Psychoneuroendocrinology (2006) 31, 407–413

ELSEVIER

PNEC

www.elsevier.com/locate/psyneuen

SHORT COMMUNICATION

Decreased brain tryptophan availability as a partial determinant of post-partum blues

K.M' Baïlara[a,b], C. Henry[a,e,*], J. Lestage[b], J.M. Launay[c], F. Parrot[d], J. Swendsen[e], A.L. Sutter[a,f], D. Roux[f], D. Dallay[f], J. Demotes-Mainard[g]

[a]*Département de Psychiatrie Adulte, CHS Charles Perrens, Bordeaux, France*
[b]*UMR 1244 INRA Université Bordeaux 2, Institut François Magendie, Bordeaux, France*
[c]*Service de Biochimie, CHU Lariboisière, Paris, France*
[d]*Service de Biochimie, CHU Bordeaux, France*
[e]*Laboratoire de psychologie clinique JE 2358, Université de Bordeaux2, Bordeaux, France*
[f]*Maternité C, CHU de Bordeaux, France*
[g]*Centre d'Investigation Clinique INSERM-CHU, Bordeaux, France*

Received 30 August 2005; received in revised form 12 October 2005; accepted 13 October 2005

KEYWORDS
Mood disorder;
Baby blues;
Aminoacid metabolism;
Materno-fetal metabolic exchange;
Indoleamine-2,3-dioxygenase;
Kynurenine;
Serotonin

Summary *Background*: The post-partum blues is a transient mood alteration affecting most women a few days after delivery. Its stereotypic pattern of symptoms and time course, peaking on post-partum day 3–5, is suggestive of biological determinants superimposed on psycho-social factors. This study was designed to evaluate the possible role of the serotonin system during this period through assessment of brain tryptophan availability.
Methods: Blood samples from 50 women were collected just before (D0) and 3 days after (D3) delivery. Based on plasma concentration of tryptophan, amino acids competing with tryptophan for transport across the blood–brain barrier and on their respective affinities for this transporter, a brain tryptophan availability index (BTAI) was calculated and its variation correlated with the intensity of post-partum blues evaluated through the Kennerley and Gath score at D3.
Results: The BTAI showed a −15% decrease between D0 and D3 ($p<0.01$, paired t-test). This decrease was not supported by a drop in plasma tryptophan since its level rather increased (+19%). There was no evidence for change in placental indoleamine-2,3-dioxygenase activity since the variation in plasma L-kynurenine (+12%) paralleled the change in tryptophan level. The decreased BTAI appeared the consequence of a dramatic increase in plasma levels of most amino acids, particularly the competitor aminoacids leucine, isoleucine, valine and tyrosine, during the early post-partum. This decrease in brain tryptophan availability was concomitant to the post-partum blues, whose intensity significantly correlated with the amplitude of BTAI variation (Pearson's coefficient −0.283, $p<0.05$).

* Corresponding author. Address: Département de Psychiatrie Adulte, CHS Charles Perrens, 121 rue de la Béchade, 33076 Bordeaux, France. Tel.: +33 556 563450; fax: +33 556 563547.
E-mail address: chenry@perrens.aquisante.fr (C. Henry).

doi:10.1016/j.psyneuen.2005.10.001

Conclusion: This study suggests that generalized, large amplitude metabolic and/or nutritional changes occurring in the early post-partum result in a transient decrease in brain tryptophan availability, partly accounting for the mood alteration referred to as the post-partum blues, a model for the triggering of puerperal mood disorder in vulnerable women.

1. Introduction

Most women experience a transient mood change in the early post-partum, referred to as the post-partum blues or baby blues (Robin, 1962; Yalom et al., 1968; Pitt, 1973; Kennerley and Gath, 1985; Iles et al., 1989; Glover et al., 1994; Sutter et al., 1997). Occurring during the first week and culminating between the 3rd and 5th days after delivery, this non-pathological feature is considered as a mild and brief depressive state. Its high incidence, together with the reproducibility of both its time course and symptomatic features, is suggestive of common psychological and/or biological determinants present in almost every pregnant woman (O'Hara et al., 1991; Da Costa et al., 2000). Besides the major psychological impact of child birth, a large number of biological mechanisms may account for mood or emotional disturbances.

