Open Access Maced J Med Sci **electronic publication ahead of print,**
published on September 10, 2017 as https://doi.org/10.3889/oamjms.2017.153

ID Design 2012/DOOEL Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences.
https://doi.org/10.3889/oamjms.2017.153
eISSN: 1857-9655
Clinical Science

Association between Beta-Sympathomimetic Tocolysis and Risk of Autistic Spectrum Disorders, Behavioural and Developmental Outcome in Toddlers

Mengühan Araz Altay[1*], Işık Görker[2], Rakhshanda Aslanova[3], Leyla Bozatlı[2], Nesrin Turan[4], Petek Balkanlı Kaplan[3]

[1]Department of Child and Adolescent Psychiatry, Edirne Sultan 1. Murat State Hospital, Edirne, Turkey; [2]Department of Child and Adolescent Psychiatry, Trakya University Faculty of Medicine, Edirne, Turkey; [3]Department of Obstetrics and Gynecology, Trakya University Faculty of Medicine, Edirne, Turkey; [4]Department of Biostatistics and Medical Informatics, Trakya University Faculty of Medicine, Edirne, Turkey

Citation: Altay MA, Görker I, Aslanova R, Bozatlı L, Turan N, Kaplan PB. Association between Beta-Sympathomimetic Tocolysis and Risk of Autistic Spectrum Disorders, Behavioural and Developmental Outcome in Toddlers. Open Access Maced J Med Sci. https://doi.org/10.3889/oamjms.2017.153

Keywords: Tocolysis; Beta-mimetics; Autism spectrum disorder; Behavioural and Developmental disorders.

***Correspondence:** Mengühan Araz Altay, MD. Department of Child and Adolescent Psychiatry, Trakya University Faculty of Medicine, Edirne Sultan 1. Murat State Hospital, Edirne. Address: Şükrüpaşa Mah. Seha Sk. No: 3, D: 39 22030, Edirne, Turkey. Tel: +905321689363. E-mail: menguhanarazaltay@gmail.com

Received: 04-May-2017; Revised: 05-Jun-2017; Accepted: 06-Jun-2017; Online first: 10-Sep-2017

Funding: This research did not receive any financial support.

Competing Interests: The authors have declared that no competing interests exist.

Abstract

AIM: To investigate whether maternal intravenous beta-mimetic tocolytic therapy increases the risk of autistic spectrum disorders (ASD) and poorer behavioural and developmental outcomes.

METHOD: Our study is a prospective case-control study among 90 children between 1.5 and three years old. Cases (n = 46) were toddlers with betamimetic tocolytic exposure; control group toddlers (n = 44) were tocolytic untreated. Treated and untreated groups were also divided into subgroups: term and preterm delivered. The gestational age of tocolytic treatment start, the dose and duration of exposure in hours were obtained from obstetric medical records. The Brief Infant-Toddler Social and Emotional Assessment (BITSEA), the Modified Checklist for Autism in Toddlers (M-CHAT) and the Denver Developmental Screening Test (DDST) tests were applied for evaluation of social, emotional problems, autism and developmental disorders.

RESULTS: Term and preterm born toddlers treated tocolytically in utero didn't demonstrate a higher risk of autistic disorders or poorer behavioural and developmental results than controls. In the preterm group, the earliest start of tocolytic treatment was correlated with toddlers lower score of the Competencies Scale (p = 0.009) and a higher score of the Problems Scale (p = 0.048). Also, we concluded that preterm membrane rupture was associated with higher ASD risk in the untreated group (p = 0.043).

CONCLUSION: Exposure to betamimetics during pregnancy was not associated with an increased risk of autism, behavioural and developmental disorders.

Introduction

Although the development of new medication methods is progressing with time, preterm birth is still an important cause of perinatal mortality and morbidity in the world [1]. About 50% of childhood neurological disorders are due to preterm birth [2]. Beta-sympathomimetics are commonly applied to postpone delivery, but it is also well known that this delaying process doesn't cause an improvement in perinatal outcomes [3, 4]. On the other hand, administration of antenatal corticosteroids enhance foetal lung maturity is associated with a decrease in perinatal morbidity and mortality [5]. Thereby, tocolytic therapy could prolong pregnancy until the administered corticosteroids effect is achieved or patient is transported to a tertiary care unit [6]. Widely used beta-mimetics could have significant maternal, foetal and neonatal side effects [7].

