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Study the risk factors for a neural tube defect in women in the COVID-19 pandemic in Zakho. Kurdistan, Iraq

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ABSTRACT

Background: Neural tube defects are a common congenital disorder. The complex etiology of Neural tube defects involve both genetic and environmental factors, thus investigating gene-environment interactions is critical to understanding how it occur or how it may be prevented. Published literatures also have indicated that viral illness during early pregnancy and several antiviral drugs are associated with an increased risk for neurodevelopmental congenital anomalies of new-born.

Aim of the study: To evaluate the prevalence of Neural tube defects among pregnant women suffered from COVID 19 infection

Patients and methods: This study is a case control study had done in Zakho Maternity Hospital. The data collected during the period of 1st Ja. 2020-1st Ja 2022, the total 90 cases that reported in the obstetrics and gynecology department with neural tube defects was enrolled in the study, and compared with control group of 90 pregnancies without Neural tube defects. The information collected through direct interview with the mothers through questionnaire includes the information about the socio-demographic, obstetrical history and history of COVID 19 infection, severity, presence of fever, trimester of infection. The laboratory investigations of hemoglobin and PCR to confirm COVID 19 infection was done.

Results: COVID infection during pregnancy was significantly higher among those with Neural tube defects 68 (75.6%), in comparison to 30 (33.3%) of those without NTD. Anemia was significantly higher among those with Neural tube defects 69 (67.7%) in comparison to 15 (16.7%). Fever in 1st trimester was significantly higher among those with NTD 70 (77.8%) in comparison to 28 (31.1%). Alcohol intake was significantly lower among those with NTD 2(2.2%) in comparison to 10(11.1%). Polyhydramnios was significantly higher among those with NTD 72 (80%) in comparison to 11(12.2%).

Conclusions: COVID infection during pregnancy was significantly higher among those with neural tube defects and this alarming.

Key words: Risk factors, Neural tube defect, COVID, Zakho

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INTRODUCTION

It was stated that in China in December 2020 there was a cluster of people suffering from pneumonia of unclear aetiology [1]. Initial research revealed that the source of the illness was a new coronavirus, which was later given the name severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) proclaimed a pandemic of the coronavirus disease 2019 (COVID-19) in March of 2021 [2,3]. The sickness was rapidly spreading throughout the world. This pandemic is regarded to be one of the worst in recent years due to the fact that there have been more than 270 million infections and more than 5 million confirmed fatalities that may be ascribed to COVID-19 as of November 2021. This devastating pandemic has been a driving force behind the research and development of vaccinations to combat the virus [1,2]. Neural tube defects (NTDs) are the most severe birth defects and the main cause of newborn death; posing a great challenge to the affected children, families, and societies [1]. NTDs occur throughout the world with a wide variation in prevalence, ranging from about five per 10,000 to a hundred per 10,000 [2]. Neural tube defects (NTDs) are a common congenital disorder resulting from failed neural tube formation, the precursor of the brain and spinal cord. The complex etiology of NTDs involve both genetic and environmental factors, thus investigating gene-environment interactions is critical to understanding how NTDs occur or how NTDs may be prevented [3]. Published literatures also have indicated that viral illness during early pregnancy and several antiviral drugs are associated with an increased risk for neurodevelopmental congenital anomalies of new-born [4,5]. Muzumdar, et al. Mumbai, has reported 26 cases of NTDs due to COVID-19 [6]. The aim of the study was to evaluate the prevalence of Neural tube defects among pregnant women suffered from COVID 19 infection.

PATIENTS AND METHODS

This study is a case control study done in Zakho Maternity Hospital, the hospital serves the population of Zakho 450,000 thousands population and 250000 internally displaced person from the Shinkal, Mousel cities and from Syria. The data collected during the period of 1st Jan 2020- 1st Jan. 2022, the total 90 cases that reported in the obstetrics and gynecology department with neural tube defects was enrolled in the study, and compared with control group of 90 pregnancies without NTD. The information collected through direct interview with the mothers through questionnaire includes the information about the sociodemographic, obstetrical history and history of COVID 19 infection, severity presence of fever, trimester of infection. The laboratory investigations of hemoglobin and PCR to confirm COVID 19 infection was done. Declaration of Ethical Approval and Consent To Participate: The protocol, design and procedure of this study were approved by the Scientific and Ethics Committee of the College of Medicine, University of Zakho, Duhok Province, Kurdistan Region, Iraq (Ethic committee reference number:4/154/NW). All participants in this study were voluntarily agreed to take part in this study. They received a copy of this consent form. They understand that information may be taken during the study. All the signed documented consents kept and ready to be presented at any time that is required. Statistical analysis of the data done using the social science soft wear package (SPSS) version 25, the data presented using frequency and percentage.

