REVIEW

Placental Barrier and Autism Spectrum Disorders: The Role of Prolactin and Dopamine on the Developing Fetal Brain

by ATMARAM YARLAGADDA, MD; GANESH ACHARYA, MD, PhD, FRCOG; JAYAPRADA KASARANENI, MBBS; CHRISTIANE S. HAMPE, PhD; and ANITA H. CLAYTON, MD

Dr. Yarlagadda is Chief of Psychiatry, Behavioral Health Services, McDonald Army Health Center, Fort Eustis, Virginia; Dr. Acharya is Professor of Obstetrics and Gynecology, UiT-The Arctic University of Norway, Consultant Obstetrician and Gynecologist, University Hospital of North Norway, Tromsø, Norway, and Visiting Professor of Obstetrics and Gynecology, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institute, Stockholm, Sweden; Dr. Kasaraneni is with Norton Healthcare, Louisville, Kentucky; Dr. Hampe is Associate Professor of Medicine, Department of Medicine, University of Washington, Seattle, Washington; and Dr. Clayton is Professor and Chair, Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, Virginia.

Innov Clin Neurosci. 2015;12(9–10):14–17

FUNDING: No funding was received for the preparation of this manuscript.

FINANCIAL DISCLOSURES: The authors have no conflicts of interest relevant to the content of this article.

DISCLAIMER: The views and opinions expressed in this article are those of the authors and do not reflect the official policy or position of the United States Army, Department of Defense, or United States Government.

ADDRESS CORRESPONDENCE TO:
Atmaram Yarlagadda, MD;
E-mail: atma@golfolks.com

KEY WORDS: Placenta, fetal brain, autism spectrum disorders (ASD), prolactin, dopamine, oxytocin, gabapentin, gene expression

ABSTRACT

Dopamine and prolactin exhibit opposite effects on lactation. However, a possible role for increased prolactin/dopamine ratio in postpartum mood and thought disorders and as a prognostic indicator of the mother's future mental health has not been well investigated. Postpartum depression is a serious condition with potentially devastating outcomes for both the mother and the infant. Early detection and treatment of this condition can have impressive results. Treatment options include antidepressant medications for mood disorders and use of antipsychotics and electroconvulsive therapy to address postpartum psychosis. Although there are obvious benefits of such treatments on the welfare of the mother and her child, broader implications of these treatments on lactation and child growth and development are not known. This review article explores a possible link between *in-utero* exposure to a high maternal prolactin/dopamine ratio and subsequent development of autism spectrum disorders. We hypothesize that a comprehensive, biologically oriented approach to the use of psychotropics in the regulation of neurotransmission during pre- and postpartum periods may result in better outcomes in this population.

INTRODUCTION

An elevated serum prolactin (PRL) level is considered to be the confirmatory test for the diagnosis of acute generalized seizures in neurology. Treatment with antipsychotics resulting in

galactorrhea also links dopamine to prolactin. Galactorrhea, seizures associated with eclampsia, depression, and psychosis are serious concerns, deserving of attention, especially in women of childbearing age. While these symptoms fall under different clinical specialties (e.g., family medicine, obstetrics/gynecology, neurology, and psychiatry), they all have a common biological link. Eclampsia serves as a good example of a peri-partum condition that deserves attention since it is complicated by seizures. Therefore, the ratio of prolactin to dopamine could be used as a diagnostic and prognostic marker. Effects of an altered dopamine/prolactin ratio while *in-utero* on the growing fetal brain may potentially lead to pervasive developmental disorders later in postnatal life.

Research is limited pertaining to women's health from a psychiatric standpoint, specifically mood and thought disorders impacting *in-utero* brain development and lactation. In this article, we explore the available research to understand the relevance of prolactin and dopamine to the development of autism spectrum disorders (ASD).

PROLACTIN, DOPAMINE, AND AUTISM SPECTRUM DISORDERS

During pregnancy, normal physiological changes occur in the pituitary gland, with hypertrophy of the gland due to lactotroph hyperplasia.[1] This has been proven by autopsy studies demonstrating evidence of hyperplasia from the first month of pregnancy to several months after delivery.[2] Hormonal evaluation becomes complicated, as changes in the pituitary gland, along with increases in binding globulin levels, occur as a normal physiological response. The highest pituitary volumes and widths of the infundibulum were observed during the first three postpartum days.[3]