One of these influences is due to cross the placenta and stimulation of b-adrenergic receptors of the foetal central nervous system during brain development [8-11], which inhibits proliferation and increases differentiation of neural cells [12]. The inability of foetal and neonatal immature tissues to desensitize this beta-mimetic exposure [13] may lead to long-term consequences like abnormalities of nervous system development [10, 11] and, followed by this, neurobehavioral deficiencies: impaired school performance, cognitive dysfunction, and psychiatric disorders [8, 14]. Recent experiments performed on rats found that catecholaminergic activity and structural changes in brain tissue, especially in the cerebellum after beta-mimetic exposure, are similar to

those in the brains of autistic patients [9, 15-17]. Also, characteristic imbalance of cardiovascular responses inherited in autistic children resembles those in beta-mimetic exposed rats [18, 19]. Recent animal studies support the conclusions of research on humans that intrauterine beta-mimetic therapy for preterm delivery could cause behavioural, cognitive disorders and increased risk of ASD in their offspring [20].

Our case-control study was designed to broaden information about the association between tocolytic betamimetic treatment; it's prolongation, doses, maternal and prenatal characteristics and adverse neuropsychiatric disorders.

Materials and Methods

Ethics

This study was approved by the local ethics committee of Trakya University, Edirne, Turkey (Protocol Number 2012/160). Written consent was obtained from all patients before they were included in the study.

Study design

Our prospective case-control study follows the offspring of mothers exposed to beta 2-adrenergic agonist use in pregnancy and untreated control groups, who delivered term or preterm. Preterm untreated groups include samples admitted to the clinic with active labour manifestations and consequently no possibility of prolonging the pregnancy. Cases and controls were included from the cohort of 1.5 to 3-year-old children born at Trakya University Obstetrics and Gynaecology Department between December 2010 and June 2013; in total 90 children (48 boys, 42 girls).

Maternal data were obtained from obstetrical records and were comprised of maternal age, obstetric history (gravida, parity), gestational age of delivery and delivery mode (spontaneous, caesarean section). Neonatal birth weight, head circumference, body length and Apgar scores were selected from neonatal records. Patients with completely available data were included in the study. Ritodrine is a beta 2-adrenergic agonist widely used for tocolysis in Turkey. Ritodrine is the generic of Prepare. Only continuous intravenous route of administration during second and third trimester of pregnancy was included in the study. Women in the treated group received intravenous Ritodrine in an initial dosage of 0.08 mg/min followed by increasing the dose by 0.04 mg/min every 15 minutes until stoppage of contractions or appearance of maternal side effects, with a maximum dosage of 0.35 mg per minute. The gestational age of pregnancy when the Ritodrine was applied, the dosage and duration of intravenous tocolysis in hours were used to explore the association between maternal exposure and potential risks for infants.

Administration of glucocorticoids for induction of lung maturity was registered in both groups. Children between the ages of 1.5 to 3 years with the following criteria were included: main spoken language Turkish; no obvious genetic defect, physical handicap or congenital chronic disease. To assess the social, emotional problems and competencies of children, the validated Turkish version of BITSEA (Brief Infant-Toddler Social and Emotional Assessment), specially designed for toddlers aged 12 to 36 months, was used [21].

The BITSEA has 42 items that combine two measuring scales: Problems Scale and Competencies Scale. Social, emotional problems are measured by the Problems Scale, which includes 31 items concerning externalizing (e.g. overactivity, aggression and defiance), internalizing (e.g. anxiety and depression), dysregulation (e.g. negative emotionality, and eating and sleeping problems), atypical behaviour and maladaptive behaviour. Social-emotional abilities like sustained attention, prosocial peer relations, compliance, imitation/play skills, mastery motivation, empathy, and social relatedness are covered by 11 items of the Competence Scale. The clinician rates each item on a 3-point scale (0 = not true/rarely, 1 = somewhat true/sometimes, 2 = very true/always). A parent can complete the BITSEA in approximately 5-7 minutes independently or 7-10 minutes as part of a structured interview [22-24]. To identify children at risk of autistic disorders M-CHAT (Modified Checklist for Autism in Toddlers) validated for Turkey [25] was applied. The M-CHAT is a standardized ASD screener, which includes 23 items concerning joint attention (proto-declarative pointing, following a point, bringing to show), responding to name, interest in other children, and imitation [26]. The DDST (Denver Developmental Screening Test) was used for the early detection of developmental disabilities. DDST examines the four areas of development: social contact, fine motor skill, gross motor skill and language [27].

