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# Non-Genetic Potential Risk Factors for Autism Spectral Disorders

KEYWORDS: ASD, maternal stress, maternal age, folic acid.

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**ABSTRACT** *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 significant cause for autism spectrum disorders. However many non genetic factors may also play an important role. The present study was therefore undertaken to investigate the potential prenatal, postnatal and other environmental risk factors for ASD. A total number of 184 individuals were studied. This study revealed that the factors with strongest evidence for an association with autism risk included advanced maternal age, stress during pregnancy, supplements taken, gestation period, parity, age gap between children and birth weight while folic acid-calcium supplement intake was found to be reducing the risk of ASD. The factors with evidence against a role in autism risk included were family history of seizures and tuberculosis, oral contraceptive, medication during pregnancy, maternal respiratory problems, maternal infection, fall during pregnancy, bleeding during pregnancy and labor induced by drugs.*

**INTRODUCTION:**

Autism Spectrum Disorders (ASD) are neuro-developmental disorders characterized by varying deficits in social interactions, communication, and learning, as well as stereotypic behaviors Others factors may alter this underlying genetic liability such as sex, IQ, and prenatal and perinatal injury (Freitag CM et al., 2007). 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 idea that preconception environmental exposures may be involved in 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. 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. The present study was therefore undertaken to investigate the potential prenatal, postnatal and environmental risk factors for ASD.

**SUBJECTS AND METHOD:**

A total number of 184 individuals were surveyed. The individuals surveyed were divided into ASD group and control group. Sample population included ASD group consisting of 92 ASD subjects and control group constituted by 92 subjects of similar age group but with no h/o ASD. For achieving the objectives of the study a Proforma was designed to collect information retrospectively from the mother. The prenatal history collected included data related to subjects mother during pregnancy period, like medication taken, stress, respiratory problems, maternal infection, fall during pregnancy, supplements taken, maternal diabetes, intake of sleeping pills during pregnancy and bleeding after first trimester. The antenatal history collected included the data of the newborn as well as data related to subjects mother during the time of parturation. It included data such as obstetric complications, type of delivery, drug induced labour, gestation, birth weight of subject. Neonatal information collected incuded habit of chewing plastic, ear infection and any other incidence during the infancy of the subject.

The data collected using the proforma was tabulated and analyzed. . Mean, standard deviation(SD) and variance were computed for quantitative data. The statistical significance of associations between various qualitative parameters was evaluated through Fisher's exect test(two tail). online calculators of statistic were used for standard deviation at www.easycalculation.com and fisher's test at www.graphpad.com.

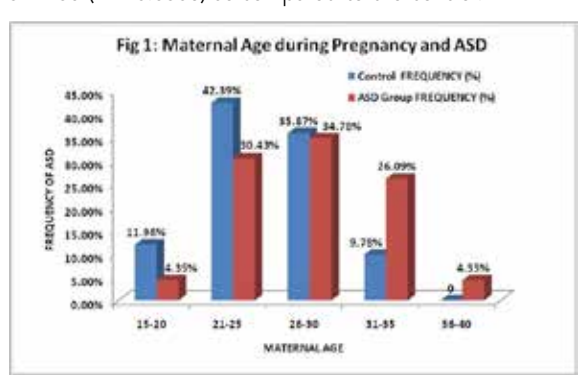
**RESULT:**

The mean present age of the ASD subjects studied was 9.02 years with standard deviation of ± 3.26and variance of 10.65. The mean age of detection of the ASD subject's studied was 2.7 years with standard deviation of ±1.76 and variance of 3.11.

**1) Pre-conception conditions:**

**a. Maternal Age:** Maternal age at pregnancy in different age intervals of both control and ASD was studied Frequency of ASD was higher in maternal age intervals of 31-35 and 36-40 years (Fig 1). The mean maternal age during pregnancy of the ASD subject's studied was 27.8 years with standard deviation of ± 5.36 and variance of 28.7. The results indicate 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.

Fig 1: Maternal Age during Pregnancy and ASD




**b. Oral Contraceptives:** The intake of oral contraceptives by the mother was also considered as a factor for the cur-

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rent study. The present study found no correlation of intake of oral contraceptives and ASD.

**c. Parity and ASD:** The frequency of ASD was higher in the first born and third born as compared to the control group. However the difference was found to be statistically insignificant (P = 0.7804 for first born and P = 1.000 for the third born).

