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Doornbos, Bennard

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Chapter 3

Sequential serotonin and noradrenalin associated processes involved in postpartum blues

Bennard Doornbos MD, Durk Fekkes PhD, M.A.C.Tanke MSc,
Peter de Jonge PhD, Jakob Korf PhD.

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Abstract

Objective: We investigated whether postpartum blues was related to changes in parameters of noradrenergic and serotonergic functioning.

Methods: From 26 healthy pregnant women blood was collected at the end of pregnancy and five days and six weeks postpartum. Serotonergic parameters were: platelet serotonin content; paroxetine binding to platelet membranes as an index of SERT activity; the serotonin precursor tryptophan in proportion to the large neutral amino acids, as an estimate of its cerebral influx. Noradrenergic indices were the noradrenaline precursor tyrosine and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG). The Kennerly and Gath blues questionnaire was applied at day five postpartum.

Results: The incidence of postpartum blues was 30%. The tryptophan ratio and serotonin content of platelets were decreased (p<0.01) at day five postpartum in all women. B_{max} paroxetine at day five was correlated with blues score (β=0.460; p=0.031). MHPG levels at six weeks were increased in women with blues (p<0.001). In a regression model MHPG at six weeks was related to blues score (β=0.477; p=0.002) and MHPG at day five (β=0.550; p=0.001), explaining >50% of the variation (R^2=0.588; p<0.001).

Conclusions: A decreased serotonergic activity was found at the fifth day postpartum in all subjects. Increased SERT activity, reflected by higher paroxetine binding to platelets might be involved in the onset of blues. The elevated MHPG levels in women with blues are compatible with a higher stress sensitivity, or a decreased stress coping in those and is suggested to be involved with the onset of depression.

Keywords: postpartum blues, postpartum depression, 3-methoxy-4-hydroxyphenylglycol, tryptophan, tyrosine, large neutral amino acids, platelet 5-HT content, paroxetine binding to platelets

Acronyms: 5-HT = serotonin; MHPG = 3-methoxy-4-hydroxyphenylglycol; LNAA’s = Large Neutral Amino Acids; tyr = tyrosine; phe=phenylalanine; SD= Standard Deviation; SERT= Serotonin Transporter
Introduction

Postpartum blues is a transient affective syndrome occurring in about half of the women (15.3% – 84%) in the first week after delivery (Gitlin and Pasnau, 1989; Henshaw, 2003). Symptoms of postpartum blues include crying, grief, anxiety, sadness, confusion, headache and also exuberance (Yalom et al., 1968; Kennerley and Gath, 1989a; Henshaw, 2003). Postpartum blues is considered as a risk factor for postpartum depression (Henshaw et al., 2004; Bloch et al., 2005). In the etiology of postpartum blues much attention has been given to the effects of the postpartum drop of estrogen and progesterone on neurophysiology and behavior (Abou-Saleh et al., 1998; Bloch et al., 2003). But, only about half of the women suffer from postpartum blues, and no consistent differences in hormone levels have been found between women with and without blues (Hendrick et al., 1998; Bloch et al., 2003). Indicating that other factors are involved in the etiology of postpartum blues.

We hypothesized that differences in serotonin (5-HT) metabolism and neurotransmission might be a factor underlying the individual risk for postpartum blues. Alterations in serotonin metabolism and transmission have been associated with affective disorders (Owens and Nemeroff, 1994; Kendler et al., 2005). In the peripartum the synthesis of both peripheral and cerebral 5-HT is limited due to the decreased availability of tryptophan, caused by the increased catabolism of tryptophan in the placenta during pregnancy (Schrocksnadel et al., 1996; Munn et al., 1998), and the immune activation and increased liver metabolism following delivery (Fuchs et al., 1996; Maes et al., 2002; Schrocksnadel et al., 2003a). Changes in tryptophan concentration (Handley et al., 1977; Abou-Saleh et al., 1999; Kohl et al., 2005; Bailara et al., 2006), tryptophan catabolism (Maes et al., 2000; Maes et al., 2002) and platelet 5-HT content (Maurer-Spurej et al., 2007) have all been associated with post partum blues. Moreover, postpartum depression has been associated with differences in functioning of the serotonin transporter (SERT) as reflected by a decreased Kd of both imipramine and paroxetine (Hannah et al., 1992b; Newport et al., 2004). During pregnancy serotonergic activity is further modulated by estrogen, progesterone and some of their metabolites (Bethea et al., 2002) resulting in a sudden change in the serotonergic neurotransmission postpartum. All together, the early postpartum period is characterized by a sudden change, mostly a reduction, of serotonergic activity and this condition may contribute to the development of mood disorders.

