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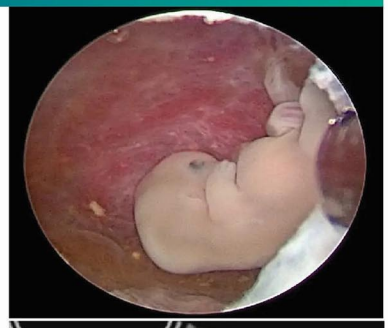
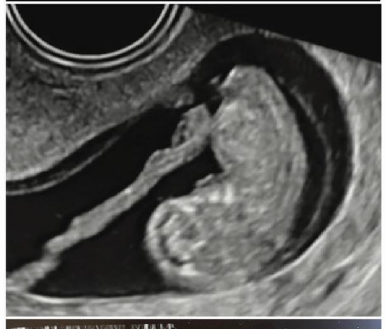
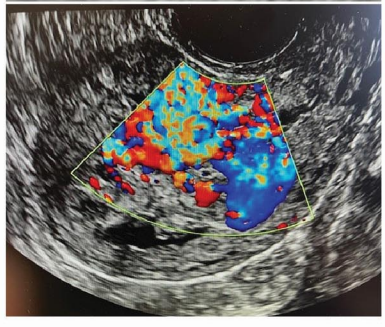
Recurrent Pregnancy Loss







4th Edition

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CHAPTER 5

Epigenetic Factors

Mayumi Sugiura-Ogasawara, Yosuke Matsumoto, Yoshihara Hiroyuki, Shinobu Goto, Tamao Kitaori

ABSTRACT

Genetic causes of recurrent pregnancy loss (RPL) are well known, whereas subtle genetic abnormalities have also been identified in euploid embryos of such cases. These abnormalities are imprinting defects like uniparental disomy of certain chromosomes and change in DNA methylation patterns in women with recurrent miscarriage (RM) as compared to controls. This alerts us to the fact that epigenetic factors may be playing a role in RPL when the karyotype of the miscarried embryo is euploid.

Keywords: Recurrent pregnancy loss, Recurrent miscarriage, Uniparental disomy, DNA methylation, Imprinting defects.

INTRODUCTION

Recurrent pregnancy loss (RPL) is defined as two or more pregnancy losses (death of the fetus) at any gestational age.[1-3] Recurrent miscarriage (RM) is defined as three or more consecutive clinical miscarriages occurring before 20 weeks post menstruation (before 22 weeks in Japan).[1] The Lancet series reported estimated frequencies of RM and RPL of 0.7 and 2.6%, respectively.[1] However, these frequencies depend on the age of the women, and in the Japanese population, this was found to be 1.1 and 5.0%, respectively.[4]

We describe in this chapter novel findings of epigenetic causes of miscarriage in euploid embryos. However, its association with RPL is still under researched. Meanwhile the reader needs to be reminded about the routine work-up recommended by guidelines. A Lancet review and ESHRE RPL guidelines recommend testing for antiphospholipid syndrome (APS), uterine anomalies and parental and embryonic abnormal karyotypes in clinical practice **(Table 1)**.[2,5] The Lancet review recommends evidence-based tests that provide results with prognostic value or with which treatment based on the results improves outcomes. Investigations of RM include testing for lupus anticoagulant, anticardiolipin antibodies, thyroid function, and performing a transvaginal pelvic ultrasound scan. Chromosome analysis of pregnancy tissue could also have explanatory value and selected couples can benefit from parental karyotyping. Newer genetic causes are being unfolded by research in this population. Single gene defects, single nucleotide polymorphism (SNP), uniparental disomy (UPD), chromosomal imprinting and now epigenetic factors may also play a role in recurrent

TABLE 1: Assessment of recurrent pregnancy loss.

Causes	*Recommended tests*	*Treatment*	*Controversy*
Antiphospholipid antibodies	• Lupus anticoagulant • Anticardiolipin antibodies	Aspirin and heparin	• Non-criteria obstetric APS • Refractory APS 20–30% • Occasional APLs
Congenital uterine abnormality	Ultrasonography	Surgery	• No evidence of improvement of the live birth rate
Parental genetic testing	Chromosome analysis	Genetic counseling PGT-SR	• No evidence of improvement of the live birth rate
Karyotyping of pregnancy tissue	Chromosome analysis	Genetic counseling PGT-A	• No evidence of improvement of the live birth rate
Hypothyroidism	TSH, TPO	Levothyroxine	• Subclinical hypothyroidism

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miscarriage wherein the POC would be reported to have a normal genetic analysis by CGH microarray.