In preeclampsia, the primary cause is thought to be abnormal placental implantation as evidenced by defective invasion of spiral arteries by extravillous cytotrophoblast cells. These abnormalities are directly influenced by the nitric oxide pathway affecting the maternal vascular tone.[4] Oxidative stress, as a result, releases oxidized lipids, free radicals, cytokines, and serum soluble vascular endothelial growth factor 1, causing endothelial dysfunction with vascular hyperpermeability and peripheral compensation for the uterine artery constriction.[5] There is evidence of human leukocyte antigen (HLA) system involvement as well. Women showing reduced levels of HLA-G and HLA- E also exhibit defective invasion of spiral arteries.[6] Vascular endothelial growth factor and placental growth factor are decreased due to increased levels of soluble fms-like tyrosine kinase 1 (sFlt1).[7]

Complex physiological changes that occur during normal pregnancy cause vasodilation of the pituitary gland and an increase in secretion of prolactin.[8] In addition to prominent roles in lactation and reproduction, prolactin has other biological functions, including the regulation of angiogenesis.[9] Since abnormal angiogenesis is thought to be the contributing factor to the development of preeclampsia, it can be hypothesized that prolactin could have significant effect on the overall course of preeclampsia in pregnant women. A prospective study from Mexico[10] reported that differences in prolactin excretion were more pronounced as the severity of preeclampsia increased, regardless of the degree of proteinuria, gestational age, and serum PRL levels. The authors therefore suggest that changes in urinary prolactin concentration accurately reflect the extent and intensity of damage to the glomerular endothelium and, probably as well, to the systemic vascular endothelium.[10] The same would apply for eclampsia, as it is a progression of preeclampsia that is complicated by seizures.

The relationship of preeclampsia and eclampsia to depression is unclear. The platelets examined in depressed patients by Nemeroff and Musselman[11] showed increased levels of 5-hydroxytryptamine 2 binding density, leading to increased vasoconstriction. Kurki et al[12] conducted a prospective study on Finnish women and observed that depression was associated with an increased risk of preeclampsia [odds ratio (OR) 2.5; 95% confidence interval (CI): 1.2–5.3]. In a case-control study in Peru by Qiu et al,[13] the authors concluded that there was an increased risk of preeclampsia in women with previous depression.

Altered lactation can occur in postpartum women who had preeclampsia or eclampsia. In a review article by Beardman et al[14] that examined excretion of antihypertensive medication into human breast milk, the authors found that, according to the available research, antihypertensive medications are present in breast milk although differences in the milk/plasma ratio are related to lipid solubility and extent of ionization of the drug at physiologic pH. Although the Committee on Drugs of the Amercian Academy of Pediatrics considers the beta-blocker atenolol compatible with breastfeeding, it appears to be concentrated in breast milk, while propranolol and labetalol are not; for that reason, propranolol and labetalol are recommended if a beta-blocker is indicated.[15] Diuretics may reduce milk volume and suppress lactation.[15]

Given the scarcity of data, breast-fed infants of mothers taking antihypertensive agents should be closely monitored for potential adverse effects.[16] Methyldopa and hydralazine have not been shown to cause harm in breastfeeding infants.[17]

In addition, a United States study by Cordero et al[18] concluded that despite all the challenges, the strongest indicator of breastfeeding success using logistic regression analysis was the intention to breastfeed. Dangat et al[19] explored changes in the composition of breast milk in women with preeclampsia and

found that long-chain polyunsaturated fatty acids and neurotrophins are increased in breast milk. Their study also showed that an increase in long chain polyunsaturated fatty acids negatively influences the child's weight as well as height.[19]

Clinical depression is estimated to occur in 10 to 15 percent of women during pregnancy, while postpartum depression occurs in about 10 to 22 percent of women.[20] In women diagnosed with moderate to severe depression, pharmacotherapy during pregnancy and during the postnatal period could have benefits for both mother and infant.[21] The usage of psychotropics for postpartum depression and psychosis has been debated over the years, since these medications can be transferred to the fetus through the placenta and via breast milk to the infant. However, most psychotropics are considered relatively safe for infants during lactation.[22] A study conducted in the United Kingdom by Howard et al[23] showed that women with nonaffective psychoses are less fertile than controls, partly because of hyperprolactinemia secondary to antipsychotic drug treatment.

