

Elevated Brain Monoamine Oxidase A Binding in the Early Postpartum Period

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Context: The early postpartum period is a time of high risk for a major depressive episode (or postpartum depression), with a prevalence of 13%. During this time, there is a heightened vulnerability for low mood because postpartum blues is common. Severe postpartum blues can herald the onset of postpartum depression. The neurobiological mechanisms to explain postpartum blues and the high risk for the onset of postpartum depression in the first few weeks after delivery are unclear. Estrogen levels drop 100- to 1000-fold during the first 3 to 4 days postpartum, and changes in estrogen levels have an inverse relationship with monoamine oxidase A (MAO-A) density. However, MAO-A levels have never been measured in the early postpartum period.

Objective: To determine whether brain MAO-A binding is elevated in the early postpartum period.

Design: Case-control study.

Setting: Tertiary care academic psychiatric hospital in Toronto, Ontario, Canada.

Participants: Fifteen healthy women who were 4 to 6 days postpartum and 15 healthy women who had not recently been postpartum underwent carbon 11-labeled har-

mine positron emission tomography scanning. All women were nonsmoking and medication free.

Main Outcome Measure: MAO-A total distribution volume, an index of MAO-A density, was measured in prefrontal cortex, anterior cingulate cortex, anterior temporal cortex, thalamus, dorsal putamen, hippocampus, and midbrain.

Results: MAO-A total distribution volume was significantly elevated (mean, 43%) throughout all analyzed brain regions during the early postpartum period.

Conclusions: Elevated MAO-A levels in the early postpartum period can be interpreted as a marker of a monoamine-lowering process that contributes to the mood change of postpartum blues. Rather than a purely psychosocial model, we propose a neurobiological model of estrogen decline, followed by elevated MAO-A binding, low mood, and subsequently a period of high risk for major depressive episodes. Our model has important implications for preventing postpartum depression and for developing therapeutic strategies that target or compensate for elevated MAO-A levels during postpartum blues.

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POSTPARTUM BLUES IS A SYNDROME of sadness that may be accompanied by mood lability, anxiety, insomnia, poor appetite, and irritability. It typically occurs within the first week after delivery and is common, occurring in 70% of new mothers.¹ Postpartum blues is important because of its relationship to the onset of clinical-level postpartum depression (PPD). Postpartum blues occurs at the beginning of a high-risk period for the onset of PPD. Women with postpartum blues have a 4-fold risk of experiencing PPD, and greater severity of postpartum blues is associated with greater risk for PPD.^{1,2} *Postpartum depression* is defined as a major depressive episode start-

ing within 4 weeks of delivery and is a major public health problem. It is common, with a prevalence of 13% within the first 3 months postpartum, and has adverse sequelae such as future maternal depressive episodes and impaired infant development.³⁻⁵ Unfortunately, the neurobiological mechanisms that may be related to mood dysregulation in the early postpartum period are unclear.

Monoamine oxidase A (MAO-A) is an enzyme primarily located on outer mitochondrial membranes and has been detected in monoamine-releasing neurons and glia.⁶ MAO-A metabolizes monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine in the brain. Excessive removal of these mono-

amines, as demonstrated by paradigms such as tryptophan depletion, inhibition of tyrosine hydroxylase, or breakdown of the storage of all 3 monoamines, is associated with low mood.⁷ Elevated MAO-A levels in affect-modulating regions is considered an important monoamine-lowering process during major depressive episodes of major depressive disorder.^{8,9} Increasing monoamine availability by blocking MAO-A is an effective treatment of depression.¹⁰

MAO-A binding is measurable using carbon 11-labeled (¹¹C) harmine and positron emission tomography (PET).^{8,9,11,12} Carbon 11-harmine has excellent qualities for measuring MAO-A binding, showing high affinity (K_i, 2nM) and high selectivity for MAO-A.¹² In humans, high brain uptake occurs, with the greatest uptake in regions with the highest MAO-A density such as cortex.¹² Metabolites of harmine are polar and do not cross the blood-brain barrier.¹³ Specific binding of ¹¹C-harmine can be fully displaced by MAO-A inhibitors in animal models.^{12,14} In humans, MAO-A inhibitors at clinically tolerable doses can displace 80% of specific binding.¹¹