Antiphospholipid syndrome, uterine anomalies, and abnormal chromosomes in either partner are established causes of RPL.[6-8] In our study, only about 30% of cases had an identifiable cause and in the remaining 69%, the causes were unexplained **(Fig. 1A)**.[7] It is well-known that the cause remains unexplained in over a half of the cases.[1] An abnormal embryonic karyotype was found in 41.1% of 482 patients for whom both conventional causes and karyotypes of aborted conceptus could be examined **(Fig. 1B)**.[9] Therefore, the prevalence of truly unexplained cases with a normal embryonic karyotype was only 24.5%. The distribution of causes depends on such characteristics as the women's age or the number of previous miscarriages and these comprise the strongest risk factors.[5] Embryonic aneuploidy is the most common cause of RPL **(Fig. 1B)**. The rate of women with a normal embryonic karyotype was significantly higher in patients with RPL compared to patients with sporadic miscarriage.[10] In our previous study, the miscarriage rate increased and the normal embryonic karyotype rate decreased according to the number of previous miscarriages. The live birth rate of patients with a previous abnormal embryonic karyotype was significantly higher than that of patients with a previous normal embryonic karyotype. The embryonic karyotype can be a good predictor of subsequent success.

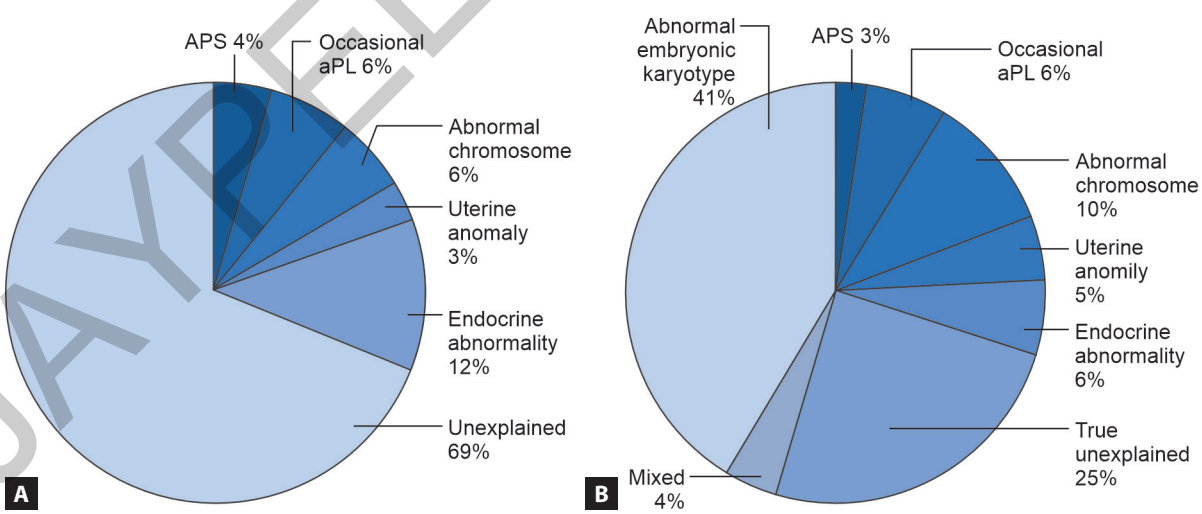
FOCUS ON RECURRENT EUPLOID MISCARRIAGE

Single nucleotide variants (SNVs), copy number variants (CNVs), epigenetics, and mitochondrial deoxyribonucleic acid (DNA) aberrations were reported to be associated with euploid miscarriage.[11,12] Regarding maternal SNPs, susceptibility genes implicated to date include those involved in the immune response, coagulation, metabolism, and angiogenesis.[11] Factor V Leiden and prothrombin mutations have been most frequently examined. Recently, Laisk et al. carried out a European ancestry genome-wide meta-analysis of RPL with each case defined as having a history of three or more consecutive miscarriages (n_{case} = 750), and they reported three significant genome-wide loci.[13] No clear association was ascertained between RPL and variants reported as significant in the systematic review.

As for genetic embryonic factors, putatively causative variants were found in a range of genes, including *CHRNA1* (cholinergic receptor nicotinic alpha polypeptide 1), *DYNC2H1* (dynein cytoplasmic 2 heavy chain 1), and *RYR1* (ryanodine receptor 1) by whole-exome sequencing or CNV studies.[12]

WHAT IS EPIGENETICS?

Epigenetics is defined as the study of heritable and stable changes in gene expression that occur through alterations



Figs. 1A and B: Comparison of the distribution of causes in 482 patients with RM, including those with an abnormal embryonic karyotype, and the 1,676 subjects of our previous study. (A) The 1,676 patients of our previous study; (B) The 482 patients with RM, including those with an abnormal embryonic karyotype.

