NYACK UNION FREE SCHOOL DISTRICT

The Effect of Maternal Autoimmune Conditions on the Risk of Gastroschisis

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ABSTRACT:

In the last decade, the US has seen in increase in the number of cases of gastroschisis. This birth defect, though survivable, can put stress on the patient and their families. With no known cause, this study was performed in order to look for a correlation between maternal autoimmune conditions and gastroschisis. Using a case-control study design, 145 cases and 1078 controls were assessed. After statistical analysis, the data suggested that there is no statistically significant indication that a maternal autoimmune condition puts a woman at greater risk for gastroschisis.

INTRODUCTION:

Gastroschisis is an abdominal wall defect in which the contents of the abdomen extrude adjacent to the umbilicus. The US sees approximately four cases per 10,000 live births (Center for Disease Control). The treatment for gastroschisis varies from case to case, however, the standard process involves the use of a silo immediately after birth, followed by reparative surgery. A silo is a vacuum sealed bag that holds the contents of the abdomen perpendicular to the baby as it lies on its back. The intention of this method is to let as much of the contents fall into place as naturally as possible. Approximately ten days later, when the patient is deemed healthy enough, doctors may intervene with a surgical procedure. This procedure, once again, is different case to case, but the overall goal is to relocate the extruding organs to their normal position. Once taken off parenteral feeding, the patient can live a healthy life, however, the number of patients who return to the hospital is rising. Approximately 40% of gastroschisis patients will experience complications such a bowel obstruction or abdominal pain. In addition, other studies have shown that gastroschisis is the leading cause of organ transplant due to damage that can occur. Prior to birth, gastroschisis is diagnosed by routine sonograms. The underlying challenge with treating gastroschisis is that there is no known cause.

Studies involving gastroschisis rely heavily on maternal interviews to investigate associations between gastroschisis and environmental exposure and diseases. The strongest and most consistent risk factor is young maternal age (Haddow, et al, 1993), certain over the counter and prescription medications such as pseudoephedrine and aspirin (Werler, et al, 2002), alcohol consumption (Bird, et al, 2009), smoking (Feldkamp, et al, 2008), and genitourinary infections during pregnancy (Feldkamp, et al, 2013).

While current research involving gastroschisis has reported many risk factors for, the question still remains unanswered. What causes gastroschisis? The health of a mother has been known to be an essential part of determining the health of the baby.

Chambers et al, (2006) published a study that involved change in paternity as a risk factor for gastroschisis. Chambers noted that preeclampsia affected the risk of gastroschisis due to its theoretical immunologic basis. The notion that systemic inflammation can play a role in the risk of gastroschisis has been suggested by Feldkamp, et al, (2008; 2015). Systemic inflammation results from a number of different causes, one source are autoimmune conditions. Autoimmune conditions such as type 1 diabetes, rheumatoid arthritis, and celiac disease can cause systemic

inflammation. Women are more likely than men to develop autoimmune disease (Fairweather, et al, 2008). The inflammation is not directly affecting the physical being of the fetus, however it may have an impact on the mechanisms that are responsible for the fetus to develop correctly. Maternal health, as a general category, and is relationship with gastroschisis is largely unstudied. Moreover, data are lacking as to whether autoimmune diseases contribute to the risk of gastroschisis.

The goal of this study was to investigate whether autoimmune conditions increased the risk factor for gastroschisis. We hypothesized that case women were more likely to be diagnosed with any type of autoimmune condition prior to or after the index pregnancy compared to control women. To accomplish this goal we had two specific aims. First, to evaluate whether case women had been diagnosed more often with any type of autoimmune disease compared to control women, and secondly, to determine the timing of autoimmune disease diagnosis relative to the birth of the index pregnancy for case and control women.

METHODS:

We used a case control study design, based on existing data from the National Birth Defects Prevention Study (NBDPS) for this study. Cases were defined as Utah mothers who participated in the NBDPS, had a pregnancy or infant diagnosed with gastroschisis and delivered between 2003-2011. All pregnancy outcomes were included (live births, stillbirths, and pregnancy terminations). Controls were Utah mothers who were randomly selected from birth certificates with a live born infant without a birth defect during the same study period and participated in the NBDPS. We excluded any case with evidence of limb-body wall complex, amniotic band sequence, ruptured omphalocele, abdominoschisis, or those poorly described. Women diagnosed with an autoimmune disease, as listed in Table 1, before or after the index pregnancy were considered exposed.

The following variables were analyzed to assess if they were confounders: maternal age, race/ethnicity, preconception body mass index, periconceptional cigarette smoking, and periconceptional alcohol use. Periconceptional time period included the three months before conception to the end of the first trimester.

The study consisted of 166 case and 1162 control subjects before we applied the

exclusion criteria. These variables were included in a logistic regression model to determine if they were confounders.Prior data indicated that the prevalence of autoimmune disease among controls was 5%. If the true odds ratio (OR) for disease in exposed subjects relative to unexposed subjects was 2.5, we would be able to reject the null hypothesis. The probability of rejecting the null hypothesis, or power, was .864. The Type I error probability associated with the test of this null hypothesis was 0.05. We used to the chi square statistic to assess whether differences were observed between case and control subjects for the demographic factors of interest. We used unconditional logistic regression to calculate the crudes OR. The OR provides information on the probability of exposure among the diseased compared to the probability of exposure among the non-diseased.

