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Research article

Mode of delivery, order of birth, parental age gap and autism spectrum disorder among Malaysian children: A case-control study

Jo Ann Andoy Galvan [a,*], Prabhagari Nair Ramalingam [b], Sapna Shridhar Patil [a], Muhammad Aminul Syahmi bin Shobri [c], Karuthan Chinna [a], Muhammad Sabri Sahrir [d], Kumarappan Chidambaram [e]

[a] School of Medicine, Faculty of Health and Medical Sciences, Taylor's University, No. 1 Jalan Taylor's, Subang Jaya 47500, Selangor, Malaysia
[b] Hospital Melaka, Jalan Mufti Haji Khalil, 75400 Melaka, Malaysia
[c] Hospital Shah Alam, Persiaran Kayangan, Seksyen 7, 40000 Shah Alam, Selangor, Malaysia
[d] Kulliyyah of Education, International Islamic University Malaysia, 53100 Jalan Gombak, Kuala Lumpur, Malaysia
[e] Department of Pharmacology, College of Pharmacy, King Khalid University, 62529, Saudi Arabia

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ABSTRACT

Rising prevalence of autism spectrum disorders (ASD) in the last decades has led research to focus on the diagnosis and identification of factors associated with ASD. This paper sought for possible factors that put children at risk for ASD. In this study, we investigated the association between ASD and parental ages, parental age gaps, birth order and birth delivery method in Malaysian population. In this school-based case control study, 465 children with ASD 464 controls participated. Questionnaires were distributed to the parents of the selected children through the respective principals. Among the tested variables, Caesarean section (OR = 1.63, 95% CI 1.20, 2.20), earlier order of birth in the family (OR = 0.68, 95% CI 0.59, 0.77) and increasing gap in parental ages (OR = 1.04, 95% CI 1.001, 1.07) were significantly associated with ASD. This study concludes that Caesarean section, earlier order of birth in the family and increasing gap in parental age are independent risk factors for developing autism among Malaysian children.

1. Introduction

According to the World Health Organization, Autism spectrum disorder (ASD) refers to a range of conditions characterized by some degree of impaired social behaviour, communication and language, and a narrow range of interests and activities that are both unique to the individual and carried out repetitively (WHO, 2019). This begins in childhood and tend to persist into adolescence and adulthood. It affects how a person acts and interacts with others, communicates and learns. Based on the systematic review conducted by Elsabbagh et al. (2012), the prevalence of this disorder has increased in the last five decades, and there are many possible explanations for this apparent increase (Elsabbagh et al., 2012). It is thought that, both genes and environment, may play important roles in ASD. The aetiology of ASD has been a topic of discussion for many years and unfortunately, is still unclear to this day. This has been one of the reasons why the management of ASD is challenging. The cause of ASD is multifactorial and even though it is thought that both genes and environment may play important roles, the recent studies focus on obstetric mode of delivery, birth order, parental age and parental age gap.

Obstetric mode of delivery has a significant impact in both early and late outcomes in a child's life. Although the causal relationship between the type of obstetric delivery and ASD is not established, there is some evidence of association between the two. It has been observed that Caesarean section tend to increase the risk of ASD (Al-Zalabani et al., 2019; Curran et al., 2015, 2016; Gregory et al., 2013).

Birth order/parity and ASD has been studied since early 1980s. Tsai and Stewart (1983) reported significant relationship between the risk of developing autism and parity, high risk in firstborn in smaller sibship and high risk in fourth-or-later born in large sibship. A meta-analysis done in 2009, showed significant relationship between birth order/parity and risk of autism; 61% increase in risk of ASD among the first-born children compared with children born third or later (Gardener et al., 2009).

* Corresponding author.
E-mail address: JoAnnAndoy.Galvan@taylors.edu.my (J.A. Andoy Galvan).

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Many studies show strong evidence that advancing paternal age at the time of birth of offspring increases the risk of autism (Durkin et al., 2008; Hultman et al., 2011; Idring et al., 2014; Reichenberg et al., 2006; Sandin et al., 2016; Wu et al., 2017). Idring et al. (2014) and Reichenberg et al. (2006) have shown advancing paternal age to be independently associated with ASD. Increased maternal age was also found independently associated with the risk of developing ASD (Larsson et al., 2005; Reichenberg et al., 2006).

Recently, parental age gap was also investigated and it showed that moderate-to-large (10 years or more) difference between the parental ages resulted in an increased risk of ASD (Sandin et al., 2016).

