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Commentary OMICS International

Autism Spectrum Disorders are not linked to β-2-Adrenergic Receptor Agonists Treatment for Preterm Labor/Asthma

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Introduction

Autism Spectrum Disorders (ASD) is a neurodevelopmental disorder comprised of repetitive behaviors and restricted interests along with communication problems during childhood [1]. The incidence of ASD has risen from 1/2000 thousand children before 1980 to approximately 1/110 by 2006 and 1/88 for the last year that data was available [2]. This increased prevalence of children diagnosed with ASD has resulted in many common agents labeled as "causal" or "associated" with this problem. Most famously, childhood vaccines such as the MMR (measles, mumps, rubella) was first said to be causal in the late 1990's but vaccination has since been demonstrated to have no correlation with ASD. The co-authors of the seminal work issued a retraction of their initial interpretation and the entire article was retracted by the Journal (Lancet) and the author rebuked [3]. More recently ASD has been linked to many factors such elevated neonatal bilirubin, oxytocin induction of labor, infection during pregnancy, exposure to beta agonist drugs (for preterm labor and asthma treatment), mental health stressors and many other factors [4]. Common issues during pregnancy can almost always be statistically "associated with" any rare disorder/disease but of course, none of these factors are causal. On the other hand, genetic research has been the most promising area as a cause for ASD [5-9]. Chromosomal abnormalities in children with ASD diagnosed by micro-array analysis and linkage to metabolic/mitochondrial disorders are being noted more frequently [10-12]. This is important because parents of such children deserve current information about ASD as it is very devastating for families and siblings alike [13].

One of the areas that received attention in the past was in utero exposure of fetuses to beta adrenergic agonist drugs (β-2AR) as they were commonly used for women in preterm labor and in pregnancies complicated by asthma. Witter et al. [14] performed a clinical literature review regarding preterm labor treatment stimulated by a basic science hypothesis that exposure to β-2AR drugs led to brain lesions in rats [15]. In an invited response by the American Journal of Obstetrics and Gynecology, the noted teratologist, Brent et al. [16] debunked the hypothesis that β-2AR was in anyway related to ASD. Furthermore, in a response to a letter to the editor by Brent et al. noted that in the original article [14] much of the evidence claimed by Witter et al. "was not present in the references cited or conflicted with the actual results reported in their literature" [17]. They also identified other "egregious omissions" in the Witter et al. [14] paper such as failure to note that preterm birth itself is strongly associated with an increased risk for ASD and that drug exposures already known to be risk factors for ASD, have their critical periods during the first trimester making the hypothesis that β-2AR used in the 2nd or 3rd trimester would lead to ASD very unlikely. As maternal fetal medicine specialists who often manage high risk pregnancies complicated by preterm labor and asthma, we have not found any relationship between β-2AR and ASD [4,18]. There is also basic science data in the rat model by investigators in our laboratories supporting clinical findings that there is no credible, reproducible evidence linking β-2AR to ASD [19]. It was reasonable to believe that this issue, based on all of the data, had been adjudicated.

Imagine, if you will, our chagrin, upon reading a recent article in Pediatrics [20] regarding a case control study which used an outpatient population registry where they "demonstrated an association" between β-2AR's and ASD. Unfortunately many of the same references previously refuted by Brent et al. [16,17] were used to bolster their findings. They even quoted Brent at al. [16] as "supporting their supposition," when in fact the Brent article says just the opposite; there is not an association between β-2AR's and ASD. Furthermore the article by Gidaya et al. [20] did not account for prematurity which is the most important pregnancy related factor with regard to ASD. Indeed, Autism is five times more common in low birth weight babies compared to those born at term [21]. As an example, we have accessed the results of an anonymous survey sent to participants who were members of several high risk pregnancy support organizations. Of the 2217 respondents, 43.5% were not treated with β-2AR medication while 46.5% did receive these drugs for preterm labor. Among treated women, 6.3% had a child diagnosed with ASD compared to 5.1% of those with no exposure to these drugs (p=0.33). In contrast, prematurity was associated with 80% of ASD cases whereas those delivered at term (≥ 37weeks gestation) accounted for only 20% children with ASD [19]. This demonstrates that prematurity is the most important gestational factor in children who are later found to have ASD. Another critical problem with the paper by Gidaya et al. [20] was they found that β-2AR use was associated with ASD even if exposure occurred before pregnancy (within 90 days of conception). Obviously, the use β-2AR prior to pregnancy cannot affect the offspring as the fetus is not yet in utero. Ultimately the data of Gidaya et al. [20] as well as the basic science and clinical studies on which the article is based did not conform to the Bradford-Hill criteria which must be fulfilled to draw a causal relationship between a disease and an environmental agent [22].

This issue needs to be laid to rest. β-2AR exposure during pregnancy does not, will not, cannot and has never caused ASD! In our view it is not fair to cause anxiety in young mothers who may in fact stop using β-2AR medications which may actually result in a preterm birth or in worsening of asthma during pregnancy with significant morbidity/mortality in the mother and fetus [23]. This is similar to what happened after the MMR vaccine scare as many mothers did not vaccinate their children. This resulted in the unvaccinated children infecting

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other children as well as causing significant childhood morbidity and mortality among the unvaccinated children themselves [24]. Many times failure to treat a disorder like preterm labor or asthma during pregnancy can be much more costly to children than the disorder itself. In this case, it is particularly true since there is no risk of ASD when β-2ARs are used during gestation.

In summary, clinicians should use β-2ARs without fear that they are related in any way to ASD. Perhaps in the future such medical literature will not to be published if it suggests ASD is related to β-2AR use in pregnancy.

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