International Journal of Reproductive BioMedicine
Volume 24, Issue no. 6, https://doi.org/10.18502/ijrm.v24i6.21461
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Original Article

Accuracy of non-invasive prenatal screening compared with amniocentesis: A retrospective study

Elham Ghadirkhomi Ph.D., Arezu Norouzi M.Sc.

Department of Genetics in Reproductive Disorders, Academic Center for Education, Culture, and Research (ACECR), Tabriz, Iran.

Corresponding Author:
Elham Ghadirkhomi; Department of Genetics in Reproductive Disorders, Academic Center for Education, Culture and Research (ACECR), Sheikh Kamal Ave., Tabriz, Iran.
Postal Code: 5166616886
Tel: (+98) 9144195679
Email: ghadirkhomi@acecr.ac.ir

Received: 7 December 2025
Revised: 30 December 2025
Accepted: 21 April 2026

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Editor-in-Chief:
Aflatoonian Abbas M.D.

Abstract

Background: One significant concern during pregnancy is the possibility of chromosomal malformations. While prenatal screenings are intended to reassure parents about the health of their unborn child, how reliable are these results when deemed suspicious?

Objective: This study aimed to evaluate the predictive accuracy of non-invasive prenatal screening tests in comparison with amniocentesis as the gold standard diagnostic method for chromosomal abnormalities.

Materials and Methods: This retrospective descriptive-analytical study was performed using medical records of 490 pregnant women who underwent amniocentesis between 2018 and 2023. Data related to first- and second-trimester maternal serum screening results, ultrasound markers, and fetal karyotype findings were extracted and analyzed.

Results: Among 490 pregnant women who underwent amniocentesis, 79 cases were suspected of chromosomal abnormalities based on combined first-trimester ultrasound criteria. Cytogenetic analysis confirmed abnormalities in only 20 of these suspected cases (25.3%). After excluding very low-risk results ($\geq$ 1:300), amniocentesis confirmed abnormalities in only 5.1% (12/234) of first-trimester and 4.5% (7/155) of second-trimester screen-positive cases. All comparisons between screening results and amniocentesis showed significant differences ($p < 0.05$).

Conclusion: These findings suggest that a more appropriate clinical approach involves the integrated use of multiple screening tools combined with genetic counseling and clear communication for prenatal care, as well as using validated noninvasive methods such as non-invasive prenatal testing before amniocentesis, thus rationally supporting parents when making decisions. Ultimately, although amniocentesis remains the most accurate diagnostic tool, the goal should be to use all available methods judiciously to minimize unnecessary interventions and psychological harm.

Keywords: *Prenatal screening, Amniocentesis, Chromosomal abnormalities, Prenatal diagnosis, Genetic counseling.*

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1. Introduction

Chromosomal anomalies during pregnancy are a significant concern; the most prevalent conditions include Down syndrome (trisomy 21), Edwards syndrome (trisomy 18), and Patau syndrome (trisomy 13). These disorders can substantially affect fetal development and quality of life for affected children and their families. Early diagnosis enables informed decision-making and appropriate pregnancy management. Therefore, screening tests have become standard tools for assessing the risk of chromosomal abnormalities during the first and second trimesters of pregnancy (1–3).

First-trimester screening typically involves noninvasive blood tests and ultrasound measurements, including nuchal translucency (NT), free β-human chorionic gonadotropin, and pregnancy-associated plasma protein A. These markers, taken together with maternal age and gestational age, provide an estimate of the risk of trisomy 21, trisomy 18, and other genetic conditions (4, 5). First-trimester screening identifies approximately 90% of Down syndrome cases, although sensitivity can differ based on the combination of markers used (2, 6). Although cell-free DNA screening has demonstrated higher detection rates for common aneuploidies, its widespread use remains limited in some settings because of cost and accessibility constraints (5, 7–9). Second-trimester screening provides additional risk assessment through maternal serum markers and complements first-trimester findings (10). Invasive diagnostic testing, however, may be recommended where screening tests indicate a high risk of chromosomal abnormalities. Among invasive prenatal diagnostic methods, amniocentesis is one of the most frequently performed procedures involving the retrieval of amniotic fluid from the fetal environment. This fluid contains fetal cells that can be analyzed to confirm the presence of chromosomal abnormalities, such as trisomy 21, with a nearly 99% accuracy rate (11). Despite its high diagnostic accuracy, amniocentesis carries a small risk of complications, such as miscarriage, and is typically only performed after abnormal screening results.