Another factor contributing to postpartum blues might be stress experienced during the delivery and subsequent days. Stress and life events are well documented risk factors for depression (Kendler et al., 1999). Virtually all kinds of stress induce activation of
noradrenergic neurons of both peripheral (sympathetic) system and the cerebral system, in particular that located in the locus coeruleus, leading to increased formation of the noradrenaline metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) (Bremner et al., 1996a; Bremner et al., 1996b). Therefore the impact of stress can to some extend be assessed by measuring MHPG in the circulation.

Here we investigate if peripartum noradrenergic and serotonergic plasma parameters are associated with postpartum blues. In contrast to most previous studies, we use a longitudinal design and combine several peripheral measures of serotonergic activity. Assessment of those parameters are limited to measurements in plasma. More direct methods like CSF-analyses or PET scanning, are difficult to perform frequently, and could be harmful for the fetus. These peripheral measures are frequently used in psychiatric research, but their translation to central functioning is not straightforward, and criticized in literature (Muller-Oerlinghausen et al., 2004).

Serotonergic activity was measured by 1.) The density and activity of 5-HT binding sites of blood platelets, as assessed by platelet paroxetine binding, which is a measure for activity of the serotonin transporter (SERT). The SERT has a key role in regulating cerebral extracellular serotonin levels; 2.) The serotonin content of the platelets, reflecting the recent serotonin production 3.) Plasma levels of the serotonin precursor tryptophan in relation to the Large Neutral Amino Acids (LNAA’s), as factor linked to central serotonin production. Noradrenaline activity was measured by plasma levels of its precursor tyrosine in relation to LNAA’s and its metabolite MHPG.

The following hypotheses were tested: 1.) Postpartum blues is associated with a decreased plasma tryptophan ratio and/or decreased platelet 5-HT levels; 2.) Serotonin transporter capacity and functioning, as reflected by platelet paroxetine binding, correlate with blues score; 3.) Women with postpartum blues experience more stress, represented by increased MHPG levels.

Subjects, Materials and methods

Subjects and experimental protocol
Twenty-six healthy pregnant women who visited the maternity clinic of the Erasmus University Medical Center in Rotterdam participated in this study, after they gave written informed consent. The protocol was approved by the ethical committee of Erasmus Medical Center. Women, all Caucasian, and aged between 21 and 35 years, were in good physical health and did not take any medication. None of the subjects
suffered from affective disorders or other mental illnesses at baseline. Blood was collected at the end of the third trimester (after 36 wk), and postpartum at day 5 and 6 weeks. The following biochemical parameters were measured: the platelet serotonin content; the paroxetine binding to platelet membranes; the plasma concentrations of the large neutral amino acids (LNAA), i.e. tryptophan, tyrosine, phenylalanine, valine, leucine and isoleucine, and the plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG). A Dutch version of the Kennerley and Gath blues questionnaire was used at the fifth postpartum day (Iles et al., 1989; Kennerley and Gath, 1989a). This questionnaire is the most used instrument for measuring blues. According to this scale women have blues when the score was higher than the mean of the whole group (Kennerley and Gath, 1989b). Because such a measure is strongly influenced by outliers, and complicates the comparisons with other samples, we use the widely used cut-off score of 12.

**Biochemical analyses**

Blood (20 ml) was collected between 9:00 and 10:30 AM in siliconated vacutainer tubes containing 0.15% K$_3$-EDTA as anticoagulant. Platelet-rich plasma was obtained by centrifugation of the blood at 90xg for 20 min at 20°C. A sample of 200 μl was frozen at –80°C for the determination of 5-HT and platelets were counted in a sample of 50 μl. The rest of the platelet-rich plasma was centrifuged at 2650xg for 20 min. The supernatant (plasma) was frozen at –80°C for the determination of amino acids and MHPG. The platelets were isolated from the pellet after two centrifugation runs, pooled and washed in 10 ml buffer (Tris-HCl 50 mM, NaCl 150 mM, Na2-EDTA 20 mM, pH 7.35) and finally frozen at –80°C for determination of paroxetine binding.

The large neutral amino acids (LNAA) tryptophan, tyrosine, phenylalanine, valine, leucine and isoleucine were analysed in the plasma samples by reversed phase high performance liquid chromatography (HPLC) after pre-column derivatisation with o-phthaldialdehyde and detected fluorometrically (Fekkes et al., 1995). The platelet 5-HT concentrations were measured by a reversed phase HPLC method described previously (Fekkes et al., 1997). Plasma free MHPG was measured by a reversed phase HPLC method after extraction using a slightly modified published procedure (Moleman and Borstrok, 1982). In short, 0.5 ml plasma, 20 μl internal standard (2 μg iso-MHPG/ml) and 3 ml ethylacetate were added to a seraclear tube containing 0.75 g NaCl and 0.1 g florisil. The tube was shaken for 20 min and centrifuged for 10 min at 2750 g. Two ml of the organic layer was evaporated to dryness at 40°C under vacuum in a Buchler Vortex Evaporator (Lenexa, KS, U.S.A.) and the residue was dissolved in 0.5 ml of the mobile phase. Ten or 20 μl samples were injected onto a reversed phase column (ODS-Hypersil, 5
μm particle size, 200 x 2.1 mm, Hewlett Packard) which was protected by a guard column (20 x 2.1 mm) of the same material. The mobile phase consisted of 50 mM sodium phosphate and 0.67 mM disodium EDTA containing 1% isopropanol, pH 2.7. The flow rate was set at 0.25 ml/min and the column temperature was 28°C. The detection system consisted of a Model 5100A Coulochem detector equipped with a 5021 conditioning cell and a 5011 high sensitivity cell (ESA, Bedford, MA, U.S.A.). The potentials for the conditioning cell and detectors 1 and 2 were +0.45, -0.05 and -0.43 V, respectively. The gain was 15 x 100 and quantification was done by measuring peak heights. The limit of detection at a signal to noise ratio of 2 was 10 fmol (approx. 2 pg) MHPG per injection. The retention times of MHPG and iso-MHPG were 7.6 and 12.8 min, respectively. The intra- and inter-day coefficients of variation of duplicate analysis of plasma samples were 2.6% (n=8) and 4.9% (n=18), respectively. The recovery of iso-MHPG added to the plasma samples was 79 ± 4% (n=14). Paroxetine binding to blood platelets was determined using \(^3\)H-paroxetine (New England Nuclear) as radioligand and clomipramine as displacing agent to correct for nonspecific binding (Klompenhouwer et al., 1990).

**Calculations**

The tryptophan ratio indicated the tryptophan availability in the brain for subsequent 5-HT synthesis. This ratio was computed with the formula: plasma tryptophan x 100/ sum of the plasma LNAA minus tryptophan. The tyrosine ratio indicated the tyrosine availability in the brain for subsequent dopamine and/or noradrenaline synthesis. This ratio was computed with the formula: plasma tyrosine x 100/ sum of the plasma LNAA minus tyrosine. The tyrosine/phenylalanine (tyr/phe) ratio was taken as index of peripheral tyrosine synthesis from phenylalanine. This ratio was plasma tyrosine/ plasma phenylalanine.

**Statistical analysis**

Data are presented as means with standard deviations (SD). Statistical analyses were done with SPSS 12.0. Data were considered to have a normal distribution when the Kolmogorov-Smirnov test was not significant. The significance level was set at 0.05. The time course of the serotonergic and noradrenergic parameters of the whole group was evaluated with repeated measures ANOVA with time (end of third term, 5 days postpartum and six weeks postpartum) as a within subject factor. Differences in the time course between blues and non-blues were subsequently analyzed with blues and non-blues as a between subject factor. Significant differences in the time course in the ANOVA test were further evaluated with a post hoc test. The hypothesis that differences in SERT capacity, and functioning are related to postpartum blues was
investigated by correlating the Bmax and the Kd of paroxetine binding to platelets with the blues score on day five postpartum. With two runs of logistic regression analyses the factors contributing to blues and the stress during the puerperium (MHPG levels at six weeks) were identified.

