Healthy Babies to Healthy Mothers

ESTD 1989
ISPAT

Volume 02 Issue 03

talkBACK

Newsletter of the Indian Society for Prenatal Diagnosis and Therapy

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INDIAN SOCIETY OF PRENATAL DIAGNOSIS & THERAPY

Foreword

Dear Esteemed Colleagues,

We hope this message finds you well and thriving in your endeavours within the field of prenatal diagnosis and treatment. As we embark on a new year filled with promise and innovation, we are delighted to share some exciting updates and developments from the Indian Society of Prenatal Diagnosis and Treatment (ISPAT) in this newsletter.

As healthcare providers dedicated to ensuring the well-being of our patients and their unborn children, we recognize the importance of staying informed about advancements in prenatal testing and diagnosis. Prenatal care plays a crucial role in identifying potential health risks and providing appropriate interventions to promote optimal outcomes for both mother and baby.

In recent years, prenatal testing and diagnosis have seen remarkable progress, offering us unprecedented insights into fetal health and development. These advancements empower us to detect, manage, and sometimes even prevent certain congenital conditions, thereby enhancing the quality of care we deliver to expectant families.

It is essential for us, as healthcare professionals, to remain abreast of the latest technologies and methodologies in prenatal testing. At ISPAT we have initiated :

1. Annual Conferences
2. New Research Initiatives
3. Continuing Education (CMEs) & webinars
4. Community Engagement
5. Member Spotlight.

As we navigate this ever-evolving field, let us remain committed to upholding the highest standards of patient-centred care. By staying informed, engaging in interdisciplinary collaboration, and prioritizing open communication with our patients, we can ensure that prenatal testing and diagnosis are integrated seamlessly into our practice, ultimately contributing to healthier pregnancies and better outcomes for all.

We extend our sincere appreciation to all ISPAT members for your unwavering dedication to advancing the field of prenatal diagnosis and treatment. Your passion, expertise, and commitment to excellence continue to inspire us all.

Thank you for your dedication to excellence in healthcare, and for your unwavering commitment to the well-being of the families we serve.

We congratulate ISPAT office bearers and specially editor Dr. Manjet Mehta for initiating the newsletter. We hope this will continue regularly.

Warm regards.

PROF. DR. NARENDRA MALHOTRA
M.B.B.S, M.D., F.I.A.J.A.G.O., F.I.C.M.U.,
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Messages

Dear ISPAT Members,

I am humbled to become the President of an organisation with such a huge Legacy.
Actually in obstetric terms. I am PREMATURE. I was to take the reins in 2025 but Destiny has put me here today.

When I look upon the past president in awe I suddenly realise that at 48 I am the youngest President of ISPAT.

The past presidents have such a high persona that it's humbling and exciting to be there in the same league.

As we all know Indian Society for Prenatal Diagnosis and Therapy, fondly called as ISPAT was established in 1989.

We are more than 3 decades from then. At that time Genetics was not what we know today, but today it's different. There is no aspect of healthcare where genetics has not touched. and most importantly "REPRODUCTION" because Genes of parents is what shapes the future progeny.

Being in this position puts a lot of responsibility on me & the team and I must say that we all are ready to take ISPAT forward to newer heights.

ISPAT would embrace all possible avenues to share knowledge plan academic events with all those organisations with whom we overlap.

We have eNewsletter, "Samvaad" series and many more activities planned for months to come.

We welcome you to become an ISPATian if not already and be part of this transformational journey.

Best regards,
Dr. Saurabh Dani
President ISPAT, 2023-25

Dear ISPAT Members,

I am delighted to share the exciting news of our inaugural newsletter launch! As your secretary, curating this edition has been a fulfilling experience, bringing together the latest updates, achievements, and highlights from our dynamic community.

In this special edition, we cast a spotlight on the ever-growing importance and applications of genetics in obstetric practice. Explore insightful articles that illuminate the transformative role of genetic insights in shaping the future of prenatal care. From breakthrough technologies to real-world applications, our newsletter unravels the evolving landscape of genetics in the realm of obstetrics, offering a comprehensive view of its impact on healthcare practices.

I extend heartfelt gratitude to all contributors and our dedicated editorial team for their hard work in bringing you this enriching content. Let's come together to celebrate this milestone and eagerly anticipate the many more editions that lie ahead.

Happy reading...

Best regards,
Dr. Manjeet Mehta
Hon. Secretary General, ISPAT

INDIAN SOCIETY FOR PRENATAL DIAGNOSIS AND THERAPY MANAGING COMMITTEE 2023 – 2025

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Remembering Dr. R. P. Soonawala

Founder President, ISPAT

A Legend in the True Sense

Rest in Peace

Today, we gather with hearts full of gratitude and admiration to honor a man whose legacy transcends the boundaries of medicine, kindness, and wisdom. Dr. Soonawala sir is not just a doctor; he is a beacon of hope, a mentor, and a symbol of compassion to all who have had the privilege to know him.

For decades, he has been a guiding light in his field, revolutionizing patient care with unparalleled expertise, while always remembering the human element that makes his work so extraordinary. His hands have healed many, but it is his heart that has touched us all. A mentor who nurtured countless young minds, he instilled in us not just the science of medicine but the art of being kind, patient, and empathetic. His gentle approach, endless patience, and dedication to the welfare of his patients and colleagues alike are qualities that make him truly one of a kind.

Dr. Soonawala sir's reputation as a leader in his field is unmatched. He has spent his life perfecting his craft, but it is his humility, humility so deep and genuine, that makes him not just a legend in medicine but a legend in humanity. His quiet strength has guided many through their darkest hours, and his wisdom continues to inspire all who follow in his footsteps.

We owe a debt of gratitude to this extraordinary man - his kindness, his passion for teaching, and his selfless dedication to the medical profession have touched more lives than we can count. His work will undoubtedly continue to echo through the years, not just in his patients' recovery but in the countless lives he has shaped and uplifted.

As we reflect on Dr. Soonawala sir's remarkable journey, we are reminded that legends are not born in the headlines but in the hearts of those who experience their grace and greatness. Today, we celebrate a legend who remains, forever, a mentor, a healer, and, above all, a truly kind soul.

Dr. Soonawala sir, your legacy will live on in each of us, as we strive to carry forward the lessons you've taught us - of compassion, expertise, and unwavering dedication. We are forever grateful to have had you as our guide. May your path always be blessed, just as you have blessed us all.

With deepest respect and gratitude,

Dr. Saurabh Dani
President, ISPAT

Dr. Manjeet Mehta
Secretary, ISPAT

Editorial

Recurrent Pregnancy Loss - Educating Ourselves to Heal Others

Recurrent pregnancy loss (RPL) remains one of the most emotionally taxing experiences for couples and one of the most complex challenges for clinicians. Defined classically as the loss of two or more consecutive pregnancies, RPL is not just a reproductive issue; it is a medical, emotional, and psychosocial crisis that demands a comprehensive, multidisciplinary approach.

Yet, even today, many couples navigate this journey with inadequate information and fragmented care. As clinicians, we are uniquely positioned to change this narrative - **through education, empathy, and evidence-based intervention.**

One of the most significant gaps in RPL care is **awareness and understanding.** Too often, investigations are either delayed or incomplete. Couples are reassured without evaluation or subjected to unnecessary interventions without clarity. The need for clinician education—across specialties—is critical. We must remain updated on evolving definitions, diagnostic pathways, and emerging evidence regarding immunological, genetic, endocrine, anatomical, and lifestyle-related contributors to RPL. Equally important is the ability to communicate this information clearly and compassionately to patients.

