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The Case for Epidemiological Investigation of the Possible Link between Combined Oral Contraceptives and Autism Spectrum Disorder

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Abstract

It is now conservatively estimated that 1 in 68 children are diagnosed with ASD in the United States. So far, no definitive cause or contributing factors have been established to account for the increase in prevalence in ASD. Combined Oral Contraceptive (COC) use is one possible risk factor for the increase in prevalence that has been overlooked in the existing biomedical and epidemiologic literature. This hypothesis is compelling due to several considerations. As the prevalence of COC use has raised so has the prevalence of ASDs. As a category of agents there are specific documented mechanisms through which COCs can affect the oocyte and/or developing embryo. As COCs are taken deliberately, exposure occurs at pharmacologically effective concentrations. The possibility exists that the effects of COC use could intensify over generations due to transgenerational transmission of altered epigenetic programming, with continued exposure across generations imparting sensitivity to developing ASDs. Lastly, the specific demographic at risk, women who are likely to have children, is the exact demographic that is taking COCs. This article calls for epidemiological investigation into the association between COC use and ASD in offspring using the Norwegian Mother and Child Cohort Study and its subset the Autism Birth Cohort.

Keywords: Autism; ASD; Oral contraceptives; COCs; Birth control; Ethinylestradiol

Introduction

It is estimated that 1 in 68 children are diagnosed with ASD in the United States. Increasing awareness and the rapidly growing number of cases of Autism Spectrum Disorder (ASD) in the United States have caused national alarm, compelling scientists to search for clues about the causes and contributing factors of ASDs. A considerable number of explanations for the rise in prevalence of ASD have been offered and yet, causal factors for ASD are still inadequately understood. Scientists agree that ASD is a complicated disorder thought to be due to interactions between genes and the environment, but as yet, there is no known cause that explains the vast majority of ASD cases.

Combined Oral Contraceptive (COC) use is one possible risk factor for the increase in prevalence that has been profoundly overlooked in the existing biomedical and epidemiologic literature. Interestingly, as the prevalence of ASD has risen over the last fifty years, so has the prevalence of the usage of COCs and other modern hormonal delivery methods such as the vaginal ring injectables, implants, and patches. Usage of oral contraceptives in the United States has increased from 1 million women in 1962 to almost 11 million women today. Because COCs were created to mimic natural human hormones and disrupt endogenous endocrine function to inhibit pregnancy, there is reason for concern that the synthetic hormonal components may be causing the harmful neurodevelopmental effects that lead to the increase in ASDs.

Unfortunately, the association between oral contraceptive use and the increase in prevalence of ASD has not been thoroughly investigated. A systematic review of the PubMed database, Annual Review database, and Google search revealed an absence of biomedical and epidemiologic literature on the link between oral contraceptive use and autism. Several different combinations of key words were used to search for articles including: oral contraceptives, combined oral contraceptives, OC, COC, the Pill, autism, autism spectrum disorder, ASD. The absence of scientific information led to the research and development of the hypothesis that oral contraceptive use is an overlooked risk factor for the development of ASD in offspring.

One aim of this article is to provide background information that supports the hypothesis that oral contraceptive use is a risk factor for the development of ASD in progeny. In addition to the temporal correlation between use of oral contraceptives and increased prevalence of ASD, it argues that the synthetic hormone Ethinylestradiol (EE2) is an endocrine disrupting chemical capable of causing harm to the endocrine system and to progeny. Because exposure concentration is directly administered and by definition pharmacologically effective, the article explores potential timing of the endocrine disruption and suggests that harmful exposure could happen to the follicle or oocyte before fertilization, to the embryo after fertilization, and/or to future generations due to both transgenerational transmission of modified epigenetic programming and the continued exposure across generations.

