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Genetic causes of sporadic and recurrent miscarriage

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Approximately 80% of miscarriages happen within the first 12 weeks of gestation. More than half of early losses result from genetic defects, usually presenting as abnormal chromosome numbers or gene rearrangements in the embryo. However, the impact of genetics on pregnancy loss goes well beyond embryonic aneuploidy. For example, the use of big data has recently led to the discovery of specific gene mutations that may be implicated in sporadic and recurrent miscarriages. Further, emerging data suggest that genetic factors play a role in conditions for which there is a causative association with recurrent pregnancy loss. Here, we summarize the evidence on the genetics of miscarriage and provide an overview of the diagnosis and prevention of genetic causes associated with sporadic and recurrent pregnancy loss. (*Fertil Steril*® 2023;120:940–4. ©2023 by American Society for Reproductive Medicine.)

Key Words: Genetic testing, genetics, miscarriage, pregnancy loss

GENETICS: A PRIMARY CONTRIBUTOR TO MISCARRIAGE

Chromosomal abnormalities are diagnosed in over 50% of first-trimester miscarriages, becoming less prevalent in second- and third-trimester losses. On karyotyping, most chromosomal abnormalities are numerical (termed aneuploidy, usually because of chromosomal nondisjunction during meiosis), including autosomal trisomies (30%–60%), triploidy (11%–13%), monosomy X (10%–15%), and tetraploidy (9%), whereas only a minority result from structural chromosome rearrangements (2%–6%) and mosaicism (8%) (1–5).

Most chromosome anomalies in sporadic miscarriages appear to arise *de novo*. During gametogenesis, abnormalities may occur because of nondisjunction, translocations, deletions, duplications, or insertions of a

chromosomal segment. These lead to numerical or structural chromosomal imbalances in either the oocyte or sperm, resulting in chromosomally abnormal embryos that are more likely to miscarry. It is important to note, however, that a plethora of embryonic chromosomal imbalances remain compatible with life, including some aneuploidies (e.g., trisomy 21 and monosomy X) and structural translocations (e.g., balanced translocations) (6).

In addition to chromosome abnormalities, defects in individual or multiple genes involved in meiosis regulation, DNA repair, and cell proliferation may impair gamete as well as embryonic development. Such changes may result directly from the expression of abnormal genes, rendering the fetus nonviable, or stem from epigenetic modifications that alter the regulatory mechanisms involved in gene expression. Furthermore, there is

evidence suggesting that imprinting disorders arising during gametogenesis may be associated with miscarriage (7).

A systematic review of 19 studies investigating cytogenetic findings of pregnancy tissue after miscarriage identified that the pooled prevalence of fetal chromosomal anomalies in women with recurrent pregnancy loss (39%, 95% CI 29%–50%, 6 studies) was comparable to that found in sporadic miscarriages (45%, 95% CI 38%–52%, 13 studies) (5). This suggests that as the number of successive pregnancy losses increases, factors other than embryonic genetic anomalies must be at play in recurrent miscarriage by rendering the endometrium inhospitable (8). These nonembryonic factors include uterine malformations, endocrine disorders, and heightened localized or systemic immunity secondary to inflammation or infection (9, 10). However, in 2%–5% of cases of recurrent miscarriage, there are underlying parental chromosomal rearrangements increasing the risk of further pregnancy loss (11–13).

Although chromosomal imbalances are a well-documented cause of miscarriage, there is a paucity of data on specific parental and fetal gene

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mutations that may increase the risk of pregnancy loss. In 2017, a systematic review of 428 case-control studies identified an association between unexplained recurrent miscarriage and 21 variants in parental genes involved in immune response, coagulation, metabolism, and angiogenesis, although the evidence was mostly of low certainty (14). More recently, however, large datasets of pregnant women have allowed for the identification of one locus on chromosome 13 associated with sporadic miscarriage (rs146350366) and 3 loci for recurrent pregnancy loss on chromosomes 9 (rs7859844), 11 (rs143445068), and 21 (rs183453668) (15).

