

A Scoping Review of Excessive Prenatal Ultrasonography as a Potential Risk Factor for Autism

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Abstract: For the past several decades, abdominal/pelvic prenatal ultrasonography (P-USG) has been the most significant technology used in obstetrics. There has been a tremendous increase in use throughout the world and there have been many improvements in the technology used. However, there are aspects of the technology such as frequency, exposure time, thermal and cavitation exposure indices, and increased acoustic output of the ultrasonic waves that possibly could be harmful to the embryo/fetus. In particular, prolonged exposure may increase susceptibility to Autism Spectrum Disorder (ASD). Along with the increasing use of P-USG, there has been a similar increase in the incidence of ASD. The diagnosis of ASD has been found to be more common in geographic areas with a more affluent ethnicity, high socioeconomic status, and high parental education. These are also areas where prenatal ultrasonography is readily available and affordable. Given that there are biophysical risks from P-USG, especially in non-medical settings, P-USG may emerge as a possible risk factor for ASD. The past history of radiography provides a historical perspective: the predominant past opinion years ago was that exposure to X-rays during pregnancy caused no significant risk to a fetus. However, the association between X-ray exposure and childhood leukemia was only established 40 years after X-ray use began. This review focuses on the literature which supports the generation of the hypothesis that excessive P-USG usage may be a factor in the etiology of ASD.

Keywords: Autism, Autistic Spectrum Disorder, Children, Behavior, Ultrasonography, Prenatal, Pregnancy

1. Introduction

The prevalence of autism spectrum disorder (ASD) has been rising markedly since the Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA) first began recording its prevalence in 1988. [1] Although genetics plays an important role, especially regarding risk, there is no definitive cause for most cases of ASD. However, the parallel increase in the use of prenatal ultrasonography (P-USG) use and the increasing prevalence of ASD is concerning enough to evaluate and determine possible connections between them. Possible biological plausibility or correlation between the two has also not been well-explored. The aim of this review specifically focuses on excessive P-USG usage and the possible development of ASD.

2. Literature Review

2.1. Brief History of P-USG

Ultrasonography was first used in the field of obstetrics/gynecology in 1958. [2] Bang and Holm [3] in 1968, reported identifying a fetal heartbeat at ten weeks of gestation. In the early 1980s, an “ultrasonic boom” [4] ensued because of the introduction of portable and affordable ultrasonic real-time devices that facilitated P-USG examinations in doctors’ clinics worldwide. [5]

Ultrasonography involves pressure waves that are greater than 20 kilohertz in frequency to make ultra-oscillating sound waves that penetrate tissue as mechanical energy. [6-8] The contact between the ultrasonic wave and the scanned tissue produces the following biophysical effects: thermal effects,

cavitation (bubbles), and acoustic pressure flow in body fluids. The intensity of an ultrasonic wave (i.e., the acoustic power per unit of area) is measured in milliwatt per square centimeter (mW/cm^2). The highest exposure intensity within the beam (i.e., spatial peak) is averaged over the time of exposure (i.e., temporal average) and is named the spatial peak temporal average. [7-11]

After ultrasound manufacturers developed output display standard (ODS) biosafety measures by displaying levels on the screens of the ultrasound devices, the Food and Drug Agency (FDA) in 1992 deregulated the acoustic output levels of clinical ultrasound systems. These new devices have higher acoustic output, produce better images and often improve diagnoses for patients. Ultrasonic acoustic output levels, emitted by the transducer for fetal, neonatal, and pediatric imaging were increased from $94 \text{ mW}/\text{cm}^2$ in 1986 [12] to $720 \text{ mW}/\text{cm}^2$ in 1992, [13] including the peak exposure through the mechanical index. These changes enhanced the potential biophysical effects exerted on the embryo and fetus. [4, 6, 11, 14]

On every newer device (since 1992) the ODS displays are composed of two indices to alert the end-user of temperature rise (thermal index) and mechanical impact. The soft tissue thermal index depends on three factors: transducer opening (i.e., beam width), beam direction, and scanning mode. The ultrasonic beam can produce heat [6, 7, 11] and cause hyperthermia [6-10] to an embryo/fetus. The mechanical or cavitation index occurs because of a more intense beam forming bubbles in soft tissue; if severe, this mechanical change may cause chemical or physical injury in tissues. [14] The acoustic output leads to radiating forces flowing in fluids which can also cause strain on tissues. [15] The responsibility of the ultrasonographer is to keep these indices as low as possible and to maintain the acoustic pressure as low as reasonably achievable (ALARA). These safety regulations, however, are clinician- and end-user dependent. [9, 10, 13] Hence, the FDA recommended that ultrasound scanning be limited for valid medical indications and conducted by professionally trained end-users. [12, 13] As this is a recommendation, there is no law in the United States or most countries that requires these.

