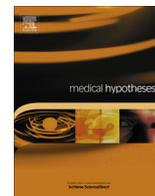


Contents lists available at [ScienceDirect](#)

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Low maternal progesterone may contribute to both obstetrical complications and autism

Patricia M. Whitaker-Azmitia*, Marci Lobel, Anne Moyer

Department of Psychology, Stony Brook University, Stony Brook, NY 11794, United States

ARTICLE INFO

Article history:
Available online xxxxx

ABSTRACT

Studies show increased autism risk among children born to mothers experiencing obstetrical complications. Although this is usually interpreted as suggesting that the obstetrical complications could be causing autism, it is possible that a single factor could be responsible for both complications and autism. We hypothesized that low levels of the hormone progesterone is responsible since it is supplied to the fetus maternally and does not only support pregnancy but also promotes brain development. Following a review of the literature, we report findings from a survey of mothers of autistic children ($n = 86$) compared to mothers of typically-developing children ($n = 88$) regarding obstetrical histories, including five obstetrical risk factors indicative of low progesterone. Using this analysis, the ASD group had significantly more risk factors than controls (1.21 ± 0.09 vs. 0.76 ± 0.08 , $p < .0001$), suggesting low progesterone. Thus, results suggest that low progesterone may be responsible for both obstetrical complications and brain changes associated with autism and that progesterone levels should be routinely monitored in at-risk pregnancies. Our hypothesis also suggests that ensuring adequate levels of progesterone may decrease the likelihood of autism.

© 2014 Elsevier Ltd. All rights reserved.

Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders defined by social and communicative deficits and restricted behaviors and occurring in an approximate male:female ratio of 4:1. The incidence in America is estimated to be 0.9/100 live births, a 7- to 9-fold increase from 20 years ago [1]. Although some of this increase can be explained by changes in diagnostic criteria, the increase cannot be explained solely by this and thus factors must be identified which contribute to autism and which also explain the increased incidence. One important factor to consider is the environment supplied by the mother during gestation.

The study of the gestational environment and autism predates the search for genetic components of ASD. Deykin and MacMahon [2] proposed that obstetrical complications could be interpreted as indicating the presence of a factor which influences both development of the fetal brain and the reproductive health of the mother. We hypothesize that a good candidate for this factor is low progesterone levels in mothers who give birth to a child with autism. Low progesterone would lead to the reproductive problems and compromised fetal brain development associated with ASD, since the only source of progesterone to the fetus is that supplied by the mother [3]. Moreover, advances in fertility and obstetrical

management may be masking progesterone deficiencies and thus also parallel the increase in autism.

Hypothesis

We are proposing that low maternal progesterone leads to both obstetrical complications and the neurodevelopmental changes in the fetal brain leading to autism.

Although in the past, much of the focus on autism research has centered on genetics [4], by re-examining and re-interpreting twin studies [5,6] researchers have increasingly hypothesized that maternal environment could be as important if not more important than genetics as a factor contributing to the disorder.

Beginning more than 30 years ago with the work of Finegan and Quarrington [7] and Deykin and MacMahon [2], many researchers have found an association between specific gestational events and autism [8–21]. Many of these events (such as fertility issues, miscarriages, bleeding, excess maternal weight gain) are known to be associated with low progesterone [22–28].

Ideally, a new hypothesis for the causes of autism should also be able to explain the gender differences in autism and the reported increased incidence over the last 20 years.

The suggestion that low progesterone is involved is a testable hypothesis. Moreover, if it can be shown that low maternal progesterone is associated with autism, prevention strategies become possible.

* Corresponding author. Tel.: +1 631 632 9899; fax: +1 631 632 7876.
E-mail address: patricia.whitaker@stonybrook.edu (P.M. Whitaker-Azmitia).

Progesterone, brain development and autism

Most importantly to our hypothesis, progesterone affects brain development in ways which may be relevant to what is already known about autism.

Progesterone as a neuroprotectant

An increased incidence of autism has been associated with immune-mediated events during early brain development [29,30]. For example, mothers giving birth to children who develop autism have an increased incidence of fevers during pregnancy [31] and an increase in first trimester viral infection and second trimester bacterial infection has been found [32]. In a primate animal model, maternal infection leads to repetitive behaviors, communication deficits and altered social behaviors [33] and several rodent models have found the same [29]. Markers of neuroinflammation, such as microglial activation, have been found in the post-mortem autism brain, further suggesting that a brain inflammation has taken place. [34,35]. Progesterone plays a role in regulating immune function and in protecting the brain from the damaging effects of infections and inflammation. Progesterone stimulates the production of regulatory T cells, preventing aspects of autoimmunity [36]. It acts as an anti-inflammatory [37] and as a regulator of antibody production [38]. Progesterone receptors are found on lymphocytes of healthy pregnancies, increasing with gestational age, but not in non-pregnant lymphocytes or the lymphocytes of women experiencing miscarriage [39]. These receptors function to increase production of certain interleukins, including IL-3, IL-4 and IL-10, as well as to increase production of some antibodies [40]. Thus, if maternal progesterone levels are sufficient, the immune system may be better able to fight an infection and any damaging effects on the developing fetal brain should have been attenuated.