Given the need for accurate prenatal risk assessment, this study compared conventional first- and second-trimester screening results with amniocentesis findings in an Iranian referral population to evaluate their clinical predictive value.

2. Materials and Methods

2.1. Study design and setting

This retrospective descriptive-analytical study was conducted using medical records of 490 pregnant women who underwent amniocentesis at the ACECR Genetic Center, Tabriz, Iran, between March 2018 and April 2023.

2.2. Sample size

The sample size was calculated using Cochran's formula for estimating proportions:

$$n = \frac{Z^2 \times p \times q}{d^2}$$

where Z represents the standard normal variate corresponding to a 95% confidence level (Z = 1.96), p is the estimated proportion based on previous similar studies, q = 1 - p, and d is the margin of

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error set at 0.05. Based on these assumptions, the minimum required sample size was calculated to be 214 participants. To improve the reliability of the findings and account for potential incomplete records, all eligible cases available during the study period were included, resulting in a final sample size of 490 participants. A flow diagram of participant selection is presented in figure 1.

2.3. Sample collection and criteria

Amniotic fluid samples were collected through standard amniocentesis procedures. Participants included pregnant women who met the inclusion criteria and provided informed consent. Inclusion criteria included pregnant women who were referred to the center by a gynecologist for amniocentesis due to various medical reasons (including the age of the mother, family history of genetic abnormalities, abnormal results of blood screenings, etc.). All referrals for amniocentesis were made in accordance with the Iranian Ministry of Health and Medical Education's national guidelines for prenatal diagnosis, according to the national prenatal diagnosis protocols and clinical recommendations in effect during the study period (2018–2023). The participants were between 19 and 43 yr old and were 15–20 wk pregnant. First- and second-trimester blood screening and ultrasound were performed for all participants. Individuals who did not wish to participate, as well as those with multiple pregnancies, were excluded from the study.