Sources: 1. Sugiura-Ogasawara et al., Fertil Steril. 2010.[7]
2. Sugiura-Ogasawara et al., Hum Reprod. 2012.[9]

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in the chromosome rather than in the DNA sequence.[14] Despite not directly altering the DNA sequence, epigenetic mechanisms can regulate gene expression through chemical modifications of DNA bases and changes to the chromosomal superstructure in which the DNA is packaged. Epigenetic features include:

- Deoxyribonucleic acid methylation
- Histone changes
- Imprinting
- Non-coding RNA sequences

Deoxyribonucleic acid methylation is a covalent modification of the nucleotide cytosine, which is heritable during cell division and is generally associated with gene silencing when methylation occurs in CpG islands of promoter sequences in which a cytosine precedes a guanosine in the 5′ to 3′ sequence.[15] DNA methylation is the best understood epigenetic modification and the clearest example of epigenetic information. This information can be copied by the enzyme DNA methyltransferase 1 (DNMT) which recognizes hemi-methylated CpG sites on newly replicated DNA and methylates the daughter-strand cytosine at the complementary CpG. Furthermore, the information can be erased, either passively during cell division or by means of an enzymatic process involving ten-eleven translocation (TET) methyl-cytosine dioxygenases, followed by glycosylation and replacement with an unmethylated cytosine.

After fertilization, cellular DNA undergoes extensive demethylation, and the level of DNA methylation is at its lowest.[16] Subsequently, the DNA undergoes cytokine-specific DNA methylation, and each cell expresses a characteristic gene that causes it to differentiate into various other cells to form tissues. DNMT knockout mice do not survive birth or die shortly thereafter, indicating that DNMT plays an important role in embryonic development.

Genome imprinting is a phenomenon in which one of the paternal or maternal genes is selectively expressed. A gene expressed from only one allele is called an imprinting gene, and it is speculated that there are 100–150 genes of this type. Imprinting genes play an important role in ontogeny, differentiation, placentation, and metabolism. Abnormal expression of imprint genes causes various diseases. Imprint gene expression is controlled within the imprinting control region (ICR), which can have a different states of DNA methylation depending on whether the father or the mother is the origin. In the IGF2/H19 (11p15.5) region, ICR1 is not methylated in the maternal allele, so the enhancer does not act, IGF2 is suppressed, and H19 is expressed. In the paternal allele, ICR1 is methylated, so IGF2 is expressed and H19 is suppressed. Epigenetic dysregulation of this region causes Beckwith–Wiedemann syndrome and Silver–Russell syndrome.[17,18]

Uniparental disomy is when the embryo expresses both chromosomes from a single parent. The classic example is hydatidiform mole where there are two sets of paternal genomes while the maternal genome is dropped. There are two types of UPD:

- *Isodisomy*—where both chromosomes from a single parent are identical copies. Its origins are often traced to a monosomic fetus that is rescued by duplication of the single parental chromosome.
- *Heterodisomy*—the two chromosomes from a single parent are non-identical. This is believed to occur in a trisomic embryo which is rescued by say the parental chromosome is dropped.

A known example is Prader–Willi and Angelman syndrome where chromosome 15 is affected.

Similarly, recessive genes may find expression in the embryo in a heterozygous couple due to uniparental disomy and be a cause of miscarriage.

Non-coding RNA sequences: These sequences may be responsible for gene expression and repressor genes thereby altering gene expression and vital protein synthesis.

EMBRYONIC EPIGENETIC FACTORS IN RECURRENT PREGNANCY LOSS

Embryonic epigenetic factors have been a focus in examining the causes of unexplained RPL. Uniparental disomies (UPDs) cause abnormal expression of imprinting genes. UPDs of various chromosomes have been detected by DNA polymorphic analysis and other methods in human individuals with chromosomal abnormalities, imprinting disturbances, and non-Mendelian inheritance of recessive genes. Maternal (mat) UPDs of chromosomes 1, 2, 4, 6, 7, 9, 10, 13–16, 21, 22, and X, and paternal (pat) UPDs of chromosomes 1, 5–8, 11, 13–16, 20–22, and X have been reported.[19] Patients with UPDs of chromosomes 1, 13, 21, and 22, which are not associated with anomalous transmission of recessive genes, had almost no clinical features. In contrast, abnormal clinical features were distinctly seen in patients with both paternal and maternal UPDs of chromosomes 14 and 15, patients with paternal UPDs of 6 and 11, and patients with mat UPDs of 2, 7, and 16. In particular, serious clinical features have been described in some cases of maternal UPD 2, paternal

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UPD 14 and maternal UPD 16. Furthermore, no UPDs of chromosomes 3, 12, and 17–19 have been found in any case to date. These findings suggest that some UPD cases may also exhibit serious abnormalities before birth, including during the periods of embryogenesis and early fetal development.

We found the involvement of maternal UPD 16 and paternal UPD 14 in euploid RM.[20,21] The polymorphic patterns of microsatellites on each chromosome were analyzed in 25 of 52 POC with a euploid karyotype **(Fig. 2A)**.[20] The patterns of the microsatellites of chromosome 16 both appeared to be of maternal origin. The results also showed that the region from the distal end of the short arm to near the middle point of the long arm of chromosome 16 (pter to D16S3107) were heterozygous, and those of the remaining region of the long arm (D16S3018 to qter) were homozygous. That is, this fetus had maternal isodisomy and heterodisomy of chromosome 16, originating from a maternal, meiosis I non-disjunction of dyad 16 that accompanied a crossover at near the middle point of the long arm.