Autism has also been suggested to be related to excitotoxicity and increased oxidative stress [41]. Progesterone can act as a neuroprotectant [42,43] in part through the production of brain-derived neurotrophic factor [44,45] and decreases in apoptosis [46]. Low levels of progesterone may also lead to low levels of its neurosteroid metabolite allopregnanolone which protects the developing brain from excitotoxic damage [47]. Finally, deficits in the development of the blood–brain barrier have been suggested to be important to the cause of autism [48], and progesterone maintains the proteins involved in blood brain barrier (BBB) development and function [49].

Progesterone and neurodevelopment

Functional brain imaging studies have determined that the brain dysfunction of autism may be related to failure in the development of cortical networks resulting in changes in connectivity in specific brain regions [50]. Progesterone plays a role in establishing neuronal connectivity [51] and cortical circuitry [52]. In animal studies, progesterone receptor knockout animals show deficits in maturation of cortical connectivity and sensorimotor integration [53]. Recent work suggests that much of the network pathology is due to axonal pathology, possibly myelination deficits [54–58] and myelination is highly dependent on progesterone [59,60]. Progesterone also has significant effects on the development of subcortical circuitry, for example in social circuitry, where progesterone receptors are highly localized in developing male brains and affect development of the medial pre-optic area of the hypothalamus [61], a region rich in oxytocin-containing neurons involved in social behaviors [62]. Progesterone also affects development of the amygdala [63], a region also involved in social circuitry. At a cellular level, progesterone promotes neurogenesis [64], synaptogenesis

and dendritic formation [65–70], again, changes which have been proposed to underlie autism [71].

Additionally, the serotonergic neurotransmitter system is often implicated in autism [72,73] and progesterone is highly involved in the development and maintenance of this system [74–76]. Since serotonin acts as a neurodevelopmental signal itself [77–79], any serotonin changes could indirectly cause many of the changes observed in autism.

Progesterone and gender differences in autism

The approximate 4:1 male:female ratio for autism may also be related to effects of progesterone. Sex hormones such as progesterone are said to exert both organizing and activating effects in the brain. Organizing effects are structural changes elicited by these hormones during brain development or during plasticity in the adult brain, while activating effects only involve changes in brain activity produced in the mature brain with no associated structural changes. Although the fetal brain has progesterone receptors, the fetus itself does not produce progesterone and the fetal brain is thus dependent on the maternal placenta supply for organizing effects to take place. A male and female fetus will receive the same amount of progesterone from the mother; however, the male fetal brain expresses progesterone receptors at critical periods, whereas the female brain has very few receptors [80]. Moreover, placentas are gender-specific and the placenta of a male fetus is more programmable and more liable to alter production of progesterone [81]. Thus, the male brain or the male-placenta may be more influenced by progesterone levels than the female brain, explaining the male preponderance in autism.

Low progesterone and the increased incidence of autism

Finally, it is important to consider whether or not there are factors in our environment or conditions in our society which lead to decreased progesterone and/or fertility which could parallel the increase in autism. Ovarian suppression (including lowered levels of progesterone) can be related to increased work load, exercise, and low-calorie dieting, even in the presence of proper menstrual cycles [82]. Increased maternal age, increased psychosocial stressors [83], and obesity may all contribute to lowered progesterone. There has also been an increase in preterm birth in the last decade [84], suggesting that low progesterone is becoming more common. The use of artificial reproductive technologies of all kinds has increased almost 40% in the last 10 years [85].

In addition, there are a number of environmental contaminants which are considered to be endocrine disruptors, particularly the xenoestrogen BisPhenol A (BPA), which has a direct effect on fertility and on brain development in animals [86]. Additional endocrine disrupting chemicals such as phthalates are also increasingly found to be present in the human body [87] and many of these compete for a progesterone receptor related to dendritic development [88]. Other toxins which are increasing in the environment, such as heavy metals, have also been linked to autism [89]. Although these may not lower progesterone directly, they could potentially be more damaging to a brain developing without adequate neuroprotection provided by progesterone.

Evaluation of the hypothesis

In order to initially test our hypothesis, we used a case-control survey approach, conducted by the Center for Survey Research at Stony Brook University comparing mothers with autistic children and those without. A list of households with children diagnosed with ASD was obtained from Great Lakes List Management

(<http://www.greatlakeslists.com/v3/>). The control group comprised biological mothers of a child who did not have ASD. This sample was matched within a limited range to the sample of mothers of children with ASD on year of child's birth, current age of mother, and geographical location. The targeted sample was drawn by GENESYS Sampling Systems (<http://www.m-s-g.com/Web/genesys/index.aspx>).

The interview required about 30 min and consisted of 75 questions, including demographic as well as detailed questions regarding pregnancy and delivery. Items of particular relevance to this study included those implicating reproductive hormones, as elaborated upon earlier: whether or not a woman was using contraception (and what type[s]) prior to the index pregnancy, whether or not she was taking oral hormonal contraceptives during the beginning of her pregnancy, infertility treatments prior to the index pregnancy, and maternal weight gain during pregnancy. Other variables likely to be related to hormonal status were also assessed, including prenatal vaginal bleeding, prenatal maternal stress, and use of medications during pregnancy. The groups are described in Table 1.