The authors suggested the need for more studies to further establish association and explore the underlying mechanism for all these findings. Therefore this study was conducted to determine the association between autism and four independent variables. This is the first study that investigated all four important risk factors: obstetric mode of delivery, birth order, parental age and parental age gap among Malaysian children studying in Primary National Schools of West Malaysia.

2. Methodology

2.1. Study design

A school-based case control study was conducted in West Malaysia to determine the association between autism and the four risk factors: mode of delivery, birth order, parental age and parental age gap.

2.2. Malaysian autism schools and ASD diagnosis

In Malaysia, Department of Social Welfare and Development categorizes autism under the big umbrella of "Learning Difficulties." whereby the autism cases are mixed with other disabilites such as: Down's syndrome, Late global Development, Attention Deficit Hyperactivity Disorder, Dyslexia, Dyscalculia and Dysgraphia. As such the data for autism could not be obtained (Ting et al., 2014). However, it is estimated that 1 in 625 children are having ASD (MOH, 2014).

In West Malaysia there are 12 Special Education Schools and 1973 National Schools with Inclusive Education Program known as Program Pendidikan Khas Integrasi (PPKI) which accomodate autism enrollees. SKPK is a special education school which caters only for children with special needs while PPKI is an inclusive education program with other regular school children. In inclusive education program (PPKI) separate classes are run under mainstream schools in both primary (Rendah) and secondary (Menengah) with integrated setting so they can interact and play with other children of their age. Admission to PPKI and SKPK require a proper medical diagnosis where children are required to be thoroughly evaluated and certified by medical specialist before they can enjoy the full services of the said facility. Diagnosis of autism is made either by using Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR 2000 and DSM-5 2013) or the 10th-Revision of International Classification of Diseases (ICD-10) (MOH, 2014).

2.3. Study population

The study population consist of 4979 ASD children enrolled in SKPK (N = 53) and PPKI (N = 4926) in the different states of West Malaysia. Confirmation of the diagnosis were inquired from the principals of these schools who admitted registration of the kids with certifications from doctors.

A total of 750 cases and 750 controls were planned for this study, the controls being in the same geographical location as the cases.

2.4. Instrument used

A questionnaire was used to obtain information from parents of students selected for this study. The questionnaire comprised two parts: Part A had questions on parents' characteristics such as age, confirmed with their birth dates, family income, and the mode of birth delivery of the child in the study. Respondents were asked to choose from 4 modes of delivery: elective cesarean section, emergency cesarean section, vacuum/forceps, or normal spontaneous delivery. Part B had questions on the child such as age, birthdate, gender, and the birth order in the family. The birth order of the child was confirmed with a tabulated birthdate of all his/her siblings. For children with ASD, healthcare personnel who made the diagnosis was noted. The initial questionnaire was written in English and was content validated by an expert panel. The validated questionnaire was then translated into the Malay language by a bilingual professor, teaching language studies in a public university. A pilot test was carried out to ensure validity and reliability of the questions in the questionnaire. In the pilot test, the parents were also asked to comment on clarity, comprehensiveness and responsiveness of the items in the questionnaire.

2.5. Data collection

Questionnaires were distributed to the parents of the selected children through the principal of the respective schools. The parents were informed that the participation in this study was voluntary and written consent was obtained from consenting parents.

2.6. Statistical analysis

All the data analyses were performed using SPSS version 24 software. Frequencies, means and standard deviations were used to summarize the date. Chi square test and t-tests were used to compare differences between cases and controls. Associations between parental ages, age gap, birth order, birth delivery method and autism spectrum disorders were tested using logistic regression analyses. For all tests, the level of significance was set at 0.05.

2.7. Ethical approval

Approval for this study was obtained from the Institutional Review Board of Taylor's University Centre for Research management and the Ministry of Education, Malaysia [KPM.600-3/2/3 Jld.34 (16); KPM.600-3/3/3 Jld.35 (37)]. All procedures performed in studies were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

3. Results

A total of 929 completed questionnaires were received from the participants. The response rate was 62%. In the sample there were 464 cases and 464 controls. The characteristics of the children and their parents in this study are shown in Table 1.

As shown in Table 1, there were significant differences in maternal age, gender, child's birth order, delivery mode and family income between the two groups. The mean mothers' age in the control group was higher compared to the ASD group. In terms of birth order 54.8% of the ASD children were first-born compared to 38.6% in the control group. In terms of delivery mode, 76.1% of the children in the control group were delivered by normal spontaneous delivery (NSD) compared to 63.7% in the ASD group and 22.6% of the children in the ASD group were delivered by emergency C-section compared to 15.1% in the control group. The two groups also differed in terms of child's gender and family income. The ASD group had more boys (82.8%) and majority had family income of more than RM 3,000 (60.6%) compared to the control group.

