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Prenatal Exposure to Synthetic Oxytocin: Risk to Neurodevelopment?

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Abstract: The neurodevelopmental risks of prenatal exposure to synthetic Oxytocin (OXT) during childbirth are relatively unexplored; however, it seems plausible that lifelong consequences could occur. This article expounds upon a pilot study (Kurth & Haussmann, 2011) that posited an association between prenatal OXT exposure and childhood onset of ADHD, suggesting neurodevelopmental disorders may be a consequence of this exposure. Study results, conclusions, and speculative impressions are discussed[1]. The potential risks of prenatal OXT exposure warrant expanded research in order to identify the specific pathophysiology involved in this dynamic and to determine if this exposure carries risks for altering child neurodevelopmental trajectory.

Keywords: Prenatal, labor induction, synthetic Oxytocin, ADHD, Neurodevelopmental

Prenatal Exposure to Synthetic Oxytocin: Risk to Neurodevelopment?

Origin of Theory

The theory of this possible association originated from over fifteen years of direct clinical observation as combined with independent, non-solicited reports provided by geographically diverse mothers during routine developmental child intakes. Specifically, these mothers voluntarily sought diagnostic clarification, evaluation, and

[1]Primary author's note: For clarification, this research originated as a Psychology Doctoral Dissertation completed at Northcentral University, Prescott Valley, Arizona.

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treatment for their biological children who either (1) demonstrated behavioral symptomology consistent with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) and/or (2) who had been previously identified by a supervising pediatrician or primary care physician as having ADHD symptoms. During these intakes, mothers responded to a series of pregnancy-related questions relevant to the child of clinical concern. Topics reviewed in depth included ease of child conception, description of the mother's health during pregnancy, gestational duration, length of labor and delivery dynamics. Included in this initial inquiry was clarification as to whether or not medication(s) had been used to induce and/or augment labor during childbirth, and specification of the medication(s) used.

With reliable frequency, the majority of mothers voluntarily self-disclosed that synthetic Oxytocin (specifically Pitocin®; heretofore referred to as OXT) had been the medical agent most often utilized during their childbirth experiences. Many mothers also provided testimonials of related childbirth complications, including extended maternal gestation, prolonged labors (including prolonged exposure to OXT), heavier newborn weight babies (i.e. >7lbs.), use of epidural anesthesia and assisted rupture of membranes. With some frequency, reports of newborn nuchal chords, low initial Apgar scores, history of fetal distress, and meconium stain were also provided by these mothers. When a majority of these children were subsequently formally evaluated (i.e. collaterally rated utilizing standardized ADHD teacher and parent rating scales) and were later confirmed by a clinician as meeting the diagnostic criteria for ADHD, these maternal reports raised questions regarding a potential association between these trends. Based on the assumption this correlation arose from circumstances other than coincidence, the pilot study discussed here ensued. The focus of this research was to determine whether prenatal OXT exposure (and/or certain other involved prenatal factors) could be identified as holding predictive potential to the future outcome of childhood ADHD.

From a Mother's Perspective

During the course of this pilot study, a number of mothers of ADHD child participants voluntarily contacted the original study authors to express their support of this research effort and to freely offer testimonials regarding their own personal experiences with obstetric OXT. For example, one mother reported an OXT exposure time during a 36 hour labor with her child, now diagnosed as having ADHD.

Another mother described an intense 23 hour OXT exposure time with her child whose complicated neurodevelopmental profile, including an ADHD diagnosis, has continued to perplex clinicians for years. Still another mother reported a 17 hour OXT exposure, after which time her child's fetal heart rate decelerated drastically, as did fetal movement, warranting a vacuum extraction attempt that resulted in an emergency C-section delivery, followed by newborn resuscitation efforts that successfully revived her child. This child was later diagnosed with ADHD.

In addition, the pilot study authors were approached by multiple medical professionals who volunteered opinions regarding their observations of common obstetric OXT usage. Consensus of these remarks conveyed that a trend toward *social induction* involving OXT usage during labor and delivery seems routine among modern birthing practices. This reported trend demonstrates a tendency for supervising medical staff to grant the social preferences of birth mothers who request elective induction in order to accommodate time schedules, etc. Such tendencies question adherence to safety standards in usage of OXT among birthing facilities, echoing the rationale for this area of research to continue.