Results and discussion

Continuous variables and their effect sizes (Cohen's *d*) are given in Table 2. The largest effect sizes in the ASD group were found for number of days born before or after due date, current level of income (ASD was associated with lower incomes) and education of the mother (mothers of ASD children were less educated). Smaller effect sizes were found for the age of mother when the child was born (ASD mothers were younger) and average prenatal distress score (ASD mothers reported more distress). Categorical variables and their effect size are given in Table 3. Variables with the largest effect sizes included: vaginal bleeding (especially in the first

Table 1
Characteristics of the study sample.

	Control (n = 88)	ASD (n = 86)
Current age of mother	47.6 ± .9 ^a	45.1 ± .9
Current age of child	18.1 ± 1.0	16.8 ± .7
Marital status		
Married	66	60
Domestic partnership	1	4
Separated	2	4
Divorced	11	13
Widowed	2	3
Never married	6	2
ASD diagnosis		
None	88	–
Asperger's syndrome	–	24
PDD	–	23
Autism	–	34
Unsure/won't say	–	5
White/caucasian	75	74
African american	4	7
Hispanic/latina	2	2
Asian	2	1
Other/mixed/won't say	4	2
Regional distribution^b		
Northeast	20	19
Midwest	24	23
South	33	30
West	11	14

Note: All respondents were biological mothers of target children.

^a Mean ± SEM.

^b Based on the US Census Bureau definition as follows: Northeast (ME, NH, VT, MA, RI, CT, NY, PA, NJ) Midwest (WI, MI, IL, IN, OH, MN, IA, MO, ND, SD, NE, KS) South (MD, DE, WV, DC, VA, NC, SC, GA, FL, KY, TN, MS, AL, OK, AR, LA, TX) West (MT, ID, WY, NV, UT, CO, AZ, NM, WA, OR, CA).

Table 2

Associations between continuous variables surrounding prenatal and delivery factors and the risk of autism spectrum disorder (ASD).

Factors measured	Calculated <i>d</i> ^a
Number of persons 18 years or older in household	0.0731
Length of labor (hours)	–0.0161
Length of time breastfeeding (months)	0.0362
Birth weight (lb)	0.1132
Birth length (in)	0.1418
Birth year of child	0.1476
Age of father when child was born	–0.01642
Age of mother when child was born	–.02138
Average prenatal distress score	0.2375
Education of mother	–0.2643
Current income level	–0.4166
Number of days born before due date	0.4289
Number of days born after due date	0.4991

Abbreviations: *d*, Cohen's *d*.

Effects that are statistically significantly different than 0 ($p < .05$) are in bold.

^a Effect sizes for *d*: .20 (small), .50 (medium), .80 (large).

Table 3

Associations between categorical variables surrounding prenatal and delivery factors and the risk of autism spectrum disorder (ASD).

Factors measured	RR ^d	OR ^e
Using forceps or vacuum for delivery	0.7000	0.5385
Received pain medication during childbirth	0.7262	0.5577
Received epidural anesthesia	0.8899	0.7936
Received medication to start contractions	0.9706	0.9429
Received other treatments to conceive ^a	1.0126	1.5542
Allergic reaction during pregnancy	1.0179	1.0357
Vaginal vs. Cesarean delivery	1.1054	1.2246
Breastfed	1.0580	1.1171
Tap or bottled water	1.0743	1.1498
Planned Cesarean delivery	1.1111	1.25
Gestational diabetes	1.1114	1.245
Vegetarian diet	1.1114	1.245
Preterm delivery	1.1275	1.2703
Cesarean delivery after labor started	1.1963	1.453
Child admitted to NICU	1.1965	1.4667
Vaginal bleeding	1.2061	1.4766
Major stressful life event^b	1.2618	1.6232
First trimester	0.8095	0.8095
Second trimester	1.2578	1.7411
Third trimester	1.333	2.000
Use of fertility drugs	1.4532	2.5105
No history of oral hormonal contraceptives	1.4908	2.4891
Other medications during pregnancy^c	1.5057	2.5171
Excess weight gain	1.6413	3.5652
Taking contraceptives when conception occurs	2.3333	9.000

Abbreviations: RR, relative risk; OR, odds ratio; NICU, neonatal intensive care unit.

^a Other treatments include donor sperm, donor eggs, or in vitro fertilization.

^b Bereavement, divorce, job loss.

^c Drugs reported: SSRI's, acetaminophen, antibiotics, pseudoephedrine. Effects that are statistically significantly different from 0 ($p < .05$) are in bold.

^d Effect sizes for RR: 1.2 (small), 1.9 (medium), 3.0 (large).

^e Effect sizes for OR: 1.5 (small), 3.5 (medium), 9.0 (large).

trimester), a major stressful event (especially in the second and third trimester), mothers taking fertility drugs to become pregnant, other medication taken during the pregnancy, excessive weight gain during the pregnancy, and the continued use of oral contraceptives while the mother was pregnant. Mothers who gained excess weight during pregnancy had odds of having a child with ASD that were about 3.6 times those of mothers who did not gain excess weight. The strongest effect was from a failure of oral contraceptives in 5 mothers, out of 30 mothers taking these contraceptives, resulting in an unintentional continued use of contraceptives while a mother was pregnant. These mothers had odds of having a child with ASD that were 9 times those of mothers without this risk factor.

