time PCR and next generation sequencing (NGS). Embryo biopsy can have deleterious impacts. There are various forms of embryo biopsy like cleavage stage biopsy, polar biopsy, inner cell mass biopsy and trophectoderm biopsy. All these procedures are time consuming and have lot of cost involved. No RCT has looked at the beneficial impact of PGS in couples with RPL. But still in Europe and the US, PGS is indicated for women with RPL and RIF [17]. Other non-invasive technologies are currently developed as an alternate to PGS such as transcryptomics, metabolomics, epigenomics and mitochondrial function tests. Many trials are ongoing, in order to select the patient population who are likely to benefit from PGS. [18, 19, 20] Three RCTs show transfer of euploid embryos following PGS significantly improves pregnancy rate.

ENDOMETRIAL SCRATCHING

Scratching of endometrium prior to embryo transfer has gained wide spread use in women posted for IVF. This procedure is supposed to increase cytokines and chemo attractants which is important for implantation. ESHRE challenges its role in RPL.

CONCLUSION

RPL is a major reproductive health issue. Full work up is needed after two pregnancy wastages. Treatment can be initiated for causes like uterine anomalies, APS, and endocrine disorders. Couples with balanced translocation can be diagnosed and counselled accordingly. Indiscriminate use of aspirin and LMWH for RPL cases should be avoided. Some people may benefit from IVIg. Paternal leukocyte immunization needs further well-designed trails. Larger trials are needed regarding the use of TNF-α inhibitors and G- CSF for its use in clinical practice. Lifestyle modifications should be implemented. Still many of the causes for RPL remain undetected and there are newer modalities of treatment available. More than anything tender loving care and psychological support can help the couple to conceive and have a healthy baby. (Stray-Pedersen 1984; Clifford et al 1997) These patients must be advised to attend special clinics for RPL as recommended by international societies and frequent visits are mandatory.

REFERENCES

1. Practice Committee of the American Society for Reproductive Medi¬cine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012;98(5):1103–1111.

2. Royal College of Obstetricians and Gynaecologists, Scientific Advisory Committee, Guideline No. 17. The Investigation and treatment of couples with recurrent miscarriage, 2011. Available from: http://www.rcog.org.uk/womens-health/clinical-guidance/investigation-and-treatmentcouples-recurrent-miscarriage-green-top-. Accessed January 10, 2017.

3. Tempfer CB, Kurz C, Bentz EK, et al. A combination treatment of prednisone, aspirin, folate, and progesterone in women with idiopathic recurrent miscarriage: a matched-pair study. Fertil Steril. 2006;86(1):145–148.

4. Gomaa MF, Elkholy AG, El-Said MM, Abdel-Salam NE. Combined oral prednisolone and heparin versus heparin: the effect on peripheral NK cells and clinical outcome in patients with unexplained recurrent miscarriage. A double-blind placebo randomized controlled trial. Arch Gynecol Obstet. 2014;290(4):757–762.

5. Hutton B, Sharma R, Fergusson D, Tinmouth A, Hebert P, Jamieson J, Walker M. Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review. BJOG: An International Journal of Obstetrics & Gynaecology. 2007 Feb;114(2):134-42.

6. Perino A, Vassiliadis A, Vucetich A, et al. Short-term therapy for recurrent abortion using intravenous immunoglobulins: results of a double-blind placebo-controlled Italian study. Hum Reprod. 1997;12(11):2388–2392.

7. Stephenson MD, Kutteh WH, Purkiss S, et al. Intravenous immu¬noglobulin and idiopathic secondary recurrent miscarriage: a mul¬ticentered randomized placebo-controlled trial. Hum Reprod. 2010;25(9):2203–2209.

8. Egerup P, Lindschou J, Gluud C, Christiansen OB; ImmuReM IPD Study Group. The effects of intravenous immunoglobulins in women with recurrent miscarriages: a systematic review of randomised trials with meta-analyses and trial sequential analyses including individual patient data. PLoS ONE. 2015;10(10):e0141588.

9. Saad FA, Rizvi Z, Sharara HA. Retrospective case-control study of the outcome of pregnancy after paternal leukocytes transfusion in cases of recurrent pregnancy loss. Qatar Medical Journal. 2013 Jun 27(1997):9.

10. Winger EE, Reed JL. Treatment with tumor necrosis factor inhibitors and intravenous immunoglobulin improves live birth rates in women with recurrent spontaneous abortion. Am J Reprod Immunol. 2008;60(1):8–16.

11. Roussev RG, Ng SC, Coulam CB. Natural killer cell functional activity suppression by intravenous immunoglobulin, intralipid and soluble human leukocyte antigen-G. Am J Reprod Immunol. 2007;57(4):262–269.

12. Santjohanser C, Knieper C, Franz C, Hirv K, Meri O, Schleyer M, Würfel W, Toth B. Granulocyte-colony stimulating factor as treatment option in patients with recurrent miscarriage. Archivum immunologiae et therapiae experimentalis. 2013 Apr 1;61(2):159-64.