3.1. Results from logistic regression analysis

Associations between parental ages, age gap, birth order, birth delivery method and autism spectrum disorders were tested using logistic

Table 1. Characteristics of respondents in this study.

Variable	Overall (n = 929)	ASD (n = 465)	Non ASD (n = 464)	p-value
Ages				
Child's age in years Mean (SD)	9.37 (1.7)	9.35 (1.7)	9.39 (1.7)	0.320
Mother's age in years Mean (SD)	39.40 (5.69)	38.95 (5.52)	39.87 (5.82)	0.016
Father's age in years Mean (SD)	42.80 (6.93)	42.48 (7.06)	43.12 (6.78)	0.460
Age gap mean in years (SD)	3.93 (4.07)	4.14 (4.37)	3.72 (3.74)	0.471
Gender				<0.001
Male	632 (68.0%)	385 (82.8%)	247 (53.0%)	
Female	297 (32.0%)	80 (17.2%)	217 (47.0%)	
Birth order				<0.001
First	434 (46.7%)	255 (54.8%)	179 (38.6%)	
Second	235 (25.3%)	126 (27.1%)	109 (23.5%)	
Third	132 (14.2%)	48 (10.3%)	84 (18.1%)	
Fourth	66 (7.1%)	23 (4.9%)	43 (9.3%)	
Fifth through eighth	62 (6.7)	13 (2.8%)	49 (10.5%)	
Delivery				<0.001
NSD	649 (69.9%)	296 (63.7%)	353 (76.1%)	
Emergency C-section	175 (18.8%)	105 (22.6%)	70 (15.1%)	
Elective C-section	64 (6.9%)	38 (8.2%)	26 (5.6%)	
Forceps/vacuum	41 (4.4%)	26 (5.6%)	15 (3.2%)	
Family Income				<0.001
≤RM 500	44 (4.7%)	8 (1.7%)	36 (8.0%)	
RM 501-2,999	379 (40.8%)	175 (37.6%)	204 (44.0%)	
≥RM 3,000	506 (54.5%)	282 (60.6%)	224 (48.0%)	

regression analyses. There were no controlled variables in this model. The results from multivariate logistic regression analysis are shown in Table 2 and the results from stepwise logistic regression analysis are shown in Table 3.

As shown in Table 2, among the tested variables, birth order and mode of delivery were statistically significant. Elective C-section (95% CI: 0.93, 2.72) was not significantly different from Emergency C-section (95% CI: 1.09, 2.21), thus both were recoded and combined as one mode of delivery in further analysis.

In the stepwise regression (Table 3), parental age gap, birth order and delivery mode were statistically significant. The odds of ASD increased with increasing age gap, ($OR = 1.04$, 95% CI 1.00, 1.07) with the odds of ASD decreased with increasing birth order ($OR = .68$, 95% CI 0.61, 0.77). In terms of delivery mode, the odds of ASD among children delivered through C-section was 1.6 (95% CI 1.2, 2.2) higher compared to delivery through NSD.

Table 2. Results from multivariate logistic regression analysis.

Variable	β	Standard error	OR (95% CI)	p-value
Mother's age	0.04	0.04	1.04 (0.97, 1.12)	0.274
Father's age	-0.03	0.04	0.97 (0.91, 1.04)	0.448
Age gap	0.06	0.04	1.06 (0.99, 1.15)	0.114
Birth order	-0.39	0.07	0.68 (0.59, 0.77)	<0.001
Birth delivery mode				0.018
Emergency C-section	0.44	0.18	1.55 (1.09, 2.21)	0.014
Elective C-section	0.46	0.28	1.59 (0.93, 2.72)	0.093
Forceps/vacuum	0.63	0.34	1.87 (0.96, 3.65)	0.067
NSD			1	

Table 3. Results from stepwise logistic regression analysis.

Variable	β	Standard error	OR (95% CI)	p-value
Age gap	0.03	0.02	1.04 (1.00, 1.07)	0.048
First in birth order	-0.38	0.06	0.68 (0.61, 0.77)	<0.001
Birth delivery mode				0.014
C-section		0.16	1.63 (1.20, 2.20)	0.002
Forceps/vacuum	0.48	0.34	1.86 (0.95, 3.63)	0.068
NSD	0.62		1	

4. Discussion

This is the first in Malaysia which investigated the associations between parental age, parental age gap, obstetric mode of delivery and birth order. Overall, the children in the ASD group and the control groups differed significantly in terms parental age gaps, birth order and birth delivery method.

