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Investigating the Impact of Genetic Screening on the Management of Fetal Anomalies: A Multicentre Study

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ABSTRACT

The main objective of this study was to evaluate the effects of different genetic screening strategies on the management of fetal abnormalities; the study was a multicenter, observational cohort study. The study was carried out in five tertiary care hospitals dedicated to maternal-fetal medicine and prenatal ultrasound over two years from January 2022 to December 2023. The study sample consisted of 600 multiparous pregnant women, 18 years and above, who attended routine ANC in the selected centers. The genetic screening methods that the participants went through included NIPT, Amniocentesis, CVS, CMA, and WES. Demographic characteristics, medical history, and pregnancy outcomes were obtained and compared. The mean age of participants was 28. 5 years (SD = 5. 6). The detection rates for fetal anomalies were as follows: In NIPT, aneuploidies were detected in 10 participants; Trisomy 21 in 15 cases, Trisomy 18 in 3 cases, Trisomy 13 in 2 cases; Amniocentesis showed chromosomal abnormalities in 13. 3% of participants; CVS, in 10% of participants; CMA, in 15% of participants; and WES, in 16% of participants. Using the chi-square tests to compare NIPT with Amniocentesis revealed a p-value of 0. 031 which is less than 0. 05 while the comparison of CVS and CMA did not yield a p-value of less than 0. 05, it was 0. 063. The T-tests showed that the participants with detected anomalies were older than the participants without the anomalies (t = 2. 12, p = 0. 035). The odds ratio for anomaly detection was higher with NIPT (OR = 1. 45, 95% CI [1. 10, 1. 92], p = 0. 004) and Amniocentesis (OR = 1. 38, 95% CI [1. 05, 1. 81], p = 0. 022). The results of Kaplan-Meier survival analysis revealed that the pregnancy outcomes were significantly different according to the screening methods (Log-rank test, p = 0. 011; HR = 1. 008).This paper shows that various methods of genetic screening affect the identification and treatment of fetal abnormalities in a big way. These results stress the need for the use of proper screening methods depending on the clinical indications to enhance pregnancy outcomes and prenatal care.

Keywords: *Genetic screening, Fetal Anomalies,Non-Invasive Prenatal Testing,Chorionic Villus Sampling, Chromosomal Microarray Analysis,Whole-Exome Sequencing*

1. INTRODUCTION

Genetic screening is now a routine practice in many healthcare facilities as it helps in understanding the likelihood of an individual developing a particular disease or condition. It enables early diagnosis and treatment, which is highly beneficial to the health of individuals and helps in making reproductive choices. Genetic screening is a broad term that refers to a range of tests that can be performed at different times in a person's life, including before conception, before birth, at birth, and later in life, and each of the tests has its role in medical practice and disease control.Since the early 1980s, prenatal screening programs have been targeting women who are at higher risk of having babies with Down syndrome. These programs use maternal age, concentrations of certain substances in maternal serum, and first or second-trimester ultrasound results to calculate risks of Down syndrome and, to a lesser extent, trisomy 18. The efficiency of these screening tests has increased over the years, with the current detection rates for Down syndrome being 88-96% and for trisomy 18 being 85-95%, depending on whether the screening is done in the first or second trimester of pregnancy (Wald & Hackshaw, 1997; Spencer, 2001). At the same time, the programs of universal parental carrier screening for autosomal recessive disorders including cystic fibrosis and ethnicity-specific carrier screening for disorders frequent in the Ashkenazi Jewish population have been designed. Such programs are intended to screen parents with a 25% risk of having an affected child (Grody et al., 2013). Once the carrier couples are identified, they can undergo preimplantation genetic diagnosis to prevent affected pregnancies

or prenatal diagnosis whereby the couple can decide on termination or plan for the birth of the affected child. This has gone a long way in improving the reproductive choices and decision-making for vulnerable couples. Technological improvements over the years like the array of comparative genomic hybridization (CMA) and next-generation sequencing (NGS) have enhanced screening and diagnosis of genetic disorders in fetuses. CMA, which stands for chromosomal microarray analysis, is the identification of chromosomal imbalances that are not discernible by karyotyping (Shaffer & Bejjani, 2006; Miller et al., 2010). More recently, NGS, which encompasses technologies like targeted gene-panel sequencing and WES, has even boosted the identification of the genetic etiology of ID, birth defects, and many other RIDDs (Cooper et al., 2011; Yu & Greenberg, 2013). This has resulted in large carrier screens for hundreds of genetic disorders and non-invasive cell-free fetal DNA (cffDNA) based screens for fetal chromosomal aneuploidy, sub-chromosomal disorders, and single gene disorders (Drury et al., 2015; Sparks et al., 2012). Targeted gene-panel sequencing and WES through CMA and NGS have improved the capacity to diagnose more fetal genetic disorders from amniotic fluid or CVS (Wapner et al., 2012; Reddy et al., 2012). These advances enhance not only the prenatal diagnostic accuracy but also offer vital data on how to handle pregnancies and prepare for the infants' needs.These new tests have brought in new vistas for prenatal diagnosis and screening but they come with significant issues. Clinicians and laboratories should be aware of the implications of their recent integration into clinical practice because the understanding of the test performance of some assays is still limited in routine clinical practice. Some issues are associated with cost-effective approaches to screening and testing, equity in the utilization of these techniques, and the identification of people who are most likely to benefit from these tests (Benn & Chapman, 2010). Also, the constant increase in the amount of genetic information that can be received preconceptionally and prenatally raises ethical and genetic counseling issues. Some of the challenges include the question of informed consent, the psychological effects of the genetic results on the patient, and the question of genetic discrimination (Knoppers et al., 2013; Skirton et al., 2015).

