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Impact of Infant Feeding Methods on the Development of Autism Spectrum Disorder

Touraj Shafai, Monika Mustafa, Jeffrey Mulari and Antonio Curtis

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Abstract

There is strong and convincing evidence that infant's sensory stimulation, which is associated with breastfeeding, contributes significantly to the infant's neurodevelopment. Our study compared the prevalence of autism spectrum disorder (ASD) in children who were breastfed, given breast milk through a bottle (breast-milk fed), or formula-fed. We reported significant association of ASD in children who were formula-fed from birth or weaned early from the breast. The statistical data revealed that increasing the duration of breastfeeding resulted in a decrease in prevalence of ASD. The odds ratio of a child not having autism was 0.27, 0.93, and 6.67 for breastfeeding for less than 6, 6–12, or longer than 12 months, respectively. There is significant evidence that this association is mediated by the ingredients of the breast milk and infant's endogenous oxytocin. Oxytocin is a neurotransmitter and neuromodulator and we postulate that oxytocin may increase neuroplasticity, synaptic connections, and alter ASD genes' expression. Animal experiments and imaging studies demonstrate the central role of oxytocin in maternal love and bonding. Currently, there are no specific treatments for patients diagnosed with autism; therefore, it is imperative to identify the risk factors that contribute to the development of ASD. In this communication, we demonstrate that lack of breastfeeding is highly associated with ASD development in children with genetic susceptibility.

Keywords: autism, neuroplasticity, oxytocin, epigenetics, breastfeeding, enriched environment

1. Introduction

The short- and long-term benefits of breastfeeding for mother and baby have been well documented [1]. The short-term benefits of breastfeeding include a lower incidence of many childhood communicable diseases, childhood lymphocytic leukemia, inflammatory bowel disease, lower incidence of type 1 diabetes, and higher IQ [2]. The long-term benefits of breastfeeding include lower incidence of noncommunicable disorders (NCDs), obesity, diabetes type 2, and hypercholesterolemia resulting in cardiovascular diseases and hypertension [2–4]. Furthermore, breastfeeding results in improved maternal health by reducing the incidence of maternal premenopausal breast and ovarian cancer as well as lowering the incidence of maternal obesity and its complications [2].

World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months and to continue breastfeeding with addition of safe and nutritious complementary food up to 2 years of age and beyond.

In the past 10 years, the global exclusive breastfeeding rate improved only marginally from 33% in 1995 to 37% in 2014. Suboptimal breastfeeding results in higher health care expenses for pediatrics and maternal care, and global productivity-related economic losses of \$302 billion or 0.49% of world gross income annually [4].

The impact of breastfeeding in lowering the incidence of mental health disorders has recently gained scrutiny. Neurodevelopmental disorders, especially autism and attention deficit disorder, are reported to be significantly associated with formula feeding [5–7]. The annual expenditure for the care of autistic children and adults in the United States is estimated to be in excess of \$120 billion [8].

The short- and long-term benefits of breastfeeding for mother and baby have been well documented. In our study, we demonstrate the mental health benefits of breastfeeding and identify early weaning and formula feeding as possible risk factors for development of ASDs in genetically susceptible children.

2. What causes autism?

Autism was reported as a distinct entity by Leo Kanner, professor of psychiatry at Johns Hopkins University in 1943. In his article “Autistic Disturbances of Affective Contact” he described 11 cases, 3 girls and 8 boys as having infantile autism. He noted that the family members were intelligent but generally they were not warm-hearted, and that the parenting style might have contributed to the development of autism. Autism spectrum disorders consist of a group of neurodevelopmental disorders, characterized by a triad of impairments in social interaction, communications, and imagination, associated with narrow range of repetitive activities. Hans Asperger, a Viennese physician, also described a type of autism that he called autistic psychopathy in 1944, which later became to be known as Asperger syndrome. However, since the original article was written in German and was not translated into English until nearly 40 years

later, there was no awareness until later when Asperger syndrome was included as a form of autism. However, a Russian neurologist, Grunya Sukharev, published an article in 1926 titled, the schzoid psychopathy in children with nearly identical description as Asperger syndrome.

The etiology of autism had been quite elusive, although there is common belief that autism has a genetic basis; however, the gene expression may be influenced by environmental factors. The genetic influence in development of autism has been shown by twin studies, where there is a high probability that monozygotic twins, who have identical genes, develop autism at a high rate. Heritability index, a measure of genetic transmission of neurobehavioral disorders, autism, hyperactivity, schizophrenia, and major depression are 0.95, 0.8, 0.8, and 0.75, respectively [9].

