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Research Article

Factors associated with fetal chromosomal aneuploidy in high-risk pregnant women

Factores asociados con la aneuploidía cromosómica fetal en mujeres embarazadas de alto riesgo

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ABSTRACT

Introduction: Chromosomal aneuploidy (CA) is one of the leading causes of miscarriage and congenital anomalies, particularly prevalent among high-risk pregnant women.

Objective: To identify the key predictors associated with fetal chromosomal aneuploidy among high-risk pregnant women.

Methods: A prospective study was conducted on 436 high-risk pregnant women at Hanoi Obstetrics and Gynecology Hospital, Vietnam, from April 2021 to December 2024. The participants underwent amniocentesis and karyotyping. Collected risk factors included maternal age, paternal age, history of miscarriage, history of giving birth to children with birth defects,


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occupational exposure to chemicals, place of residence, and abnormal fetal ultrasound findings. Statistical analysis was performed using both univariate and multivariate logistic regression.

Results: The overall rate of chromosomal aneuploidy was 11.2%, with trisomy 21 being the most common (42.9%). In the univariate analysis, statistically significant risk factors associated with CA included: maternal age ≥ 35 (OR = 2.3; p = 0.007), paternal age ≥ 40 (OR = 2.1; p = 0.033), and abnormal ultrasound findings (OR = 2.2; p = 0.017). In multivariate analysis, only abnormal ultrasound findings remained statistically significant (OR = 2.06; p = 0.022).

Conclusion: Advanced paternal age and abnormal fetal ultrasound findings serve as important predictors for screening fetal chromosomal aneuploidy in high-risk pregnant women.

Keywords: amniocentesis; chromosomal aneuploidy; high-risk pregnancy; prenatal screening; prenatal ultrasonography.

RESUMEN

Introducción: La aneuploidía cromosómica (AC) es una de las principales causas de aborto espontáneo y anomalías congénitas, particularmente prevalente entre las mujeres embarazadas de alto riesgo.

Objetivo: Identificar los principales predictores asociados con la aneuploidía cromosómica fetal en mujeres embarazadas de alto riesgo.

Métodos: Se llevó a cabo un estudio prospectivo en 436 mujeres embarazadas de alto riesgo en el Hospital de Obstetricia y Ginecología de Hanói, Vietnam, desde abril de 2021 hasta diciembre de 2024. Las participantes se sometieron a amniocentesis y cariotipo. Los factores de riesgo recogidos incluyeron: edad materna, edad paterna, antecedentes de aborto espontáneo, antecedentes de parto de hijos con defectos congénitos, exposición ocupacional a productos químicos, lugar de residencia y hallazgos anormales en ecografías fetales. Se realizó un análisis estadístico utilizando regresión logística univariante y multivariante.

Resultados: La tasa general de aneuploidía cromosómica fue del 11,2 %; la trisomía 21 fue la más común (42,9 %). En el análisis univariante, los factores de riesgo estadísticamente significativos asociados con la AC fueron: edad materna ≥ 35 años (OR= 2,3; p= 0,007), edad paterna ≥ 40 años

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(OR= 2,1; p= 0,033) y hallazgos ecográficos fetales anormales (OR= 2,2; p= 0,017). En el análisis multivariante, solo los hallazgos ecográficos anormales se mantuvieron estadísticamente significativos (OR= 2,06; p= 0,022).

Conclusión: La edad paterna avanzada y los hallazgos ecográficos fetales anormales actúan como predictores importantes para el cribado de la aneuploidía cromosómica fetal en mujeres embarazadas de alto riesgo.

Palabras clave: amniocentesis; aneuploidía cromosómica; embarazo de alto riesgo; cribado prenatal; ecografía prenatal.

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INTRODUCTION

Chromosomal abnormalities (CA) are among the most common causes of congenital anomalies, miscarriages, and stillbirths, and are the first or second most frequent indications for prenatal invasive testing.[1] Among them, common aneuploidies such as trisomy 21 (Down syndrome), trisomy 18, and trisomy 13 are frequently observed, particularly among high-risk pregnant populations.[2]

According to statistics, the rate of fetal chromosomal abnormalities is increasing, especially in high-risk pregnant women.[3] One of the most recognized and well-established risk factors is advanced maternal age, typically defined as age ≥ 35 years, due to the increasing frequency of chromosomal anomalies with maternal age. ACOG (American College of Obstetricians and Gynecologists) estimates that the risk of Down syndrome is 1 in 350 at age 35, rising to 1 in 100 at age 40, and 1 in 30 at age 45.[4] Multiple studies have confirmed that women aged 35 and older have a significantly higher incidence of fetal chromosomal anomalies than younger women.[5]