The Impact of Parental Age on Genetic Anomalies

Female age is by far the strongest risk factor for miscarriage, with the probability of pregnancy loss being highest at the extremes of women's reproductive lives (i.e., <20 years and ≥40 years) (16, 17). Although it is thought that the increased risk of miscarriage in teenage pregnancies may be associated with a plethora of contributing factors, including substance abuse (18), because female age advances beyond 40 years, the frequency of genetic abnormalities in the oocyte and embryo rapidly becomes the leading cause of pregnancy loss, resulting in an exponential rise in sporadic and recurrent miscarriage rates (16, 19).

The effect of paternal age on the risk of miscarriage appears to increase with time, and male partners aged ≥40 years exhibit on average 69% higher odds of miscarriage compared with those aged 20–29 years (odds ratio 1.69, 95% CI 1.18–2.43) (17). This results partly from an overall decline in reproductive function, including lower testicular activity and altered reproductive hormone secretion as men age. However, male age also has a crucial effect on sperm chromosome number and structure (20, 21), DNA integrity (22, 23), gene mutation rates (24), and epigenetic defects (21). Although the mechanisms underlying these associations remain incompletely elucidated, data suggest a putative role for increased reactive oxygen species compounded by impaired antioxidant and DNA repair mechanisms as age advances (23, 25).

GENETIC LINKS TO ESTABLISHED CAUSES OF RECURRENT MISCARRIAGE

There is a strong association between recurrent pregnancy loss and underlying maternal conditions thought to render the decidua inhospitable to the implanting embryo. Such hostility to the blastocyst may result from local anomalies in the endometrial immune-endocrine environment or from a generalized state of heightened systemic immunity. Examples of chronic disorders associated with recurrent miscarriage include inherited and acquired thrombophilia, subclinical hypothyroidism, thyroid autoimmunity, polycystic ovary syndrome (PCOS), and prolactin disorders (13). This section examines the genetic mechanisms underpinning the etiology of these conditions in the context of miscarriage.

Inherited Thrombophilia

Inherited thrombophilia includes Factor V Leiden mutations, protein C and S deficiencies, antithrombin deficiency, and prothrombin gene mutations, all of which exhibit an autosomal dominant inheritance pattern (26, 27). Collectively, this group of conditions affects approximately 5% of the general population (26). Although the mechanisms through which inherited thrombophilia may increase the risk of miscarriage remain understudied, it is thought that an underlying hypercoagulable state exerts a prothrombotic effect on the placental microvasculature, leading to placental failure (28). However, the evidence of this association is stronger for second-trimester losses than for those occurring before 12 weeks of gestation (13, 28). In addition, heparin treatment has not been shown to decrease the risk of miscarriage in women with inherited thrombophilia (28).

Acquired Thrombophilia

Antiphospholipid syndrome (APS), an acquired thrombophilia marked by the presence of autoimmune antiphospholipid antibodies, has no recognized pattern of inheritance. Yet, despite not being directly passed on from parents to their progeny, there is evidence to suggest a genetic predisposition for APS. This includes, for example, the existence of familial clusters of APS cases, affected monozygotic twins, and an increased prevalence of antiphospholipid antibodies in family members of people with APS (29). Associations between specific genes and recurrent miscarriage in the context of APS remain elusive, however, and difficult to tease out in diseases of multifactorial etiology. Yet, recent data suggest a causative role for the human leukocyte antigen system, located on the short arm of chromosome 6, as well as genes involved in hemostasis, the immune response, apoptosis, and thyroid function (29–32).

Thyroid Dysfunction And Autoimmunity

Subclinical hypothyroidism and the presence of thyroid autoantibodies have well-established associations with recurrent pregnancy loss (13, 33). However, there is an overall lack of data on the genetic mechanisms predisposing women to thyroid dysfunction concurrently with recurrent miscarriage. Recent evidence suggests that women with moderately high thyroid-stimulating hormone levels (>2.5 mIU/L) combined with low plasma mannose-binding lectin levels and HLA-DRB1*03 positivity may be associated with increased odds of positivity for at least one thyroid autoantibody and spontaneous miscarriage, but such an association has not been identified in recurrent pregnancy loss (34).