Among biological determinants, functional alterations in the serotonin system have long been associated with mood disorders (Lucki, 1998), and also with impaired control of emotion (Mann, 1999). Brain serotonin synthesis is highly dependent on brain tryptophan availability. Tryptophan is an essential amino acid provided by food and transported into the brain through the high affinity LAT1/r4F2hc L-system transporter (Kanai et al., 1998; Prasad et al., 1999). Tryptophan availability in the brain is also dependent on the competition with large neutral amino acids occurring at the blood-brain barrier (Pardridge, 1979; Smith, 2000; Verrey, 2003). The change in tryptophan bioavailability is a rate-limiting step in brain serotonin synthesis and triggers mood alteration in animals and human. Rapid tryptophan depletion is a model for depressive symptoms (Moore et al., 2000) and tryptophan supplementation (or a reduced diet of competitor amino acids) leads to an improved mood and social status in primates (Moskowitz et al., 2001). The risk of post-partum depression is associated with a tryptophan hydroxylase gene polymorphism (Sun et al., 2004). Moreover, there is some evidence that plasma tryptophan concentrations progressively decrease during pregnancy and return to normal after delivery (Schröcksnadel et al., 1996, 2003; Maes et al., 2001). Recently, Kohl et al. (2005) showed an increase in plasma tryptophan and kynurenine after delivery, with an impaired tryptophan-to-kynurenine ratio in women experiencing baby blues.

During the post-partum period, many factors may account for possible changes in brain tryptophan availability. Among these factors, indoleamine-2,3-dioxygenase (IDO, that transforms tryptophan into L-kynurenine) activity may explain changes in level of tryptophan.

There could be at least two distinct sources of IDO activity in the post-partum context: (i) the immune system (Maes et al., 2002), where IDO transcription is induced under appropriate inflammatory cytokine stimulation (including inflammation related to delivery); and (ii) the placenta, since IDO is highly expressed in the syncytiotrophoblast (Kudo and Boyd, 2000; Santoso et al., 2002; Sedlmayr et al., 2002; Baban et al., 2004), and IDO is considered to play a local immunosuppressive role and to participate in materno-fetal tolerance (Munn et al., 1998; Mellor et al., 2002). In the latter hypothesis, abrupt removal of placenta might lead to withdrawal of IDO activity in the early post-partum. In addition, the liver enzyme tryptophan 2,3-dioxygenase (TDO), another tryptophan catabolizing pathway, may also undergo change in activity during the post-partum period, due to increased corticosteroid levels (Comings et al., 1995).

This study was therefore designed to correlate the intensity of baby blues, as assessed by the Kennerley and Gath rating scale (1989), with the intensity of metabolic changes determining brain tryptophan availability.

2. Methods

2.1. Subjects

Fifty pregnant women were enrolled in this study. Pathological pregnancies were not considered for inclusion, and obstetrical complications as well as surgical delivery were exclusion criteria. Informed consent was obtained and the study was approved by the local ethics committee. Blood samples were

collected upon arrival at hospital (Maternité C, CHU de Bordeaux) just before delivery (D0), then three days after (D3) delivery, before the subject was discharged.

2.2. Psycho-social assessment

Psycho-social data, including mother's age, parity, weeks of pregnancy and history of mood disorders were obtained during interviews performed by a trained psychologist using the Mini International Neuropsychiatric Interview (MINI, version 5), an abbreviated structured psychiatric interview providing criteria for axis I mood disorders of the DSM-IV.

2.3. Intensity of baby blues

Mood assessment was performed at day 3 using the Kennerley and Gath Blues Scale (1989), translated into French by Glangeaud-Freudenthal et al. (1995). The 28 items address symptoms specific for baby blues, thus providing a baby blues intensity score.