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Advanced maternal age is a principal risk factor due to its impact on oocyte quality, leading to meiotic nondisjunction errors during cell division.[6]

In addition to age, other risk factors include environmental exposure to toxic chemicals, history of miscarriage, paternal age, family history of birth defects, and previous birth of children with congenital anomalies — all of which are associated with increased risk of fetal chromosomal abnormalities.[7,8,9,10,11] Abnormal ultrasound markers (e.g., increased nuchal translucency, absent nasal bone, single umbilical artery, shortened femur, etc.) have been shown to have predictive value for trisomy, with a sensitivity of approximately 60–70% when combined with serum biochemical screening.[12] Moreover, maternal exposure to environmental toxins during pregnancy — including industrial solvents, pesticides, and heavy metals — has been linked to fetal anomalies and chromosomal abnormalities as highlighted in recent epidemiological studies.[13]

In Vietnam and other Southeast Asian countries, prenatal genetic screening programs are still inconsistently implemented, and access to cytogenetic testing remains limited to urban centers. Regional data on chromosomal abnormalities in high-risk pregnancies are scarce, underscoring the need for locally relevant evidence to guide national prenatal care policies. Therefore, this study was conducted to evaluate factors associated with fetal chromosomal aneuploidy in high-risk pregnant women.

METHODS

Study population and design

This was a prospective analytical observational study conducted on 436 high-risk pregnant women at Hanoi Obstetrics and Gynecology Hospital, Vietnam, from April 2021 to December 2024. Participants were enrolled consecutively based on predefined inclusion criteria. The inclusion criteria consisted of:

(1) Maternal age ≥ 35: Women aged 35 and above are directly associated with an increased risk of chromosomal abnormalities due to declining reproductive function.


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(2) Abnormal ultrasound findings: Specific abnormalities that may indicate high risk, such as increased nuchal translucency or structural malformations. These are considered important predictive markers for the risk of chromosomal abnormalities in subsequent pregnancies.

(3) History of miscarriage: Recurrent miscarriage is considered a risk factor for chromosomal anomalies.

(4) Exposure to toxic chemicals: Harmful substances that can damage DNA and lead to genetic disorders. All participants provided written informed consent before inclusion in the study. The minimum sample size was calculated based on the formula for estimating the proportion in descriptive research:

$$n = \frac{Z^2_{1-\alpha/2} \cdot p(1-p)}{d^2}$$

In which:

Z1–α/2 = 1.96 (with 95% confidence level);

p = 0.114 is the estimated rate of chromosomal abnormalities in high-risk pregnant women according to Li H *et al*.;[14]

d = 0.03 is the desired margin of error.

Based on this formula, the required minimum sample size was approximately 432 participants. This study collected data from 436 pregnant women who met the inclusion criteria.

Research Procedures

The research process was carried out in the following steps:

Selection of study subjects: Pregnant women who visited Hanoi Obstetrics and Gynecology Hospital, Vietnam, between April 2021 and December 2024 were screened and selected according to inclusion criteria.

Eligible participants were thoroughly informed about the study objectives, procedures, benefits, and potential risks. Only those who agreed to participate signed written informed consent forms.


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Medical data were collected from medical records and structured interviews. Collected variables included maternal and paternal age, obstetric history, occupation, residential area, exposure to environmental risks, abnormal ultrasound findings, and relevant genetic indicators.

Participants who met the criteria were referred for amniocentesis under ultrasound guidance between gestational weeks 16 and 20. Amniotic fluid samples were analyzed at the hospital's genetics laboratory using Giemsa banding technique (G-banding) for the purpose of chromosomal karyotyping.

Data collection and analysis followed standardized protocols.

Variables

Dependent variable: Presence of fetal chromosomal abnormalities (yes/no), determined based on karyotyping results from amniotic fluid samples.

Independent variables:

Maternal age: < 35 years / ≥ 35 years

Paternal age: < 40 years / ≥ 40 years

History of miscarriage: Yes / No

History of giving birth to a child with congenital anomalies: Yes / No

Occupation involving exposure to hazardous chemicals during pregnancy: Yes / No

Place of residence: Urban / Rural

Abnormal fetal ultrasound findings: Yes / No

Indicators include increased nuchal translucency (NT ≥ 3 mm), hypoplastic nasal bone, fetal cardiac anomalies, and other structural malformations (based on prenatal screening between 12–22 weeks of gestation).

