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Original Article

Congenital anatomical variants in human fetal embryological development and its risk factors in low-resource setting: A longitudinal study

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ABSTRACT

Objectives: We aimed to determine the variants of congenital anomalies in human fetal development using ultrasound diagnosis, its associated risk factors, and the outcome of such pregnancies.

Material and Methods: This longitudinal study was conducted at a secondary health facility in north-central Nigeria. A total of 250 consenting pregnant women between 12 and 28 weeks of gestation were recruited, and each had a detailed history taken, an ultrasound scan to screen for fetal congenital anatomic variants, packed cell volume (PCV), and a 75-g oral glucose tolerance test at 24–28 weeks of gestation. All participants were followed up until delivery, and data analysis was done with SPSS version 21.0 (Chicago, IL, USA).

Results: Ultrasound-diagnosed congenital anatomical malformations were found in 29 participants (11.6%), and all were confirmed at birth. Of the 29 cases with congenital malformation, 15 (51.7%) were males. Maternal characteristics that were significantly associated with the risk of fetal congenital anomalies included age ($p < 0.001$), hypertension in pregnancy ($p < 0.001$), ingestion of herbal medication during pregnancy ($p < 0.001$), previous history of unexplained neonatal death ($p < 0.001$), and elevated blood glucose level ($p < 0.001$).

Conclusion: The study shows a high incidence of congenital anomalies, especially among pregnant women with medical disorders in pregnancy. Also, there is a need to discourage the use of herbal medications during pregnancy.

Keywords: Birth defects, Congenital abnormalities, Pregnancy outcomes, Prenatal diagnosis, Risk factors

INTRODUCTION

The macroscopic and microscopic structures of the human body and their characteristics follow an observed pattern of normality; therefore, deviations from this pattern produce anatomical variations or abnormalities, which may be congenital or acquired. Every year, about 3.0%–6.0% of infants worldwide are born with a severe congenital disability.[1] These defects affect infants irrespective of race, ethnicity, or birthplace. In a report, an estimated 303,000 newborn deaths occurring within the first 4 weeks of life were attributed to congenital anomalies.[2] Also, congenital anomalies represent a significant global disease burden among children, accounting for 25 million disability-adjusted life years (DALYs) worldwide.[3] The prevalence of fetal congenital anomalies in Nigeria varies from 0.4% in the south-south,[4,5] 6.2% in the south-west,[6] and 5.8% in the north-west[7] compared to 3.0% in the USA,[8] 2.0–3.0% in the United Kingdom,[9] and 2.5% in India.[10]

Furthermore, it was reported that the prevalence is limited to gross anomalies seen in live births, while anomalies resulting in miscarriages or minor anomalies not routinely screened were missed.[1] The actual prevalence is higher than was reported.[1] Depending on the type and severity of the congenital anomaly, it may not result in death but contribute

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to long-term disability, potentially significantly impacting individuals, families, healthcare systems, and societies.[11]

The advent of ultrasonography provides noninvasive access to the prenatal diagnosis of congenital anomalies. It has resulted in a significant improvement in the diagnosis and care of affected fetuses and neonates.[12] The antenatal diagnosis of these anomalies prepares the parturient, her partner, the family, and the healthcare personnel for the challenges and possible solutions during and after delivery. Ultrasonography is safe for both the parturient and the fetus during the evaluation of the external and internal anatomy of the fetus for major congenital anomalies as well as soft markers of chromosomal anomalies and genetic syndromes.[13] In Nigeria, available reports on the pattern of occurrence and distribution of these anomalies are mostly limited to retrospective analysis and a few studies that looked at congenital malformations at birth.[5–7] Thus, the burden of prenatally diagnosed congenital malformation in Nigeria remains largely unknown. We, therefore, aimed to determine the variants of congenital anomalies in human fetal development using ultrasound diagnosis, its associated risk factors, and the outcomes of such pregnancies in a secondary health facility in north-central Nigeria.