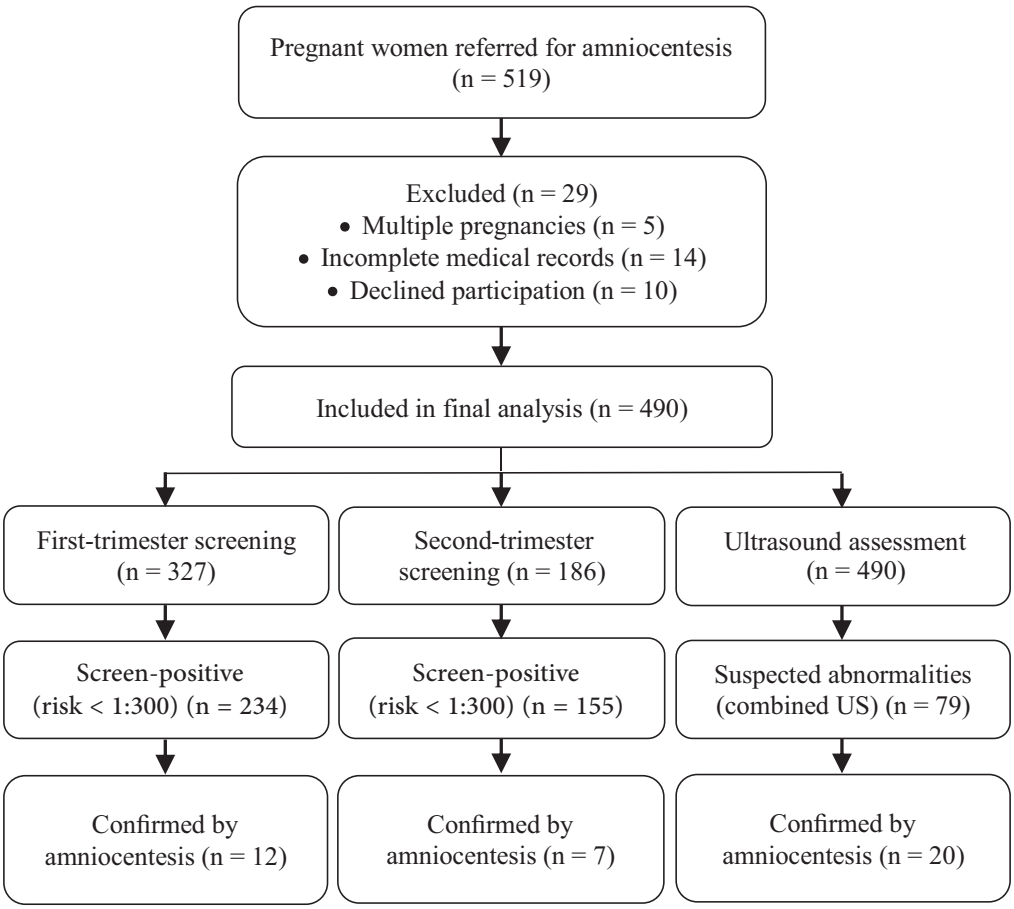

Figure 1. Flow diagram of participant selection and study design.

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2.4. Ethical Considerations

This study was retrospective and based on previously collected medical records obtained during routine clinical care between 2018 and 2023. Ethical approval for retrospective data analysis and publication was obtained from the research ethics committee of Avicenna Research Institute, Tehran, Iran (Code: IR.ACECR.AVICENNA.REC.1403.018). All participants' data were anonymized, and no identifying information was used. The study protocol complied with the principles of the Declaration of Helsinki.

2.5. Statistical Analysis

For the data analysis, results from chromosomal tests, ultrasound parameters, blood screenings, and any relevant clinical history were gathered. SPSS software (version 27.0.1) was used to analyze the data. Continuous variables (e.g., maternal age, NT, crown-rump length [CRL], fetal heart rate [FHR]) were treated as numerical data, while categorical variables (e.g., risk categories, referral reasons, karyotype results) were expressed as frequencies and percentages. Descriptive statistics are presented as mean ± standard deviation or frequency (percentage). The independent samples *t* test was used to compare continuous variables between groups. A two-tailed $p < 0.05$ was considered statistically significant, and 95% confidence intervals (CIs) were calculated for all mean differences.

3. Results

330 participants were referred to the laboratory due to high-risk findings in first- or second-trimester screening, 70 for check-ups (due to advanced maternal age or their request), 45 due to high NT levels, and 45 for various reasons, including genetic abnormalities. Table I presents the reasons for referral and the age of those referred to the laboratory.

3.27% of the participants were < 20 yr old, 11.02% of the participants were between 20 and 25 yr old, 16.33% of the participants were between 25 and 30 yr old, 17.14% of the participants were between 30 and 35 yr old, 26.73% of the participants were between 35 and 40 yr old, and 15.51% of them were > 40 yr old. First, the ultrasound results from the first-trimester screening, including NT, CRL, and FHR, were examined. Table II presents the number of samples suspected of Down syndrome or other chromosomal abnormalities.

According to the results in table II, 39 samples based on CRL value, 19 samples based on NT value, and 25 samples based on FHR value can be suspected of chromosomal abnormalities. Based on the combined assessment of 3 ultrasound criteria, a total of 79 samples were suspected of chromosomal abnormalities. Cytogenetic analysis of amniotic fluid in these samples confirmed the presence of chromosomal abnormalities in only 20 samples (Table III).

Table IV illustrates the correlation between ultrasound-based suspected chromosomal abnormality results and those obtained from amniocentesis.

The results presented in table IV indicate that the $p < 0.05$ at the 95% CI, suggesting a statistically significant difference between the ultrasound criteria and the amniocentesis results. These findings imply that relying solely on ultrasound criteria may not be sufficient for accurate screening of chromosomal abnormalities. This discrepancy is particularly

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evident among participants who underwent amniocentesis due to elevated NT measurements, where only 5 out of 45 suspected cases were confirmed positive by amniocentesis. The inaccuracy and inability of ultrasound results to diagnose chromosomal abnormalities have led doctors to rely on the results of blood screening tests to make decisions. At this stage, based on the results of pregnancy-associated plasma protein A as well as other indicators, such as the mother's age, the risk of chromosomal abnormalities is determined. By reviewing the relevant data, 327 samples have undergone first-trimester screening tests, and 186 samples have undergone second-trimester screening tests. Among the 327 women who underwent first-trimester screening and subsequent amniocentesis, 93 women (28.4%) had a calculated risk in the low-risk range (≥ 1:300). The remaining 234 women (71.6%) had either an elevated risk (< 1:300) or an indeterminate result warranting further investigation. It is this latter group of 234 women that constituted the clinically relevant screen-positive population. Of these 234 women, only 12 (5.1%) had confirmed chromosomal abnormalities on karyotyping (positive predictive value [PPV] = 5.1%, 95% CI: 2.8–8.7).