Statistical analysis

All data were analyzed using SPSS software version 27.0 (IBM Corp., Armonk, NY, USA). Quantitative variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) if non-normally distributed. Categorical variables were described using frequency and percentage. Group differences were assessed using the Chi-square test (χ^2). The associations between risk factors and fetal chromosomal abnormalities were evaluated using both


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univariate and multivariate binary logistic regression analyses. Results were expressed as odds ratios (ORs) with 95% confidence intervals (95% CI). A p-value < 0.05 was considered statistically significant.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committees of the Institute of Genome Research, Vietnam (No: 10-2019/NCHG-HĐĐĐ, dated October 30, 2019), and Hanoi Medical University, Vietnam (No: 668/GCN-HĐĐĐNCYSH-ĐHYHN, dated March 29, 2023). Informed consent was obtained by distributing the consent forms and obtaining signed agreement from all participants involved in the study.

RESULTS

Characteristics of study participants

The mean maternal age was 29.9 ± 5.8 years and the mean paternal age was 32.0 ± 5.8 years. The proportion of mothers aged ≥ 35 accounted for 21.8% (95 cases), while fathers aged ≥ 40 accounted for 12.8% (56 cases). The proportion of women with a history of miscarriage was 25.9% (n = 113). A total of 2.1% of participants (n = 9) were engaged in occupations involving exposure to harmful chemicals during pregnancy. Regarding the history of giving birth to children with birth defects, 3.7% of the women reported such a history. Abnormal findings on prenatal ultrasound were noted in 45.2% of cases (n = 197). Women residing in rural areas accounted for 39.9% (n = 174), while the remaining 60.1% lived in urban or other areas (table 1).


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Table 1 - Characteristics of study participants (n = 436)

Characteristics	Number (n)	Percentage (%)
Maternal age (years)	29.9 ± 5.8	
≥ 35	95	21.8
< 35	341	78.2
Paternal age (years)	32.0 ± 5.8	
≥ 40	56	12.8
< 40	380	87.2
History of miscarriage		
Yes	113	25.9
No	323	74.1
Occupation involving exposure to chemicals		
Yes	9	2.1
No	427	97.9
History of giving birth to a child with defect		
Yes	16	3.7
No	420	96.3
Abnormal prenatal ultrasound		
Yes	197	45.2
No	239	54.8
Residence in rural area		
Yes	174	39.9
No	262	60.1

Chromosomal aneuploidy rate

Among the 436 pregnancies, 49 cases (11.2%) were identified with chromosomal aneuploidy (table 2). The specific distribution of aneuploidy types was as follows: trisomy 21 (Down syndrome): 21/49 cases (42.9%), trisomy 18: 8/49 cases (16.3%), trisomy 13: 1/49 case (2.0%), and sex chromosome aneuploidies (XO, XXY, XYY, XXX): 18/49 cases (36.7%). Other rare chromosomal abnormalities such as 69, XXY were identified in 1/49 case (2.0%).


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Table 2 - Karyotype results of 436 amniocentesis samples

Karyotype Result	Number (n)	Percentage (%)
Normal (46,XX or 46,XY)	387	88.8
Abnormal	49	11.2
47,XX or XY, +13	1	2.0
47,XX or XY, +18	8	16.3
47,XX or XY, +21	21	42.9
45,XO	8	16.3
47,XXX/XXY/XYY	10	20.4
69,XXY	1	2.0

Analysis of risk factors associated with chromosomal aneuploidy

In the univariate analysis (table 3), several factors showed statistically significant differences between groups with and without chromosomal aneuploidy. The rate of aneuploidy among mothers aged ≥ 35 years was 18.9%, higher than that of the < 35 years group (9.1%), with an OR = 2.3; 95% CI: [1.2 – 4.4]; p = 0.007. Similarly, the rate of fetal aneuploidy in the paternal age group ≥ 40 years was 19.6%, compared to 10.0% in those < 40 years, OR = 2.1; 95% CI: [2.1 – 4.6]; p = 0.033. Ultrasound abnormalities also showed a significant difference between groups, with aneuploidy occurring in 15.2% of cases with abnormal ultrasound findings compared to 7.9% in the normal group, OR = 2.2; 95% CI: [1.2 – 4.1]; p = 0.017. Other variables, including history of miscarriage, congenital anomalies in previous offspring, occupational chemical exposure, and residential area, were not statistically significant (p > 0.05).