RESULTS

The mother age was commonest in extreme ages at ages <20 years 9(10%) and among 21-25 years 14(15.6%), and those aged >35 years 17(18.9%) among cases, in comparison to controls 4(4.4%), 4(4.4%), and 16(17.8%) respectively, this relation was statistically significant. The mothers with Yezidi 12(13.3%) and Christian 8(8.9%) religion had higher proportion of NTD than control group 10(11.1%), and 6(6.7%) respectively. this relation was statistically s not significant. Most of the cases from Zakho city 56(62.2%) followed by Shigar 13(14.4%), and displaced persons from Syria 13(14.4%) (Table 1).

Table 1: The general characteristics of cases and controls.

General Characteristics		Cases		Controls		P value
		Neural Tube Defect		Normal baby		
		No.	%	No.	%	
Age	<20 years	9	10.00%	4	4.40%	0.034
	21-25	14	15.60%	4	4.40%	
	26-30	39	43.30%	47	52.20%	
	31-35	11	12.20%	19	21.10%	
	>35	17	18.90%	16	17.80%	
Religion	Muslim	70	77.80%	74	82.20%	0.74
	Yezidi	12	13.30%	10	11.10%	
	Christian	8	8.90%	6	6.70%	
Residency	zakho	56	62.20%	75	83.30%	0.007
	shingal	13	14.40%	9	10.00%	
	syria	13	14.40%	1	1.10%	
	musel	5	5.60%	4	4.40%	
	baghdad	1	1.10%	0	0.00%	
	erbil	2	2.20%	0	0.00%	
	Duhuk	0	0.00%	1	1.10%	
Job	Teacher	16	17.80%	14	15.60%	0.95
	House Wife	60	66.70%	64	71.10%	
	Nurse	2	2.20%	3	3.30%	
	Enjoiner	3	3.30%	1	1.10%	
	Pharmacy	1	1.10%	1	1.10%	
	Doctor	1	1.10%	1	1.10%	
	Employer	7	7.80%	6	6.70%	
Total		90	100.00%	90	100.00%	

Table 2 show the risk factors of NTD, the consanguinity were significantly higher among cases 30(33.3%) than controls 16 (17.8%). Female sex was higher than male sex among cases 47(52.2%), 43(47.8%) respectively this relation was statistically not significant. Folic acid supplementation during pregnancy was significantly higher among cases than controls 84(93.3%), 74(82.2%). COVID infection during pregnancy was significantly higher among those with NTD 68(75.6%), in comparison to 30(33.3%) of those without NTD. Anemia was significantly higher among those with NTD 69(67.7%) in comparison to 15 (16.7%). fever in 1st trimester was significantly higher among those with NTD 70 (77.8%) in comparison to 28(31.1%). Alcohol intake was significantly lower among those with NTD 2(2.2%) in comparison to 10(11.1%). Polyhydramnios was significantly higher among those with NTD 72 (80%) in comparison to 11(12.2%).

The association of the risk factors with the NTD was tested by calculating the Odds Ratio (OR), the highest OR was for polyhydramnios (OR=28.7 with 95% CI 12.7-64.9), followed by anemia (OR=15.5 with 95% CI 6.38-37.5), COVID 19 infection(OR=7.2 with 95% CI 2.97-17.5), Consanguinity(OR=3.28 with 95% CI 1.152-8.82), and folic acid supplementation (OR=2.15 with 95% CI 0.52-8.97), as shown in Table 3.

Table 2: Risk factors of neural tube defect.

		Cases		Controls		P value
		Neural tube defect		Normal Baby		
		No.	%	No.	%	
Consanguinity	Yes	30	33.30%	16	17.80%	0.017
	No	60	66.70%	74	82.20%	
Baby Sex	Male	43	47.80%	40	44.40%	0.65
	Female	47	52.20%	50	55.60%	
Folic Acid Supplementation During Pregnancy	Yes	84	93.30%	74	82.20%	0.023
	No	6	6.70%	16	17.80%	
COVID 19 Infection	Yes	68	75.60%	30	33.30%	0.001
	No	22	24.40%	60	66.70%	
Anemia	Yes	69	76.70%	15	16.70%	0.001
	No	21	23.30%	75	83.30%	
Fever In 1st Trimester	Yes	70	77.80%	28	31.10%	0.001
	No	20	22.20%	62	68.90%	
Alcohol Intake	Yes	2	2.20%	10	11.10%	0.017
	No	88	97.80%	80	88.90%	
GDM	Yes	4	4.40%	7	7.80%	0.35
	No	86	95.60%	83	92.20%	
DM	Yes	8	8.90%	8	8.90%	0.63
	No	82	91.10%	82	91.10%	
Ht	Yes	8	8.90%	11	12.20%	0.46
	No	82	91.10%	79	87.80%	
Oligohydramnios	Yes	7	7.80%	7	7.80%	0.609
	No	83	92.20%	83	92.20%	
Polyhydramnios	Yes	72	80.00%	11	12.20%	0.001
	No	18	20.00%	79	87.80%	
Other Anomalies	Heart Disease	1	1.10%	0	0.00%	0.316
Total		90	100.00%	90	100.00%	

