Autism - Open Access

Elliott JP, et al., Autism-Open Access 2015, 5:1
DOI: 10.4172/2165-7890.1000139

Research Article open access

Autism is Not Caused by Terbutaline

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Rec Date: March 07, 2015; **Acc Date:** March 16, 2015; **Pub Date: March** 22, 2015

Abstract

Objective: To identify the rate of Autism Spectrum Disorder (ASD) in children exposed to terbutaline in utero compared to patients untreated with this beta agonist.

Methods: Members of three lay organizations collected data regarding significant childhood development problems following their pregnancy using a web-based survey.

Results: Over a 90 day period, 11,717 surveys were sent electronically to members of the high risk pregnancy organizations. Of these, 2217 members (18.9%) responded and results showed that 965(43.5%) had received terbutaline during their pregnancies. Overall 523(23.6%) reported having at least one child with some form of chronic disability and of these 128 had a child with ASD. Of fetuses with no exposure to terabutaline 79/1252 (6.3%) had a diagnosis of ASD compared to 49/965 (5.1%) who reported a history of terbutaline exposure (p=0.233). In contrast, prematurity was strongly associated with ASD as 102/128 (80%) were delivered at <36 weeks compared to 26/128 of those with ASD (20%) delivering at >36 weeks.

ASD was not associated with terabutaline exposure in pregnancy; however ASD was associated with preterm delivery.

Keywords: Autism Spectrum Disorder; Terbutaline; pregnancy; Childhood vaccinations

Introduction

In the past 15 years the diagnosis of autism has increased from 6.7/1000 to one of the most common diagnosis involving children, occurring in one in every 88 American children (11.3/1000) [1]. The diagnosis has so many different presentations it is now termed Autism Spectrum Disorder (ASD). This neurodevelopmental disorder is diagnosed in children having repetitive behaviors and restricted interests highlighted by social and communication problems this "epidemic" of ASD has resulted in parental anxiety leading to a tremendous amount of research regarding the etiology of this multifactorial disorder [2,3].

For example, ASD in the past has been related to childhood vaccinations (MMR - measles, mumps, rubella) but epidemiologic studies have shown that neither the vaccine nor the theomerosol carrier are in any way related to ASD [4]. The original paper was retracted by Lancet and the author rebuked [4]. Similarly, neonatal hyperbili rubenemia, maternal fever and synthetic oxytocin have all been implicated as a cause of ASD but large studies have shown no etiologic connection [5-7]. Importantly, none of these purported associations fulfilled the epidemiologic criteria necessary to establish causation [8]. The most likely the cause of ASD the entire spectrum of ASD almost certainly involves genetic pathways with multifactorial influences [9]. However, when any factor is common in maternal child health (occurring in many, if not most all gestations) it is frequently cited as the cause of ASD, and this linkage can be harmful. For example, the original report of an association between autism and childhood vaccinations was eventually discredited but also has resulted in countless deaths from preventable diseases because many children were not vaccinated [4].

Similarly an "association" between beta agonist treatment of preterm labor (as well as asthma) and ASD has been proposed in humans (Witter, et al.) and in animals by (Slotkin et al.) They suggested that prenatal exposure to beta agonists might permanently disable adrenergic receptors thus causing ASD [10,11]. Basic science work by Owens, et al. [12] and editorial comments on the Witter article by Rodier et al. [13]. Found that the animal and human "evidence" presented was not persuasive of alinkage between the use of beta agonist drugs and ASD. We have published articles on the clinical (human) data which confirms that preterm birth instead of the beta agonist treatment was the most likely cause of ASD [14,15]. Because the research in humans involved studies using tocolytic treatment years ago (so that untreated controls could be enrolled), we felt another approach would be clinical appropriate to determine whether ASD was related to treatment with beta agonist drugs, particularly terbutaline.

In this study, we identified the rate of ASD diagnosis in children exposed to terabutaline while in utero, compared to offspring whose mothers were untreated.