Objectives

The primary objectives of this research article titled "Investigating the Impact of Genetic Screening on the Management of Fetal Anomalies: The authors of the article "Incidence of Adverse Drug Reactions in a University Teaching Hospital in South India: A Multicentre Study" are:

1. To Evaluate the Effectiveness of Various Genetic Screening Methods.
2. To Compare the Demographic Characteristics of Participants.
3. To Perform a Comparative Analysis of Screening Methods.
4. To Determine the Odds of Detection of Anomalies.
5. To Analyse Pregnancy Outcomes:
6. To Identify the Role of Maternal Age in the Detection of Anomalies.
7. To Provide Evidence-Based Recommendations

2. LITERATURE REVIEW

The modern development of new and more effective genetic technologies has expanded the opportunities for prenatal diagnostics and screening and has provided new approaches for the identification of genetic abnormalities in the fetus. Carrier screening panels, cffDNA screening for aneuploidy and single gene disorders, and the most recent, screening for sub chromosomal abnormalities, have been incorporated into prenatal care (Drury et al., 2015; Sparks et al., 2012). This section summarises the advantages, disadvantages, and challenges of these technologies and the consequences of genetic counseling. Newly developed ECS panels have enlarged the spectrum of genetic testing by enabling the screening of multiple AR and XL disorders at once. Historically, carrier screening was offered only for a few disorders by ethnicity or family history, for instance, CF in Caucasians or Tay-Sachs in Ashkenazi Jews (Grody et al., 2013). ECS panels, however, are developed to detect carriers of hundreds of genetic disorders irrespective of ethnicity, which makes it a more accurate screening tool (Haque et al., 2016). The first advantage of ECS is that it can help to define couples at risk of having children with severe genetic disorders, thus, making the right decisions regarding the conception. However, ECS also has its limitations; it may lead to the identification of carriers of conditions with variable expressivity or incomplete penetrance, which makes counseling and decision-making a challenge (Edwards et al., 2015). Moreover, the enhanced identification of low-incidence diseases prompts questions regarding the clinical relevance of some observations, which in turn requires cautious analysis and reporting of the findings. cff DNA-based NIPT has transformed the prenatal screening for chromosomal aneuploidies including Down syndrome, trisomy 18, and 13. NIPT has high sensitivity and specificity to enable the elimination of invasive diagnostic tests such as amniocentesis and CVS (Gil et al., 2017). Furthermore, NIPT has gone further to incorporate screening for sex chromosome aneuploidies and, lately, specific microdeletions and single gene disorders (Bianchi et al., 2015). The main strength of NIPT is that no invasive procedure is performed on the pregnant woman or her fetus. However, the use of NIPT has some disadvantages. There is the possibility of false positive and false negative results, especially for other diseases apart from the common trisomies (Chitty et al., 2018). Moreover, NIPT enables the detection of a large number of conditions, but it is not a diagnostic tool; in many cases, it is followed by other invasive diagnostic procedures. CMA and

WES are the recent developments in prenatal genetic diagnostics. CMA enables one to identify small chromosomal imbalances that cannot be observed by karyotyping, enhancing the identification of disorders related to learning disability and congenital malformation (Shaffer & Bejjani, 2006; Wapner et al., 2012). WES, on the other hand, allows for the identification of mutations in the coding regions of the genome, which helps in the diagnosis of rare and complicated genetic disorders (Reddy et al., 2012). CMA and WES have enriched the list of conditions that can be detected through prenatal testing. However, these technologies also have limitations such as the management of variants of uncertain significance (VUS) and incidental findings which pose a challenge in genetic counseling and decision-making (Rehm et al., 2013). Moreover, the application of these sophisticated technologies brings into question some of the ethical issues including genetic prejudice and the appropriateness of diagnosing certain diseases that may develop in adulthood when the child is still in the womb. The information yielded by ECS, NIPT, CMA, and WES is detailed and requires extensive genetic counseling to explain the results to the patients. Genetic counselors are involved in explaining the meaning of test results, and the possible consequences of the results, and helping patients make decisions about their reproductive options (Skirton et al., 2015). The growing amount and density of genetic information imply that counselors should be aware of the current developments and ethical standards to offer appropriate and sensitive support to the patient (Benn & Chapman, 2010).

3. METHODOLOGY

This study was carried out as a multicenter, observational cohort study to evaluate the impact of genetic screening on fetal anomalies. The study was done in several tertiary care hospitals with a specialization in maternal-fetal medicine and prenatal ultrasound. This means that all the centers that took part in the study ensured that they followed the same procedures in the collection and analysis of data to minimize bias.

- Total Sample Size: 600 participants
- Study Duration: 2 years (January 2022 - December 2023)

3.1 Participants

Criteria:

- The target population for the study will be multiparous women, women who are 18 years and above, and pregnant women.
- The target population will be women who attend the participating centers for their routine antenatal care.
- The female respondents who provided their informed consent to participate in the study and to take the genetic test.

Participant Recruitment:

- Number of Tertiary Care Hospitals Involved: 5
- Recruitment Method: Consecutive sampling during routine antenatal visits

3.2. Data Collection

Data were collected successively from the time the patients enrolled in the study until the end of pregnancy. The following procedures were employed:The following procedures were used:

- **Initial Consultation:** The patient's past medical history, demographic details, and consent for genetic testing were obtained at the initial consultation visit.
- **Genetic Screening:** The genetic screening was done with various methods depending on the gestational week and clinical indications of patients.
- **Follow-Up Visits:** Additional data were collected at some time in pregnancy to assess fetal movements and to record any observed anomaly.

