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ORIGINAL ARTICLE

Global Trends in Prenatal Mosaicism Research: Insights from a Bibliometric Analysis (1980–2023)

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Abstract

Background: The coexistence of at least two cell lines with different genetic structures (chromosomal or single gene mutation) originating from the same zygote in an organism is defined as mosaicism. This study aimed to present a medical perspective by examining scientific articles published on diagnosis of prenatal mosaicism from a perinatal and genetic perspective with statistical methods.

Methods: The source of our study is the Web of Science (WoS) database. The articles indexed between 1980-2023 were included in our research in the database, and the studies of 2024 were not included since the effect factors are not clear yet. While searching the database, the words "Prenatal Mosaicism" were used as keywords

Results: We reached a total of 2124 publications by analyzing the WoS database using the term "prenatal mosaicism". When the citations of the documents written about prenatal mosaicism are evaluated, we found that the highest citation was made in 2022. Co-citation analysis has shown that there are 9932 authors investigating the issue of prenatal mosaicism. Collaboration and citation collaboration was observed between Mackay Memorial Hospital, National Taiwan University and National Yang Ming University. Prenatal screening and Aneuploidy were found the strongest relationship with prenatal mosaicism.

Conclusions: It is observed that the publications related prenatal mosaicism are associated with prenatal diagnosis and screening and this diagnosis has the highest publication, citation and impact power.

Key words: Prenatal Diagnosis, Mosaicism, Genetics, Bibliometry

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INTRODUCTION

Prenatal diagnostic methods describe tests developed with the aim of detecting chromosomal structural and numerical anomalies and ensuring healthy offspring. These tests have methodological, reproducibility, consistency, sensitivity and specificity differences among themselves. The differences in methods and the accuracy of their application methods affect genetic counseling and perinatal management. The reliability of the ideal diagnostic test should be high. The selection of the test should be determined by considering the fetal week, the competence of the center performing the test and the family's preference.

Fetuses requiring prenatal diagnosis are determined by family history, obstetric history, genetic history, various biochemical and sonographic tests. Chorionic villus sampling, amniocentesis, fetal skin biopsies and cordocentesis are used for diagnosis. None of these tests can diagnose all fetal anomalies, which test to be selected should be determined specifically for the pregnancy. Patients should be informed in a way that they understand the limitations of genetic tests, that possible genetic results cannot be recognized in some cases, and that genetic disorders can cause very different clinical and phenotypic results. The diagnosis of mosaicism, which is a prenatal genetic diagnosis, explaining it to the family and predicting its clinical results may involve various difficulties.

Basically, chromosomal anomalies can be examined in two groups as structural and numerical. The most frequently observed chromosomal numerical anomalies are aneuploidies that contain extra or missing chromosomes. Sometimes, extra chromosome sets that are multiples of 23 chromosomes can be encountered (triploidy, tetraploidy, etc.). In an organism, the coexistence of at least two cell lines with different genetic structures (chromosomal or single gene mutation) originating from the same zygote is defined as mosaicism. Abnormalities in the number of chromosomes can be mosaic, which means that the abnormal number of chromosomes is not present in all cell lines. Mosaicism occurs with at least one mitotic error. A mosaic individual can be formed when a genetic anomaly occurs with a new mutation in the mitotic divisions of a zygote with a normal genetic structure and these cells continue to divide, or mosaicism can occur with a second mutation during the mitotic divisions of an anomalous gamete that was formed with a meiotic error (1).

In CVS (Chorion villus sampling) and amniocentesis, which are frequently used in prenatal diagnosis, classical karyotyping methods are routinely applied, and the ability of these methods to recognize aneuploidies is quite strong. Sometimes, if there is no mosaicism in the specific fetal cell line obtained by prenatal testing, mosaicism in the fetus may not be detected by karyotype analysis. Chromosomal mosaicism rates detected by amniocentesis, CVS and cordocentesis may be quite different from each other due to the different areas from which the cell material is obtained. While mosaicism is less common in amniocentesis samples (0.25-0.50%), it is more common in chorionic villus sampling (1-3.2%) (2-5). When preimplantation genetic tests (PGT) performed within the indication in assisted reproductive treatments are also evaluated as diagnostic tests, the incidence of chromosomal aneuploidies increases. In series where PGT results are screened retrospectively, chromosomal mosaicism is encountered at quite high and variable rates (29.1-50%). (6,7).

As can be seen, the incidence of chromosomal mosaicism varies according to many clinical and laboratory factors such as the type of test, the cell series taken, and the age of the pregnant woman. Factors that make mosaicism diagnosis difficult also reduce the chance of predicting prenatal results. Categorization is possible according to the reasons for false positive or negative results in prenatal diagnoses of mosaic individuals and the diagnostic laboratory methods. It can be thought that the diagnosis of mosaicism will increase with the development of the frequency and reliability of the prenatal tests used, and academic progress will be made in this direction.

The number of perinatal and genetic studies on mosaicism in prenatal diagnosis is increasing day by day. Studies can be grouped according to the verification of diagnoses, the variety and reliability of the methods used to establish the diagnosis. The aim of this study is to conduct a holistic bibliometric analysis of academic articles examining prenatal mosaicism and to present a comprehensive data with existing publications.

MATERIALS AND METHODS

The source of our study is the Web of Science (WoS) database and includes the Korean journal database, core collection index, Russian Science Citation Index and Sci ELO (Scientific Electronic Library Online) citation index.

The articles indexed between 1980-2023 were included in our research in the database, and the studies of 2024 were not included since the impact factors are not clear yet. While searching the database, the words "Prenatal Mosaicism" and "Prenatal Mosaicism Diagnosis" were used as keywords. Datawrapper free open web-based application was used to visualize global research productivity. VOS-viewer 2019 program was used to determine the scientific relevance of the data.