Another topic that merits exploration is the potential relationship between the prolactin-dopamine ratio exposure *in utero* and the development of pervasive developmental disorders in children. It can be hypothesized that a placental barrier exists for pervasive developmental disorders (PDD), such as the one described by Holmes et al[24] for stress hormone influence on fetal mice brain. This team showed evidence in mice of fetal growth reduction along with development of mood disorders later in life, supporting the hypothesis that placental 11-beta-HSD2 is an essential barrier to maternal glucocorticoids.[24] Muhle et al[25] performed a review that yielded convincing evidence for multiple interacting genetic factors as the main causative determinants of autism. They also noted that data from whole-genome screens in multiplex families suggest interactions of at least 10 genes in the causation of autism.[25] In a study by Yrigollen et al,[26] the authors examined the allelic associations between genetic variants in six genes (oxytocin [OXT], oxytocin receptor gene [OXTR], prolactin [PRL], prolactin ligand receptor [PRLR], dopamine beta hydroxylase [DβH, and Finkel-Biskis-Jinkins (FBJ) murine osteosarcoma viral oncogene homolog B (FosB) and found that they are involved in the control of maternal and affiliative behaviors. The results showed an association between the PRL ligand and the prolactin receptor, which have allelic associations with ASD. This might suggest the direct involvement of the PRL pathway and possible indirect effects of other pathways with which PRL interacts. The study also revealed an allelic association between ASD and the OXTR.[26]

We conclude that in order to understand the genetic etiology of PDD, we need further genetic mapping of parents and their children who are diagnosed with PDD spectrum conditions. So far, according to a review article by Lim et al[27] that examined fetal animal model studies conducted on rats, mice, and rhesus monkeys, hormonal fluctuations in pregnant animals affect neural control of social functioning.[27] In rat models, it was shown by Kennett et al[28] that oxytocin stimulates prolactin secretion leading to a positive oxytocin-prolactin feedback loop. This induces the dopamine-prolactin negative feedback loop, thus impacting two separate feedback loop systems.[28]

Rodent models, as described by Lim et al, showed that low levels of oxytocin influenced social recognition and social bonding,[27] and it was disregulated in people with PDD.[29] A human study found that autistic children did have significantly lower levels of plasma oxytocin compared to age-matched normal subjects.[30] Another study showed that autistic patients do in fact have a decrease in plasma oxytocin, but showed an increase in the pro-hormone of oxytocin.[31] These findings contribute directly to the growing evidence of the involvement of OXT in the formation of affiliated behaviors in general and their disruption in ASD, and indirectly to hypotheses of possible connections between the OXT and GABA systems, the latter being consistently implicated in ASD. It has been studied that during labor, the stress on the mother and baby make the blood brain barrier (BBB) in the child more permeable to lipid insoluble molecules. Therefore, any exogenous oxytocin administered during labor can cross the BBB into the newborn's brain, consequently influencing social behavior.[32]

CONCLUSION

In summary, placenta being the most invasive tissue, to establish the hypothesized altered genetic transcription as the cause for complex phenotypic expressions in PDD, hormonal and environmental causes need to be ruled out. A pilot study to compare the ratios of prolactin/dopamine and oxytocin/GABA in gestational periods (20–40 weeks) as well as in the placenta would, in our opinion, provide valuable insights into the etiology of PDD. Alternative approaches may include the measurement of autoantibodies directed to the GABA-generating enzyme, glutamate decarboxylase 65 (GAD65), which have been detected in the serum of 60 percent of autistic children.[33] Whether these autoantibodies inhibit GAD65 function as has been proposed for GAD65Ab in stiff person syndrome[34] remains to be established.

REFERENCES

1. Karaca Z, Kelestimur F. Pregnancy and other pituitary disorders (including GH deficiency). *Best Pract Res Clin Endocrinol Metab.* 2011;25(6):897–910.
2. Scheithauer BW, Sano T, Kovacs KT, et al. The pituitary gland in pregnancy: a clinicopathologic and immunohistochemical study of 69 cases. *Mayo Clin Proc.*