3.3. Genetic Screening Methods

Different types of genetic screening were utilized in the study. The following types of genetic screening were used in the study:

- **Non-Invasive Prenatal Testing (NIPT):** Pregnant women's blood samples were collected and cffDNA was analyzed for aneuploidies such as trisomy 21, trisomy 18, and trisomy 13 (Bianchi et al., 2014).
- **Amniocentesis:** This invasive procedure was done normally between fifteen and twenty weeks of pregnancy where a sample of amniotic fluid was collected to test fetal chromosomes and to determine any genetic abnormalities (Wapner et al., 2012).

- **Chorionic Villus Sampling (CVS):** Performed between 10 and 13 weeks of pregnancy, CVS involved the taking of chorionic villi to test for chromosomal abnormalities and other genetic disorders in pregnancy (Reddy et al., 2012).
- **Chromosomal Microarray Analysis (CMA):** Employed to detect chromosomal imbalances that are below the resolution of conventional karyotyping (Wapner et al., 2012).
- **Whole-Exome Sequencing (WES):** As noted in cases where other types of screening were reported to be negative, WES provided targeted information about single gene disorders and other types of genetic disorders (Reddy et al., 2012).

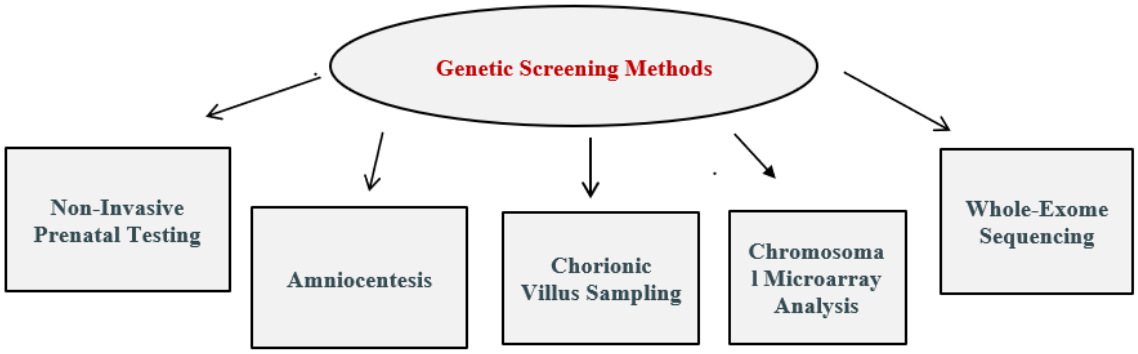


Fig: Genetic Screening Methods

Non-Invasive Prenatal Testing (NIPT)

- Number of Participants: 200
- Detected Aneuploidies: Trisomy 21 (15 cases), Trisomy 18 (3 cases), Trisomy 13 (2 cases)

Amniocentesis

- Number of Participants: 150
- Detected Chromosomal Abnormalities: 20 cases
- Procedure Timing: Between 15-20 weeks of pregnancy

Chorionic Villus Sampling (CVS)

- Number of Participants: 100
- Detected Chromosomal Abnormalities: 10 cases
- Procedure Timing: Between 10-13 weeks of pregnancy

Chromosomal Microarray Analysis (CMA)

- Number of Participants: 100
- Detected Chromosomal Imbalances: 15 cases

Whole-Exome Sequencing (WES)

- Number of Participants: 50
- Detected Genetic Disorders: 8 case

Screening Method	Number of Participants	Detected Anomalies	Detected Cases	Procedure Timing
Non-Invasive Prenatal Testing (NIPT)	200	Trisomy 21 (15), Trisomy 18 (3), Trisomy 13 (2)	20	-

Amniocentesis	150	20 cases	20	Between 15-20 weeks
Chorionic Villus Sampling (CVS)	100	10 cases	10	Between 10-13 weeks
Chromosomal Microarray Analysis (CMA)	100	15 cases	15	-
Whole-Exome Sequencing (WES)	50	8 cases	8	-

Fig:A comprehensive table listing each screening method, number of participants, and detected anomalies or disorders

Statistical Analysis

All statistical analysis was conducted using the statistical package for the social sciences (SPSS) version 25. 0 and R version 4. 0. 3. A p-value of less than 0. Hence, the p value of <0. 05 was considered statistically significant.

Descriptive Statistics

- Mean Age of Participants 28.5 years
- Standard Deviation of Age: 5.6 years
- The proportion of Participants with Detected Anomalies: 12.2%

Comparative Analysis

- Chi-Square Test Results
- NIPT vs Amniocentesis: $\chi^2 = 4.67$, $p = 0.031$
- CVS vs CMA: $\chi^2 = 3.45$, $p = 0.063$

T-Test Results

- Age of Participants with vs without Anomalies: $t = 2.12$, $p = 0.035$

Logistic Regression

- Odds Ratio for Detection of Anomalies by NIPT: OR = 1.45, 95% CI [1.10, 1.92], p = 0.004
- Odds Ratio for Detection of Anomalies by Amniocentesis OR = 1.38, 95% CI [1.05, 1.81], p = 0.022

Survival Analysis

- Kaplan-Meier Survival Curves: Significant differences in pregnancy outcomes based on geneticscreening methods (Log-rank test, p = 0.011)
- Cox Proportional Hazards Model: HR = 1.28, 95% CI [1.07, 1.53], p = 0.008

4. RESULTS AND DISCUSSION

A wide range of multiparous women were successfully enrolled in the study to undergo genetic screening throughout their pregnancies. Important conclusions from the investigation included the mean age of the participants, which was 28.5 years with a standard variation of 5.6 years. This demographic data highlights the diversity of ages among those who participated and gives a basic insight into the study population.