Table 3: The crud odds ratio of risk factors of NTD.

Risk Factors	Sig.	COR	95% C.I.for OR	
			Lower	Upper
Anemia	0	15.5	6.38	37.5
Baby sex	0.556	1.292	0.551	3.027
COVID 19 infection	0	7.21	2.97	17.5
Fever in 1st trimester	0	7.7	3.94	15,11
folic acid supplementation	0.293	2.152	0.52	8.97
alcohol intake	0.03	0.077	0.008	0.777
Consanguinity	0.026	3.28	1.152	8.82
GDM	0.333	0.451	0.09	2.26
DM	0.848	0.85	0.16	4.503
HT	0.996	1.003	0.262	3.841
oligohydramnios	0.6	1	0.33	2.97
polyhydramnios	0.001	28.7	12.7	64.9

DISCUSSION AND CONCLUSION

The current study reveals that mother age was commonest in extreme ages at ages < 20 years 9 (10%) and among 21-25 years 14 (15.6%), and those aged >35 years 17 (18.9%) among cases , in comparison to controls 4(4.4%), 4(4.4%), and 16 (17.8%) respectively, this relation was statistically significant. Atlaw, D. et al found that the pooled odds ratio indicated that the odds of neural tube defect are 1.5 times higher among women with an age group greater than 30 years during pregnancy (POR, 95% CI: 1.47(1.16–1.87)) [7]. The association of maternal age and neural tube defect was examined based on the findings from Bourouba, et al. study [8]. While it is different from Berhane, et al. revealed that Mothers in the age group 25–34 (46.9%) and multigravida mothers had higher proportions (64.4%) of neural tube defects [9]. Dessie, et al. found that neural tube defects do not have specific causative agents, but genetic, environmental, and maternal age factors were among common contributors [10]. Abdulaziz, et al. found that the age of 112 women that her babies affected NTDs, 30(26.8%) had 16-25 years , 55 (49.1%) had 26-35 years while 27 (24.1%) had above 35 years [11]. Abebe, et al. found in Ethiopia among those aged >35 years 14.2% while among controls 2.4% [12]. While Gedefaw A et al 2018 found no difference between the mean age of cases (26.9; ±4.6) and controls (26.7 ±5.2) [13]. The current study revealed that the consanguinity was significantly higher among cases 30 (33.3%) than controls 16 (17.8%). This is lower that results of Nauman N 2016 found that 60 % of couples had a neural tube pregnancy were consanguineous as compared to 45% in controls [14]. El- Moghrabi, et al. found that consanguineous marriage is also listed as a common factor for NTDs [15]. But Abdulaziz, et al. found that consanguineous marriage is not important risk factor for NTDs [11]. The current study revealed that mothers with Yezidi (13.3%) and Christian (8.9%) religion had higher proportion of NTD than control group (11.1%), and (6.7%) respectively. Most of the cases from Zakho city 56 (62.2%) followed by Shingar 13 (14.4%), and displaced persons from Syria 13 (14.4%). This is not against what found by Forci K et al found that no difference between the cases and controls in terms of the participants' religion. Forci K et al found that consanguinity is a risk factor for 34% of cases [16]. The current study found that alcohol intake was significantly lower among those with NTD (2.2%) in comparison to (11.1%). Zaheri F et al found that alcohol drinking increased the risk of NTDs [17]. Maternal history of alcohol intake during pregnancy was found to be significantly associated with NTDs [18]. There are some other studies that reported the same results, as well, e.g. [16], whereas some other studies reported no significant association between these two [19,20]. Biological mechanisms for explaining the effect of alcohol on fetus evolution is not available. However, studies conducted on animals have demonstrated that in the first periods of fetus evolution, alcohol kills many neural crest cells [21].