RESULTS

General Features and Global Productivity

We reached a total of 2124 publications by analyzing the WoS database using the term "Prenatal Mosaicism" and "Prenatal Mosaicism Diagnosis". In our study, we excluded 71 studies of 2024 from evaluation, since the citations were not yet completed. We have listed the date of the remaining 2124 articles published from the past by 2023, and we saw that the first article was published in 1982. This study presented prenatal cytogenetic analyses in a cross-sectional manner retrospectively in a single center and determined the true mosaicism rates (8). The articles were written in 21 different languages, the most widely used was English, which accounts for about 97.9 % of all articles. Most of the documents (78.1 %) were research articles, followed by reviews and meeting abstracts (Table 1). We analyzed the distribution of the documents written about prenatal mosaicism in the branches of science, we saw that there were studies in 40 different fields in total, we found that the branch of science that carried out the most studies was genetics heredity. The field of genetics and heredity was followed by obstetrics and gynecology, reproductive biology, pediatrics, biochemistry molecular biology and medicine general internal respectively (Table 2). The number of documents written about prenatal mosaicism was increasing every year. Since 1999, a large number of documents have been published every year, and the most productive year was 2022 (Figure 1). 123 articles were published in 2022, although the majority of these publications were research articles. The most cited research article of these years was the "Genome-Wide Fetal Aneuploidy Detection by Maternal Plasma DNA Sequencing" published in the Obstetrics and Gynecology (9).

2124 articles have been published on prenatal mosaicism in the field of genetics and heredity. 701 of these articles were published by the Prenatal Diagnosis, Tawanese Journal of Obstetrics Gynecology and American Journal of Medical Genetics. The most cited year for the articles on prenatal mosaicism published in the Prenatal Diagnosis at 2022. Among the publications on prenatal mosaicism in this journal, the most cited article was " Cytogenetıc Results From The Unıted-States Collaboratıve Study on CVS." (10)

We evaluated the countries in which articles written about prenatal mosaicism were prepared, and found the most productive countries as the United States of America (USA), China and Taiwan. About 26.5 % of all publi-

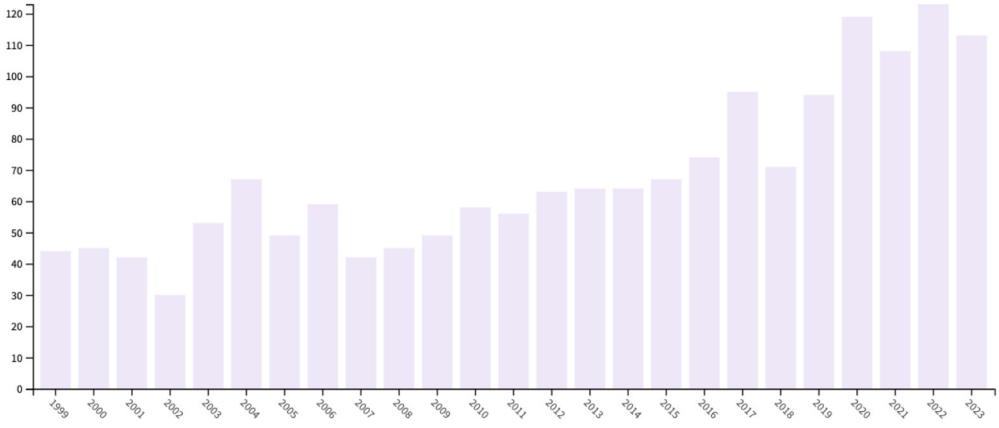

Figure 1: Graph of publications about Prenatal Mosaicism by years.

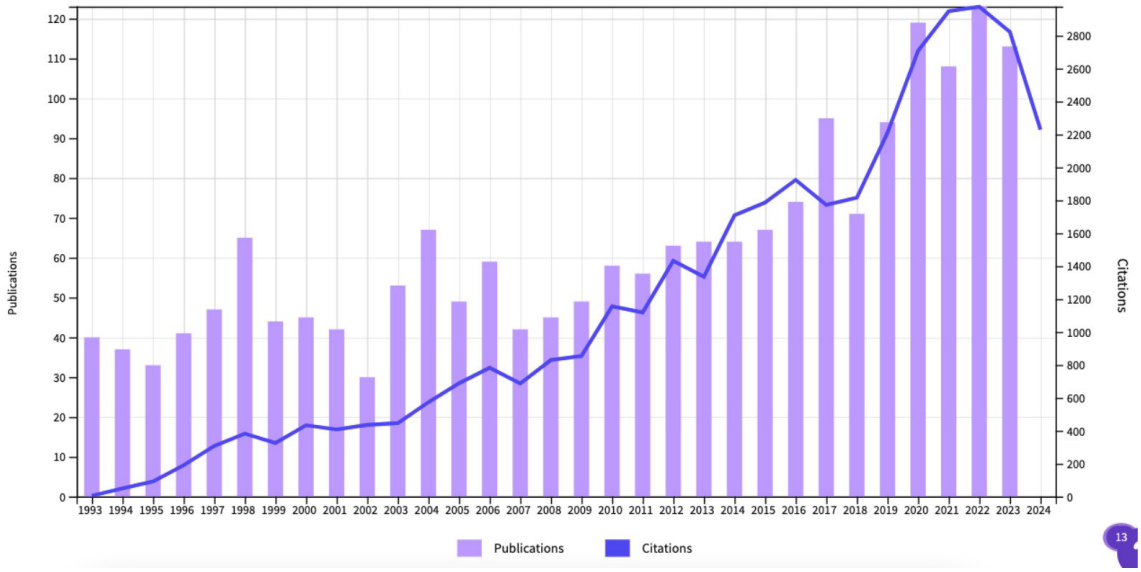

Figure 2: Graph of citations about Prenatal Mosaicism by years.