The emotional distress faced by couples with RPL cannot be overstated. These are not isolated clinical events but cumulative losses, each bringing its own grief and fear. As clinicians, recognizing this psychological burden is as important as managing the medical one. Our approach must be sensitive, trauma-informed, and affirming. Referrals for mental health support should be normalized and integrated into the care pathway—not offered as an afterthought.

The good news is - we have options. Genetic counseling, thrombophilia workups, endocrine evaluations, uterine imaging, and immunological assessments can reveal treatable causes in a significant number of cases. For those with unexplained RPL, emerging data supports interventions such as progesterone supplementation and close surveillance in early pregnancy. Importantly, most couples with RPL ultimately go on to have successful pregnancies, especially with tailored care.

And that brings us to **hope.** In the face of repeated loss, hope may feel fragile—but when supported by science and compassion, it is powerful. Our role is not only to diagnose and treat, but to walk alongside couples, offering clarity, continuity, and confidence in the journey ahead.

As clinicians, let us commit to moving beyond reassurance to **real readiness** - educating ourselves to ask the right questions, initiate the right workups, and offer the right words. Because when we do, we not only improve outcomes - we help restore hope.

Dr. Veronica Arora
Consultant
Genetics

Dr. Neharika Malhotra
Rainbowivf
Agra

Recurrent Pregnancy Loss: A Case Study Involving Balanced Translocation in a Non-Consanguineous Couple

INTRODUCTION:

Recurrent pregnancy loss (RPL) is a deeply distressing experience for couples, often bringing both emotional and physical burdens. Defined as the loss of two or more pregnancies before the 20th week of gestation, RPL affects approximately 1-2% of couples trying to conceive. While causes such as anatomical anomalies, hormonal imbalances, and immunological disorders are frequently implicated, genetic abnormalities are a significant but often underdiagnosed contributor to early pregnancy losses.

This article presents a detailed case study of a non-consanguineous couple who experienced two unexplained miscarriages. It explores the diagnostic process, eventual genetic diagnosis, and reproductive options available. The case underscores the importance of genetic testing, especially microarray and parental karyotyping, in identifying chromosomal abnormalities and guiding reproductive planning.

CASE SUMMARY

A non-consanguineous couple presented with a history of two first-trimester miscarriages. Both pregnancies had ended in missed abortions around 8–10 weeks of gestation. Detailed investigations were conducted following the second miscarriage to identify potential causes.

INVESTIGATIONS AND INITIAL WORKUP:

- Hormonal assessments: Including thyroid function tests, prolactin levels, and luteal phase progesterone, were all within normal limits.
- Immunological tests: Screening for antiphospholipid antibody syndrome (APLA), lupus anticoagulant, and other immunological factors yielded negative results.
- Anatomical assessment: A pelvic ultrasound and hysterosalpingogram (HSG) showed a normal uterine cavity, ruling out uterine malformations or synechiae.

Despite an exhaustive workup, no cause for the pregnancy losses could be determined. The couple was advised to try conceiving again with reassurance. However, when the third pregnancy also ended in a missed abortion at around 9 weeks, the clinicians decided to further investigate the genetic basis of the recurrent losses.

GENETIC TESTING OF THE ABORTUS

For the third miscarriage, the products of conception (POC) were sent for chromosomal microarray analysis (CMA), a more sensitive technique than traditional karyotyping. CMA does not rely on cell culture and thus avoids issues like culture failure and maternal cell contamination, which can compromise the accuracy of karyotyping results.

MICROARRAY FINDINGS:

- **Duplication on Chromosome 9**
- **Deletion on Chromosome 11**

CN State	Type	Chr.No.	Cytoband Start	Size (kbp)	No. of genes	Genomic Coordinates	Interpretation
3	GAIN	9	32,737	p24.3.21.1	145	arr[GRCh37] 9p24.3p21.1 {203,862_32,940,}X3	PATHOGENIC
2	LOSS	11	1,074	q25	13	arr[GRCh37] 11q25 {133,864,938_134,938,470}XI	PATHOGENIC

Interpretation: CMA Analysis shows about 32,737kbp (^32MB) ***duplication on chromosome 9***, spanning 9p24.3-21.1 region, and about 1,074kbp (2MB) ***deletion on chromosome 11*** spanning 11q25 region, corresponding to a deletion-duplication syndrome referred to as a translocation.

Fig 1: Microarray report showing duplication on chromosome 9, and deletion on chromosome 11

These findings were suggestive of an ***unbalanced chromosomal rearrangement*** in the fetus. Such rearrangements often result from one parent carrying a ***balanced translocation***, which in itself does not usually cause health issues for the carrier but can lead to unbalanced gametes and, consequently, miscarriages or children with congenital anomalies.

PARENTAL KARYOTYPING AND DIAGNOSIS

Following the abnormal microarray report from the fetal tissue, the couple underwent ***peripheral blood karyotyping*** to assess for balanced translocations.

FINDINGS:

- The ***father*** was found to be a carrier of a ***balanced reciprocal translocation between chromosomes 9 and 11.***
- The ***mother's karyotype was normal.***

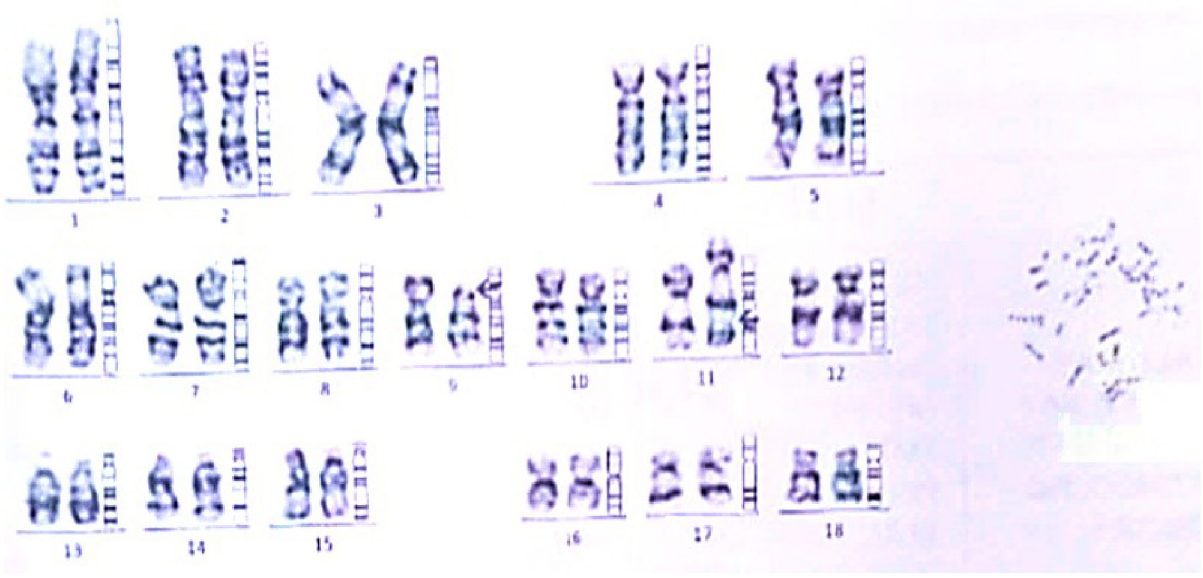

Fig 2: 46, XY, t(9;11)(p24.3; q25) Karyotype of father showing balanced translocation of chromosomes 9 and 11.