Findings in our study showed an association between autism and mode of delivery, the odds of autism is higher among those born via C-section compared to those born via normal deliveries. Our results concur with the findings from the study conducted by Al-Zalabani et al. (2019), in which the OR value was reported to be 2.9, after adjusting for potential confounders. This finding is similar to the results reported in the systematic review by Curran et al. (2015). Some theories that were postulated to explain this association are: oxytocin dysregulation, missed exposure to mother's bacteria, lesser stress of labour, and neurotoxicity brought by the anaesthesia.

Oxytocin is a peptide secreted in pulses during labour by the mother's hypothalamus which reaches the baby via the bloodstream. Perinatal oxytocin level is shown to influence child's development of social behaviour, social interaction and sexual behaviour (Gialloreti et al., 2014). If a mother delivers the baby by cesarean, it arrests the normal oxytocin production. Kids delivered by mothers via C-section are known to have significantly lower plasma levels of oxytocin compared to those born via vaginal delivery (Husarova et al., 2016). The disruption of the oxytocinergic system caused by Cesarean section might affect the baby's brain development which might lead to the development of autism. It has also been hypothesized that children with ASD have different gut microbiota than the general population. Babies born via vaginal birth are exposed to mother's bacteria in comparison to those born via C-section, who are exposed to skin bacteria (Dominguez-Bello et al., 2010). It is possible that this alteration in the microbiota is a factor in psychological development of autism as it has been shown that altered microbiota in animals cause a change in behavior (Cryan and Dinan, 2012).

Babies born via C-section are more vulnerable to stress as the labor from vaginal birth is shown to prime the hypothalamic pituitary adrenal axis and the immune system that protect babies' development (Cho and Norman, 2013). The neurotoxic effects of general anesthesia from the C-section procedure is also associated with autism risk. A study done by Chien et al. (2015) showed a 52% increased risk of autism in neonates born via C-section involving general anesthesia compared to those born via vaginal delivery. Some researchers argue that the reasons for cesarean section might be the cause of autism and not the procedure itself (Guinchat et al., 2012; Bilder et al., 2009). The underlying factors (such as failure to progress in labour, fetal distress, multiple pregnancies and breech presentation) should be studied in detail. In contrary, a case control study done by Polo-Kantola et al., in 2014 which suggested Elective Casarean section and not Emergency C-section significantly raised autism risk among children in Finland (Polo-Kantola et al., 2014). Hence it is still inconclusive whether the C-section procedure itself or the medical conditions that necessitated the C-section is the factor associated with autism development.

In our study it was not possible to trace back the reasons for emergency C-sections. Future studies considering the reasons for emergency C-section, instead of just the procedure only, will be more useful in determining the real cause.

Based on our results, the first-born children seem to be at higher risk of ASD compared to the later ones. However, existing literature provides a mixed result on the association between birth order and ASD. In their case control study, Cagatay et al. (2019) demonstrated a significant difference for being the first-born child in the ASD group. A meta-analysis by Gardener et al. (2009) revealed an association between autism risk and being the first-born child. Our results concur with those of a study by Deykin and MacMahon (1980) in which a higher risk for ASD was reported in the first-born children compared to the controls. However, the common agreeable conclusion is that, ASD risk is higher in firstborn in smaller sibship and in fourth-or-later born in larger sibship(Tsai and Stewart, 1983; Bolton et al., 1997) (Turner et al., 2011). One possible reason for this pattern could be that parents may be worried of having another child after their first-born child was autistic. This phenomenon is known as the "stoppage rule"(Lord et al., 1991) (Bolton et al., 1997) (Gardener et al., 2009). One short coming of this study is that information on sibship was not gathered.

Many studies have associated both paternal and maternal age in the development of autism in their children (Reichenberg et al., 2006; Sandin et al., 2016). In our study, we found a significant association between maternal age and autism, butnot with paternal age, in the univariate analysis. But when tested in multivariate analysis, it was the age gap that made the difference, independently of the parent's ages. Larsson et al. (2005) displayed similar findings as our study when corrected for other variables In a recent meta-analysis of 27 studies, Wu et al. (2017) reported that increased maternal and paternal ages were associated with 41% and 55% increased risk of autism. However, the authors cautioned that the studies they pooled were highly heterogenous, hence the results may not be that accurate.