Social, demographic and environmental risk factors were evaluated systematically through structured diagnostic interviews with parents. Family size, educational level of parents, single parenthood, adoptive parent, the death of a parent, separation from mother, maternal mental health, medical disorders and nicotine exposure during pregnancy, television exposure of toddlers were analysed.

Statistics

Results were analysed by the Pearson Chi-Square test, Fisher's exact test, unpaired Student T-test, the nonparametric Mann-Whitney-U-test and

multivariate analysis of variance (MA-NOVA) with the psychosocial risk score as a control variable. A p-value of less than or equal to 0.05 was considered significant.

Results

To exclude the possible effect of preterm birth on the neuropsychiatric development, children were distributed into preterm and term delivered groups. Concerning maternal age, gestational week of delivery, birth weight, head circumference, body length and Apgar scores between treated and untreated children in term and preterm groups, there was found to be no difference (Table 1).

Table 1: Maternal and perinatal characteristics of the sample

	Term Birth (Gest. age ≥ 37 weeks)			Preterm Birth (Gest. age < 37 weeks)		
	Untreated (n = 24)	Treated (n = 22)	p	Untreated (n = 20)	Treated (n = 24)	P
Maternal age (y)	29.8 ± 5.7	27.7 ± 4.8	0.195*	30.1 ± 6.6	27.9 ± 5.9	0.174**
Gestational weeks	39 ± 1.4	37 ± 8.3	0.553*	31 ± 10.9	28.9 ± 11.6	0.553*
Birth weight (g)	3022 ± 494	3193 ± 425	0.180**	2427 ± 1001	2178 ± 860	0.255**
Head circumference (cm)	33.7 ± 1.8	34 ± 1.2	0.286*	31.3 ± 10.9	30 ± 3.9	0.286*
Body length (cm)	49 ± 0.5	49.7 ± 2.3	0.346*	44.9 ± 5.9	44.9 ± 5.5	0.986*
Apgar score 1st minute	8.7 ± 0.7	8.9 ± 0.2	0.673**	7.7 ± 1.8	7.6 ± 2	0.882**
Apgar score 5th minute	9.8 ± 0.4	9.9 ± 0.2	0.333**	9.3 ± 1.1	9.1 ± 1.2	0.783**

Values presented as Mean ± SD; *, Unpaired t-test; **, Mann-Whitney U test.

Social, demographic and environmental risk factors defined as family size, educational level of parents, attending of kindergarten, single parenthood, adoptive parent, death of parent, separation from mother, maternal mental health, medical disorders and nicotine exposure during pregnancy, television exposure, maternal infection during pregnancy, preterm membrane rupture and delivery mode were compared in preterm and term groups with and without tocolysis.

Table 2: Social, demographic and environmental factors

N (%)	Term Birth (Gest. age ≥ 37 weeks)			Preterm Birth (Gest. age < 37 weeks))		
	Untreated (n = 24)	Treated (n = 22)	P	Untreated (n = 20)	Treated (n = 24)	P
Elementary Family	19 (79)	16 (73)	0.869*	13 (6)	15 (63)	1.000*
Low educational level of mother	12 (50)	12 (55)	0.990*	14 (70)	19 (79)	0.727*
Low educational level of father	10 (42)	7 (32)	0.700*	12 (60)	14 (58)	1.00*
Attending kindergarten	0 (0)	2 (9)	0.223	0 (0)	0 (0)	-
Separation from mother	2 (8)	1 (5)	1.000**	0 (0)	4 (16)	0.114**
Maternal mental disorder during pregnancy	3 (13)	3 (14)	1.000**	6 (30)	3 (13)	0.261**
Maternal medical disorder during pregnancy	7 (29)	8 (36)	0.837*	10 (50)	10 (42)	0.804*
Maternal nicotine exposure during pregnancy	1 (4)	2 (9)	0.600**	15 (75)	19 (79)	1.000**
Television exposure of the toddlers	18 (75)	18 (82)	0.725**	17 (85)	16 (67)	0.294**
Maternal infection during pregnancy	2 (8)	5 (23)	0.234**	3 (15)	6 (25)	0.477**
Preterm membrane rupture	0 (0)	1 (5)	0.478**	4 (20)	12 (50)	0.081*
Cesarean section	16 (67)	12 (55)	0.590*	15 (75)	12 (50)	0.166*

