ORIGINAL ARTICLE

Exploring prenatal risk factors associated with congenital anomalies among newborns in national referral hospital, Indonesia

Lisa Novianti, OBGYN[1,2], Rima Irwinda, PhD[1,2]

[1]Department of Obstetrics and Gynecology Faculty of Medicine Universitas Indonesia, [2]Dr. Cipto Mangunkusumo Hospital, Jakarta

ABSTRACT

Introduction: Congenital anomalies (CAs) account for approximately 8 to 15% of perinatal deaths and 13 to 16% of neonatal deaths. Congenital anomalies are a significant public health issue in Indonesia, affecting approximately 59.3 per 1,000 live births. The three most frequent malformations were hydrocephalus (21%), cleft lip and cleft palate (9.2%) and Down Syndrome (9.2%).

Materials and Methods: A retrospective case-control study was conducted at Dr. Cipto Mangunkusumo General Hospital, Jakarta, between September 2023 and October 2024. Data from 552 births were analysed, including 97 cases of congenital anomalies (CAs). Maternal, fetal, and environmental factors were assessed using medical records and documented clinical histories. Statistical analyses included descriptive statistics, cross-tabulations, binary logistic regression, and multivariable logistic regression.

Results: The prevalence of CAs was 17.6%. Significant maternal risk factors included a history of congenital anomalies (OR = 3.7, 95% CI: 0.88–16.00) and severe anemia (OR = 4.37, 95% CI: 2.48–7.69). Environmental risks, such as drug use in the first trimester (OR = 3.43, 95% CI: 2.01–5.86), passive smoking (OR = 4.10, 95% CI: 1.89–8.90), and pesticide exposure (OR = 3.92, 95% CI: 1.26–12.17), were also significant. Folic acid supplementation showed a significant protective effect against congenital anomalies (OR = 0.56, p = 0.001), although the usage rate remained low (35.5%).

Conclusion: This study found a significant association between congenital anomalies and risk factors such as passive smoking, exposure to pesticides, and chemicals. It highlights the importance of ongoing community health education to prevent and manage these predisposing risk factors.

KEYWORDS:
Congenital anomaly, maternal factors, epigenetics

INTRODUCTION

Congenital anomalies (CAs), commonly referred to as birth defects, are prenatal conditions characterized by structural, functional, behavioral, or metabolic abnormalities that develop during fetal development. Present at birth, these abnormalities can significantly affect an infant's health, growth, and ability to thrive. They pose a significant global health challenge, contributing to pregnancy losses, stillbirths, and neonatal deaths, while also causing lifelong disabilities that affect individuals, families, and healthcare systems.[1-2] Globally, an estimated 8 million infants are born each year with major congenital anomalies, accounting for approximately 6% of all live births and leading to nearly 300,000 deaths in the first month of life.[3] According to the Centers for Disease Control and Prevention (CDC), approximately one in 33 infants is affected by a congenital anomaly, contributing to 8–15% of perinatal deaths and 13–16% of neonatal deaths.[4-5] Congenital anomalies are a significant public health concern in Indonesia, with an estimated prevalence of 59.3 per 1,000 live births, translating to approximately 263,154 affected infants annually. A study conducted at Dr. Cipto Mangunkusumo General Hospital in Jakarta reported that 8 out of every 1,000 live births involved congenital heart disease (CHD), with approximately 50,000 infants born with CHD annually in Indonesia.[6] The three most frequent malformations were hydrocephalus (21%), cleft lip and cleft palate (9.2%) and Down's Syndrome (9.2%).[6] Congenital anomalies continue to represent a substantial global health burden, with emerging regional data indicating a rising trend in prevalence. Notably, in South Korea, the prevalence of congenital anomalies doubled between 2006 and 2014, reflecting broader global epidemiological patterns.[7-8] Similar increases have been observed in Indonesia, where records from Dr. Cipto Mangunkusumo General Hospital show a 1.5-fold increase in cases compared to 2016. These trends highlight the urgent need for further research and intervention, particularly in low- and middle-income countries where congenital anomalies are often overlooked as a public health priority.[9]