An inverse relationship exists between changes in estrogen levels and MAO-A density. In assays of cell lines, rodents, and monkeys, interventions that lower estrogen levels are associated with greater MAO-A levels, MAO-A messenger RNA, or MAO-A activity.¹⁵⁻¹⁸ In a model using a human neuroblastoma cell line transfected with estrogen receptor complementary DNA, estrogen receptor activation correlates with decreased MAO-A activity.¹⁸ In investigations comparing ovariectomized Sprague-Dawley rats treated with placebo or estrogen, the placebo condition was associated with greater MAO-A activity in regions with high MAO-A density such as amygdala,¹⁹ hypothalamus,¹⁹ and locus ceruleus.¹⁵ In ovariectomized macaque monkeys, estradiol administration reduced MAO-A messenger RNA in the dorsal raphe nucleus.¹⁷ In another study¹⁶ of ovariectomized macaque monkeys, 1 month of estradiol administration reduced MAO-A protein in the midbrain by approximately 50%.

In the early postpartum period, estrogen levels drop 100- to 1000-fold during the first 3 to 4 days postpartum.^{3,20,21} Given the decline in estrogen during the first 4 days postpartum, the relationship between estrogen decline and elevation of MAO-A synthesis, and the link between greater MAO-A levels and lower mood, we hypothesized that elevated MAO-A binding occurs during the early postpartum period, when postpartum blues tend to happen, in brain regions participating in affect regulation. Because the rationale for the hypothesis is based on an abrupt decline in estrogen levels throughout the brain, we also hypothesized that elevated MAO-A binding would be present throughout all analyzed brain regions.

METHODS

PARTICIPANTS

Fifteen healthy women who were 4 to 6 days postpartum (mean [SD] age, 33 [7] years) and 15 age-matched healthy women who had not recently been postpartum (mean [SD] age, 31 [4] years)

completed the protocol. In the postpartum group, all women were breastfeeding, 2 women had delivered via cesarean section, and 1 woman had delivered twins vaginally. Nine women had 1 previous child. In the control group, 3 women were nulliparous, 5 had 1 previous child, and 7 had 2 previous children. Those who had children were 3 to 8 years postpartum, and all those had breastfed their children in the past. Two women had undergone cesarean sections. Among control patients, performance of ¹¹C-harmine PET imaging was performed throughout the menstrual cycle, with 10 images in the follicular phase.

All women in the study were nonsmoking, had no history of neurotoxin use, and underwent a urine drug screen. The absence of any past or present DSM-IV Axis I disorders was determined using the Structured Clinical Interview for DSM-IV nonpatient edition²² and the Hamilton Scale for Depression.²³ The study and recruitment procedures were approved by the Research Ethics Board for Human Subjects at the Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada. Each woman underwent a single session of ¹¹C-harmine PET scanning within the first week of giving birth (4-6 days postpartum). The radioactive half-life of carbon 11 is 20 minutes. Women refrained from breastfeeding for more than 13 half-lives of the radiotracer (>260 minutes) after injection (a cutoff point similar to that in other investigations of the early postpartum period²⁴). Radioactivity in breast milk was measured at approximately 250 minutes after injection and was indistinguishable from background activity at that time. A Geiger counter measurement performed at the chest surface in all women gave similar results.