Finally, as shown in Table 4, risk factors for mothers in each group which are considered to indicate a suboptimal hormonal maternal environment were combined into a Total Hormonal Risk Factor. Five factors associated with low progesterone were included: vaginal bleeding, two indicators of low fertility – use of fertility drugs and not using contraceptives before pregnancy [22,23], excess weight gain (progesterone is inversely related to weight gain; 26), and taking oral contraceptives when pregnancy begins (effectiveness of contraception relies on a functional progesterone/progesterone receptor feedback system). Using this analysis, the ASD group had significantly more hormonal risk factors suggestive of low progesterone (1.21 ± 0.09) than controls (0.76 ± 0.08 , $p < .0001$).

The strongest of the low progesterone factors identified was the number of women giving birth to a child with autism who experienced contraceptive failure. Interestingly, a similar result was found by Juul-Dam et al. [12] who reported that 12% of children with autism were conceived while their mothers were taking an oral contraceptive. In our results, 5 out of 30 mothers of autistic children became pregnant while on oral contraceptives, while only 1 out of 46 mothers of control children did (16.7% vs. 2.2%).

Contraceptives can be a combination of synthetic estrogens and progestins or progestins alone. In either case, efficacy is based on suppression of ovulation through stimulation of progesterone receptors either in the hypothalamus (inhibiting gonadotropin releasing hormone) or the pituitary (preventing release of luteinizing hormone and follicle stimulating hormone) [90]. It is not known how oral contraception failure occurs, when they are taken regularly, however, we are proposing that a failure of this feedback loop could be responsible. This failure could be due to changes in the sensitivity or functioning of the progesterone receptor. Interestingly, an increased incidence of progesterone receptor-related ovarian and uterine cancers in families of autistic children have been reported [91]. In future, progesterone receptor genetics could be examined in mothers and children to test this possibility. Conversely, exposure to contraceptives could have a direct teratogenic effect on the developing fetus. Although physical malformations from progestin intake early in pregnancy have not been found [92], to our knowledge no behavioral teratology studies have been done.

Of the low progesterone factors, excess maternal weight gain had the second strongest effect on the occurrence of autism. This has also recently been reported in two other studies [21,25].

Our findings show an increased incidence of autism after fertility treatments. Others have looked at the role of assisted conception in autism and a recent review has concluded that these techniques do not add to the increase in autism [93]. However, the studies examined in that review included any assisted reproductive techniques (ART), and did not examine the use of fertility drugs separately, which we have done. We also found no effect of other ART, such as in vitro fertilization. None of the studies, including ours, directly addressed the question of whether or not mothers who give birth to children with autism have greater infertility problems than others. However, we did find that that the mothers of ASD children were significantly less likely to have

previously used oral hormonal contraception in general (35% vs. 52%), suggesting suboptimal fertility may be present. Together, the findings of an increased use of fertility treatments and an absence of hormonal birth control treatments suggest low progesterone in the maternal environment.

An increased incidence of vaginal bleeding and autism has been reported previously [8,9,12,19] and our results are consistent with those. There are a number of causes of bleeding during pregnancy, but in our sample, when bleeding was in the second or third trimester, placental abnormalities (such as previa or abruption) or early labor are most likely. These conditions may result in hypoxia, or placental insufficiency, which has been shown to have an effect on a number of developmental disorders, including schizophrenia. Since the placenta is the sole source of progesterone for the developing fetus, the recent observation of histological differences in placentas from newborns who develop autism offers further support for our hypothesis [94].

There are other factors, not used in our five factor Total Hormonal Risk Factor score, which could also indicate altered progesterone – higher reported stress, earlier birth and higher incidence of infections. Beversdorf et al. [16] found a higher incidence of prenatal maternal stressors, including divorce, job loss, and bereavement at gestational weeks 25–28 in pregnancies resulting in a child with autism. We found higher prenatal distress in the ASD group. These findings could indicate lower progesterone as the neurosteroid allopregnanolone is dependent on progesterone levels. This neurosteroid is known to be a GABA agonist, decreasing anxiety and stress in the mother [69]. Allopregnanolone is also neuroprotective against excess HPA activation, particularly important to a developing brain [95]. Secondly, progesterone plays a role in the onset of parturition either by directly activating receptors in the placenta or through inhibition of oxytocin [96]. As gestation continues, it is generally believed that loss of progesterone, or of progesterone receptors, leads to parturition [97,98]. In either case, lower progesterone levels may explain the increased incidence of earlier births.

There are several findings which others have reported which we failed to replicate. However, our sample uses a case control approach, and changes in some demographic factors (such as maternal age) would not be evident. For example, we found no effect of paternal age. The possible role of parental age in autism is complicated by the fact that delayed child-bearing has increased at the same time as autism has increased, and it is not clear how these may be related [99]. Our study also found a small effect of lower socioeconomic status while most studies in the United States have found an effect of higher socioeconomic status and more education. However, a recent study in a population in Sweden, where there is universal health care, also found autism risk to be associated with a lower socioeconomic status and suggested that previous American studies showed biases based on access to services [100]. Lower socioeconomic status could be a variable contributing to the increased obstetrical complications. However, in our sample this may not be the case, as the birth weights of the ASD group was not significantly different from the typically developing children and low birth weight is a principal outcome of lowered social economic status and lower education [101].