A balanced translocation involves the exchange of segments between two chromosomes without any gain or loss of genetic material. While the individual is phenotypically normal, the risk lies in gamete formation. During meiosis, the segregation of chromosomes may lead to gametes with ***unbalanced chromosomal content***, resulting in recurrent miscarriage or children with congenital anomalies.

REPRODUCTIVE OPTIONS FOR THE COUPLE

With the diagnosis of a ***balanced translocation in the father***, the couple was counseled extensively about their reproductive options. The goal was to maximize the chance of a healthy pregnancy while minimizing the emotional and physical toll of repeated pregnancy losses.

1. **Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR):**

   - ***PGT-SR*** is an advanced form of embryo screening available during ***in vitro fertilization (IVF).***
   - Embryos created via IVF are biopsied at the blastocyst stage, and their chromosomal structure is analyzed to identify those with balanced or normal karyotypes.
   - Only chromosomally normal or balanced embryos are selected for transfer, significantly reducing the risk of miscarriage.

Advantages:

- Reduces the risk of unbalanced conceptions.
- Increases the likelihood of a successful live birth.
- Avoids the emotional trauma of miscarriage.

Limitations:

- Cost and access to IVF and PGT-SR.
- Not all embryos may be suitable for testing or transfer.
- IVF success rates vary with maternal age and other factors.

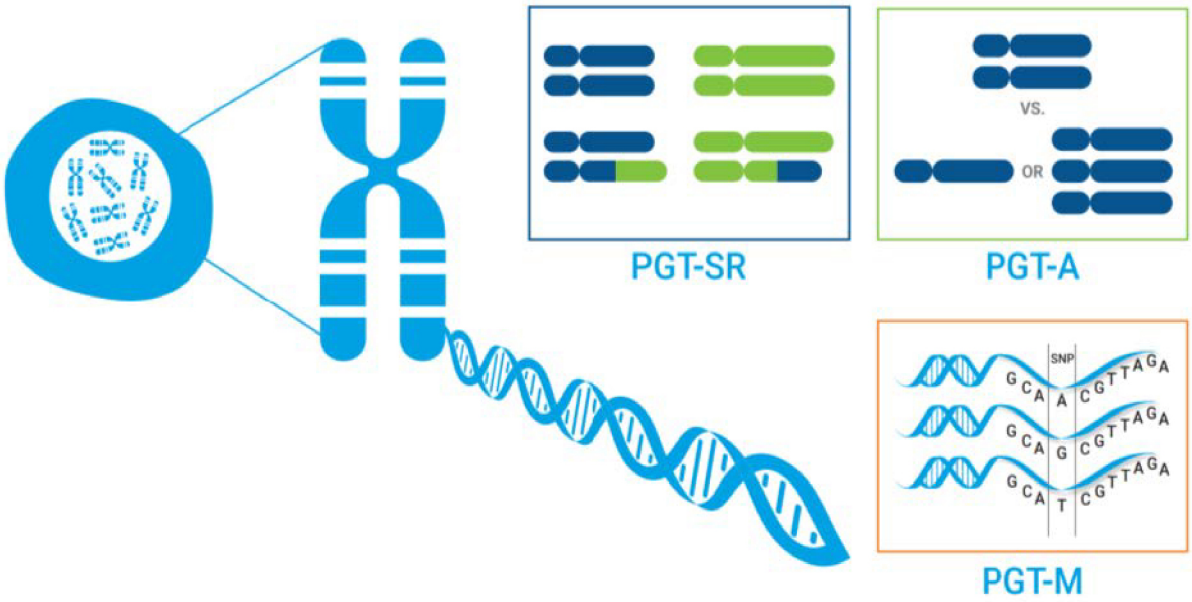

Fig 3: Preimplantation Genetic Testing (PGT) PGT-A for Aneuploidies, PGT-SR for Structural Rearrangements, and PGT-M for Monogenic Disorders

2. Prenatal Diagnostic Testing:

If the couple chooses to conceive naturally, ***prenatal diagnostic tests*** such as:

- ***Chorionic Villus Sampling (CVS)*** (at 10–13 weeks), or
- ***Amniocentesis*** (at 15–18 weeks), can be offered to detect chromosomal abnormalities in the fetus.

Advantages:

- Allows continuation of natural conception.
- Provides definitive diagnosis during early gestation.

Limitations:

- Invasive with a small risk of miscarriage.
- Detection comes only after conception, which may lead to difficult decisions if abnormalities are found.

3. Use of Donor Gametes:

- ***Donor sperm*** could be considered to eliminate the risk associated with the paternal balanced translocation.
- While this option guarantees the genetic abnormality is avoided, it also raises significant emotional, ethical, and legal considerations.

DISCUSSION:

This case underscores several crucial lessons in the evaluation and management of recurrent pregnancy loss:

1. **Genetic Testing is Crucial:**

   - In couples with unexplained recurrent losses, ***genetic testing of fetal tissue*** should be considered, particularly after the second or third loss.
   - ***Chromosomal microarray*** is now the ***preferred method*** for testing abortus material due to its higher resolution and reliability.

2. **Parental Karyotyping is Essential in Missed Abortions:**

   - If a chromosomal abnormality is detected in the POC, ***both partners should undergo karyotyping*** to detect possible balanced translocations.
   - Balanced translocations are found in approximately 2-5% of couples with RPL.

3. **Tailored Reproductive Counseling:**

   - Identification of a balanced translocation enables appropriate ***genetic counseling*** and discussion of ***reproductive options***, including IVF with PGT-SR.
   - This allows couples to make informed decisions that align with their emotional, ethical, and financial considerations.

TAKEAWAY MESSAGE

- In cases of ***first-trimester missed abortions***, particularly recurrent losses, ***karyotyping of the couple*** should be a standard part of the evaluation.
- When investigating the cause of miscarriage, ***chromosomal microarray of abortus material*** is the ***test of choice.*** It avoids pitfalls such as culture failure and maternal contamination, which are limitations of traditional karyotyping.
- A genetic diagnosis opens up ***new reproductive avenues*** for affected couples and prevents the emotional and physical toll of repeated losses.

CONCLUSION

Recurrent pregnancy loss is a multifaceted issue requiring a systematic and empathetic approach. Genetic abnormalities, particularly balanced translocations, represent a significant and often overlooked cause. With advancements in genetic testing technologies such as microarray and PGT-SR, clinicians can now offer more accurate diagnoses and tailored reproductive solutions. This case exemplifies the power of combining clinical vigilance with modern diagnostics to provide clarity and hope to couples navigating the difficult path of recurrent miscarriage.

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Genetic Causes in Recurrent Pregnancy Loss

ABSTRACT

Recurrent pregnancy loss (RPL), defined as the loss of two or more consecutive pregnancies, affects approximately 1-2% of couples attempting to conceive. While multiple etiologies contribute to RPL, genetic factors play a significant role in its pathogenesis. This article explores the genetic mechanisms underlying RPL, including chromosomal abnormalities, single-gene disorders, and polymorphic variations that may predispose individuals to recurrent pregnancy loss. Understanding these genetic factors is crucial for advancing diagnostic strategies and improving patient outcomes.