IMAGE ACQUISITION AND ANALYSIS

For the region of interest (ROI) method, each woman underwent magnetic resonance (MR) imaging using a 1.5-T imaging system (Signa; GE Medical Systems, Milwaukee, Wisconsin), including fast spoiled gradient echo, T1-weighted images, and x, y, and z voxels of 0.78, 0.78, and 1.5 mm, respectively. The ROIs were determined on MR images that were coregistered to each integral ¹¹C-harmine PET image using a mutual information algorithm.²⁵ Regions of interest were determined on the MR image using a semiautomated method in which regions on a template MR image are transformed to the individual MR image via a series of transformation and deformation parameters that match the template image to the coregistered MR image,²⁶ followed by selection of gray matter voxels within the ROI.²⁷ The location of the ROI was verified by visual assessment of the ROI on the coregistered MR image and the integrated ¹¹C-harmine PET image. We sampled regions that are involved in mood regulation²⁸ such as prefrontal cortex and hippocampus, as well as anterior cingulate cortex, anterior temporal cortex, dorsal putamen, thalamus, and midbrain. MAO-A total distribution volume (V_T) was measured using the 2-tissue compartment model⁸ and the method by Logan et al.²⁹ For the voxelwise analysis, parametric images of ¹¹C-harmine V_T were generated by an application of the graphic method by Logan et al,²⁹ including a plasma input function. Application of the model was performed on the 3-dimensional dyadic wavelet-transformed dynamic PET image using designed software (ROMI; Vivian Rakoff Neuroimaging Centre, Toronto, Ontario, Canada).²⁷ This approach overcomes noise susceptibility when solving linear models in real space and is reliable across regions of different receptor density in the presence of noise.³⁰ Each parametric map was spatially normalized by a standard template (Montreal Neurological Institute, Montreal, Quebec, Canada) using statistical parametric mapping normalization and coregistration tools (SPM2; Department of Cognitive Neurology, Wellcome Trust Centre for Neuroimaging, London, En-

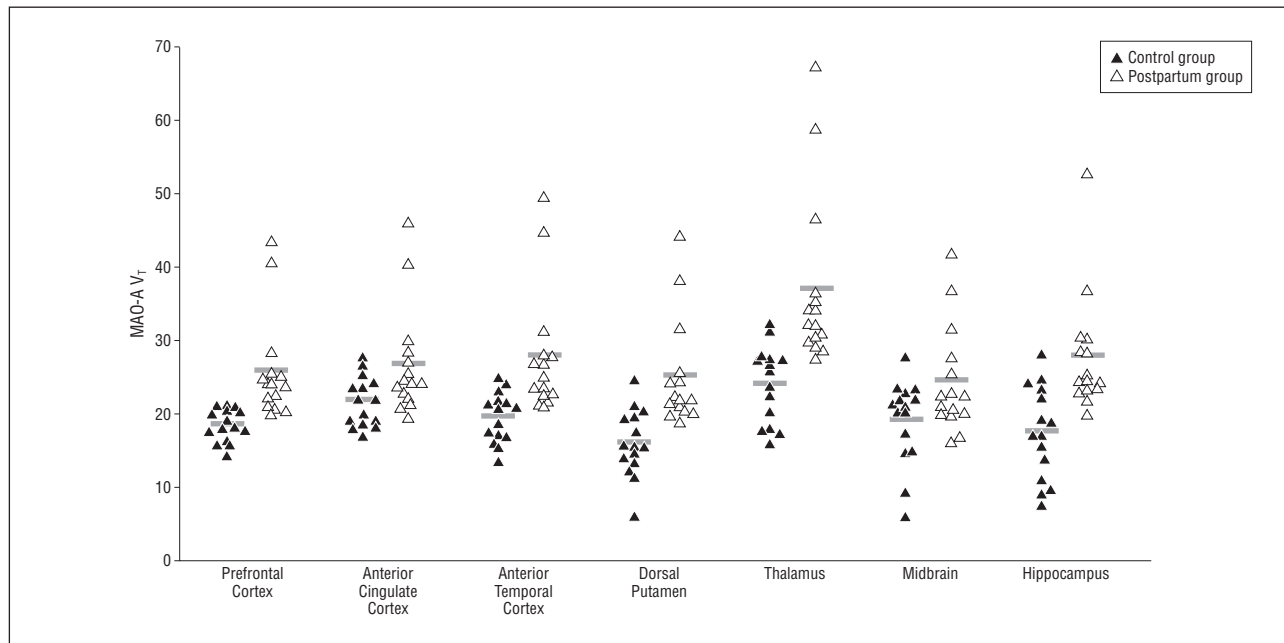


Figure 1. Comparison of monoamine oxidase A (MAO-A) binding between the early postpartum and the control groups. On average, MAO-A total distribution volume (V_T) was elevated by 43% during the early postpartum period. Differences between the 2 groups were statistically significant in each brain region (range, $P < .001$ to $P = .04$; independent-samples t test). Gray bars indicate mean MAO-A V_T values.

gland) and a ligand-specific template for ^{11}C -harmine.³¹ The images were then spatially smoothed using a gaussian filter (8-mm full width at half maximum).