Overview of ADHD

ADHD Etiology

The genesis of ADHD continues to baffle researchers. Despite studies arguing the *heritability* of this disorder (Biederman & Faraone, 2005; Faraone et al. 2005), including familial genetic interaction (Jain et al. 2012) and translational evidence of gene variants linked to ADHD (Williams et al. 2010), no genetic test for ADHD yet exists (American Psychiatric Association [APA], 2000). Thus, the definitive etiology of this commonly diagnosed neurodevelopmental disorder remains unknown. Sprich-Buckminster, Biederman, Milberger, Faraone and Lehman (1993) suggested ADHD may result as part of a non-genetic mechanism. Barkley (1998, 2006) and Goldstein (1999) agreed ADHD may involve injury to soft brain tissue as attributable to the interaction of combined genetic and biological factors.

It has long been suggested that ADHD may be a consequence of *early neural insult* (Still, 1902; Lillienfeld, Pasamanick, and Rogers, 1955), with implications that neural damage at critical developmental stages may be associated with later ADHD onset (Milberger,

Biederman, Faraone, Guite, and Tsuang, 1997). A healthy body of research has linked ADHD to complications in pregnancy and delivery (Boyce, Smith, and Castro, 1999; Faraone and Biederman, 1998; Milberger et al., 1997; Mulkins, 1993; Spadafore, 1997), without specifying prenatal OXT involvement. Biological mothers of children with ADHD have been found to have comparatively higher rates of *pregnancy and delivery complications* (Bhatia, Nigram, Bohra, and Malik, 1991), along with issues in labor length and fetal distress (Buka, Tsuang, and Lipsitt, 1993; Hartsough and Lambert, 1983; Mick, Biederman, Faraone, and Kleinman, 2002).

Still others (Ben-Amor et al. 2005: Bhat, Grizenko, Amor, and Joober, 2005) associated perinatal and obstetric complications with fetal distress and neurological insult. According to Nass (1995), a study by the National Perinatal Collaborative Project found birth asphyxia increased risk of childhood ADHD. *Environmental factors*, including smoking during pregnancy (Rodriguez and Bohlin, 2005; Neuman et al. 2007) and complications during pregnancy, delivery and infancy (Gustafsson and Källén, 2011) have also been suggested as contributing to ADHD onset.

Brake, Sullivan, and Gratton (2000) suggested ADHD may result from perinatal distress and frontal lobe damage. Hypoxic and/or anoxic injury in ADHD has been implied (O'Dougherty, Neuchterlein, and Drew, 1984), along with *prefrontal cortex abnormalities* (Barkley, Murphy, and Bush, 2001; DuPaul, Barkley, and Connor, 1998; Schweitzer et al. 2000; Semrud-Clikeman et al. 2000) and dysregulated blood flow (Gustafsson, Thernlund, Ryding, Rosen & Cedarblad, 2000), suggesting vasoconstriction may play a key role. Recently, impaired neural networks dysregulating prefrontal cortex activity were discovered in individuals diagnosed with ADHD (Bush, 2010; Vance et al. 2007), while animal researchers observed aberrations in neurotransmitter release affecting networks governed by prefrontal cortex functioning (Levy, 2009; Arnsten, 2009). However, a specific explanation for these anomalies in ADHD has not been determined.

While these multiple studies imply an origin of early neurological insult, a signature mechanism in this disorder has yet to be isolated. Claycomb, Ryan, Miller, and Schnakenberg-Ott (2004) remarked that studies examining the potential risks of labor-induction related toxicities and adverse neurodevelopmental outcomes, such as ADHD, have been omitted in the scientific literature. Studies examining prenatal exposure to OXT as potentially associated with ADHD have been lacking, according to a research summary by Kurth (2012).