Results

Blues score
Blues scores varied from 2 – 21. The average score was 9.0 ± 5.4. Eight Participants (30%) had a score >12 and were considered to suffer from postpartum blues.

Biochemical parameters of the whole group
Data of the serotonergic and noradrenergic activity of the whole group are summarized in Table 1. All data were normally distributed (with a z-score of the skewness and the kurtosis < 1.96 and a non-significant Kolmogorov-Smirnov test) and were therefore analyzed with repeated measures ANOVA. The tryptophan ratio decreased significantly postpartum (p<0.01) and returned to prepartum levels after six weeks. The tyrosine ratio increased significantly postpartum (p<0.05) and also returned to prepartum levels at six weeks. The tyr/phe ratio increased significantly at day 5 (p< 0.05) and after six weeks, (p<0.01) compared with pregnancy. MHPG levels decreased significantly postpartum i.e. five days (p<0.05) and six weeks (p<0.01). The 5-HT content of platelets decreased at day five postpartum (p<0.01), and increased to the prepartum levels after six weeks. 5-HT content of platelets did not correlate with tryptophan ratio at any time. No changes were found in Kd and Bmax of paroxetine-binding at the platelet membrane over time.

Table 1. Biochemical parameters of all subjects (n=26) at the end of third trimester, 5 days postpartum, and six weeks postpartum

<table>
<thead>
<tr>
<th></th>
<th>Third trimester</th>
<th>5 days postpartum</th>
<th>6 weeks postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tryptophan ratio</td>
<td>8.99 ± 1.73</td>
<td>7.29 ± 1.50</td>
<td>8.50 ± 1.41</td>
</tr>
<tr>
<td>Tyrosine ratio</td>
<td>13.80 ± 1.70</td>
<td>15.20 ± 2.05</td>
<td>13.67 ± 3.54</td>
</tr>
<tr>
<td>Tyrosine/phenylalanine ratio</td>
<td>1.12 ± 0.13</td>
<td>1.30 ± 0.16</td>
<td>1.39 ± 0.50</td>
</tr>
<tr>
<td>Platelet Kd paroxetine (nM)</td>
<td>0.17 ± 0.09</td>
<td>0.14 ± 0.06</td>
<td>0.16 ± 0.07</td>
</tr>
<tr>
<td>Platelet Bmax paroxetine (fmol/mg protein)</td>
<td>1635 ± 506</td>
<td>1428 ± 432</td>
<td>1576 ± 751</td>
</tr>
<tr>
<td>MHPG (ng/ml)</td>
<td>3.69 ± 0.91</td>
<td>3.29 ± 0.88</td>
<td>2.92 ± 0.85</td>
</tr>
<tr>
<td>5-HT content platelets (nmol/10^9 platelets)</td>
<td>2.96 ± 1.01</td>
<td>2.19 ± 0.88</td>
<td>3.19 ± 1.16</td>
</tr>
</tbody>
</table>

Subsequently, the biochemical data were analyzed with repeated measures ANOVA in blues and non blues as between subject factor. This revealed a between-subject effect in MHPG levels (p<0.001). Post hoc analyses showed a significant decrease in MHPG levels in the non blues group six weeks postpartum compared to the blues group which remained at the same level. Data is presented in Table 1. No between-groups differences in the time-course of the serotonergic parameters were found with repeated measures ANOVA.

* Significant time effect in repeated measures ANOVA.

- Differs significantly from 5 days postpartum.
- Differs significantly from 6 weeks postpartum.
- p<0.05.
- p<0.01.
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The $B_{\text{max}}$ of platelet membrane paroxetine binding at day 5 correlated significantly with blues score (Pearson, 0.460, p<0.05). The scatter plot is shown in fig 2. The $K_d$ did not correlate with the blues score (Pearson corr: 0.041, p=0.855).