For the 186 women who underwent second-trimester screening, 31 (16.7%) had a low-risk result (≥ 1:300). The remaining 155 women (83.3%) had elevated or indeterminate risk and underwent amniocentesis. In this group, 7 cases (4.5%) were confirmed positive (PPV = 4.5%, 95% CI: 2.0–9.0).

Table V shows that a significant difference was observed between the risk of the first and second-trimester screening tests and the results of the amniocentesis test. This means that the presence of chromosomal abnormalities cannot be confirmed with certainty based on the high risk of blood screening. In general, a significant difference in variables were observed in the results of the first and second-trimester screening and amniocentesis test. Additionally, by considering other variables that influence chromosomal disorders (Table V), it was found that there was a significant difference between the results, indicating that the presence of chromosomal abnormalities cannot be determined solely from an individual's history.

Table I. Reasons for referral and age of participants

Year	High risk for Down syndrome	Intermediate risk for Down syndrome	Check-up	High NT	Other reason	Total	Age of participants	Frequency	Percentage of frequency
2018	37	24	25	10	6	102	< 20	16	3.27
2019	63	13	23	14	3	116	21–25	54	11.02
2020	39	17	15	0	6	77	25–30	80	16.33
2021	56	32	7	13	13	121	30–35	133	27.14
2022	19	10	0	5	12	46	35–40	131	26.73
2023	14	6	0	3	5	28	≥ 40	76	15.51

NT: Nuchal translucency

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Table II. Number of samples suspected of chromosomal abnormalities

Year	Out of normal range		
	84 ≤ CRL ≤ 45	3.5 ≤ NT	170 ≤ FHR ≤ 120
2018	102	97	94
2019	112	111	114
2020	75	75	75
2021	99	115	113
2022	29	19	25
2023	23	27	27
Total	39	19	25

CRL: Crown-rump length, NT: Nuchal translucency, FHR: Fetal heart rate

Table III. The positive results of amniocentesis based on the reason for referral

Year	Reason for referral	Pregnancy week	Ultrasound results			Risk tresomy 21	Age	Miscarriage or certain genetic diseases
			CRL (mm)	NT (mm)	FHR (min)			
2018	Down risk	15w	57	1.8	170	1:36	48	No
2018	Down risk	17W+3d	52	1.3	172	1:108	33	No
2018	Down risk	15W	58	1.7	163	1:12	40	1 abortion case
2018	High NT	15W+3d	77	4.4	165	1:2	43	No
2019	Down risk	18W+3d	75	1.9	149	1:8	45	1 abortion case
2019	Down risk	18W	57	1.4	140	1:196	39	1 abortion case
2019	High NT	19W	62	5	145	1:250	43	No
2020	Down risk	15W	65	1.2	169	1:66	37	No
2020	Down risk	19w+5d	69	2.4	155	1:219	24	No
2020	Down risk	15W+6d	51	1.1	166	1:75	39	2 abortion cases
2021	Down risk	16W	46	1.6	172	1:50	42	No
2021	High NT	19W+3d	54	3.15	148	1:61	22	No
2022	Down risk	19W+5d	63	1.9	170	1:234	37	No
2022	Down risk	15W+1d	53	1.05	170	1:101	42	3 abortion cases
2022	Down risk	18W+2d	40	2	155	1:2	44	1 abortion case
2022	Down risk	17W+3d	56	1.3	134	1:4	36	No
2022	High NT	15W+2d	79	2.28	160	1:150	35	1 abortion case
2023	High NT	18W	81	2.9	151	1:1200	29	No
2023	High NT	16W	67	2.48	155	1:151	40	No
2023	Down risk	19W	55	2.4	144	1:8	39	No

CRL: Crown-rump length, NT: Nuchal translucency, FHR: Fetal heart rate

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Table IV. Comparison of ultrasound markers (NT, CRL, FHR) and combined assessment with amniocentesis outcomes