STATISTICAL ANALYSIS

The primary analysis was an independent-samples t test comparing regional MAO-A V_T between the 2 groups for the ROI and voxelwise analyses. Significance for the post hoc analysis was calculated using nonparametric Mann-Whitney test. For the voxelwise analysis, the cluster threshold for size was applied as a threshold for significance. The voxelwise t statistic was applied to voxels having reasonably high levels of MAO-A binding as reflected by V_T values exceeding 10.

RESULTS

COMPARISON OF MAO-A V_T BETWEEN THE POSTPARTUM GROUP AND THE CONTROL GROUP

Our main finding is significantly elevated MAO-A V_T (mean, 43%; range, $P < .001$ to $P = .04$, independent-samples t test) throughout all analyzed brain regions (prefrontal cortex, anterior cingulate cortex, anterior temporal cortex, thalamus, dorsal putamen, hippocampus, and midbrain) during the early postpartum period (**Figure 1**). The comparison remains significant with application of the Mann-Whitney test (range, $P < .001$ to $P = .02$) and omission of the highest 2 values (range, $P < .001$ to $P = .05$) except for the midbrain, which was near trend ($P = .15$ and $P = .13$, respectively) for these additional analyses. For the postpartum group, the mean (SD) estradiol levels were 603 (601) pg/mL (to convert estradiol level to picomoles per liter, multiply by 3.671). For the postpartum group, the mean (SD) Hamilton Scale

for Depression score (17-item scale) was 7 (4). The mean (SD) Edinburgh Postnatal Depression Scale score was 5.6 (3.4).

Because the fifth day after delivery is when postpartum blues is most severe,³² a post hoc analysis was conducted to compare MAO-A V_T on day 5 postpartum ($n = 9$) vs days 4 and 6 postpartum ($n = 6$). Based on the Mann-Whitney test, MAO-A V_T was significantly greater on day 5 vs days 4 and 6 in the regions assessed. The mean (SD) MAO-A V_T on day 5 vs days 4 and 6, and the significance were as follows: prefrontal cortex (29.13 [8.30] vs 22.09 [1.60], $P < .01$), anterior cingulate cortex (30.33 [8.60] vs 22.70 [1.82], $P < .02$), anterior temporal cortex (31.71 [10.05] vs 23.29 [2.12], $P < .02$), dorsal putamen (28.70 [8.69] vs 21.11 [1.30], $P < .04$), thalamus (42.33 [14.03] vs 30.70 [2.27], $P < .03$), hippocampus (31.92 [9.27] vs 23.05 [1.76], $P < .004$), and midbrain (28.63 [7.53] vs 19.58 [2.22], $P < .004$).

GLOBAL ELEVATION OF MAO-A V_T IN POSTPARTUM BRAIN

The voxel comparison of MAO-A V_T in the postpartum group vs the control group reveals clusters of significantly elevated MAO-A binding throughout all analyzed postpartum brain regions (**Figure 2**). The individual voxel threshold was set at $P < .05$. A total of 86 412 voxels comprised a single cluster, which had a cluster-corrected significance of $P = .03$. This cluster included the entire cortex, subgenual cingulate cortex (Cg 25, Brodmann area 25), hippocampus, and dorsal and ventral striatum.

Protein binding was unrelated to the variation in MAO-A V_T in the postpartum group because it did not significantly correlate with MAO-A V_T ($r^2 = 0.02$,