As stated earlier, we found a significant association between maternal age and autism in the univariate analysis. But when tested in multivariate analysis, it was the age gap that made the difference, independently of the parent's ages. The wider is the age gap between the parents, the higher is the risk of ASD in their children. A similar finding was reported by Sandin et al. (2016) that the risk of ASD to be high among parents with age gaps of ten years or more. However, a cohort study by Croen et al. (2007), reported no significant association between ASD and parents age gap. Studies on parental age gap and ASD are limited. This warrants the need for further studies on this presumed risk factor for ASD.

Our study had several limitations. This is a case control study hence, making a causal inference is difficult. A longitudinal study design would have been a better option to study factors associated with ASD. Also, in this school-based study, the cases were from schools who are in the better spectrum of the disorder and the severe cases were not represented. The relationship between birth-order with their respective sibship size needs further exploration. Research exploring not only the obstetric mode of delivery but also underlying indications of the respective procedure need to be carried out. Potential risk factors to ASD and possible indications of C-section during the pregnancy and intrapartum or postpartum period must be taken into consideration for future studies.

5. Conclusions

Our study found significant associations between autism and obstetric mode of delivery, birth order and parental age gap. Children of parents with wider age gap, first-born and delivered through emergency C-section are at higher risk of ASD.

Declarations

Author contribution statement

J. Andoy-Galvan: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

P. Ramalingam and M. bin Shobri: Performed the experiments; Wrote the paper.

S. Patil and K. Chinna: Analyzed and interpreted the data; Wrote the paper.

K. Chidambaram: Conceived and designed the experiments.

M. Shari: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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References

Al-Zalabani, A.H., Al-Jabree, A.H., Zeidan, Z.A., 2019. Is Cesarean section delivery associated with autism spectrum disorder? Neurosciences (Riyadh) 24 (1), 11–15.

Bilder, D., Pinborough-Zimmerman, J., Miller, J., McMahon, W., 2009. Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. Pediatrics 123 (5), 1293–1300.

Bolton, P.F., Murphy, M., Macdonald, H., Whitlock, B., Pickles, A., Rutter, M., 1997. Obstetric complications in autism: consequences or causes of the condition? J. Am. Acad. Child Adolesc. Psychiatr. 36 (2), 272–281.

Cagatay, U., Aysegul, T., Zeynep, G., Ozden, S.U., 2019. Birth order and reproductive stoppage in families of children with autism spectrum disorder. Psychiatr. Clin. Psychopharmacol. 29 (4), 509–514.

Chien, L.N., Lin, H.C., Shao, Y.H., Chiou, S.T., Chiou, H.Y., 2015. Risk of autism associated with general anesthesia during cesarean delivery: a population-based birth-cohort analysis. J. Autism Dev. Disord. 45, 932–942.

Cho, C.E., Norman, M., 2013. Cesarean section and development of the immune system in the offspring. Am. J. Obstet. Gynecol. 208, 249–254.

Croen, L., Najjar, D., Fireman, B., Grether, J., 2007. Maternal and paternal age and risk of autism spectrum disorders. Arch. Pediatr. Adolesc. Med. 161 (4), 334–340. Retrieved from.

Cryan, J.F., Dinan, T.G., 2012. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat. Rev. Neurosci. 13, 701–712.

Curran, E.A., O'Neill, S.M., Cryan, J.F., Kenny, L.C., Dinan, T.G., Khashan, A.S., Kearney, P.M., 2015. Research Review: birth by caesarean section and development of autism spectrum disorder and attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. J. Child Psychol. Psychiatry) 56 (5), 500–508.

Curran, E.A., Cryan, J.F., Kenny, L.C., Dinan, T.G., Kearney, P.M., Khashan, A.S., 2016. Obstetrical mode of delivery and childhood behavior and psychological development in a British cohort. J. Autism Dev. Disord. 46 (2), 603–614.

Deykin, E.Y., MacMahon, B., 1980. Pregnancy, delivery, and neonatal complications among autistic children. Am. J. Dis. Child. 134, 860–864.

Dominguez-Bello, M.G., Costello, E.K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., Knight, R., 2010. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc. Natl. Acad. Sci. Unit. States Am. 107, 11971–11975.

Durkin, M., Maenner, M., Newschaffer, J., Lee, L., Cunniff, C., Daniels, J., et al., 2008. Advanced parental age and the risk of autism spectrum disorder. Am. J. Epidemiol. 168 (11), 1268–1276.