INTRODUCTION

Recurrent pregnancy loss remains a distressing condition for both patients and clinicians. The etiology of RPL is multifactorial, encompassing anatomical, endocrine, immunological, infectious, and genetic causes. Among these, genetic abnormalities are particularly significant as they can lead to implantation failure, embryonic lethality, or structural defects incompatible with life. Genetic evaluations and counseling have become integral to the management of RPL, allowing for risk assessment and personalized therapeutic interventions.

CHROMOSOMAL ABNORMALITIES IN RPL

1. Parental Chromosomal Abnormalities

Balanced chromosomal translocations, including reciprocal translocations and Robertsonian translocations, are found in 2-5% of couples experiencing RPL. These abnor malities may lead to unbalanced gametes, resulting in conceptions with chromosomal imbalances that are often nonviable.

- **Reciprocal Translocations:** Exchange of genetic material between nonhomologous chromosomes can result in partial trisomy or monosomy in the offspring.
- **Robertsonian Translocations:** Fusion of two acrocentric chromosomes leads to fertility challenges and an increased risk of chromosomal imbalances in embryos.

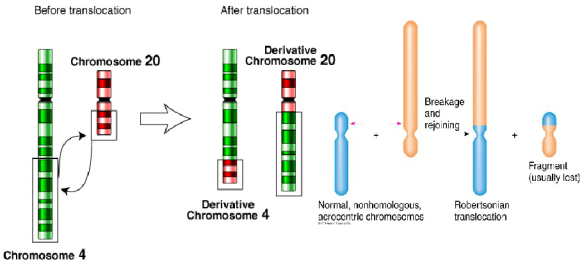

Fig 1: Balanced Reciprocal Translocation. Robertsonian Translocation

2. Embryonic Aneuploidy

Most early pregnancy losses result from embryonic aneuploidy, with approximately 50-70% of first-trimester miscarriages associated with chromosomal abnormalities. The most common aneuploidies include:

- **Trisomies** (e.g., trisomy 16, 21, 18, and 13)
- **Monosomy X** (Turner syndrome)
- **Triploidy and Tetraploidy**

The likelihood of embryonic aneuploidy increases with maternal age due to meiotic nondisjunction events in oocytes.

SINGLE-GENE DISORDERS AND RPL

1. Thrombophilia-Related Mutations

Several inherited thrombophilic conditions are implicated in RPL, as they contribute to placental insufficiency and thrombotic events. Notable mutations include:

- **Factor V Leiden (F5 1691G>A):** Increases the risk of venous thromboembolism and placental microthrombosis.
- **Prothrombin G20210A Mutation:** Associated with increased coagulation activity.
- **MTHFR C677T and A1298C Mutations:** Affect homocysteine metabolism, leading to hyperhomocysteinemia and vascular complications.

2. Autoimmune and Endocrine Gene Variants

- **HLA-G Variants:** Abnormal maternal-fetal immune tolerance due to altered HLA-G expression is implicated in RPL.
- **FOXL2 Mutations:** Affect ovarian function and are linked to premature ovarian insufficiency, potentially contributing to pregnancy loss.

3. Congenital Disorders and Syndromic Associations

- **COL1A1 and COL1A2 Mutations:** Associated with osteogenesis imperfecta, which may predispose affected pregnancies to intrauterine demise.
- **GATA2 and TBX1 Variants:** Contribute to congenital heart defects that may result in fetal loss.

Epigenetic Influences in RPL

Beyond direct genetic mutations, epigenetic alterations such as DNA methylation and histone modifications influence pregnancy viability. Dysregulation of imprinting genes, such as those in the H19/IGF2 locus, has been linked to placental dysfunction and miscarriage.

Advances in Genetic Testing for RPL

Recent advances in molecular genetics have enhanced our ability to diagnose genetic causes of RPL.
Techniques include:

- **Karyotyping:** Used for detecting balanced and unbalanced chromosomal translocations in parents.
- **Molecular Testing (PCR & Sanger Sequencing):** Useful to detect point mutations known to cause RPL.
- **Chromosomal Microarray (CMA) and Next-Generation Sequencing (NGS):** Provide high-resolution detection of chromosomal imbalances in embryonic tissue.
- **Whole-Exome Sequencing (WES):** Identifies pathogenic mutations in single genes associated with RPL.

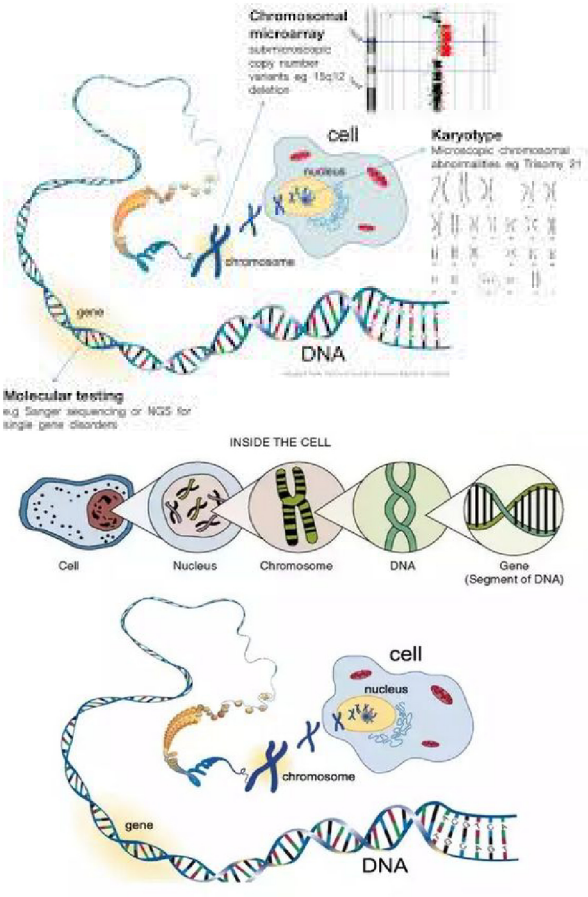

Fig 1: Various Genetic Technologies available

Genetic Counseling and Management Strategies

For couples with identified genetic abnormalities, reproductive options include:

- **Preimplantation Genetic Testing (PGT):** Helps select chromosomally normal embryos during in vitro fertilization (IVF).
- **Donor Gametes:** Considered when one partner has a significant genetic risk factor.
- **Prenatal Diagnostic Testing:** Includes chorionic villus sampling (CVS) and amniocentesis for early detection of fetal genetic abnormalities.

CONCLUSION:

Genetic factors are a predominant cause of recurrent pregnancy loss, with chromosomal abnormalities, single-gene mutations, and epigenetic changes contributing to pregnancy failure. Advances in genetic diagnostics, including next-generation sequencing and preimplantation genetic testing, have significantly improved the management of RPL. Further research into the genetic underpinnings of RPL will enhance our ability to provide personalized reproductive care and improve pregnancy outcomes for affected couples.