Conclusions and future directions

Lower levels of progesterone in pregnancies leading to autism could explain the cellular and morphological brain changes seen in autism, as well as explain the gender ratio and the increased incidence of autism. We have tested and corroborated our hypothesis indirectly by determining the Total Hormonal Risk Factor in a population of mothers with autistic children. A more direct test is

Table 4
Analyses of hormonal risk factors related to progesterone and autism.^a

	Control	ASD
Total hormonal risk factor score ^b	0.7614 ± .07580	1.2093 ± .09227
$p < .0001$		

^a Continued use of oral contraceptives, excess weight gain, vaginal bleeding, fertility treatments, no previous use of contraceptives.

^b Mean of the average number of risk factors in each group ± SEM.

now necessary. In the future, it may be worthwhile to monitor the levels of progesterone in pregnancies, especially in women who have previously given birth to a child with autism, or who have experienced previous obstetrical complications. In addition, there are polymorphisms of the progesterone receptor which lead to disturbances in the health of a pregnancy [102] which could also be monitored in mothers and children. The hypothesis could also be further tested in an animal model of lowered progesterone and programmable effects of progesterone could be examined in a post-mortem brain sample.

More importantly, identifying changes in the in utero environment leading to an increased risk of autism can more immediately be translated into prevention and treatment strategies than can genetic changes. The current work is thus a return to studies on identifying causes of autism which have a therapeutic potential – restoring appropriate progesterone levels may decrease the incidence of autism.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

This research was supported through a seed Grant from the Center for Survey Research at Stony Brook University. The authors are grateful for the assistance of the Center's Director, Dr. Leonie Huddy.