The causes of congenital anomalies are diverse, ranging from genetic and environmental factors to maternal health conditions. Known prenatal risk factors include maternal infections such as cytomegalovirus, rubella, and toxoplasmosis; exposure to hazardous substances like chemicals, radiation, air pollution, pesticides, and heavy metals; and maternal characteristics such as advanced age, smoking, obesity, chronic illnesses, and gestational diabetes.[10-12] Despite advances in understanding these factors, 40–60% of congenital anomalies still have no clearly identified cause.[13]

This article was accepted:
Corresponding Author: Rima Irwinda
Email: rima.irwinda@gmail.com

Genetic testing is not part of routine screening in Indonesia and is not covered by national health insurance, limiting access to this essential diagnostic tool for many individuals. In Indonesia, however, research into the prenatal risk factors contributing to congenital anomalies remains limited, leaving significant gaps in understanding and prevention strategies. Few studies have examined the roles of genetic, environmental, and maternal health factors in influencing the prevalence of congenital anomalies. This study aims to address these gaps by exploring prenatal risk factors associated with congenital anomalies, with the goal of informing effective preventive measures and improving prenatal care practices in Indonesia.

MATERIALS AND METHODS

This retrospective case-control study was conducted at Dr. Cipto Mangunkusumo General Hospital, Jakarta, to investigate prenatal risk factors associated with congenital anomalies. Data collection included cases documented between September 2023 and October 2024. Participants were selected based on medical records and previously documented clinical information from the hospital. Inclusion criteria included individuals diagnosed with specific congenital anomalies, such as spina bifida, anencephaly, meningo-/encephalocele, congenital cataract, cleft palate, cleft lip, cleft lip and palate, hypospadias, epispadias, talipes, reduction deformity, atresia ani with or without fistula, omphalocele, gastroschisis, and conjoined twins. Patients with incomplete medical records or those not meeting these diagnostic criteria were excluded from the study.

Data were obtained by reviewing medical records for the specified period. The data collection process was conducted continuously and rigorously, with daily monitoring by trained data collectors and oversight from the principal investigator and supervisory team to ensure completeness and accuracy. Following collection, the data underwent cleaning, coding, and entry into EpiData Manager, and were subsequently exported to SPSS Version 25.0 for statistical analysis. The outcome variable—fetal congenital anomalies—was examined in relation to the mode of delivery. Classification of congenital anomalies was based on the International Classification of Diseases, 10th Revision (ICD-10). Prevalence was calculated by dividing the number of documented congenital anomaly cases (numerator) by the total number of live and stillbirths (denominator) within the study setting and time frame. Descriptive and inferential statistics were employed, including frequency distribution, cross-tabulations, binary logistic regression, and multivariable logistic regression analyses. Exposure variables with a p-value ≤ 0.20 in bivariate analysis were included in the multivariable model to assess their association with congenital anomalies. Adjusted odds ratios (AOR) with corresponding 99% confidence intervals and p-values were reported. Statistical significance was determined based on 99% confidence intervals that did not include the null value, and results were presented in both textual and tabular formats.

RESULTS

A total of 552 births were recorded between September 2023 and October 2024 at Dr. Cipto Mangunkusumo General Hospital, with 97 cases of congenital anomalies (17.6%). The median maternal age was 27 years, ranging from 14 to 45 years. The majority of mothers of affected infants were aged 26–35 years (38%), had a low level of education (55.7%), and were in the low-to-middle socioeconomic category (58.8%). Among deliveries, caesarean sections accounted for 63% of cases, and diabetes was observed in 5.97% of mothers. Table I summarize the sociodemographic characteristics.

Maternal Factors

Maternal factors such as a history of congenital anomalies in previous pregnancies and severe anaemia were strongly associated with an increased risk of congenital anomalies, as shown in Table II. Among the mothers included in the study, 25% had a history of a malformed child, and notably, 25% of these mothers gave birth to another child with a congenital anomaly. Similarly, severe anaemia (Hb ≤ 7 g/dL) was identified as a significant factor, with 32.97% of the mothers experiencing severe anemia and resulting in malformed infants.