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Immunological Causes of Recurrent Pregnancy Loss (RPL)

INTRODUCTION

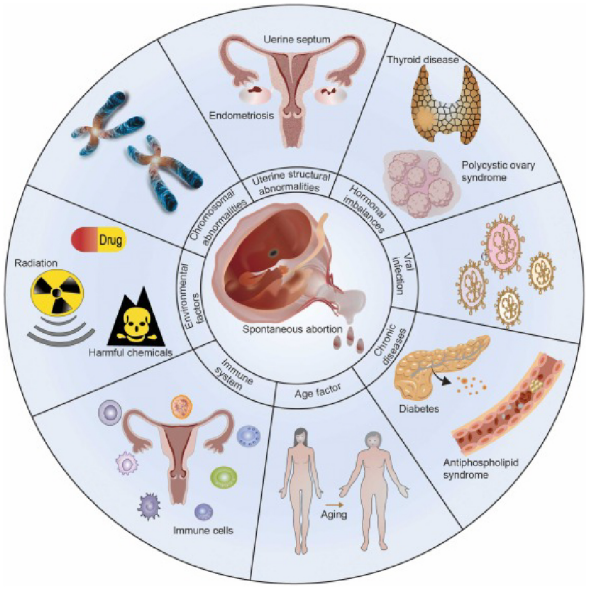
Recurrent pregnancy loss (RPL), defined as two or more consecutive pregnancy losses before 20 weeks of gestation, affects a significant number of women and can have profound emotional and psychological consequences. Understanding the underlying causes of RPL is crucial for effective management and treatment. Among the various factors contributing to RPL, immunological causes have gained increasing attention in recent years. Immunological mechanisms that may contribute to RPL, including autoimmune disorders, alloimmune responses, and the role of cytokines and natural killer (NK) cells.

OVERVIEW OF RECURRENT PREGNANCY LOSS

Definition and Prevalence

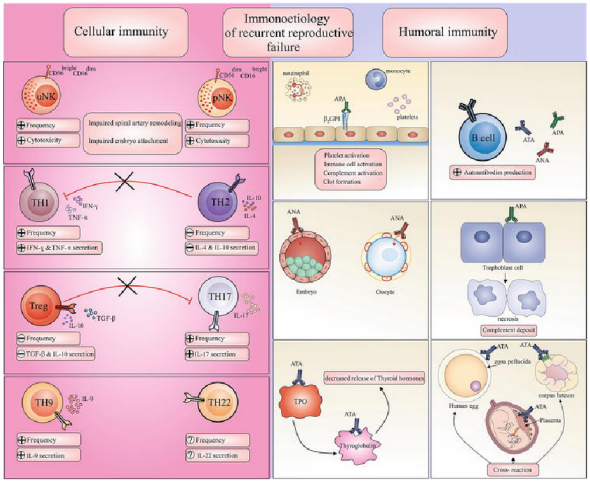
Recurrent pregnancy loss is a distressing condition experienced by 1-2% of couples trying to conceive. The definition of RPL varies, but most clinicians consider two or three consecutive losses as the threshold for diagnosis. Identifying the cause of RPL is essential for guiding therapeutic interventions and providing psychological support.

Etiological Factors



The causes of RPL are multifaceted and can be classified into several categories:

- **Genetic Factors:** Chromosomal abnormalities in either parent can lead to embryonic development issues.
- **Anatomical Factors:** Uterine abnormalities, such as septate uterus or fibroids, can interfere with implantation and growth.
- **Endocrine Factors:** Hormonal imbalances, including thyroid dysfunction and polycystic ovary syndrome (PCOS), can affect pregnancy viability.
- **Infectious Factors:** Certain infections can compromise pregnancy maintenance.
- **Immunological factors:** Autoimmune disorders and alloimmune responses are increasingly recognized as significant contributors to RPL.



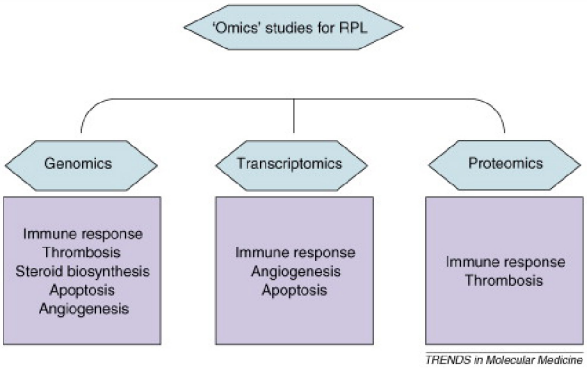
IMMUNOLOGICAL MECHANISMS IN RPL

1. Autoimmune Disorders

Autoimmune disorders occur when the immune system mistakenly attacks the body's own tissues. In the context of pregnancy, these disorders can disrupt normal immuno logical tolerance and contribute to RPL. Key autoimmune disorders associated with RPL include:

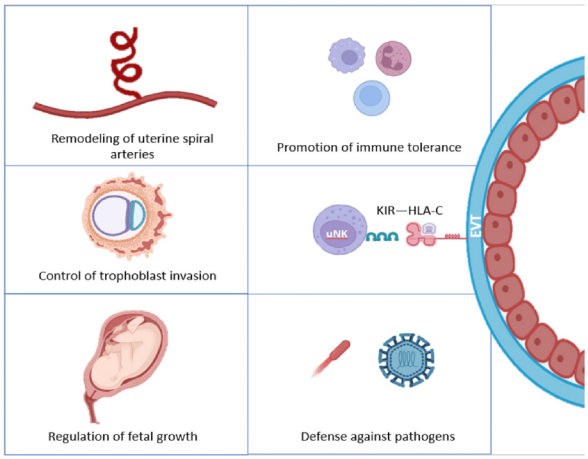
- **Antiphospholipid Syndrome (APS):** Characterized by the presence of antiphospholipid antibodies, APS is a major contributor to RPL. These antibodies can induce thrombosis, leading to placental insufficiency and fetal loss.
- **Systemic Lupus Erythematosus (SLE):** Women with SLE may experience increased risks of RPL due to immune dysregulation and the presence of antiphospholipid antibodies.
- **Thyroid Autoimmunity:** Thyroid antibodies can interfere with normal thyroid function, potentially impacting fetal development and contributing to pregnancy loss.

2. Alloimmune Responses



During pregnancy, the maternal immune system must tolerate the semi-allogeneic fetus (half maternal and half paternal antigens). Disruption in this tolerance can lead to RPL. Alloimmune factors include:

- **Maternal-Fetal Immune Interaction:** Trophoblast cells from the placenta express paternal antigens that are recognized as foreign by the maternal immune system. A failure in the immune tolerance mechanism can lead to an immune response against these cells, resulting in implantation failure or early pregnancy loss.



- **Natural Killer (NK) Cells:** NK cells are critical in the early stages of pregnancy, playing a role in trophoblast invasion and remodeling maternal blood vessels. Dysregulation of NK cell activity can lead to inadequate placentation and subsequent pregnancy loss.

3. Cytokine Imbalances

Cytokines are signaling molecules that mediate immune responses. The balance of pro-inflammatory and anti-inflammatory cytokines is crucial for a successful pregnancy. In RPL, an imbalance in cytokines can occur:

- **Pro-inflammatory Cytokines:** Elevated levels of cytokines such as TNF-alpha and IL-6 can lead to an inflammatory environment detrimental to embryo implantation and development.
- **Anti-inflammatory Cytokines:** Cytokines like IL-10 are essential for promoting a tolerogenic environment. Deficiencies in these anti-inflammatory cytokines may contribute to immune activation against the embryo.

