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The link between oral contraceptive use and prevalence in autism spectrum disorder

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ABSTRACT

Autism spectrum disorder (ASD) is a group of developmental disabilities that include full syndrome autism, Asperger's syndrome, and other pervasive developmental disorders. The identified prevalence of ASD has increased in a short time period across multiple studies causing some to conclude that it has reached epidemic proportions in the U.S.

Many possible explanations for the rise in numbers of individuals diagnosed with ASD have been offered and yet, causes and contributing factors for ASD are inadequately understood. Current evidence suggests that both genetics and environment play a part in causing ASD.

One possible risk factor for the increase in prevalence has been profoundly overlooked in the existing biomedical and epidemiologic literature. As the prevalence of ASD has risen in the last sixty years, so has the prevalence of the usage of the oral contraceptives and other modern hormonal delivery methods. In 1960 about one million American women were using oral contraceptives, today close to 11 million women in the U.S. use oral contraceptives. Eighty-two percent of sexually active women in the U.S. have used oral contraceptives at some point during their reproductive years. Thus, the growth in use of progesterone/estrogen-based contraceptives in the United State has reached near-ubiquitous levels among women in the child-bearing age range.

The suppression of ovulation produced by estrogen–progesterone is an indisputable abnormality. It is logical to consider the outcome of the ovum that would have been normally released from the ovary during ovulation. To date there is no comprehensive research into the potential neurodevelopmental effects of oral contraceptive use on progeny. The issue has been only sparsely considered in the biomedical literature. This article hypothesizes that the compounds, estrogen and progesterone, used in oral contraceptives modify the condition of the oocyte and give rise to a potent risk factor that helps explain the recent increase in the prevalence of ASD's.

This hypothesis does not propose to delineate the cause of autism. Rather, it attempts to explain the recent dramatic increase in prevalence and point the way for further study that will lead to causal examination.

Introduction

Autism spectrum disorder (ASD) is a developmental disability that is lifelong. It is defined by psychiatric diagnostic criteria that include deficits in social communication and social interaction and restricted, repetitive patterns of behavior, activities and/or interests [1]. Typically, initial signs and symptoms are noticeable in the early developmental period. However, behavioral patterns and social deficits might not be recognized as indications of ASD until a child is unable to handle social, educational, occupational, or other significant life-stage demands. Functional deficiencies sometimes develop over time and often vary among persons with ASD's [2].

The identified prevalence of ASD has increased across multiple studies in a short period of time causing some to say that it has reached epidemic proportions. The Centers for Disease Control and Prevention (CDC) reports that the estimated prevalence of ASD in the Unites States has increased roughly 29% since 2008, 64% since 2006, and 123% since 2002 [3]. Many potential explanations for the escalation in numbers of individuals diagnosed with ASD have been presented and yet, underlying causes and contributing factors for ASD are poorly understood. Current evidence proposes that both genetics and environment play a part in causing ASD [4]. And, yet, sixty years have passed since scientists first

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identified and described autism and the causes of ASD's are still unknown.

As the prevalence of ASD has risen in the last sixty years, so has the prevalence of the usage of the oral contraceptives and other modern hormonal delivery methods such as the injectables, patch, vaginal ring, and implants. Although dosage has changed from the earliest version of the oral contraceptive, the two compounds used, progesterone and estrogen, are still the same. In 1960 about one million American women were using oral contraceptives. Today close to 11 million women in the United States use oral contraceptives as their principle method of contraception [5]. It is reported that 82% of sexually active women in the United States have used oral contraceptives at some point during their reproductive years [6]. Thus, the growth in use of progesterone/estrogen-based contraceptives in the United State has reached near-ubiquitous levels among women in the child-bearing age range.

Strikingly, the increase in the prevalence of oral contraceptive use in the past 60 years coincides with the recent dramatic rise in autism and ASD prevalence. Does the correlation suggest a risk factor for ASD? The suppression of ovulation produced by estrogen–progesterone is an indisputable abnormality. It is logical to consider the outcome of the ovum that would have been normally released from the ovary during ovulation. When exposed to the hormonal compounds in the oral contraceptives, does the oocyte die or does it survive? If it survives, is it altered in any way? To date there is no comprehensive research into the potential neurodevelopmental effects of oral contraceptive use on progeny. Indeed, the issue has been only sparsely considered in the biomedical literature. The compounds used in oral contraceptives may modify the condition of the oocyte and give rise to the risk factor that explains the recent increase in the prevalence of ASD's.