In the 1980s, the first diagnostic ultrasound imaging devices evolved into using digital two-dimensional (2D) arrays. This advancement was followed, in the 1990s, by real-time processable three-dimensional (3-D) and four-dimensional (4-D) arrays, which is 3-D visualization that also captures motion. Both 3-D and 4-D arrays require an increase in the dwell time. [16]

In addition to the prolonged dwell time, Doppler ultrasonography, whether pulsed or color overflow, elevates the thermal index. [17]

2.2. Brief History of ASD

In 1943, the child psychiatrist Kanner [18] was the first to characterize autism as extreme social isolation and intolerance for change; he used the term “auto,” meaning “self” in Greek, to describe “early infantile autism.” Kanner also emphasized the rarity of infantile autism with 150 cases per 20,000

“troubled children” observed over a 30-year career.

In 1944, Asperger [19] described autistic-like behavior in young boys with decreased social and communicative interactions combined with ordinary intelligence and language attainment. In 1966, an epidemiological survey in the County of Middlesex, England by Lotter [20] revealed that the prevalence of “autistic” cases was 4.5 per 10,000 population and was more common in boys.

In 1970, Treffert [21] from the state of Wisconsin in the United States published a 5-year study (conducted from 1962 to 1967) that investigated the prevalence of infantile autism, which was rare at a prevalence of 0.7 cases per 10,000 population. In the Treffert study, the ordinal position of the autistic child was not the first-born male. The total prevalence of infantile autism in addition to childhood psychosis and psychotic disorders with brain damage was 4.8 cases per 10,000 population, which was similar to Lotter’s figures of prevalence rates in England.

2.3. Recent Prevalence of ASD

ASD has undergone various diagnostic modifications; [22-27] however, the prevalence of ASD grew exponentially and globally within the last 40 years. [28-53]

In 2010, Baxter et al. [54] estimated the prevalence of autism in the Global Burden of Disease Study as 52 million. In 2016, Vos et al. [55] revised the estimate to 62 million ASD cases, which was an increase of 10 million ASD cases worldwide in 6 years.

In comparing the two studies of Kogan et al. the estimated prevalence by parental report of currently diagnosed ASD in the 3–17 years age group was 1 in 91 in 2007. [56] This prevalence increased to 1 in 40 in 2016. [57]

Over the course of the past two decades, the increase in ASD prevalence has been controversial; some investigators [51] conclude that the observed increase in ASD may have been mainly related to “diagnostic shifting” and improved professional and public education and awareness of autism, whereas other investigators state that the increase in ASD is primarily because of increased referrals and earlier diagnosis of ASD. [52]

Recent research has shown that more developed countries [58] and higher socioeconomic populations [59] have a greater prevalence of ASD. A study from California reported that ASD is associated with higher parental education. [60] From 2002 to 2010, the CDC annual surveillance revealed unaltered racial and ethnic variances in ASD prevalence; white children maintained the highest prevalence whereas Hispanic children remained the lowest. [61] Likewise there were higher usage of ultrasonic examinations in more affluent populations with higher health insurance coverage. [59]

3. Results

3.1. Prenatal Ultrasonography and ASD-Evidence for Possible Link

Although an “ultrasound boom” [62] coincided with an

“autistic epidemic,” [46, 63, 64] causation between the two has yet to be investigated completely. Some research on the correlation between ASD and P-USG however has been done.

In 2010, in a retrospective American study of children born from 1995 to 1999, Grether *et al.* [65] found that ultrasonic exposure in the second trimester of pregnancy was not a risk factor for ASD. In 2012, Stoch *et al.* [66] from Australia examined an existing controlled study to evaluate the correlation between childhood ASD diagnosis and randomized prenatal ultrasonic exposure. Of 2,834 randomly selected single pregnancies, 1,415 pregnancies underwent one ultrasonic scan at 18 weeks of gestation whereas 1,419 pregnancies underwent several second- and third-trimester scans at 18, 24, 34, and 38 weeks. ASD rates did not show a significant variation between a single second-trimester scan versus several ultrasound scans in the second and third trimesters.