2.4. Measurement of aminocid, kynurenine and serotonin concentrations, and evaluation of brain tryptophan bioavailability

High performance liquid chromatography with electrochemical detection was used to measure plasma tryptophan (free and total) and total blood serotonin, and with fluorimetric detection for plasma L-kynurenine and neopterin concentrations. Colorimetric measurement after ion-exchange chromatography and ninhydrine derivatization was used for plasma amino acid assessment. Concentrations were expressed in μM.

The brain tryptophan availability index (BTAI) was calculated according to the Michaelis model for substrate competition on enzymes or transporters, taking into account:

- the total plasma tryptophan concentration (since the brain amino acid transporter LAT1/r4F2hc shows a far higher affinity for tryptophan than the albumin carrier, both free and bound tryptophan must be considered in modeling its transport across the blood–brain barrier) (Pardridge, 1979);
- the blood concentration of competitor aminoacids (CA), i.e. valine, isoleucine, leucine, tyrosine, phenylalanine and methionine;
- the respective affinities (K_m) of the blood–brain barrier transporter LAT1/r4F2hc for tryptophan and competitor amino acids (derived from Smith, 2000, in μM): valine 210, isoleucine 56, leucine 29, tyrosine 64, phenylalanine 11, methionine 40, and tryptophan 15):

$$\mathrm{BTAI} = (\mathrm{Try}/K_{\mathrm{mTry}})/\mathrm{sum}(\mathrm{CA}/K_{\mathrm{mCA}})$$

2.5. Statistical analysis

Pre- and post-partum values were compared using the paired Student's *t*-test. Pearson's correlation was used to correlate the Kennerley and Gath (1989) post-partum blues score (dependent variable) with the amplitude of BTAI change between D0 and D3.

3. Results

The total plasma tryptophan concentration exhibited a mild (+19%) increase while free circulating tryptophan was unchanged. However, an abrupt increase in plasma competitor amino acid concentrations, reaching +77% for isoleucine, +55% for leucine and +52% for tyrosine (see Table 1), led to a reduction in brain tryptophan availability. Given the normal range for plasma amino acid concentrations in non-pregnant adults, this post-partum rise seemed to be a return to normal values after a period of gravidic down-regulation.

Thus, the BTAI decreased between pre-term and post-partum (by −15%, $p<0.01$), concomitant to the occurrence of post-partum blues symptoms. The change in BTAI (D3–D0) was significantly and negatively correlated with the intensity of post-partum blues as assessed through the Kennerley and Gath score (Pearson's correlation coefficient −0.283, $p<0.05$) (see Fig. 1).

Regarding tryptophan metabolism, plasma kynurenine (+12%) and total blood serotonin (+16%) concentration only slightly increased in the early post-partum, both paralleling the increase in plasma tryptophan concentration, while plasma neopterin remained unaltered.

4. Discussion

This study shows that a decrease in brain tryptophan availability acts as a determinant for the post-partum blues.

The robust symptomatology and limited variability of post-partum blues is suggestive of possible biological determinants, superimposed on either psychological or social factors (O'Hara et al.,

Table 1 Mean values (from our 50 pre- (D0) and post-partum (D3) subjects) for plasma amino acids, L-kynurenine, neopterin, and total blood serotonin concentrations (in μM), together with the brain tryptophan availability index (BTAI).

