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Abstract

Introduction: Postpartum Depression (PPD) affects up to 19% of all women after parturition. The nonapeptide oxytocin (OXT) is involved in adjustment to pregnancy, maternal behavior and bonding. Our aim was to examine the possible association between plasma OXT during pregnancy and the development of PPD symptoms.

Method: 74 healthy, pregnant women were included in this prospective study. During the third trimester of pregnancy and within two weeks after parturition PPD symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS). Blood samples for plasma OXT assessment were collected in the third trimester. Following the literature, participants with postpartum EPDS scores of 10 or more were regarded as being at risk for PPD development (rPPD group). In a logistic regression analysis plasma OXT was included as a potential predictor for being at risk for PPD. Results were controlled for prepartal EPDS score, sociodemographic and birth-outcome variables.

Result: Plasma OXT concentration in mid-pregnancy significantly predicted PPD symptoms at two weeks postpartum. Compared to the no-risk-for-PPD group, the rPPD group was characterized by lower plasma OXT concentrations.

Conclusion: To our knowledge, this is the first study to show an association between prepartal plasma OXT concentration and postpartal symptoms of PPD in humans. Assuming a causal relationship, enhancing OXT release during pregnancy could serve as a potential target in prepartum PPD prevention and help to minimize adverse effects of PPD on the mother-child-relationship.

Keywords: postpartum depression; oxytocin; pregnancy; EPDS; adaptation to motherhood

Introduction

Postpartum Depression (PPD) affects up to 19% of all mothers and adversely influences maternal adaptation to motherhood (Gavin *et al*, 2005) with negative effects on child development, as children of depressive mothes are more vulnerable to develop mental disorders in later life (Grace *et al*, 2003).

The etiology of PPD is closely related to psychological determinants and experiences during pregnancy (O'Hara and Swain, 1996). Identification of psychological risk factors for PPD has been an important issue in the recent years. Major identified risk factors are a history of previous PPD or affective illnesses in general, stressful life events, lack of social support and low self-esteem (Beck, 2006; Robertson *et al*, 2004). Additionally, the early postpartum period is seen as a time of increased emotional vulnerability, partly caused by dysregulations of the endocrinological homeostasis (Wisner and Stowe, 1997). Due to the challenging reorganization of physiological processes that comes along with pregnancy and parturition, research started to address endocrine factors as potential determinants in the etiology of PPD. From animal models of PPD, we know that withdrawal from high doses of estradiol and progesterone, comparable to the respective amounts available during pregnancy, is followed by depression-like symptoms (Green *et al*, 2009). Addtionally, the regulation of the hypothalamic-pituitary-adrenal (HPA) axis seems to be disturbed in women with PPD (Brummelte and Galea, 2010) or short periods of Postpartum Blues (Ehlert *et al*, 1990). However, existing findings are not consistent (Bloch *et al*, 2003). One biological parameter that has not yet been considered in PPD etiology, is the nonapeptide oxytocin (OXT). OXT is synthesized in the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus and released peripherally into the blood and centrally into different brain regions (Gimpl and Fahrenholz, 2001). In context of pregnancy, OXT is known for its

involvement in the process of delivery (Russell *et al*, 2003) and its physiological role in the onset and maintenance of lactation (Sala and Althabe, 1968).

Beyond its physiological functions in the periphery, animal studies provide evidence for a major role of OXT in behavioral adaptation to pregnancy and motherhood. Characteristic maternal behaviors (pup-grooming, hover over offspring, respond latency) are impaired, if OXT availability is diminished (Higuchi and Kaba, 1997; Olazabal and Young, 2005; Pedersen *et al*, 2006). Furthermore, maternal OXT functioning influences reciprocal affective behaviors between mother and offspring in mammalian species (Nelson and Panksepp, 1998). Recently, this association was also shown in humans. Parents showing more affectionate and stimulatory behaviors in interactions with their children were characterized by higher plasma OXT concentrations (Gordon *et al*, 2010). Further, Feldman et al. (2007) reported associations between prepartum assessed OXT concentrations and postpartum maternal adaptation. The maternal plasma OXT level, measured during early and late pregnancy, as well as in the first month postpartum, predicted maternal behavior (mother's gaze at infant, motherese vocalizations, affectionate touch) in interaction with the child. A study assessing plasma OXT twice during pregnancy showed higher postpartum maternal-fetal attachment-scores in women with a OXT rise between the first and third trimester compared to women with stable or decreasing patterns of OXT (Levine *et al*, 2007). In non-pregnant women, OXT is known to promote interpersonal relationships and enhance feelings of love and trust (Heinrichs and Domes, 2008).

Based on current evidence, lower OXT levels in pregnancy could result in impaired emotional adaptation to motherhood, which is a major risk factor for PPD development and subsequently affects the quality of maternal behavior (Murray *et al*, 1993; Stein *et al*, 2010). Therefore, the aim of the present study was to assess a potential association between OXT during pregnancy and postpartum PPD symptoms in a sample of healthy pregnant women. We expected, that lower plasma OXT levels during the third trimester of pregnancy would

result in an increased risk for PPD, as assessed postpartum. Results could help to elucidate the

etiopathology of PPD and provide new targets for prepartal prevention of PPD.

Methods

Subjects

Data was collected within a larger longitudinal study conducted with 100 pregnant women in the area of Basel, Switzerland. All participants were recruited between their 21st and 32nd week of gestation. Recruitment-methods included local newspaper announcements, promotion of the study at local hospitals and a call for participants on local TV. A detailed study description was given to all interested women and, if any arised, questions were answered. All participants were screened for the following inclusion criteria: (a) no current mental illness, (b) no severe medical complications (acute or chronic physical diseases, such as gestational diabetes, metabolic diseases, hypertension and thyroid dysfunction), (c) no signs of fetal malformation, (d) a pre-pregnancy BMI below 32, (e) no smoking beyond the 10th week of gestation and (f) good knowledge of German language. Data for analyses of the present paper was available for 73 participants, of which 16 were characterized by at least one lifetime depressive episode. All cases with a lifetime episode of depression were dated back more than two years before participation in the study. A flowchart of dropouts is displayed in Figure 1. Comparisons between the 73 women providing complete data and the 27 excluded women indicated no significant differences on age, parity, socioeconomic status and PPD symptoms. Informed written consent was obtained from all participants. The study protocol was approved by the local ethics committee and is consistent with the revised Helsinki Declaration of 1975.

Blood sampling and OXT measurement

All blood samples were obtained between the 30th and 34th week of gestation. Participants visited the study centre for an experimental session, which included blood sampling and other physiological assessments. The samples for the OXT assessment were collected at the beginning of the session, starting between 1 pm and 3 pm. Participants were seated on a examination couch and a study nurse sampled 2.7 ml of blood into vacutainer tubes containing lithium heparin and 108 μl of Aprotinin (BioChemica, Germany). Tubes were kept on ice and centrifuged within 10 minutes at 6 °C at 3000g for 10 min. Supernatants were pipetted into safe-lock devices and stored at -80 °C until analysis.

Samples were analyzed at the Department of Behavioural Neuroendocrinology, Max Plank Institute of Psychiatry, Munich, Germany, using a radioimmunoassay, as described elsewhere (Landgraf *et al*, 1995). This assay was reported to have an antiserum-cross-reactivity of less than 0.7%, with a detection limit of 0.1 pg per sample. All samples were analyzed in duplicates. The intra-assay and inter-assay coefficients of variability were 6-8% and 8-10%, respectively.

Assessment of demographic and psychological characteristics

After inclusion, participants were interviewed for assessing possible present, recent or life-time depression and anxiety disorders using the German translation of corresponding sections of the Computer Assisted Personal Interview (CAPI) version of the Composite International Diagnostic Interview (Wittchen *et al*, 1998; Wittchen and Pfister, 1997; World Health Organization, 1990) and general socioeconomic data.

Depressive symptoms were assessed within two weeks after delivery using the Edinburgh Postnatal Depression Scale (EPDS), a scale originally developed as a screening measure for depression, showing good reliability (split-half: 0.82; standardized α = .81) (Bergant *et al*, 1998). Ten items, dealing with typical PPD symptoms are answered on a 4-point scale. As a

control variable the prepartal EPDS score was assessed between the 32nd and 34th week of gestation.

Information on length of gestation and birth outcome were collected from medical records.

Data analyses

All variables were checked for normal distribution, missing data and outliers (defined as more than two standard deviations below or above the mean) by the Kolmogorov-Smirnof test and visual inspection. Outliers were checked for validity and excluded if reasonable. If necessary, variables were subjected to transformation by natural logarithm before further analyses. Differences on demographic, biological and psychological characteristics between included and excluded study participants were tested by t and χ^2 tests. Participants were divided into a risk-for PPD group (rPPD) and a no-risk-for PPD group (nPPD), according to the respective postpartum EPDS score. Based upon the proposals of Bergant et al. (1998) and Jardri et al. (2006), the chosen cut-off score for being at risk for PPD was 10 or more within the first two weeks postpartum. T and χ^2 tests were computed between the groups, to identify possible confounders among the demographical and medical variables. Descriptive statistics of EPDS scores and OXT values are reported. The postpartal EPDS scores of nursing and not nursing mothers were compared using the t-test. The bivariate correlation was computed between the pre- and postpartal EPDS score. The association between OXT and PPD symptoms was tested by conducting a binary logistic regression analysis with the group variable as outcome variable and OXT concentration as the potential predictor in the first run. In a second run the prepartal EPDS score was added, to control for potential confounding by previous depressive symptoms. Further analyses were computed including OXT concentration as the first predictor and other potential predictors, identified through previous group comparisons. Due to the expected, unequal group sizes, every logistic regression analysis was conducted with

not more than two predictors, of which the first one was always OXT concentration. Because accurate classification of participants is difficult when groups are not evenly split, primary emphasis was placed on prediction rather than classification of being at risk for PPD. Data was analyzed using SPSS 16.0.2 for Mac OS X. The level of significance for all analyses was set at $\alpha = .05$.

Results

Sample and group characteristics

Demographic and pregnancy-related sample and group characteristics are displayed in Table 1. A group variable was introduced according to the postpartum EPDS score. Fourteen participants were identified as having a postpartum EPDS score of 10 or more and were assigned to the rPPD group, representing a higher risk for the development of PPD. The remaining 59 participants were assigned to the nPPD group. Groups were tested for significant differences regarding sociodemographic and birth characteristics. Groups differed only in length of gestation. Participants in the rPPD group had a significantly shorter length of gestation ($M = 39.02$ weeks) compared to participants in the nPPD group ($M = 39.73$ weeks) ($T(71) = 2.049$; $P < .05$). Therefore length of gestation was included as a potential mediator in further analysis of the relationship between OXT and PPD symptoms.

Pre- and postpartal EPDS scores

Postpartal EPDS scores did not differ between nursing and not nursing mothers ($T(69) = 0.025$; $P = .98$). Prepartal EPDS scores (Range 0-17) were significantly correlated with

postpartal EDPS scores (Range 0-22) ($r = .232$; $p = .048$). Mean prepartal and postpartal total EPDS scores were 4.77 and 5.85 respectively.

Plasma OXT concentrations

Plasma OXT concentrations had a range of 14.39-245.71 pg/ml and mean OXT concentration for the overall sample was 80.81 pg/ml (SD = 48.81 pg/ml). Three outliers with OXT values above 200 pg/ml were identified. Information on these three subjects did not provide a clear reason for exclusion of these cases or any indication for invalidity of assessments. Therefore, they were retained in the analyses. All further analyses were conducted with the log-transformed OXT concentrations to assure normal distribution. The bivariate correlation between prepartal EPDS scores and OXT concentrations was not significant ($r = -.086$; $p = .467$).

The association between OXT concentration in pregnancy and postpartum PPD symptoms

The test statistics of the logistic regression analyses, with OXT predicting PPD symptoms are displayed in Table 2. Plasma OXT level significantly predicted PPD symptoms (Exp (b) = .290; $p < .05$). The coefficient of association between OXT concentration and PPD was below one, indicating lower OXT levels in the rPPD group and higher OXT levels in the nPPD group. The addition of the prepartal EPDS score as a further covariate in a second analysis did not improve the model fit ($\Delta\chi^2$ (1) = 0.302; $P > .05$). According to the results of descriptive statistics, length of gestation was tested as a potential mediator in a third analysis. Length of gestation did not predict PPD symptoms (Exp (b) = .931; $p > .05$) and the model fit did not improve either ($\Delta\chi^2$ (1) = 3.507; $P > .05$).

With OXT as predictor of PPD symptoms, 83.6% of the sample was classified correctly into the nPPD and rPPD group. To visualize the difference in OXT values between the groups, mean OXT concentrations are displayed in Figure 2.

Repeated analyses excluding the three cases with outlying OXT concentrations did not change the results.

Discussion

In line with our hypothesis, we could show that OXT during pregnancy was negatively associated with a positive screen on the EPDS at greater than or equal to 10, indicating a higher risk for the development of PPD. This suggests an increased occurrence of depressive symptoms in the first two weeks after delivery in individuals with low plasma OXT concentrations during pregnancy. The relationship persisted after controlling for prepartal EPDS scores.

Our findings are in agreement with the only human study addressing the link between plasma OXT during pregnancy and postpartal maternal behavior. Plasma OXT concentrations during pregnancy were found to be positively associated with a set of maternal bonding behaviors, such as positive affect and gaze in interactions, as well as cognitive attachment representations towards the newborn in the early postpartum period (Feldman *et al*, 2007). In women suffering from PPD the same behaviors are impaired, accompanied by feelings of overload and difficulties in emotional attachment development towards their child (Beck, 2006; Martins and Gaffan, 2000). Correspondingly studies with rodents report deficits in maternal behavior, such as less protective behavior and less pup-licking, and longer latencies in postpartal onset of maternal behavior in animals with decreased central OXT availability (Pedersen *et al*, 2006; van Leengoed *et al*, 1987). Non-human primate mothers show increased maternal affiliation towards offspring when central OXT is enhanced (Holman and

Goy, 1995). The present findings are also in agreement with human studies reporting relationships between plasma OXT, assessed in the 2nd and 6th month postpartum and affectionate maternal behavior during mother-child interactions (Gordon *et al*, 2010). Again, mothers' OXT concentrations were positively correlated with the behavioral indicators of attachment, such as motherese vocalization, affectionate touch and positive affect. As anxiety and excessive preoccupation are other important symptoms of PPD, our results also match reports of OXT working anxiolytic and enhancing positive emotional affiliation in non-pregnant humans (Uvnas-Moberg, 1998). There is also evidence for decreased plasma OXT concentrations in individuals suffering from Major Depression or reporting increased depressive symptoms (Frasch *et al*, 1995; Ozsoy *et al*, 2009; Scantamburlo *et al*, 2007).

The herein observed prevalence of subjects above cutoff resembles those of other studies using the same screening instrument. Here we identified 19.18% of the sample having an EPDS score of 10 or more. Other comparable studies found a rate of 20% at 5 days postpartum (Bergant *et al*, 1998) and 16% at two months postpartum (Yim *et al*, 2009).

Group comparisons revealed a significantly shorter gestation among women within the rPPD group. In women with lower OXT availability in pregnancy the oxytocinergic inhibition of the HPA axis could be decreased. Decreased HPA axis inhibition would enhance the exponential increase of placental corticotropin-releasing factor that promotes the onset of labour (Smith, 1998). However, the length of gestation variable did not reach significance in the following prediction of PPD symptoms. It remains to be elucidated, if length of gestation plays a mediating role in the relationship between OXT and PPD in samples including premature deliveries.

The range of OXT concentrations found in the present sample, is in line with those of previous studies (Dawood *et al*, 1979; De Geest *et al*, 1985). One often mentioned issue concerning OXT assessment in human samples is that central OXT release is not necessarily related to peripheral OXT release and therefore associations between centrally regulated

psychological variables and peripheral measured OXT should be handled with caution (Jones *et al*, 1983; Landgraf and Neumann, 2004). However, in animals, there are also studies accounting for joint control mechanisms of central and peripheral OXT release in context of fear-related stress responses (Wotjak *et al*, 1998) and for autostimulatory effects at the level of the hypothalamus, in terms of peripheral OXT release activation by centrally released OXT (McKenzie *et al*, 1995; Neumann *et al*, 1994). Given the current evidence from animal studies and the difficulties in the determination of central OXT release in humans, it appears justifiable to revert to peripheral OXT assessment. This is supported by several findings reporting relations between peripheral OXT in humans and various psychological constructs, all representing aspects of human affiliation and attachment (Feldman *et al*, 2007; Light *et al*, 2004; Tops *et al*, 2007; Wismer Fries *et al*, 2005).

The mechanisms behind the observed association between OXT and PPD symptoms remain to be elucidated. Although we cannot rule out residual confounding by unknown factors, the prospective design and the inclusion of pre-pregnancy EPDS scores as a covariate make a causal relationship imaginable. There already exists evidence that OXT concentrations are lower in mothers characterized by depressive symptoms and negative affect during pregnancy, when assessed postpartum (Light *et al*, 2004). Further, OXT is known to reduce psychological and physiological stress responses (Heinrichs *et al*, 2003) and to inhibit hyperactive fear-responses of the amygdala (Labuschagne *et al*, 2010). There is also evidence that the properties of endocrine systems during pregnancy have programming functions for the postpartal period (Meinlschmidt *et al*, 2010; Pop *et al*, 1993). Transferred to our case, the interplay between low OXT, its effects on amygdala reactivity and the HPA axis in pregnancy could indicate an increased reactivity to stressful stimuli at that time and promote the development of depressive symptoms after birth, when mothers are challenged by a bulk of potentially stressful new conditions. Additionally, expectations of the social environment and the growing demands of the child may promote feelings of fear and insecurity. Notably, a

study comparing the symptomatology of postpartum and non-postpartum depression found more anxious features among the investigated PPD group (Hendrick *et al*, 2000). As we know from animal studies, besides the general importance of OXT in the formation of social bonds in females (Insel, 1997), the positive feedback mechanism of the oxytocinergic system is supposed to provide long lasting stimulation of maternal behaviors after parturition (DaCosta *et al*, 1996). It may be less efficient, if OXT availability is diminished. Adopted to human mothers, this would be reflected by the difficulties depressed mothers have in implementing maternal behaviors and forming a relationship with their child (Beck, 1995; Cooper and Murray, 1998). Considering the profound physiological challenge caused by endocrinological changes over the course of gestation and the following abrupt shift after parturition, it is not possible to form a biological model for PPD development, that accounts for all contributing factors yet. Future studies should try to experimentally modify OXT concentrations in mid-pregnancy, to verify, whether OXT during pregnancy contributes to the generation of depressive symptoms during the postpartum period.

There are some limitations of the study. First, our finding needs to be confirmed in future studies with more than one OXT assessment over the course of pregnancy to clarify, if the relationship is specific to OXT concentrations between the 30th and 34th week of gestation. Studies assessing OXT at different stages of gestation report the possibility of individually different patterns of OXT fluctuations over time, arguing that there might be a functional difference between women with stable OXT levels and those with rising ones (Dawood *et al*, 1979; Levine *et al*, 2007). But high intra-individual stability of values has been reported also (Feldman *et al*, 2007; Leake *et al*, 1981; van der Post *et al*, 1997). From our point of view, the present results refer to plasma OXT levels between the 30th and 34th week of gestation only, as we did not assess potential alterations in peripheral OXT release over the course of gestation. Second, the sample consisted of women with mostly medium to high socioeconomic status. Consequently results need to be replicated with more heterogenous

samples. Third, PPD symptoms were assessed by questionnaire (EPDS), which should be complemented in future studies by structured or standardized interviews to verify the presence of a diagnosis of PPD. It should be noted that as yet, estimations of the sensitivity and specificity of the EPDS to detect PPD vary across studies, warranting further attention of this issue (Eberhard-Gran *et al*, 2001; Gaynes *et al*, 2005; