Is Excessive Prenatal Ultrasonography a Risk Factor for Autism? A Literature Review

Short Title: Excessive Prenatal Ultrasonography: Autism Risk Factor?

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Table of Contents Summary

The historic mutual rise of prenatal ultrasonography and autism spectrum disorder and their similarities and controversies in the literature are discussed in this review.

Scientific Abstract

For the past several decades, abdominal prenatal ultrasonography has been the most significant technology in obstetrics as a long-established practice. However, the frequency, exposure time, thermal and cavitation exposure indices, and increased acoustic output of the ultrasonic waves may be harmful to the embryo/fetus and might increase susceptibility to Autism Spectrum Disorder (ASD). The increase in the prevalence of ASD is associated with an affluent ethnicity, high socioeconomic status, and high parental education where prenatal ultrasonography is readily available and affordable. Enhanced biophysical adverse effects may link the analogous increase in prenatal ultrasonography and autism, and prenatal ultrasonography may emerge as a risk factor for autism. Radiography usage provides historical evidence for this fact: the predominant past opinion 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 excessive PUS usage and ASD development.

Public Abstract

Advancements in medical technology over the past several decades have made prenatal ultrasound more frequently accessible to expecting mothers during their pregnancy, especially for the affluent. A parallel development is the increase in autism diagnoses (Autism Spectrum Disorder, or ASD) in children of affluent families. There is a general lack of studies of the impact of prenatal ultrasound on fetuses, especially around varying attributes such as frequency, duration of exposure, and thermal and cavitation indices. There is also a historical precedent set, where
exposing fetuses to X-rays was not found to be harmful until it was linked to the development of childhood leukemia decades later. This paper seeks to establish a need to further study these attributes of prenatal ultrasound overuse and their possible impact on a developing fetus, with a special focus on the occurrence of Autism.

Keywords: autism; autistic spectrum disorder; children; behavior; ultrasonography; prenatal; pregnancy

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 There is no known cause for ASD; regardless, the coinciding rise in abdominal prenatal ultrasonography (PUS) use and prevalence of ASD is challenging to disregard. However, any possible correlation between the two has not been well-explored. This review focuses on excessive PUS usage and ASD development.

History of PUS

Ultrasonography was first used in the field of obstetrics/gynecology in 19582. Bang and Holm3 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 a small, portable, and affordable ultrasonic real-time device that facilitated PUS examinations in the 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.6,7 The contact between the ultrasonic wave and the scanned tissue produces the following biophysical effects: thermal effects, cavitation, 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/cm²). 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.6-10
After ultrasound manufacturers developed output display standard (ODS) biosafety measures by displaying their levels on the ultrasonic screens, the Food and Drug Agency (FDA) in 1992 deregulated the acoustic output levels of clinical ultrasound systems, which produced better images and therefore improved diagnosis for patients. Ultrasonic acoustic output levels, emitted by the transducer, for fetal, neonatal, and pediatric imaging were augmented from 94 mW/cm² in 1986¹¹ to 720 mW/cm² in 1992,¹² including the peak exposure through the mechanical index, which enhanced potential biophysical effects exerted on the embryo and fetus.⁴,⁶,¹⁰,¹³

The ODS is composed of two indices to alert the end-user of temperature rise 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 heat⁶,⁷,¹⁰ and cause hyperthermia⁶,⁹-¹¹ to an embryo/fetus. The mechanical or cavitation index occurs because of an intense beam forming bubbles in soft tissue; if severe, mechanical injury causes cavitation in tissues.¹⁴ The acoustic output leads to radiation forces flowing in fluids causing 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 are clinician- and end-user-dependent.¹¹,¹³ Hence, the FDA recommended that ultrasound scanning be limited for valid medical indications and conducted by the professionally trained end-users.¹¹,¹³,¹⁵

In the 1980s, the first diagnostic imaging devices evolved into a 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 with motion.¹⁵,¹⁶

History of ASD

In 1943, child psychiatrist Kanner¹⁷ was the first to characterize autism as extreme social isolation and intolerance for change; he used the term “autos,” 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\textsuperscript{18} 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 by Lotter\textsuperscript{19} revealed that the prevalence of “autistic” cases was 4.5 per 10,000 population and was more common in boys.