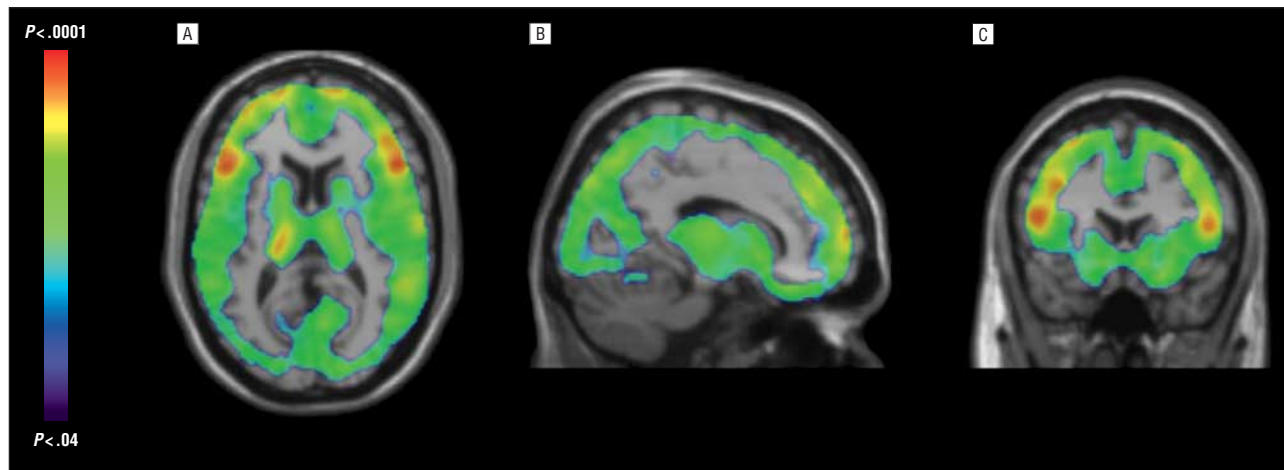


Figure 2. Parametric maps of elevated monoamine oxidase A binding in the postpartum group vs the control group. Maps are superimposed on a T1-weighted magnetic resonance image that is normalized to the T1-weighted template (SPM2; Department of Cognitive Neurology, Wellcome Trust Centre for Neuroimaging, London, England). A, Transverse. B, Sagittal. C, Coronal. The individual voxel threshold was set at $P < .05$; a total of 86 412 voxels comprised a single cluster, which had a cluster-corrected significance of $P = .03$.

$P = .62$). Injected mass of tracer did not differ significantly between the groups (mean [SD], 2.64 [1.04] vs 2.65 [1.21] μg).

COMMENT

To our knowledge, this is the first investigation of MAO-A binding in any species during the early postpartum period. The primary finding is significantly elevated MAO-A binding throughout all analyzed brain regions in the early postpartum period (days 4-6) in healthy women. A secondary finding is that MAO-A V_T is significantly greater on day 5 vs days 4 and 6 throughout the brain. Elevated MAO-A binding in the early postpartum period argues for a new model to understand postpartum sadness and has direct clinical implications for preventing PPD.

MAO-A V_T can be viewed as an index of MAO-A levels. Changes in MAO-A levels parallel changes in MAO-A activity during paradigms of hormone administration.³³ The acute rise in MAO-A levels during the early postpartum period (Figure 1) can be interpreted as an important monoamine-lowering process, which is associated with sad mood. This provides the foundation for a new neurobiological model of postpartum blues in humans involving a rapid estrogen decline, followed by a rapid rise in MAO-A levels in affect-modulating brain structures, with subsequent sad mood and symptoms of postpartum blues (Figure 3). Estrogen removal is associated with a rise in indexes of MAO-A levels,¹⁵⁻¹⁹ and the findings herein argue that this is highly relevant to the early postpartum period in humans. Consistent with the proposed neurobiological model, MAO-A binding was highest on day 5 postpartum, the day most strongly associated with the lowest mood in most investigations of postpartum blues.³²

There was some variation in MAO-A binding during the early postpartum period. This is not purely attributable to outlying values because the regional elevations in MAO-A binding during the early postpartum period were significant after nonparametric testing (or alterna-

tively after removing the 2 women with the highest values). The primary reason for variability seems to be time of imaging, because women on day 5 had higher MAO-A binding values than on days 4 and 6. However, women with the highest and fifth-highest MAO-A values subsequently experienced new postpartum onset of major depressive episodes. There may be variation in sensitivity to estrogen decline that also relates to these changes.