	Mean concentration (μmol/l)		% Change (D3 vs D0)	*t* test statistics	Mean value in non-pregnant adults
	D0, before delivery	D3, 3 days after delivery		D3 vs D0 (*p*)	
Total plasma tryptophan	35.13 (±10.2)	41.75 (±8.5)	19	0.0001	
Free plasma tryptophan	8.04 (±2.3)	8.15 (±2.2)	1	0.785	
Total blood serotonin	659 (±340.4)	763 (±334.9)	16	0.009	
Neopterin	5.58 (±2.4)	5.43 (±2.8)	−3	0.682	
L-kynurenine	1.61 (±0.5)	1.8 (±0.4)	12	0.002	
Valine	146 (±31.5)	208 (±40.5)	42	0.0001	188
Isoleucine	36.4 (±12.3)	64.3 (±19.0)	77	0.0001	54
Leucine	71.5 (±20.4)	110.8 (±30.1)	55	0.0001	106
Tyrosine	32.2 (±9.0)	49.1 (±12.9)	52	0.0001	52
Phenylalanine	44.9 (±9.3)	54.7 (±11.9)	22	0.0001	56
Methionine	23.9 (±5.9)	30.7 (±8.9)	28	0.0001	30
Taurine	41.2 (±24.6)	49.0 (±25.7)	20	0.019	66
Threonine	190.0 (±58.6)	230 (±73.8)	21	0.0001	130
Serine	80.5 (±20.9)	124,5 (±109.5)	55	0.005	112
Glutamate	55.71 (±26.9)	52.96 (±37.3)	−5	0.156	58
Glycine	129 (±47.3)	202 (±63.6)	57	0.0001	243
Alanine	303 (±94.5)	404 (±127.0)	33	0.0001	336
Citrulline	15.03 (±6.6)	26.17 (±8.0)	74	0.0001	29
Aminobutyric acid	12.52 (±8.1)	24.86 (±11.3)	99	0.0001	20
Cysteine	47.08 (±12.3)	54.57 (±12.4)	16	0.0001	47
Brain tryptophan availability index (BTAI)	0.27 (±0.08)	0.23 (±0.07)	−15	0.003	

Mean values in non-pregnant adults are indicated in the right column.

1991; Da Costa et al., 2000). Our study shows a rapid increase in total plasma tryptophan levels (+19% within the first 3 post-partum days), in line with the results recently published by Kohl et al. (2005). Surprisingly, this 19% increase in plasma tryptophan levels in the early post-partum does not result in an increased but rather in a decreased brain tryptophan availability (−15%). This is supported by high-amplitude variations in the concentration of competitor amino acids, particularly valine, leucine, isoleucine and tyrosine, resulting in a significantly impaired transport of tryptophan across the blood-brain barrier. Thus, simply measuring plasma tryptophan levels could lead to a misleading interpretation of the biological data.

The amplitude of changes in biological parameters may appear weaker (mean −15% reduction in BTAI) than under experimental

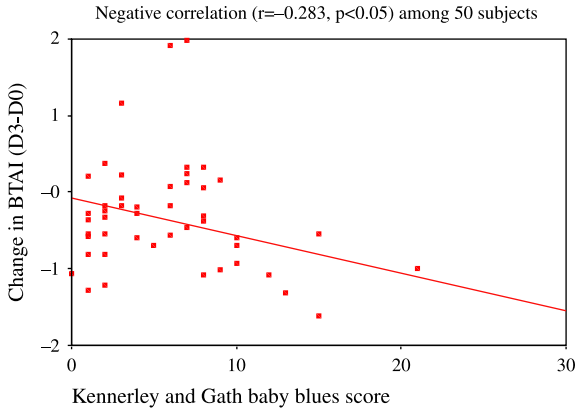

Figure 1 Individual values among the 50 subjects for the intensity of baby blues (as assessed through the Kennerley and Gath score) as a function of the amplitude of the variation (D3-D0) in brain tryptophan availability index (BTAI), showing a negative correlation (Pearson's coefficient −0.283, $p<0.05$).

condition inducing mood alteration (e.g. the robust attenuation of plasma tryptophan during rapid tryptophan depletion by consuming a tryptophan-free amino acid drink). However, the baby blues is a transient physiological mood change, not a pathological state such as depression (and there can be no guarantee that artificial depletion accurately models a physiological mechanism). Finally, changes in BTAI reflect individual differences, and their correlation with the intensity of symptoms is the salient point, rather than their mean amplitude.

Certain determinants might account for such a change in this overall increase in the plasma concentration of almost all amino acids. Pregnancy and delivery are associated with major nutritional and metabolic events (Schoengold et al., 1977). Many factors may interfere with amino acid metabolism, including changes in hormonal status, physical activity during delivery, stress- or lactation-related adaptation and changes in feeding behavior (Handley et al., 1977, 1980; More et al., 2003). Moreover, removal of both fetus and placenta abruptly interrupt the materno-fetal exchanges. Some data suggest that fetal metabolism is responsible for the drop in the maternal plasma amino acid levels observed during pregnancy, since fetal growth retardation is correlated with a lesser reduction in circulating amino acids (Cetin et al., 1996; Cetin, 2003). Other mechanisms might account for this major rise in amino acids, including their release through protein catabolism at the onset of lactation (More et al., 2003). However, our data suggest that plasma amino acid levels rapidly return to normal after a period of gravidic down-regulation, which would be in line with changes associated with the withdrawal of materno-fetal metabolic exchanges. Further studies focusing on the impact of nutritional and metabolic factors during this early post-partum period might therefore contribute to a better understanding of the underlying mechanism.

