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STRESS DURING PREGNANCY AND LACK OF CALCIUM AND FOLIC ACID INCREASES RISK OF AUTISM SPECTRAL DISORDER IN OFFSPRING

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ABSTRACT

The idea that preconception environmental exposures may be involved in Autism Spectrum Disorders (ASD) etiology arose in the 1970s from a retrospective case-control study of ASD that found a statistically significant difference in parental occupational exposure to chemicals during the preconception period 1. ASD are neurodevelopmental disorders characterized by varying deficits in social interactions, communication, and learning, as well as stereotypic behaviors. Over the past years, research into environmental risk factors for autism has grown dramatically, bringing evidence that an array of non-genetic factors acting during the prenatal period may influence neurodevelopment 2. The present study was therefore undertaken to investigate the potential prenatal risk factors for ASD. A total number of 184 individuals were studied. In the present study, factors that have demonstrated significant increases in ASD risk, include advanced maternal age and stress during pregnancy while folic acid and calcium supplement intake was found to be reducing the risk of ASD. Factors that showed insignificant increase in frequency or no association with ASD were intake of medications, fall, respiratory problems and bleeding during pregnancy.

Key Words: ASD, Maternal stress, Maternal age, Folic acid

INTRODUCTION

Autism spectrum disorders (ASDs) are complex conditions, with combinations of milder social abnormalities and communication impairment and less rigid interest restrictions. Genetic factors may be the most significant cause for autism spectrum disorders. Others factors may alter this underlying genetic liability such as sex, IQ, and prenatal and perinatal injury[1]. From the earlier research works, it is known that ASD is not caused by a single factor. Both genetic and environmental factors have the potential to increase the risk of ASD. The present study was undertaken to investigate potential prenatal and perinatal factors risk factors for ASD.

SUBJECTS AND METHOD

To achieve the objective of the study, 184 individuals were surveyed. The individuals surveyed were divided into ASD group and control group. The sample population included ASD group consisting of 92 ASD subjects and control group constituted by 92 subjects of similar age group but with no history of ASD. For achieving the objectives of the study a Proforma was designed to collect information about Prenatal and perinatal factors studied included medications taken, supplements taken during pregnancy, maternal stress, respiratory problems, fall during pregnancy and bleeding during pregnancy. The data collected using the proforma was tabulated and analyzed. For quantitative data, mean and standard deviation were computed. The statistical significance of associations between the various qualitative parameters was evaluated through Fisher's exact test *(two tail)*.

RESULT

ASD subjects studied had a mean age of 9.02 ± 3.26 years. The mean age of detection of the ASD subject's studied was 2.7 ±1.76 years with a variance of 3.11. The following prenatal factors were studied.

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1. **Maternal Age:** We observed that with advanced maternal age, the risk of having a child with ASD increase. Age of pregnancy in different age intervals of both control and ASD is tabulated (Table 1). The frequency of ASD was higher in maternal age intervals of 31-35 and 36-40 years. The mean maternal age during pregnancy of the ASD subject's studied was 27.8 ± 5.36 years and a variance of 28.7. The results indicate a significantly higher frequency of 26.09% ASDs in children born to mothers in age interval of 31 – 35 (*P = 0.0306*) as compared to the control.
2. **Intake of medication during pregnancy and ASD:** The present study showed an increase in the frequency of ASD in offspring of mothers who consumed medication during the first trimester of pregnancy. The study indicates that higher frequency of 39.13% of history of intake of medication in the mothers of ASD as compared to the control (28.57%). The difference was found to be statistically insignificant *(P=0.4312)*.
3. **Stress during pregnancy and ASD:** Stress on mothers during pregnancy was another factor studied. Mothers of the subjects were interrogated for physical and mental stress during their pregnancy, in both the control and ASD group. The frequency of stress during pregnancy was found to be higher in mothers of ASD group as compared to those in the control group. The difference is found to be statistically significant *(P=0.0257)*.
4. **Respiratory problems during pregnancy and ASD:** To evaluate the role of the hypoxic condition of a mother during pregnancy, we analyzed the sample population for respiratory problems during pregnancy. The present study found no correlation between respiratory problems during pregnancy and ASD.
5. **Maternal infection during pregnancy and ASD:** Infection of the mother may be also a source of impeding the growth of the fetus, which can be a potential risk factor for ASD in offspring. The present study found no correlation between maternal infections during pregnancy and ASD (*P = 0.6887)*.
6. **Fall during pregnancy and ASD:** This factor was studied to see if the physical impact of fall during pregnancy can be a potential risk factor. The frequency of ASD was higher in 13.04% of the mothers who had a fall during pregnancy as compared to the control. However, the difference was found to be statistically insignificant *(P=0.1226)*.
7. **Intake of supplements during pregnancy and ASD:** Different types of supplements are necessary for growth and development of the fetus. The vital supplements include vitamins, folic acid, iron, and calcium. The present study tried to evaluate the effect of not consuming folic acid or calcium or both. Most of the mothers of ASD subjects had not consumed folic acid and calcium supplements (52%) as compared to the control (5.5%). The difference was found to be statistically highly significant *(P=0.0039)*.
8. **Bleeding during Pregnancy:** The present study found no correlation between maternal bleeding during pregnancy and ASD *(P = 0.4898)*.