Foetal Factors

As presented in Table III, foetal factors such as birth weight, maturity, and type of birth were examined. Congenital anomalies were more common in preterm infants, with preterm birth showing a significant association (OR = 17.052, 95% CI: 10.95–26.54). Infants with a birth weight under 1,500 grams had an incidence of 0.97%, while anomalies occurred in 72% of live births and 40% of preterm infants. Stillbirths were more frequent in cases than controls (OR = 14.58, 95% CI: 8.98–23.68), although this did not reach statistical significance. Gender showed no notable association.

Environmental, Family History, Exposure to Different Chemicals, and Maternal Illness

Environmental exposures, family history, and maternal conditions were assessed for their association with congenital anomalies, as shown in Table IV. Factors significantly contributing to congenital anomalies included the absence of folic acid supplementation, drug use during the first trimester, and pesticide exposure. Mothers who did not take folic acid had a higher likelihood of congenital anomalies (OR = 0.56, 95% CI: 0.39–0.83).

The main reason for non-compliance is the lack of adequate antenatal care (ANC). Women who miss regular ANC visits often lack information about the importance of folic acid, leading to lower adherence. This issue is especially common in rural and underserved areas, where logistical barriers and financial constraints limit access to essential prenatal care. Socioeconomic factors, such as the cost of prenatal vitamins, hinder folic acid uptake, especially among low-income women.[14]

Moreover, side effects such as nausea, bloating, and gastrointestinal discomfort discourage some women from adhering to folic acid supplementation.[15] Additionally, misinformation and lack of awareness contribute

Table I: Sociodemographic characteristics of the participants of the study

Characteristics	Group	n (%)	
		Cases	Controls
Age (years)	≤20	3 (3.1)	22 (4.8)
	21–25	31 (32.0)	159 (35.0)
	26–35	37 (38.1)	152 (33.4)
	≥36	26 (26.8)	122 (26.8)
Education	<12 years	54 (55.7)	254 (55.8)
	≥12 years	43 (44.3)	201 (44.2)
Socioeconomic status	Low–Middle	57 (58.8)	191 (42.0)
	High–Very High	40 (41.2)	264 (58.0)
ANC visits	Regular	19 (20.5)	304 (66.8)
	Irregular	78 (79.5)	151(33.2)
Delivery	Caesarean section	58 (63)	354 (77.8)
	Spontaneous	39 (37)	101 (22.1)
Maternal comorbidities	Diabetes mellitus	5 (5.97)	9 (1.9)
	Asthma	1 (1.49)	91 (20.0)
	Graves' disease	2 (2.99)	63 (13.8)
	Preeclampsia	2 (2.47)	131 (28.8)
	Autoimmune	3 (2.50)	68 (14.9)
	None	84 (64.18)	93 (20.4)

Table II: Maternal factors associated with congenital anomalies

Characteristics	n (%)		OR (95% CI)
	Cases	Controls	
Age (years)			0.43 (0.22 to 0.83)
≤20	3 (3.1)	22 (4.8)	
21–35	68 (70.1)	311 (68.4)	
≥35	26 (26.8)	122 (26.8)	
Socioeconomic status			1.51 (0.92 to 2.50)
Low–Middle	57 (58.8)	191 (42.0)	
High–Very High	40 (41.2)	264 (58.0)	
History of malformation			34.1 (28.36 to 58.12)
Yes	25 (25.7)	15 (3.3)	
No	72 (74.3)	440 (96.7)	
Severe anaemia (Hb ≤7 g/dL)			6.95 (4.36 to 11.23)
Yes	32 (32.9)	22 (4.8)	
No	65 (67.1)	433 (95.1)	

Note: OR = odd ratio

Table III: Foetal factors associated with congenital anomalies

Characteristics	n (%)		OR (95% CI)
	Cases	Controls	
Birth weight			1.21 (0.62 to 2.38)
<2500 g	39 (40.1)	282 (62)	
≥2500 g	58 (50.9)	173 (38)	
Type of birth			14.58 (8.98 to 23.68
Live births	70 (72.2)	410 (98.4)	
Stillbirths	27 (27.8)	45 (1.6)	
Gender			0.81 (0.63 to 1.44)
Male	45 (47)	282 (62)	
Female	52 (53)	173 (38)	
Maturity			17.05 (10.95 to 26.54)
Preterm	68 (70.9)	182 (40)	
Full term	29 (29.1)	273 (60)	

Note: OR = odd ratio

Table IV: Environmental, family history, exposure to different chemicals, and maternal illness