In the past 40 years, a number of environmental toxins were considered to be the main culprit in the development of autism. Prenatal factors, including maternal folate deficiency and short interpregnancy intervals, do not appear to be causal factors [10]. Perinatal factors, newborn jaundice, breech presentation, and prematurity do not seem to be responsible for autism development. Multiple gene theory and second hit theory which advocate ASD genes induce increased susceptibility to environmental toxins have also been refuted as a cause of autism.

The fraudulent report of finding measles viruses in the guts of 12 children with autism, published in Lancet in 1998, therefore linking autism to MMR vaccine was retracted by the coauthors in 2004 and by the journal's editor in 2010. Allegations that vaccine's ingredients (thimerosal, aluminum) are responsible for the epidemic of autism have been soundly refuted by epidemiological studies and there is no scientific basis that there is a causal association between vaccines and autism [11].

In the past 20 years, multidisciplinary research has resulted in better understanding of the complex nature of ASDs. The multicenter study reported by Sanders et al. on the association of copy number variations, characterized by submicroscopic deletions or duplications on chromosomes in the individuals with ASDs, demonstrate the genetic etiology of this disorder [12–14]. However, there is evidence that a number of individuals with CNV genotype have normal phenotypes, indicating incomplete gene penetrance and the influence of environmental factors [12].

3. The role of oxytocin in infant's brain development

There is significant evidence that oxytocin plays a major role in the development of the mammalian brain [1]. Oxytocin, a neuropeptide is secreted by the paraventricular (PVN) and supraventricular (SON) nuclei in the hypothalamus. Oxytocin was thought to be only a parturition hormone, which initiates the uterine contractions during childbirth and the myoepithelial cells in the breast, pushing breast milk from the alveoli through the milk ducts during breastfeeding. However, animal experiments have generated significant evidence that oxytocin plays a major role in the development of the mammalian's central nervous system. Oxytocin is implicated in both romantic and maternal love and all aspects of reproduction and breastfeeding. Romantic and maternal love are some of the most inspiring manifestations of human behavior and responsible for the survival of our species. Additionally, oxytocin is a neurotransmitter and neuromodulator and implicated in neuroplasticity of the infant's central

nervous system. There are numerous oxytocin receptors in the central nervous system and the peripheral tissues. However, there are separate oxytocin receptors for romantic and maternal love [1].

Oxytocin is generated by the specialized neuroendocrine cells in the hypothalamus, which are activated by the sensory nerves in the infants' oral mucosa and released during breastfeeding. Additionally, oxytocin is released during skin-to-skin contact with the mother due to sensory nerves responding to warmth, touch, and stroking by the mother [15]. The sensory nerves enter the spinal cord or brain stem and connect to the nucleus tractus solitarius (NTS). Furthermore, oxytocin release is triggered by the breast milk/food in the infant's stomach, which results in the release of cholecystokinin in the gut. Cholecystokinin stimulates the release of oxytocin by activating the sensory vagal nerve fibers, which results in central and peripheral oxytocin release [1, 15].

The endogenous release of oxytocin results in behavioral changes in both mother and baby, including bonding and attachment. Additionally, oxytocin stimulates the sense of well-being and suppresses the HPA axis [10, 15].

4. Environmental influence on the infant's brain development

Anthropological studies clearly demonstrate the necessity of the closeness of the mother-baby dyads. The statement by famous anthropologist, Sarah Blaffer Hrdy that "for species such as primates, the mother is the environment" holds very true. Primates such as monkeys, apes, and humans are referred to by scientists as the "carrying mammals" versus the "nested mammal" because of the difference in the sugar and the fat contents of their breast milk and feeding frequency. The human infant's central nervous system depends on the microenvironment that is similar to the maternal uterine environment, which is full of sensory exchanges involving warmth, sound, movement, transportation, feeling, touch, smell, and access to the nutrients in the mother's breast milk.

Anthropological studies indicate that the mammalian brain development requires an enriched environment with the mother providing breast milk, emotional and physical support and protection. This is in contrast to a mother who is formula-feeding her infant with little or no emotional and physical support. The infant is not held by the mother or the caretaker, she is frequently ignored and sometimes is physically or emotionally abused. This type of environment which we call a toxic environment frequently results in developmental delay, lower IQ, and neurodevelopmental disorders. The elegant experiments by Volkmar and Grenough demonstrate the effect of environmental enrichment in laboratory rats, which resulted in more complexity and dendritic branching of the visual cortex [16]. Furthermore, Weaver et al. [17] have shown that epigenetic factors can induce gene activation by histone acetylation without changing the DNA sequence. Therefore, histone acetylation results in gene activation in the offspring when they reach maturity.

Imaging studies (**Figure 1**) comparing the activation of oxytocin receptor sites in formula and breastfeeding mothers demonstrate significant enhancement of oxytocin receptors in breastfeeding

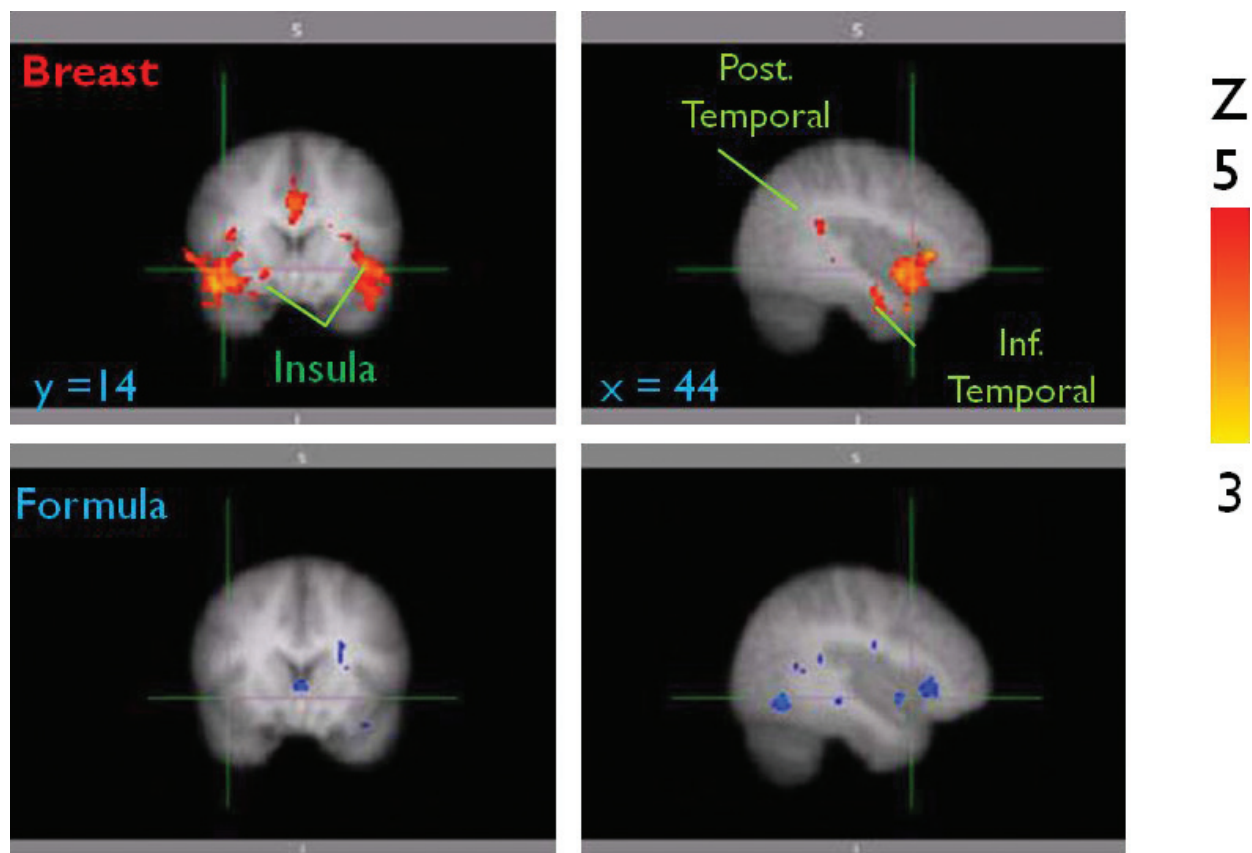


Figure 1. Comparison of the functional MRI studies of breastfeeding and formula feeding mothers after viewing the pictures of their own infants. Oxytocin receptors are significantly enhanced in breastfeeding mothers.

mothers, which correlates with greater neural response [1]. Furthermore, higher plasma and salivary oxytocin levels are reported in breastfeeding compared to formula feeding mothers, 36% in plasma and 23% in saliva, respectively [18]. We hypothesize that an increase in brain oxytocin level may improve learning, speech, cognition, parental attachment, and emotional ties. Additional support for the beneficial effect of oxytocin in premature infants is reported from the University of Chicago hospitals. Premature infants, who received sensory stimulations, including auditory, tactile, visual, and vestibular, gained more weight and were discharged home sooner than the control group who did not receive any sensory or only tactile stimulation. Measurements of salivary cortisol levels in the infants showed a decline in the infants associated with ATVV (auditory, tactile, visual, and vestibular) stimulation corresponding to the rise in blood oxytocin level (**Figure 2**).

In the past decade, there has been credible evidence that ASDs are associated with oxytocin dysfunction [19]. Modahl et al. [20] reported lower serum oxytocin in children with ASDs. Additionally, oxytocin infusion to adults with ASD resulted in temporary improvement in some of their symptoms [21, 22]. However, it is generally believed that oxytocin does not cross the blood-brain barrier. Therefore, trials of oxytocin nasal spray, which would bypass the blood-brain barrier was attempted for a period of 6 weeks to adults with ASD, which resulted only in temporary improvements in some of the autistic symptoms [23]. These findings indicate that oxytocin has a critical function during the first 5 years of life when the accelerated brain growth occurs.

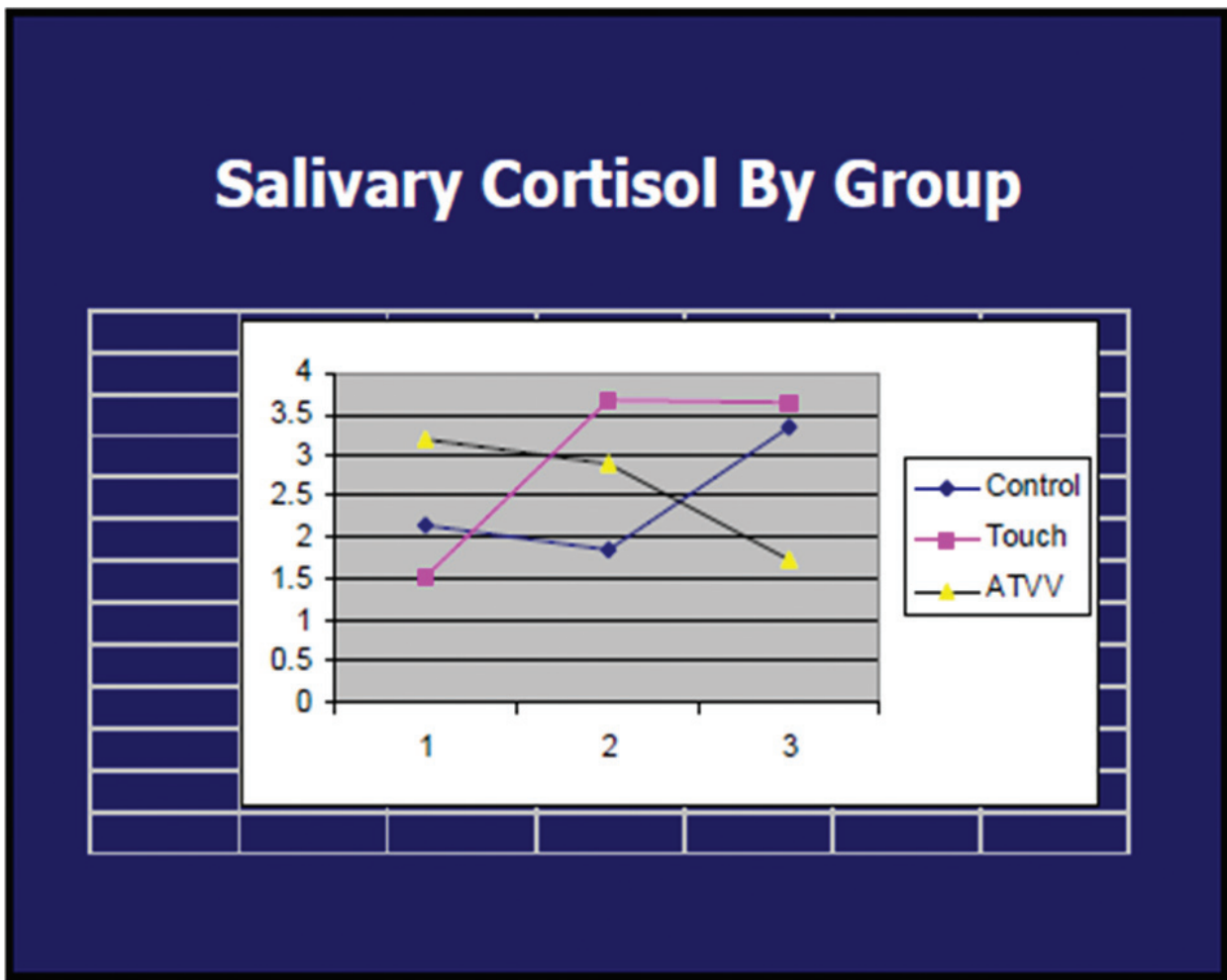


Figure 2. Salivary cortisol levels in three groups of premature infants, showing a decline associated with ATVV sensory stimulation, which corresponds to a rise in serum oxytocin.

Population genetic studies have shown that structural alteration of oxytocin are responsible for development of autism [24]. Finally, genetic alterations in oxytocin receptor protein are reported to be associated with ASDs [25].

5. Industrialization, global conflicts, the rise of formula feeding, and autism

It is commonly believed that the rate of breastfeeding in the industrialized nations sank to its lowest level after the 1950s and began to climb in the past 20–30 years. We assume that autism has always existed, but not recognized until the 1940s when it was described independently by Leo Kanner and Hans Asperger. However, it is clear that throughout our history, the prevalence of ASDs was quite low, due to the high rate of breastfeeding and sensory interaction between the mother and her infant. There is clear evidence that there is an increase in the prevalence of ASDs, especially in the United States that in recent years has reached alarming numbers. However, expansion of diagnostic criteria and diagnostic substitution may explain

the increase in ASDs diagnosis in the United States. Furthermore, the prevalence of autism is lower in other industrialized nations because of higher rates of breastfeeding and paid maternity leave. In parts of Africa and the Middle East, infants are breastfed for 4 years and they report lower rates of autism.

Historically, the first description of autism was reported independently by three physicians, Grunya Sukharev from Russia, Leo Kanner from the United States, and Hans Asperger from Austria at about the same time. The authors do not describe possible cause(s) for autism and no mention of the type of feedings during infancy. However, we know of the desperate conditions of populace in Russia and Austria. In the United States, many women were working in the factories and the infants were fed cow's milk or powdered milk. There are no reliable statistics on the breastfeeding rates in the mid-twentieth century. However, cow's milk or powdered milk feeding became very popular in Europe and the United States. Many women chose injection of a prolactin inhibitor after childbirth to prevent producing any breast milk. In the 1980s, the formula companies began aggressive marketing of infant formulas directly to the consumers. This resulted in World Health Organization's campaign to counter the formula industry by the passage of the Code of Ethics of Marketing of Breast Milk Substitutes, followed by Baby-Friendly Hospital Initiative.

In the past 20 years, improved public awareness of many benefits of breastfeeding for mother-baby dyads has resulted in higher breastfeeding initiations [3]. This is especially true in college-educated mothers and middle-class families. The rates of breastfeeding in the United States vary greatly by race, ethnicity, parents' income, parents' education, and the community support. Many college-educated mothers elect to breastfeed their babies and exclusive breastfeeding rates in this population at 6 months stands at 16%. The rate of breastfeeding is inversely associated with families' income. Therefore the breastfeeding rates for the families at or above 6 times poverty line at 6 months is 21%, for those at 4.2 times poverty line is 20% and for those below the poverty line is 12%. Accordingly, the breastfeeding rates by mothers at six times above the poverty line, those between 4.2 times, and those below the poverty line are at 21, 20, and 12%, respectively [26]. Breastfeeding rates also vary greatly among the racial groups, whites are at 19%, Hispanics at 16%, and African Americans are at 9% at 6 months [26].

The United States WIC program, Women, Infants and Children, which funds nutrition program for pregnant mothers and children, who are below the 180% poverty level, began providing infant formulas beginning in 1974 to the WIC recipients. The WIC program was enacted in 1972 following a White House Conference on the ill-effects of poverty on pregnancy and the well-being of breastfed infants. During the first 2 years, the program was very successful in eliminating malnutrition in pregnant women and their babies.

However, for the past three generations the great majority of WIC recipients have received free formula for their infants for 1 year. The WIC population has the lowest breastfeeding rates in the United States and numerous interventions to improve breastfeeding rates in this population have not been effective.

There are numerous benefits of exclusive breastfeeding to both mother and her infant, which are attributed to the ingredients of breast milk [2]. However, recent research and genomic studies demonstrate that the infant's social environment may play a significant role in her

brain development. The environmental factors may be positive, including high socioeconomic status (SES), high maternal IQ, breastfeeding, and mother-infant sensory interactions. Negative environmental factors include poverty, formula feeding, lack of high school and college education, absence of mother-baby sensory interaction, neglect, and abuse.

Fragile X syndrome is the most common inherited cause of intellectual disability and the focus of intense research on multiple levels from molecular to the cognitive functions and the IQ of the individuals. Fragile X syndrome is caused by CGC (dinucleotide) repeats on the X chromosome, replacing the FMRP (fragile X mental retardation protein) gene, which results in autism. However, environmental enrichment results in a favorable outcome in some of these children. The IQ of the boys with fragile X syndrome is known to be higher in association with parental responsiveness to the child, having educational material in the home and parental efforts to provide developmental enrichment [27]. The association of home environment with IQ is larger than any other variables, including the child's level of FMRP and mean parental IQ.

There is clear and convincing evidence that oxytocin has a major role in the development of oxytocin system, connecting the periaqueductal gray matter (PAG), the limbic system and the lateral orbitofrontal cortex, which are identified with maternal behavior [1]. Furthermore, the oxytocin system appears to include a number of pathways, especially in the limbic system, which are affected in various degrees in individuals with ASDs.

6. Association of early weaning and formula feeding with autism

Tanoue and Oda [28] first reported the association of early weaning and autism over 25 years ago. The authors also noted that in their study population, autism was more common in the lower socioeconomic class. The result of a survey comparing the rates of autism in three groups of children was reported by Schultz et al. [29]. The children who were breastfed for 6 months had a lower incidence of autism than the group who were fed formula without DHA&ARA supplementation. However, the group of children who were given formulas supplemented with DHA&ARA also had a lower rate of autism. We strongly believe that the study was flawed because it was conducted in 2004, only 2 years after DHA&ARA supplementation of infant formulas. The diagnosis of autism is usually confirmed in children who are older than 3–4 years old.

6.1. Methods

In this communication, we hypothesize that breastfeeding and nurturing result in a decrease in autism diagnosis. In order to explore this hypothesis, we conducted a confidential written survey of parents to ascertain the association of parent's reported ASD diagnosis with the duration of breastfeeding, breast milk, or formula feeding. The study focused on the children who were 2–8 years old at the time of the survey and to include only formulas supplemented with DHA and ARA. The survey did not include any questions regarding the brand of the formulas used, because of possible frequent formula changes as well as difficulty recalling the brand name of formulas. Our study was based on an anonymous written retrospective survey which was conducted from our offices. The survey forms were made available from our

offices. The completed survey forms were returned through fax to our office. Statistical analysis was performed using binary logistic regression analysis on the data of the children who were breastfed or formula-fed and those who received breast milk via a bottle. In each group there were a number of children who did not have autism. The children without ASD diagnosis were used as the “control group.” The odds ratios, *P*-values, and confidence intervals were calculated in relation to the duration of breastfeeding, formula feeding, or breast milk feeding using binary regression analysis.

6.2. Results

One hundred and forty-five parents responded to our survey. Eighty-five parents reported no ASD diagnosis and 60 parents reported that their child had ASD diagnosis. The children were divided into three groups. The infants who were formula-fed from birth were placed in the formula-fed group. The infants who were breastfed from birth were placed in the group of breastfed children, regardless of the length of breastfeeding. Twelve of the 60 children who were formula-fed from birth had ASD diagnosis as shown in **Table 1**. Twenty-six were reported to have been breastfed from less than 2 weeks to greater than 2 years and reported to have a diagnosis of autism as shown in **Table 1**. The survey results demonstrate that increasing the duration of breastfeeding is associated with a decline in ASD diagnosis as shown in **Table 2**. The statistical data reveal that children who were breastfed longer than 12 months are 6.67 times less likely to have autism diagnosis than children who were breastfed less than 12 months as shown in **Table 3**. Breastfeeding of less than 6 months duration was significantly associated with autism diagnosis. Twenty-two out of 64 children who were fed breast milk through a bottle were reported to have ASD diagnosis as shown in **Table 4**. The odds ratio analysis of the association of breast milk feeding and ASD diagnosis is shown in **Table 5**. This survey indicates that increasing the duration of breast milk feeding was not associated with a significant decrease in autism diagnosis. We believe that the infants who are bottle-fed with breast milk or formula have little sensory interaction with the mother or caregiver during the feeding **Table 6**. We hypothesize that breast milk feeding is associated with lower oxytocin release and oxytocin receptors in the infant’s central nervous system. Similarly, in children who were formula-fed and had ASD diagnosis, less sensory interaction between mother-baby during bottle feeding and absence of maternal hormones, especially estrogens, in the infant’s feeding result in lower oxytocin and its

Children with ASD diagnosis	Children without ASD diagnosis	Total
Number of formula-fed children		
12	22	34
Number of breastfed children		
21	26	47
Number of breast milk fed children		
22	42	64
55	90	145

Table 1. Number of breastfed children with ASD diagnosis should be 21 and without ASD diagnosis should be 26 autism relative to the feeding methods, breastfeeding, breast milk, or formula feeding.

Duration of breastfeeding	Number of children with ASD diagnosis	Number of children without ASD diagnosis
<2 months	8	2
2–3.99 months	4	1
4–5.99 months	2	2
6–8.99 months	4	0
9–11.99 months	2	2
12–14.99 months	2	8
15–17.99 months	2	3
18–23.99 months	2	0
>24 months	0	3

Table 2. Number of children with and without ASD diagnosis relative to the duration of breastfeeding.

Months of breastfeeding	Odds ratio	P-value	95% confidence intervals
<6	0.27	0.04	(0.08–0.95)
6–11.99 months	0.93	0.94	(0.14–6.23)
>12 months	6.67	0.009	(1.61–26.47)

Table 3. Odds ratios of association of breastfeeding duration and ASD diagnosis.

Duration of breast milk feeding	With ASD diagnosis	Without ASD diagnosis
<2 months	4	8
2–3.99 months	4	6
4–5.99 months	4	4
6–8.99 months	4	8
9–11.99 months	4	5
12–14.99 months	0	5
15–23.99 months	2	2
>24 months	0	4

Table 4. Number of children with and without ASD relative to the duration of breast milk feeding.

receptors in the infant’s brain [30]. The presence of estrogens as well as other maternal hormones in the breast milk has been well documented. Johnson et al. and Champagne et al. have reported that estrogens are transcriptional promoters of oxytocin and oxytocin receptor’s gene in experimental animals [31, 32]. The absence of estrogens in the infant’s feeding or the use of oxytocin blockers in experimental animals results in lower endogenous oxytocin and oxytocin receptors [30–32]. Oxytocin and estrogens have regulatory influence on the oxytocinergic system and have been shown to alter many aspects of cellular function and differentiation as well as potential to remodel the nervous system [33, 34]. Additionally, oxytocin is a neurotransmitter and

Months of breast milk feeding	Odds ratios	P-value	95% confidence interval
<6 months	0.67	0.37	(0.11–4.31)
6–11.99 months	1.08	0.08	(0.35–3.40)
>12 months	3.67	0.12	(0.69–19.56)

Table 5. Odds ratios of association of breast milk feeding duration and prevalence of ASD diagnosis.

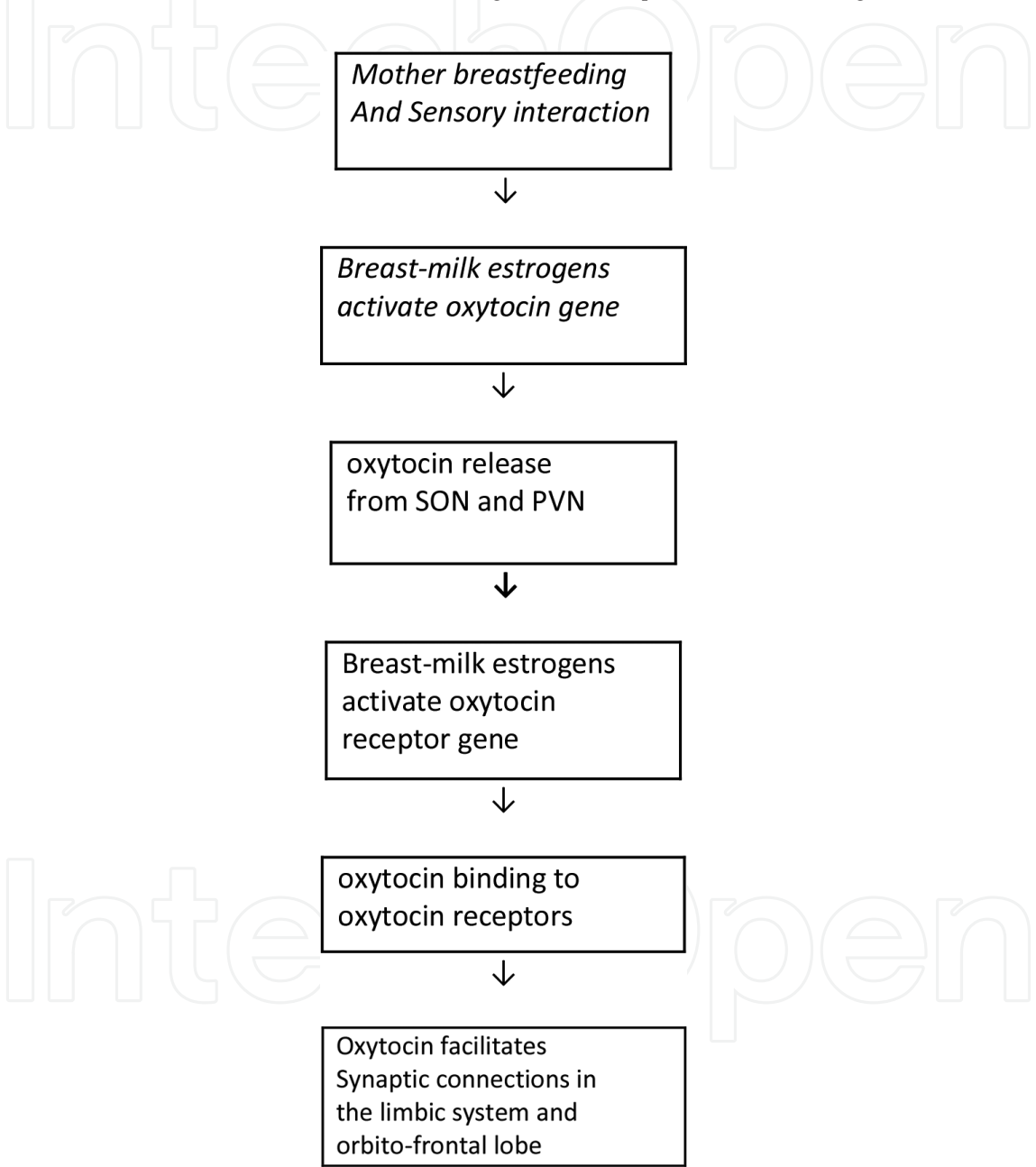


Table 6. Cascade of oxytocin system activation in the newborn infants.

neuromodulator and may increase neuroplasticity, synaptic connections, and alter ASD genes expression.

There is clear and convincing evidence that links the ingredients of breast milk and infant's sensory stimulation during breastfeeding to lowering the prevalence of autism. However,

there are questions raised that infants who are later diagnosed to have autism may have dysregulated breastfeeding behavior [35]. A small retrospective study of the association of autism and dysregulated breastfeeding behavior revealed that the majority of infants in this study who developed autism were breastfeeding well and a few who were identified as having dysregulated breastfeeding behavior were breastfeeding more often and quite vigorously [35].

In this communication, we demonstrate the association between breastfeeding and decline in prevalence of ASD. We further believe that this effect is mediated by an increase in the endogenous oxytocin in the infant's central nervous system [1, 13, 15]. The elegant experiments by Krol et al. demonstrate the significance of breastfeeding and oxytocin increase in the central nervous system of infants with CD-38 gene variation. CD-38 gene encodes the enzyme system that releases the oxytocin from the hypothalamic neuroendocrine cells. The individuals who have two copies of the C allele of the enzyme release less oxytocin than the individuals with the A (normal) allele and therefore are at risk of developing ASD [36]. Furthermore, the infants with CC allele of the enzyme who were not breastfed showed less eye contact with their caregiver at 6 months, an early sign of autism, while the infants who were exclusively breastfed continued to maintain normal eye contact with their mother. The author state that oxytocin in the breast milk is absorbed in the infant's intestinal tract and cross the blood-brain barrier. However, this appears to be very unlikely because breast milk contains small amounts of oxytocin, 8 pg/ml in the first few days, and decreases with increased milk production. It is believed that oxytocin is digested in the infant's digestive tract and even if it is absorbed into the blood stream, it does not cross the blood-brain barrier [10]. We postulate that the rise of oxytocin in the infant's central nervous system is due to the presence of estrogens in the breast milk acting as transcriptional promoter of oxytocin gene. We believe that the finding is further indication that breastfeeding provides protection against autism development.

In this communication, we demonstrate the evidence supporting our hypothesis that breastfeeding for 1 year or more is highly associated with reduced prevalence of autism and identify the lack of breastfeeding as a risk factor for the development of ASD in genetically susceptible children.

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The opinions stated in this communication are only the opinions of the authors. The authors declare no competing interest.

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