References

- [1] Hertz-Picciotto I, Delwiche L. The rise in autism and the role of age at diagnosis. *Epidemiology* 2009;20:84–90.
- [2] Deykin EY, MacMahon B. Pregnancy, delivery, and neonatal complications among autistic children. *Am J Dis Child* 1980;134:860–4.
- [3] Hill M, Parížek A, Jirásek JE, Jirkovská M, Dusková M, Klímková M, et al. Is maternal progesterone actually independent of the fetal steroids? *Physiol Res* 2010;59:211–24.
- [4] Chamak B. Autism: overestimation of the genetic origins. *Med Sci (Paris)* 2010;26:659–62.
- [5] Gronborg TK, Schendel DE, Parner ET. Recurrence of autism spectrum disorders in full- and half-siblings and trends over time: a population-based cohort study. *JAMA Pediatr* 2013;167:947–53.
- [6] H.V. Bohm, M.G. Stewart, M. Healy. On the autistic spectrum disorder concordance rates of twins and non-twin siblings. *Med Hypotheses*. (2013) [Epub ahead of print].
- [7] Finegan JA, Quarrington B. Pre-, peri-, and neonatal factors and infantile autism. *J Child Psychol Psychiatry* 1979;20:119–28.
- [8] Gillberg C, Gillberg IC. Infantile autism: a total population study of reduced optimality in the pre-, peri-, and neonatal period. *J Autism Dev Disord* 1983;13:153–66.
- [9] Mason-Brothers A, Ritvo ER, Guze B, et al. Pre-, peri-, and postnatal factors in 181 autistic patients from single and multiple incidence families. *J Am Acad Child Adolesc Psychiatry* 1987;26:39–42.
- [10] Bolton PF, Murphy M, Macdonald H, Whitlock B, Pickles A, Rutter M. Obstetric complications in autism: consequences or causes of the condition? *J Am Acad Child Adolesc Psychiatry* 1997;36:272–81.
- [11] Burd L, Severud R, Kerbeshian J, Klug G. Prenatal and perinatal risk factors for autism. *J Perinat Med* 1999;27:441–50.
- [12] Juul-Dam N, Townsend J, Courchesne E. Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population. *Pediatrics* 2001;107:E63.
- [13] Wilkerson DS, Volpe AG, Dean RS, Titus JB. Perinatal complications as predictors of infantile autism. *Int J Neurosci* 2002;112:1085–98.
- [14] Bilder D, Pinborough-Zimmerman J, Miller J, McMahon W. Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. *Pediatrics* 2009;123:1293–300.
- [15] Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. *Arch Gen Psychiatry* 2004;61:18–27.
- [16] Beversdorf DQ, Manning SE, Hillier A, et al. Timing of prenatal stressors and autism. *J Autism Dev Disord* 2005;35:471–8.
- [17] Larsson HJ, Eaton WW, Madsen KM, et al. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. *Am J Epidemiol* 2005;161:916–25.
- [18] Maimburg RD, Vaeth M. Perinatal risk factors and infantile autism. *Acta Psychiatr Scand* 2006;114:257–64.
- [19] Brimacombe M, Ming X, Lamendola XM. Prenatal and birth complications in autism. *Matern Child Health* 2007;11:73–9.
- [20] Burstyn I, Sithole F, Zwaigenbaum L. Autism spectrum disorders, maternal characteristics and obstetric complications among singletons born in Alberta, Canada. *Chronic Dis Can* 2010;30:125–34.
- [21] Dodds L, Fell DB, Shea S, Armson BA, Allen CA, Bryson S. The role of prenatal, obstetric and neonatal factors in the development of autism. *J Autism Dev Disord* 2011;41:891–902.
- [22] Konno T, Graham AR, Rempel LA, et al. Subfertility linked to combined luteal insufficiency and uterine progesterone resistance. *Endocrinology* 2010;151:4537–50.
- [23] Young SL, Lessey BA. Progesterone function in human endometrium: clinical perspectives. *Semin Reprod Med* 2010;28:5–16.
- [24] Wiebe ER, Trussell J. Contraceptive failure related to estimated cycle day of conception relative to the start of the last bleeding episode. *Contraception* 2009;79:178–81.
- [25] Krakowiak P, Walker CK, Bremer AA, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. *Pediatrics* 2012;129:e1121–8.
- [26] Lagiou P, Lagiou A, Samoli E, Hsieh CC, Adami HO, Trichopoulos D. Diet during pregnancy and levels of maternal pregnancy hormones in relation to the risk of breast cancer in the offspring. *Eur J Cancer Prev* 2006;15:20–6.
- [27] Szekeres-Bartho J, Reznikoff-Etievant MF, Varga P, Pichon MF, Varga Z, Chauat G. Lymphocytic progesterone receptors in normal and pathological human pregnancy. *J Reprod Immunol* 1989;16(3):239–47.
- [28] Haas DM, Ramsey PS. Progesterone for preventing miscarriage. *Cochrane Database Syst Rev* 2008;2:CD003511.
- [29] Patterson PH. Immune involvement in schizophrenia and autism: etiology, pathology and animal models. *Behav Brain Res* 2009;204:313–21.
- [30] Patterson PH. Maternal infection and immune involvement in autism. *Trends Mol Med* 2011;17:389–94.
- [31] Zerbo O, Iosif AM, Walker C, Ozonoff S, Hansen RL, Hertz-Picciotto I. Is maternal influenza or fever during pregnancy associated with autism or developmental delays? Results from the CHARGE (Childhood Autism Risks from Genetics and Environment) study. *J Autism Dev Disord* 2013;43:25–33.
- [32] Atladóttir HO, Thorsen P, Østergaard L, Schendel DE, Lemcke S, Abdallah M, et al. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. *J Autism Dev Disord* 2010;40:1423–30.
- [33] Bauman MD, Iosif AM, Smith SE, Bregere C, Amaral DG, Patterson PH. Activation of the maternal immune system during pregnancy alters behavioral development of rhesus monkey offspring. *Biol Psychiatry* 2013 [Epub ahead of print].
- [34] Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. *Ann Neurol* 2005;57:67–81.
- [35] Morgan JT, Chana G, Pardo CA, et al. Microglial activation and increased microglial density observed in the dorsolateral prefrontal cortex in autism. *Biol Psychiatry* 2010;68(4):368–76.
- [36] Lee JH, Ulrich B, Cho J, Park J, Kim CH. Progesterone promotes differentiation of human cord blood fetal T cells into T regulatory cells but suppresses their differentiation into Th17 cells. *J Immunol* 2011;187:1778–87.
- [37] Wang J, Zhao Y, Liu C, Jiang C, Zhao C, Zhu Z. Progesterone inhibits inflammatory response pathways after permanent middle cerebral artery occlusion in rats. *Mol Med Rep* 2011;4:319–24.
- [38] Hughes GC, Clark EA, Wong A. The intracellular progesterone receptor regulates CD4+ T cells and Tcell-dependent anti-body responses. *J Leukoc Biol* 2013;93:369–75.
- [39] Szekeres-Bartho J, Balasch J. Progestagen therapy for recurrent miscarriage. *Hum Reprod Update* 2008;14:27–35.
- [40] Druckmann R, Druckmann MA. Progesterone and the immunology of pregnancy. *J Steroid Biochem Mol Biol* 2005;97(5):389–96.
- [41] Essa MM, Braidy N, Vijayan KR, Subash S, Guillemin GJ. Excitotoxicity in the pathogenesis of autism. *Neurotox Res* 2013;23:393–400.
- [42] Wright DW, Kellermann AL, Hertzberg VS, et al. ProTECT: a randomized clinical trial of progesterone for acute traumatic brain injury. *Ann Emerg Med* 2007;49:391–402.
- [43] Xiao G, Wei J, Yan W, Wang W, Lu Z. Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: a randomized controlled trial. *Crit Care* 2008;12:R61.
- [44] Cekic M, Johnson SJ, Bhatt VH, Stein DG. Progesterone treatment alters neurotrophin/proneurotrophin balance and receptor expression in rats with traumatic brain injury. *Restor Neurol Neurosci* 2012;30:115–26.
- [45] Jodhka PK, Kaur P, Underwood W, Lydon JP, Singh M. The differences in neuro-protective efficacy of progesterone and medroxyprogesterone acetate correlate with their effects on brain-derived neurotrophic factor expression. *Endocrinology* 2009;150:3162–8.
- [46] Cutler SM, Cekic M, Miller DM, Wali B, VanLandingham JW, Stein DG. Progesterone improves acute recovery after traumatic brain injury in the aged rat. *J Neurotrauma* 2007;24:1475–86.
- [47] Yawno T, Hirst JJ, Castillo-Melendez M, Walker DW. Role of neurosteroids in regulating cell death and proliferation in the late gestation fetal brain. *Neuroscience* 2009;163(3):838–47.
- [48] Theoharides TC, Zhang B. Neuro-inflammation, blood-brain barrier, seizures and autism. *J Neuroinflammation* 2011;8:168–77.