Prevalence of ADHD

According to the CDC (2010), the prevalence of ADHD within the United States is reportedly as high as 1 in every 10 children between the ages of 14 and 17, with parent reports of greater than 5.5% per year increases in this diagnostic profile among this age group (CDC, 2010). An explanation for this steady diagnostic increase remains unknown. Prevalence rates of ADHD among U.S. children ages 5-17 have risen from 6.9% in 1998-2000 to 9% through 2007-2009 (Akinbami, Liu, Pastor & Reuben, 2011). Presently, 1 in every 10 children in this age group has confirmed ADHD, representing an increase of 1 million more children diagnosed since 2003 (CDC, 2010). Exceeding previous annual estimates (Mandell, Thompson, Weintraub, De Stefano, and Blank, 2005), this trend is rather alarming, since ADHD rates are reportedly nearly 20% among community sampled school-age children (Rowland, Lesesne, and Abramowitz, 2002); a finding that raises questions around ADHD's undetermined origin.

Neurodevelopmental and Behavioral Profile of ADHD

The current description of ADHD's neurodevelopmental profile includes deficits in cognitive executive functioning (Baddeley, 1986; Barkley, 2006; Diamond, 2005). Some suggest ADHD may be the by-product of unexplained disruption of functioning in neural areas that are associated with regulating active working memory; areas responsible for necessary, routine tasks such as time tracking, planning, organization, etc. (Arnsten & Li, 2005; Barkley, 2006) and for processing information (Levine, 2002). Diamond (2005) defined ADHD's "dysexecutive" profile (p. 808) as reflective of active working memory deficits linked to birth trauma, head injury and/or exposure to environmental toxins, yet did not refer to any specific prenatal exposure as possibly associated in this outcome.

The challenges and adversities that children diagnosed with ADHD encounter are multifaceted. Within the academic arena, these children typically contend with issues related to underachievement, exhibiting symptoms of cognitive sluggishness (McBurnett, Pfiffner, and Frick, 2001), delays in information processing (Milich, Balentine, and Lynam, 2001), speech and language issues (Cantwell and Baker, 1992), problems with short-term memory, organization, time tracking, initiation and completion of tasks, inhibition of motor activity and problems in planning and sequencing (Nigg, Blaskey, Huang-Pollock, and Rappley, 2002). In addition, nearly 60% of children diagnosed with

ADHD evidence co-morbid learning disabilities (Barkley, 2004).

Within the social/emotional realm, ADHD children can display maturational lags by several years, with behavioral symptoms of aggression, conduct problems, irresponsibility, and a tendency to be disruptive and loud (Barkley, 2004). They also exhibit externalizing behaviors of oppositional/defiance and a tendency to argue (Crystal, Ostrander, Chen, and August, 2001; Diamond, 2005; Hodgens, Cole, and Boldizar, 2000). Additional social/emotional characteristics of children with ADHD may include passivity, shyness, and social withdrawal (Hodgens et al, 2000; Milich et al, 2001) along with increased levels of anxiety, mood instability, and sleep disruption (Wolraich et al, 2005), as well as problems in general unhappiness and low self-esteem (Diamond, 2005). Children with ADHD may demonstrate greater susceptibility to family problems and disrupted relationships later in life, as well as to alcohol and substance abuse, traffic violations, accidents, and frequent emergency room visits (Barkley, 2004). Unfortunately, health insurance coverage for children diagnosed with ADHD is typically restricted, owing to these inherent emotional and physical risks (Wolraich, et al, 2005).

These studies portray the multiple challenges that children with ADHD may experience, and provide support for the impression that some type of neural insult could account for the cognitive deficiencies and behavioral disruptions characteristic of this neurodevelopmental disorder. Simultaneously, these combined reports raise question as to whether an unidentified environmentally-based agent, possibly introduced during crucial developmental times, contributes to adverse neurodevelopmental outcomes (Nigg, 2005).

Overview of Synthetic Oxytocin (OXT)

Utilization of OXT

In 2008, over 4 million births were registered in the United States; over 95% of these births were physician-attended in hospitals; nearly one million of which reported having been labor induced (Martin et al. 2005). According to a study by Mealing, Roberts, Ford, Simpson and Morris (2009), worldwide labor induction rates since 1990 have increased exponentially, including approximately 50% of all U.S. labors (Moleti, 2009). Researchers Martin, Kirmeyer, Osterman, and Shepherd (2009) reported the percentage of late preterm births for which labor was induced more than doubled from 1990 to 2006, reflecting a 20% increase during this time. The majority of all induced

labors have routinely relied upon OXT (specifically Pitocin®) as the chief medical agent (Mealing, et al., 2009). This exogenous polypeptide hormone is utilized to induce or augment complicated childbirth (American College of Obstetrics and Gynecology [ACOG]), 2009). While precise rates of OXT use in the U.S. have not been recently quantified, a report by Hayes and Weinstein (2008) suggests overall rates of OXT usage may be as high as 33.2%.