Polycystic Ovary Syndrome

A recent systematic review showed a 59% average increase in the odds of miscarriage in women with PCOS compared with women without PCOS (odds ratio 1.59, 95% CI 1.11–2.28) (35). The etiology of PCOS is thought to be multifactorial and closely associated with that of obesity,

hyperandrogenism, hyperinsulinemia, and endometrial cancer (36). Data suggest genetic predispositions to PCOS that are highly heritable, but there is a paucity of research on specific genes involved in the etiology of miscarriage in the context of PCOS (37, 38). Importantly, miscarried fetuses of women with PCOS appear to exhibit a higher rate of chromosomal anomalies compared with non-PCOS controls (61.3% vs. 52.7%, respectively), although the mechanisms underlying this association remain unclear (39).

Prolactin Disorders

Abnormal serum prolactin levels have been implicated in recurrent miscarriage (13). Although there is a growing body of evidence investigating the genetics of prolactin disorders (40), we did not find studies focusing specifically on the genetics of miscarriage in the context of hyperprolactinemia.

DIAGNOSING GENETIC CAUSES OF MISCARRIAGE

Genetic tests enable the identification of chromosomal and subchromosomal genetic anomalies responsible for pregnancy loss. Historically, karyotyping has been the most commonly used genetic test for the identification of chromosomal imbalances resulting in miscarriage. It involves obtaining parental blood or pregnancy tissue, culturing cells, and analyzing their chromosomes in the metaphase stage of mitosis. In the context of recurrent miscarriage, karyotyping of pregnancy tissue yields inconclusive results in up to 20%–40% of cases because of the absence of fetal tissue or contamination with maternal cells. In addition, karyotyping for cytogenetic testing of pregnancy tissue after the loss of euploid female fetuses can lead to false-negative results in up to 22%–33% of samples (4, 13, 41).

Chromosomal microarray analysis (CMA) diagnoses submicroscopic genetic abnormalities that remain undetected using karyotyping. It can be performed using array comparative genomic hybridization or single nucleotide polymorphism genotyping. Compared with karyotyping, CMA offers improved resolution, detecting molecular gains or losses of DNA down to 10 kilobases within the genome. It is also less likely to yield inconclusive or false-negative results. In a systematic review of 9 studies comparing conventional karyotyping and CMA, the investigators identified a 13% increase in the detection rate of chromosome abnormalities using CMA (42). These reasons have led the European Society of Human Reproduction and Embryology to recommend array comparative genomic hybridization as the preferred method for cytogenetic testing of fetal tissue (12).

In recent years, cytogenetic testing has evolved to include next-generation sequencing, whole genome screening, and whole exome screening, featuring enhanced resolution to identify single nucleotides in small amounts of tissue using high-throughput assays. This yields large volumes of data that are often difficult to interpret. Such tests are also

expensive, and their applicability to cytogenetics of miscarriage has not been fully elucidated (12).

Fetal Genetic Testing

Cytogenetic analysis of fetal tissue should be offered to individuals sustaining their third and subsequent miscarriages. This often yields a merely explanatory result that warrants no further action when the risk of recurrence in future pregnancies is low (e.g., trisomy). Where unbalanced translocations are identified on fetal cytogenetics, however, parental karyotyping should be undertaken to rule out balanced chromosome rearrangements, which increase the risk of further losses (13).

Parental Genetic Testing

Parental chromosome rearrangements are involved in approximately 2%–5% of recurrent miscarriage cases, of which most are balanced translocations (12, 13). The cost-effectiveness of parental karyotyping in the absence of fetal cytogenetics is unclear because the odds of having a subsequent healthy child without assisted conception remain favorable (43). However, where fetal cytogenetic testing renders inconclusive results or is impossible because of a lack of suitable tissue, guidance recommends parental karyotyping. In addition, couples found to have a genetic abnormality should be referred for genetic counseling for discussion of the risks of future pregnancy and management options, including preimplantation genetic testing (PGT), prenatal testing (e.g., amniocentesis, chorionic villi sampling, and noninvasive testing), gamete donation, adoption, fostering, or remaining childless (12, 13).