Characteristics	n (%)		OR (95% CI)
	Cases	Controls	
Folic acid			0.56 (0.39-0.83)
Yes	34 (35.1)	223 (49)	
No	63 (64.9)	232 (51)	
Drug use in 1st trimester			3.0 0(1.88-5.07)
Yes	39 (40.2)	39 (8.7)	
No	58 (59.7)	416 (91.3)	
Smoking			5.31 (0.50 to 56.24)
Yes	29 (30)	45 (9.9)	
No	68 (70)	410 (90.1)	
X-ray exposure			0.69 (0.05-8.48)
Yes	27 (28)	5 (1)	
No	70 (72)	450 (99)	
Pesticide exposure			
Yes	39 (40)	47 (10.3)	1.46 (0.80 – 2.28)
No	58 (60)	408 (89.7)	
Diabetes mellitus			
Yes	43 (45)	212 (46.6)	1.12 (0.77-1.62)
No	54 (55)	243 (53.4)	
Maternal illness			
Yes	51 (53)	173 (38)	1.30 (0.80-2.10)
No	46 (47)	282 (62)	

Note: OR = odd ratio

Table V: Multivariate analyses of factors associated with congenital anomalies

Characteristics	AOR	95% CI
Age	2.35	1.036–5.642
History of malformation	3.7	0.88–16.00
Severe anaemia	4.37	2.48-7.69
Birth weight	2.65	1.15-8.63
Maturity	2.39	2.30-2.49
Drug use during the 1st trimester	3.43	2.01–5.86
Smoking	4.10	1.89–8.90
Folic acid use	0.63	0.24–0.74
Pesticide exposure	3.92	1.26–12.17

Note: AOR = Adjusted Odd ratio

significantly to low folic acid intake. Cultural beliefs and traditional practices also play a role in minimizing the perceived need for modern supplements. Studies indicate that women with limited knowledge about folic acid supplementation are less likely to follow medical recommendations and may rely on non-medical remedies16 Drug use during the first trimester was strongly associated with anomalies (OR = 3.0, 95% CI: 1.88–5.07). Pesticide exposure also increased the risk, though the effect size was moderate (OR = 1.46, 95% CI: 0.80–2.28).

Several pesticides have been associated with fetal anomalies. Organophosphates, such as chlorpyrifos, are linked to developmental neurotoxicity, including lower IQ and motor impairments in offspring. Triazines, such as atrazine, have been associated with low birth weight and defects in the heart, urinary system, and limbs.

Although smoking and x-ray exposure were observed more frequently in cases, they did not show statistically significant associations. Similarly, maternal diabetes and other illnesses did not demonstrate strong correlations with congenital anomalies in this study population.

Multivariate Analyses

The Cox multivariate model identified several significant factors associated with congenital anomalies, as shown in Table V. Unidentified medication used during the first trimester demonstrated a strong association with congenital anomalies (OR=3.43, 95% CI: 2.01–5.86). Passive smoking was the most significant factor, with an adjusted odd ratio of 4.10 (95% CI: 1.89–8.90), followed by pesticide exposure (OR=3.92; 95% CI: 1.26–12.17). While factors such as severe anaemia, low birth weight, maturity, and folic acid use showed trends toward significance, they did not retain statistical significance in the multivariate model.

DISCUSSION

This study identified key factors associated with CAs, highlighting maternal, foetal, and environmental contributors. A history of congenital anomalies and severe anaemia in mothers were significant risks, with severe anaemia linked to nearly one-third of cases. Preterm birth showed the strongest foetal association, while other factors like low birth weight and stillbirths were less significant. Environmental risks included unidentified medication use during the first trimester, passive smoking, and pesticide

exposure, with passive smoking showing the highest hazard ratio. Notably, 64.5% of mothers in this study did not receive folic acid supplementation, potentially reflecting gaps in antenatal care and knowledge, as evidenced by the lack of antenatal care follow-up in a significant portion of both cases and controls. While the absence of folic acid supplementation showed a protective trend, it did not retain significance in the multivariate model.