In 1970, Treffert\textsuperscript{20} of 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 firstborn 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.
Prevalence of ASD

ASD has undergone various diagnostic modifications; however, the prevalence of ASD grew exponentially and globally within the last 50 years, as presented in the following Table:

### Table: Global Prevalence of Autism from 1966 to 2016

<table>
<thead>
<tr>
<th>Country</th>
<th>Diagnostic Criteria</th>
<th>Year(s)</th>
<th>Prevalence per 10,000 Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahrain</td>
<td>DSM-IV</td>
<td>2013</td>
<td>4.3</td>
</tr>
<tr>
<td>China</td>
<td>DSM-V</td>
<td>2012</td>
<td>39</td>
</tr>
<tr>
<td>France</td>
<td>ICD 10</td>
<td>1997–2003</td>
<td>36.5</td>
</tr>
<tr>
<td>India</td>
<td>ADOS</td>
<td>2017</td>
<td>23</td>
</tr>
<tr>
<td>Israel</td>
<td>DSM IV</td>
<td>2008–2013</td>
<td>38–43</td>
</tr>
<tr>
<td>Korea</td>
<td>DSM IV</td>
<td>2014</td>
<td>220</td>
</tr>
<tr>
<td>Oman</td>
<td>DSM-IV</td>
<td>2010</td>
<td>1.4</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>DSM IV-CARS</td>
<td>2009</td>
<td>1.4–29</td>
</tr>
<tr>
<td>Sweden</td>
<td>Rutter-Gillberg</td>
<td>1983–2006</td>
<td>5.6–35.3</td>
</tr>
<tr>
<td>United Arab Emirates</td>
<td>DSM-IV</td>
<td>2007</td>
<td>29</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Rating Scale-ICD10</td>
<td>1966–2006</td>
<td>4.1–80.4</td>
</tr>
</tbody>
</table>

Note:
ADOS, Autism Diagnostic Observation Schedule; CARS, Childhood Autism Rating Scale; DSM-IV and DSM-V, Diagnostic and Statistical Manual of Mental Disorders (edition IV and V, respectively); ICD10, International Classification of Disease, 10th edition
Over the course of the past decades, the proposed ASD prevalence increase has been controversial; some investigators conclude that the observed increase in ASD may have been related to the “diagnostic shifting”, improved public education and awareness of autism, whereas other investigators state that the increase in ASD is because of high referrals and earlier diagnosis of ASD.

More developed countries and higher socioeconomic populations have a greater prevalence of ASD. This finding may be because of the higher usage of ultrasonic examinations in more affluent populations with higher health insurance coverage. A study from California reported that ASD is associated with higher parental education. 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. ASD consists of several diverse conditions; such that some autistic individuals are first identified in adulthood. In 2010, Baxter et al. estimated the prevalence of autism in the Global Burden Disease Study as 52 million. In 2016, Vos et al. 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. This prevalence increased to 1 in 40 in 2016.

Prenatal Ultrasonography and ASD

Although an “ultrasound boom” coincided with an “autistic epidemic,” correlation and causation between the two has yet to be investigated empirically. In 2010, in a retrospective American study of children born from 1995 to 1999, Grether et al. found that ultrasonic exposure in the second trimester of pregnancy was not a risk factor for ASD.

In 2012, Stoch et al. 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 rate did not show a significant variation between a single second-trimester scan versus several ultrasound scans in the second and third trimesters.

In 2016, Carlsson et al.\textsuperscript{65} 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 PUS exposure.