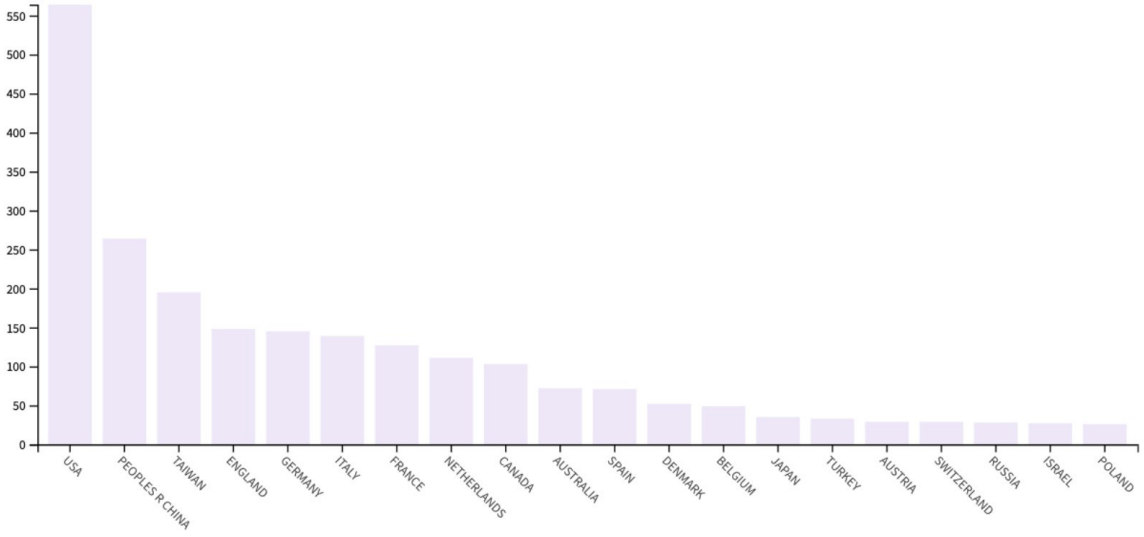

Figure 3: The top ten publishing country bar charts on Prenatal Mosaicism.