1990;65(4):461–474.
3. Dinc H, Esen F, Demirci A, et al. Pituitary dimensions and volume measurements in pregnancy and post partum. MR assessment. *Acta Radiol.* 1998;39(1):64–69.
4. Fisher SJ, McMaster M, Roberts M. *Chesley's Hypertensive Disorders in Pregnancy.* Waltham, MA: Academic Press; 2009.
5. Roberts JM. Endothelial dysfunction in preeclampsia. *Semin Reprod Endocrinol.* 1998;16(1):5–15.
6. Colbern GT, Chiang MH, Main EK. Expression of the nonclassic histocompatibility antigen HLA-G by preeclamptic placenta. *Am J Obstet Gynecol.* 1994;170(5 Pt 1):1244–12450.
7. Genbacev O, DiFederico E, McMaster M, Fisher SJ. Invasive cytotrophoblast apoptosis in pre-eclampsia. *Hum Reprod.* 1999;14 Suppl 2:59–66.
8. Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: structure, function, and regulation of secretion. *Physiol Rev.* 2000;80(4):1523–1631.
9. Struman I, Bentzien F, Lee H, et al. Opposing actions of intact and N-terminal fragments of the human prolactin/growth hormone family members on angiogenesis: an efficient mechanism for the regulation of angiogenesis. *Proc Natl Acad Sci U S A.* 1999;96(4):1246–1251.
10. Leanos-Miranda A, Marquez-Acosta J, Cardenas-Mondragon GM, et al. Urinary prolactin as a reliable marker for preeclampsia, its severity, and the occurrence of adverse pregnancy outcomes. *J Clin Endocrinol Metab.* 2008;93(7):2492–2499.
11. Nemeroff CB, Musselman DL. Are platelets the link between depression and ischemic heart disease? *Am Heart J.* 2000;140(4 Suppl):57–62.
12. Kurki T, Hiilesmaa V, Raitasalo R, et al. Depression and anxiety in early pregnancy and risk for preeclampsia. *Obstet Gynecol.* 2000;95(4):487–490.
13. Qiu C, Sanchez SE, Lam N, et al. Associations of depression and depressive symptoms with preeclampsia: results from a Peruvian case-control study. *BMC Womens Health.* 2007;7:15.
14. Beardmore KS, Morris JM, Gallery ED. Excretion of antihypertensive medication into human breast milk: a systematic review. *Hypertens Pregnancy.* 2002;21(1):85–95.
15. Schaefer C. *Drugs During Pregnancy and Lactation.*Waltham, MA: Academic Press; 2007:680–684
16. Moser M. Working group report on high blood pressure in pregnancy. *J Clin hypertens.* 2001;3:2.
17. Brown CM, Garovic VD. Drug treatment of hypertension in pregnancy. *Drugs.* 2014;74(3):283–296.
18. Cordero L, Valentine CJ, Samuels P, et al. Breastfeeding in women with severe preeclampsia. *Breastfeed Med.* 2012;7(6):457–463.
19. Dangat K, Kilari A, Mehendale S, et al. Preeclampsia alters milk neurotrophins and long chain polyunsaturated fatty acids. *Int J Dev Neurosci.* 2014;33:115-21.
20. Kim J, Riggs KW, Misri S, et al. Stereoselective disposition of fluoxetine and norfluoxetine during pregnancy and breast-feeding. *Br J Clin Pharmacol.* 2006;61(2):155–163.
21. Kristensen JH, Ilett KF, Rampono J, et al. Transfer of the antidepressant mirtazapine into breast milk. *Br J Clin Pharmacol.* 2007;63(3):322–327.
22. Tripathi BM, Majumder P. Lactating mother and psychotropic drugs. *Mens Sana Monogr.* 2010;8(1):83–95.
23. Howard L, Webb R, Abel K. Safety of antipsychotic drugs for pregnant and breastfeeding women with non-affective psychosis. *BMJ.* 2004;329(7472):933–934.
24. Wyrwoll CS, Holmes MC. Prenatal excess glucocorticoid exposure and adult affective disorders: a role for serotonergic and catecholamine pathways. *Neuroendocrinology.* 2012;95(1):47–55.
25. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. *Pediatrics.* 2004;113(5):e472–486.
26. Yrigollen CM, Han SS, Kochetkova A, et al. Genes controlling affiliative behavior as candidate genes for autism. *Biol Psychiatry.* 2008;63(10):911–916.
27. Lim MM, Bielsky IF, Young LJ. Neuropeptides and the social brain: potential rodent models of autism. *Int J Dev Neurosci.* 2005;23(2–3):235-243.
28. Kennett JE, McKee DT. Oxytocin: an emerging regulator of prolactin secretion in the female rat. *J Neuroendocrinol.* 2012;24(3):403–412.
29. Andari E1, Duhamel JR, Zalla T, et al. Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *Proc Natl Acad Sci U S A.* 2010;107(9):4389–4394.
30. Modahl C, Green L, Fein D, et al. Plasma oxytocin levels in autistic children. *Biol Psychiatry.* 1998;43(4):270-7.
31. Green L, Fein D, Modahl C, et al. Oxytocin and autistic disorder: alterations in peptide forms. *Biol Psychiatry.* 2001;50(8):609–613.
32. Saunders H, Habgood M, Dziegielewska K. Barrier mechanisms in the brain: immature brain. *Clin Exp Pharmacol Physiol.* 1999;26:85–91.
33. Rout UK, Mungan NK, Dhossche DM. Presence of GAD65 autoantibodies in the serum of children with autism or ADHD. *Eur Child Adolesc Psychiatry.* 2012;21(3):141–147.
34. Raju R, Foote J, Banga JP, et al. Analysis of GAD65 autoantibodies in Stiff-Person syndrome patients. *J Immunol.* 2005;175(11):7755–7762. ■