MATERIAL AND METHODS

Study design and settings

The study was a hospital-based longitudinal study conducted at the General Hospital, Ilorin, a secondary healthcare center in north-central Nigeria, between 1 September 2019 and 31 December 2020.

Study participants

Study participants were antenatal clinic attendees at the study site between 12 and 28 weeks gestation with ultrasound screening for fetal congenital malformations. The inclusion criteria included a presentation for an anomaly scan at 12–28 weeks gestation and willingness to deliver at the study site. Women who did not undergo an anomaly scan, those who had ultrasonography before 12 weeks or after 28 weeks of gestation, and those who did not deliver at the study site were excluded.

Sample size estimation

The minimum sample size was calculated using the formula for observational studies[14] at a power of 95% and 5% level of precision. Using a proportion of 6.2% in a previous study in Nigeria,[6] and an anticipated attrition rate of 20%, we obtained a minimum sample size of 215. However, 250 participants were recruited to improve the strength of the study.

Sampling methods

The participants were recruited by simple random sampling using the ballot system by picking from a box containing wrapped paper bearing a "yes" or "no" each; all participants also had a 75g oral glucose tolerance test at 24–28 weeks gestation and were subsequently followed up for pregnancy outcomes.

The ultrasound machine

Product: Ultrasound Scanner

Brand: Sonostar Technology Company Limited, Guangzhou, China

Model: SS-7

Serial Number: 80070080531

Probe: Curvy Linear (3.5 MHz)

Data collection

All women who presented for ultrasonography were counseled for the study and screened for participation eligibility. Eligible women willing to participate signed an informed consent form and were recruited into the study. After that, anomaly scans were carried out by a trained sonologist; the major and minor congenital anomalies visible with the aid of the ultrasound machine were documented. Anomalies of interest included cardiac and neural tube defects, craniofacial abnormalities like cleft lip and palate, anencephaly, achondroplasia, and hydrocephalus. After that, all participants had a 75g oral glucose tolerance test done at 24–28 weeks gestation and other routine laboratory investigations and clinical examinations. All participants were followed up at the antenatal clinic using the regular departmental protocol; labor was managed actively, and they had routine postpartum care. After delivery, the neonatologist examined all the newborns to confirm the previous ultrasound-diagnosed malformation and detect other malformations that were possibly missed during ultrasonography. Neonates with congenital anomalies compatible with life were transferred to the special care baby unit for further treatment by the necessary sub-specialists. All the participating pregnant women received counseling on congenital anomalies before and after the ultrasound evaluation. Prior to the commencement of the study, a pretested study proforma was used to obtain relevant information (risk factors for congenital malformations, antenatal history, ultrasound findings, oral glucose tolerance tests) and was updated at delivery. The proforma was pretested among a cohort of 10 pregnant women who were not included in the data before the commencement of the study.

Statistical analysis

The collected data were sorted, entered into a computer, and analyzed using Statistical Package for Social Science version 21.0 (SPSS Inc., Chicago, IL, USA). The prevalence of congenital anatomical variants was reported as a proportion (the number of congenital anatomical variants over the number of deliveries from the recruited participants). A chi-square was used to identify risk factors associated with the presence of congenital anatomical variants, and variables that were significant along with maternal age were entered into a binary logistic regression to identify the predictors of congenital anatomical variants. The level of statistical significance was set at $p < 0.05$.

Ethical approval

Institutional ethical approval for the study was obtained from the ethical review committee of the General Hospital Ilorin, Nigeria, with approval number GHI/ADM/134/VOL.I/108-30/8/19, and all participants signed a written informed consent.

RESULTS

A total of 250 pregnant women had anomaly scans during the study period, out of which 29 had congenital anomalies, giving a prevalence of 11.6%. The mean maternal age was 30.8 ± 3.8 years old; 163 (65.2%) had tertiary education; 18 (7.2%) had chronic hypertension, among whom 13 (72.2%) have been hypertensive for less than 5 years; and 38 (15.2%) has used herbal preparations in index pregnancy [Table 1].