Carlsson *et al.* [67] from Sweden analyzed the frequency of ASD in 30,000 children born from 1999 - 2003. In the study, 14,726 single pregnancies were randomly exposed to one ultrasonic scan at 12 weeks of gestation, and 14,596 pregnancies were exposed to several ultrasonic scans at 18, 24, 34, and 38 weeks of gestation. There was no significant difference in the ASD occurrence between early and late P-USG exposure.

Despite these negative studies from the past, there have not been any recent studies that have studied outcomes from the more powerful P-USG devices that have been developed in the last two decades. In addition, mainly due to current proper obstetrics practice, there has not been published research on the incidence of ASD in large populations where no P-USG was done during the pregnancy.

Recently, however, in 2013, World Federation for Ultrasound in Medicine and Biology, [68] International Society of Ultrasound in Obstetrics and Gynecology, Asian Federation Societies of Ultrasound in Medicine, American Institute of Ultrasound in Medicine (AIUM), British Medical Ultrasound Society, and European Federation Societies for Ultrasound in Medicine and Biology agreed on the safety and prudent use of P-USG by applying the following conditions:

- Limit fetal exposure time.

- Restrict pulsed Doppler ultrasound use to clinically required indications.

- Maintain the thermal index to less than 1.

- Use as short as possible exposure time (no longer than 5-10 min), and never exceeding a total of 60 minutes. [13, 68]

In this statement, the acoustic output threshold was also defined; therefore, the AIUM and other societies incorporated the “as low as reasonably achievable” (i.e., ALARA) principle in its guidelines to monitor and maintain the acoustic output. [69-72]

3.2. The Triple Hit Hypothesis

The severity of ASD varies from mild to severe. Casanova explains this spectrum in the “triple hit” hypothesis [73, 74] wherein the development of autism is determined by the different interaction of three factors: the vulnerable stage of

brain development, genetic susceptibility, and environmental impact, especially during the first trimester. Williams and Casanova [74] hypothesized that the severity of ASD depends on the timing, duration, and intensity of P-USG scanning to the embryo/fetus.

In July 2016, Webb *et al.* [75] retrospectively analyzed a modification of Casanova’s hypothesis by analyzing a possible association between ASD severity and P-USG exposure within the first trimester of pregnancy in fetuses genetically predisposed to ASD. Genetic predisposition was determined based on the presence or absence of ASD-associated copy number variations (CNVs) with structural duplications or deletions of deoxyribonucleic acid (DNA) base pairs in the genome sequence. [76]

The results of the Webb *et al.* [75] study supported the hypothesis that male ASD children with CNVs, who were exposed to first-trimester ultrasound, had a considerably reduced non-verbal intelligence quotient and more repetitive behaviors than male ASD children with CNVs without ultrasound exposure. It also demonstrated that first-trimester P-USG exposure influences the outcome diversity in ASD children, whether CNVs were present or not. This variation was not associated with social affective impairment but increased parental reports of repetitive behaviors. The study suggested that the diversity in ASD symptoms may partially result from ultrasonic exposure during early prenatal development in children with particular genetic susceptibilities.

The AIUM Bioeffects Committee [77] responded to Webb’s [75] study, by emphasizing that the study results did not determine a causal relationship between ultrasound use and autism. It advocated that P-USG can be safely performed by qualified sonographers and clinicians for valid medical causes, and P-USG exposure can be reduced when the ALARA principle is applied. In this response to the Webb study no data or other information was provided to definitively refute the study’s findings or to provide data about how often ALARA is followed.

3.3. Safety of P-USG

Biosafety studies of P-USG on the embryo/fetus have been controversial, and the studies can be categorized into advocates, [69, 71, 78, 79] neutralists, [6, 80, 81] and questioners. [82-83] Abramowitz [11, 78, 79] highlights the positive safety record reports of P-USG on the human fetus and indicates that no scientific studies to date have shown any resulting fetal impairment. Additionally, the AIUM and ACOG have issued several reports on the prospective biological adverse effects of P-USG that have assured its safety. [68-71]

Brightness modulation (B-mode) scanners, used in the mid-1990s, are the source of the prevalent safety verification of P-USG. [11, 66, 80, 81] The new devices such as pulsed Doppler, color flow, or scanners produce 10- to 15-fold higher acoustic outputs than those of the earlier 1990s scanners; however, there are only a few epidemiological biosafety studies on the use of these new devices. [80, 82, 83]