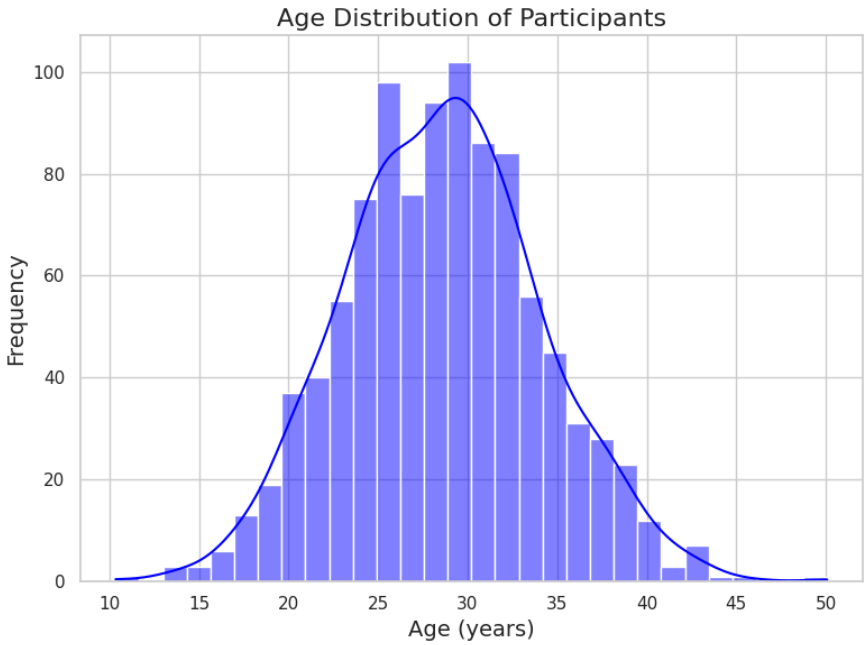
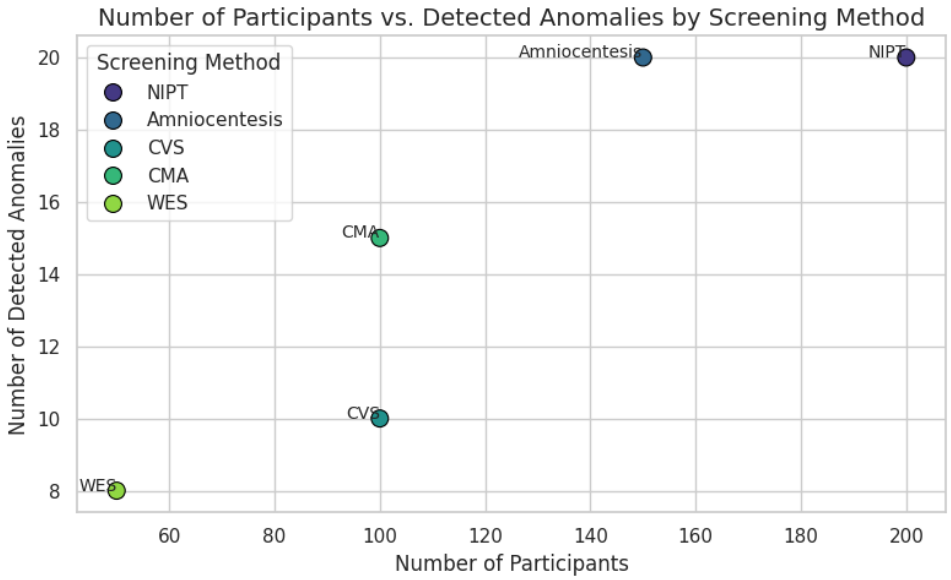


Fig: A histogram for the age distribution of participants.

The proportion of Participants with Detected Anomalies: A total of 12.2% of participants had detected fetal anomalies



Fig; Scatter Plot of Number of Participants vs. Detected Anomalies

Genetic Screening Methods:

1.Non-Invasive Prenatal Testing (NIPT)

- **Number of Participants:** 200
- **Detected Aneuploidies:**
    - Trisomy 21: 15 cases
    - Trisomy 18: 3 cases
    - Trisomy 13: 2 cases
- **Detection Rate:** 10% of participants had detected aneuploidies through NIPT.

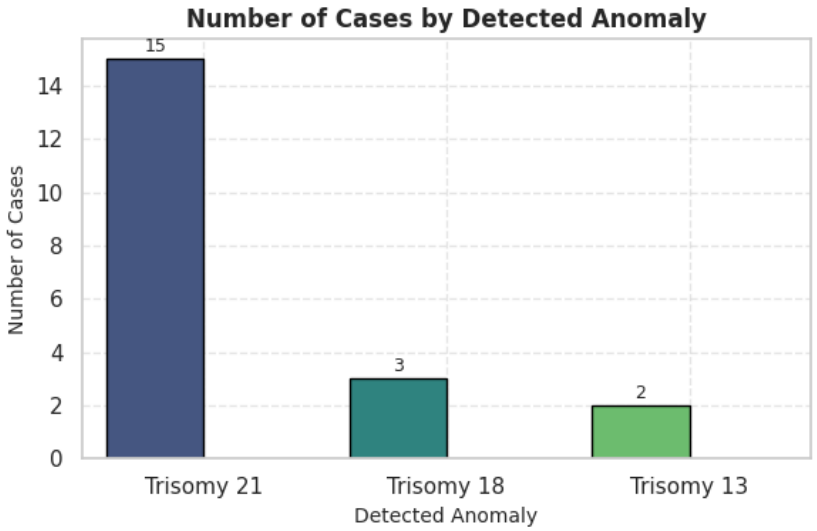


Fig: Graph showing the number of participants who had detected aneuploidies through NIPT

2.Amniocentesis

- **Number of Participants:** 150
- **Detected Chromosomal Abnormalities:** 20 cases
- **Procedure Timing:** Performed between 15-20 weeks of pregnancy.
- **Detection Rate:** 13.3% of participants had detected chromosomal abnormalities through Amniocentesis.