13. Scarpellini F, Sbracia M. Use of granulocyte colony-stimulating factor for the treatment of unexplained recurrent miscarriage: a randomised controlled trial. Hum Reprod. 2009;24:2703–2708.

14. Carlini T, Paoli D, Pelloni M, Faja F, Dal Lago A, Lombardo F, Lenzi A, Gandini L. Sperm DNA fragmentation in Italian couples with recurrent pregnancy loss. Reproductive biomedicine online. 2017 Jan 1;34(1):58-65.

15. Saccone G, Schoen C, Franasiak JM, Scott RT Jr, Berghella V. Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscar¬riage: a systematic review and meta-analysis of randomized, controlled trials. Fertil Steril. 2017;107(2):430–438.

16. Munne S, Lee A, Rosenwaks Z, Grifo J, Cohen J. Diagnosis of major chromosome aneuploidies in human preimplantation embryos. Hum Reprod. 1993;8(12):2185–2191.

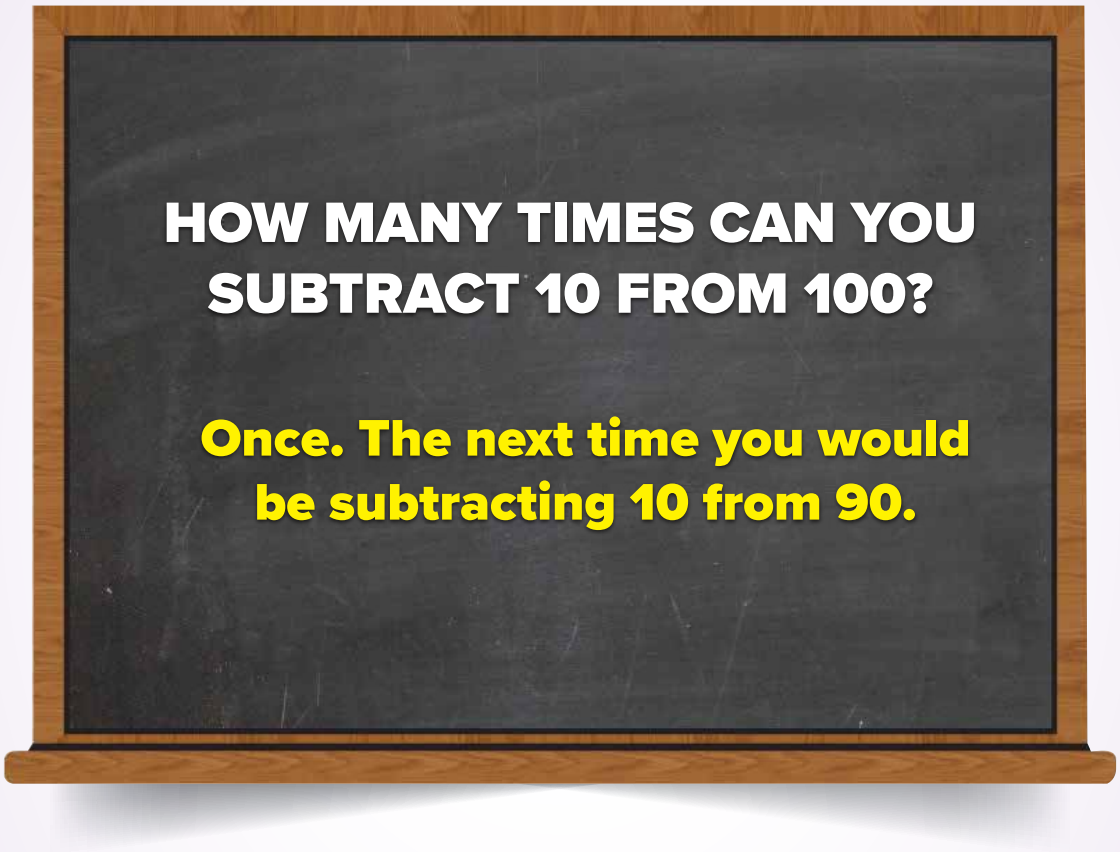
17. Sermon K, Capalbo A, Cohen J, et al. The why, the how and the when of PGS 2.0: current practices and expert opinions of fertility specialists, molecular biologists, and embryologists. Mol Hum Reprod. 2016;22(8):845–857.

18. Brezina PR, Anchan R, Kearns WG. Preimplantation genetic testing for aneuploidy: what

technology should you use and what are the differences? J Assist Reprod Genet. 2016;33(7):823–832.

19. Geraedts J, Sermon K. Preimplantation genetic screening 2.0: the theory. Mol Hum Reprod. 2016;22(8):839–844.

20. Yang Z, Liu J, Collins GS, et al. Selection of single blastocysts for fresh transfer via standard morphology assessment alone and with array CGH for good prognosis IVF patients: results from a randomized pilot study. Mol Cytogenet. 2012;5(1):24.



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