An additional aim is to suggest and outline further epidemiological investigation into the association between maternal use of COCs and risk of ASD in children. It proposes using a large cohort like the Norwegian Mother and Child Cohort Study (MoBa) and its subset, the Autism Birth Cohort (ABC), as a basis by which the hypothesis could be tested effectively, affordably and in a rapid time-frame. MoBa is an ongoing long-term prospective cohort study of 110,000 pregnant Norwegian women and their children [1]. The ABC, a MoBa sub-set, was created to address the natural history of ASD and to investigate genetic and pre- or perinatal environmental factors for ASD causation [2]. The ABC also studies the interplay between genes and

environment. More than 108,000 children are constantly screened through questionnaires, referrals and a national patient registry.

COCs are a Potential Risk Factor for ASD

One of the compounds found in COCs is the synthetic estrogen called Ethinylestradiol (EE2). EE2 is a known Endocrine Disrupting Compound (EDC) capable of causing harmful effects to the endocrine system and to progeny [3-7]. Recent studies have shown that EDCs have the potential to do harm by adversely affecting the sensitive hormonal pathways that regulate reproductive function in a variety of species including humans [8-11]. The National Institute for Environmental Health Sciences (NIEHS, 2014) reports that EDCs may disturb the endocrine system and produce adverse developmental, reproductive, neurological, and immune effects in humans and wildlife. The NIEHS [12] indicates that research also shows that the highest risk of endocrine disruption occurs during prenatal and early postnatal development when organ and neural systems are being created. Humans might be exposed to EDCs through foods, beverages, pesticides, and cosmetics, but the case with EE2 is particularly striking because EE2 exposure in female humans occurs at a pharmacologically effective dose, administered every day, for extended periods of time. Moreover, since COCs were developed to mimic natural human hormones and disrupt endogenous endocrine function to prevent pregnancy, there is reason for concern that the EE2 component may be causing the harmful neurodevelopmental effects that lead to the increase in ASDs.

Hormones and their signaling pathways are essential to regular functioning of all tissues and organs in invertebrate and vertebrate species. Normal communication of the endocrine system can be disrupted by exogenous substances like EDCs in three different ways [12]. First, they can mimic a natural hormone and lock onto a receptor within the cell. The disrupter may give a stronger signal than the natural hormone or give a signal that happens at the wrong time. Second, substances can bind to a receptor within a cell and prevent the appropriate hormone from binding. This causes the normal signal to fail to occur and the body to fail to properly respond. The third way that a disruptor can negatively influence normal communication is that it can interfere with or block the way natural hormones and receptors are made or controlled. If the endocrine disruptor inhibits or stimulates the endocrine system, then decreased or increased amounts of hormone may be produced. Even small amounts of a disruptor may have a detectable effect [12]. And, even small amounts of endocrine disruptor chemicals delivered over time may have a cumulative effect [12].

EDCs have the same attributes as hormones [10]. They possess the ability to be active at low concentrations and like endogenous hormones, they are able to bind to receptors at very low concentrations [10]. Therefore, endocrine disruption can occur from low-dose exogenous hormone exposure or from hormonally active substances that interfere with receptors for other hormonally assisted processes. In addition, some EDCs are able to interact with multiple hormone receptors concurrently. They can work simultaneously to create additive or synergistic effects not observed with the individual compounds [10]. EDCs can act on a number of physiological processes in a tissue specific manner. And, as with endogenous hormones, it is often not feasible to extrapolate low-dose effects from the high-dose effects of EDCs [10]. Thus the mimicry of E2 and the information that such compounds can cause harmful effects on reproduction and the endocrine system provide mechanistic evidence that EE2 found in oral contraceptives may adversely affect the oocyte or developing embryo.

The World Health Organization recently issued the State of the Science of Endocrine Disrupting Chemicals 2012. In the comprehensive report, they comment on the point that we are just beginning to comprehend the mechanisms through which EDC exposure can modify the development of specific tissues that lead to increased vulnerability to diseases and disorders later in life [10]. In addition, we are just beginning to appreciate the essential roles that hormones play in neurodevelopment, including the neuroendocrine circuits that control physiology and sex-specific behavior that could result in behavioral and psychiatric conditions and disorders. However, it is known that early development, when hormones are regulating cell changes to create tissues and organs, is a sensitive time-frame for EDC action. An EDC that is present during developmental programming could upset normal hormone levels and lead to changes in development. These developmental modifications may or may not be evident at birth. They may show up later in life.