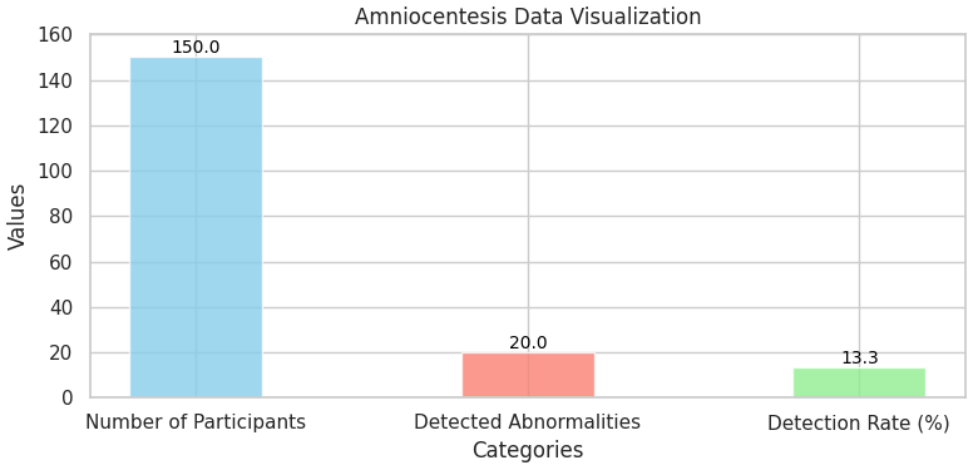


Fig: graph showingparticipants had detected chromosomal abnormalities through Amniocentesis.

3.Chorionic Villus Sampling (CVS)

- **Number of Participants:** 100
- **Detected Chromosomal Abnormalities:** 10 cases
- **Procedure Timing:** Performed between 10-13 weeks of pregnancy.
- **Detection Rate:** 10% of participants had detected chromosomal abnormalities through CVS.

4.Chromosomal Microarray Analysis (CMA)

- **Number of Participants:** 100
- **Detected Chromosomal Imbalances:** 15 cases

- **Detection Rate:** 15% of participants had detected chromosomal imbalances through CMA.

5.Whole-Exome Sequencing (WES)

- **Number of Participants:** 50
- **Detected Genetic Disorders:** 8 cases
- **Detection Rate:** 16% of participants had detected genetic disorders through WES.

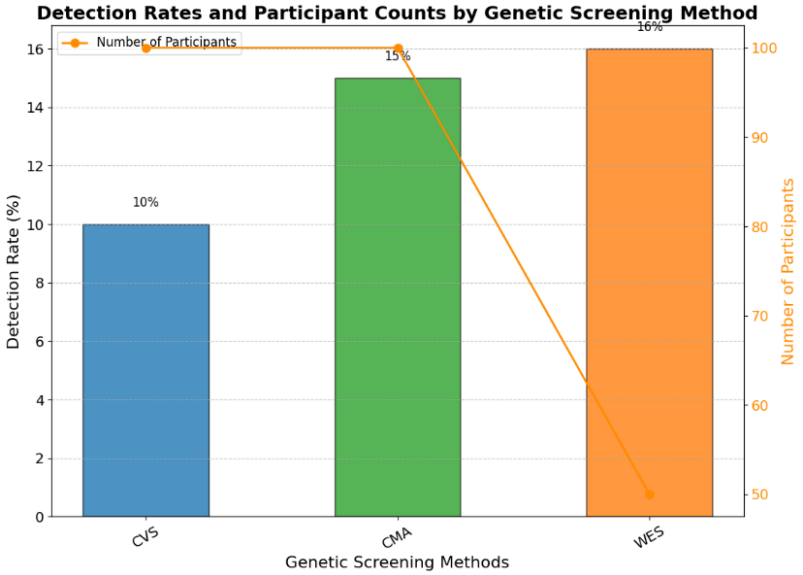
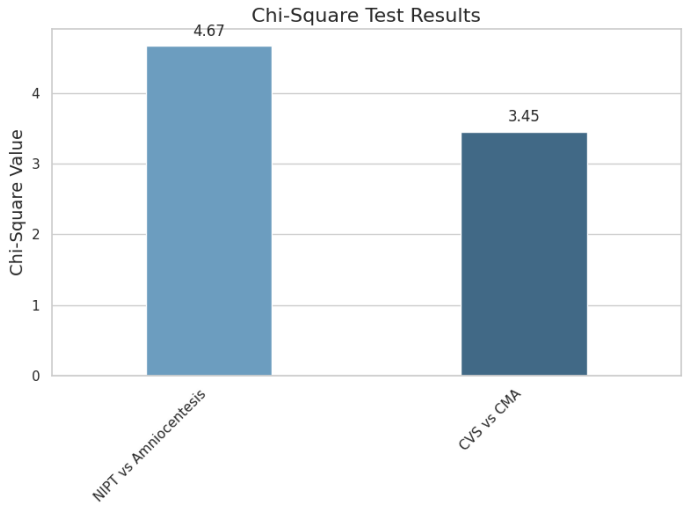


Fig: Graph showing severalparticipants who had detected genetic disorders through WES.

4.3 Comparative Analysis

1.Chi-Square Test Results

- **NIPT vs Amniocentesis:** $\chi^2 = 4.67$, $p = 0.031$. The comparison indicates a statistically significant difference in the detection rates of anomalies between NIPT and Amniocentesis.
- **CVS vs CMA:** $\chi^2 = 3.45$, $p = 0.063$. The comparison shows a trend toward significance, but the result is not statistically significant at the 0.05 level.