Elsabbagh, M., Divan, G., Koh, Y., Kim, Y., Kauchali, S., Marcín, C., Montiel-Nava, C., Patel, V., Paula, C., Wang, C., Yasamy, M.T., Fombonne, E., 2012. Global prevalence of autism and other pervasive developmental disorders. Autism Res. 5 (3), 160–179.

Gardener, H., Spiegelman, D., Buka, S.L., 2009. Prenatal risk factors for autism: comprehensive meta-analysis. Br. J. Psychiatry.

Gialloreti, L.E., Benvenuto, A., Benassi, F., Curatolo, P., 2014. Are caesarean sections, induced labor and oxytocin regulation linked to Autism Spectrum Disorders? Med. Hypotheses 82 (6), 713–718.

Gregory, S.G., Anthopolos, R., Osgood, C.E., Grotegut, C.A., Miranda, M.L., 2013. Association of autism with induced or augmented childbirth in North Carolina birth record (1990-1998) and education research (1997-2007) databases. JAMA Pediatr.

Guinchat, V., Thorsen, P., Laurent, C., Cans, C., Bodeau, N., Cohen, D., 2012. Pre-, peri- and neonatal risk factors for autism. In: Acta Obstetricia et Gynecologica Scandinavica.

Hultman, C.M., Sandin, S., Levine, S.Z., Lichtenstein, P., Reichenberg, A., 2011. Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. Mol. Psychiatr. 16 (12), 1203–1212.

Husarova, V.M., Lakatosova, S., Pivovarciova, A., Babinska, K., Bakos, J., Durdiakova, J., et al., 2016. Plasma oxytocin in children with autism and its correlations with behavioral parameters in children and parents. Psychiatr. Invest. 13, 174–183.

Idring, S., Magnusson, C., Lundberg, M., Ek, M., Rai, D., Svensson, A.C., et al., 2014. Parental age and the risk of autism spectrum disorders: findings from a Swedish population-based cohort. Int. J. Epidemiol. 43 (1), 107–115.

Larsson, H.J., Eaton, W.W., Madsen, K.M., Vestergaard, M., Olesen, A.V., Agerbo, E., et al., 2005. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. Am. J. Epidemiol. 161 (10), 916–925.

Lord, C., Mulloy, C., Wendelboe, M., Schopler, E., 1991. Pre- and perinatal factors in high-functioning females and males with autism. J. Autism Dev. Disord. 21 (2), 197–209.

MOH, 2014. Management of Autism Spectrum Disorder in Children and Adolescents. Putrajaya, Malaysia. Retrieved from. http//www.moh.gov.my.

Polo-Kantola, P., Lampi, K., Hinkka-Yli-Salomäki, S., Gissler, M., Brown, A., Sourander, A., 2014. Obstetric risk factors and autism spectrum disorders in Finland. J. Pediatr. 164 (2), 358–365.

Reichenberg, A., Gross, R., Weiser, M., Bresnahan, M., Silverman, J., Harlap, S., et al., 2006. Advancing paternal age and autism. Arch. Gen. Psychiatr. 63 (9), 1026–1032.

Sandin, S., Schendel, D., Magnusson, P., Hultman, C., Surén, P., Susser, E., et al., 2016. Autism risk associated with parental age and with increasing difference in age between the parents. Mol. Psychiatr. 21 (5), 693–700.

Ting, T., Neik, X., Lee, L.W., 2014. Prevelance, diagnosis, treatment and research on autism spectrum disorders (Asd) in Singapore and Malaysia. Int. J. Spec. Educ. 29 (3), 82–92.

Tsai, L.Y., Stewart, M.A., 1983. Etiological implication of maternal age and birth order in infantile autism. J. Autism Dev. Disord. 13 (1), 57–65.

Turner, T., Pihur, V., Chakravarti, A., 2011. Quantifying and modeling birth order effects in autism. PloS One 6 (10), e26418.

World Health Organization, 2019. WHO | Autism Spectrum Disorders. WHO [Internet] [cited 2019 Dec 27]; Available from: https://www.who.int/news-room/fact-sheets/detail/autism-spectrum-disorders.

Wu, S., Wu, F., Ding, Y., Hou, J., Bi, J., Zhang, Z., 2017. Advanced parental age and autism risk in children: a systematic review and meta-analysis. Acta Psychiatr. Scand. 135 (1), 29–41.