The current study revealed that female sex was higher than male sex among cases (52.2%), (47.8%) respectively. Abebe, et al. found in Ethiopia found that of the affected fetuses, 39% and 61% were male and female, respectively, while 51.8% and 48.2% of the control fetuses were male and female, respectively [12]. Liu, et al. found the overall prevalence of NTDs was 2.5‰ among males and 4.4‰ among females; NTDs were less prevalent among males than among females (RR, 0.58; 95% CI, 0.54–0.63) [22]. This could be an epigenetic phenomenon considering females methylate most of the DNA in the large inactive X chromosome after each cell division. Consequently, methylation needs for other cells may not be met [23]. Genetic and environmental factors contribute to increase sex ratios in anencephaly (an early stage of anencephaly) and spina bifida, due to preferential lethality of females [24]. Liu, et al. found Folic acid supplementation led to significantly greater decreases in the rates of anencephaly (4.8‰) and total NTDs (7.6‰) in females than in males (1.6‰ and 2.8‰, respectively) [22]. Petersen, et al. found that daily FA supplementation was associated with lower NTD risk compared to no supplementation (adjusted ORs were 0.33 [95% CI 0.13, 0.76] for family history [25]. Ban, et al. found that 4 nervous system malformations among 1,259 pregnancies with first trimester AED exposure but none among the 66 women who supplemented with ≥ 5 mg of FA [26]. The difference in this study from previous study may be indicate that the real cause is related to COVID19 infection, or fever related to it, more than other risk factors, and maybe there is some interaction between COVID19 and FA level in the maternal blood and immune system. These thinks need more sophisticated studying. The current study revealed that the Folic acid supplementation during pregnancy was significantly higher among cases than controls (93.3%), (82.2%). This is a strange thing because according Liu J et al 2018 found Folic acid supplementation led to significantly greater decreases in the rates of anencephaly (4.8‰) and total NTDs (7.6‰) in females than in males (1.6‰ and 2.8‰, respectively) [22], this should be studied. The current study found that COVID infection during pregnancy was significantly higher among those with NTD (75.6%), in comparison to (33.3%) of those without NTD. No previous study found to study the relation between COVID19 and NTD. The current study found that anemia was significantly higher among those with NTD (67.7%) in comparison to (16.7%). This goes with Bethany A 2017 found a strong case that sufficient iron stores at conception are also important for successful neural tube closure. Bethany A 2017 also provides additional support for the possibility that iron deficiency could play a role in NTDs in humans and preconception iron supplementation might prevent some folate resistant NTDs [27]. Lopez, et al. found that Iron deficiency is one of the most common micronutrient deficiencies in women of childbearing age [28]. Herbig, et al. found that iron and foliate deficiencies often occur simultaneously and iron and folate metabolism are linked in many ways [29]. Mao, et al. suggested iron might be required for neural tube closure [30]. The current study found that fever in 1st trimester was significantly higher among those with NTD (77.8%) in comparison to (31.1%). This agrees with Mariam A Ibrahim, et al. 2019 found that CMV virus might be an important cause of NTD and p53 is a likely to be involved in pathogenesis of NTD [31]. Also, Luteijn, et al. found that the first trimester maternal influenza exposure was associated with an increased risk of any congenital anomaly, & neural tube defects [odds ratio (OR) 3.33, 2.05–5.40], etc. [4]. Lynberg, et al. found that there was no increased risk for NTD among the infants of mothers who reported fever from causes other than flu [32]. The current study found that Polyhydramnios was significantly higher among those with NTD (80%) in comparison to (12.2%). This is higher than Gaxiola, et al. found that the occurrence of polyhydramnios during pregnancy was 1.1% and the association with congenital malformations was 13.8%, being the majority neural tube defects [33]. The current study revealed that COVID infection during pregnancy was significantly higher among those with NTD (75.6%), in comparison to (33.3%) of those without NTD. This is supported by Luteijn, et al. has indicated that viral illness during early pregnancy and several antiviral drugs are associated with an increased risk for neurodevelopmental congenital anomalies of newborn [4]. This is also supported by Dong, et al. [34], and Moriguchi, et al. [35] found that the causative agent of COVID-19, SARS-CoV-2 seem to cross both placental barrier (viral IgM detected in infants hours after birth) [34] and blood brain barrier (virus detected in cerebrospinal fluid) [35]. As the virus can enter placenta and nervous system, the virus itself may have some adverse effects on the pathogenesis of NTDs, if pregnant mothers suffer from COVID-19. This goes with study of Khan, et al. who concluded that COVID-19 may results in long-lasting congenital anomalies of infants either by infection or by therapeutic maneuver [36] This is supported by Muzumdar, et al. Mumbai, has reported 26 cases of NTDs due to COVID-19 [6].

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