Exposure timing is of interest and importance. When does exposure to the endocrine disruptor EE2 in COCs disrupt the endocrine system? COC's were designed to disrupt the endocrine system throughout the month to keep a woman from becoming pregnant. During this disruption, what happens to follicles or the oocytes? As they are repeatedly exposed to the compound EE2, does this modify or change either or both of them? It is conceivable that with contraceptive EE2 exposure alteration in follicles or oocytes occurs, since data from animal models suggest that hormonal compounds do cause changes in follicular, [13,14] embryonic, and fetal development [15,16]. Hormonal compounds are also found to exert long-term effects on endogenous sex hormone levels [17,18]. Does repeated exposure to the synthetic hormone EE2 cause harmful changes to human follicles and/or oocytes as well? If so, in this case, the adverse effects of disruption would happen even before fertilization occurs.

COCs are reported to be 99.9% effective if used properly (Planned Parenthood, 2014). Less than 1 out of 100 women will get pregnant each year if they always take the pill each day as directed. Moreover, about 9 out of 100 women will get pregnant each year if they don't always take the pill each day as directed (Planned Parenthood, 2014). Combining these mathematical considerations, out of the 11 million U.S. women using COCs, up to 100,000 may get pregnant while continuing to take EE2 after oocyte fertilization. Those embryos would then be directly exposed to pharmacologic doses of EE2. It is conceivable that exposure to EE2 could adversely affect the developing embryo. And, the time-frame for COC wash-out is not clear even after cessation of contraceptive ingestion [19]. Even if there is full drug wash-out, persisting toxicological, genetic, and epigenetic effects are possible. Harmful EE2 exposure could then occur after fertilization and during early development of the embryo.

There is also the potential for some EDCs to produce effects that can cross generations, meaning that exposure may affect not only the development of the first offspring but also their offspring over generations [10,20-22]. This means that effects of EDCs could increase over generations due to both transgenerational transmission of the modified epigenetic programming, and the continued exposure across generations possibly imparting disease sensitivity later in time. Michael Skinner's laboratory works on the epigenetic effects of EDCs. Using rodent models, they study how endocrine disruptors instigate epigenetic inheritance of diseases. Skinner [21] points out that endocrine disruptors are one of the largest groups of specific toxicants

shown to disturb normal endocrine signaling and to promote epigenetic transgenerational inheritance of disease susceptibility. Thus, the ability of ancestral exposures to promote disease susceptibility greatly complicates the possible threat to the health of subsequent generations, through exposure to EDCs such as EE2 [23].

The Need for Epidemiological Study into the Association

The WHO [10] suggests that exposed animal studies impart essential information on exposure levels, early effects, and clinical neurotoxicity of EDCs, because the mechanisms, fundamental effects, and outcomes of exposure are frequently analogous to those found in human beings.

Animal studies provide the opportunity to control exposure dose, environmental conditions, and genetic factors in a precise way. However, when considering these data the problem exists of having to extrapolate data from animal to human populations. Certain human disorders involving high-level cognitive function, like autism, may not occur in animals. It is also difficult to extrapolate animal doses to human doses due to differences in pharmacokinetics and pharmacodynamics. Thus, different species vary in their pharmacologic and physiologic responses to exposure to the same drugs. Toxicologic studies are very helpful, and yet, uncertainty exists as to whether or not the animal findings can be generalized to humans.

In vitro systems, such as cell and organ cultures are also helpful but limited. Again, these are artificial systems and it is difficult to extrapolate from artificial systems to whole human organisms.

Overall, while animal studies of the effects of EE2 in animals clearly document direct adverse pharmacologic, physiologic, and toxicologic effects of that agent, the stipulations mentioned preclude being able to directly extrapolate from in vitro and in vivo animal studies to humans. Because of these limitations, conclusions as to whether or not a substance like EE2 found in COCs is a risk factor for developing ASD require observations in human populations. Since it is not ethically possible to randomize humans to harmful exposures, nonrandomized observations are necessary. Thus far, there has not been comprehensive research into the potential neurodevelopmental effects of oral contraceptive use on offspring.