Among the possible determinants of such a rapid change in plasma tryptophan concentrations, we hypothesized the activity of the tryptophan-catabolizing enzyme indoleamine-2,3-dioxygenase (IDO), which degrades tryptophan in the L-kynurenine pathway. However, our data show no evidence for such a mechanism since interruption of IDO activity would result in a decrease in L-kynurenine. In contrast, post-partum changes in blood levels of L-kynurenine (+12%), consistent with the data from Kohl et al. (2005) and serotonin (+16%) paralleled variations in plasma tryptophan concentrations (+19%), suggesting that both kynurenine and serotonin pathways remain unaffected. Similarly, these markers are not suggestive of significant changes in TDO activity.

Taken together, this study suggests that rapid changes in plasma amino acid levels occur in the early post-partum, possibly due to discontinuation of materno-fetal metabolic exchanges. As a consequence of the dramatic rise in plasma competitor amino acid concentrations, and in spite of a mild increase in plasma tryptophan levels, transport of tryptophan across the blood-brain barrier is reduced a few days after delivery. Such an abrupt withdrawal of brain tryptophan in the early post-partum (mean −15% between pre- and post-partum), with its expected consequences on the function of the serotonin system, is concomitant to, and may play a role in, triggering the mood alteration associated with impaired control of emotions referred to as the post-partum blues.

A psycho-social assessment was performed on the same population (M'Bailara et al., 2005). In a logistic regression model including the three blocks of factors, both the biological determinant (change in brain tryptophan availability index, ANOVA $F=3.293$; $p=0.010$) and the psychological factors (stress and self-esteem, ANOVA $F=3.24$; $p=0.015$), but not the social factor (age, pairing, marital status, ANOVA $F=0.377$; $p=0.77$) were partial determinants of the increased Kennerley and Gath score.

A better clinical and biological assessment of the baby blues that represents a stereotypic mood change could be a model to understand the mechanisms responsible for post-partum mood episodes. The same mechanisms might trigger a real mood disorder in women with genetic vulnerability.

Acknowledgments

This work was funded by grants from CHU de Bordeaux (Appel d'Offres Interne 2001) and Lilly-CNRS, and was carried out with the support of Conseil Régional d'Aquitaine, Université de Bordeaux-2 and Centre d'Investigation Clinique INSERM/CHU de Bordeaux.

References

Baban, B., Chandler, P., McCool, D., Marshall, B., Munn, D.H., Mellor, A.L., 2004. Indoleamine 2,3-dioxygenase expression is

restricted to fetal trophoblast giant cells during murine gestation and is maternal genome specific. J. Reprod. Immunol. 61, 67–77.

Cetin, I., 2003. Placental transport of amino acids in normal and growth-restricted pregnancies. Eur. J. Obstet. Gynecol. 110, S50–S54.

Cetin, I., Ronzoni, S., Marconi, A.M., Perugino, G., Corbetta, C., Battaglia, F., Pardi, G., 1996. Maternal concentrations and fetal–maternal concentration differences of plasma amino acids in normal and intrauterine growth-restricted pregnancies. Am. J. Obstet. Gynecol. 174, 1575–1583.

Comings, D.E., Muhleman, D., Dietz, G., Sherma, M., Forest, G.L., 1995. Sequence of human tryptophan 2,3-dioxygenase (TDO2): presence of a glucocorticoid response-like element of a GTT repeat and an intronic CCCCT repeat. Genomics 29, 390–396.