- [49] Ishrat T, Sayeed I, Atif F, Hua F, Stein DG. Progesterone and allopregnanolone attenuate blood-brain barrier dysfunction following permanent focal ischemia by regulating the expression of matrix metalloproteinases. *Exp Neurol* 2010;226(1):183–90.
- [50] Minshew NJ, Keller TA. The nature of brain dysfunction in autism: functional brain imaging studies. *Curr Opin Neurol* 2010;23(2):124–30.
- [51] Sanchez AM, Flamini MI, Polak K, Palla G, Spina S, Mannella P, et al. Actin cytoskeleton remodelling by sex steroids in neurones. *J Neuroendocrinol* 2011;24:195–201.
- [52] Jahagirdar V, Wagner CK. Ontogeny of progesterone receptor expression in the subplate of fetal and neonatal rat cortex. *Cereb Cortex* 2010;20(5):1046–52.
- [53] Willing J, Wagner CK. Sensorimotor development in neonatal progesterone receptor knockout mice. *Dev Neurobiol* 2013 [Epub ahead of print].
- [54] Brun CC, Nicolson R, Lepore N. Mapping brain abnormalities in boys with autism. *Hum Brain Mapp* 2009;30(12):3887–900.
- [55] Zikopoulos B, Barbas H. Changes in prefrontal axons may disrupt the network in autism. *J Neurosci* 2010;30(44):14595–609.
- [56] Carmody DP, Lewis M. Regional white matter development in children with autism spectrum disorders. *Dev Psychobiol* 2010;52(8):755–63.
- [57] Shukla DK, Keehn B, Müller RA. Tract-specific analyses of diffusion tensor imaging show widespread white matter compromise in autism spectrum disorder. *J Child Psychol Psychiatry* 2011;52(3):286–95.
- [58] Steinman G. Predicting autism at birth. *Med Hypotheses* 2013;81(1):21–5.
- [59] Baulieu E, Schumacher M. Progesterone as a neuroactive neurosteroid, with special reference to the effect of progesterone on myelination. *Steroids* 2000;65:605–12.
- [60] Garcia-Segura LM, Melcangi RC. Steroids and glial cell function. *Glia* 2006;54(6):485–98.
- [61] Wagner CK, Nakayama AY, De Vries GJ. Potential role of maternal progesterone in the sexual differentiation of the brain. *Endocrinology* 1998;139(8):3658–61.
- [62] Gil M, Bhatt R, Picotte KB, Hull EM. Sexual experience increases oxytocin receptor gene expression and protein in the medial preoptic area of the male rat. *Psychoneuroendocrinology* 2013;38(9):1688–97.
- [63] Breton AB, Austin KJ, Leedy MG, Alexander BM. Effects of progesterone and RU486 on the development and expression of adult male sexual behaviour and gene expression in the amygdala and preoptic area of the hypothalamus. *Reprod Fertil Dev* 2012;24(7):916–22.
- [64] Barha CK, Ishrat T, Epp JR, Galea LA, Stein DG. Progesterone treatment normalizes the levels of cell proliferation and cell death in the dentate gyrus of the hippocampus after traumatic brain injury. *Exp Neurol* 2011;231(1):72–81.
- [65] Woolley CS, McEwen BS. Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle in the rat. *J Comp Neurol* 1993;336:293–306.
- [66] McEwen BS, Woolley CS. Estradiol and progesterone regulate neuronal structure and synaptic connectivity in adult as well as developing brain. *Exp Gerontol* 1994;29(3–4):431–6.
- [67] Sakamoto H, Ukena K, Tsutsui K. Effects of progesterone synthesized de novo in the developing Purkinje cell on its dendritic growth and synaptogenesis. *J Neurosci* 2001;21:6221–32.
- [68] Romeo RD, Waters EM, McEwen BS. Steroid-induced hippocampal synaptic plasticity: sex differences and similarities. *Neuron Glia Biol* 2004;1(3):219–29.
- [69] Sá SI, Lukoyanova E, Madeira MD. Effects of estrogens and progesterone on the synaptic organization of the hypothalamic ventromedial nucleus. *Neuroscience* 2009;162(2):307–16.
- [70] Baudry M, Bi X, Aguirre C. Progesterone–estrogen interactions in synaptic plasticity and neuroprotection. *Neuroscience* 2013;239:280–94.
- [71] Wegiel J, Kuchna I, Nowicki K, et al. The neuropathology of autism: defects of neurogenesis and neuronal migration, and dysplastic changes. *Acta Neuropathol* 2010;119(6):755–70.
- [72] Chugani DC. Serotonin in autism and pediatric epilepsies. *Ment Retard Dev Disabil Res Rev* 2004;10(2):112–6.
- [73] Azmitia EC, Singh JS, Whitaker-Azmitia PM. Increased serotonin axons (immunoreactive to 5-HT transporter) in postmortem brains from young autism donors. *Neuropharmacology* 2011;60(7–8):1347–54.
- [74] Lima FB, Bethea CL. Ovarian steroids decrease DNA fragmentation in the serotonin neurons of non-injured rhesus macaques. *Mol Psychiatry* 2010;15(6):657–68.
- [75] Bethea CL, Smith AW, Centeno ML, Reddy AP. Long-term ovariectomy decreases serotonin neuron number and gene expression in free ranging macaques. *Neuroscience* 2011;192:675–88.