*, Continuity correction; **, Fisher's exact test.

Among the samples, there were no toddlers with single parenthood, adoptive parent or deceased parent. Concerning other factors, no differences between treated and untreated groups were obtained (Table 2).

The same pattern of results was seen in tocolytically treated and untreated preterm and term children according to psychomotor skills, ASD risk, competencies and Problems Scale (Table 3).

Table 3: Autism risk, psychomotor development, emotional problems and competencies in term and preterm children exposed to tocolysis and untreated controls

N (%)	Term Birth (Gest. age ≥ 37 weeks)			Preterm Birth (Gest. age < 37 weeks)		
	Untreated (n = 24)	Treated (n = 22)	P	Untreated (n = 20)	Treated (n = 24)	P
Autism risk	5 (20.8)	3 (13.6)	0.702**	6 (30)	4 (16.7)	0.472**
Psychomotor developmental disabilities	2 (8.3)	0 (0)	0.490**	3 (15)	4 (16.7)	1.000**
Mean ±SD						
Competencies scale	19.54 ± 4.032	20.36 ± 1.293	0.847*	18.85 ± 4.017	19.5 ± 3.464	0.810*
Problems scale	10.08 ± 5.233	10.95 ± 4.933	0.389*	12.40 ± 5.491	13.21 ± 6.827	0.812*

*, Mann-Whitney U test; **, Fisher's exact test.

Regarding tocolytic treatment start time, dosage or duration of pharmacotherapy no significant differences in the risk for ASD, psychomotor skills in preterm and term children groups were found (Table 4).

Table 4: Risk of ASD and psychomotor development disabilities associated with beta 2-adrenergic exposure during pregnancy

	Without Risk of ASD	With Risk of ASD	p*	Without Psychomotor Developmental Disabilities	With Psychomotor Developmental Disabilities	p
Beginning of tocolysis (gestational week)	31.6 ± 6.4	31.7 ± 3.5	0.842	31.54 ± 6.20	32.20 ± 4.97	0.612
Duration of tocolysis (hours)	39.5 ± 53.2	13.9 ± 27.7	0.307	33.35 ± 46.69	59.25 ± 63.82	0.332
Cumulative dosis of tocolysis (gr)	713.2 ± 474.8	1109.1 ± 926.5	0.426	414.1 ± 581.9	226.7 ± 300.9	0.320

Values presented as Mean ± SD; *, Mann-Whitney U Test.

In the preterm group, the earliest start of the tocolytic treatment is associated with the higher score on the Problems Scale. The later the treatment is applied, the higher the score of the Competencies Scale in preterm born toddlers (Table 5).

Table 5: Correlation of emotional problems and competencies with beta 2-adrenergic exposure during pregnancy

	Preterm (N = 24)				Term (N = 22)			
	Competencies scale		Problem scale		Competencies scale		Problem scale	
	r	p	r	P	r	p	R	P
Beginning of tocolysis (gestational week)	0.521	0.009**	-0.408	0.048***	-0.243	0.275	0.351	0.109
Duration of tocolysis (hours)	0.046	0.831	-0.131	0.543	-0.036	0.875	-0.096	0.671
Cumulative dosis of tocolysis (mg)	0.045	0.0834	0.071	0.741	0.113	0.617	-0.221	0.322

*, Spearman's rho; **, Statistically significant p < 0.01; ***,Statistically significant p < 0.05.