Given the lack of research on the effects of oral contraceptive use on progeny, it is impossible at this point to specify a mechanistic link between oral contraceptives and autism. This fact represents a meaningful limitation to the hypothesis presented in this review. However, recent research already suggests that the current understanding of the pharmacology of oral contraceptives may be over-simplified. It has been proposed, for example, that epigenetic side-effects of pharmaceuticals may be involved in the etiology of cancer, heart disease, neurological and cognitive disorders, obesity, infertility, and sexual dysfunction [7]. It has also been suggested that epigenetic assays be incorporated into the safety assessment of all pharmaceutical drugs, which might lead to new mechanistic insights in the future [7]. Finally, new evidence is emerging that oral contraceptive use directly and deleteriously affects both the ovaries and the ova [8]. Thus, we are at a point where some concrete mechanistic hypotheses may be achievable in the near future.

In a generalized form the link between oral contraceptive use and the increased prevalence of ASD may be understood using Alfred Kudson's multiple hit hypothesis, which was first developed in considering the ontogeny of retinoblastoma [9]. Using this hypothesis, in the context of neurodevelopmental disorders such as ASD's, the oocyte suffers the first insult with its exposure, in situ in the ovary, to the hormonal compounds in the oral contraceptives. This insult might include aberrant retention of the oocyte for too long a time period, direct effects in the oocyte of estrogen/progesterone receptor activation, or the secondary triggering of an abnormal hormonal milieu in the corpus luteum. The second insult might be in the pre-existing ovum or occur subsequently over the lifespan, and might include genetic, environmental, or epigenetic factors. The combination of the two "hits" will lead to autism in the offspring. It is important to note that this hypothesis does not propose to delineate the cause of autism. It only attempts to explain the recent increase in prevalence and point the way for further study that will lead to causal examination (see Fig. 1).

The CDC model for risk assessment requires that for a risk factor to make a notable contribution to population changes in the prevalence of ASD during a short time period, three conditions have to be met [10]. The factor has to be quite prevalent in the population, its presence has to have increased substantially, and it must be strongly associated with ASD [10]. This review suggests that the oral contraceptives meet the first two conditions and hypothesizes that the third condition will also be met with further scientific inquiry into the association between the prevalent use of oral contraceptives and the increased prevalence in ASD's.

This article considers the increase in prevalence of ASD, examines potential explanations for the increase, identifies the proposed risk involved with the oral contraceptives, surveys the prevalence of usage of the oral contraceptives, and then hypothesizes that the use of the oral contraceptives may modify the condition of the oocyte producing a risk factor that explains the significant increase in ASD prevalence.

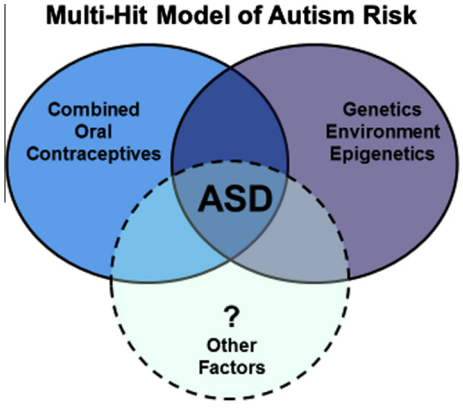

Fig. 1. Multi-hit model of autism risk. The model proposes that Autism Spectrum Disorders (ASD's) can arise from a coincidental occurrence of several physiologic insults in a single individual. Specifically, the model hypothesizes that use of combined oral contraceptives (blue oval) confers risk for developing an ASD, when occurring in conjunction with a second (or more) additional risk factor. Known risk factors might include genetic, environmental, or epigenetic factors (purple oval). In addition, the presence of other unknown risk factors in the same individual might be necessary for development of an ASD (dashed circle).

Increased prevalence of ASD

Based on data from multiple studies, including the Centers for Disease Control and Prevention's (CDC) Autism and Developmental Disabilities Monitoring (ADDM) Network, the identified prevalence of ASD's in the United States has increased significantly in a short time period [3] (see Table 1).

The ADDM Network is made up of a group of programs that are funded by the CDC to estimate the number of children who have ASD and other developmental disabilities currently living in different parts of the United States. The goals of the network are to define the population of children with ASD, compare and

Table 1
Identified prevalence of autism spectrum disorder*.

Surveillance year	Birth year	Prevalence per 1000 children	This is about 1 in X Children
2000	1992	6.7	1 in 150
2002	1994	6.6	1 in 150
2004	1996	8.0	1 in 125
2006	1998	9.0	1 in 110
2008	2000	11.3	1 in 88
2010	2002	14.7	1 in 68

* Adapted from ADDM Network 2000–2010.

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