**d. Age gap between the autistic children and other siblings:** In the sample population the age gap varied from 1-7 years. The mean of age gap of the ASD subject's studied was 4.2 years with standard deviation of ± 1.47 and variance of 2.18. The frequency of ASD was observed to be higher in those with larger age gap of 4- 7 years as compared to the control. However the difference was found to be statistically insignificant (P=0.3482 for 4 yrs and P=0.2756 for 6 & 7years).

**2) During Pregnancy(Prenatal risk factors):**

**a. Medication taken during pregnancy and ASD:** The study indicates that higher frequency of 39.13% of h/o 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).

**b. Stress during pregnancy and ASD:** Mothers of the subjects were interrogated for physical and mental stress during their pregnancy, in both the control and ASD group. Frequency of stress during pregnancy was found to be higher in mothers of ASD group as compared to those in control group. The difference is found to be statistically significant (P=0.0257).

**c. Respiratory problems during pregnancy and ASD:** The present study found no correlation between respiratory problems during pregnancy and ASD.

**d. Maternal infection during pregnancy and ASD:** The present study found no correlation between maternal infections during pregnancy and ASD (P = 0.6887).

**e. Fall during pregnancy and ASD:** The frequency of ASD was higher in 13.04% of the mothers who had a fall during pregnancy as compared to the control (Fig. 3.20). The difference was found to be Statistically Insignificant (P=0.1226).

**f. Supplements taken during pregnancy and ASD:** Different types of supplements are necessary for growth and development of the foetus. The vital supplements include vitamins, folic acid, iron and calcium. 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).

**g. Bleeding during Pregnancy:** The present study found no correlation between maternal bleeding during pregnancy and ASD (P = 0.4898).

TABLE 1: ASSOCIATION OF PRENATAL AND PERINATAL FACTORS WITH FREQUENCY OF ASD

| Factors | | Frequency | | Significance (fishers exact test) |
|---|---|---|---|---|
| Control Group | | ASD Group | | |
| PRECONCEPTION AND PRENATAL FACTORS | 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 |
| | Bleeding during pregnancy | 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 | 9.52% | 26.09% | *P = 0.0306 |
| | 36-40 yrs | 0% | 4.35% | |
| POSTNATAL AND NEONATAL FACTORS | Normal Delivery | 66.67% | 73.91% | P=0.7937 |
| | Obstetric complications | 21.95% | 13.04% | P=0.1226 |
| | post term births | 4.76% | 13.04% | P=0.1226 |
| | low birth weight(less than 1.9kg) | 1.30% | 16.65% | ***P=0.0018 |
| | Labour inducing drugs | 31.71% | 40.91% | P=0.4444 |
| | Chewed Plastic Toys in Infancy | 15.79% | 30.43% | P=0.1077 |
| | Insufficient Attention Received By Child | 9.52% | 13.04% | P=0.4869 |

* Significant

** and *** highly significant

**3) Postnatal/Neonatal – Other environmental risk factors:**

**a. Type of Delivery and ASD:** This factor was studied to assess if stress on the child during normal delivery, use of forceps or suction during normal delivery could be a risk factor for ASD. Present study revealed increased frequency of ASD in those mothers who had normal delivery (73.91%) as compared to the control group. However the difference is found to be statistically insignificant (P=0.7937).

**b. Labour Induced by Drugs and ASD:** Labour inducing drugs may be a potential risk factor for ASD. Therefore this factor was also studied. Labour was induced by drugs in 40.91% of ASD group which was higher than that of control group (31.71%) (Fig: 3.26). However the difference was found to be statistically insignificant (P=0.4444).

**c. Gestation Period and ASD:** Gestation period was evaluated to see if there is significance with pre and post term births. Frequency of post term births was found to be higher in the ASD group (13.04%) as compared to the control (4.76%). However the difference was found to be statistically insignificant (P=0.1226).