Left-handedness, speech delays, and dyslexia have been found to be possible P-USG associated neurological findings. [81-83] The hypothesis for these is that the P-USG generated heat may raise the maternal core temperature. Thus, thermal heat cannot dissipate due to the lack of poorly developed blood circulation in the embryo/fetus, respectively, inactivating fetal enzymes. [83]

A survey of the FDA acoustic output data was grouped into three time periods: 1984-1989, 1992-1997 and 2005-2010. The survey revealed a chronological increase in ultrasonic energy power and in Doppler mode utilization in fetal ultrasonic scanning. Doppler modes produce a significant rise in bone thermal index compared to the B-mode. Two ultrasonic factors affect tissue heating-mainly the ultrasonic energy output but also the higher mean frequency of the transducer which penetrates and is absorbed by the tissue resulting in augmented heating. [84]

A case-controlled study was conducted by Rosman et al. [85] with three groups of patients: ASD; developmentally delayed; and neurotypical. This study showed a higher mean ultrasonic penetration rate in the ASD group in the first and second trimester, with no statistical difference of other ultrasonic variables. The depth of tissue penetration can be recorded and counted on the P-USG image, however, how the depth of tissue penetration was calculated continues to be controversial.

Ultrasonic devices have calipers that are regularly used to improve image resolution at the expense of tissue penetration. Rosman et al. showed that in the first trimester an increase of 0.9 cm in the mean depth of ultrasonic penetration was observed in the ASD group compared to both the neurotypical and developmentally delayed groups. The higher mean depth of penetration denotes that greater than expected heat dissipation occurred at 3.5-megahertz transducer frequency and has affected fetal neural tissue development in ASD patients. [103-105]

Ten years after the implementation of the ODS (the standard device display), a Swedish assessment of display use competence [86] revealed that only 33% of daily P-USG end-users could comprehend the mechanical and thermal indices, 28% were aware of the location of safety indices on their screen, and merely 22% knew how to modify the energy output on their machine. The inadequate knowledge of end-users of ultrasound devices of the biosafety indices or even their display screen appearance is widespread among medical professionals in many countries. [87-90]

In some locations throughout the world, the current clinical practice is to scan all pregnant women who have low- or high-risk pregnancies at every prenatal clinic visit, which may amount to 10 scans per pregnancy. [11, 79, 80]

Perhaps much more worrisome is the proliferation of companies that provide souvenir or keepsake fetal ultrasounds. This has expanded into a major industry and the ultrasounds are conducted by nonmedical personnel. [91-94] The FDA [95] and the European Committee for Medical Ultrasound Safety, [96] strongly deter this nonmedical practice. Despite these warnings, there has not yet been a

legal ban created in most countries to stop this likely very risky practice.

4. Discussion

In 1966, before the advent of the first portable sonogram devices for P-USG, the incidence of ASD was 3 to 4 patients per 10,000 population. [20] By 2005, although various diagnostic criteria were implemented, the ASD incidence had increased to 30–40 patients per 10,000 population. [97]

The literature review that was done for this report demonstrated two facts- there has been both an increase in the use of P-USG and an increase in ASD. This current study did not do any correlation analyses as they have been done before with mixed results as noted before. There have been numerous reports of correlations between different situations (paternal age) or environmental factors, such as pesticide use. [98] None of these correlation studies, especially those about environmental factors, have found them to be direct causes of ASD. However, the history of one medical procedure should serve as a warning: the association of radiographic imaging during pregnancy and later childhood leukemia was only established by MacMahon in 1962– forty years since the beginning of radiographic imaging. [99]

As recently as 2013, results from the evaluation of randomized data of P-USG usage from insurance sources in the United States revealed an average of 4–5 prenatal scans per pregnancy with a 30%–50% increase in the utilization rate. [100] This data, however, does not include information about the number of customers who received “keepsake” ultrasounds from private un-regulated companies or in what trimester these scans were done.

Based on the findings from this review, the authors recommend that un-regulated P-USG scans be banned and for those medically indicated reasons, the ALARA principles should be followed by well-trained ultrasonographic technicians. The tendency to conduct a P-USG scan for every prenatal visit, which mostly involves low-risk pregnancies, is not medically indicated and is contrary to the American College of Obstetrics and Gynecology (ACOG) and AIUM safety guidelines. [70, 71]

A P-USG viability scan at 8–10 weeks of gestation should take a very brief dwell time. A second scan to evaluate morphology at 22–24 weeks of gestation ought to be as short as possible.