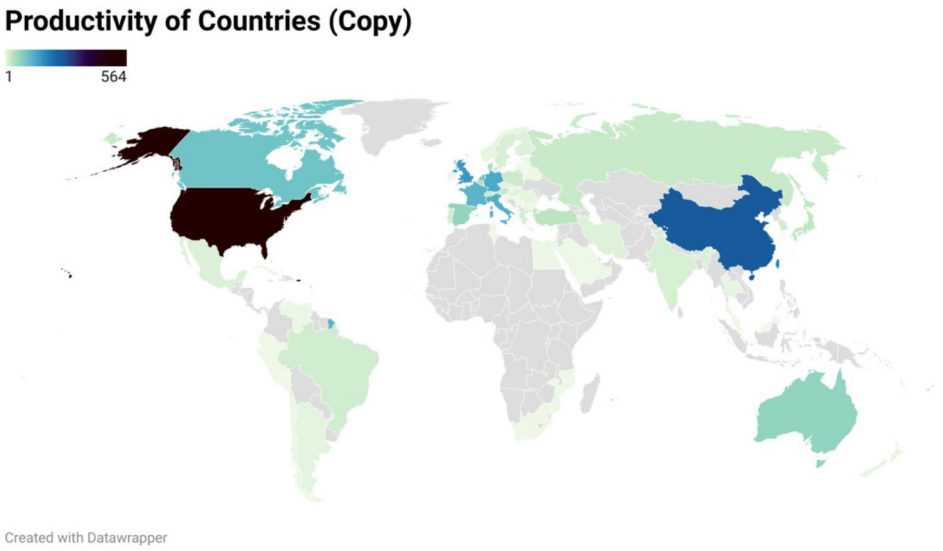

Figure 4: Prenatal Mosaicism publication density according to the countries

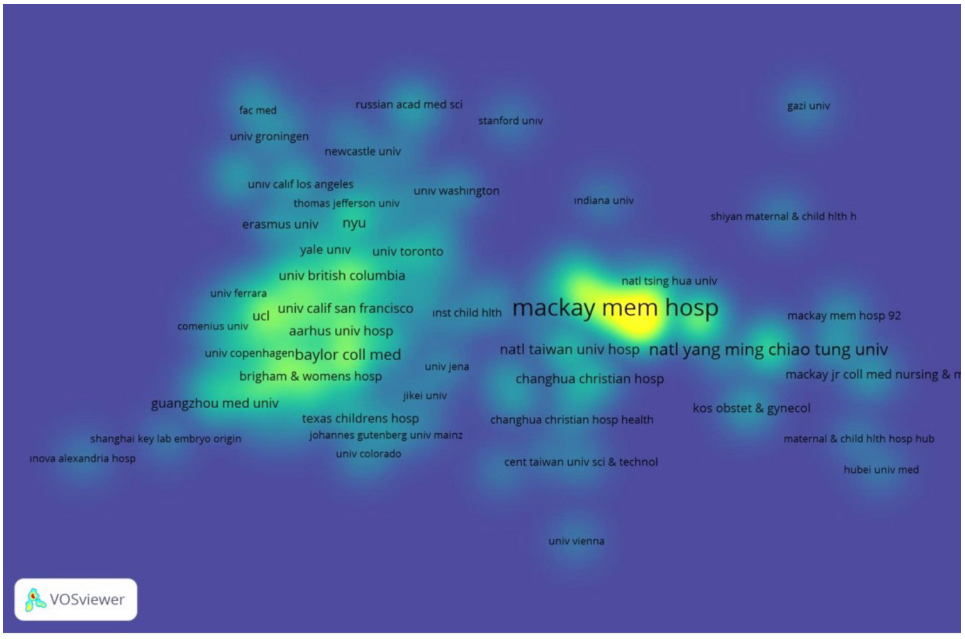

Figure 5: Intensity map of the cooperation analysis of the institutes

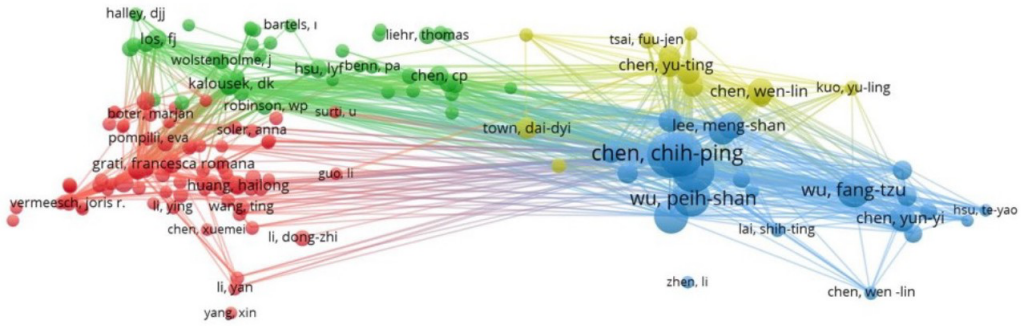

Figure 6: Network visualization map of co-citation analysis of active authors

cations were produced in the USA (Figure 3). We found that the productivity of African countries and Central Asian Countries countries are very low on prenatal mosaicism. The most productive countries were in North America and Europe (Figure 4).

Productivity of Authors and Institutions

We compared authors' productivity, institutions, and H-Index. Chen CP, Ming Chi University Technology, Taiwan was found most productive researcher. The 10 most productive authors and countries are presented in Table 3. We also compared the productivity of universities and organizations in the WoS database. The most productive organisation was the Mackay Memorial Hospital host 165 (7.7%) publications in the field of prenatal mosaicism. (Figure 5).

Authorship and Institutions Co-citation

Co-citation analysis has shown that there are 9932 authors investigating the issue of prenatal mosaicisim. Organizations that published at least 5 documents about prenatal mosaicisim and received 5 citations were classified, 176 out of a total of 2749 organizations were found to meet these requirements. Among these 176 organizations, the most active was determined as Mackay Memorial Hospital, Taiwan. Collaboration and citation collaboration were observed between Mackay Memorial Hospital, National Taiwan University and National Yang Ming University. Organizations belonging to the European Union countries and USA were cooperating among themselves around the USA. (Figure 5).

Authors' collaborations were evaluated, a total of 9932 authors with at least 10 publications on perinatal mosaicism were separated. After this filtering, 44 active authors were identified, and their cooperation was evaluated among themselves. Collaboration clustering around 5 active authors was detected. Of these five writers Chen Chih Ping, Wang Wayseen and Grata Fancesca Romana were the most active and collaborative (Figure 6).

Articles written about prenatal mosaicism were reviewed and the most cited, average number of citations per year, authors and publishers were examined. The document by Bianchi DW M. Genome-Wide Fetal Aneuploidy Detection by Maternal Plasma DNA Sequencing was the first in terms of total number of citations and average number of citations per year (10). The 10 most cited articles are presented in Table 5. The citation relations between the articles were indicative of the tendencies of the publishers and the authors. When the citations of the articles were examined on a yearly basis, it was observed that the most cited articles were written between 2018-2020 (Figure 7).

Productivity of Journals

Journals containing publications on prenatal mosaicism were examined in terms of the number of publications and citations they received. Fifteen journals with the largest number of articles are presented in Table 6 with their publication numbers and impact factors. 864 journals publishing on prenatal mosaicism were examined, the 90 most active journals with at least 10 articles were found. It was observed that the Prenatal Diagnosis printed 19.8 % of the articles published on prenatal mosaicism. The 2023

impact factor of this journal is 2.7, and its effectiveness on genetics and heredity seems to be high (Figure 8).

International Collaboration

When the researches published by countries on prenatal diagnosis were examined, the most active country was determined as the USA. Collaborations of countries on research were also examined. The intersection point of all researcher countries was the USA. China, Taiwan, France and England were the countries that cooperated most with the USA (Figure 9). A collaborative connection was formed around China. In this cluster Australia, Belgium and South Korea were also included. (Figure 9).

Table 1. Publication types of prenatal mosaicism literature between 1982-2023

Research Areas	Number of Publication	% of 2124
Article	1877	78.1
Review	202	8.4
Proceedings Paper	43	1.7
Letter	119	4.9
Editorial Material	47	3.4
Meeting Abstracts	73	3.1
Note	71	0.8
Book Chapter	22	0.5
Early Access	3	0.2
Corrections	5	0.1

Table 2. The top ten research areas of documents in prenatal mosaicism according to Web of Science database between 1982-2023

Research Areas	Number of Publication	% of 2124
Genetics Heredity	1194	56.5
Obstetrics and Gynecology	960	45.1
Reproductive Biology	96	4.5
Pediatrics	92	4.3
Biochemistry Molecular Biology	89	4.1
Medicine General Internal	88	4.1
Medicine Research Experimental	75	3.5
Cell Biology	50	2.1
Radiology Nuclear Medicine	46	1.9
Acoustics	41	1.6

Table 3. The first ten authors by record count in prenatal mosaicism literature between 1982-2023

Authors	Institution	Record Count	% of 2124	H-index
Chen CP	Ming Chi Univ Technol, Dept Mat Engn, New Taipei City 24301, Taiwan	164	7.7	16
Chern SR	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	132	6.2	15
Wang W	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	119	5.6	17
Wu PS	Gene Biodesign Co Ltd, Taipei, Taiwan	88	4.1	10
Chen SW	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	78	3.6	10
Wu FT	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	69	3.2	8
Lee CC	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	58	2.7	13
Chen YY	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	47	2.2	8
Pan CW	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	45	2.1	9
Chen WL	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	44	2.0	11

Mem: Memorial, Hosp: Hospital, Dept: Department, Med: Medicine, Res: Research

Table 4. The top ten funding organisations by number of prenatal mosaicism literature

Institutions	Number of Publication	% of 2124
Mackay Memorial Hospıtal Taipeı Taiwan	119	5.6
Ministry Of Science and Technology Taiwan	86	4.0
Unıted States Department of Health Human Services	81	3.8
National Institutes of Health USA	76	3.5
National Natural Science Foundation Of China	47	2.2
Spanish Government	30	1.4
Eunice Kennedy Shriver National Institute of Child Health and Human Development	29	1.3
National Key Research Devalopment Program of China	25	1.1
National Science and Technology Council Taıwan	24	1.1
The National Institute of General Medical Sciences	11	0.5

USA: United States of America

Trend Topics

While reviewing the articles on prenatal mosaicism, we also identified new trends and topics in this regard. Frequently used keywords in the articles on prenatal mosaicism, the frequency of these words and their interrelationships would provide insight into new research topics. The words genetic counselling, prenatal diagnosis and genetic counselling identified the subjects with the strongest association with prenatal diagnosis. Aneuploidiy, trisomy, non-invasive prenatal testing, placenta, QF-PCR, were found to be the types of clinical and laboratory conditions that had the strongest relationship with prenatal mosaicism. The most frequently repeated clinical analyzes in the articles on prenatal mosaicism were observed as prenatal screening and non-invasive prenatal testing (Figure 10).

