RESEARCH ARTICLE

Association of congenital abnormalities with maternal risk factors; an ultrasound based case-control study

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Abstract

Objective: To determine the association between foetal congenital abnormalities and maternal risk factors, including family history and consanguinity.

Method: The case-control study was conducted from December 2022 to May 2023 at the Radiology Department of Jinnah Postgraduate Medical Center, Karachi, and Tanveer Ultrasound Clinic, Karachi, after approval from the ethics review committee of Bahria University of Health Sciences, Karachi. The sample comprised pregnant women aged 18-40 years who were divided into foetuses with structural abnormalities group A and foetuses with normal structural development in control group B. Sonoscape S22 and Toshiba Aplio 500 ultrasound systems were used to detect congenital abnormalities. Maternal risk factors were assessed and associations were explored. Data was analysed using SPSS 23.

Results: Of the 120 women, 60(50%) were in each of the two groups. Maternal age, family history of birth defects and a history of consanguinity were highly associated with an increased risk of congenital abnormalities ($p<0.05$). Diabetes mellitus, hypothyroidism and asthma had significant inverse associations with congenital abnormalities ($p<0.05$).

Conclusion: Sociodemographic factors like age and risk factors played a significant role in the development of congenital abnormalities.

Key Words: Congenital abnormalities, Risk factors, Consanguinity.

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Introduction

Globally, 295,000 newborns die at 4 weeks or prior due to complications associated with congenital abnormalities, which have been defined by the World Health Organisation (WHO) as any structural or functional anomalies that are present at birth.[1] The health burden of congenital abnormalities is significantly higher in developing countries compared to the developed ones, and have a profound impact not just on the families, but on the overall disease burden of a society.[2]

Congenital abnormalities can result due to potential risk factors varying from maternal age and infections to drug abuse. Moreover, nicotine, caffeine, medicinal drugs along with nutritional status of the mother, especially the use of folic acid, play a significant role.[3] A population-based study in the United States identified various congenital abnormalities in foetuses, especially if the mother suffered from diabetes mellitus (DM) or gestational diabetes mellitus (GDM).[4] This association is further supported by mechanistic evidence showing how maternal hyperglycaemia during early organogenesis contributes to diabetic embryopathy and causes anencephaly, spina bifida and congenial heart diseases.[5]

Consanguineous marriages are identified in literature as another major risk factor for birth defects[6], which seem to be more common due to the homozygosity of harmful recessive genes.[6,7]

To our knowledge, there is a scarcity of data in Pakistan on the maternal risk factors associated with the incidence of congenital abnormalities. The current study was planned to fill the gap in literature by determining the association between foetal congenital abnormalities and maternal risk factors, including family history and consanguinity.

Subjects and Methods

The case-control study was conducted from December 2022 to May 2023 at the Radiology Department of Jinnah Postgraduate Medical Center (JPMC), Karachi, and Tanveer Ultrasound Clinic (TUC), Karachi, after approval from the ethics review committee of Bahria University of Health Sciences, Karachi. The sample was raised using purposive sampling technique. The sample size was calculated using Open Epi sample size calculator.[8] The