The polymorphic patterns of microsatellites on each chromosome were analyzed in 81 of 164 POC with a euploid karyotype.[21] In one of the two cases, the polymorphic patterns of chromosome 14 both appeared to be of paternal origin **(Fig. 2B)**. The patterns of the distal end of the long arm were homozygous, and those of the remaining region were heterozygous. That is, this fetus had paternal UPD 14, originating from a meiosis I nondisjunction. In the other case, the polymorphic patterns of the distal one third of the long arm of chromosome 7 were uniparental (maternal) in origin whereas those of the remaining region of this chromosome were biparental **(Fig. 2C)**. These findings thus suggested that this chromosome might have originated from a chromatid exchange between the long arms of paternal and maternal chromosome 7 at the first mitotic division. These findings suggest the possibility that some UPDs may cause euploid miscarriage. *However, the frequency of UPDs is speculated to be low in patients with RPL.*

Most complete hydatidiform moles are embryos with two paternal-derived genomes. These cystic malformations do not have a fetal component and are characterized by hydropic villous stroma and hyperplasia of chorionic villi. A *KHDC3L* mutation in components of the subcortical maternal complex of the oocyte was found in a patient with recurrent hydatidiform moles and there was found to be a genome-wide DNA methylation loss in oocytes and persistent imprinting defects after fertilization.[22]

Deoxyribonucleic acid methylation in gene regulatory regions, such as in enhancers and promoters, is closely associated with gene expression, including that of lineage-specific genes.[23,24] Dynamic epigenetic reprogramming ensures the correct development of an embryo during early embryogenesis.[25,26] Recent studies documented altered DNA methylation in certain sets of genes, such as imprinting loci, in the chorionic villi of RM, or sporadic miscarriage after *in vitro* fertilization.[27-29] In addition, a genome-wide DNA methylation analysis in decidua revealed that hypomethylation of CAMP Responsive Element Binding Protein 5 (*CREB5*) appeared to be a risk factor for RPL by causing dysfunction of trophoblast cells.[30] These studies indicate that aberrant epigenetic regulation of maternal decidua and fetal villi tissue is involved in early embryogenesis. However, information on aberrant DNA methylation in association with RM is still limited. In addition, decidua and villi have different DNA methylation profiles.[31]

We investigated genome-wide DNA methylation profiles in both chorionic villi and decidual tissues from POC of patients with euploid RM compared with the same tissues from control women who underwent artificial abortions (AAs) in the same gestational week ($n = 5$ each) group.[32] We found that 13,426 and 5,816 CpG sites were differentially methylated in chorionic villi and decidua, respectively. DNA methylation profiles of chorionic villi, but not decidua, in RM patients were clearly distinct from those of the AA controls **(Figs. 3A and B)**. Among the differentially methylated genes, the enhancer region of *SPATS2L* was significantly more methylated in RM patients ($n = 19$) than in AA controls ($n = 19$; mean methylation level, 52.0% vs. 28.9%, $p < 0.001$), resulting in reduced expression of SPATS2L protein in the patients. Functionally, depletion of *SPATS2L* in extra-villous trophoblast cells reduced their invasion and migration abilities. There was a clear positive correlation between DNA methylation levels in *SPATS2L* and gestational weeks in both RM and AA groups ($R^2 = 0.217$ and $R^2 = 0.485$ in RM and AA, respectively) **(Fig. 3C)**. Our data indicate that in particular, the chorionic villi of RM patients exhibit distinct DNA methylation profiles compared with normal pregnancies and that this changed DNA methylation status may impede the progression of embryo development via the altered expression of such genes as *SPATS2L* in the villi. However, all patients had live births even though the mean number of previous miscarriages was 4.7 (range 3–7, not shown). Patients with methylation abnormalities in the villi might