According to Grobman (2007), elective inductions have also recently increased. These inductions typically involve OXT and are often characterized by prolonged labors requiring epidural anesthesia to allay consequential pain. OXT's rapidly growing usage in routine childbirth prompted Johanson, Newburn and Macfarlane (2002) to argue "The medicalisation of childbirth has gone too far," (p. 892). Although a clear rationale for this increase in obstetric protocol remains unknown, changes in management of labor and delivery practices have been considered as accounting for the rising trend in labor inductions (Martin, et al, 2009). Broad variability in obstetric practices as managed across birthing facilities, possibly attributable to institutional autonomy may, at least in part, account for the observed increase in this procedure (Clark, Simpson, Knox & Garite, 2009). Since OXT was first medically introduced in 1955 (Curtis, 1993), the potential drug-fetal impact has not been carefully considered as posing neurodevelopmental risk.

Concerns in OXT Utilization

OXT's original role in expediting complicated childbirth (ACOG, 2009) is to effectively stimulate uterine contractions. However, if its dosage goes mismanaged, the potential fetal risk-benefit ratio of this dynamic could be overlooked (Engstrom, 1959). While use of this obstetric drug has been long respected throughout the medical community, inconsistencies in its routine administration have been raised as concerns (Clark, et al., 2009). For example, OXT intravenous overflow issues have been implicated in adverse fetal outcomes (Amoore and Adamson, 2003; Wallace, 1996; Wilson and Sullivan, 2004). OXT dosages are routinely incrementally increased "with no apparent risk" if uterine contractions are inadequate and "fetal status is reassuring," (Cunningham et al. 2010, p. 507). In 2009, Wei, Luo, Xu, and Fraser concluded the risk of uterine hyperstimulation during labor was substantially increased with OXT administration, possibly associated with negative effects on fetal oxygen status and abnormal patterns in fetal heart rate. Dawood, Ylikorkala, and Fuchs (1980)

reported low disappearance rates of buccal (orally administered) oxytocin levels from the plasma after discontinuation of labor induction drugs.

Issues of Neurodevelopmental Impact

OXT-induced contractions have been described as being hypertonic; promoting a prenatal atmosphere of intra-uterine hyperstimulation and increased pressure on the fetal head which repeats as these prolonged contractions intensify (Caldeyro-Barcia & Sereno, 1961). This labor dynamic fosters considerable concern regarding impact to the still-developing fetal brain. For example, intrapartum head compression has been implicated in an outcome of fetal neurological injury; linked to fetal hypoxia and ischemic injuries and evidenced by low initial Apgar scores (Schifrin and Ater, 2006). In addition, issues of neural oxygen deprivation (Engstrom, 1959), hypoxia and asphyxia (Clark, et al., 2009), bradycardia (Simpson and James, 2008), fetal intolerance (Joy and Scott, 2009), cord compression (Cunningham, et al., 2005) and insufficient fetal blood supply (Caldeyro-Barcia and Sereno, 1961) have all been considered as arising from OXT-induced contractions. Still other studies have interpreted fetal distress as associated with OXT induction/augmentation during labor (Akoury, 1991; Bidgood and Steer, 1987; Satin, 1992), implying a potential risk to long-term neurological impairment (Bors-Koefoed, et al., 1998. However, none of these efforts have arrived at a definitive conclusion regarding involvement of prenatal OXT exposure specific to neurodevelopmental outcomes such as ADHD.

Brackbill (1979) found sustained neurological post-birth vulnerability to labor and delivery medications, cautioning even a single acute administration could promote cellular migration, aberrations and/or cellular death, risking an evolving developmental disruption. Higetag and Barbas (2006) suggested pressure-induced neural convolutions may impose architectural imprints on the fetal brain, altering cortical topography. Finally, potential adverse reactions of "bradycardia, premature ventricular contractions and other arrhythmias and permanent CNS or brain damage in the fetus…due to increased (maternal) uterine motility" are represented in OXT's pharmaceutical disclosure statement (JHP Pharmaceuticals, 2007, p.1). According to Hirst, Walker, Yawno and Palliser (2009) prenatal stress accounting for fetal brain injury can result in long term neurological impairment.