The medical history for all prenatal visits necessitates the acquisition of information regarding previous P-USG scans, and patients must be cautioned at these visits to avoid commercial ultrasounds. The maternal temperature should be recorded prior to and during especially if ultrasonic scanning time may be prolonged. [101] The mother should also be provided with appropriate information about risks and benefits and informed signed consent done before undergoing P-USG scanning. When ultrasonically scanning the patient, the ultrasonographer must be required to monitor and to document the number of scans, the thermal and mechanical indices, the acoustic output, and the dwell

time. There are also P-USG procedures that should be used only on rare occasions because there are now better alternatives. For example, there are maternal blood biomarkers such as cell-free DNA [102] that are available to test for aneuploidy that can readily replace ultrasonic nuchal translucency examinations which may take up to 45 minutes to complete.

Acoustic output increased between 1991 and 2010 and peak negative pressure in B-mode imaging nearly doubled. Flint et al have shown that the automated ALARA usage sustains exceptionally low fetal acoustic exposure with improved imaging quality. As a result, the automation of the ALARA method is recommended to reduce the end-user impact on P-USG biosafety. [103]

Although ASD research has focused on genetics, medical, and environmental causes, and delineated multiple risk factors and associations; a definite biophysical etiology of ASD has yet to be identified. Studies have demonstrated excessive neuron production throughout the first two years of life in patients with ASD. It is hypothesized that this is due to an aberrant prenatal event in the uterine environment. [104-110] A maternal infection during pregnancy, often with fever, may alter brain development programming during embryonic/fetal life through maternal immune activation (MIA) dysregulation. [111]

The study by Rosman et al. [85] regarding the association of prenatal ultrasonography and ASD is an essential step in the research on the impact of P-USG usage on the fetus; however, case-controlled studies have limitations.

The possible long-term P-USG effects [6-8] on the embryo/fetus related to the acoustic output of new ultrasonic devices, [16, 17, 83, 84] its overuse in clinical practice [11, 79] and the commercial fetal video souvenirs [91-94] remain unknown.

Regulatory reforms should be implemented to improve professional end-users' knowledge of ultrasonic biosafety parameters and details about proper use of devices. It has been proposed but not universally implemented that all medical ultrasonographers must be licensed, and this license must be renewed periodically through complete training with a practical examination. [86-90] The popular practice of commercial fetal video scanning of pregnant women, [91-94] should also be regulated by laws for maternal and fetal safety.

Prenatal ultrasonography, an important obstetrical tool, is not a commercial fetal video keepsake and its usage needs to be medically indicated and restricted to safeguard the lives of our future children.

As the global coronavirus disease 2019 pandemic [112] has disrupted standard healthcare access and delivery, [113] there is further scope to conduct epidemiological studies with a natural control group.

5. Conclusion

Global collaborative obstetric/pediatric epidemiological multicenter studies to investigate the number and duration of P-USG performed during pregnancy and the prevalence rate

of ASD, is strongly advised and long overdue.

The coronavirus disease pandemic offers a unique opportunity to compare the last quarter births of 2019 with the natural control group of 2020, due to reduced frequency of hospital visits and likely decreased number of P-USG performed, and the prevalence rate of ASD in the two groups. Further research with these types of data sets may delineate a correlation between excessive in-utero-ultrasonic exposure and the development of childhood ASD.

Abbreviations

AIUM: American Institute of Ultrasound in Medicine
ALARA: as low as reasonably achievable

ADOS: Autism Diagnostic Observation Schedule ACOG: American College of Obstetrics and Gynecology ASD: autism spectrum disorder

CARS: Childhood Autism Rating Scale

CDC: Centers for Disease Control and Prevention CNV: copy number variation

DNA: deoxyribonucleic Acid

DSM: Diagnostic and Statistical Manual of Mental Disorders FDA: Food and Drug Agency

ICD10: International Classification of Disease, 10th Edition

P-USG: abdominal prenatal ultrasonography

MI: Mechanical Index

MRI: magnetic resonance imaging ODS: output display standard

TI: Thermal Index

All authors have approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interest Statement

The authors have no conflicts of interest relevant to this article to disclose.

Dedication

The authors dedicate this article to Professor Rabi Sulayman, MD, Prior Chair of the Department of Pediatrics, Chicago Medical School. He was loved by his patients and families and was an inspiration to all the health care workers he encountered.

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Biography

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