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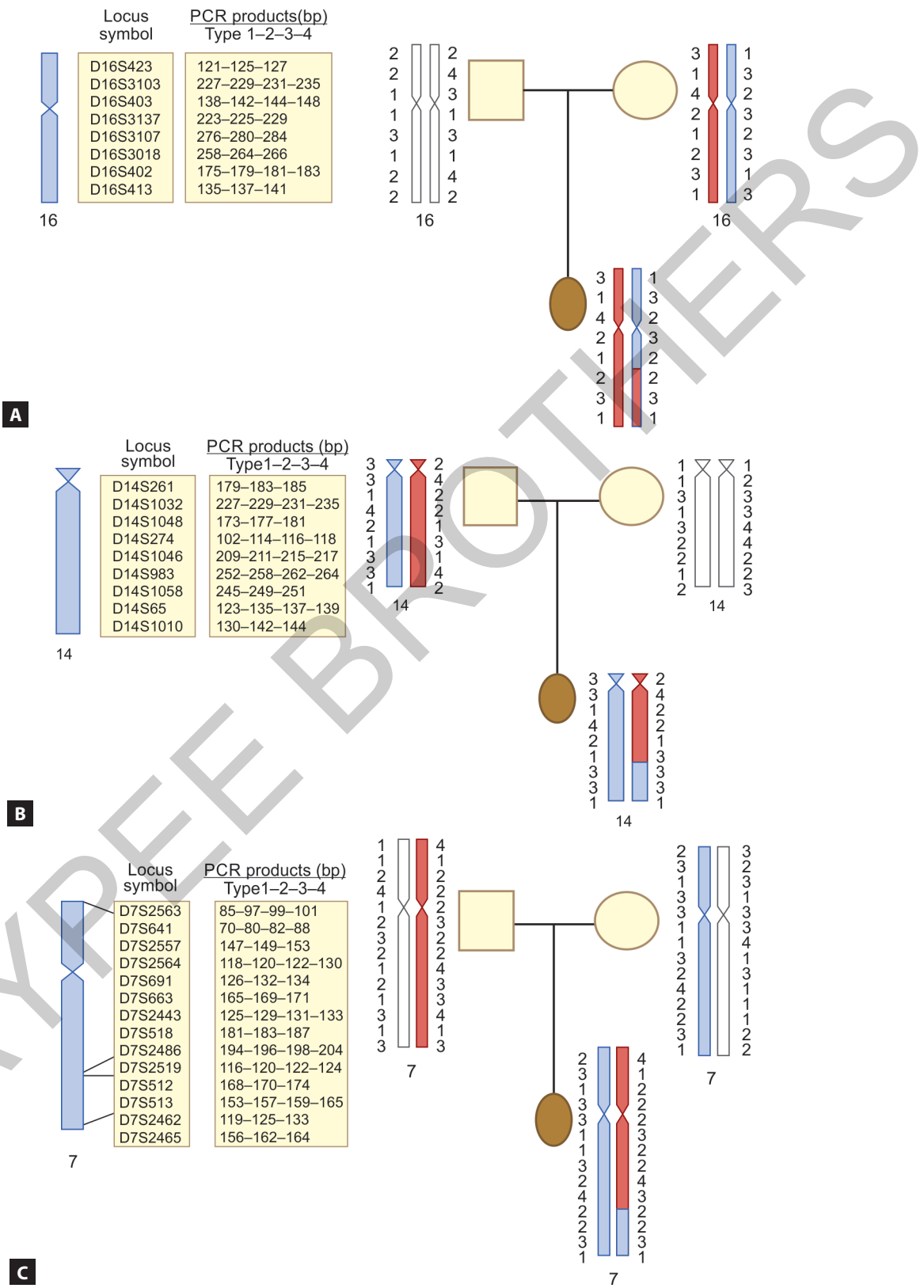

Figs. 2A to C: Uniparental disomy.

