Is cortisol the underlying mediator of prenatal risk factors associated with autism spectrum disorders?

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Review

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Is cortisol the underlying mediator of prenatal risk factors associated with autism spectrum disorders?

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Abstract

Introduction

Autism spectrum disorder is a neurodevelopmental condition that exhibits itself in children with impaired communication, sensory and learning problems. It is established that autism spectrum disorder is an inheritable disorder with rates of autism varying with gender in a ratio of approximately four males to every one female.

The debate over the genetic causes of autism continues with the variations in autistic phenotype being due to a combination of genetics and a range of environmental factors. Many of the risk factors for autism spectrum disorder occur prenatally and include a plethora of conditions but not limited to the following factors; age of parents, infections, asthma and autoimmune conditions, gestational diabetes, iron deficiency, obesity, anxiety, stress and depression.

This review investigates the possible role of excess prenatal cortisol in the development of autism spectrum disorder in children who may be genetically predisposed to the detrimental effects of excess cortisol and appraises many of the reported prenatal risk factors which are either caused by excess cortisol or contribute to elevated cortisol during gestation.

Conclusion

If cortisol is an environmental contributor to the development of autism spectrum disorder, many of the risk factors (i.e. stress, iron deficiency, uncontrolled asthma) that result in the elevation of cortisol during pregnancy are treatable and such a greater awareness is required by practitioners to understand that high cortisol levels should raise the same concerns during gestation as does elevated glucose levels.

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Introduction

Autism spectrum disorder (ASD) is a neurological condition defined as a pervasive developmental disorder (PDD) of children. Clinicians and researchers use the term ASD to include autism, Asperger's syndrome and PDD not otherwise specified and has been defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V, American Psychiatric Association). ASD is characterised by an inability to communicate, emotional detachment, and sensory changes with obsessive and repetitive behaviours. Because criteria for diagnosing ASD relies primarily on the impaired communication skills of the affected child, ASD is rarely determined before the child is 4–6 years of age.

We know from twin study research that genetic influence can be the main attribution of ASD[1]; however, the gene or set of genes involved are yet to be identified. This review exposes a number of prenatal factors that exert strong influence over cortisol levels during gestation and neurodevelopment of the foetus where cortisol may significantly reduce the function of amine neurotransmitters such as serotonin[2], which is vital for brain growth and development, and therefore may contribute to neurological problems such as the development of ASD.

Discussion

The author has referenced some of her own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Cortisol metabolism, production and function

Cortisol is a stress hormone that is released in increasing quantities as pregnancy progresses (for review, see Rose'Meyer[2]). The release of cortisol (or glucocorticoids) begins with corticotrophin-releasing hormone (CRH) and arginine-vasopressin production in the hypothalamus which then stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary and consequent release of cortisol from the adrenal cortex. Cortisol is carried in the blood attached to the cortisol binding protein (CBP) and free (unbound) cortisol is considered the bioactive form of cortisol. Cortisol is metabolised to cortisone by the enzyme 11β-hydroxysteroid dehydrogenase-2 (11β-HSD2) which is found in the kidney and adipose tissues (and placenta). Cortisone can also be converted to cortisol by the enzyme 11β-HSD1 which is located in a range of tissues including liver, adipose tissue, blood and brain. Cortisol exerts negative feedback on the hypothalamus to reduce the release of CRH. The endocrine system that controls cortisol release and

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regulation is referred to as the human hypothalamic-pituitary-adrenal (HPA) axis[2].

Cortisol enters the cells where it interacts with intracellular glucocorticoid receptors which then bind to glucocorticoid response elements in the DNA to regulate gene transcription. Cortisol regulates metabolism and as such has a wide range of effects in every organ of the body. Glucocorticoids stimulate the rapid mobilisation of glucose, amino acids and fat from storage sites that make them available for use as energy as well as for synthesis into new products. Glucocorticoids, particularly at high concentrations, have mineralocorticoid activity which causes fluid retention and can increase blood pressure and can also cause insulin resistance resulting in glucose intolerance.

Glucocorticoids have an anti-inflammatory effect where they suppress the immune cell activity to limit an immune response in traumatised tissues. Cortisol has an important role in developing and maintaining brain function and is involved in prefrontal cortical cognitive function, specifically for working memory and has multiple effects on human behaviour such as sleep patterns, mood and the reception of sensory input[3].