One recent study considers various maternal early life factors associated with hormone levels and the possibility of having a child with ASD [24]. Lyall et al. [24] also point to the lack of thorough and complete research into the risks associated with pre-gravid oral contraceptive use. Lyall's [24] study from 2011 references three articles on similar topics from the seventies and one contemporary paper: Vessey, Torrey, Rothman, and Mucci [25-28]. None of these earlier studies investigated or established an association between COCs and ASDs. Although Lyall's [24] study reported no significant effect of oral contraceptive use prior to pregnancy in their statistically corrected data based on modeling population, their uncorrected data presented a trend toward an increased risk of autism in users of oral contraceptives. The results of this aspect of their investigation remain inconclusive and further research will either replicate their finding or provide new insight.

The need for human epidemiological investigation into the association between COC use and ASD is motivated by the firmly grounded hypothesis that COC use is a risk factor for ASD in offspring. In the realm of environmental risk factors this hypothesis is compelling due to several considerations. First, as a category of agents there are specific documented mechanisms through which COCs can affect the oocyte and/or developing embryo. Second, exposure concentration is directly administered and by definition pharmacologically effective. And, it may be of greater magnitude than other environmental exposures that largely occur through passive secondary mechanisms. The possibility exists that the effects of EE2 could intensify over generations due to transgenerational transmission of altered epigenetic programming and the continued exposure across generations possibly imparting sensitivity to developing ASDs. Lastly, the specific demographic at risk, women who are likely to have children, is the exact demographic that is taking COCs, specifically during child-bearing years ("first principles"). In addition, the possibility exists that careless use of the pill regimen (missing days) may allow embryos to be exposed to ongoing dosing of EE2.

Norwegian Mother and Child Cohort (MoBa) as an example

Further epidemiological investigation into the association between maternal use of COCs and risk of ASD in children is necessary. How would such a study proceed? It is compelling to consider, as an example, using a large cohort like the Norwegian Mother and Child Cohort Study (MoBa) and its subset, the Autism Birth Cohort (ABC), as a basis by which the hypothesis could be tested effectively, affordably and in a rapid time-frame. MoBa is an ongoing long-term prospective cohort study of 110,000 pregnant Norwegian women and their children [1]. Enrollment was from 1999 to 2008. The ABC, a MoBa sub-set, was created to address the natural history of ASD and to investigate genetic and pre- or perinatal environmental factors for ASD causation [2]. The ABC also studies the interplay between genes and environment. The cohort is used to assist discovery of biomarkers with potential to facilitate early recognition and treatment of ASDs. The ABC employs a significant, unselected birth cohort. Cases are prospectively determined through population screening. More than 108,000 children are constantly screened through questionnaires, referrals and a national patient registry.

While longitudinal population-based cohorts are often challenged with retaining participants and the continuous investment needed to launch and maintain a program until results are achieved, the ABC has some advantages that improve the likelihood of success. Emigration is less customary in Norway than in many other nations. Socialized medicine and national registries simplify capturing cases and facilitate follow-up on cases. Lastly, there is national perception of the cohort as a significant contribution to science and public health. All of these positive attributes of the MoBa and the ABC enhance the probability of an efficacious study.

This article calls for an epidemiological study that would investigate the association between COC use and the subsequent risk of ASD in offspring. One possible approach is illustrated using the Norwegian Mother and Child Cohort Study (MoBa) and subset, the Autism Birth Cohort (ABC). Available data through linkage of MoBa data with the Norwegian Prescription Registry and ABC data demonstrate the feasibility of estimating the risk and evaluating the association between COC use and ASD. There are several strengths to a study conceptualized and implemented along these lines. They are as follows: cohort design; population-based recruitment of participants; large sample size; the combination of screening, questionnaires and referrals; registry linkage for ASD cases; and linkage to the Norwegian Prescription Registry.