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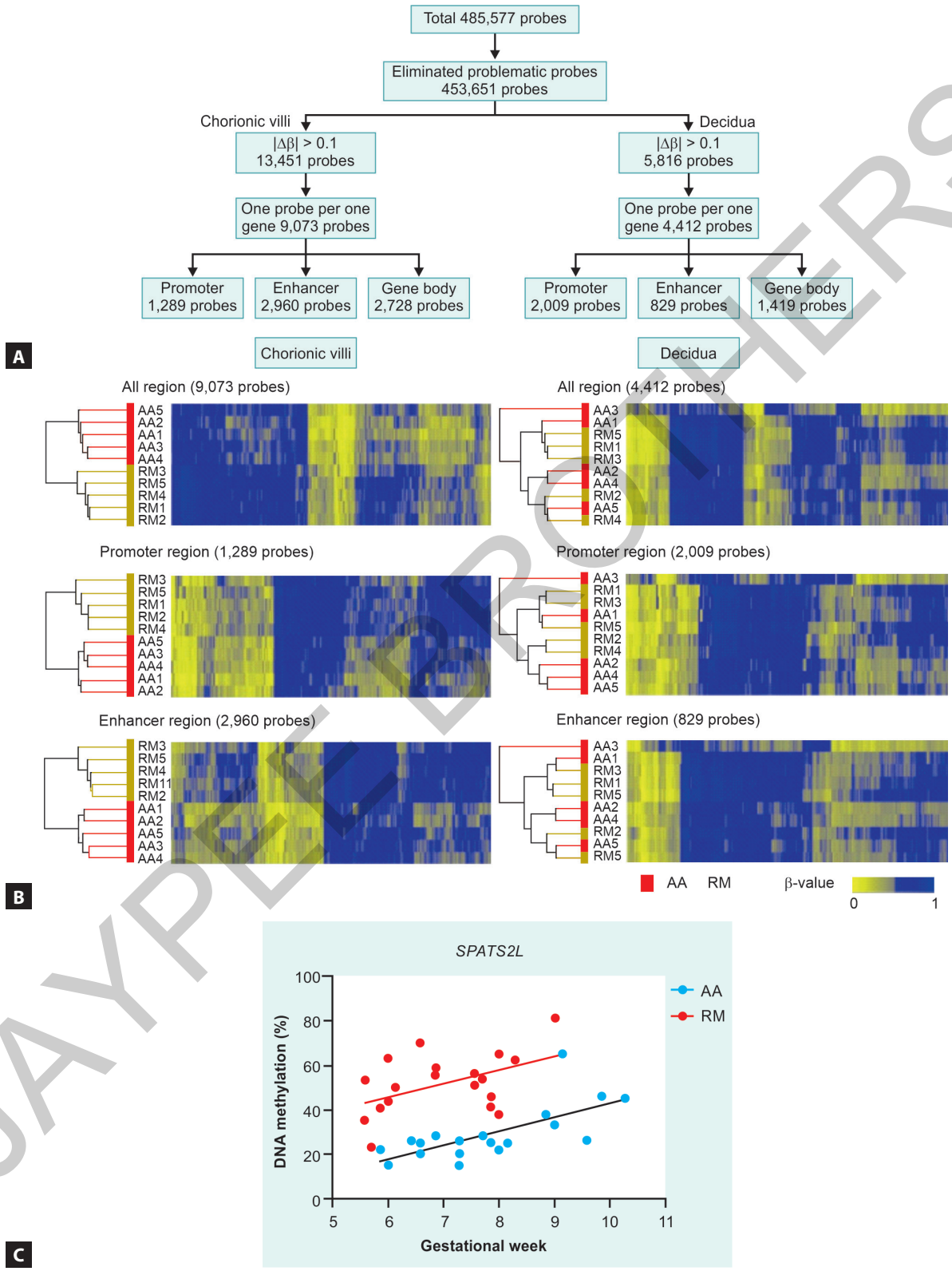

Figs. 3A to C: DNA methylation profile of chorionic villi of control AA and RM. (AA:artificial abortion; DNA: deoxyribonucleic acid; RM: recurrent miscarriage)

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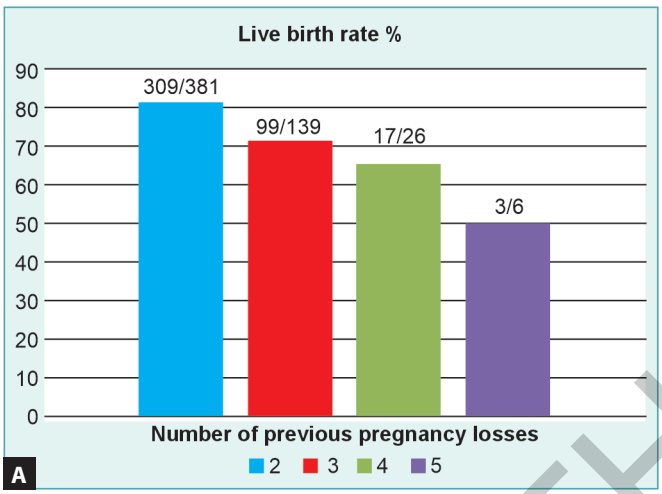