CAN WE ELIMINATE GENETIC FACTORS IN MISCARRIAGE?

There is no known intervention to prevent embryonic genetic defects. In the context of medically assisted reproduction, however, it is possible to perform PGT before deciding which embryos to transfer. This usually involves a biopsy of cells taken at the blastocyst stage in the laboratory, followed by embryo cryopreservation while awaiting PGT results. In the context of unexplained recurrent pregnancy loss, the evidence suggests that performing PGT for aneuploidies does not accrue any clinical improvement in live birth and is not cost effective (44). In addition, studies report a rate of embryo mosaicism ranging between 4% and 90%, raising uncertainties about discarding possibly normal embryos (19).

Preimplantation genetic testing for monogenic disorders (PGT-M) or PGT for chromosomal structural rearrangements (PGT-SR) is an option for couples with genetic defects linked to an increase in the risk of miscarriage. The use of PGT-M virtually eliminates the chance of having children affected by the condition for which the embryos are tested. For PGT-SR rearrangements, questions of cost-effectiveness remain unanswered, although the evidence suggests a reduction in miscarriage rates (12). In England, the National Health Service funds up to 3 cycles of in vitro fertilization with PGT-M and PGT-SR in couples carrying genetic abnormalities,

provided the female partner's age is lower than 40 years, even in the absence of an absolute cause of infertility. Those with previously affected children remain eligible for state-funded treatment (45).

THE FUTURE OF MISCARRIAGE GENETICS

The past 3 decades have witnessed rapid improvements in the diagnosis and prevention of genetic defects causing miscarriage. Current technology for genetic testing of embryos relies largely on invasive procedures. Recent evidence has identified embryonic DNA in the culture media of blastocysts, leading to rising interest in noninvasive PGT techniques. These require validation in future trials, but it is possible that by eliminating the need for embryo biopsy, noninvasive PGT may in time prove a cheaper and safer alternative (46).

In addition to molecular-based techniques, artificial intelligence models on the basis of large morphokinetic datasets have been tested to determine their accuracy in the prediction of embryo ploidy status and miscarriage risk. However, there is heterogeneity between artificial intelligence models owing to the use of a variety of databases and annotation systems between clinics. This makes external validation studies difficult to perform, and to date, noninvasive ploidy prediction models remain experimental, with results requiring confirmation by invasive techniques in clinical practice (47).

In the future, it is likely that gene-disease association studies will continue to unveil causal pathways through which genetic defects may contribute to disease phenotypes in which miscarriage is included, in isolation or alongside other manifestations (e.g., preeclampsia and thrombotic disease) (48). Furthermore, as the impact of different genetic variants becomes clearer, it may be possible to use polygenic risk scores to screen for individuals' risk of sustaining miscarriage, whether sporadic or recurrent, although the use of such tools remains controversial (49).

Although to date there has been no such thing as a "miscarriage gene," the discovery of causal associations between genetic aberrations and pregnancy loss may ultimately allow for the correction of these anomalies through gene therapy, although presently such aspirations remain merely speculative.

BALANCING HOPE AND ETHICAL CONSIDERATIONS IN GENETIC TESTING FOR MISCARRIAGE PREVENTION

The use of genetic testing in reproductive medicine raises important ethical considerations. In a time of ever-growing reproductive inequalities, access to healthcare remains uneven across the world and often within nations. Few countries offer state-funded PGT-M and PGT-SR, and where this is available, stringent eligibility criteria exist (45). Unequal access to medically assisted procreation to prevent miscarriage for preventable genetic conditions may further exacerbate social and reproductive inequalities (17).