Table 5. The top ten most cited manuscripts about prenatal mosaicism

No	Article	Author	Journal Name/ Published	TC	ACY
1	Genome-Wide Fetal Aneuploidy Detection by Maternal Plasma DNA Sequencing	Bianchi DW, Platt LD, Goldberg JD, Abuhamad AZ, Sehnert AJ et al.	Obstet Gynecol, 2012	493	37.9
2	Somatic Mutation, Genomic Variation, and Neurological Disease	Poduri A, Evrony GD, Cai X, Walsh CA.	Science, 2013	410	34.1
3	Fanconi Anemia and Its Diagnosis	Auerbach AD	Mutation Research, 2009	408	25.5
4	Neurofibromatosis Type 2 (NF2): A Clinical and Molecular Review	Evans DG	Orphanet Journal of Rare Diseases, 2009	337	21.6
5	Mechanisms of mosaicism, chimerism and uniparental disomy identified by single nucleotide polymorphism array analysis	Conlin LK, Thiel BD, Bonnemann CG, Medne L, Ernst LM, et al.	Human Molecular Genetics,2010	329	21.9
6	Prenatal testing in ICSI pregnancies: incidence of chromosomal anomalies in 1586 karyotypes and relation to sperm parameters	Bonduelle M, Van Assche E, Joris H, Keymolen K, Devroey P et al.	Human Reproduction, 2002	312	13.5
7	Chromosomal mosaicism confined to the placenta in human conceptions	Kalousek DK, Dill FJ.	Science,1988	307	7.5
8	Cytogenetic results from the U.S. Collaborative Study on CVS	Ledbetter DH, Zachary JM, Simpson JL, Golbus MS, Pergament E et al.	Prenatal Diagnosis, 1992	285	8.6
9	Non-invasive prenatal testing for trisomies 21, 18 and 13: clinical experience from 146,958 pregnancies	Zhang H, Gao Y, Jiang F, Fu M, Yuan Y, et al.	Ultrasound in Obstetrics & Gynecology, 2015	261	26.1
10	Non-invasive prenatal testing for aneuploidy: current status and future prospects.	Benn P, Cuckle H, Pergament E	Ultrasound in Obstetrics & Gynecology, 2015	230	10.55

TC: Total Citation; ACY: Average Citations per Year

Table 6. The first fifteen journal by number of publications and citations on prenatal mosaicism

Journal Name	No	% of 2124	JIF
Prenatal Diagnosis	421	19.8	2.7
Taiwanese Journal of Obstetrics Gynecology	163	7.6	1.9
American Journal of Medical Genetics, Part A	117	5.5	1.7
American Journal of Medical Genetics	87	4.1	3.6
Molecular Cytogenetics	52	2.4	3.5
Journal of Medical Genetics	43	2.0	3.5
Clinical Genetics	41	1.9	2.9
American Journal of Human Genetics	35	1.6	10.5
European Journal of Human Genetics	33	1.5	5.3
Frontıers In Genetıcs	32	1.5	1.1
Fetal Diagnosıs and Therapy	31	1.4	1.6
Ultrasound in Obstetrics Gynecology	29	1.3	6.1
European Journal of Medical Genetics	27	1.2	1.6
Genetics in Medicine	23	1.1	8.8
Cytogenetic and Genome Research	22	1.0	1.7
No: Number of publications; JIF: Journal Impact Factor			

DISCUSSION

Mosaicism in Amniocentesis

Amniotic fluid cells originate from various fetal anatomic organs, such as the reproductive system, respiratory apparatus, and epithelial system. Samples may also contain fragments of maternal tissue, maternal blood, and placental or membrane cells. In routine karyotyping, mosaicisms can sometimes be limited to a single cell or culture and are often disregarded as cell culture or chromosome preparation artifacts ("pseudomonasity") (11).

Mosaicism can be detected at different stages of cytogenetic evaluation in amniocentesis. Most often this is considered as an artifact in cell culture (12). Another remarkable frequency of mosaic cells detected in amniocentesis is the detection of two or more colonies. These cells can be observed in culture or in a single sample. However, this should not be observed in different cultures of the same amniocentesis (13). The more important situation in which mosaic cells are detected is the presence of two or more cells with the same chromosome abnormality distributed in two or more independent cultures. It is likely that these cases represent true mosaicism present in fetal tissues (1).

Mosaicism in Chorionic Villus Sampling

In the early stages of fertilization, tissue and organ differentiation begins and during this time, the development of extra-embryonic tissues occurs (14). It is thought that errors occurring during mitosis of extra-embryonic cells may also be related to mosaicism and that this probability is higher than embryonic cell lines (15). Chorionic villi consist of two layers. There is a mesenchymal area inside and a trophoblastic layer outside. It is thought that the mesenchymal layer is more closely related to embryo development (16).