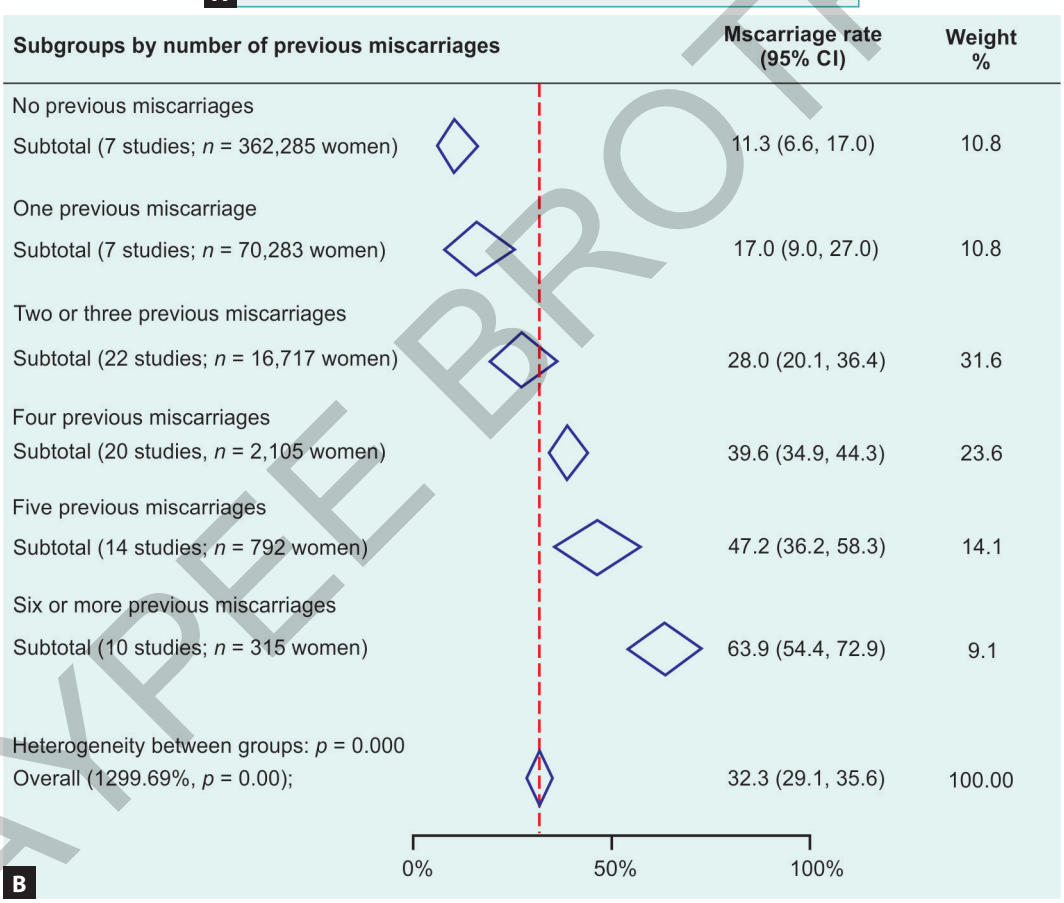

Figs. 4A and B: Live birth rate according to the number of previous pregnancy losses.
Sources: 1. Katano et al., Fertil Steril. 2013.[33]
2. Coomarasamy et al., 2021.[5]

have a favorable prognosis, as might patients with embryo aneuploidy.[10]

The rates of subsequent live birth rates in patients with an unexplained cause, including patients with an abnormal embryonic karyotype, who had previously had two, three, four, and five miscarriages were about 80%, 70%, 60%, and 50% with no medication, respectively **(Figs. 4A and B)**.[33,34] For such patients, the cumulative

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live birth rate was 85%, which should provide some encouragement for individuals undergoing genetic counseling.[7]

CONCLUSION

Genetic aberrations identified in miscarried euploid embryos can be single gene defects, uniparental disomy or improper DNA methylation. These epigenetic factors may be responsible for unexplained RPL. Although, these factors are currently studied in research setting only, it will open up a new avenue of investigation in unexplained RPL.

DISCLOSURE

None of the authors have any conflicts of interest to report.