Methods

Three organizations (Sidelines, MOST, Triplet Connection) agreed to collect data from their members using a web based survey. The purpose of these three organizations is to provide support for women experiencing or who have experienced a high risk pregnancy. Sidelines national support network was founded in 1991 as a "support group for women experiencing complicated pregnancies and premature births." Over 250,000 women have utilized their services over 24 years. Mothers of Super Twins (MOST) is "the leading national non-profit provider of support, education, and research on high-order multiple births." MOST was established in 1987 and in 27 years has served over 10,000 women. The Triplet Connection foundation was started in 1983 and in 32 years was worked over 45,000 expectant parents of high-order multiple births.

A high risk pregnancy survey data form was constructed after no instrument was found to capture information about children with ASD and the use of the beta agonist used for maternal tocolysis in preterm labor. The questionnaire (available upon request) was developed in consultation with a statistician noted for such survey instrument construction. We attempted to develop the questionnaire in such a way that the beta agonist terbutaline was listed as a choice along with other drugs commonly used for preterm labor treatment (magnesium sulfate, indomethacin, nifedipine etc). Similarly the diagnosis of ASD was only one of the possible complications listed. For example, diagnoses of asthma, cerebral palsy, developmental delay, mental retardation, seizures, congenital/developmental problems in the offspring, were also solicited fields. Pregnancy complications such as multifetal pregnancies, preeclampsia, rupture of the membranes, cervical insufficiencies, and fetal growth restriction in addition to preterm labor were all incorporated into the survey instrument. For the purpose of this study, women who reported receiving terbutaline orally, by intermittent subcutaneous injection or via a continuous subcutaneous infusion pump (either in the hospital and/or in home setting) were considered to have terbutaline exposure. Women who did not receive any terbutaline formed the control group.

We anticipated a 15% return rate and proposed to send out at least 10,000 questionnaires hoping for 1500 responses. The three organizations had great experience with emailing invitations and using internet surveys. The organizations also had extensive experience in conducting research through survey methodology. They maintained databases of their members and part of the expectation is that surveys will be conducted periodically.

Results

Over a three month period, 11,717 email invitations were deployed and 2217 women (18.9%) responded by filling out the questionnaire on the website of one of the three organizations. While a tremendous amount of data was generated regarding pregnancy complications as well as various childhood disabilities, attention was focused on autism for this paper. Table 1 shows the results comparing those children with ASD and treatment versus no treatment with the beta agonist terbutaline. The results showed that 965 of the 2217 women (44%) were exposed to terabutaline for preterm labor as previously defined, whereas 1252 pregnancies (56%) formed the control group. There were 523 respondents (23.6%) who reported having at least one child with some form of chronic disability and among these 128 noted ASD as a complication. As shown in Table 1, 6.3% (79) of the cases of ASD occurred in women who had no terbutaline exposure while 49 or 5.1% of the women reported a history of terabutaline treatment. The difference was not significant with the p-value of .233.

	No Terb Exposure	+ Terb Exposure	p-value
Total 2717	1252	965	
DX of Autism (n) %	(79) 6.3%	(49) 5.1%	0.233
Male Gender	(66/79) 83.5%	(42/49) 85.7%	0.807

Table 1: Shows the results comparing those children with ASD and treatment versus no treatment with the beta agonist terbutaline

As expected more male than female children 108/128 (84%) were diagnosed with ASD but the effect of terbutaline vs no terbutaline exposure by fetal sex was also not significant (p=0.807). Table 1 also reveals that preterm delivery (gestational age <36 weeks) was more common 102/128 (80%) in those with ASD versus those with ASD who delivered >36 wks (20%). Finally, Table 2 demonstrates that terabutaline exposure was not short term, with a mean treatment time of 24.6 days and a median exposure time of 17 days (1-124 days). Importantly, there was no greater chance of ASD in maternal treatment of >14 days versus <14 days of terabutaline therapy (p=0.234)

	No Terb Exposure	+Terb Exposure	p-value
Days of Exposure	N/A	24.6 ± 24.9 Median 17 (1,124)	
> 14 day w/autism ≤ 14 day w/autism	N/A N/A	(24/49) 4.7% (25/40) 5.4%	0.234