This body of research justifies further exploration of the

neurodevelopmental impact of prenatal OXT exposure for children. In addition, these collective reports suggest safety risks for the fetus during routine OXT administration, especially under circumstances of prolonged exposure, should be more carefully reviewed. Recently, similar concerns have prompted the Institute for Safe Medication Practices to list OXT as a "high alert medication," (Miller, 2009). While collaborative efforts seem warranted to properly evaluate safe OXT management in its role during labor and delivery (Miller, 2009), the need to quantify the potential risks of perinatal OXT exposure to the course of long-term childhood neurodevelopment cannot be ignored (Simpson and Knox, 2009).

Pilot Study Review

Objective

Trends in ADHD prevalence, as combined with a series of independent reports by biological mothers of children diagnosed with ADHD regarding their OXT-assisted childbirths, prompted a pilot investigation aimed at examining a potential relationship between these two factors. Ultimately, this study sought to determine whether prenatal exposure to OXT may risk lifelong neurodevelopmental sequelae specific to an ADHD outcome.

Method

As previously published (Kurth & Haussmann, 2011), a total of 300 informational study packets were distributed to parents of children attending regionally diverse private and public schools, and those whose children either were or had been treated as patients at pediatric and mental health clinics throughout the U.S. The study invited parents to voluntarily consent to participate via authorization of release of relevant records pertinent to the study rationale. Seeking a sizeable group of heterogeneous participants, ages 3-25 (including siblings), with clinically confirmed ADHD, per DSM-IV-TR criteria (APA, 2000), along with an equivalent group of non-affected (i.e. not diagnosed with ADHD) participants as controls, a final recruited group (N=172) was secured. Signed consents by mothers authorized study access to archival, maternal medical labor and delivery records and respective newborn nursery records of child study participants. Records were gathered from parent-identified birthing facilities, then reviewed and abstracted by trained, independent raters for presence of variables as selected from the relevant literature.

Study variables consisted of 17 select obstetric complications (which included prenatal OXT exposure, either by labor induction and/or by augmentation), presence or non-presence of a confirmed child ADHD diagnosis, a first-degree family history of ADHD (parent self-reported), and child gender. From the retrieved and coded data, four comparison groups emerged, distinguished as (1) children with ADHD and OXT exposure; (2) children with ADHD and no OXT exposure; (3) non-affected children with OXT exposure and (4) non-affected children with no OXT exposure. Statistical analyses relied on PLUM ordinal regression, chi-square, independent samples t test and step-wise multiple regression to investigate the potential power of each variable to predict future ADHD onset via an ex post facto, quasi-experimental design.

Results

In support of the pilot study hypothesis, Kurth and Haussmann (2011) found a predictive correlation of 67.1% (p<.001) between prenatal OXT exposure and ADHD onset within the OXT group of children diagnosed with ADHD (see Figure 1). Stepwise multiple regression analyses yielded predictive trends in maternal gestation length, labor length and OXT exposure time. Medically documented frequencies in use of epidural anesthesia (69.2% or 119 cases), assisted rupture of membranes (43.6% or 75 cases), neonate oxygen supplementation (37.2% or 64) and nuchal cord events (27.9% or 48) were also observed. Although not statistically significant, heavier newborn weight (i.e. >7lbs.) occurred frequently in cases.

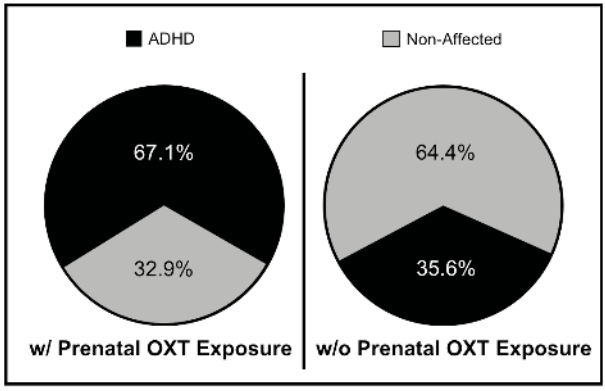

Figure 1. Frequency and Comparison of Prenatal OXT Exposure among ADHD vs. Non-Affected participants

Note: *Prenatal OXT Exposure* refers to maternal labor induction/augmentation via medical administration of synthetic oxytocin. *Non-Affected* refers to participants without a confirmed diagnosis of ADHD. $\chi^2 = 16.99$, $p < .001$.