In Table 2, 7 (2.8%) had diabetes using fasting blood sugar and 5 (2.0) using the 2-hour postprandial evaluation, and 59 (23.9%) pregnant women had anemia (packed cell volume of <30%).

Pregnancy outcomes of the study participants showed that 34 (13.6%) had cesarean sections while 216 (86.4%) had spontaneous vaginal deliveries. Among the babies at birth, 22 (8.8%) weighed < 2,500g, 199 (79.6%) weighed between 2,500 and 3,900g, and 29 weighed ≥4,000g, while 159 (63.6%) were females. Among the participants' newborns, 29 (11.6%) had congenital anomalies. Among the congenital malformations, seven (24.2%) were omphalocele (minor) and six (20.7%) were polydactyl [Figure 1].

In Table 3, there was a significant association between the occurrence of fetal congenital anomalies and maternal age ($p < 0.001$), fasting blood sugar ($p < 0.001$), and 2-hour postprandial levels ($p < 0.001$).

In Table 4, the statistically significant predictors of fetal congenital anomalies using the binary logistic regression were maternal hypertension (p = 0.004), ingestion of herbal

Table 1: Bio-social characteristics and identifiable risk factors for congenital anomalies among participants.

Variable	Frequency n = 250 (%)
Age (years)	
≤35	227 (90.8)
>35	23 (9.2)
Mean ± SD	30.8 ± 3.8
Level of education	
None	2 (0.8)
Primary	7 (2.8)
Secondary	78 (31.2)
Tertiary	163 (65.2)
Hypertension	
Yes	18 (7.2)
No	232 (92.8)
Medication for hypertension (n = 18)*	
Alpha-methyldopa	16 (88.8)
Nifedipine	4 (22.2)
Duration of hypertension (n = 18)	
≤5 years	13 (72.2)
>5 years	5 (27.8)
Herbal medication during pregnancy	
Yes	38 (15.2)
No	212 (84.8)
Oral contraceptive use	
Yes	11 (4.4)
No	239 (95.6)
Previous congenitally abnormal child	
Yes	10 (4.0)
No	240 (96.0)
Previous unexplained neonatal death	
Yes	15 (6.0)
No	235 (94.0)
Parity	
Nulliparous	59 (23.6)
Primiparous (1)	43 (17.2)
Multiparous (2–4)	143 (57.2)
Grand multiparous (>4)	5 (2.0)

*Multiple answers allowed; SD: Standard deviation

Table 2: Oral glucose tolerance tests and packed cell volume among the recruited pregnant women.

Variables	Frequency n = 250 (%)
Fasting Blood Sugar	
Normal	239 (95.6)
Pre-diabetes	4 (1.6)
Diabetes	7 (2.8)
2-hour Postprandial	
Normal	237 (94.8)
Impaired glucose tolerance	8 (3.2)
Diabetes	5 (2.0)
Packed Cell Volume	
<30%	59 (23.6)
≥30%	191 (76.4)

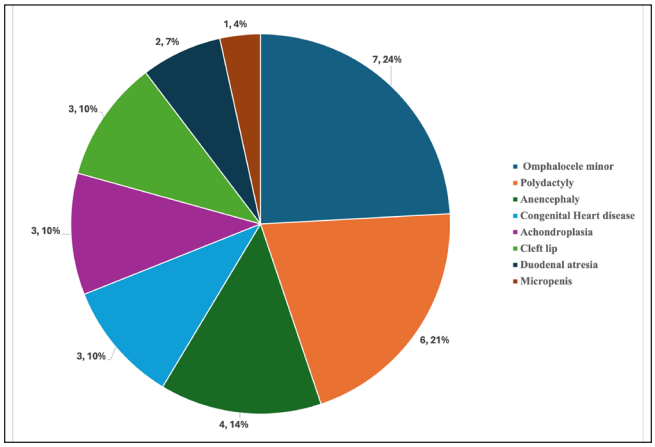

Figure 1: Distribution of congenital anatomical variants among neonates with congenital anomalies.