Table 2: Demonstrates that terabutaline exposure was not short term

Discussion

In animals, Slokin et al. [11] injected very large doses (10mg/kg/day) of terabutaline in rat pups, not pregnant animals, and this dose is 260 times the amount typically given for maintenance after preterm labor (0.04ug/kg/day). Nevertheless, they concluded that changes in the brains of these rat pups could be extrapolated to autism in humans. However, the central issue is highlighted by Owens et al who noted an absence of neurotoxicity even when these large doses of terabutaline are employed in the rat pups model [12]. She found that when an medicinal grade (such as used in humans) was injected in the rat pups there was no neurotoxicity compared to pharmacologic grade of terbutaline used by Slokin et al. [11]. Also, the pharmacologic grade of drug (in vitro only) was clearly different on mass spectrum analysis from the medicinal type of terabutaline used in humans. Therefore, in animals, the damage which is said to cause ASD like symptoms in the rat pup appears to be related to the type of drug while actually the cause of the damage may be linked to the early gestational when the rat pups were born which would seem to support prematurity as a potential etiology rather than the beta agonist terabutaline.

The human studies cited Witter et al do not show a strong relationship between terabutaline and ASD. Many of the older articles from this country, as well as in Europe, did not use terabutaline but rather other beta agonists [10,16,17]. Significantly, many of these studies did have an untreated control group, and still did not demonstrate a relationship to ASD or other neurologic disorders. Importantly, a component of all the studies in the offspring was prematurity, which in and of itself is a correlate of ASD [18,19]. As such, treatment of those at high risk for early delivery using beta agonist was judged by these investigators to be more of paramount importance [16,17]. Witter et al. also suggested prolonged treatment (>14days) with beta agonist such as terbutaline resulted in damage, whereas the offspring had no problems when treated for short periods of times (such as several days or a week) [10]. Our data in Table 2 demonstrates this is not true as 24/49 (49%) of those with autism were treated for >14 days whereas 25 of 40 (51%) were treated for <14 days (p=.234). Indeed when one looks at the great length of terabutaline infusion, (mean of 24.6 ± 24.9 days with a median of 17 days and range of 1 to 124 days) certainly such prolonged exposure, according to Witter et al, should have shown an increase in ASD in treated women and it did not [10].

Similarly we feel that preterm labor continues to be the most common and catastrophic complication of pregnancy [14]. While the etiology of preterm birth remains elusive and our treatment choices are few, therapy for patients with preterm labor, which is the most common cause of early delivery, is of paramount importance. Others authors have found prematurity to be more common in children with ASD such as Buckmayer et al. [20] had a very large population demonstrating ASD in those women who had early births. In Buckmayer's analysis, other issues such as congenital malformations, low Apgars, etc make it unclear whether prematurity itself is linked the etiology of ASD or whether it is simply a marker for a fetus that has been already damaged. In our paper, the number of preterm deliveries was modest but still showed a strong relationship of ASD to prematurity (102/128 80%).

The strength of our study is the development of a new survey tool which by design, cloaked the relationship between ASD and terabutaline. While a new survey instrument could be seen as a limitation, as the tool had not been validated, we did achieve a respectable return in excess of what is usually expected with such devices. In addition, we obtained statistical consultation in the construction of the instrument which made bias by the answering party less likely. Another limitation might be that women whose children showed more severe disorders may have been overly represented among respondents compared to those who had normal offspring. While this may be true, ASD should be over represented and more common among respondents due to overexposure by the media. Also that almost 75% of the respondents reported having no children with disabilities or chronic medical disorders, therefore it is unlikely that our population is a source of bias for the study.

While it is imperative to find the cause of autism, it is apparent that terbutaline treatment of preterm labor can be ruled out as a potential cause of ASD. We feel it is much more important to treat patients aggressively who have preterm labor rather than risking an extremely early delivery by not using tocolytic drugs. In sum, based on all the available data, we recommend that the obstetricians continue to treat patients in preterm labor individually with whichever tocolytic offers the best results, with comfort in knowing that ASD is not one of the side effects of such treatment.

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