Study Population and Cohort Design

In recent years, there has been growing recognition that exposures and experiences before and during fetal life may have significant and long-lasting effects that might even last into adult life. Therefore, an appealing use of the cohort design is to employ long-term cohort studies of childhood health and disease. The MoBa, a nation-wide population-based pregnancy cohort, was begun in 1999 [1]. At the end of recruitment in 2008, 90,700 mothers, 72,100 fathers, and 108,500 children were enrolled. The last child included in the cohort was born in 2009. The MoBa is unique in that it is the only comprehensive population-based prospective cohort with available data necessary to explore gene-environment-timing interactions. It is also able to follow the course of neurodevelopmental disorders such as autism. The ABC is a model for exploring the role of genetic and environmental factors in ASD.

Measures of ASD

The data for ASD in the MoBa sub-set ABC already exist and are available. Potential ASD cases within the MoBa cohort are identified through four ways: screening questionnaires are administered at 36 months, 5 years and 7 years; professional referrals are made by the Norwegian healthcare system; self-referrals are obtained from parents; and connections are made with the Autism Database managed by the Norwegian National Institute of Public Health [2]. ABC also identifies individual's cases through the Norwegian Patient Registry. The ABC controls are randomly selected from participants in MoBa and then matched to potential cases by date of birth.

When children with ASD or potential ASD are detected through any of these four ways, they are invited to participate in a clinical assessment that includes highly reliable and valid research-standard instruments for diagnosing ASD. Assessments are made without knowledge of prior questionnaire responses. Instruments include the Autism Diagnostic Interview and the Autism Diagnostic Observation Schedule. Clinical diagnoses are derived from interviews, test results, and parental information. DSM-IV criteria based, the case definitions include Autistic Disorder (299.00), Asperger's Syndrome (299.80), and Pervasive Developmental Disorder Not Otherwise Specified (299.80) [2].

The registry includes ICD-9 codes used by Norwegian health services. ASD case definition of the ABC study includes Childhood Autism (F84.0), Atypical Autism (F84.1), Asperger's Syndrome (F84.5), Other Pervasive Developmental Disorder (F84.8), Pervasive Developmental Disorder, Unspecified (F84.9) [2].

Measures of COC Use

Measures of COC use are also readily available in the MoBa cohort. MoBa study participants were recruited from 1999 through 2008 in Norway [1] While scheduling a free-of-charge routine prenatal health check at 17–20 weeks of gestation, women were identified for eligibility. Before the scheduled ultrasound, women were mailed an invitation to join the study. Informed consent and enrollment took place at the ultrasound examination. About 42% of all pregnant women in Norway were invited to participate in the MoBa study. Of those invited, 39% consented to join the study. During enrollment, participants were given a self-administered questionnaire. From the questionnaire data, information was collected that included demographic characteristics, reproductive health history, medication history, disease history, socioeconomic status, and lifestyle factors. Self-administered questionnaires served as follow-up measures.

Data on maternal contraceptive use is available through MoBa by a linkage with prescription data from the Norwegian Prescription Registry (NorPD). The registry includes individual-level data on all prescribed and dispensed medications through pharmacies to non-institutionalized individuals in Norway. As of January 2004, Norwegian law insists that all pharmacies must provide electronic data for all dispensed prescriptions. Data quality measures are in place for assuring the NorPD is accurate and complete [29]. Contraceptive exposure is also characterized by type and route of administration: combination OC, progestin-only OC, vaginal ring, transdermal, injectable, implant and hormonal-based intrauterine device. They are also characterized by formulation.

Analysis

The main analysis concerns assessing the association between maternal use of COCs and no use of COC and the occurrence of ASD in the offspring. Never before have so many individuals taken such powerful drugs (COCs) of their own accord over such a prolonged period of time for an objective other than for the control or management of a disease. It is rational to question the potential developmental effects of COC use.