Table 3: Association between maternal sociodemographic variables and laboratory parameters and the occurrence of congenital anomalies.

Variable	Congenital anomalies		χ^2	*p*-value
	Yes n (%)	No n (%)		
Age (years)				
Mean ± SD	33.28 ± 3.86	30.52 ± 3.71	3.748[t]	<0.001
Level of Education				
None	1 (50.0)	1 (50.0)	5.319[F]	0.130
Primary	2 (28.6)	5 (71.4)		
Secondary	9 (11.5)	69 (88.5)		
Tertiary	17 (10.4)	146 (89.6)		
Parity				
Nulliparous (0)	2 (3.4)	57 (96.6)	6.259[F]	0.081
Primiparous (1)	7 (16.3)	36 (83.7)		
Multiparous (2–4)	20 (14.0)	123 (86.0)		
Grand multiparous (>4)	0 (0.0)	5 (100.0)		
Fasting blood sugar				
Normal	22 (9.1)	221 (90.9)	51.882[F]	<0.001
Diabetes mellitus	7 (100.0)	0 (0.0)		
Two-hour postprandial blood glucose				
Normal	24 (9.8)	221 (90.2)	38.881[F]	<0.001
Diabetes	5 (100.0)	0 (0.0)		
Packed Cell Volume				
<30%	5 (8.5)	54 (91.5)	0.736	0.391
≥30%	24 (12.6)	167 (87.4)		

χ^2: Chi square test; F: Fisher's exact test; t: Independent Samples T test; *: *p*-value < 0.05; SD: Standard deviation

medication during pregnancy (p = 0.002), and maternal 2-hour postprandial blood glucose level (p < 0.001).

DISCUSSION

Our study shows a prevalence of 11.6% for fetal congenital anatomic variants, higher than reports from local studies in Nigeria that ranged from 0.4% to 6.2% [4–7,15]. It is also higher than studies in Baghdad, which ranged from 7.76 to 12.36 per 1,000.[16,17] This higher prevalence of fetal congenital anomalies obtained in this study may be due to differences in the study methodology, as these reference studies were reports from physical examination of newborns after birth with the exclusion of abortuses, unlike this present study, which performed ultrasonographic evaluation of fetuses.

According to this study, congenital malformations are higher among older women (> 35 years). The preponderance of fetal anatomic variants among parturients aged over 35 years in this study may be related to the observation that with advanced maternal age, the oocytes become increasingly likely to form embryos with an imbalance in their chromosome content, resulting in increased risks of anatomic variants.[18] This observation was corroborated by Singh *et al.*[14] and Zhang *et al.*,[19] who reported an association

Table 4: Predictors of fetal congenital anomaly using binary logistic regression.

Variable	B	*p*-value	AOR (95% CI)
Maternal Age	0.075	0.373	1.077 (0.914–1.270)
Gender of the fetus			
Male	0.101	0.874	1.107 (0.315–3.891)
Female[REF]			1
Maternal Hypertension			
Yes	3.532	<0.001*	4.200 (1.405–21.383)
No[REF]			1
Duration of hypertension	0.192	0.872	1.825 (0.082–8.619)
Use of Alpha-methyldopa			
Yes	1.757	0.809	2.796 (1.330–5.181)
No[REF]			1
Use of Nifedipine			
Yes	0.026	0.973	1.027 (0.221–4.848)
No[REF]			1
Maternal Packed Cell Volume			
<30	−0.458	0.514	0.633 (0.160–2.504)
≥30[REF]			1
Maternal Fasting Blood Sugar			
Diabetic	0.768	0.543	2.464 (0.045–7.524)
Normal[REF]			1
Two-hour Postprandial glucose			
Diabetic	0.303	0.815	1.355 (0.111–17.149)
Normal[REF]			1
Herbal medication during pregnancy			
Yes	2.695	0.001*	4.803 (1.141–5.916)
No[REF]			1
Previous unexplained neonatal death			
Yes	1.130	0.323	3.279 (0.583–8.47)
No[REF]			1