We did not detect any statistically significant difference between toddlers with and without ASD risk, concerning the maternal age, gestational week of delivery, birth weight, head circumference and body length. In the tocolytically treated group with the risk of

ASD, the Apgar score at the 5th minute was significantly lower than in the group without risk of ASD (Table 6).

Table 6: Characteristics of treated and untreated samples with and without ASD risk

	Untreated			Treated		
	Without Risk of ASD	With Risk of ASD	p*	Without Risk of ASD	With Risk of ASD	P
Maternal age	30.7 ± 5.8	27.5 ± 6.3	0.175	28.15 ± 5.6	26 ± 3.41	0.365
Gestational weeks	36.2 ± 3	35.6 ± 3.8	0.593	34.7 ± 4.4	33.5 ± 4.6	0.476
Birth weight (g)	2785 ± 769.9	2685 ± 946.8	0.759	2696 ± 838.2	2485 ± 973.1	0.625
Head circumference (cm)	32.8 ± 2.4	32.3 ± 4.3	0.648	32.1 ± 3.4	31.4 ± 4.4	0.783
Body length	47.3 ± 4.1	47.2 ± 6.5	0.417	47.4 ± 4.6	45.8 ± 6.4	0.634
Apgar score 1st min	8.7 ± 1.5	8.6 ± 0.8	0.504	8.3 ± 1.6	8.0 ± 1.4	0.118
Apgar score 5th min	9.5 ± 0.9	9.8 ± 0.4	0.454	9.6 ± 0.8	9.0 ± 1.4	0.045**

Values presented as Mean ± SD; *, Spearman's rho; **, Statistically significant p < 0.01; ***, Statistically significant p<0.05.

In addition to defining the psychosocial and environmental influence on ASD risk in treated and untreated samples, toddlers with and without risk of autism were compared according to their family size, educational level of parents, attending kindergarten, separation from mother, maternal mental health, medical disorders and nicotine exposure during pregnancy, television exposure, preterm membrane rupture delivery mode. In untreated groups, preterm membrane rupture was associated with ASD risk; however, in children with tocolytic treatment, maternal nicotine exposure during pregnancy was higher in the group with the risk of autism (Table 7).

Table 7: Association of social demographic and environmental factors with ASD risk

	Untreated					Treated				
N (%)	Without Risk of ASD		With Risk of ASD		P	Without Risk of ASD		With Risk of ASD		P
Elementary Family	25	75.8	7	63.6	0.457*	25	64.1	6	85.7	0.399*
Low educational level of mother	18	54.5	8	72.7	0.480*	26	66.6	5	71.4	1.000*
Low educational level of father	17	51.5	5	45.5	1.000**	18	46.2	3	42.9	1.000*
Attending kindergarten	0	0	0	0	-	1	2.6	1	14.3	0.284*
Separation from mother	0	0	2	18.2	0.058*	4	10.3	1	14.3	1.000*
Maternal mental disorder during pregnancy	5	15.2	4	36.4	0.195*	5	12.8	1	14.3	1.000*
Maternal medical disorder during pregnancy	12	36.4	5	45.5	0.724*	14	35.9	4	57.1	0.407*
Maternal nicotine exposure during pregnancy	5	15.2	1	9.1	1.000*	4	10.3	3	42.9	0.06*
Television exposure of the toddlers	27	81.8	8	72.7	0.669*	27	69.2	7	100	0.165*
Preterm membrane rupture	1	3	3	27.3	0.043***	0.043	30.8	1	14.3	0.654*
Cesarean section	22	66.7	9	81.8	0.461*	21	53.8	3	42.9	0.694*

*, Mann-Whitney U Test; **, Statistically significant p < 0.05.

Discussion

Our study is directed at analysing the relation between beta-sympathomimetic treatment, time of start, duration and dose of tocolytic treatment administration and toddler's risk of autistic spectrum disorders, behavioural and developmental outcomes. Moreover, it is focused on the possible influence of psychosocial risks and comedications like calcium channel blockers, magnesium sulphate and glucocorticoids on brain development. Unlike previous research that follows children with poor neurophysiologic and performance including autism [14, 28, 29], we selected a random group of patients delivered in our clinic during an 18-month period. Previous studies have demonstrated an increased risk of ASD and educational problems in prematurely born infants; however, the role of preterm birth itself could not be ignored [30, 31].