REFERENCES

1. Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet. 2021;397(10285):1658-67.
2. ESHRE Guideline Group on RPL; Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, et al. ESHRE guideline: recurrent pregnancy loss: an update in 2022. Hum Reprod Open. 2023;2023(1):hoad002.
3. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril. 2013;99:63.
4. Sugiura-Ogasawara M, Ebara T, Yamada Y, Shoji N, Matsuki T, Kano H, et al. Adverse pregnancy and perinatal outcome in patients with recurrent pregnancy loss: Multiple imputation analyses with propensity score adjustment applied to a large-scale birth cohort of the Japan Environment and Children's Study. Am J Reprod Immunol. 2019;81(1):e13072.
5. Coomarasamy A, Dhillon-Smith RK, Papadopoulou A, Al-Memar M, Brewin J, Abrahams VM, et al. Recurrent miscarriage: evidence to accelerate action. Lancet. 2021;397(10285):1675-82.
6. Farquharson RG, Pearson JF, John L. Lupus anticoagulant and pregnancy management. Lancet. 1984;28:228-9.
7. Sugiura-Ogasawara M, Ozaki Y, Kitaori T, Kumagai K, Suzuki S. Midline uterine defect size correlated with miscarriage of euploid embryos in recurrent cases. Fertil Steril. 2010;93:1983-8.
8. Sugiura-Ogasawara M, Ozaki Y, Sato T, Suzumori N, Suzumori K. Poor prognosis of recurrent aborters with either maternal or paternal reciprocal translocation. Fertil Steril. 2004;81:367-73.
9. Sugiura-Ogasawara M, Ozaki Y, Katano K, Suzumori N, Kitaori T, Mizutani E. Abnormal embryonic karyotype is the most frequent cause of recurrent miscarriage. Hum Reprod. 2012;27:2297-2303.
10. Ogasawara M, Aoki K, Okada S, Suzumori K. Embryonic karyotype of abortuses in relation to the number of previous miscarriages. Fertil Steril. 2000;73:300-4.
11. Kaur M, Kaur R, Chhabra K, Khetarpal P. Maternal candidate gene variants, epigenetic factors, and susceptibility to idiopathic recurrent pregnancy loss: A systematic review. Int J Gynaecol Obstet. 2023;162(3):829-41.
12. Colley E, Hamilton S, Smith P, Morgan NV, Coomarasamy A, Allen S. Potential genetic causes of miscarriage in euploid pregnancies: a systematic review. Hum Reprod Update. 2019;25(4):452-72.
13. Laisk T, Soares ALG, Ferreira T, Painter JN, Censin JC, Laber S, et al. The genetic architecture of sporadic and multiple consecutive miscarriage. Nat Commun. 2020;11:5980.
14. Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A. An operational definition of epigenetics. Genes Dev. 2009;23(7):781-3.
15. Feinberg AP. The Key Role of Epigenetics in Human Disease Prevention and Mitigation. N Engl J Med. 2018;378(14):1323-34.
16. Shinjo K, Kondo Y. Epigenetics. J Japan Med Assoc. 2023;152:50-55.
17. Brown KW, Villar AJ, Bickmore W, Clayton-Smith J, Catchpoole D, Maher ER, et al. Imprinting mutation in the Beckwith-Wiedemann syndrome leads to biallelic IGF2 expression through an H19-independent pathway. Hum Mol Genet. 1996;5(12):2027-32.
18. Gicquel C, Rossignol S, Cabrol S, Houang M, Steunou V, Barbu V, et al. Epimutation of the telomeric imprinting center region on chromosome 11p15 in Silver-Russell syndrome. Nat Genet. 2005;37(9):1003-7.
19. Engel E. Uniparental disomies in unselected populations. Am J Hum Genet. 1998;63:962-6.
20. Kondo Y, Tsukishiro S, Tanemura M, Sugiura-Ogasawara M, Suzumori K, Sonta SI. Maternal uniparental disomy of chromosome 16 in a case of spontaneous abortion. J Hum Genet. 2004;49(4):177-81.
21. Tsukishiro S, Li QY, Tanemura M, Sugiura-Ogasawara M, Suzumori K, Sonta SI. Paternal uniparental disomy of chromosome 14 and unique exchange of chromosome 7 in cases of spontaneous abortion. J Hum Genet. 2005;4:112-7.
22. Demond H, Anvar Z, Jahromi BN, Sparago A, Verma A, Davari M, et al. A KHDC3L mutation resulting in recurrent hydatidiform mole causes genome-wide DNA methylation loss in oocytes and persistent imprinting defects post-fertilisation. Genome Med. 2019;11(1):84.

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23. Kim K, Doi A, Wen B, Ng K, Zhao R, Cahan P, et al. Epigenetic memory in induced pluripotent stem cells. Nature. 2010;467:285-90.
24. Roadmap Epigenomics Concorsium. Integrative analysis of 111 reference human epigenomes. Nature. 2015;518:317-30.
25. Guo H, Zhu P, Yan L, Li R, Hu B, Lian Y, et al. The DNA methylation landscape of human early embryos. Nature. 2014;511:606-10.
26. Smith ZD, Chan MM, Humm KC, Karnik R, Mekhoubad S, Regev A, et al. DNA methylation dynamics of the human preimplantation embryo. Nature. 2014;511:611-5.
27. Hanna CW, McFadden DE, Robinson WP. DNA methylation profiling of placental villi from karyotypically normal miscarriage and recurrent miscarriage. Am J Pathol. 2013;182:2276-84.
28. Zheng HY, Tang Y, Niu J, Li P, Ye DS, Chen X, et al. Aberrant DNA methylation of imprinted loci in human spontaneous abortions after assisted reproduction techniques and natural conception. Hum Reprod. 2013;28:265-73.
29. Liu Y, Tang Y, Ye D, Ma W, Feng S, Li X, et al. Impact of Abnormal DNA Methylation of Imprinted Loci on Human Spontaneous Abortion. Reprod Sci. 2018;25:131-9.
30. Yu M, Du G, Xu Q, Huang Z, Huang X, Qin Y, et al. Integrated analysis of DNA methylome and transcriptome identified CREB5 as a novel risk gene contributing to recurrent pregnancy loss. E Bio Med. 2018;35:334-44.
31. Robinson WP, Price EM. The human placental methylome. Cold Spring Harb Perspect Med. 2015;5:a023044.
32. Matsumoto Y, Shinjo K, Mase S, Fukuyo M, Aoki K, Ozawa F, et al. Characteristic DNA methylation profiles of chorionic villi in recurrent miscarriage. Sci Rep. 2022;12(1):11673.
33. Katano K, Suzuki S, Ozaki Y, Suzumori N, Kitaori T, Sugiura-Ogasawara M. Peripheral natural killer cell activity as a predictor of recurrent pregnancy loss: a large cohort study. Fertil Steril. 2013;100(6):1629-34.
34. Devall AJ, Coomarasamy A. Sporadic pregnancy loss and recurrent miscarriage. Best Pract Res Clin Obstet Gynaecol. 2020;69:30-9.

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