In addition, the line between embryo selection to prevent aneuploidy and using genetic testing to select the "best"

possible child may be difficult to navigate, often bringing into conflict the principles of autonomy, beneficence, and nonmaleficence. This is apparent in cases where genetic conditions affect male and female children differently (e.g., Lynch syndrome). When, after PGT-M, all embryos test positive for the condition, parents may be tempted to request sex selection of the available embryos on the basis of their perception of how severe the phenotype may be in each sex. Although some defend that the precedence in such cases should be given to the principle of procreative beneficence, whereby parents could select an embryo that will give them the best chance of having a child who is expected to have the least probability of complications, the assembly of ethics committees by regulatory bodies is often necessary to guide clinical decision-making in these complex cases (49, 50).

CONCLUSION

Miscarriage is caused most commonly by genetic abnormalities. In recent decades, the scientific knowledge of the genetic pathways underpinning pregnancy loss has increased, as has our ability to diagnose and prevent genetically linked miscarriages. Yet, there remains an urgent need for additional research into gene-disease associations, which may pave the way for targeted interventions in the future.

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REFERENCES

- Muñoz M, Arigita M, Bannasar M, Soler A, Sanchez A, Borrell A. Chromosomal anomaly spectrum in early pregnancy loss in relation to presence or absence of an embryonic pole. *Fertil Steril* 2010;94:2564–8.
- Soler A, Morales C, Mademont-Soler I, Margarit E, Borrell A, Borobio V, et al. Overview of chromosome abnormalities in first trimester miscarriages: a series of 1,011 consecutive chorionic villi sample karyotypes. *Cytogenet Genome Res* 2017;152:81–9.
- Eiben B, Bartels I, Bähr-Porsch S, Borgmann S, Gatz G, Gellert G, et al. Cytogenetic analysis of 750 spontaneous abortions with the direct-preparation method of chorionic villi and its implications for studying genetic causes of pregnancy wastage. *Am J Hum Genet* 1990;47:656–63.
- Lomax B, Tang S, Separovic E, Phillips D, Hillard E, Thomson T, et al. Comparative genomic hybridization in combination with flow cytometry improves results of cytogenetic analysis of spontaneous abortions. *Am J Hum Genet* 2000;66:1516–21.
- van den Berg MMJ, van Maarle MC, van Wely M, Goddijn M. Genetics of early miscarriage. *Biochim Biophys Acta* 2012;1822:1951–9.
- Hassold T, Hunt P. To err (meiotically) is human: the genesis of human aneuploidy. *Nat Rev Genet* 2001;2:280–91.
- Tomizawa SI, Sasaki H. Genomic imprinting and its relevance to congenital disease, infertility, molar pregnancy and induced pluripotent stem cell. *J Hum Genet* 2012;57:84–91.
- 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.
- Turocy JM, Rackow BW. Uterine factor in recurrent pregnancy loss. *Semin Perinatol* 2019;43:74–9.