B: Coefficient of Binary Logistic Regression; AOR: Adjusted odds ratio; 95% CI: 95% Confidence Interval; REF: Reference group; *: Statistically significant.

between advanced maternal age and fetal anatomic variants. The risk of congenital anomalies is also higher among multiparous women when compared to nulliparous women or women with low parity. This observation is also consistent with a study by Feng *et al*.[20]

Medical disorders such as diabetes mellitus and chronic hypertension, mainly when poorly controlled, have been associated with an increased risk of congenital anomalies. This study shows that factors associated with fetal congenital anomalies included maternal hypertension, ingestion of herbal medication during pregnancy, and maternal 2-hour postprandial blood glucose level. The observed association between maternal chronic medical disorders (hypertension and diabetes mellitus) and fetal anatomic variations corroborates the report by Morrison *et al*.[21] The poor glycemic control of diabetes mellitus, especially in early pregnancy when organogenesis begins, increases the risk for anomalies, especially congenital cardiac malformations.[22,23] Also, it has been reported that maternal chronic hypertension significantly increases the risk of developing renal, limb, and lip/cleft/palate congenital anomalies. In contrast, the risk is further exacerbated by superimposed eclampsia.[24,25] This observation is also in keeping with a study in Iraq that showed an increased risk of congenital anomalies in a parturient with poorly controlled hypertension and diabetes.[26] Herbal medications are well advertised in Nigeria, and they are widely believed to have little or no side effects since they are obtained from natural sources. In addition, most herbal medications sold do not go through the standard pharmaceutical regulatory processes. Therefore, there is an increased risk of adulteration and contamination with products such as arsenic, known to be fetotoxic.[27] Ingestion of herbal medication, especially during the first trimester, increases the risk of congenital malformations.[24] The process of organogenesis in the face of ingesting herbal preparations whose composition and effects on the reproductive system are largely unclear may explain the relationship. Thus, herbal ingestion during pregnancy may cause harm, including congenital anomalies.[27] The most common congenital anomalies in this study were omphalocele minor, polydactyly, and anencephaly, similar to a report in Nigeria by Akinmoladun *et al*.[6]

The strength of this study included being a longitudinal study that involved a cohort of 250 pregnant women who had ultrasonography for the presence of congenital anatomic variants or otherwise and were all followed up until delivery. However, this study has some limitations; pregnancy less than 12 weeks was not included, possibly missing the early congenital anatomic variants that may end up as abortuses. Besides, this is a single hospital-based study and may not reflect what is obtained across the country. The outcomes of managing the babies born with congenital anatomic variants were also not reported.

CONCLUSION

The study shows a high incidence of congenital anomalies, emphasizes the need for adequate antenatal counseling and routine anomaly ultrasound scans, especially among women with hypertension in pregnancy, and discourages using herbal medication, particularly during pregnancy.

AUTHORS' CONTRIBUTION

AM was responsible for the concept, design, data collection, interpretation, drafting, and approval of the final draft; AOO was in charge of the concept, design, data interpretation, drafting, and approval of the final draft; AD was involved with the concept, design, data interpretation, drafting, and approval of the final draft; FOA was responsible for the design, data collection, drafting, and final draft approval; ASA was in charge of the concept, design, data interpretation, drafting, and approval of the final draft; and IOR was responsible for the concept, design, data interpretation, drafting, and approval of the final draft.

Ethical approval

The research/study approved by the Institutional Review Board at General Hospital Ilorin, Kwara State, Nigeria, number GHI/ADM/134/VOL.I/108, dated 30/8/19.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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