Cells obtained by CVS may be taken from placental or fetal cell lines. The obtained material can be examined cytogenetically by direct cell preparation or by cell culture

and multiplication. When placental mosaicism and fetal mosaicism cannot be distinguished, confirmation by amniocentesis or cordocentesis may be necessary. Cases where confirmation cannot be made are called limited placental mosaicism. Approximately 87% of mosaicism detected by CVS is limited to the placenta, while the rest is true fetal mosaicism (17). The karyotype obtained by amniocentesis analyzes the genetic structure of a heterogeneous group of cells derived from embryonic ectoderm and amniotic ectoderm and mesoderm and should be interpreted accordingly. Therefore, the possibility of missing a hidden mosaic line even with high cell rates in amniocentesis should not be ignored.

Mosaicism present in both cytotrophoblast and mesenchyme is mainly of meiotic origin and the absence of any normal cells in a layer also increases the probability of meiotic origin of the abnormality (18,19). Fluorescence in situ hybridization (FISH) can be used as a laboratory method with higher reliability in amniocentesis evaluation when the diagnosis cannot be confirmed by CVS cytogenetics. In cases where amniocentesis results are controversial and fetal blood sample is evaluated by cordocentesis, FISH is useful in genetic counseling due to its advantage of providing rapid results. FISH studies using probes specific to the relevant chromosome offer the advantage of direct and rapid evaluation of large numbers of uncultured cells and at the same time elimination of artefacts caused by cell culture.

Laboratory Techniques in Diagnosis of Mosaicism

For the diagnosis of chromosomal mosaicism in prenatal diagnosis, FISH, Quantitative Fluorescence Polymer Chain Reaction (QF-PCR) and various chromosomal microarray tests (Array Comparative Genomic Hybridization-aCGH, Single Nucleotide Polymorphism-SNP array) can be used. Each test may have advantages and disadvantages over the other. FISH analysis using a subset of specific probes for the most common chromosomal aneuploidies (13, 18, 21, X and Y) can be used to evaluate the presence of these conditions in homogeneous or mosaic form in prenatal samples.

FISH eliminates the contamination and time disadvantages of cell culture and provides rapid evaluation. It can also provide high reliability results without the need for the metaphase cell counting step required to detect low mosaic levels (20). In addition to its diagnostic success, the FISH technique also has several limitations. The first of these is the inadequacy of hybridization. This may be related to the inadequacy of the obtained material or the preparation of the probe. The second limitation is the contamination of maternal tissue and blood during the acquisition of the material. Another limitation is that the results are obtained only with the relevant probe and narrow-spectrum data are obtained. Therefore, in order to use the correct probe, the clinician should be aware of the prenatal conditions that he strongly suspects (21).

QF-PCR is a DNA-based test for the detection of common aneuploidies by amplification of repeat sequences at specific polymorphic loci. It is a highly reliable test for the diagnosis of aneuploidy and a powerful test for the detection of mosaicism and maternal contamination (22). During QF-PCR, an allelic pattern consisting of two identical repeat sites within the same chromosomal region is diagnostic of two copies of the target region, whereas three peaks or two peaks in a 2:1 ratio within the same chromosomal region are indicative of trisomy for the target region. The detection of maternal cell contamination, triploidy and mosaicism at a rate as low as 15% is an important advantage of these techniques. During this test, maternal contamination can be detected by comparing maternal and fetal alleles (23, 24).

Multiplex Ligation-Based Probe Amplification (MLPA) tests, which are PCR-based and less labor intensive than FISH and less expensive, can detect trisomies and mosaicism. In MLPA, the free ends of the probes are complementary to the primers in the target regions. MLPA is designed to determine the relative abundance of up to 40 to 45 nucleic acid targets. The use of MLPA for prenatal diagnosis includes the detection of aneuploidies, common microdeletion syndromes, and subtelomeric copy number alterations, the identification of marker chromosomes, and the detection of familial copy number alterations in single genes (25). The success of MLPA in the diagnosis of mosaicism may vary depending on the prenatal situation. MLPA has the ability to use multiple probes for each chromosome. When the fetal sex is male, the possibility of maternal contamination can be determined by X chromosome detection. However, the ability to detect triplolypsies in female fetuses is limited. The recommended approach to examine the possibility of maternal contamination in amniotic fluid samples is to determine fetal hemoglobin (Hb) levels in samples with macroscopic red cell contamination, and these are tested

only in samples with fetal Hb levels of 85% or greater by MLPA (26).

Another test that can be used in prenatal diagnosis is microarray tests. In the microarray method, the strength of the signals from the probes is automatically determined to provide information about the copy number of that region of the genome. Microarray analysis can detect aneuploidies of all 23 chromosomes as well as submicroscopic copy number abnormalities (such as microdeletions and microduplications) throughout the genome (27). Genomic alterations can be detected reproducibly at appropriate weeks of pregnancy with high resolution. It can also detect chromosomal abnormalities that routine prenatal chromosomal assessment methods cannot detect and copy number abnormalities of undetermined clinical significance (28,29). It may be difficult to detect mosaicism below a certain level (~10-20%) with microarray analysis. This limitation is not specific to Chromosomal Microarray Analysis and is in fact a general difficulty for all genetic tests. When microarray analysis is performed with cell culture materials for prenatal diagnosis, the probability of detecting mosaicism in microarray analysis may be higher in samples obtained without direct culture, since the probability of proliferation of healthy cell lines is high (30). However, when microarray analysis is performed on fresh CVS, feto-placental mosaicism, which is present in approximately 1-2% of all samples, may pose analytical difficulties since the differentiation in cytotrophoblastic and mesenchymal tissue is lost separately when DNA is extracted. Detection of mosaicism with limited copy number changes in cytotrophoblasts on microarray may pose diagnostic difficulties (31).