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Table 3 - Univariate analysis of factors associated with fetal chromosomal aneuploidy (n = 436)

Variables		Chromosomal aneuploidy		OR, [95 % CI]	p
		Yes n (%)	No n (%)		
Maternal age (years)	≥ 35	18 (18.9)	77 (81.1)	2.3 [1.2 - 4.4]	0.007
	< 35	31 (9.1)	310 (90.9)		
Paternal age (years)	≥ 40	11 (19.6)	45 (80.4)	2.1 [1.1 – 4.6]	0.033
	< 40	38 (10.0)	342 (90.0)		
History of miscarriage	Yes	12 (10.6)	101 (89.4)	0.9 [0.5 – 1.8]	0.809
	No	37 (11.5)	286 (88.5)		
Occupational chemical exposure	Yes	- (0.0)	9 (100.0)	-	0.606
	No	49 (11.5)	378 (88.5)		
Congenital anomalies in prior child	Yes	2 (12.5)	14 (87.5)	1.13 [0.25 – 5.14]	0.698
	No	47 (11.2)	373 (88.8)		
Abnormal ultrasound findings	Yes	30 (15.2)	167 (84.8)	2.2 [1.2 – 4.1]	0.017
	No	19 (7.9)	220 (92.1)		
Residence in rural area	Yes	16 (9.2)	158 (90.8)	0.70 [0.37 - 1.32]	0.271
	No	33 (12.6)	229 (87.4)		

In the multivariate logistic regression model (table 4), only the variable abnormal ultrasound findings showed a statistically significant association with chromosomal aneuploidy. Cases with abnormal ultrasound findings had a higher risk of chromosomal abnormalities, with an OR = 2.06; 95% CI: 1.11 – 3.82; p = 0.022. Other variables, including maternal age ≥ 35 (OR = 2.28; p = 0.078), paternal age ≥ 40 (OR = 1.05; p = 0.925), history of miscarriage (OR = 0.73; p = 0.399), and history of congenital anomalies in previous children (OR = 1.29; p = 0.758) did not show statistically significant associations in the model (p > 0.05).


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Table 4 - Multivariate analysis of factors associated with fetal chromosomal aneuploidy (n=436)

Variables	OR	95% CI	p-value
Maternal age ≥ 35	2.28	0.91 – 5.68	0.078
Paternal age ≥ 40	1.05	0.36 – 3.06	0.925
History of miscarriage	0.73	0.35 – 1.51	0.399
History of child with malformation	1.29	0.26 – 6.33	0.758
Abnormal ultrasound findings	2.06	1.11 – 3.82	**0.022**

DISCUSSION

In this study, the overall prevalence of fetal chromosomal abnormalities was 11.2% (49/436). Among these, trisomy 21 was the most frequent, accounting for 42.9%, followed by trisomy 18 (16.3%) and trisomy 13 (2.0%). Sex chromosome abnormalities (XO, XXY, XYY, XXX) constituted 36.7%, while other structural rearrangements were rare. These rates are comparable to the findings of *Seaton SE* et al.[15] who reported in their EUROCAT analysis that trisomy 21 represented approximately 60–70% of all prenatally detected chromosomal abnormalities, while trisomy 18 and 13 accounted for roughly 25% and ≤1 0%, respectively.

Another study based on non-invasive prenatal testing from nearly 68,763 samples also demonstrated a higher detection rate for trisomy 21 compared to trisomy 18 and 13, consistent with our cytogenetic findings.[16] A possible biological explanation for these differences may lie in the inherent properties of each trisomy. Trisomy 21 may allow for better fetal tolerance of an additional chromosome, enabling survival into late gestation or live birth. In contrast, trisomy 13 and 18 are more likely to result in early miscarriage or neonatal death.[17] Additionally, although monosomy X (Turner syndrome) is a common chromosomal abnormality, its low survival rate during gestation results in a very low proportion among ongoing pregnancies.[18] The chromosomal distribution observed in our study aligns well with patterns reported in other prenatal screening models and corresponds closely with data from both European and North American populations.[15,16] These results affirm the reliability of our findings and emphasize the importance of cytogenetic


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classification in guiding genetic counseling and designing targeted prenatal screening strategies for high-risk pregnancies.

In the univariate analysis, several clinical and paraclinical factors were found to be significantly associated with fetal chromosomal abnormalities. Specifically, maternal age ≥ 35 and paternal age ≥ 40 were associated with a higher risk of chromosomal abnormalities. The rate of chromosomal abnormalities in mothers aged ≥ 35 was 18.9%, compared to 9.1% in those aged < 35 (OR = 2.3; 95% CI: [1.2–4.4]; p = 0.007). These findings are consistent with previous studies suggesting that advanced maternal age is a well-established independent risk factor for aneuploidies, particularly trisomy 21.[3,4] At the cellular level, the "maternal age effect" is primarily due to the prolonged arrest of oocyte development. Female oocytes complete meiosis I only shortly before ovulation, following a long dormancy phase (from prophase I to metaphase I). Over time, the meiotic apparatus undergoes age-related deterioration.