Table 1: Autoimmune diseases	
Autoimmune Disease	ICD9 Code
Type 1 Diabetes	250.01
Rheumatoid Arthritis	714
Celiac Disease/Ulcerative Colitis	570.0
Lupus	710.0
Multiple Sclerosis	340
Vasculitis	446
Eczema	692
Alopecia Areata	704.09
Polymyalgia Rheumatica (related to giant cell arteritis)	725
Sjögren's Syndrome	710.2
Graves Disease	242.0
Pernicious Anemia	281.0
Guillain-Barré Syndrome	357.0
Vitiligo	709.01
Psoriasis	696
Biliary Cirrhosis	571.6
Hashimoto's Disease	245.2
Antiphospholipid	289.81
Hemolytic Anemia	283.0
Idiopathic thrombocytopenic purpura (ITP)	287.31
Polymyositis	710.4
Dermatomyositis	710.3
Scleroderma	701.0
Antiphospholipid syndrome	289.81
Myasthenia gravis	358.0
Autoimmune hepatitis	571.42
Myocarditis	422.0
Reactive arthritis	099.3

Table 1: List of the possible autoimmune conditions along with ICD9 codes.

RESULTS:

After assessing the data, a clear outcome was observed. There was no positive correlation between maternal autoimmune conditions and the risk of gastroschisis. Table 2 is a display of characteristics among case and control subjects. Case subjects were more likely to be There is only one case with an autoimmune condition. The crude OR= 2.5 (95%CI 0.26 to 24.1). An adjusted OR was not feasible due to only one case with autoimmune disease.

Characteristic	*Category*	*Case (n)*	*%*	*Control (n)*	*%*	
	Utah	**145**	**100**	**1078**	**100**	**Chi square p value**
Maternal race/ethnicity						0.008
	Non-Hispanic White	106	73.1	897	83.2	
	Hispanic	23	15.9	119	11	
	Other	16	11	62	5.8	
Maternal age (yrs)						<0.001
	<20	36	24.8	46	4.3	
	20-24	68	46.9	272	25.2	
	25-29	35	24.1	402	37.3	
	≥30	6	4.1	358	33.2	
Maternal BMI NIH						0.007
	Underweight	9	6.3	64	6	
	Normal	104	73.2	641	60.4	
	Overweight	22	15.5	210	19.8	
	Obese	7	4.9	146	13.8	
Gestational diabetes						0.102
	No	144	99.3	1040	96.9	
	Yes	1	0.7	33	3.1	
Maternal education (yrs)						<0.001
	0-12	81	56.3	293	27.2	
	>12	63	43.8	784	72.8	
Maternal smoking B1P3						<0.001
	No	111	76.6	975	90.4	
	Yes	34	23.4	101	9.4	
	Missing	0	0	2	0.2	
Illicit drug use B1P3						<0.001
	No	48	76.2	348	93.3	
	Yes	15	23.8	25	6.7	
Alcohol B1P3						<0.001
	No	97	66.9	916	85	
	Yes	48	33.1	158	14.7	
	Missing	0	0	4	0.4	
Autoimmune disease						0.416
	No	144	99.3	1074	99.7	
	Yes	1	0.7	3	0.3	

Table 2: Frequency and proportion of case and control maternal demographic factors.

DISCUSSION:

Overall, we found an non-statistically significant increased risk between maternal autoimmune conditions and gastroschisis. Because gastroschisis is a birth defect that occurs most commonly in women less than 25 years of age, it may be difficult to investigate this in women who have not had the opportunity to develop an autoimmune condition. It is also important to note the age range at which a woman may develop an autoimmune condition is not the same as the range they may be at a greater risk of having a baby with gastroschisis. This results in a possible scenario of a mother giving birth to a baby with gastroschisis and either not knowing about a present autoimmune condition, or not developing one until later on. In addition possible explanation for this finding can be seen in a population-based study conducted in 2012 by Anderson, et al. This study showed, in a population of individuals with a certain autoimmune condition, the majority (26.8%) were in the age group 75-79.

Several limitations are noted. We used NBDPS data were limited to one state. It is also known that the NBDPS only receives maternal interviews from about two thirds of those asked to participate. In addition, there is potential recall bias due to the fact that mothers are asked to recall their experiences. The fact that interviews were conducted 24 months after delivery leaves opportunity for incorrect information to be recalled. During pregnancy there are accepted and unaccepted behaviors. It may also be difficult for an expecting mother to admit that an unacceptable behavior took place during the pregnancy. However, maternal interviews were conducted by trained interviewers, each interviewer used computer assisted questionnaire to ensure the questions were asked in the same way. Cases were clinically reviewed by geneticists to determine if the case met eligibility criteria. Cases were excluded if there was a known chromosomal or genetic condition, and all pregnancy outcomes were included (NBDPS).

Further research should continue in the direction of maternal health, in addition to physical, environmental exposures. The health of a mother has been known to be an essential part of determining the health of the baby. When considering what may increase the chances of inflammation, assuming it may have an effect on the risk of gastroschisis, autoimmune conditions are consistently overlooked. The inflammation is not directly affecting the physical being of the fetus, however it may have an impact on the mechanisms that are responsible for the fetus to develop correctly. This study focused specifically on women having autoimmune

conditions before pregnancy. Women should be monitored after pregnancy to see if later on an autoimmune condition is developed.

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