Regression modeling indicated that the blues score was predicted by $B_{\text{max}}$ paroxetine at day 5 postpartum ($\beta=0.562$) explaining 30% of the variance ($R^2 = 0.316$; Adjusted $R^2 = 0.275$) in a significant model ($F_{(1,18)}=7.840$, p=0.012). MHPG levels at six weeks were related to MHPG levels at five days and blues score explaining more than 50% of the variation ($R^2$ of 0.588, adjusted $R^2$ of 0.551) in a highly significant model ($F_{(2,22)}=15.729$, p<0.001). Both models are shown in table 2. The temporal relations between the different parameters indicated by the regression models are depicted in figure 3.

Discussion

The present study indicates a decreased serotonergic activity in all women during the first postpartum week, as illustrated by a decreased tryptophan ratio and a decreased 5-HT content of platelets. The decrease in serotonergic activity was not associated with the occurrence of postpartum blues. However, the significant correlation between $B_{\text{max}}$ paroxetine-binding to platelets and blues scores suggests that differences in serotonin transporter functioning might intensify the effect of those changes in serotonergic metabolism thereby increasing the vulnerability for blues. MHPG levels remain high in the women with blues, and depressive symptoms were related to both blues scores and increased MHPG levels, indicative for persistent activity of the sympathetic nervous system or both in women with blues.

Strong points of this study are the longitudinal design with the assessment of several indices of both serotonergic and noradrenergic functioning and blues score. A serious point of criticism is the uncertain relationship between peripheral and central parameters of serotonergic and noradrenergic functioning (as summarized by (Muller-Oerlinghausen et al., 2004)) However, a relation between peripheral and central functioning has been reported for tryptophan ratio and central serotonergic functioning (Russo et al., 2005); 5-HT platelet content and psychopathology (Mann et al., 1992; Russo et al., 2005); and the amount of platelet 5-HT transporters (SERT) and central SERT functioning (Rausch et al., 2005; Uebelhack et al., 2006) although the correlations in these studies were low (0.3-0.6), and the relation was influenced by several other factors, as for instance gender (the strongest correlations were found in women.) Platelets have a circulating half life of 11 days. Therefore platelet data at 5 days postpartum do not fully represent the changes in this period. Summarizing: the data on serotonergic metabolism of platelets should be interpreted with care. Approximately about 35-60% of the peripheral MHPG has cerebral origin (Yoshimura et al., 2004).
Peripheral MHPG may serve as index for stress responsiveness because both the peripheral sympathetic nervous system and the central locus coeruleus are similarly activated by stress.

Other limitations of the study concern 1) the single assessment of blues, limiting the evaluation of the delivery induced changes in affective functioning; 2) the lactation status was not assessed. Lactation status is associated with postpartum depression and the lactation hormones prolactin and oxytocin influence stress reactivity and might thus have influenced MHPG levels (Carter et al., 2001; Grattan, 2001). 3) the sleep pattern was not investigated. The sleep quality is disturbed during the puerperium (Ross et al., 2005; Parry et al., 2006) what might lead to increased serotonergic activity or vice versa (Adrien, 2002). These disturbances in sleep pattern have been associated with the onset of depression (Ross et al., 2005; Parry et al., 2006).

Several authors have reported a reduced puerperal tryptophan ratio (Schrocksnadel et al., 2003a; Kohl et al., 2005; between the tryptophan ratio and postpartum blues, Abou-Saleh et al., 1999; Maes et al., 2002; Kohl et al., 2005) and the decreased puerperal tryptophan ratio, respectively. This could be due to the small sample size in the studies in the specific days that the blood samples were collected. The reduced puerperal tryptophan ratio is most likely caused by the increased immune activation in the first days post delivery, leading to activation of the tryptophan catabolising enzyme Indoleamine deoxygenase (IDO) (Maes et al., 2002). However, some other studies did not find a relation between immune activation and IDO activity and suggested that the decreased tryptophan ratio is induced by hepatic tryptophan pyrrolase (Schrocksnadel et al., 2003a; Schrocksnadel et al., 2003b) or the relatively larger increase in the concentration of the other Large Neutral Amino Acids competing for transport over the blood brain barrier (Bailara et al., 2006).