**d. Birth Weight and ASD:** The birth weight of ASD ba-

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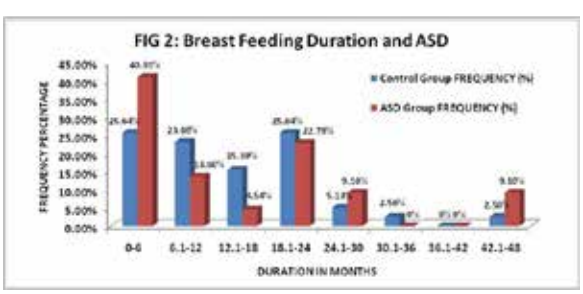
bies was either higher or had low birth weight as compared to the normal. The mean of birth weight of the ASD subject's studied was 3.03kg with standard deviation of ± 0.85 and variance of 0.72 as compared to the control where mean birth weight was 2.95kg with standard deviation of ± 0.48 and variance of 0.23. Significantly higher frequency (P=0.0018) of low birth weight of 1-1.9kg in the ASD group as compared to the control. Higher frequency of high birth weight of 4 – 4.9 kg observed in the ASD group was found to be statistically insignificant (P=0.229).

**e. Chewed Plastic Toys in Infancy:** Lead poisoning is the leading health risk associated with chewing on plastic. Therefore this factor was studied to asses if ingestion of toxic components from plastic toys during infancy can act as a risk factor. We recorded a high frequency of positive history of chewing of plastic toys in infancy, in the ASD group (30.43%) as compared to the control. However the difference was found to be statistically insignificant (P=0.1077).

**f. Day Care and Risk of ASD:** We analyzed this factor as ASD children may be subjected to emotional insecurity if sent to Day care centres at early. The present study found no correlation between day care and risk of ASD.

**g. Insufficient Attention Received By Child:** The study revealed that 13.04% subjects of that of ASD group received insufficient attention as compared to 9.52% subjects in control(Fig:3.34). However the difference is considered to be statistically insignificant (P=0.4869).

**h. Breast feeding Duration:** The mean breast feeding duration in the ASD subject's studied was 1.45 yrs with standard deviation of ± 1.13 and variance 1.27. The present study revealed higher frequency of mothers who breast fed their child for a shorter duration of 0 – 0.5 yrs in the ASD group (40.91%) as compared to the control (Figure 2). However the difference was found to be statistically insignificant (P=0.2046). We also noted higher frequency of mothers who breast fed their child for a longer duration of 3.5 -4 yrs in the ASD group (9.10%) as compared to the control. However the difference was also found to be statistically insignificant (P=0.0581).




**DISCUSSION:**

Factors that showed potential risk for causing or increasing frequency of ASD were maternal age, stress during pregnancy, supplements taken, gestation period, parity, age gap between children and birth weight. There were also some factors that had no association with ASD which includes family history with seizures and tuberculosis, oral contraceptive, medication during pregnancy, respiratory problem during pregnancy, maternal infection, fall during pregnancy, type of water consumed, bleeding during pregnancy, labour induced by drugs.

The present study revealed significantly higher frequency of ASD (P = 0.0058) in the males as compared to the control group. Our results are consistent with the findings of Fombonne E et al., 2005, which reported that ASD affects males four times more than females. The cause for this difference is not well understood. Several theories have been proposed, among which the involvement of the sex chromosome in the etiology of ASD, and the role of hormonal influences in utero are suggested (Boron et al., 2011). However, none of these theories has been confirmed yet. Recent Genetic studies demonstrate that females are protected from the effects of heritable and de-novo ASD risk variants and compelling work suggests that sex chromosomal genes and/or sex hormones, especially testosterone, may modulate the effects of genetic variation on the presentation of an autistic phenotype.

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 very crucial factor in determining the neurological development of the fetus. This study indicate significantly higher frequency of 26.09% of ASDs in children born to mothers in age interval of 31 – 35 as compared to the control. Our findings are consistent with the findings of Croen LA et al., 2007; Kolevzon A et al., 2007 and Gardener H, 2009, which state that older parents may be statistically more likely to have children with autism. Study of Sandin S et al., 2012, reports that children of mothers older than 35 years had 30% increased risk for autism.

Another potential risk factor observed in our study was parity and age gap between siblings. The frequency of ASD was higher in the first born and third born as compared to the control group. However the difference was found to be statistically insignificant. The frequency of ASD was observed to be higher in those with age gap of 4, 6 and 7 years as compared to the control. The difference was found to be statistically insignificant. Nevertheless, study of Chaste P and Leboyer M, 2012, showed that risk of ASD was high for first born children. Increased risk was also found first-born children compared with children born third or later (Bouvard MP et al.,1995).