10. Vomstein K, Feil K, Strobel L, Aulitzky A, Hofer-Tollinger S, Kuon RJ, et al. Immunological risk factors in recurrent pregnancy loss: guidelines versus current state of the art. *J Clin Med* 2021;10:869.
11. De Braekeleer M, Dao TN. Cytogenetic studies in couples experiencing repeated pregnancy losses. *Hum Reprod* 1990;5:519–28.
12. ESHRE Guideline Group on RPL, Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, et al. [ESHRE guideline] ESHRE guideline: recurrent pregnancy loss: an update in 2022. *Hum Reprod Open* 2023;2023:hoad002.
13. Regan L, Rai R, Saravelos S, Li TC, Royal College of Obstetricians and Gynaecologists. Recurrent Miscarriage - Green-top Guideline No. 17. *BJOG*; 2023.
14. Perez N, Ostojić S, Kapović M, Peterlin B. Systematic review and meta-analysis of genetic association studies in idiopathic recurrent spontaneous abortion. *Fertil Steril* 2017;107:150–9.e2.
15. 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.
16. Magnus MC, Wilcox AJ, Morken NH, Weinberg CR, Häberg SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. *BMJ* 2019;364:l869.
17. Quenby S, Gallos ID, Dhillion-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;397:1658–67.
18. Tung I, Beardslee J, Pardini D, Chung T, Keenan K, Hipwell AE. Adolescent childbirth, miscarriage, and abortion: associations with changes in alcohol, marijuana, and cigarette use. *J Child Psychol Psychiatry* 2020;61:104–11.
19. Brosens JJ, Bennett PR, Abrahams VM, Ramhorst R, Coomarasamy A, Quenby S, et al. Maternal selection of human embryos in early gestation: insights from recurrent miscarriage. *Semin Cell Dev Biol* 2022;131:14–24.
20. Sartorelli EMP, Mazzucatto LF, de Pina-Neto JM. Effect of paternal age on human sperm chromosomes. *Fertil Steril* 2001;76:1119–23.
21. Kaltsas A, Moustakli E, Zikopoulos A, Georgiou I, Dimitriadis F, Symeonidis EN, et al. Impact of advanced paternal age on fertility and risks of genetic disorders in offspring. *Genes* 2023;14:486.
22. Alshahrani S, Agarwal A, Assidi M, Abuzenadah AM, Durairajanayagam D, Ayaz A, et al. Infertile men older than 40 years are at higher risk of sperm DNA damage. *Reprod Biol Endocrinol* 2014;12:103.
23. du Fossé NA, van der Hoorn MP, van Lith JMM, le Cessie S, Lashley ELO. Advanced paternal age is associated with an increased risk of spontaneous miscarriage: a systematic review and meta-analysis. *Hum Reprod Update* 2020;26:650–69.
24. Ma RH, Zhang ZG, Zhang YT, Jian SY, Li BY. Detection of aberrant DNA methylation patterns in sperm of male recurrent spontaneous abortion patients. *Zygote* 2023;31:163–72.
25. Johnson SL, Dunleavy J, Gemmill NJ, Nakagawa S. Consistent age-dependent declines in human semen quality: a systematic review and meta-analysis. *Ageing Res Rev* 2015;19:22–33.
26. Liu X, Chen Y, Ye C, Xing D, Wu R, Li F, et al. Hereditary thrombophilia and recurrent pregnancy loss: a systematic review and meta-analysis. *Hum Reprod* 2021;36:1213–29.
27. Khan S, Dickerman JD. Hereditary thrombophilia. *Thromb J* 2006;4:15.
28. Quenby S, Booth K, Hiller L, Coomarasamy A, de Jong PG, Hamulák EN, et al. Heparin for women with recurrent miscarriage and inherited thrombophilia (ALIFE2): an international open-label, randomised controlled trial. *Lancet* 2023;402:54–61.
29. Barinotti A, Radin M, Cecchi I, Foddai SG, Rubini E, Roccatello D, et al. Genetic factors in antiphospholipid syndrome: preliminary experience with whole exome sequencing. *Int J Mol Sci* 2020;21:9551.
30. Sugiura-Ogasawara M, Omae Y, Kawashima M, Toyo-Oka L, Khor SS, Sawai H, et al. The first genome-wide association study identifying new susceptibility loci for obstetric antiphospholipid syndrome. *J Hum Genet* 2017;62:831–8.
31. Sipak O, Rył A, Grzywacz A, Laszczyńska M, Szymański S, Karakiewicz B, et al. Molecular analysis of HLA-G in women with high-risk pregnancy and their partners with regard to possible complications. *Int J Environ Res Public Health* 2019;16:982.