A sub-group analysis might explore the relationship between the route of administration and/or the formulation of the contraceptive and occurrence of offspring with ASD. Most combination birth control pills today contain between 20 micrograms (low dose pills) to 30/35 micrograms of EE2. However, there are some higher-dose pills that do contain up to 50 micrograms and there is one low dose pill, Lo Loestrin that only has 10 micrograms of EE2. Non-oral hormonal contraceptives such as patches and implants also contain EE2 at different doses. The NuvaRing steadily releases 15 micrograms of EE2 daily into the body over a period of 21 days. The Ortho Evra Patch delivers 20 micrograms of EE2 each day for a duration of 7 days, yet because of the way the body absorbs this hormone, the overall exposure to the EE2 in the patch is comparable to a daily 50 micrograms birth control pill. Since there are many formulations and dosage is not consistent, sub-group analysis would seem to be necessary.

Another sub-group analysis might investigate contraceptive exposure during the distinct developmental periods of susceptibility. Timing of contraceptive exposure can be derived from dispensed prescription data and from information from the mother's questionnaire about the use of medicine. It can then be characterized into discrete periods of hormonal contraceptive exposure according to last date of use before conception. In a recent study, Maternal hormonal contraceptive use and offspring overweight or obesity, Jensen [30] created an exposure window period for each hormonal contraceptive filled by employing the date that the prescription was filled and the number of dispensed daily doses. This type of analysis might provide information about when endocrine disruption occurs. However, due to the limited generations involved in the study, addressing the issue of the transmission of modified epigenetic programming is problematic.

Potential Confounders

Factors that may influence a potential association between maternal COC use and the development of ASD in children should be taken

into account. Parental age, parental education, folic acid supplementation, maternal illness and medications, smoking, COC formulations, and reliability of ASD subtype diagnoses need to be considered and adjustments made to the analysis.

A trend has been observed over the years that parents are waiting longer to begin having children. Some scientists wonder if being older is a risk factor for having a child with ASD. Recent epidemiologic studies have found conflicting results [31-36]. Therefore, parental age may be considered a confounder.

A positive association with ASD and parents with higher education has led some scientists to propose higher status as a risk factor [37]. Scientists question whether the increase is due to a true increase or identification disparities. Two questions arise. Do educated parents have a disproportionate influence on autism awareness, or does the risk of autism increase with a higher socioeconomic status? And, is a knowledgeable and determined parent of a child with ASD more likely to obtain an informed diagnosis? Since higher education and social status are still being questioned, education might be a cofounder and should be adjusted.

Studies have reported that supplementation with folic acid around the time of conception decreases the risk for the development of neural tube defects in children [38,39]. And, daily supplementation of folic acid has been recommended for women planning to become pregnant. This led Surén et al. to investigate the association between maternal use of folic acid and the development of ASD in offspring. Since Surén's main finding was that maternal use of folic acid supplements was associated with a lower risk of developing autism in offspring, folic acid supplementation should be accounted for and analysis adjusted.

Maternal illness and medication use during pregnancy is readily obtained from questionnaires and from the Medical Birth Registry. These should be accounted for in the analysis. Adjustments for maternal illness should be made for the presence of anxiety, depression, diabetes, epilepsy, and preeclampsia. Separate adjustments need to be made for use of medications for treating these illnesses during pregnancy. In addition, adjustments should be made for use of any hormone therapy and if in vitro fertilization was used to become pregnant. Of note, previous scientists who have used the cohort found that none of the adjustments for maternal illness and medication made any significant difference [40]. They concluded that this may be a reflection of the fact that pregnant women in the cohort were mostly healthy and therefore, had minimal medication use during pregnancy.

Maternal smoking should also be taken into account. It is well known that smoking during pregnancy affects the baby's health. The nicotine, carbon monoxide, and other poisons inhaled from a cigarette are carried through the bloodstream and go directly to the baby. Smoking while pregnant lowers the amount of oxygen available to the mother and to the growing baby. Smoking increases the baby's heart rate. It increase the chances of miscarriage and stillbirth. Smoking increases the risk for babies to be born prematurely and/or born with low birth weight. Smoking is known to increase the risk of developing respiratory problems. It also increases the likelihood of birth defects. Consequently, cases where the mother smoked during pregnancy need to be adjusted in analysis.