The postpartum period is characterized by complex hormonal changes and represents a general risk for the onset of major depressive episodes in women. Other reproductive events such as the premenstrual state or the perimenopausal transition period are associated with an increased risk for mood disorders.³⁴ Postpartum blues represents a major risk factor for developing PPD, and severe postpartum blues can be viewed as a prodromal stage for PPD.^{2,35,36} From this perspective, preventing severe symptoms of depressed mood during the early postpartum period may be helpful for PPD prophylaxis. Given the new neurobiological model presented herein, a key strategy to prevent PPD is to interfere with the acute rise in MAO-A or loss of multiple monoamines. Increasing single monoamines has been an intervention strategy with limited benefit for postpartum mood disorders.^{37,38} Although the selective serotonin inhibitor sertraline hydrochloride was more effective than placebo in a pilot study³⁸ of preventing PPD in a small sample of women with a prior episode of PPD, the primarily norepinephrine reuptake inhibitor nortriptyline hydrochloride was not significantly more effective than placebo.³⁷ The present study provides a specific rationale for increasing multiple monoamines rather than targeting a single monoamine in PPD prophylaxis.

Early MAO inhibitors target MAO-A and MAO-B in the brain and periphery.⁶ The adverse effects from MAO inhibition in the periphery of a hypertensive crisis associated with dietary tyramine led to reduced use of these treatments.⁶ However, more recent developments (eg, the use of selective reversible MAO-A inhibitors such as moclobemide and the transdermal patch application of