Da Costa, D., Larouche, J., Drista, J., Brender, W., 2000. Psychosocial correlates of prepartum and postpartum mood. J. Affect. Disord. 59, 31–40.

Glangeaud-Freudenthal, M.C., Sutter, A.L., Guillaumont, C., Bourgeois, M., 1995. Questionnaire du "blues" du postpartum, version française du maternity blues de Kennerley H et Gath D. Ann. Med. Psychol. 153, 337–341.

Glover, V., Liddle, P., Taylor, A., Adams, D., Sandler, M., 1994. Mild hypomania (the highs) can be a feature of the first postpartum week. Association with later depression. Br. J. Psychiatry 164, 517–521.

Handley, S.L., Dunn, T.L., Baker, J.M., Cockshott, C., Gould, S., 1977. Mood changes in puerperium, and plasma tryptophan and cortisol concentrations. Br. Med. J. 2, 18–20.

Handley, S.L., Dunn, T.L., Waldron, G., Baker, J.M., 1980. Tryptophan, cortisol and puerpural mood. Br. J. Psychiatry 136, 498–508.

Iles, S., Gath, D., Kennerley, H., Maternity Blues II, 1989. A comparison between post-operative women and post-natal women. Br. J. Psychiatry 155, 363–366.

Kanai, Y., Segawa, H., Miyamoto, K., Uchino, H., Takeda, E., Endou, H., 1998. Expression cloning and characterization of a transporter for large neutral amino acids activated by the heavy chain of 4F2 antigen (CD98). J. Biol. Chem. 273, 23629–23632.

Kennerley, H., Gath, D., 1985. Maternity blues reassessed. Psychiatry Dev. 1, 1–17.

Kennerley, H., Gath, D., 1989. Maternity blues I–II. Br. J. Psychiatry 155, 356–362, see also pp. 367–373.

Kohl, C., Walch, T., Huber, R., Kemmler, G., Neurauter, G., Fuchs, D., Södler, E., Schröcksnadel, H., Sperner-Unterweger, B., 2005. Measurement of tryptophan, kynurenine and neopterin in women with and without postpartum blues. J. Affect. Disord. 86, 135–142.

Kudo, Y., Boyd, C.A.R., 2000. Human placental indoleamine 2,3-dioxygenase: cellular localization and characterization of an enzyme preventing fetal rejection. Biochem. Biophys. Acta 1500, 119–124.

Lucki, I., 1998. The spectrum of behaviors influenced by serotonin. Biol. Psychiatry 44, 151–162.

Maes, M., Ombelet, W., Verkerk, R., Bosmans, E., Scharpe, S., 2001. Effects of pregnancy and delivery on the availability of plasma tryptophan to the brain: relationships to delivery-induced immune activation and early anxiety and depression. Psychol. Med. 31, 847–858.

Maes, M., Verkerk, R., Bonaccorso, S., Ombelet, W., Bosmans, E., Scharpe, S., 2002. Depressive and anxiety symptoms in the early puerperium are related to increased degradation of tryptophan into kynurenine, a phenomenon which is related to immune activation. Life Sci. 71, 1837–1848.

Mann, J.J., 1999. Role of serotoninergic system in the pathogenesis of major depression and suicidal behavior. Neuropsychopharmacology 21, 99S–105S.

M'Bailara, K., Swendsen, J., Glatigny-Dallay, E., Dallay, D., Roux, D., Sutter, A.L., Demotes-Mainard, J., Henry, C., 2005. Le baby-blues: caractérisation clinique et influence de variables psychosociales. Encéphale 31, 331–336.

Mellor, A.L., Chandler, P., Lee, G.K., Johnson, T., Keskin, D.B., Lee, J., Munn, D.H., 2002. Indoleamine 2,3-dioxygenase, immunosuppression and pregnancy. J. Reprod. Immunol. 57, 143–150.

Moore, P., Landolt, H.P., Seifritz, E., Clark, C., Bhatti, T., Kelsoe, J., Rappaport, M., Gillin, J.C., 2000. Clinical and physiological consequences of rapid tryptophan depletion. Neuropsychopharmacology 23, 601–622.