Maternal infections were measured with nonspecific indicators, including maternal recall of fever and/or other symptoms and information archived in medical records Association of medication during pregnancy with autism risk is indicated in the study of Gardener H (2009). 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 Gardner H 2009. This study shows higher frequency of 39.13% of the mothers in ASD group had taken medication during pregnancy as compared to the control. However the difference was found to be statistically insignificant.

Strongest evidence of maternal hypertension and ASD risk is indicated in the studies of Gardener H,et al., 2009. Important revelation of this study was the association of maternal stress during pregnancy and increased risk of ASD. Frequency of stress during pregnancy was found to be significantly higher in mothers of ASD group as compared to those in control group. Studies of Rai D et al.,(2012), also reveled 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.

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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 as compared to the control. This study reinforces the findings of Schmidt R. J et al., 2012, 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 (2014) also support that higher maternal intake of certain nutrients and supplements like folic acid has been associated with 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 (Kočovská E et al., 2012). ). On the basis of these results, we argue that though the high frequency of ASD shows no statistically significance, possibly the important role of vitamin D and folic acid cannot be overlooked.

Frequency of post term births was found to be higher in the ASD group as compared to the control. However the difference was found to be statistically insignificant. We observed significantly higher frequency of low birth weight of 1-1.9kg in the ASD group as compared to the control. Our studies are agreeing to the findings of earlier studies which state that increased risk of ASD is related to preterm birth which is mediated primarily by prenatal and neonatal complications that occur more commonly among preterm infants (Buchmayer S et al.,2008; Fudenberg HH et al., 1996; Pinto-Martin JA et al., 2011).

Lead poisoning is the leading health risk associated with chewing on plastic. Plastic toys contain many toxic components including lead. In the present study we recorded a high frequency of positive history of chewing of plastic toys in infancy, in the ASD group as compared to the control. Toxicants, such as heavy metals, pesticides and chemicals, can damage cells by converging on similar biochemical pathways to produce adverse effects, such as increasing oxidative stress, depleting glutathione and impairing cellular signalling (Li Z, et al., 2007). Exposures to environmental toxicants, such as mercury, lead, arsenic, polychlorinated biphenyls and toluene, are known to cause neurodevelopmental disorders (Grandjean P, et al., 2006). Exposures to environmental toxicants have also been implicated in ASD (Palmer RF, et al., 2009; Windham GC et al., 2006; Roberts EM et al., 2007).

Our study indicates that there is no association between ASD and parental factors such as working mother, sending the child to day care or insufficient attention by Parents. Our study supports the reports of research that state that bad parenting is not responsible for increasing the risk of ASD. The present study also found no correlation of family h/o seizures, TB, intake of oral contraceptives, Respiratory problems during pregnancy or maternal infections during pregnancy. However many research findings are contrary to our findings. Studies of Atladottir HO et al., 2010) supports the hypothesis that this infection triggers a vulnerability to develop autistic disorder in the foetus who supported by the evidence from results with rodent models. It seems that gestational viral infections trigger a maternal immune response, which can perturb foetal brain development, at least in part through interleukin-6 (Bradstreet JJ, et al., 2007). Association of maternal gestational diabetes, maternal bleeding during pregnancy and maternal medication with ASD is suggested in the study of Bouvard MP et al., 1995. Autism is unlikely to be caused by a single obstetric factor. The increased prevalence of obstetric complications among autism cases is most likely due to the underlying genetic factors or an interaction of these factors with the environment (Glasson EJ, 2004).

The present study revealed higher frequency of mothers who breast fed their child for a shorter duration of 0 – 0.5 yrs in the ASD group as compared to the control. We also noted higher frequency of mothers who breast fed their child for a longer duration of 3.5 -4 yrs in the ASD group as compared to the control. This difference was also found to be statistically insignificant. Breastfeeding may also be beneficial to the emotional development of the autistic child, since it provides a special opportunity for autistic children to experience close physical and emotional contact. Prolonged duration of sucking may be attributed to the emotional security which the ASD child may be seeking from the mother

Heterogeneity in some studies may be on account of methodological limitations that have impaired the precision and validity of results as 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 while folic acid-calcium supplement intake was found to be reducing the risk of ASD. The factors with evidence against a role in autism risk included were intake of medications, fall, respiratory problems and bleeding during pregnancy.

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