Mosaicism in Non-Invasive Prenatal Test (NIPT) using Cell Free DNA (cfDNA)

NIPT is based on the detection of cfDNA fragments in the maternal peripheral blood. cfDNA fragments are released during a series of cellular processes including apoptosis, necrosis and microparticle secretion from all organs. These fragments may originate from maternal cells or from the destruction of cytotrophoblasts. cfDNA can be detected in maternal peripheral blood from the fifth week of gestation and decreases to undetectable levels a few hours after birth (32, 33). Current NIPT procedures cannot be performed without modern molecular technologies (e.g. next-generation sequencing). This method can be used to screen for Trisomies 13, 18 and 21 as well as sex chromosome aneuploidy and single-gene disorders. Measurement of the fetal cfDNA fraction in maternal blood is necessary for the accuracy and quality of the test. It is important to ensure that placental cfDNA is sufficiently measurable in maternal plasma to produce a meaningful result. Early gestational weeks, increasing parity, maternal age, vitamin B12 deficiency, active autoimmune diseases and maternal obesity are identified as some of the factors that reduce the detectable fetal fraction (34, 35).

In most cases where NIPT is performed or the test is performed, trophoblastic DNA is identical to DNA in fetal tissues. Although highly sensitive and specific, an important limitation is pregnancies with placental confinement mosaicism (36). In addition, biological causes such as maternal malignancy, fetoplacental mosaicism, or non-identical vanishing twins may also cause incorrect estimation of fetal status (37). Karyotype studies evaluating the reliability of the test have shown that NIPT may give false-positive results in 1/1100 of fetuses with postnatal normal genomes and false-negative results in 1/61. The above reasons may play a role in misleading results. It should be kept in mind that especially in cases where the karyotype of the placenta is misleading, there may be different karyotypic anomalies in different regions of the placenta itself (38, 39).

The most recent development in prenatal genetic evaluation is observed as the definition of NIPT and microarray analysis methods. The current trend in prenatal testing is characterized by a major shift from invasive sampling to the use of noninvasive or less invasive peripheral blood testing. Today, NIPT is observed to be the most likely candidate to replace invasive testing. Nevertheless, the technique continues to require validation with invasive testing, especially in cases where the diagnosis can be variable, such as mosaicism, due to the disadvantage of cell dominance from the placental area. Even in cases where invasive testing is used, the diagnosis of chromosomal mosaicism in the preimplantation period and prenatal stage in in vitro fertilization is full of uncertainties and many factors must be taken into account to establish the correct diagnosis.

REFERENCES

1. Grati FR. Chromosomal mosaicism in human feto-placental development: implications for prenatal diagnosis. J Clin Med. 2014;3(3):809-37.
2. Li S, Shi Y, Han X, Chen Y, Shen Y, Hu W, et al. Prenatal diagnosis of chromosomal mosaicism in over 18,000 pregnancies: a five-year single-tertiary-center retrospective analysis. Front Genet. 2022;13:876887.
3. Kang H, Wang L, Xie Y, Chen Y, Gao C, Li X, et al. Prenatal diagnosis of chromosomal mosaicism in 18,369 cases of amniocentesis. Am J Perinatol. 2024;41(Suppl 1):e2058-e2068.
4. Goldberg JD, Wohlferd MM. Incidence and outcome of chromosomal mosaicism found at the time of chorionic villus sampling. Am J Obstet Gynecol. 1997;176(6):1349-52; discussion 1352-3.
5. Hsu LY, Yu MT, Richkind KE, Van Dyke DL, Crandall BF, Saxe DF, et al. Incidence and significance of chromosome mosaicism involving an autosomal structural abnormality diagnosed prenatally through amniocentesis: a collaborative study. Prenat Diagn. 1996;16(1):1-28.
6. Wu L, Jin L, Chen W, Liu JM, Hu J, Yu Q, et al. The true incidence of chromosomal mosaicism after preimplantation genetic testing is much lower than that indicated by trophectoderm biopsy. Hum Reprod. 2021;36(6):1691-1701.
7. Baart EB, Martini E, van den Berg I, Macklon NS, Galjaard RJ, Fauser BC, et al. Preimplantation genetic screening reveals a high incidence of aneuploidy and mosaicism in embryos from young women undergoing IVF. Hum Reprod. 2006;21(1):223-33.
8. Najafzadeh TM, Cahill TC, Dumars KW. Prenatal detection of chromosomal mosaicism. Prenat Diagn. 1982;2(1):7-12.
9. Bianchi DW, Platt LD, Goldberg JD, Abuhamad AZ, Sehnert AJ, Rava RP; MatErnal BLood IS Source to Accurately diagnose fetal aneuploidy (MELISSA) Study Group. Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. Obstet Gynecol. 2012;119(5):890-901.
10. Ledbetter DH, Zachary JM, Simpson JL, Golbus MS, Pergament E, Jackson L, et al. Cytogenetic results from the U.S. Collaborative Study on CVS. Prenat Diagn. 1992;12(5):317-45.
11. Benn PA. Prenatal diagnosis of chromosomal abnormalities through chorionic villus sampling and amniocentesis. In: Genetic Disorders and the Fetus. 2015. p. 178-266.
12. Hsu LY, Perlis TE. United States survey on chromosome mosaicism and pseudomosaicism in prenatal diagnosis. Prenat Diagn. 1984 Spring;4 Spec No:97-130.
13. Weng C-Y, Chu S-Y, Li T-Y, Fang J-S, Lee M-L. Genetic counseling on amniocyte level II mosaicism. Tzu Chi Med J. 2011;23(4):149-50.
14. Knöfler M, Haider S, Saleh L, Pollheimer J, Gamage TKJB, James J. Human placenta and trophoblast development: key molecular mechanisms and model systems. Cell Mol Life Sci. 2019;76(18):3479-96.
15. Levy B, Hoffmann ER, McCoy RC, Grati FR. Chromosomal mosaicism: origins and clinical implications in preimplantation and prenatal diagnosis. Prenat Diagn. 2021;41(5):631-41.
16. Bianchi DW, Wilkins-Haug LE, Enders AC, Hay ED. Origin of extraembryonic mesoderm in experimental animals: relevance to chorionic mosaicism in humans. Am J Med Genet. 1993;46(5):542-50.
17. Benn P, Malvestiti F, Grimi B, Maggi F, Simoni G, Grati FR. Rare autosomal trisomies: comparison of detection through cell-free DNA analysis and direct chromosome preparation of chorionic villus samples. Ultrasound Obstet Gynecol. 2019;54(4):458-67.
18. Wolstenholme J. Confined placental mosaicism for trisomies 2, 3, 7, 8, 9, 16, and 22: their incidence, likely origins, and mechanisms for cell lineage compartmentalization. Prenat Diagn. 1996;16(6):511-24.
19. Chiesa J, Hoffet M, Rousseau O, Bourgeois JM, Sarda P, Mares P, et al. Pallister-Killian syndrome [i(12p)]: first prenatal diagnosis using cordocentesis in the second trimester confirmed by in situ hybridization. Clin Genet. 1998;54(4):294-302.
20. Feldman B, Ebrahim SA, Gyi K, Flore LA, Evans MI. Rapid confirmation of previously detected prenatal mosaicism by fluorescence in situ hybridization in interphase uncultured amniocytes. Genet Test. 2000;4(1):61-3.
21. Hultén MA, Dhanjal S, Pertl B. Rapid and simple prenatal diagnosis of common chromosome disorders: advantages and disadvantages of the molecular methods FISH and QF-PCR. Reproduction. 2003;126(3):279-97.
22. Mann K, Ogilvie CM. QF-PCR: application, overview and review of the literature. Prenat Diagn. 2012;32(4):309-14.
23. Nicolini U, Lalatta F, Natacci F, Curcio C, Bui TH. The introduction of QF-PCR in prenatal diagnosis of fetal aneuploidies: time for reconsideration. Hum Reprod Update. 2004;10(6):541-8.
24. Sreelakshmi KN. Medical genetics for practicing obstetricians. J Obstet Gynaecol India. 2020;70(1):6-11.
25. Willis AS, van den Veyver I, Eng CM. Multiplex ligation-dependent probe amplification (MLPA) and prenatal diagnosis. Prenat Diagn. 2012;32(4):315-20.
26. Van Opstal D, Boter M, de Jong D, van den Berg C, Brüggenwirth HT, Wildschut HI, et al. Rapid aneuploidy detection with multiplex ligation-dependent probe amplification: a prospective study of 4000 amniotic fluid samples. Eur J Hum Genet. 2009;17(1):112-21.
27. Wright D, Carey L, Battersby S, Nguyen T, Clarke M, Nash B, et al. Validation of a chromosomal microarray for prenatal diagnosis using a prospective cohort of pregnancies with increased risk for chromosome abnormalities. Genet Test Mol Biomarkers. 2016;20(12):791-8.
28. Shaffer LG, Dabell MP, Rosenfeld JA, Neill NJ, Ballif BC, Coppinger J, et al. Referral patterns for microarray testing in prenatal diagnosis. Prenat Diagn. 2012;32(6):611.
29. Levy B, Wapner R. Prenatal diagnosis by chromosomal microarray analysis. Fertil Steril. 2018;109(2):201-12.
30. Hall GK, Mackie FL, Hamilton S, Evans A, McMullan DJ, Williams D, et al. Chromosomal microarray analysis allows prenatal detection of low level mosaic autosomal aneuploidy. Prenat Diagn. 2014;34(5):505-7.
31. Karampetsou E, Morrogh D, Ballard T, Waters JJ, Lench N, Chitty LS, et al. Confined placental mosaicism: implications for fetal chro-