Notably, the cohesin complex – responsible for maintaining chromatid cohesion – gradually degrades with age, resulting in weakened chromosomal attachment and increased segregation errors.[19] During meiosis I, failure in proper homologous chromosome pairing or crossing-over can lead to nondisjunction.[20] Research on older women's oocytes has shown a higher incidence of premature chromatid separation – a common mechanism for trisomy formation.[20] Furthermore, age-related decline in spindle checkpoint fidelity can result in chromosomal missegregation that is not corrected in time.[20] Cellular aging is also linked to telomere shortening and reduced gene expression regulation, both of which may contribute to meiotic failure and aneuploidy formation.[20] Collectively, these mechanisms explain why increasing maternal age correlates with higher rates of chromosomal anomalies.[21] Advanced maternal age is associated with a higher risk of embryo aneuploidy, miscarriage, and birth defects such as Down, Edwards, and Patau syndromes. However, in this multivariate model, maternal age ≥ 35 did not remain statistically significant (aOR = 2.28; p = 0.078), likely due to confounding from limited sample size in the ≥35 age group (95/436 cases). Nonetheless, this study confirms the importance of maternal age and adverse obstetric history when interpreting prenatal ultrasound abnormalities and providing genetic counseling to high-risk pregnant women.


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Similarly, paternal age ≥ 40 was also associated with an increased risk of chromosomal abnormalities, with OR = 2.1; 95% CI: [1.1 – 4.6]; p = 0.033, suggesting a potential role of de novo mutations associated with advanced paternal age, as previously reported in molecular genetic studies.[22] In addition, increasing evidence has indicated that advanced paternal age contributes to a higher risk of inherited diseases in offspring.[9] One study found a correlation between paternal age and reduced sperm quality and function.[9] Genetic abnormalities such as DNA mutations, chromosomal aneuploidies, and epigenetic alterations—including gene silencing or disruption of essential genes—have all been linked to advanced paternal age.[9]

Notably, abnormal ultrasound findings were the only variable that remained statistically significant in the multivariate regression model, with OR = 2.2; 95% CI: [1.2 – 4.1]; p = 0.017. This finding aligns with prior studies reporting that abnormal ultrasound features—such as increased nuchal translucency, hypoplastic nasal bone, or structural anomalies—are strong predictors of chromosomal abnormalities, particularly trisomy 21 and other early- or mid-trimester aneuploidies.[12] The biological basis of these associations lies in the impact of chromosomal abnormalities on embryonic development. Such anomalies can disrupt organogenesis and result in various congenital malformations. At the cellular level, chromosomal imbalances (either due to excess or deficiency) interfere with gene expression and disrupt key pathways involved in differentiation and cellular interaction during organ formation.[23] Other factors such as history of miscarriage, rural residence, or occupational exposure to chemicals did not show a significant association with fetal chromosomal abnormalities. This could be due to limited sample size, resulting in a low frequency of these variables and thus insufficient statistical power.

This study has several limitations that should be considered. First, the relatively small sample size may affect the accuracy of estimates regarding associations between risk factors and fetal chromosomal abnormalities. Second, the study did not categorize the specific types or severity of ultrasound abnormalities, and did not fully control for multiple potential confounders such as infertility history, reproductive treatments, body mass index (BMI), or family genetic background. Finally, the assessment of occupational chemical exposure was based on self-reported data, which


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lacked quantitative validation and may have introduced reporting bias, potentially affecting conclusions drawn about this variable.

In conclusion, among the 436 high-risk pregnant women included in the study, the prevalence of fetal chromosomal abnormalities was 11.2%. Maternal age ≥ 35, paternal age ≥ 40, and particularly abnormal ultrasound findings were identified as major risk factors. These results underscore the critical role of prenatal ultrasound in the screening of congenital anomalies and support informed decision-making for early diagnosis in high-risk pregnancies. Future studies with larger sample sizes and prospective longitudinal designs are necessary to validate these findings and to optimize chromosomal abnormality screening strategies in clinical practice.

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Conflicts of interest

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Data Availability Statement

The database is available to readers upon request to the corresponding author at the following email address: truongdt@vmmu.edu.vn