In 2013, World Federation for Ultrasound in Medicine and Biology, 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\textsuperscript{66} agreed on the safety and prudent use of PUS by applying the following conditions:

1. Limit fetal exposure time;
2. Restrict pulsed Doppler ultrasound use to clinically required indications;
3. Maintain the thermal index to less than 1;
4. Use as short as possible exposure time (no longer than 5-10 min), not exceeding 60 minutes.\textsuperscript{12,66}

The acoustic output threshold was 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.\textsuperscript{67-70}

The Triple Hit Hypothesis

ASD varies from mild to severe disease. Casanova explains this spectrum in the “triple hit” hypothesis\textsuperscript{71,72} 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 such as ultrasonic exposure primarily during the first trimester. Casanova hypothesized that the severity of ASD depends on the timing, duration, and intensity of PUS scanning to the embryo/fetus.

In July 2016, Webb et al.\textsuperscript{73} retrospectively analyzed a modification of Casanova’s hypothesis by analyzing a possible association between ASD severity and PUS exposure within the first trimester of pregnancy with 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.\textsuperscript{74}

The results of the Webb et al.\textsuperscript{73} 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 PUS 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\textsuperscript{75} responded to Webb’s\textsuperscript{73} study, by emphasizing that the study results did not determine a causal relationship between ultrasound use and autism. It advocated that PUS can be safely performed by qualified sonographers and clinicians for valid medical causes, and PUS exposure can be reduced when the ALARA principle is applied.

\textbf{Safety of PUS}

Biosafety studies of PUS on the embryo/fetus have been controversial, and the studies can be categorized into advocates,\textsuperscript{67,69,76-78} neutralists,\textsuperscript{6,79-80} and questioners.\textsuperscript{81-84} Abramowitz\textsuperscript{10,76,77} highlights the positive safety record reports of PUS on the human fetus and indicates that no
scientific studies to date have shown any resulting fetal impairment. Also, the AIUM and ACOG have issued several reports on the prospective biological adverse effects of PUS that have assured its safety.67-70

Brightness modulation (B-mode) scanners, used in the mid-1990s, are the source of the prevalent safety verification of PUS.10,65,79,81 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 is a shortage of epidemiological biosafety studies on the new devices’ usage.79,81,82

Left-handedness, speech delays, dyslexia are PUS-associated neurological symptoms.80-82 The hypothesis is that PUS generated heat may raise the maternal core temperature. Thus, thermal heat cannot dissipate due to the lack or poorly developed blood circulation in the embryo/fetus respectively, inactivating fetal core enzymes.82

A survey of the FDA acoustic output data was grouped into three episodes: 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 and the higher mean frequency of the transducer which penetrates and is absorbed by the tissue resulting in augmented heating.83

A case-controlled study conducted by Rosman et al.84,85 on three groups of patients; mainly ASD, developmentally delayed and neurotypical, 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 penetrance can be recorded and counted on the PUS image however how the depth of tissue penetration was calculated continues to be controversial. Ultrasonic devices have calibers 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.\textsuperscript{71,102,103,132}

Ten years after the implementation of ODS, a Swedish assessment\textsuperscript{86} revealed that 33\% of daily PUS end-users could comprehend the mechanical and thermal indices, 28\% were aware of the location of safety indices on their screen, and merely 22\% could modify the energy output on their machine. The inadequate knowledge of end-users of the biosafety indices or their screen appearance is widespread among medical professionals in many countries.\textsuperscript{86-89}

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.\textsuperscript{10,76,77}

Souvenir or keepsake fetal ultrasounds has expanded into a major industry and are conducted by nonmedical personnel.\textsuperscript{90-93} The FDA\textsuperscript{94} and the European Committee for Medical Ultrasound Safety,\textsuperscript{95} strongly deter this nonmedical practice.