Index	95% CI for mean difference	T-value	P-value
NT criteria			
High risk Down syndrome	(0.0213, 0.1157)	5.23	0.000
Intermediate risk	(0.0125, 0.1337)	6.24	0.000
Check-up	(0.0248, 0.1230)	2.53	0.012
Other reason	(0.1423, 0.3475)	4.39	0.000
Total	(0.0204, 0.2261)	3.94	0.000
CRL criteria			
High risk down	(0.0314, 0.1394)	4.68	0.000
Intermediate risk	(0.1570, 0.3484)	5.50	0.000
Check-up	(0.1846, 0.3841)	4.66	0.000
Other reason	(0.1320, 0.4903)	3.50	0.001
Total	(0.0723, 0.1328)	6.44	0.000
FHR criteria			
High risk down	(0.0214, 0.1436)	2.42	0.013
Intermediate risk	(0.0294, 0.1176)	5.02	0.000
Check-up	(0.0233, 0.1796)	4.15	0.000
Other reason	(0.0423, 0.2478)	2.36	0.018
Total	(0.0239, 0.0974)	5.48	0.000
Combined assessment of 3 ultrasound criteria			
High risk down	(0.0525, 0.1353)	4.46	0.000
Intermediate risk	(0.1320, 0.4903)	3.50	0.001
Check-up	(0.0185, 0.1529)	2.54	0.013
Other reason	(0.0305, 0.3251)	2.43	0.019
Total	(0.0841, 0.1567)	6.51	0.000

Independent samples *t* test, significance level set at $p \leq 0.05$. CRL: Crown-rump length, NT: Nuchal translucency, FHR: Fetal heart rate, CI: confidence interval

Table V. Correlation of blood screening results and maternal risk factors with confirmatory amniocentesis findings

Variables	95% CI for the mean difference	T-value	P-value
Stage			
First-trimester	(0.6226, 0.7450)	22.01	0.000
Second-trimester	(0.7199, 0.8480)	24.17	0.000
Maternal risk factors			
History of miscarriage	(0.2348, 0.3244)	12.26	0.000
Family relationship	(0.8975, 1.0174)	32.17	0.000
IDDM	(0.00907, 0.04807)	2.88	0.004
Smoke	(0.02324, 0.05840	4.56	0.000
RH	(0.3272, 0.4197)	15.87	0.000

Independent samples *t* test; significance level set at $p \leq 0.05$. IDDM: Insulin-dependent diabetes mellitus, RH: Rhesus factor, CI: confidence interval

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4. Discussion

This study examined the effectiveness of noninvasive screening methods, such as blood tests and ultrasounds performed during the first and second trimesters, in predicting chromosomal abnormalities compared to the more invasive procedure of amniocentesis. This issue has generated significant conversation in prenatal care regarding the dependability of these screening techniques in relation to conventional diagnostic tests. Primarily, the research emphasizes the restricted diagnostic precision of ultrasound indicators, especially NT, CRL, and FHR. Despite being widely used in the first trimester, ultrasound-based assessments yielded a significant number of false positives. Only 20 out of 79 cases flagged as suspicious by ultrasound were confirmed to have chromosomal abnormalities through amniocentesis, underscoring its low PPV. This aligns with prior research that cautions against over-reliance on ultrasound findings alone without confirmatory testing (2, 11). The blood tests from the first and second trimesters seem more specific than ultrasound, but they still have their downsides. For those identified as high-risk based on serum markers, only a few confirmed chromosomal issues through amniocentesis (12 in the first trimester and 7 in the second). This finding is consistent with previous large-scale real-world studies, which indicate that although first- and second-trimester serum screening tests can detect a substantial proportion of trisomy 21 cases, they are insufficient for a definitive diagnosis (5, 6).

The psychological toll of false-positive screening results is substantial and well-documented. Maternal anxiety following a high-risk screening result can persist throughout pregnancy and may adversely affect prenatal attachment and postpartum mental health (12–14). In the present cohort, over 75% of invasive procedures performed for abnormal ultrasound findings, and approximately 87% of those performed for high-risk serum screening, yielded normal karyotypes. This high false-positive rate underscores the critical need for robust pre-test counseling and shared decision-making to mitigate iatrogenic psychological harm.