DISCUSSION

The present study evaluated the risk that a child will develop autism increases monotonically with the age of the mother. This study revealed that maternal age during pregnancy is a very crucial factor in determining the neurological development of the fetus. This study indicates a significantly higher frequency of 26.09% of ASDs in children born to mothers in age interval of 31 – 35 (*P = 0.0306*) as compared to the control. The present study is consistent with the findings of Croen LA et al,[3] Kolevzon A et al.,[4] and Gardener[5] which state that older parents may be statistically more likely to have children with autism. Study of Sandin S et al.,[6] reports that children of mothers older than 35 years had 30% increased the risk for autism.

Association of medication during pregnancy with autism risk is indicated in the study of Gardener[4]. According to his study, maternal medication use was associated with a 46% increased risk. The present study, however, does not agree with the study of Gardener[4]. This study shows a higher frequency of 39.13% of the mothers in ASD group had taken medication during pregnancy as compared to the control (28.57%). However, the difference was found to be statistically insignificant *(P=0.4312)*.

Strongest evidence of maternal hypertension and ASD risk is indicated in the studies of Gardener[4]. The important revelation of this study was the association of maternal stress during pregnancy and increased the risk of ASD. The frequency of stress during pregnancy was found to be significantly higher in mothers of ASD group as compared to those in the control group (*P=0.0257)*. Studies of Rai D et al.,[7] also revealed that exposure to stressful life events during the prenatal period is associated with an increased risk of offspring ASD. Whether this association is causal or reflects the risk of autism with severe depression during pregnancy requires further research.

The nutritional supplements taken were found to be having a positive influence in decreasing the ASD risk, as per the present study. Most of the mothers of ASD subjects had not consumed all supplements (21.74%) as compared to the control. This study reinforces the findings of Schmidt R. J et al.,[8] which indicated that women who consume the recommended daily dosage of folic acid, the synthetic form of folate or vitamin B-9, during the first month of pregnancy may have a reduced risk of having a child with autism. Studies of Lyall K, et al.,[2] also support that higher maternal intake of certain nutrients and supplements like folic acid has been associated with a reduction in ASD risk. Vitamin D deficiency – either

during pregnancy or early childhood – may be an environmental trigger for ASD in individuals genetically predisposed for the broad phenotype of autism[9].

The factors with the strongest evidence against a role in autism risk included maternal bleeding, intake of medications, respiratory problem and fall during pregnancy. However, meta-analysis of Gardner[10] identified fetal distress as potential risk factors for ASD and showed significant 81% elevated risk of ASD in relation to maternal bleeding during pregnancy. The mechanism underlying the suggested association with maternal medication use is also unclear, due to the variety of medications consumed during pregnancy and assessed in these studies.

Heterogeneity in some studies may be on account of methodological limitations that have impaired the precision and validity of results of most studies include small sample size, non-normal control groups, broad disease definition, and retrospective parental recall of exposures which may result in the high possibility of recall bias. Thus, the rising prevalence of ASD, coupled with the severe emotional and financial impact on the families, underscores the need for large, prospective, population-based studies with the goal of elucidating the modifiable risk factors, particularly those during the prenatal period.

CONCLUSION

Many factors may have a potential for increasing the risk of ASD. ASD is influenced by both genetic and environmental factors, and the risk increases most likely due to the underlying genetic factors or an interaction of these factors with the environment. In other words, ASD is a complex disorder resulting from the combination of genetic and environmental factors. Those having genetic susceptibility may be more vulnerable to develop ASD when exposed to the environmental risk factors. In the present study, the factors with the strongest evidence for an association with autism risk included advanced maternal age and stress during pregnancy. The study also indicates that folic acid and calcium supplement intake was found to be reducing the risk of ASD. The factors with the strongest evidence against a role in autism risk included were the intake of medications, fall, respiratory problems and bleeding during pregnancy.

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TABLE 1: Association of Prenatal Factors with Frequency of ASD in Offspring

Factors	Frequency		Significance (fishers exact test)
	Control Group	ASD Group	
Intake of Medication during pregnancy	28.57%	39.13%	*P=0.4312*
Stress during pregnancy	11.90%	30.43%	**P=0.0257*
Respiratory Problems During Pregnancy	14.29%	8.70%	*P = 0.4168*
maternal infection during pregnancy	7.32%	4.35%	*P = 0.6887*
fall during pregnancy	4.76%	13.04%	*P=0.1226*
Frequency of bleeding	19.05%	14.28%	*P = 0.4898*
Not taken Folic acid and calcium	5.50%	52.00%	***P = 0.0039*
Maternal age: 31-35 yrs 36-40 yrs	 9.52% 0%	 26.09% 4.35%	**P = 0.0306*

*Significant
** Highly significant