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calculation assumed a 95% confidence level, 80% power, and a 1:1 case-control ratio. The required sample size was further inflated by 20%[9] to improve the reliability of the analysis. The sample comprised pregnant women aged 18-40 years. Those excluded were pregnant women with a history of intrauterine death, missed abortion and gestational age <11 weeks. After taking informed consent from all the subjects, they were divided into foetuses with structural abnormalities group A and foetuses with normal structural development in control group B. Data was collected using a well-structured questionnaire administered by the interviewer. Accessible prenatal records were also reviewed. At the time of presentation all the participants underwent a single detailed diagnostic obstetric ultrasound examination. Scans were taken at different gestational ages (1st, 2nd and 3rd trimester) depending on the timing of referral. Examinations were performed using the Sonoscape S22 Colour Doppler Ultrasound System manufactured by SonoScape Medical Corp., Shenzhen, Guangdong, China. This is a trolley-based shared-service ultrasound platform equipped with an 18.5-inch HD LED monitor, 3D/4D imaging capability, and real-time panoramic imaging, with an approximate frequency range of 1–7 MHz and the Toshiba Aplio 500, a trolley-based Colour Doppler Ultrasound System manufactured by Canon Medical Systems Corporation, Otawara, Tochigi, Japan. The system is equipped with a 19-inch HD monitor, 3D/4D imaging capability, and real-time panoramic imaging, supporting convex transducers with an approximate frequency range of 1–7 MHz. A standardized foetal abnormality screening protocol based on International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) guidelines was used with systematic examination of the central nervous system (CNS), face, spine, thorax and heart, abdomen, limbs, placenta, umbilical cord and amniotic fluid.[10] Due to the multicentre nature of the study, the scans were performed at the two centres each by a single consultant radiologist, but, formal inter-observer variability analysis was not performed. Real time ultrasound results were used to diagnose congenital abnormalities, and an average of three measurements of each parameter were taken to minimise intra-observer bias. Complex cases were examined by a senior consultant radiologist.

Data was analysed using SPSS 23. Chi-square test was used to determine the association of congenital abnormalities with age, parity, use of folic acid, history of consanguinity, DM, hypertension (HTN), hypothyroidism, asthma, family history of birth defect, and history of stillbirths or miscarriages. Fisher's exact test was used to determine the association of congenital abnormalities with multiple pregnancy, use of antenatal supplements, hyperthyroidism, cardiac disease, epilepsy, psychiatric disease and kidney disease. Binary logistic regression was used to determine the strength of association with factors associated with congenital abnormalities. P<0.05 was considered significant.

Results

Of the 120 women, 60(50%) were in each of the two groups. In group A, 26(43.3%) women were aged 30-34 years. In group B, 27(45%) women were aged 25-29 years (p=0.003) (Table 1).

DM, hypothyroidism and asthma demonstrated significant differences in distribution between the groups (Table 2) No significant associations were observed for cardiac disease, epilepsy, psychiatric illness or kidney disease (p>0.05).

Congenital abnormalities and a family history of birth defects had a significant association (p=0.002), while no

Table-1: Distribution and association of congenital abnormalities with age and maternal risk factors (n=60).

Maternal Risk Factors	Population				p-value
	Case		Control		
	n	%	n	%	
AGE (Years)					
≤ 20	1	1.7	3	5	0.003**
21-24	11	18.3	8	13.3	
25-29	9	15	27	45	
30-34	26	43.3	17	28.3	
35-40	13	21.7	5	8.3	
PARITY					
1st child	10	16.7	19	31.7	0.090
2nd child	12	20	14	23.3	
> 2 children	38	63.3	27	45	
MULTIPLE PREGNANCY					
Yes	1	1.7	2	3.3	1.000
No	59	98.3	58	96.7	
USE OF FOLIC ACID					
Yes	37	61.7	43	71.7	0.245
No	23	38.3	17	28.3	
USE OF ANTENATAL SUPPLEMENTS					
Yes	54	90	58	96.7	0.272
No	6	10	2	3.3	
HISTORY OF CONSANGUINITY					
Yes	32	53.3	15	25	0.001**
No	28	46.7	45	75	

*p<0.05, **p<0.01

Table 2: Distribution and association of congenital abnormalities with maternal comorbidity profile.

Maternal Comorbidity	Population				p-value
	Case		Control		
	n	%	n	%	
DIABETES MELLITUS					
Yes	11	18.3	24	40	0.009**
No	49	81.7	36	60	
HYPERTENSION					
Yes	19	31.7	14	23.3	0.307
No	41	68.3	46	76.7	
THYROID DISEASE					
Yes Hypothyroidism	2	3.33	12	20	0.004**
Hyperthyroidism	1	1.7	3	5	0.309
No Thyroid Disease	57	95	45	75	
CARDIAC DISEASE					
Yes	3	5	1	1.7	0.619
No	57	95	59	98.3	
EPILEPSY					
Yes	3	5	2	3.3	1.000
No	57	95	58	96.7	
ASTHMA					
Yes	6	10	18	30	0.006**
No	54	90	42	70	
PSYCHIATRIC DISEASE					
Yes	3	5	2	3.3	1.000
No	57	95	58	96.7	
KIDNEY DISEASE					
Yes	1	1.7	1	1.7	1.000
No	59	98.3	59	98.3	

*p<0.05, **p<0.01

Table-3: Distribution and association of congenital abnormalities with family history of birth defects and history of stillbirth or miscarriage.

	Maternal Risk Factors				p-value
	Cases		Controls		
	N	%	N	%	
Family History of Birth Defects					
Yes	17	28.3	4	6.7	0.002**
No	43	71.7	56	93.3	
History of Still Birth or Miscarriage					
Yes	27	45	21	35	0.264
No	33	55	39	65	

p<0.05, **p<0.01

significant association was observed with respect to a history of stillbirths or miscarriages (p=0.264) (Table 3).

Binary logistic regression analysis showed that a history of consanguinity and a family history of birth defects increased the risk congenital abnormalities, while DM, hypothyroidism and asthma had significant inverse associations with congenital abnormalities (Table 4).

Table-4: Binary logistic regression of factors associated with congenital abnormalities.

Maternal Risk Factors	OR [95% CI]	p-value
HISTORY OF CONSANGUINITY		
Yes	3.429 [1.582 – 7.433]	0.002**
No	1	1
FAMILY HISTORY OF BIRTH DEFECTS		
Yes	5.535 [1.736 – 17.646]	0.004**
No	1	1
DIABETES MELLITUS		
Yes	0.337 [0.146 – 0.775]	0.010*
No^R	1	1
HYPOTHYROIDISM		
Yes	0.138 [0.029 – 0.647]	0.012*
No^R	1	1
ASTHMA		
Yes	0.259 [0.095 – 0.710]	0.009*
No^R	1	1

*p<0.05, **p<0.01, OR: Odds ratio, CI: Confidence interval, R: Reference category.

Discussion

The current study identified several associations between maternal factors and congenital abnormalities. Most cases of congenital abnormalities were found in mothers aged 30-34 years, while most of the control group were aged 25-29 years. This suggests that advancing maternal age may increase the risk of congenital abnormalities, which is a widely accepted idea in the medical community. A case-control surveillance study in Hungary deduced that maternal age >35 and <20 have high incidence of congenital abnormalities.[11] Oloyede et al. found statistically significant association between high maternal age (35-40 years) and increased incidence of congenital malformations (CMFs) in their observational cross-sectional study in a teaching hospital in Nigeria. They found 78 foetuses with major CMFs among 9,698 pregnancies in which ultrasound scan was done across all three trimesters of pregnancy. This increased risk was thought to be related to an increase in chromosomal meiotic errors like aneuploidy.[12]

CMF was observed to be prevalent in 38(63.3%) women with parity >2 in the current research, although the results were not statistically significant. Adri et al. also found significant correlation between multiparity and occurrence of congenital abnormalities.[13] This is most

likely because high parity is associated with higher maternal age and aggravated risk of obstetric complications, like pregnancy-induced HTN, GDM and anaemia.[14] Two of such factors were also seen in the current study; maternal age and HTN. However, because high parity is more common in lower socioeconomic groups, the effect of this parameter on foetal morbidity cannot be separated from the confounding effects of socioeconomic determinants. Other studies have also documented the increased incidence of congenital abnormalities with increase in parity.[14-16] However, Hossain et al. did not find substantial connection between parity and congenital abnormalities, which was contrary to the current results.[17]

There was no significant difference in the occurrence of multiple (twin) pregnancies between the cases and controls, reflecting the general understanding that while multiple pregnancies carry higher risks, their overall prevalence is low. Recent data supports this finding, showing that the risk posed by multiple pregnancies does not significantly impact the overall incidence of congenital abnormalities.[18]

Majority of the participants 80(66.7%) in the current study used folic acid, although congenital abnormalities were still found in 37(61.7%) of these foetuses.