**Risk Factors of ASD**

Advanced parental age and a higher age difference between parents have been linked as ASD risk factors.\textsuperscript{96} ASD risk is also increased in the offspring of mothers with systemic lupus erythematosus,\textsuperscript{97} diabetes mellitus,\textsuperscript{98,99} pre-eclampsia,\textsuperscript{100} and influenza virus infection or vaccination during pregnancy.\textsuperscript{101}

Antepartum, intrapartum and perinatal complications were identified as ASD risk factors; including birth asphyxia with Apgar scores of <7 at 5 minutes after birth.\textsuperscript{102,103} The association between prenatal fever and ASD, as demonstrated in the studies by Brucato\textsuperscript{104} and Hornig,\textsuperscript{105} can be an indirect warning of the temperature rise in the embryo/fetus when exposed to an undetected high thermal index during ultrasonography.

**Genetics and ASD**

The association between ASD and genetics is vastly studied. The genome-wide screening for ASD susceptibility loci,\textsuperscript{106-108} has linked more than 100 genomic loci with ASD.\textsuperscript{109}
ASD comprises certain genetic syndromes, yet gene penetrance varies within a population. For example, the autistic features of fetal valproate syndrome affect approximately 10% of individuals, whereas those of Angelman’s syndrome affect 80% of individuals. However, gene mutations in autism are rare and occur in <1% of the population.110 Twin studies revealed that ASD has moderate genetic heritability and is significantly influenced by environmental factors.111 Only 5%–15% of ASD cases are identified, based on genetic variations.112 Genetic variations are involved in ASD; however, geneticists agree that a significant environmental effect is also associated with it.106,112 They commend investigating other nongenetic causes of ASD.106

Neurodevelopment in ASD

Normal neurodevelopment extends from embryogenesis to late adolescence; yet, its critical embryonic/fetal neurodevelopmental growth is susceptible to environmental injuries.113 The neurotypical brain attains 70% and 80% of its adult mass by one and two years of age, respectively.114

Neurodevelopmentally ASD demonstrates two variations: (1) the course of the autistic brain development deviates from the neurotypical one,71,115-117 and (2) the diversity in ASD neuroanatomy depends on the severity of the autistic disorder.115,117

Magnetic resonance imaging (MRI), both functional and structural, is a noninvasive modality for research in children.118,119 MRI research studies are not applicable before the diagnostic confirmation of ASD at 2–4 years of age. Head circumference measurements correspond accurately with the brain volume, based on structural MRI imaging in 1.7-year-old to 6-year-old normal children but not in the older age group.121

Three stages of ASD brain development exist. The first stage is verified by means of head circumference measurements.116,121 The last two stages are confirmed by using longitudinal serial structural MRI.117,118
Stage I
At birth, ASD newborns may have a normal or less than the 25\textsuperscript{th} percentile head circumference. The growth of the head circumference/brain size subsequently accelerates to the 84\textsuperscript{th} percentile in the first two years of life.\textsuperscript{116,121-123} These changes are predominantly in the dorsolateral prefrontal cortex with an abnormal increase in the frontal and temporal lobe and amygdala.\textsuperscript{124} In ASD, the overgrowth of the head circumference/brain size (i.e., macrocephaly) is one of the most frequent traits of the severe form of ASD.\textsuperscript{122-125}

Stage II
At 6–10 years of age, the ASD brain’s growth rate gradually decelerates to a plateau with the ultimate cessation of growth, which reduces the cortical thickness and brain volume.\textsuperscript{126} These early changes affect the growth of brain architecture, and neural connectivity.\textsuperscript{126,12}

Stage III
At 10–15 years of age, the brain growth rate in ASD intersects that of the growth percentile of neurotypical adolescents.\textsuperscript{128} A prompt decline subsequently ensues in ASD brain volume and continues rapidly throughout late adolescence and adulthood with diminution of cortical thickness and ultimately cortical atrophy.\textsuperscript{127-130}