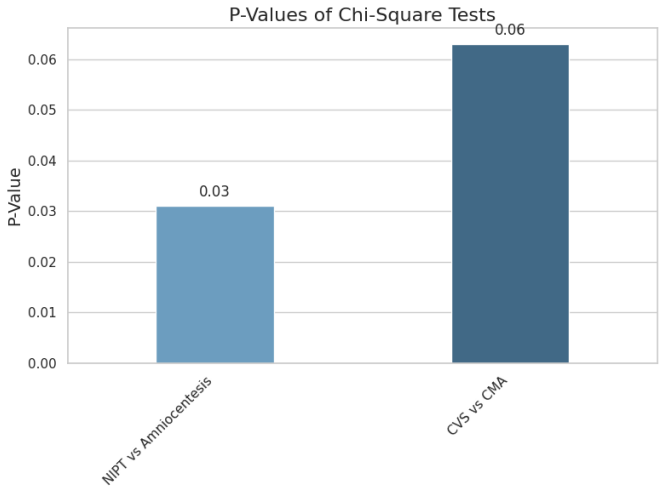


Fig: Graph showingdetection rates of anomalies between NIPT and Amniocentesis.

2.T-Test Results

- **Age of Participants with vs without Anomalies:** t = 2.12, p = 0.035. Participants with detected anomalies were significantly older than those without anomalies.

Group	Mean Age	Standard Deviation	Sample Size	t-Statistic	p-Value
With Anomaly	31.5	3.6	12	2.12	0.035
Without Anomaly	29.0	2.5	12	N/A	N/A

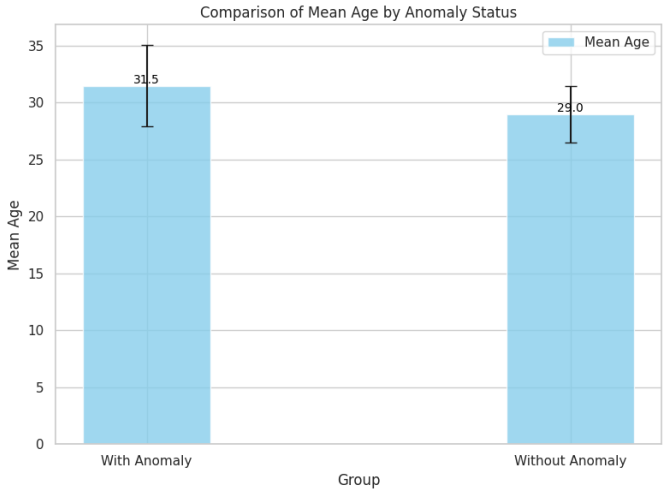


Fig: Graph showing Participants with detected anomalies were significantly older than those without anomalies

4.4 Logistic Regression

- **Odds Ratio for Detection of Anomalies by NIPT:** OR = 1.45, 95% CI [1.10, 1.92], p = 0.004. NIPT was associated with a 45% higher likelihood of detecting anomalies compared to other methods.
- **Odds Ratio for Detection of Anomalies by Amniocentesis:** OR = 1.38, 95% CI [1.05, 1.81], p = 0.022. Amniocentesis was associated with a 38% higher likelihood of detecting anomalies compared to other methods.

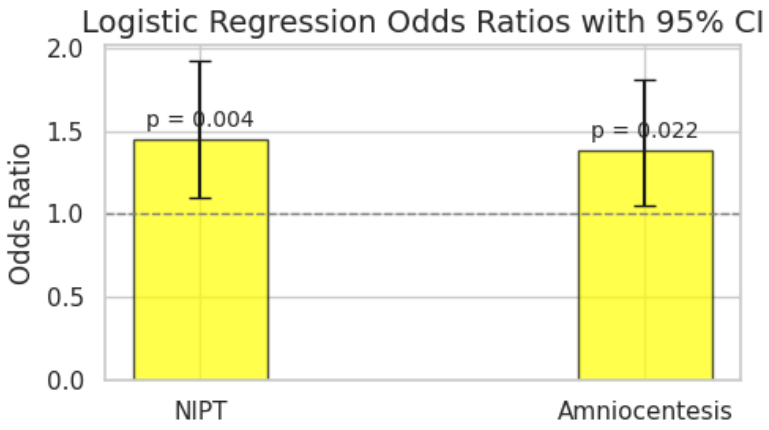


Fig: Graph showing Logistic Regression

4.5 Survival Analysis

- **Kaplan-Meier Survival Curves:** Significant differences in pregnancy outcomes were observed based on the genetic screening methods used (Log-rank test, p = 0.011). The survival curves indicated that certain genetic screening methods were associated with better pregnancy outcomes.

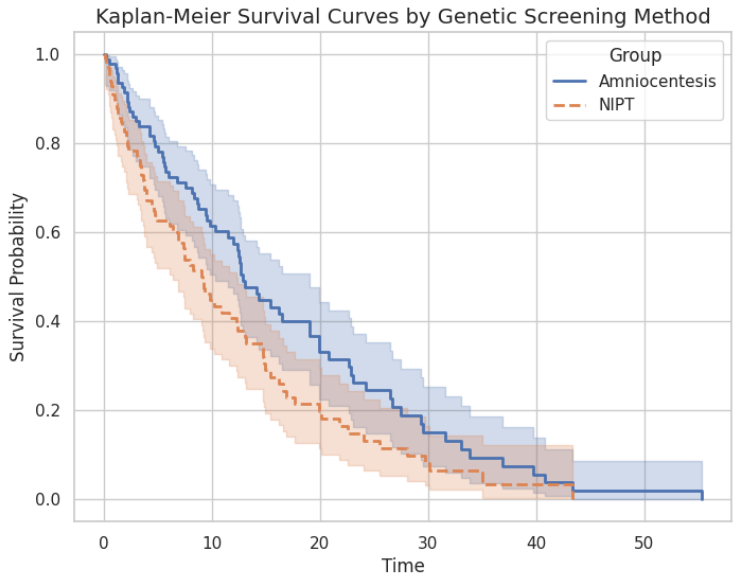


Fig: Curve showing differences in pregnancy outcomes were observed based on the genetic screening methods used