Teratogens disrupt organ development during the critical period of organogenesis in early pregnancy, a stage when the embryo is highly susceptible to environmental exposures despite being protected by extra-embryonic membranes.[17-18] These agents can penetrate the placenta and interact with maternal and fetal genetic profiles, modifying biochemical pathways and morpho-functional patterns, which influence susceptibility to malformations. Mechanisms such as oxidative stress, endocrine disruption, hyperacetylation, and alterations in folate metabolism are common pathways through which teratogens induce developmental disruptions.[19] For example, pesticide exposure during the first eight weeks of gestation can interfere with neuronal proliferation, synaptogenesis, and neurotransmitter regulation, increasing the risk of structural and neurodevelopmental anomalies.[20-22]

Maternal behaviors such as smoking further exacerbate these risks. Active and passive smoking during early pregnancy increase oxidative stress, leading to cellular damage and disruptions in essential pathways like Notch and Wnt, which are crucial for embryonic development.[23] Additionally, inadequate folic acid intake significantly raises the likelihood of congenital anomalies, particularly neural tube defects, due to its role in DNA synthesis and cell division during organogenesis.[24-25] A recent meta-analysis has demonstrated that folic acid supplementation reduces the risk of congenital anomalies by up to 77% (OR 0.23; 95% CI: 0.16–0.32).[26]

Our study identified several maternal, foetal, and environmental factors associated with congenital anomalies, many of which align with findings from previous research. Similar to the study by Maritska et al conducted in Indonesia, we observed that maternal smoking and exposure to chemicals, such as pesticides, were significant risk factors.[27] Additionally, studies conducted in Iraq and Egypt also reported a strong association between maternal smoking—both active and passive—during the first three months of pregnancy and the occurrence of birth defects, particularly cleft lip with or without cleft palate.[28-29] The differences in the prevalence of smoking-related congenital anomalies between these regions and Indonesia may be due to cultural variations in smoking practices and second-hand smoke exposure. Additionally, Maritska et al. reported congenital digestive system anomalies as the most prevalent type, whereas our study focused more broadly on risk factors and did not categorize specific anomaly types.[27]

Several studies have shown that gestational diabetes is strongly associated with foetal growth abnormalities, as maternal hyperglycaemia leads to increased glucose levels in the embryo, resulting in oxidative stress and apoptosis.[30-32] However, our findings did not reveal a significant association between diabetes mellitus and congenital anomalies. This lack of association may be attributed to the fact that most diabetes patients in our study population were already under the care of internal medicine specialists before pregnancy, potentially achieving better glycaemic control.

Sunitha et al.'s research in South India also highlighted maternal age and consanguinity as significant contributors to congenital anomalies, particularly in high-risk pregnancies.[33] Our study identified maternal age >35 years as a risk factor but did not examine consanguinity due to cultural and demographic differences. Indonesia, being a predominantly Muslim country, does not permit consanguineous marriages. As a result, there were no cases of consanguinity recorded in our dataset, and therefore this variable was not included in the analysis. However, in Indonesia, TORCH screening remains relatively expensive and is not covered by government health insurance, resulting in limited available data; therefore, it was not included in our analysis.

Findings from African studies, including Moges et al and Abebe et al, also resonate with our results.[26,34] Moges et al identified folic acid deficiency, maternal illness, and drug use as significant risk factors, findings consistent with our study's emphasis on the protective role of folic acid and the risks associated with unidentified medication use.[26] Abebe et al specifically noted pesticide exposure and passive smoking as major contributors, similar to our results. Interestingly, while smoking did not appear significant in bivariate analysis in our study, it emerged as a significant factor in multivariate analysis.[34]

The umbrella review by Lee et al reinforced the global relevance of environmental and genetic risk factors.[35] Congenital anomalies were linked to maternal exposure to air pollution, toxic chemicals, and smoking, all of which align with our findings on pesticides and smoking. The review also emphasized the preventive role of folic acid supplementation, consistent with our study's findings. The observed association between genetic factors and congenital anomalies in Lee et al.'s review was not within the scope of our study, suggesting an area for further exploration in future research.[35]

Cultural practices and healthcare accessibility in Indonesia influence the findings of this study, particularly the high exposure to passive smoking despite low rates of active smoking among mothers and the limited folic acid supplementation, reflecting gaps in antenatal care and awareness. These findings highlight the need for public health campaigns to reduce passive smoking, regulate pesticide use, and promote safe medication practices during pregnancy. Improving antenatal care to ensure consistent folic acid supplementation and addressing teratogenic risks can significantly reduce the burden of congenital anomalies. However, the study's single-hospital design limits generalizability, and potential recall bias from self-reported data may affect accuracy. Future research should explore multi-center studies for a broader understanding of congenital anomalies in Indonesia.