Cortisol and gestation

The reproductive hormones oestrogen and progesterone are released in increasing concentrations from the placenta as pregnancy progresses, oestrogen in particular drives the increased production of cortisol through altering CBP production, upregulating 11β-HSD1 levels or directly stimulating the pituitary gland, causing an overall rise in plasma cortisol[2]. Pregnancy is characterised by relative hypercortisolism due to the placental production of CRH[4] and cortisol levels at the time of delivery are 2.5-fold higher than non-pregnant women. However, due to a rise in CBP levels, as gestation proceeds the bioavailable cortisol remains at non-pregnant levels until approximately 25 weeks of gestation and then increases[5]. During pregnancy, peripheral CRH rises due to the release of this hormone from the placenta which causes significant increases in ACTH and total cortisol levels[6]. Placental CRH is identical to hypothalamic CRH in structure; however, unlike the effect that cortisol has on the promoter region in the hypothalamus to reduce CRH release, in the placenta, cortisol activates the promoter region to increase placental CRH release[7]. Elevated cortisol levels in early pregnancy alter placental production of CRH levels in the third trimester and increases the risk of preterm delivery[8]. Exposure to stress during early pregnancy accelerates the rise in placental CRH and reduces the length of gestation[9]. Similar effects have been observed in women administered with corticosteroids in the first trimester[10]. A feature of excess natural or synthetic glucocorticoids during gestation results in preterm delivery with lower median birth weights[11].

Changes in the function of the HPA axis due to parity or pregnancy specific experiences can result in varying foetal exposure to glucocorticoids with steeper decline in morning cortisol levels observed in women who are in their first pregnancy[12].

The foetus is principally protected from elevated cortisol levels through the catabolic action of placental 11β-HSD2 activity[13], and as cortisol levels increase during gestation the levels of placental 11β-HSD2 increases. However, measurement of sex differences on placental 11β-HSD levels in full term births shows that 11β-HSD1 activity (converting cortisone to cortisol) in placentas from male foetuses is greater than female foetuses, with no differences in 11β-HSD2 expression[14].

Maternal salivary cortisol differs by foetal sex with elevated cortisol levels occurring in women carrying male foetuses from 24 to 30 weeks when compared with women carrying female foetuses then crossing over to higher maternal cortisol in women carrying female foetuses to term[15].

Placental 11β-HSD2 deficiency causing overexposure of the foetus to maternal glucocorticoids has been linked to lower birth weights[11] and idiopathic intrauterine growth restriction with an attenuated cortisone to cortisol ratio observed in the umbilical artery[16].

Conditions known to elevate cortisol

Although cortisol is important for the regulation of metabolism its levels will rise during infections. Plasma corticosteroid levels regulate the immune system against invading pathogens and elevated cortisol levels decrease the number of circulating lymphocytes and monocytes. Cortisol plays an important role in promoting an appropriate response to acute infection where the rise in cortisol is proportional to the severity of the illness and can rise up to six times basal levels[17]. The release of cortisol is due to the discharge of inflammatory cytokines from white blood cells involved in the pathogenic response. Periodontal disease has been linked to adverse pregnancy outcomes including preterm birth, low birth weight, preeclampsia and gestational diabetes[18]. Also, in the presence of oxidative stress, the anti-inflammatory effects of cortisol are diminished to cause cortisol resistance[19]. During pregnancy the degree of oxidation stress increases as the pregnancy progresses with increases in advanced oxidation products observed during the first and second trimesters compared with non-pregnant women[20,21].

Salivary cortisol has higher evening levels and is elevated in pregnant stressed women (morning levels not different) and may be related to vaginal bleeding during gestation[22]. Furthermore, maternal depression

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or anxiety are known to contribute to neurodevelopmental disorders in the child, which could be due to exposure to excess cortisol in utero[23]. A summary of symptoms of excess cortisol levels during pregnancy can be seen in Table 1.

Outcomes of excess cortisol for child and mother

Excess cortisol during gestation has been shown to cause pathological hyperactivation of the HPA axis as well as elevation of stress hormones in the offspring[24]. Similar effects have been reported for children with autism, who demonstrated a more variable circadian rhythm as well as statistically significant elevations in cortisol following exposure to a novel, non-social stimulus. However, morning fasting levels of cortisol appear to be lower than IQ and age-matched children[25]. The overall view is that circadian disturbances of cortisol production occur in ASD affected individuals.

Autism prenatal risk factors

It is well established that ASD babies are small for gestational age and preterm[26] which in itself suggests that these children represent a subset of babies subjected to elevated prenatal cortisol. These children are at an elevated risk of developing ASD depending on when during gestation they are affected by excess cortisol or they may be genetically predisposed to be sensitive to excess cortisol. A number of prenatal risk factors for the development of ASD have been identified in epidemiological studies (for review, see Rose'Meyer[2]). Identified maternal risk factors for autism include gestational diabetes and vaginal bleeding during pregnancy as well as drug use, infectious agents and nutritional excesses or deficiencies[27]. Other epidemiological studies have identified increased age of parents, obesity, asthma, stress, infections and inflammatory disorders as prenatal risk factors for ASD (for review, see Rose'Meyer[2]). Many of the listed prenatal risk factors for ASD are an outcome of cortisol excess in the mothers or have the potential to alter cortisol levels either directly through stimulating cortisol release from the adrenal glands, modifying the HPA axis or indirectly through modulating 11β-HSD1/2 expression.