- [76] Rivera HM, Bethea CL. Ovarian steroids increase PSD-95 expression and dendritic spines in the dorsal raphe of ovariectomized macaques. *Synapse* 2013;67(12):897–908.
- [77] Lauder JM. Ontogeny of the serotonergic system in the rat: serotonin as a developmental signal. *Ann N Y Acad Sci* 1990;600:297–313.
- [78] Mazer C, Muneyyirci J, Taheny K, Raio N, Borella A, Whitaker-Azmitia PM. Serotonin depletion during synaptogenesis leads to decreased synaptic density and learning deficits in the adult rat: a possible model of neurodevelopmental disorders with cognitive deficits. *Brain Res* 1997;760(1–2):68–73.
- [79] Whitaker-Azmitia PM, Druse M, Walker P, Lauder JM. Serotonin as a developmental signal. *Behav Brain Res* 1996;73(1–2):19–29.
- [80] Wagner CK. Progesterone receptors and neural development: a gap between bench and bedside? *Endocrinology* 2008;149:2743–9.
- [81] Mueller BR, Bale TL. Sex-specific programming of offspring emotionality after stress early in pregnancy. *J Neurosci* 2008;28:9055–65.
- [82] Ellison PT. Human ovarian function and reproductive ecology: new hypotheses. *Am Anthropol* 1990;92:933–52.
- [83] Kalantaridou SN, Makriganakis A, Zoumakis E, Chrousos GP. Stress and the female reproductive system. *J Reprod Immunol* 2004;62(1–2):61–8.
- [84] Hall NR. What agent should be used to prevent recurrent preterm birth: 17-P or natural progesterone? *Obstet Gynecol Clin North Am* 2011;38(2):235–46.
- [85] Halpert J. Altering the primal environment: health effects associated with assisted reproductive technologies. *Environ Health Perspect* 2012;120(10):a390–5.
- [86] Hajszan T, Leranath C. Bisphenol A interferes with synaptic remodeling. *Front Neuroendocrinol* 2010;31(4):519–30.
- [87] Wolff MS, Teitelbaum SL, Windham G, et al. Pilot study of urinary biomarkers of phytoestrogens, phthalates, and phenols in girls. *Environ Health Perspect* 2007;115(1):116–21.
- [88] Matsunaga H, Mizota K, Uchida H, Uchida T, Ueda H. Endocrine disrupting chemicals bind to a novel receptor, microtubule-associated protein 2, and positively and negatively regulate dendritic outgrowth in hippocampal neurons. *J Neurochem* 2010;114(5):1333–43.
- [89] Desoto MC, Hitlan RT. Sorting out the spinning of autism: heavy metals and the question of incidence. *Acta Neurobiol Exp (Wars)* 2010;70(2):165–76.
- [90] Rivera R, Jacobson I, Grimes D. The mechanism of action of hormonal contraceptives and intrauterine devices. *Am J Obstet Gynecol* 1999;181:1263–9.
- [91] Ingudomnukul E, Baron-Cohen S, Wheelwright S, Knickmeyer R. Elevated rates of testosterone-related disorders in women with autism spectrum conditions. *Horm Behav* 2007;51(5):597–604.
- [92] Carmichael SL, Shaw GM, Laurent C, Croughan MS, Olney RS, Lammer EJ. Maternal progestin intake and risk of hypospadias. *JAMA. Pediatrics* 2005;159(10):957–62.
- [93] Hvidtjørn D, Schieve L, Schendel D, Jacobsson B, Svaerke C, Thorsen P. Cerebral palsy, autism spectrum disorders, and developmental delay in children born after assisted conception: a systematic review and meta-analysis. *Arch Pediatr Adolesc Med* 2009;163:72–83.
- [94] Walker CK, Anderson KW, Milano KM et al. Trophoblast inclusions are significantly increased in the placentas of children in families at risk for autism. *Biol Psychiatry* 2013 [epub ahead of print].
- [95] Brunton PJ, Russell JA. Endocrine induced changes in brain function during pregnancy. *Brain Res* 2010;1364:198–215.
- [96] Mesiano S, Wang Y, Norwitz ER. Progesterone receptors in the human pregnancy uterus: do they hold the key to birth timing? *Reprod Sci* 2011;18:6–19.
- [97] Lockwood CJ, Stocco C, Murk W, Kayisli UA, Funai EF, Schatz F. Human labor is associated with reduced decidual cell expression of progesterone, but not glucocorticoid, receptors. *J Clin Endocrinol Metab* 2010;95:2271–5.
- [98] Hill M, Pařízek A, Jirásek RJE. Reduced progesterone metabolites in human late pregnancy. *Physiol Res* 2011;60:225–41.
- [99] Shelton JF, Tancredi DJ, Hertz-Picciotto I. Independent and dependent contributions of advanced maternal and paternal ages to autism risk. *Autism Res* 2010;3:30–9.
- [100] Rai D, Lewis G, Lundberg M, et al. Parental socioeconomic status and risk of offspring autism spectrum disorders in a Swedish population-based study. *J Am Acad Child Adolesc Psychiatry* 2012;51(5):467–76.
- [101] Cardwell MS. Stress: pregnancy considerations. *Obstet Gynecol Surv* 2013;18(2):119–29.
- [102] Su MT, Lee IW, Chen YC, Kuo PL. Association of progesterone receptor polymorphism with idiopathic recurrent pregnancy loss in Taiwanese Han population. *J Assist Reprod Genet* 2011;28(3):239–43.