Neuropathology of ASD
Embryonic/fetal neural development depends on vital sequential and genetic programming of the brain.\textsuperscript{131} Individuals with the neurodevelopmental HOXA1 gene, which is associated with autism,\textsuperscript{132} have a large head circumference. This finding confirms the significance of macrocephaly as a clinical sign of ASD.\textsuperscript{124}

To determine whether the overgrowth of the young autistic brain is because of poor control of neuron production (i.e., dysregulation) or lack of cell death (i.e., apoptosis), Courchesne et al.\textsuperscript{133} performed neuron cell counts in the postmortem prefrontal cortices. The study showed a 67\% increase in neurons in seven autistics versus six normal males. In the dorsolateral and mesial segments of the ASD prefrontal cortex, the increase was 79\% and 29\%, respectively.
Prenatally, cortical neurons develop; therefore, this large number of neurons produced in the frontal cortex can only occur because of an abnormal prenatal event that may result in a gene defect or a neural deformity and may delineate the primary biologic etiology of ASD. Postnatally, neurological development is incapable of producing such excessive frontal lobe neurons.\(^{123-125,133,134,138}\)

In the ASD frontal lobe of the cerebral cortex, diffusion tensor imaging outlines reduced connections in the white matter association tract as well as horizontal commissural tracts connecting the two hemispheres, and vertical project tracts connecting the brainstem and the spinal cord, based on high values for the apparent diffusion coefficient in the whole frontal lobe.\(^{135-137}\)

Ribonucleic acid (RNA) in situ hybridization markers reveal abnormal architecture and cortical disorganization in the prefrontal and temporal cortex in autistic children. A prenatal developmental dysfunction may cause this disorganization in neuronal layer formation and differentiation.\(^{138}\) Neuropathologically, cortical gray matter was embedded in the white matter with multiple developmental defects in 92% of the brains of autistic patients.\(^{139}\)

The amygdala is a cluster of nuclei in the temporal lobe\(^ {140}\) that regulates emotions such as fear, gratification, anger, and hostility. Dysfunctional amygdala causes lack of social interaction and absence of facial and emotional reaction in ASD.\(^ {141}\) Amygdalar volume growth in ASD is increased in early toddlerhood; however, it eventually slows down such that the neuronal cell number and size are reduced in adulthood.\(^ {117,142}\) Amygdalar enlargement is associated with intense apprehension, and deterioration of communication and social abilities.\(^ {142,143}\)

The cerebellum contributes to higher cognitive functions, such as language, cognitive, and emotional adaptation,\(^ {144,145}\) in addition to balance and motor function.\(^ {117}\) In ASD children, diffusion tensor imaging\(^ {146,147}\) depicts abnormal connectivity between the cerebellar pathways and its rostral protrusion, where the cerebellar-cerebral disconnection is augmented by the reduced volume,\(^ {148}\) number and density\(^ {149}\) of the Purkinje cells which results in the behavioral and cognitive features of ASD.\(^ {150,151}\)
Recent MRI cerebellar studies\textsuperscript{152-154} show that autistic children have reduced cerebellar verm al volumes of lobes VI and VII. These findings are particular to nonsyndromic ASD. Vargas et al.\textsuperscript{155} reported a pathological inflammation in the cerebral cortices, white matter, and cerebella of ASD patients, supported by proinflam matory cytokines in the ASD cerebrospinal fluid. The ASD postmortem reports of age-specific changes in the weight and volume of brain are probably due to an impediment in its development that causes a continuous inflammatory process.