Considering this, we divided patients into tocolytically treated and untreated term and preterm groups, to compare not only tocolytic but also prematurity with risk of ASD, behavioural and developmental disabilities. We compared similar groups to exclude the obstetric, social, demographic and environmental risk factors from influencing the outcome. The present study did not find any association between tocolytic exposure and subsequent development of autistic disorders among term and preterm born infants. Also, we consider that neither the time of treatment start nor the duration and dosage of beta-sympathomimetic exposure is correlated with increased risk of ASD. Recent studies have demonstrated controversial and inconclusive results. Connor at al. [32] found evidence of an association between tocolytic exposure and risk of autistic disorders in dizygotic twins. Pitzer's group [14] also indicated the impairment of motor skills, cognitive and socio-emotional development and a higher rate of psychiatric disorders in tocolytic treated term born children, whereas, Croen at al. [28] did not indicate concordance of autistic disorders and beta-sympathomimetic treatment in utero.

Also, we consider that time of treatment start, dose and duration of beta-sympathomimetic exposure did not affect the risk of psychomotor development in both term and preterm groups. However, in the preterm group, tocolytic treatment start time affects the Competencies Scale score, which reflects the socially competent functioning of toddlers and Problems Scale, which assesses behavioural types like externalizing, internalizing and dysregulation. The start of the tocolytic treatment in the earliest weeks of gestation is associated with a lower score on the Competencies Scale; consequently, it contributes to significantly lower levels of competencies. The earlier the treatment is applied, the higher the score on the Problems Scale in preterm born toddlers. Pitzer at al. [14] reported an increased level of social, emotional problems in 2-, 4-, 5- and 8-year old children exposed to beta-sympathomimetic treatment in utero. But in term born group, Polowczyk at al. [33] reported significantly higher rates of psychopathology in children exposed to tocolysis with beta-sympathomimetics.

Furthermore, Hadders-Algra at al. [34] also found higher rates of poor school performance in children prenatally exposed to the tocolytic treatment.

In our study, we examined toddlers between 1.5 and three years old, which gave us the possibility of diagnosing and treating them at an early stage of autistic disability. Also, we also controlled possible confounding factors like the psychosocial and environmental influence on ASD risk in treated and untreated samples. We conclude that preterm membrane rupture is associated with higher ASD risk in untreated groups; however, in tocolytically treated children maternal nicotine exposure during pregnancy was concordant with increased autistic disorders risk. Moore and colleagues [35] did not find any similarity between premature membrane rupture and ASD; however, Joseph at al. [36] and Dudova et al. [37] did. The literature concerning maternal nicotine exposure during pregnancy shows different results: some authors demonstrate an association between harmful exposure and subsequent autism disorder [38, 39], others indicate association close to nil [40-42]. However, it is well known that tocolytic maintenance treatments do not improve perinatal outcome and should not be applied for the management of preterm labour in general practice [43]. Ritodrine is still widely used in Turkey for more than two days in preterm labour treatment. With this in mind, we can conclude that further evaluation of maintenance tocolytic treatments' long-term effects are needed, to recognize potential harmful effects on offspring.

Study Limitations: There are some limitations in our study. Since our study was conducted in a centre which delivers tertiary healthcare service, our patients might have a different clinical picture. It arose from a single centre and therefore was subject to selection bias. The small number of subject is another limitation of our study. More extensive and multicenter studies are required to fully understand the relationship between beta-mimetic exposure on child development.

In conclusion, our study is directed at analysing the relation between beta-sympathomimetic treatment, time of start, duration and dose of tocolytic treatment administration and toddlers risk of ASD, behavioural and developmental outcomes. The present study did not find any association between tocolytic exposure and subsequent development of autistic disorders, behavioural or developmental disabilities among term and preterm born infants. Besides this study consider that neither the time of treatment start nor the duration and dosage of beta-sympathomimetic exposure is correlated with increased risk of ASD. Considering that currently available data reveals contentious results, further thorough research is needed to clarify any possible influence of beta-mimetic exposure on child development.

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