32. Królik M, Wrześniak M, Jezela-Stanek A. Possible effect of the HLA-DQ2/DQ8 polymorphism on autoimmune parameters and lymphocyte subpopulation in recurrent pregnancy losses. *J Reprod Immunol* 2022;149:103467.
33. Rao M, Zeng Z, Zhou F, Wang H, Liu J, Wang R, et al. Effect of levothyroxine supplementation on pregnancy loss and preterm birth in women with sub-clinical hypothyroidism and thyroid autoimmunity: a systematic review and meta-analysis. *Hum Reprod Update* 2019;25:344–61.
34. Yang Y, Li J, Zhou Y, Dai W, Teng W, Shan Z. TSH/miR-17-5p/ZNF367 axis is related to spontaneous abortion in patients with TSH above 2.5 mIU/L. *J Mol Endocrinol* 2021;67:121–34.
35. Bahri Khomami M, Joham AE, Boyle JA, Piltonen T, Silagy M, Arora C, et al. Increased maternal pregnancy complications in polycystic ovary syndrome appear to be independent of obesity-A systematic review, meta-analysis, and meta-regression. *Obes Rev* 2019;20:659–74.
36. Joham AE, Norman RJ, Stener-Victorin E, Legro RS, Franks S, Moran LJ, et al. Polycystic ovary syndrome. *Lancet Diabetes Endocrinol* 2022;10:668–80.
37. Gorsic LK, Dapas M, Legro RS, Hayes MG, Urbanek M. Functional genetic variation in the anti-Müllerian hormone pathway in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2019;104:2855–74.
38. Brower MA, Hai Y, Jones MR, Guo X, Chen YI, Rotter JJ, et al. Bidirectional Mendelian randomization to explore the causal relationships between body mass index and polycystic ovary syndrome. *Hum Reprod* 2019;34:127–36.
39. Li Y, Wang L, Xu J, Niu W, Shi H, Hu L, et al. Higher chromosomal aberration rate in miscarried conceptus from polycystic ovary syndrome women undergoing assisted reproductive treatment. *Fertil Steril* 2019;111:936–43.e2.
40. Chang S, Copperman AB. New insights into human prolactin pathophysiology: genomics and beyond. *Curr Opin Obstet Gynecol* 2019;31:207–11.
41. Bell KA, Van Deerlin PG, Haddad BR, Feinberg RF. Cytogenetic diagnosis of “normal 46,XX” karyotypes in spontaneous abortions frequently may be misleading. *Fertil Steril* 1999;71:334–41.
42. Dhillion RK, Hillman SC, Morris RK, McMullan D, Williams D, Coomarasamy A, et al. Additional information from chromosomal microarray analysis (CMA) over conventional karyotyping when diagnosing chromosomal abnormalities in miscarriage: a systematic review and meta-analysis. *BJOG* 2014;121:11–21.
43. Barber JC, Cockwell AE, Grant E, Williams S, Dunn R, Ogilvie CM. Is karyotyping couples experiencing recurrent miscarriage worth the cost? *BJOG* 2010;117:885–8.
44. Murugappan G, Ohno MS, Lathi RB. Cost-effectiveness analysis of preimplantation genetic screening and in vitro fertilization versus expectant management in patients with unexplained recurrent pregnancy loss. *Fertil Steril* 2015;103:1215–20.
45. Kay AC, Wells J, Hallowell N, Goriely A. Providing recurrence risk counselling for parents after diagnosis of a serious genetic condition caused by an apparently de novo mutation in their child: a qualitative investigation of the PRE-GCARE strategy with UK clinical genetics practitioners. *J Med Genet* 2023;60:925–31.
46. Leaver M, Wells D. Non-invasive preimplantation genetic testing (niPGT): the next revolution in reproductive genetics? *Hum Reprod Update* 2020;26:16–42.
47. Bamford T, Barrie A, Montgomery S, Dhillion-Smith R, Campbell A, Easter C, et al. Morphological and morphokinetic associations with aneuploidy: a systematic review and meta-analysis. *Hum Reprod Update* 2022;28:656–86.
48. Bortoletto P, Lucas ES, Melo P, Gallos ID, Devall AJ, Bourne T, et al. Miscarriage syndrome: linking early pregnancy loss to obstetric and age-related disorders. *EBiomedicine* 2022;81:104134.
49. Polyakov A, Amor DJ, Savulescu J, Gyngell C, Georgiou EX, Ross V, et al. Polygenic risk score for embryo selection-not ready for prime time. *Hum Reprod* 2022;37:2229–36.
50. Savulescu J. Procreative beneficence: why we should select the best children. *Bioethics* 2001;15:413–26.