CONCLUSION

Maternal socio-demographic factors, such as education, socioeconomic status, and ANC visits, were not significantly associated with CAs. However, maternal smoking, pesticide and chemical exposure, and unidentified medication use during the first trimester were significant risk factors, while folic acid supplementation showed a protective effect despite low usage rates in Indonesia. Improving antenatal care, promoting folic acid supplementation through food fortification, and ensuring safe medication use during pregnancy are essential for congenital anomalies prevention.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

ACKNOWLEDGEMENTS

The authors are deeply grateful to the patients for their invaluable participation, which has helped advance understanding in this field.

FUNDING

None

REFERENCES

1. DeSilva M, Munoz FM, McMillan M, Kawai AT, Marshall H, Macartney KK, et al. Congenital anomalies: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2016; 34(49): 6015-26.
2. Kancherla V, Oakley GP, Jr., Brent RL. Urgent global opportunities to prevent birth defects. Semin Fetal Neonatal Med 2014; 19(3): 153-60
3. Christianson A, Howson CP, Modell B. March of Dimes: global report on birth defects, the hidden toll of dying and disabled children. 2005.
4. Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005. MMWR Morb Mortal Wkly Rep 2008; 57(1): 1-5
5. Cherian AG, Jamkhandi D, George K, Bose A, Prasad J, Minz S. Prevalence of congenital anomalies in a secondary care hospital in South India: A cross-sectional study. J Trop Pediatr 2016; 62(5): 361-7.
6. WHO. 2023. Indonesia: Neonatal and Child Health Profile.
7. Kim MA, Yee NH, Choi JS, Choi JY, Seo K. Prevalence of birth defects in Korean livebirths, 2005-2006. J Korean Med Sci 2012; 27(10): 1233-40.
8. Ko JK, Lamichhane DK, Kim HC, Leem JH. Trends in the prevalences of selected birth defects in Korea (2008–2014). Int J Environ Res Public Health 2018; 15(5).
9. Oliveira-Brancati CIF, Ferrarese VCC, Costa AR, Fett-Conte AC. Birth defects in Brazil: Outcomes of a population-based study. Genet Mol Biol 2020; 43(1): e20180186.
10. Al-Dewik N, Samara M, Younes S, Al-jurf R, Nasrallah G, Al-Obaidly S, et al. Prevalence, predictors, and outcomes of major congenital anomalies: A population-based register study. Scientific Reports 2023; 13(1): 2198.
11. Harris BS, Bishop KC, Kemeny HR, Walker JS, Rhee E, Kuller JA. Risk factors for birth defects. Obstet Gynecol Surv 2017; 72(2): 123-35.
12. Lin H, Luo MY, Luo JY, Zeng R, Li YM, Du QY, Fang JQ. Demographic characteristics and environmental risk factor exposure of birth defects in pregnant women: A population-based study. Biomed Environ Sci 2019; 32(1): 51–7.
13. El Koumi MA, Al Banna EA, Lebda I. Pattern of congenital anomalies in newborn: a hospital-based study. Pediatr Rep. 2013; 5(1): e5.
14. Titaley CR, Rahayu E, Damayanti R, Dachlia D, Sartika RAD, Ismail A et al. Association between knowledge and compliance of taking iron/folic acid supplements during pregnancy. Asian Journal of Pharmaceutical and Clinical Research 2017; 10: 177-82.
15. Atmadani RN, Akrom A, Ananda D, Saputri LY, Puspitasari AA, Urbayatun S. Supports and Barriers Regarding the Iron-Folic Acid Supplementation Adherence Level in Anemic Pregnant Women: Indonesian's Perspective. MKMI 2024; 20(2): 46-5.
16. Yismaw AE, Tulu HB, Kassie FY, Araya BM. Iron-folic acid adherence and associated factors among pregnant women attending antenatal care at Metema District, Northwest Ethiopia. Front Public Health 2022; 10; 978084.