Reported means in the total sample demonstrated: OXT exposure time (*M*=5 hours); maternal labors (*M*=10 hours); maternal gestation mean (*M*=39 weeks); newborn weight (*M*=7.7oz.). The mean of OXT exposure time in the ADHD group, however, emerged greater (*M*=6 hours) than the mean of OXT exposure time in the Non-Affected group (*M*=3 hours). Similarly, within the ADHD group, the mean of maternal labor measured greater (*M*=12 hours) as compared to this variable's mean as measured within the Non-Affected group (*M*=9 hours).

Group comparisons yielded male dominance trends within the total sample (58.7% males, N=101, vs. 41.3% females, N=71) and also within both the ADHD and the non-Affected groups (64.8% ADHD males, N=57 vs. 35.2% ADHD females, N=31; 52.3% Non-Affected males, N=44 vs. 47.7% Non-Affected females, N=40). Results from the Non-Affected group w/o prenatal OXT exposure (N=56) also revealed more males (N=34) as compared to females (N=22) (see Figure 2). In addition, more males represented the total prenatal OXT-exposed group (N=36) as compared to the groups with no OXT exposure (N=25).

By contrast, the OXT-exposed Non-Affected group demonstrated a greater female propensity (64.3% females, N=18 vs. 35.7% males, N=10). Also, from the total female ADHD group (N=31) a greater number of females demonstrated a history of prenatal OXT exposure (81% OXT females, N=25) as compared to those of this group with no OXT exposure (19% non-OXT females, N=6). There was no significance revealed upon statistical analysis of genetic predisposition throughout any of the groups.

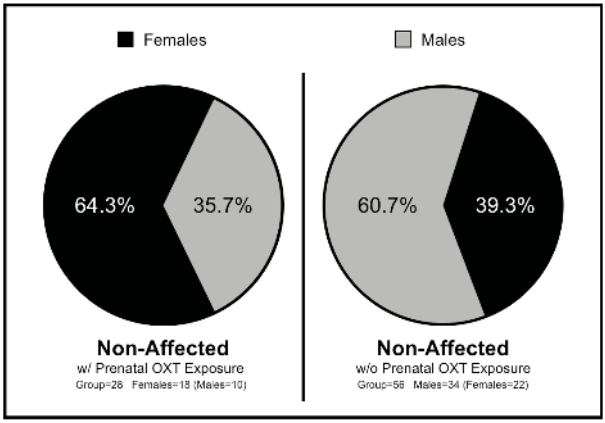

Figure 2. Gender distribution in Non-Affected group w/ and w/o prenatal OXT exposure

Note: *Non-Affected* refers to those participants without a confirmed diagnosis of ADHD. χ^2 value = 4.677 .031 , $p < .05$.

Pilot Study Conclusions

These preliminary results suggest prenatal exposure to OXT nearly doubles the vulnerability to future onset of ADHD in children who are birthed by this means. Furthermore, these findings imply it may be possible for other neurodevelopmental outcomes to arise from this exposure. An expansion of this study should be launched to more carefully investigate the specific pathophysiology involved in this observed association.

Speculative Underpinnings

Given the relative risk of prenatal OXT exposure to affect future onset of ADHD, as was demonstrated by these pilot findings, considerable questions arise as to the precise pathogenesis underlying this dynamic. Since a specific mechanism(s) involved in this association has yet to be identified, and since isolating such mechanism(s) represented a pursuit well beyond the scope of this original study, several speculative impressions are proposed that warrant further research.