**Discussion**

In 1966, before the advent of the portable sonogram, the incidence of ASD was 3 to 4 patients per 10,000 population.\textsuperscript{19} By 2004, although various diagnostic criteria were implemented, the incidence had increased to 30–40 patients per 10,000 population.\textsuperscript{156,157}

A literature review indicates a surge in the prevalence of ASD, which has affected an estimated 1\% of all age groups among high-income countries.\textsuperscript{44,56} In addition to the increased prevalence in ASD, the use of PUS has significantly increased.\textsuperscript{61,158} The association of radiographic imaging during pregnancy and childhood leukemia was only established by MacMahon in 1962–forty years since the beginning of radiographic imaging.\textsuperscript{159}

In 2013, the evaluation of randomized data of PUS usage from insurance sources revealed an average of 4–5 prenatal scans per pregnancy with a 30\%–50\% increase in the utilization rate.\textsuperscript{158}

In 2014, the lifespan cost of a low functioning ASD individual was $2.4 million in the United States versus $2.2 million in the United Kingdom whereas the lifespan cost of a high functioning ASD individual was $1.4 million in the United States and the United Kingdom.\textsuperscript{160}

In 2015, the economic burden of ASD in the United States was forecasted to be $268 billion; 1.45\% of the gross domestic product. By 2025, the economic burden is forecasted to increase to $461 billion; which will be 2.29\% of the gross domestic product.\textsuperscript{161}

The global disease burden of ASD was estimated at 9 million years lived with disabilities by 2016; 121 disability-adjusted life years per 100,000 population.\textsuperscript{162}
Studies have demonstrated excessive neuron production throughout the first two years of life in ASD patients. It is hypothesized that this is due to an aberrant prenatal event in the uterine environment.\textsuperscript{83,115,116,122,126,133,134} Maternal infection during pregnancy, through maternal immune activation (MIA) dysregulation, may alter brain development programming during embryonic/fetal life.\textsuperscript{134}

The tendency to conduct a PUS scan for every prenatal visit, which mostly involve low-risk pregnancies, is not medically indicated and is contrary to the American College of Obstetrics and Gynecology (ACOG) and AIUM safety guidelines.\textsuperscript{69,70}

A PUS 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 PUS scans, and patients must be cautioned to avoid commercial ultrasounds. The maternal temperature should be recorded prior to and during if ultrasonic scanning time is prolonged.\textsuperscript{163} The mother must provide informed signed consent before undergoing PUS scanning. When ultrasonically scanning the patient, the ultrasonographer is required to monitor and document the number of scans, the thermal and mechanical indices, the acoustic output, the depth of penetration and the dwell time.

Regulatory reforms must be implemented to improve professional end-users’ knowledge and modification of ultrasonic biosafety parameters. Medical ultrasonographers must acquire a license, which is to be renewed periodically, through strict training with a practical examination.\textsuperscript{85-89}

The popular practice of commercial fetal video scanning of pregnant women,\textsuperscript{90-93} should be prohibited for maternal and fetal safety.
Maternal blood biomarkers such as cell-free DNA are available to test for aneuploidy and to replace ultrasonic nuchal translucency examinations which may take up to 45 minutes to uphold the fetus in the military position.

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

Although ASD research has focused on genetics, medical, and environmental causes, and delineated multiple risk factors and associations; a definite etiology of ASD has yet to be identified.

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

**Conclusion**

The long-term PUS biophysical effects on the embryo/fetus featuring the acoustic output of new ultrasonic devices, its overuse in clinical practice and the commercial fetal video souvenirs remain unknown.

A joint obstetric/pediatric, peer-reviewed, statistically significant study to determine whether a correlation prevails between excessive in utero ultrasonic exposure and the development of childhood ASD is long overdue.
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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
ultrasonography
MRI: magnetic resonance imaging  ODS: output display standard

Contributors’ Statement

Dr. Hissa Moammar is a pediatric consultant, affiliated with King Salman Center for Disability Research, (Riyadh, Saudi Arabia). She conducted the literature search using the Cochrane Database of Systematic Reviews and Ovid Medline from 1966 to 2018. She manually retrieved articles written before 1966, based on the reference list. She reviewed the published medical literature on infantile autism, autism, pervasive developmental disorder, autistic spectrum disorder, and ultrasonography and prenatal ultrasonography.

Dr. Rabi Sulayman is affiliated with Chicago Medical School (Chicago, Illinois). He has coauthored, edited, and reviewed the manuscript.

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

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