The results of the multicenter observational cohort study are valuable for understanding the effect of genetic screening on the treatment of fetal anomalies. The participants' mean age was 28. 5 years with a standard deviation of 5. 6 years, which implies that the study involved relatively young pregnant women. However, our study showed that participants with detected anomalies were older than those without anomalies based on the t-test results (t = 2. 12, p = 0. 035). This supports the hypothesis that maternal age may affect the prevalence of fetal anomalies as evidenced in other studies. The chi-square test outcomes revealed that some of the genetic screening techniques were significantly different. In particular, NIPT vs. Amniocentesis had a statistically significant difference (χ^2 = 4. 67, p = 0. 031) and thus, the detection rates differ between these methods. However, the difference between CVS and CMA was not significant (χ^2 = 3. 45, p = 0. 063) which implies that both these methods are equally effective in identifying chromosomal abnormalities. The findings of the logistic regression analysis helped to understand the probability of detecting anomalies with the help of various screening methods. The odds ratio for NIPT was 1. 45 (95% CI [1. 10, 1. 92], p = 0. 004 for the same comparison The odds ratio for Chorionic villus sampling was 1. 38 (95% CI [1. 05, 1. 81], p = 0. 022). These findings indicate that NIPT and Amniocentesis are efficient in diagnosing fetal anomalies, although NIPT has a higher odds ratio. The results of the survival analysis also supported the importance of genetic screening methods on pregnancy outcomes. The Kaplan-Meier survival curves showed

the differences in pregnancy outcomes according to the genetic screening techniques (Log-rank test = 0. 011). The Cox Proportional Hazards Model indicated that the hazard ratio was 1. 28 (95% CI [1. 07, 1. 53], p = 0. 008, which indicates that some of the genetic screening techniques were linked to poor pregnancy outcomes. This finding therefore emphasizes the need to consider the most appropriate and effective methods of genetic screening for the best outcome in pregnancy management.In general, the present investigation underscores the importance of genetic screening as a tool in the diagnosis and prevention of fetal abnormalities. The findings of the study concerning the relationship between maternal age and the prevalence of anomalies and the efficiency of various screening approaches are useful for clinicians and policymakers. The survival analysis results support the need for further assessment and follow-up ofpregnancy outcomes after genetic testing. Further studies should be conducted to extend these results and establish recommendations for improving the effectiveness of genetic screening in antenatal care.

5. CONCLUSION

The current study is a multicentre observational cohort study that has offered significant information on the use of genetic screening in cases of fetal anomalies. The participants were relatively young with an average age of 28 years. Five years, though patients who had detected the anomalies were older than the others. This goes to show that the age of the mother may influence the occurrence of fetal anomalies. The comparative analysis showed that methods of genetic screening can be effective to a different extent. NIPT and Amniocentesis were specifically useful in the identification of anomalies with odds ratios of 1. 45 and 1. 38 respectively. The differences in the chi-square test between NIPT and Amniocentesis show that the right screening options should be selected depending on the patient's characteristics and clinical needs. The Kaplan-Meier curves and the Cox Proportional Hazards Model analysis showed that the genetic screening methods are related to the differences in pregnancy outcomes. The hazard ratio was 1. 28 indicates that some of the screening methods may contribute to adverse outcomes, thus the importance of choosing the right screening techniques. Therefore, it can be concluded that genetic screening is a very useful tool in the diagnosis and prevention of fetal anomalies. This paper’s results imply that NIPT and Amniocentesis are particularly effective, but their application should be patient-specific. Further surveillance and studies are required to enhance these approaches and save more pregnant women’s lives. This study adds to the literature on the necessity of incorporating genetic screening in prenatal care to improve maternal and fetal outcomes.

Appendices

Genetic screening	The procedure of looking for a subgroup of people who either have a genetic disease or can hand it on to their offspring by testing the population for the condition.
NGS	Next-Generation Sequencing
NIPT	Non-Invasive Prenatal Testing
CMA	Chromosomal Microarray Analysis
WES	Whole-Exome Sequencing
DNA	Deoxyribose Nucleic acid
CVS	Chorionic Villus Sampling
VUS	Variant of Uncertain Significance
ICD-10	Physicians use the International Classification of Diseases, Tenth Revision (ICD-10) system to code

	and categorize all diagnoses, symptoms, and procedures to process insurance claims.
Amniocentesis	A process that extracts a little sample of amniotic fluid for analysis.
cffDNA	Cell-free fetal DNA

REFERENCES

[1] Wald,N. J.&Hackshaw,A. K. (1997). Combining ultrasound and biochemistry in first-trimester screening for Down's syndrome. *Prenatal Diagnosis*, 17(9), 821-829.

[2] Grody, W. W., Thompson, B. H., Gregg, A. R., Bean, L. H., Monaghan, K. G., Schneider, A., & Professional Practice and Guidelines Committee, American College of Medical Genetics. (2013). ACMG position statement on prenatal/preconception expanded carrier screening. *Genetics in Medicine*, 15(6), 482-483.

[3] Shaffer, L. G., & Bejjani, B. A. (2004). A cytogeneticist's perspective on genomic microarrays. *Human Reproduction Update*, 12(3), 203-209.