DIAGNOSIS OF IMMUNOLOGICAL CAUSES OF RPL

1. Clinical Evaluation

A thorough clinical evaluation is essential for diagnosing immunological causes of RPL. This includes:

- **Medical History:** A detailed reproductive history, including the number of losses, timing, and any associated symptoms.
- **Autoimmune Screening:** Testing for antiphospholipid antibodies, thyroid antibodies, and other relevant autoimmune markers.

2. Immunological Testing

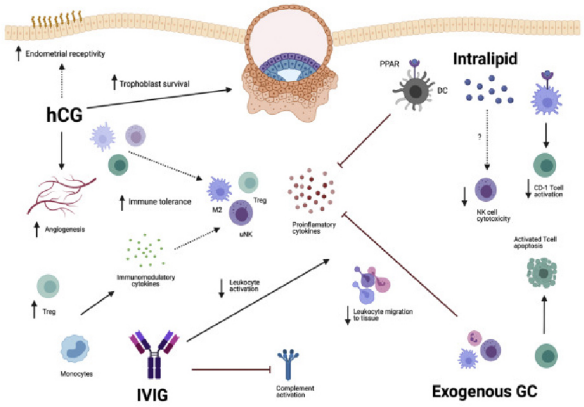
Specific tests can help identify underlying immunological issues:

- **Antiphospholipid Antibodies:** Screening for these antibodies can confirm APS.
- **Thyroid Function Tests:** Assessing thyroid hormone levels and antibodies can reveal thyroid dysfunction.

3. Genetic Testing

In some cases, genetic testing may be warranted to identify chromosomal abnormalities that could contribute to RPL.

Management of Immunological Causes of RPL



1. Intravenous Immunoglobulin (IVIG)

Mechanism: IVIG is thought to modulate immune responses, enhancing regulatory T cell (Treg) activity and reducing pro-inflammatory cytokines.

Efficacy: Some studies suggest that IVIG may improve pregnancy outcomes in women with a history of RPL, particularly those with autoimmune conditions. However, more robust clinical trials are needed to establish definitive efficacy.

2. Corticosteroids

Mechanism: Corticosteroids can suppress immune responses and reduce inflammation. They are often used in patients with autoimmune disorders that contribute to RPL.

Efficacy: The use of corticosteroids has shown promise in improving outcomes for women with conditions like APS or SLE. However, the potential risks of long-term steroid use must be carefully considered.

3. Antiphospholipid Syndrome Management

For women diagnosed with APS, treatment typically involves anticoagulation therapy, including:

- **Low-dose Aspirin:** Helps reduce the risk of clot formation.
- **Heparin:** Often used in conjunction with low-dose aspirin to prevent thromboembolic complications.

4. Natural Killer (NK) Cell Therapy

Mechanism: NK cells play a crucial role in implantation and placentation. Dysregulated NK cell activity can contribute to RPL.

Efficacy: Some studies suggest that therapies aimed at modulating NK cell activity may improve outcomes. However, the evidence is still evolving, and more research is needed to clarify the role of NK cells in RPL.

5. Cytokine Therapy

Mechanism: Cytokine therapies aim to restore the balance of pro-inflammatory and anti-inflammatory cytokines in the maternal environment.

Efficacy: Research is ongoing to determine the most effective cytokine interventions for RPL. Therapies target ing specific cytokines may hold promise but require further investigation.

6. Supportive Care

Providing emotional and psychological support to women experiencing RPL is crucial. Counseling, support groups, and mental health resources can help women cope with the emotional toll of recurrent losses.

CURRENT RESEARCH AND FUTURE DIRECTIONS

Clinical Trials

Numerous clinical trials are exploring the efficacy of various immunotherapeutic approaches in RPL. These studies aim to establish guidelines for the use of immunotherapy in this context, assessing both safety and efficacy.

Personalized Medicine

As our understanding of the immunological factors contributing to RPL deepens, the future of treatment may shift toward more personalized approaches. Tailoring immunotherapy based on individual immune profiles may enhance treatment success.

Integrative Approaches

Combining immunotherapy with lifestyle modifications, nutritional support, and psychological counseling may offer a holistic approach to managing RPL. Addressing both physical and emotional well-being is crucial for improving outcomes.

CONCLUSION

Immunological causes of recurrent pregnancy loss represent a complex interplay of autoimmune disorders, alloimmune responses, and cytokine imbalances. Understanding these mechanisms is vital for effective diagnosis and management. By recognizing the potential immunological factors contributing to RPL, healthcare providers can offer targeted interventions that may improve pregnancy outcomes. Ongoing research is necessary to further elucidate the immunological pathways involved in RPL and to develop more effective therapeutic strategies.

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Prognostication of Pregnancy in RPL

INTRODUCTION

Recurrent pregnancy loss (RPL) ,in United states ,is defined as two or more consecutive failed clinical pregnancies documented by ultrasound or histopathology, while, in United Kingdom,it is defined as having three or more consecutive early pregnancy losses. Up to 50 percent of cases of recurrent pregnancy loss lack a clear etiology (1).However extensive evaluation after two first trimester miscarriages is must for the prognostication of future pregnancies. Recurrent pregnancy loss is categorized into primary and secondary types. Primary, recurrent pregnancy loss occurs in women who have never given birth to a live infant. Secondary recurrent pregnancy loss occurs in women who have given birth to a live infant(2).

PROGNOSTICATION

pregnancy after RPL depends on the nature of previous pregnancy loss . period of gestation at the time of demise, presence or absence of cardiac activity at time of presentation, biochemical markers ,presence of any Mullerian anomaly, family history etc.

Recurrent pregnancy loss (RPL) carries a tremendous negative emotional and psychological negative impact on couples. It is associated with depression, anxiety, and low self-esteem. Increasing maternal age, as well as the number of previous miscarriages, appear to be the most influential independent risk factors for having further pregnancy losses.

It is necessary to understand aetiologies of RPL for its prognostication and management. Common causes of RPL are Genetic, Anatomic, Endocrine, Antiphospholipid antibody syndrome, Immunological and Environmental factors.

Management of patient depends on the time at which patient presented first in the clinic whether pregnancy is ongoing or Patient is planning her pregnancy with history of RPL.

EVALUATION AND MANAGEMENT

a). Complete biochemical studies should be performed to rule out diabetes, thyroid problems [3],hyperpro lactinemia or any underlying medical problem. Women with second trimester miscarriage may be offered testing for Factor V Leiden, prothrombin gene mutation and protein S deficiency.

Consultation with a physician or endocrinologist is necessary for the management of uncontrolled thyroid conditions and diabetes. Patients with elevated thyroid peroxidase antibodies are at high risk for RPL and should be managed appropriately.

b). If patient presents in pregnant state, ultrasound can prognosticate the pregnancy.

1. The appearance of yolk sac and/or gestational sac- too small, too large or irregular is poor prognostic marker. Picture 1
2. Cardiac activity - fetal heart rate less than 90 beats per min is a marker of poor outcome. Picture 2. Lagging behind as per sonographic expectations according to gestational age picture
3. Assessment of vascularity of corpus luteum can predict corpus luteum insufficiency.
4. Cervical assessment can be done to rule out cervical insufficiency or incompetency.

c). If patient presents in Non pregnant state

1. Assessment of the Uterine Anomalies should be done by Pelvic ultrasound, and Hysteroscopy.
   MRI is also valuable in identifying congenital uterine anomalies.[4].Though 3D ultrasound can diagnose most of the uterine anomalies.