We found a decreased platelet 5-HT content at day 5 postpartum, which was not related with the onset of blues. It has been recently reported that women with a postpartum depression had a decreased platelet 5-HT content (Maurer-Spurej et al., 2007). The reason they found a relation might be attributed to peculiar aspects of the latter study namely, a different method for measuring the 5-HT content; the longer sampling time...
B<sub>max</sub> of paroxetine binding to platelets in the first postpartum week correlated positively with blues scores. Two studies (Newport et al., 2004; Hannah et al., 1992a) reported an association between postpartum depression and the K<sub>d</sub> of imipramine or paroxetine, suggesting the presence of a different genetic SERT variant in women who get depressed. In non-puerperal depressed patients a decreased number of SERT binding sites has often been reported (as summarized by (Owens and Nemeroff, 1994)). This may appear opposite to what we found. However, the changes in depressed patients may reflect the end-stage of a long patho-physiological process, whereas the present changes were detected at the beginning of a transient affective syndrome.

The data on serotonergic functioning suggests that women with blues have a relatively higher SERT activity, which might result in a low synaptic 5-HT content. A decrease in brain tryptophan levels postpartum might lead to a further decrease in the synaptic 5-HT content, thus impairing serotonergic neurotransmission in women with blues and increasing the vulnerability to develop affective symptomatology. The decrease in serotonergic metabolism might also lead to a decrease in the serotonin product melatonin, which is also thought to be involved in the onset of depression.

MHPG, blues and tyrosine ratio
We are the first to report data on puerperal course of MHPG. One study investigating MHPG levels in cerebrospinal fluid (CSF) in pregnant women (Altemus et al., 2004) reported decreased MHPG levels when compared to non pregnant women.

The previously reported increase in puerperal increase in tyrosine ratio’s (Abou-Saleh et al., 1999; Maes et al., 2001; Bailara et al., 2006) might be the result of an increase of intestinal absorption, protein breakdown from hydroxylation of phenylalanine. The latter was supported by the significantly increased tyr/phe ratio. The relatively decreased tyrosine levels at six weeks with a constant tyr/phe ratio might point to an increased utilization of tyrosine for synthesis of proteins, hormones (thyroxine and triiodothyronine), or catecholamines. However MHPG levels, reflecting catecholamine turnover, were apparently independent of tyrosine levels, as they did not correlate. Presumably, tyrosine levels did not vary to an extend that they became rate-limiting for catecholamine synthesis and most likely also not for triiodothyronine synthesis. Changes in synthesis both hormones have been associated with depression.
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The longitudinal study design allows the modeling of the sequential changes in mood and various biochemical parameters revealing a consistent relation between blues and noradrenergic metabolism. This increased noradrenergic metabolism might be related to depression at six weeks postpartum according to a personal observation of the clinician who performed the study. He noted depressive symptoms in five women at six weeks postpartum. All these women had blues. The women with blues and depressive symptoms both had increased levels of MHPG. The apparent causality in this triangular relation can have two forms: 1.) Women with blues experience more stress and thus have higher MHPG levels. Due to this stress women develop subsequent depressive symptoms. The relation between blues and MHPG levels is thus mediated by stress. 2.) Women with blues are more vulnerable for depressive symptoms. Due to the depression women get stressed (and get increased MHPG levels). So the relation between blues and MHPG levels is primarily mediated by depression. The sequence of events has to be further clarified in a study in which the temporal changes in mood and noradrenergic functioning are assessed more frequently, for example on a weekly base, with a systematic assessment of depressive symptoms at six weeks postpartum.

Conclusion

In summary, the present study indicates that: 1.) Individual differences in serotonin transporter functioning together with a low plasma tryptophan ratio might synergistically affect brain 5-HT function postpartum, which seems to increase the vulnerability for blues. 2.) Women with postpartum blues have increased noradrenergic activity at six weeks postpartum which might be indicative for higher levels of perceived stress. This is suggested to be either a causal factor or a consequence of later depression. 3.) Whether these monoamine mediated effects are amplified by rapid hormonal fluctuations during the postpartum period or by the stress experienced by the delivery or that their combination contributes to labile affect postpartum (Halbreich, 2005) remains as yet to be elucidated.

Acknowledgements

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