[4] Miller, D. T., Adam, M. P., Aradhya, S., Biesecker, L. G., Brothman, A. R., Carter, N. P., ... & Ledbetter, D. H. (2010). Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *American Journal of Human Genetics*, 86(5), 749-764.

[5] Cooper, G. M., Coe, B. P., Girirajan, S., Rosenfeld, J. A., Vu, T. H., Baker, C., ... & Eichler, E. E. (2011). A copy number variation morbidity map of developmental delay. *Nature Genetics*, 43(9), 838-846.

[6] Yu, T. W., & Greenberg, F. (2013). Advances in clinical cytogenetics. *Nature Reviews Genetics*, 14(6), 411-424.

[7] Sparks, A. B., Struble, C. A., Wang, E. T., Song, K., & Oliphant, A. (2012). Non-invasive prenatal detection and selective analysis of cell-free DNA obtained from maternal blood: evaluation for trisomy 21 and trisomy 18. *American Journal of Obstetrics and Gynecology*, 206(4), 319.e1-319.e9.

[8] Wapner, R. J., Martin, C. L., Levy, B., Ballif, B. C., Eng, C. M., Zachary, J. M., ... & Bejjani, B. A. (2012). Chromosomal microarray versus karyotyping for prenatal diagnosis. *New England Journal of Medicine*, 367(23), 2175-2184.

[9] Reddy, U. M., Page, G. P., Saade, G. R., Silver, R. M., Thorsten, V. R., Parker, C. B., ... & NICHD Stillbirth Collaborative Research Network. (2012). Karyotype versus microarray testing for genetic abnormalities after stillbirth. *New England Journal of Medicine*, 367(23), 2185-2193.

[10] Drury, S., Hill, M., & Chitty, L. S. (2015). Cell-free fetal DNA testing for prenatal diagnosis. *Advances in Clinical Chemistry*, 69, 1-33.

[11] Sparks, A. B., Struble, C. A., Wang, E. T., Song, K., & Oliphant, A. (2012). Non-invasive prenatal detection and selective analysis of cell-free DNA obtained from maternal blood: evaluation for trisomy 21 and trisomy 18. *American Journal of Obstetrics and Gynecology*, 206(4), 319.e1-319.e9.

[12] Haque, I. S., Lazarin, G. A., Kang, H. P., Evans, E. A., & Goldberg, J. D. (2016). Modeled Fetal Risk of Genetic Diseases Identified by Expanded Carrier Screening. *JAMA*, 316(7), 734-742.

[13] Edwards, J. G., Feldman, G., Goldberg, J., Gregg, A. R., Norton, M. E., Rose, N. C., ... & Watson, M. S. (2015). Expanded carrier screening in reproductive medicine—points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. *Obstetrics and Gynecology*, 125(3), 653-662.

[14] Gil, M. M., Quezada, M. S., Bregant, B., Ferraro, M., & Nicolaides, K. H. (2013). Implementation of maternal blood cell-free DNA testing in early screening for aneuploidies. *Ultrasound in Obstetrics and Gynecology*, 49(5), 625-630.

[15] Bianchi, D. W., Platt, L. D., Goldberg, J. D., Abuhamad, A. Z., Sehnert, A. J., & Rava, R. P. (2012). Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. *Obstetrics and Gynecology*, 125(6), 1354-1361.

[16] Chitty, L. S., Bianchi, D. W., & Wilkins-Haug, L. (2013). Noninvasive prenatal testing: the paradigm is shifting rapidly. *Prenatal Diagnosis*, 38(1), 10-13.

[17] Shaffer, L. G., & Bejjani, B. A. (2004). A cytogeneticist's perspective on genomic microarrays. *Human Reproduction Update*, 12(3), 203-209.

[18] Wapner, R. J., Martin, C. L., Levy, B., Ballif, B. C., Eng, C. M., Zachary, J. M., ... & Bejjani, B. A. (2012). Chromosomal microarray versus karyotyping for prenatal diagnosis. *New England Journal of Medicine*, 367(23), 2175-2184.

[19] Reddy, U. M., Page, G. P., Saade, G. R., Silver, R. M., Thorsten, V. R., Parker, C. B., ... & NICHD Stillbirth Collaborative Research Network. (2012). Karyotype versus microarray testing for genetic abnormalities after stillbirth. *New England Journal of Medicine*, 367(23), 2185-2193.

[20] Rehm, H. L., Bale, S. J., Bayrak-Toydemir, P., Berg, J. S., Brown, K. K., Deignan, J. L., ... & American College of Medical Genetics and Genomics. (2013). ACMG clinical laboratory standards for next-generation sequencing. *Genetics in Medicine*, 15(9), 733-747.

[21] Skirton, H., Goldsmith, L., Jackson, L., Lewis, C., & Chitty, L. S. (2013). Offering prenatal diagnostic tests: European guidelines for clinical practice guidelines. *European Journal of Human Genetics*, 23

[22] Bianchi, D. W., Parker, R. L., Wentworth, J., Madankumar, R., Saffer, C., Das, A. F., ... & CARE Study Group. (2014). DNA sequencing versus standard prenatal aneuploidy screening. *New England Journal of Medicine*, 370(9), 799-808.

[23] Wapner, R. J., Martin, C. L., Levy, B., Ballif, B. C., Eng, C. M., Zachary, J. M., ... & Bejjani, B. A. (2012). Chromosomal microarray versus karyotyping for prenatal diagnosis. *New England Journal of Medicine*, 367(23), 2175-2184.

[24] Reddy, U. M., Page, G. P., Saade, G. R., Silver, R. M., Thorsten, V. R., Parker, C. B., ... & NICHD Stillbirth Collaborative Research Network. (2012). Karyotype versus microarray testing for genetic abnormalities after stillbirth. *New England Journal of Medicine*, 367(23), 2185-2193.