More, C., Bhattoa, H.P., Bettembuk, P., Balogh, A., 2003. The effects of pregnancy and lactation on hormonal status and biochemical markers of bone turnover. Eur. J. Obstet. Gynecol. Reprod. Biol. 106, 209–213.

Moskowitz, D.S., Pinard, G., Zuroff, D.C., Annable, L., Young, S.N., 2001. The effect of tryptophan on social interaction in everyday life: a placebo-controlled study. Neuropsychopharmacology 25, 277–289.

Munn, D.H., Zhou, M., Attwood, J.T., Bondarev, I., Conway, S.J., Marshall, B., Brown, C., Mellor, A.L., 1998. Prevention of allogenic fetal rejection by tryptophan catabolism. Science 281, 1191–1193.

O'Hara, M.W., Schlechte, J.A., Lewis, D.A., Wright, E.J., 1991. Prospective study of postpartum blues biologic and psychosocial factors. Arch. Gen. Psychiatry 48, 801–806.

Pardridge, W.M., 1979. The role of blood–brain barrier transport of tryptophan and other neutral amino acids in the regulation of substrate-limited pathways of brain amino acid metabolism. J. Neural Transm. 15, 43–54.

Pitt, B., 1973. Maternity blues. Br. J. Psychiatry 122, 431–433.

Prasad, P.D., Wang, H., Huang, W., Kekuda, R., Rajan, D.P., Leibach, F.H., Ganapathy, V., 1999. Human LAT1, a subunit of system L amino-acid transporter: molecular cloning and transport function. Biochem. Biophys. Res. Commun. 255, 283–288.

Robin, A.M., 1962. Psychological changes associated with childbirth. Psychiatry Q. 36, 129–150.

Santoso, D.I., Rogers, P., Wallace, E.M., Manuelpillai, U., Walker, D., Subakir, S.B., 2002. Localization of indoleamine 2,3-dioxygenase and 4-hydroxynonenal in normal and pre-eclamptic placentae. Placenta 23, 373–379.

Schoengold, D.M., DeFiore, R., Parlett, R.C., 1977. Free amino acids in plasma throughout pregnancy. Am. J. Obstet. Gynecol. 131, 490–499.

Schröcksnadel, H., Baier-Bitterlich, G., Dapunt, O., Wachter, H., Fuchs, D., 1996. Decreased plasma tryptophan in pregnancy. Obstet. Gynecol. 88, 47–50.

Schröcksnadel, K., Widner, B., Bergant, A., Neurauter, G., Schennach, H., Schröcksnadel, H., Fuchs, D., 2003. Longitudinal study of tryptophan degradation during and after pregnancy. Life Sci. 72, 785–793.

Sedlmayr, P., Blaschitz, A., Wintersteiger, R., Semlitsch, M., Hammer, A., MacKenzie, C.R., Walcher, W., Reich, O., Takikawa, O., Dohr, G., 2002. Localization of indoleamine 2,3-dioxygenase in human female reproductive organs and the placenta. Mol. Hum. Reprod. 8, 385–391.

Smith, Q.R., 2000. Transport of glutamate and other amino-acids at the blood–brain-barrier. J. Nutr. 130, 1016S–1022S.

Sun, H.S., Tsai, H.W., Ko, H.C., Chang, F.M., Yeh, T.L., 2004. Association of tryptophan hydroxylase gene polymorphism with depression, anxiety and comorbid depression and anxiety in a population-based sample of postpartum Taiwanese women. Genes Brain Behav. 3, 328–336.

Sutter, A.L., Leroy, V., Dallay, D., Verdoux, H., Bourgeois, M., 1997. Post-partum blues and mild depressive symptomatology at days tree and five after delivery. A French cross sectional study. J. Affect. Disord. 44 (1), 1–4.

Verrey, F., 2003. System L: heteromeric exchangers of large, neutral amino acids involved in directional transport. Pflugers Arch. Eur. J. Physiol. 445, 529–533.

Yalom, I., Lunde, D., Moos, R., Hamburg, D., 1968. 'Post-partum blues syndrome': a description and related variables. Arch. Gen. Psychiatry 18, 16–27.