Neural Injury Dynamics

First, it is strongly suspected that long-term neurodevelopmental issues may arise for children as the result of prenatal exposure to toxins medically introduced within the intrauterine environment. For example, it seems possible that dynamics inherent during exposure to medical agents commonly utilized during labor and delivery may act and/or interact in a somewhat teratogenic manner, especially when use of these agents during prolonged labors fosters an extended fetal exposure. For example, liberal prenatal use of OXT and/or epidural anesthesia may adversely impact the developing fetus in any number of ways that could compromise the innate toxinsulation of its immature fetal brain. It is speculated that neurodevelopmental risks specific to prenatal OXT exposure may involve the following scenarios: Genetic variants and/or epigenetic triggering; faulty hormonal imprinting (fostering trans-generational imprinting); uterine hyperstimulation (disrupting fetal oxygen and/or restricting cerebral blood flow, leading to vasoconstriction, asphyxia and/or hypoxic-ischemic injury); direct neural soft tissue insult and intracranial pressure linked to prolonged uterine contractions and/or an interplay of any of these factors.

Epigenetic Influence

Epigenetics, heritable but potentially reversible modifications of gene expression and genomic imprinting, play a fundamental role in fetal development and functioning within the placenta (Hales, Grenier, Lalancette, and Robaire, 2011). During critical fetal developmental times, the biological mother's exposure experience to obstetric medications may risk disrupting the balance in expressed genes, possibly challenging the fetus's ability to compensate, risking fetal growth abnormalities (Piedrahita, 2011). Researchers have discussed the possibility that exogenous exposures or manipulations may affect fetal development specific to potential dysregulation of early epigenetic programming (Hales, et al., 2011). This possibility is especially concerning in light of translational research findings involving OXT exposure in prairie voles (Carter, Boone, Pournajafi-Nazarloo & Bales, 2009). Specifically, it has been suggested that exogenous oxytocin risks maternal-fetal blood-brain barrier crossover issues by triggering differential exposure to fetal hypoxia during alterations in intensity of OXT-induced contractions (Carter, et al., 2009).

Directions for Future Research

It is worthy of mention that the Non-Affected group of study participants exposed to OXT during labor and delivery was comprised of nearly twice the number of females as compared to males. This finding raises question as to whether a gender-specific vulnerability to this exposure exists, whereby females carry an innate resilience and males a greater susceptibility to the impact of this exposure. One plausible explanation for these gender differences in ADHD outcome could involve the role of estrogen as a neuroprotectant for females, and this possibility should be further explored. It may also be that female ADHD behavioral symptomology is not as readily recognized as compared to that of their male counterparts, fostering later diagnoses for females. Issues of birth weight respective to gender specificity and/or some other predisposing prenatal factor(s) may also influence sex-specific diagnostic outcomes, and future research should devote itself to exploring the keys behind these measurable trends.

Given these pilot results, a modification of this study as examined through the lens of a possible association to other child neurodevelopmental outcomes, such as Autism Spectrum Disorders (ASD) seems entirely plausible. For example, Wahl (2004) recently

questioned whether dynamics associated in the management of obstetric OXT might contribute to ASD and other similar behavioral disorders. Efforts to pursue such a re-examination should be encouraged, which would seem timely in light of the current focus on etiology of ASD within the scientific community.

Human studies exploring the consequences of exogenous exposures such as prenatal OXT to maternal-fetal epigenetic programming also appear to be lacking. While future research is warranted to illuminate the long-term childhood effects of chemical exposures during labor and delivery, it seems possible that some disturbance or alteration to epigenetic programming during crucial fetal developmental times (Mehler, 2008) may be linked specifically to prenatal OXT exposure. For example, the synergistic properties of OXT, when used in tandem with epidural anesthesia, may play a key role in upsetting the normal template of epigenetic programming for childhood neurodevelopment and this possibility should be more carefully investigated. In addition, issues involving family genetic predisposition to certain neurodevelopmental diagnoses may increase epigenetic vulnerability to this exposure, and this factor should be carefully weighed in future studies.

As previously discussed, issues of vasoconstriction, antenatal oxygenation, and breach of the placental blood-brain barrier are dynamics potentially associated in OXT exposure that seem ripe for human studies and also for translational researchers to pursue. It seems plausible any of these combined influences may weaken or deplete fetal adaptation reserves, playing a key role in the alteration of child neurodevelopmental trajectory. Co-occurring involvement of epidural anesthesia, nuchal chord events and newborn birth weight should also be measured against the frequency and intensity of prenatal OXT exposure, as should maternal demographics such as maternal age, SES, race, level of education, etc. as such factors may play a key role.