mosomal analysis using microarray comparative genomic hybridization. Prenat Diagn. 2014;34(1):98-101.

32. Gahan PB. Circulating nucleic acids in plasma and serum: diagnosis and prognosis in cancer. EPMA J. 2010;1(3):503-12.

33. Okoror CEM, Arora S. Prenatal diagnosis after high chance non-invasive prenatal testing for trisomies 21, 18 and 13, chorionic villus sampling or amniocentesis? - Experience at a district general hospital in the United Kingdom. Eur J Obstet Gynecol Reprod Biol X. 2023;19:100211.

34. Kinnings SL, Geis JA, Almasri E, Wang H, Guan X, McCullough RM, et al. Factors affecting levels of circulating cell-free fetal DNA in maternal plasma and their implications for noninvasive prenatal testing. Prenat Diagn. 2015;35(8):816-22.

35. Hui L, Bethune M, Weeks A, Kelley J, Hayes L. Repeated failed non-invasive prenatal testing owing to low cell-free fetal DNA fraction and increased variance in a woman with severe autoimmune disease. Ultrasound Obstet Gynecol. 2014;44(2):242-3.

36. Benn P, Cuckle H, Pergament E. Non-invasive prenatal testing for aneuploidy: current status and future prospects. Ultrasound Obstet Gynecol. 2013;42(1):15-33.

37. Bianchi DW, Chudova D, Sehnert AJ, Bhatt S, Murray K, Prosen TL, et al. Noninvasive prenatal testing and incidental detection of occult maternal malignancies. JAMA. 2015;314(2):162-9.

38. Henderson KG, Shaw TE, Barrett IJ, Telenius AH, Wilson RD, Kalousek DK. Distribution of mosaicism in human placentae. Hum Genet. 1996;97(5):650-4.

39. Verma RS, Babu A. Human chromosomes principles and techniques. McGraw-Hill Inc.; Milano, Italy: 1995. pp. 24–26. Chapter 2.16.

Abbreviations list

CVS: Chorionic Villus Sampling
PGT: Preimplantation Genetic Testing
MLPA: Multiplex Ligation-Based Probe Amplification
FISH: Fluorescence In Situ Hybridization

Ethics approval and consent to participate

The data presented in the study were obtained from publicly available search databases and did not require ethics committee approval.

Consent for publication

The research does not contain personal data and does not require consent.

Availability of data and materials

Data for the research can be obtained from the web of science database.

Competing interests

There is no conflict of interest regarding the research.

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Authors' contributions

Idea/Concept: EY, SY. Design:EY. Control/Supervision EY, YC. Data Collection And/Or Processing: EY, EsY, EE. Analysıs And/Or Interpretation: EY, EsY. Literature Review: SY, YC. Writing The Article: EY. Critical Review: SY, YC. References And Fundings: SY. Materials: EsY. Other: EE.

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