17. Cassina M, Salviati L, Di Gianantonio E, Clementi M. Genetic susceptibility to teratogens: state of the art. Reprod Toxicol 2012; 34(2): 186-91.
18. Mazzu-Nascimento T, Melo DG, Morbioli GG, Carrilho E, Vianna FSL, Silva AA, Schuler-Faccini L. Teratogens: a public health issue - a Brazilian overview. Genet Mol Biol 2017; 40(2): 387-97.
19. Giavini E, Menegola E. Biomarkers of teratogenesis: suggestions from animal studies. Reprod Toxicol 2012; 34(2): 180-5.
20. Wager JL, Thompson JA. Development and child health in a world of synthetic chemicals. Pediatr Res 2024.
21. Goasdoué K, Miller SM, Colditz PB, Björkman ST. Review: The blood-brain barrier; protecting the developing fetal brain. Placenta 2017; 54: 111-6.
22. Iqubal A, Ahmed M, Ahmad S, Sahoo CR, Iqubal MK, Haque SE. Environmental neurotoxic pollutants: review. Environ Sci Pollut Res 2020; 27(33): 41175-98.
23. Liszewski W, Ritner C, Aurigui J, Wong SS, Hussain N, Krueger W, et al. Developmental effects of tobacco smoke exposure during human embryonic stem cell differentiation are mediated through the transforming growth factor-β superfamily member, Nodal. Differentiation 2012; 83(4): 169-78.
24. Rosenquist TH. Folate, homocysteine and the cardiac neural crest. Dev Dyn 2013; 242(3): 201-18.
25. Scholl TO, Johnson WG. Folic acid: influence on the outcome of pregnancy. Am J Clin Nutr 2000; 71(5 Suppl): 1295s-303s .
26. Moges N, Sisay Chanie E, Anteneh RM, Zemene MA, Gebeyehu AA, Belete MA, et al. The effect of folic acid intake on congenital anomalies. A systematic review and meta-analysis. Front Pediatr 2024; 12: 1386846
27. Maritska Z, Aswadi T. Risk factors of congenital anomalies in South Sumatera, Indonesia. Biosci Med 2020; 4: 60-9.
28. Ameen SK, Alalaf SK, Shabila NP. Pattern of congenital anomalies at birth and their correlations with maternal characteristics in the maternity teaching hospital, Erbil city, Iraq. BMC Pregnancy and Childbirth 2018; 18(1): 501.
29. Shawky R, Sadik D. Congenital malformations prevalent among Egyptian children and associated risk factors. World Pumps 2011; 12: 69-78.
30. Al-Shwyiat RMM, Radwan AM. Fetal anomalies in gestational diabetes mellitus and risk of fetal anomalies in relation to pre-conceptional blood sugar and glycosylated hemoglobin. J Mother Child 2022; 26(1): 73-7.
31. Mirabelli M, Chiefari E, Tocci V, Greco E, Foti D, Brunetti A. Gestational diabetes: Implications for fetal growth, intervention timing, and treatment options. Curr Opin Pharmacol 2021; 60: 1-10.
32. Moreli JB, Santos JH, Lorenzon-Ojea AR, Corrêa-Silva S, Fortunato RS, Rocha CR, et al. Hyperglycemia differentially affects maternal and fetal DNA integrity and DNA damage response. Int J Biol Sci 2016; 12(4): 466-77.
33. Sunitha T, Rebekah Prasoona K, Muni Kumari T, Srinadh B, Laxmi Naga Deepika M, Aruna R, Jyothy A. Risk factors for congenital anomalies in high risk pregnant women: A large study from South India. Egypt J Med Hum Genet 2017; 18(1): 79-85.

34. Abebe S, Gebru G, Amenu D, Mekonnen Z, Dube L. Risk factors associated with congenital anomalies among newborns in southwestern Ethiopia: A case-control study. PLoS One 2021; 16(1): e0245915.

35. Lee KS, Choi YJ, Cho J, Lee H, Lee H, Park SJ, et al. Environmental and genetic risk factors of congenital anomalies: An umbrella review of systematic reviews and meta-analyses. . J Korean Med Sci 2021; 36(28): e183.