Prenatal OXT as an Early Diagnostic Marker

From a clinical perspective, it may be beneficial to engineer a standardized instrument as an instrument designed to assess maternal labor and delivery dynamics from the context of child prenatal histories. The utility of this scale would be in its role as a useful information-gathering protocol for clinicians aimed at identifying early markers of neurodevelopmental disorders, such as ADHD, used at the point of initial developmental intake. This clinical

tool could facilitate a more thorough assessment of children whose symptoms appear neurodevelopmental in nature, potentially expedite earlier detection of neurodevelopmental risk in children, and pave the way for earlier intervention in clinical services and follow-up treatment.

Discussion

The pilot study by Kurth and Haussmann (2011) sought to better understand whether prenatal exposure to OXT may be considered as a risk factor to future long-term neurodevelopmental outcomes specific to ADHD. Consistent with this hypothesis, a relationship between these two factors appears to have emerged.

It is likely a complex constellation of multiple factors are involved in this association, coloring it as more complicated than what was feasible to examine within the limited scope of the recent pilot effort. Some form of fetal hypoxic-ischemic cerebral injury as potentially linked to uterine hyperstimulation during OXT-assisted labors, as combined with epigenetic triggering, OXT blood-brain crossover issues and estrogen mediated gender vulnerability are all speculative underpinnings considered as possibly contributing to long-term neurodevelopmental outcomes. While these issues are scientifically explored, implications for enhanced clinical strategies to more thoroughly assess for ADHD, relying on developmental (i.e. prenatal and childbirth histories) is implied.

Summary

When a maternal labor becomes complicated and an unborn child's life is determined to be at risk, it seems reasonable to expedite its delivery via reliable medical interventions. Current trends in society suggest that personal expectations and preferences also play a role in the use of OXT. However, it is crucial that protocols for childbirth interventions, especially those involving OXT, be executed in terms of safety first as a priority over personal preferences for social conveniences. Furthermore, it is imperative these routine labor and delivery procedures be implemented with a fuller understanding regarding the potential risks involved so as to safeguard and ensure a healthy life-long development for the unborn child.

The birth experience is an intense event in and of itself. When this life entry encounter is compounded by circumstances that warrant OXT utilization, as-yet-unknown mechanisms involved in this exposure may set the stage for neurodevelopmental consequences;

quite possibly triggering pathophysiological reactions that result in future difficulties for a child with such exposure.

The results yielded by this pilot research suggest common obstetric practices may need to be reassessed. OXT usage in common birthing practices should be exercised with greater caution. As efforts are launched to unravel the specific risks involved in this exposure, measures that ensure safe labor and delivery and minimize risks for long-term neurological outcomes should be pursued with considerable vigor. Meanwhile, practitioners who attend childbirth are urged to more carefully consider the long-term benefits vs. risks of OXT-assisted routine labor and delivery protocols. While this opinion is not intended to imply rationale for restriction or prohibition of OXT usage within the obstetric community, its focus is to invite a groundswell of research to address its potential to risk impact to normal childhood neurodevelopmental trajectory.

The long-term neurodevelopmental risks of prenatal exposure to synthetic oxytocin (OXT) remains relatively understudied and poorly understood; it is likely its precise impact to the unborn fetus is multifaceted and complicated. Kurth and Haussmann's (2011) recent exploration appears to have illuminated that this specific prenatal exposure may pose a contributing factor to an ADHD diagnostic outcome. While a direct cause and effect relationship between prenatal OXT exposure and alterations in neurodevelopmental trajectory cannot be determined at this time, the increasing prevalence of routine prenatal OXT usage during labor augmentation/induction as measured alongside the steadily rising incidence of ADHD seems more than coincidental. Moreover, when considering the body of research that documents this exposure may contribute a neural impact for the fetus, a relationship between these factors seems only logical to further explore.

Results of this pilot effort justifiably prompt a host of inquiries and opinions regarding the potential for prenatal OXT exposure to carry specific risks that could alter the normal course of child neurodevelopmental trajectory. As this early research has resulted in more unanswered questions than definitive answers, it seems only logical that future research continue in this vein, aimed at clarifying and illuminating the potential long-term consequences involved in this exposure.

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