A multicentre prospective study by Dong et al.[19] emphasised the protective effects of folic acid, highlighting that folic acid should be started one-and-a-half months before the conception (optimal initiation time 1.5 months; optimal range: 1.1-1.9) with a duration of 4 (3.7-4.4) months in order to achieve lowest risk of birth defects. Another study also emphasised the importance of appropriate timing and duration of folic acid supplementation in reducing the risk of congenital abnormalities.[20] However, the present study did not collect data on the timing, dosage or duration of folic acid use. As such, either the current subjects did not start taking folic acid before conception, as recommended,[19] because of lack of awareness, or they were not taking the prescribed dose because they did not realise the importance of correct dosing.

The current study revealed that maternal diabetes was more prevalent in controls (40%) compared to cases (18.3%). This is contradictory to the available evidence that is supportive of the well-known fact that high blood sugar levels during pregnancy can have harmful effects on foetal development.[21-23]

Chronic diseases, like hypothyroidism and asthma, were more frequent in controls (20% and 30%, respectively) compared to cases (3.3% and 10%, respectively) in the current study. This is in contradiction with the common finding that chronic diseases in mothers are linked to higher incidence of congenital abnormalities in the foetuses.[24] Yland et al. found in a sample of 190,520 pregnancies no association between diagnosis, control or severity of asthma with abortions, stillbirths or CMFs.[25] Contradictory results were seen in recent studies, which reported significant association of congenital abnormalities with the timing of diagnosis of hypothyroidism in the mother.[26,27] The current study also showed statistically non-significant increases in cases with HTN (31.7%) compared to controls (23.3%). Similar results were observed in other studies.[14, 28]

A strong association was observed between family history of birth defects and congenital abnormalities, as well as between consanguinity and these abnormalities in the current study. Consanguineous marriages are thought to contribute significantly to the chance of congenital defects. The probability of a child inheriting a recessively inherited disorder is greater among related parents, and this risk rises as the connection grows closer. In the current study, 39.2% of the parents were related. Furthermore, the rate of abnormalities in consanguineous and non-consanguineous marriages in the current study was 53.3% and 46.7%, respectively. The incidence of abnormalities had a significant association with the inbreeding coefficient and was greater in couples who were consanguineous than in non-consanguineous marriages. This aligns with studies highlighting the genetic risks associated with family history and consanguineous marriages.[13,15,23,29]

The logistic regression analysis revealed significant associations between family history of birth defects, consanguinity and congenital abnormalities in the current study. DM, hypothyroidism and asthma showed reduced odds of congenital abnormalities (OR <1). Contradictory to the current study, a meta-analysis by Wu et al. reported higher risk of congenital abnormalities with maternal diabetes.[30] Shahmirzady et al. reported increased risk of congenital abnormalities with consanguinity and family history of birth defects, which was similar to the current study.[31] Arijo et al. reported lower odds of congenital abnormalities with maternal diabetes, like the current study, although highly significant results were obtained for consanguinity, which was also in agreement with the current study.[32]

In the current study, the association between maternal comorbidities and congenital abnormalities may have been strongly influenced by confounders related to disease awareness, medical management, access to ANC,

particularly glycaemic and hormonal control, and should not be interpreted as protective. As data on disease severity, treatment adherence, and level of metabolic or hormonal control was not available, residual confounding could not be fully addressed. This represents a key limitation of the study and may explain the inverse associations observed. Together with a small sample size, the limitations mean the findings cannot be generalized. Further research is required to validate the results and to understand potential confounding factors or unique population characteristics.

Conclusion

Congenital abnormalities were found to be significantly associated with maternal age, family history of birth defects and consanguineous marriages.

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AUTHORS' CONTRIBUTIONS:
JAA: Concept, design, drafting, data acquisition, analysis, interpretation and final approval.
AQ: Editing, critical review and accountability and integrity of work.
AS: Drafting, data analysis and interpretation.
SK: Drafting.