Table 1 Symptoms of excess cortisol during pregnancy[2,35]

Central obesity
Round face
Abdominal striae
High blood glucose
Muscle weakness
Hirsutism and acne
Psychological disturbances
Spontaneous bruising
Ecchymosis
Poor wound healing
Hypertension
Obesity and weight gain

How cortisol mediates prenatal risk factors for autism spectrum disorder

Conditions in the mother including gestational diabetes and hypertension have been identified as risk factors for ASD and other developmental disorders[28] and represent conditions that can be caused by excess cortisol. Prenatal factors such as advanced maternal and paternal age, obesity, have been associated with the risk of ASD. Increased waist circumference associated with advancing age even in the absence of weight gain and obesity are associated with increased cortisol production[2].

Vaginal bleeding during gestation is a risk factor associated with ASD[27] which has been linked to excess cortisol during gestation[22]. Another risk factor for ASD that has been identified is maternal asthma where studies found that asthma caused consequences such as gestational diabetes, preeclampsia, hypertensive disorders and low birth weight[29]. Uncontrolled asthma associated with reduced placental 11β-HSD2 activity significantly increases foetal cortisol levels[30].

Infections and autoimmune diseases have also been reported as factors that are associated with ASD. Experiencing an infection in the first or second trimester requiring hospitalisation is associated with an increased risk of autism[31]. Infections have been reported to increase cortisol as previously discussed[17]. The role of infection in contributing to neurodevelopmental disorders could be attributed to the magnitude of the maternal immune response to the infection rather than a direct action of the infectious agent. A higher rate of autoimmune diseases have been found in families with one member having ASD suggesting that problems with immune function could be a factor in the development of ASD, speculatively due to cytokine-induced dysregulation of the HPA axis.

Iron deficiency has been reported to elevate cortisol levels in pregnant women through increased synthesis of CRH, resulting in increased risk of preterm labour, hypertension and preeclampsia[32]. ASD is associated also with parental psychiatric history with respect to stress, depression and anxiety[28]. Prenatal depression and psychological stress are associated with elevated cortisol levels, prematurity and low birth weights and increased rates of cognitive and behavioural problems in the children[23].

Timeframe for risk of developing autism spectrum disorder during gestation

The time points of gestation which conferred the greatest risk of ASD have been reported in several studies. In one study, the effect of prenatal stress and risk of ASD was calculated for women exposed to hurricanes in the state of Louisiana

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between the years 1980 and 1995[33]. This research found that the greatest risk of stress-induced ASD was at 5–6 months (20–28 weeks). Beversdorf and colleagues[34] also investigated the timing of risk during gestation for ASD and reported that the highest incidence of prenatal stressors associated with the embryological age that coincides with altered development of the cerebellum associated with ASD occurred at 21–32 weeks of gestation with a peak at 25–28 weeks. These two studies suggest a common time period during gestation that confers an increased risk of ASD. Stress is linked to increased cortisol production[22] and as previously discussed women carrying male foetuses have elevated cortisol levels from 24 to 30 weeks when compared with women carrying female foetuses[15] and as such may contribute to the increased rate of ASD in males.

Conclusion

This review investigates the prenatal risk factors associated with ASD with respect to how they alter cortisol levels during gestation. Excess cortisol during gestation is well established to cause neurodevelopmental disorders in children. The prevalence of ASD is predominately associated with males (4:1). Investigations of gender differences in cortisol production and placental protection from cortisol show that the greatest concentrations of cortisol in males coincide with greatest risk for ASD late in the second trimester gestation. If cortisol is an environmental contributor to the development of ASD, many of the risk factors (i.e. stress, iron deficiency and uncontrolled asthma) that result in the elevation of cortisol during pregnancy are treatable and such a greater awareness is required by practitioners to understand that high cortisol levels should raise the same concerns during gestation as does elevated glucose levels.

Abbreviations list

ACTH, adrenocorticotropic hormone; ASD, autism spectrum disorder; CBP, cortisol binding protein; CRH, corticotrophin-releasing hormone; HPA, hypothalamic-pituitary-adrenal; HSD, hydroxysteroid dehydrogenase; PDD, pervasive developmental disorder.

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