Another possible confounder is that different delivery methods and different formulations of COCs were prescribed. There are many different estrogens and even more progestins available on the market today. And, there are many ways to combine them into contraceptive formulations. Exposure data is available and can be characterized by method of deliver and formulation type. Jensen [30] characterized hormonal contraceptives according to the Norwegian guidelines found in the Anatomical Therapeutic Chemical Classification System. Methods of delivery include COCs, progestin-only oral contraceptives, vaginal ring, transdermal, implant, injectables, and hormonal intrauterine device. All hormonal contraceptives with an estrogenic agent contain EE2. These include COCs, the vaginal ring, and the transdermal contraceptive. Different progestin types used alone or in combination with EE2 should also be characterized. Data should be adjusted for different routes of administration and for different formulations.

Reliability of ASD subtype diagnoses may present a limitation. Some studies report that clinical distinctions among categorical diagnostic ASD subtypes are not reliable, even across sites using standardized diagnostic instruments with well-documented fidelity. In using ASD diagnosis data from the ABC cohort, Surén et al. report a limitation to their study was the reliance on subtype diagnosis of ASD. They point out that in the United States ASD subtype diagnoses have not been found reliable across assessment sites. However, their own validation of registry diagnoses indicated that even though the subtype diagnoses were less reliable than for ASD as a whole, there was still a high level of agreement for autistic disorder diagnoses, which was their primary interest. Considering the difficulties with reliable diagnoses of ASD subtypes, this should be considered a potential confounder.

As pointed out by Surén and colleagues, the main limitations to epidemiologic studies of ASD prevalence in the ABC are ascertainment and sampling bias of ASD cases in the cohort. The authors of this prior study attributed most of the discrepancies in their study to reliance on subtype diagnoses of ASD and lower response rates among parents with severely autistic children. The article also pointed out that prevalence in ASD is lower in the cohort population than the prevalence reported from the United Kingdom and the United States. However, they found that the ASD prevalence is also lower in the general population in Norway. Of note, women in Norway prefer the IUD (30%) to oral contraceptives (21%) [41,42].

Conclusion

This article presents background information that supports the hypothesis that oral contraceptive use is a risk factor for the development of ASD in progeny. It argues that the synthetic hormone ethinylestradiol (EE2) is an endocrine disrupting chemical capable of adversely affecting sensitive hormonal pathways that regulate reproductive function and harmfully affecting offspring. The article examines potential timing of the endocrine disruption and suggests that harmful exposure could happen to the follicle or oocyte before fertilization, to the embryo after fertilization, and/or to future generations due to both transgenerational transmission of modified epigenetic programming and the continued exposure across generations. Considering the increased prevalence in ASD and the lack of scientific investigation into the association of oral contraceptive use and ASD, this article calls for further epidemiologic study.

This article also illustrates one approach to executing an epidemiological assessment of the COC hypothesis of ASD prevalence. This type of study will provide the means to test for a positive association between maternal COC use and the development of ASD in offspring. The strengths to such a study are many. They include the following: cohort design; population-based recruitment of

participants; large sample size; the combination of screening, questionnaires, and referrals; existing databases; registry linkage for ASD cases; and linkage to the Norwegian Prescription Registry. There is also the ability to compare the study sample with a nationwide sample.

There are some weaknesses to such a proposed study. Confounders exist, ethnic subgroups might not be representative of all relevant populations, and there may be gaps in the data. Differences in diagnoses might reflect regional variations. It may be the case, for example, that in some regions, children diagnosed with ASD receive different services than others with ASD diagnoses. Or, it may be that in different regions the diagnosis of an ASD might be avoided as more stigmatizing than diagnoses of PDD-NOS or Asperger Syndrome. However, its feasibility, affordability, and potential to address the effects of COC use on progeny, make for a compelling example of a first step in testing the COC hypothesis.

The main analysis of the proposed study is concerned with assessing the association between maternal exposure to COCs as compared to no COC exposure and the occurrence of ASD in the offspring. If, as hypothesized, the proposed study establishes a link between COCs and ASD, this information would be invaluable to women of child-bearing age evaluating birth control options. Considering the increased prevalence of ASD this information has a sense of urgency for those women and their progeny.

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