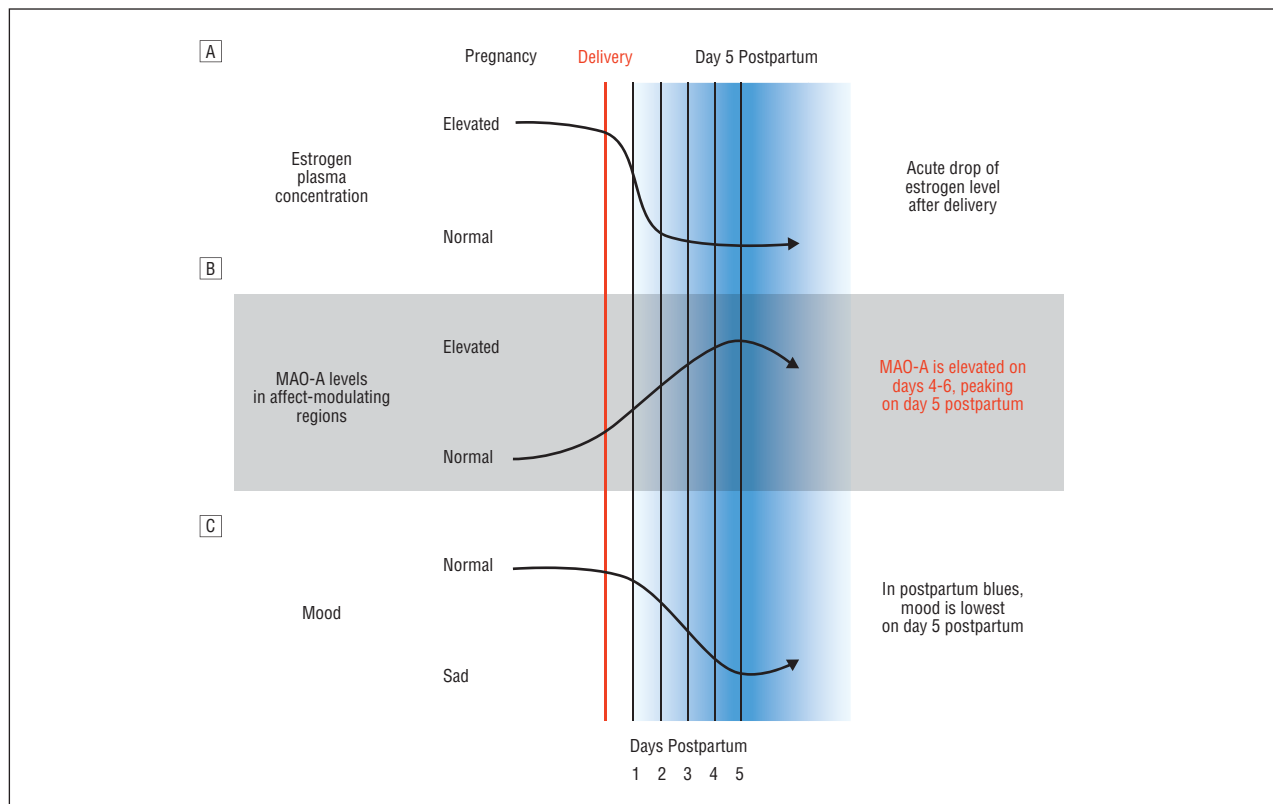


Figure 3. Monoamine model of postpartum blues. A, After delivery, estrogen levels drop 100- to 1000-fold; the estrogen decline is greatest during the first 3 to 4 days postpartum, with a modest decline thereafter. B, Monoamine oxidase A (MAO-A) levels are significantly greater in the early postpartum period, with a peak on day 5 postpartum. C, In the early postpartum period, up to 70% of mothers experience sadness, mood lability, anxiety, insomnia, poor appetite, and irritability, with mood being lowest on day 5 postpartum.

MAO-B inhibitor selegiline hydrochloride) show much more favorable adverse-effect profiles. Other emerging advances in this drug class are compounds for which the parent is inactive but is metabolized into the active MAO inhibitor in the brain, creating a favorable brain to periphery distribution ratio.⁶

Interventions on components of this model of estrogen decline, increased MAO-A density, and decreased monoamine concentrations should be considered to prevent severe postpartum blues and to reduce the risk of subsequent PPD. Given the need to develop treatments that are compatible with breastfeeding, the intake of dietary supplements of monoamine precursors in the early postpartum period would be a promising strategy to maintain a sufficient balance of monoamines during this time. For example, the administration of precursor supplements such as the amino acids tryptophan for serotonin and tyrosine for norepinephrine and dopamine should be investigated for the prevention of severe postpartum blues and PPD.

Further additions to this model are expected over time. There is consistent evidence for the involvement of gonadal steroid function in neuromodulation.³⁹⁻⁴¹ Estrogens are implicated as powerful modulators of human emotional processing via mechanisms such as estrogen nuclear receptors, second-messenger pathways like the cyclic adenosine monophosphate and mitogen-activated protein kinase system, and calcium homeostasis.^{42,43} Alterations in the regulation of progesterone, cor-

tisol, and melatonin levels may also contribute to postpartum mood changes.⁴⁴ For example, mice experience γ -aminobutyric acid A receptor downregulation by progesterone during pregnancy and a subsequent rebound in the early postpartum period.^{45,46} Genotypes may be discovered that influence the degree to which MAO-A levels increase in the early postpartum period, and this will add detail to the model, although evidence to date suggests that a simple single-genotype relationship to MAO-A level or activity is unlikely.^{3,32} Among environmental variables, social stressors have an important role in the risk for postpartum mood disorders.

Some limitations are typical in ligand PET and brain imaging studies in humans. MAO-A V_T is an index of MAO-A density that reflects total binding. This measure is computationally efficient and is the most stable and least variable measure of ¹¹C-harmine binding.¹¹ However, 15% of this measure reflects free and nonspecific binding in healthy people,⁸ so it is assumed that free and nonspecific binding do not elevate tremendously during the early postpartum period.¹¹ Elevation of MAO-A V_T may also reflect greater affinity of MAO-A, although this would not affect our interpretation because greater affinity of MAO-A for monoamines would be expected to facilitate monoamine loss.

The dramatic elevation of MAO-A binding in affect-modulating brain regions of healthy women during the first week postpartum indicates a key neurobiological mechanism for postpartum blues. Our findings have ex-

citing potential for preventing postpartum mood disorders. Several strategies could be used to prevent lowered mood in new mothers by therapeutically targeting elevated MAO-A levels or by compensating for the presence of elevated MAO-A levels. These include inhibiting MAO-A, increasing multiple monoamines with antidepressants, and administering dietary amino acids that are precursors for the monoamines metabolized by MAO-A. Less invasive strategies such as administration of amino acid precursors have potential for women at low risk of developing PPD, whereas interventions such as MAO-A inhibitors could be considered for those at high risk.

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