In fact, the majority of high-risk cases identified in this study were not confirmed by amniocentesis, illustrating the emotional and ethical damage caused by premature or poorly communicated screening results. While ultrasound and laboratory tests have some connection to amniocentesis results, they do not solely guarantee accurate diagnoses. This discrepancy highlights the need for clear and compassionate communication when discussing screening results with individuals. The use of terms like “high risk” must be carefully contextualized, with clinicians offering absolute risk estimates and explaining the probabilistic nature of screening, not deterministic outcomes. Without this clarity, individuals may misinterpret the results as a definitive diagnosis, leading to undue stress or premature decisions (14, 15). That is why it is important to look at a mix of clinical info, lab results, and imaging together. This method lines up with the best practices and the latest prenatal screening guidelines (5).

What is really clear is that no single factor, like a woman’s age or past miscarriages, can reliably predict chromosomal issues on its own. Even though non-invasive methods have their limits, amniocentesis is still the go-to for prenatal testing, with almost 99% accuracy in finding chromosomal problems (2). Since it is invasive and carries a small risk of miscarriage, it is usually recommended only when tests point to a high chance of chromosomal issues. This way, we get the best certainty in diagnosis while keeping risks low. It is noteworthy that, as demonstrated

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in table III, all confirmed cases of chromosomal abnormalities in this cohort were identified among women with either a high-risk screening result (risk < 1:300) or an elevated NT measurement. This observation underscores the fundamental value of prenatal screening programs in effectively triaging patients for invasive diagnostic testing. Conversely, the performance of amniocentesis in women with low-risk screening results (risk ≥ 1:300) or those referred solely for maternal age without additional risk factors highlights a potential deviation from evidence-based practice. Such practices expose women to the procedure-related risk of miscarriage, estimated at approximately 1 in 500 to 1 in 1000 in contemporary practice (16) without a proportionate increase in diagnostic yield. Strict adherence to national guideline thresholds for offering invasive testing is therefore essential to minimize iatrogenic harm and optimize the risk-benefit ratio of prenatal care.

Based on the study findings, several key recommendations can enhance the accuracy, effectiveness, and emotional safety of prenatal screening practices.

First, clinicians should adopt a combined risk assessment strategy, integrating maternal age, medical history, ultrasound findings, and blood screening results to better estimate the likelihood of chromosomal abnormalities before recommending invasive procedures like amniocentesis. Second, genetic counseling must be embedded in prenatal care, especially following abnormal screening outcomes, to ensure individuals fully understand the distinction between screening and diagnostic tests and can make informed decisions. To further aid understanding, healthcare providers should implement decision-support tools, such as visual aids or interactive risk calculators, which help individuals contextualize risk in relation to population norms. Additionally, where resources allow, non-invasive prenatal testing should be considered as a second-tier screening method, beneficial for reducing unnecessary amniocentesis in low-risk pregnancies (5, 17). Finally, mental health support and psychological reassurance should be included in prenatal consultations to help manage the anxiety and stress often triggered by uncertain or high-risk screening results.

This study has several important limitations. First, its retrospective design relies on the accuracy and completeness of medical records. Second, and most critically, the study cohort consists exclusively of women referred for invasive diagnostic testing, introducing significant selection (verification) bias. Women with screen-negative results who did not undergo amniocentesis and subsequently delivered healthy infants are not represented in this analysis. Consequently, the true negative predictive value of screening cannot be assessed, and the findings are not generalizable to the general low-risk obstetric population.

5. Conclusion

While first- and second-trimester screening are essential components of prenatal care for early risk stratification, their limited specificity can lead to significant parental anxiety and unnecessary invasive procedures. A balanced clinical approach (integrating multiple screening modalities, adhering to evidence-based guidelines, and providing comprehensive genetic counseling) is essential to optimize detection of chromosomal abnormalities while minimizing psychological and procedural harms.

Data Availability

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Author Contributions

E. Ghadirkhomi and A. Norouzi designed the study and conducted the research. They also collected and evaluated data from medical records and analyzed the study data. A. Norouzi drafted the manuscript, and E. Ghadirkhomi critically reviewed and revised the manuscript for important intellectual content. Both authors approved the final version of the manuscript and take responsibility for the integrity and accuracy of the work.

Acknowledgments

The authors would like to thank the staff of the ACECR Genetic Center, Tabriz, Iran, for their assistance in data collection and technical support. This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. ChatGPT (OpenAI) was used solely for language editing, grammar correction, and improvement of manuscript readability. All scientific content, data analysis, interpretation of results, and final manuscript approval were performed by the authors. The authors also thank all individuals who contributed to this study but did not meet the criteria for authorship.

Conflict of Interest

The authors declare that there is no conflict of interest.

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