   Congenital and acquired uterine abnormalities causing RPL could be managed surgically. Some of the surgical procedures are hysteroscopic septum resection, lysis of adhesions, myomectomy, and repair of a bicornuate uterus.(Hysteroscopy picture)
2. Immunologic Work Up in the form of Measurement of antiphospholipid antibody anticardiolipin antibody, lupus anticoagulant, and anti-beta 2 glycoprotein should be done for patients with RPL.

   Patients with autoimmune disease are treated with aspirin and LMWH, and it appears to improve pregnancy outcomes. However, in women with thrombophilias, this treatment may improve maternal outcomes but does not prevent RPL. The new treatment options, including drugs like TNF (tumor necrosis factor-alpha) inhibitors and granulocyte colony-stimulating factor (G-CSF) are also beneficial but still under trial.
3. Genetic Evaluation of couple by doing Karyotype to be offered to recognize underlying balanced, reciprocal, or Robertsonian translocations or mosaicism that might be transmitted to the fetus, causing RPL.

   In couples with chromosomal abnormalities, genetic counseling is needed. Couples should be educated on the potential likelihood of having fetal chromosomal abnormalities in future pregnancies. They may choose to proceed with prenatal genetic testing, such as preimplantation genetic diagnosis, chorionic villus sampling, or amniocentesis to identify genetic anomalies in the fetus and decide about further treatment options.
4. Screening of sperm DNA testing is recommended.

5. Women with recurrent miscarriage should be advised to maintain a BMI between 19 and 25 kg/m 2, smoking cessation, limit alcohol consumption andlimit caffeine to less than 200 mg/day.

Evaluation of products of Conception (POC)

Using chromosome microarray analysis adds significantly to RPL assessment. Genetic evaluation of miscarriage tissue obtained at the time of the second and subsequent pregnancy losses should be offered to all couples with two or more consecutive pregnancy losses. The combination of a genetic evaluation on miscarriage tissue with an evidence-based assessment for RPL will identify a probable or definitive cause in over 90 percent of miscarriages.

CONCLUSION:

Management of recurrent RPL stresses the role of team-based interprofessional care for affected patients involving skilled Gynecologist, Radiologist, Genetic counsellor, Fetal medicine expert, Physician ,Endocrinologist etc

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Understanding NK Cells

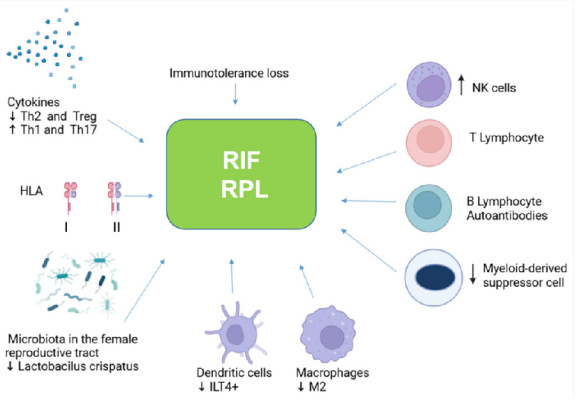
INTRODUCTION

The immune system plays an essential role in normal implantation, maternal-placental fetal crosstalk, and embryo development ,thus, immunological alterations can be responsible for RPL and RIF. The local immune response can also be impaired by vaginal dysbiosis (VD). VB has been involved in several pregnancy complications, such as miscarriage, preterm birth, and adverse outcomes in vitro fertilization (IVF).

The innate immune response functions as the initial line of defense against pathogens, encompassing mechanisms such as phagocytosis, endocytosis, secretion of lytic granules and protective peptides, and the release of proinflammatory cytokines, chemokines, lipid enzymes, metabolites, nitrogen, and oxygen radicals, all of which play crucial roles in the inflammatory process. Furthermore, innate immunity contributes to tissue homeostasis and remodeling.

In the last decade Natural Killer cells have been studied in peripheral blood and uterus in order to determine if there are specific characteristics of Natural Killer cells associated with miscarriage. Different authors have described an increased number of uterine and peripheral blood Natural Killer cells in women with recurrent miscarriages compared to control women. However, its relationship with miscarriage has not been confirmed.

In patients with recurrent miscarriage a lack of inhibition of decidua Natural Killer cells can be observed, which leads to a more activated state characterized by higher levels of proinflammatory cytokines. In peripheral blood, it has been also reported a dysfunctional cytokine production by Natural Killer cells, with an increase of interferon-γ levels and a decrease of Interleukin-4.



The figure illustrates the major elements studied in RIF and RPL.

What Are NK Cells?

Natural Killer (NK) cells are part of the body's first line of immune defense. Unlike other immune cells, they don't need prior exposure to identify what doesn't belong. While they're known for fighting infections and abnormal cells, they also play a surprisingly important role in early pregnancy.

NK Cells in Pregnancy: Two Types

There are two kinds of NK cells we talk about:

Peripheral NK cells (pNK) – found in the bloodstream

Uterine NK cells (uNK) – located in the lining of the uterus
Interestingly, the NK cells in the uterus are different from those in the blood. Uterine NK cells are more focused on creating a healthy environment for the embryo rather than destroying anything foreign.

What Do NK Cells Do in a Healthy Pregnancy?

During early pregnancy, uterine NK cells help the placenta form and encourage blood vessels in the uterus to adapt. This helps ensure the developing embryo gets the nutrients and oxygen it needs.

Instead of attacking the embryo, these cells actually support implantation and placental growth by releasing helpful molecules like VEGF and IL-8. When everything is balanced, NK cells are pregnancy helpers-not threats.

How NK Cells Might Be Involved in Recurrent Pregnancy Loss (RPL)

Recurrent pregnancy loss refers to having two or more miscarriages, and in some women, NK cells may be part of the puzzle.

Here's what research has suggested:

Some women with RPL seem to have higher numbers of NK cells.

In others, the NK cells may be overactive, releasing too many inflammatory chemicals or attacking the embryo.

There's also a theory that the way NK cells interact with fetal cells-especially through specific gene combinations (like KIR receptors on NK cells and HLA-C on fetal cells)-can affect pregnancy outcomes.

Still, these ideas are not universally agreed upon, and the science is far from settled.

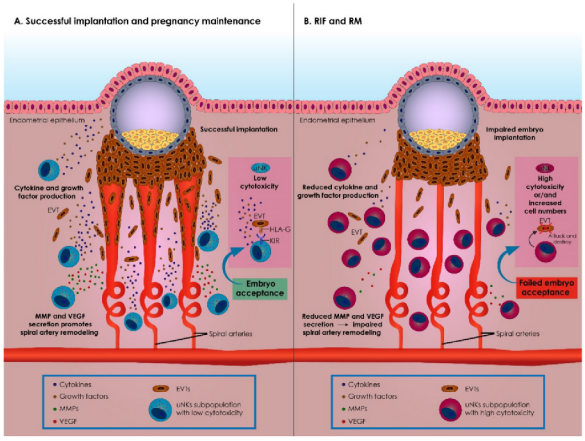


Figure shows a summary of the role of uterine natural killer (uNK) cells on the events entailed in successful embryo implantation and maintenance of a pregnancy, as well as on the pathophysiological mechanisms involved on recurrent implantation failure (RIF) and recurrent miscarriage (RM), respectively.

Testing and Treatment – Still Up for Debate

Testing for NK cell levels or activity is controversial. Blood tests are more common, but they don't always reflect what's going on in the uterus. Biopsies of the uterine lining can give more accurate information but aren't routinely done.

Treatments aimed at calming down NK cells—such as steroids, IVIG, or intralipids—have been tried in some women with RPL. However, the evidence is mixed, and many specialists don't recommend these treatments unless part of a clinical trial.

FINAL THOUGHTS

NK cells clearly have an important role in early pregnancy, especially in helping the placenta develop. When they're not working properly, they might contribute to recurrent miscarriage-but this doesn't happen in all cases. There's still a lot we don't understand, and more research is needed before routine testing or treatment becomes standard.

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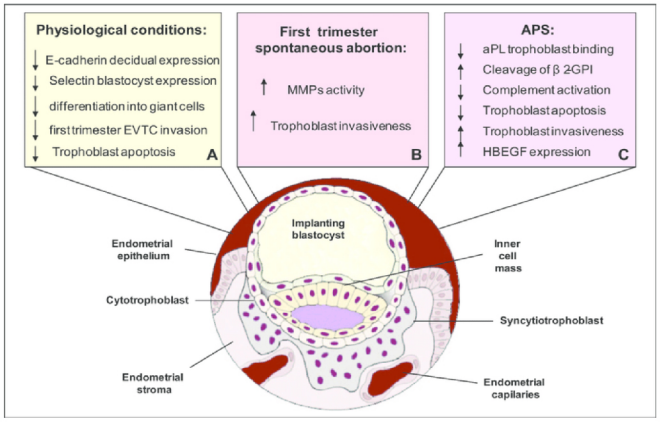
Illustrations depicting mechanisms of therapies

HOW HEPARIN HELPS ?.

This figure summarizes heparin's known effects in both physiological (A) and pathological (B, C) in vitro models of trophoblast invasion. .



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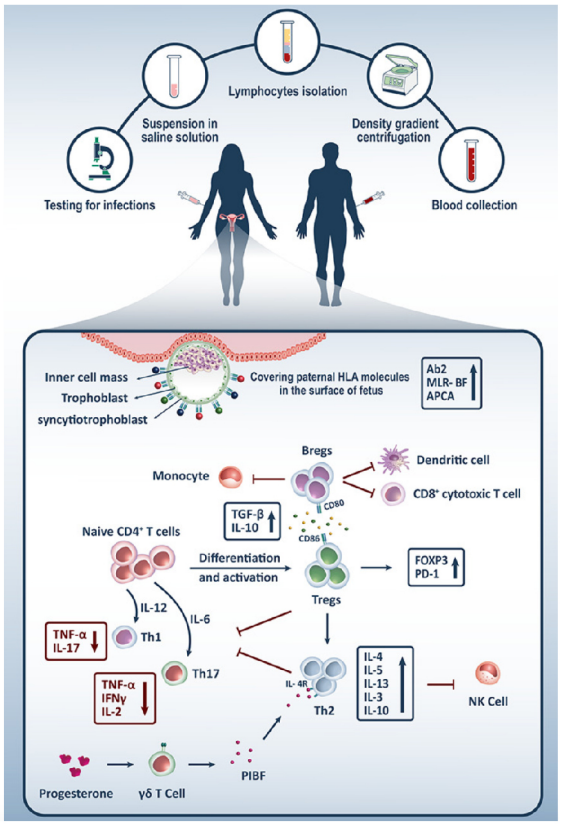

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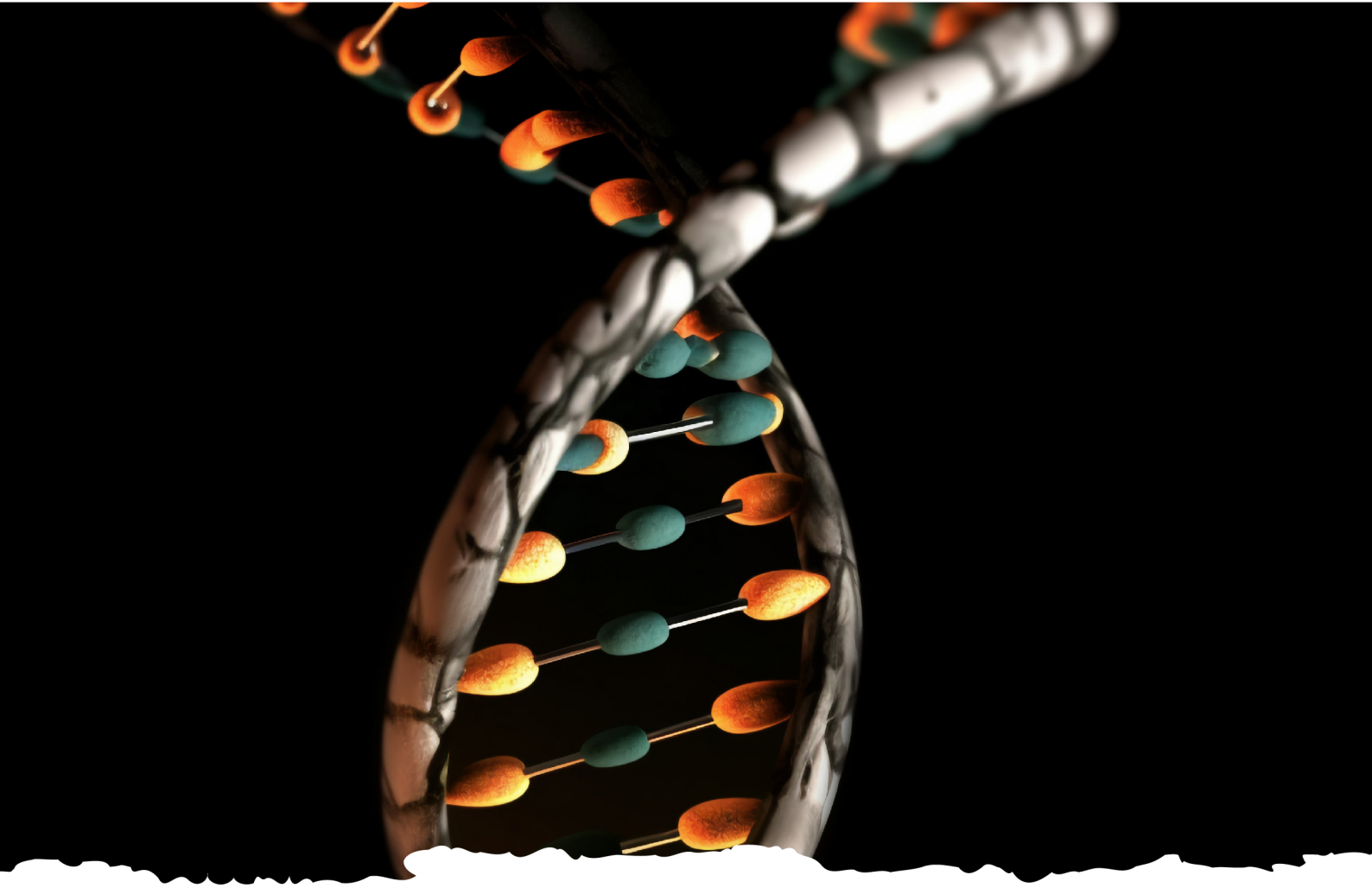

Think Genetics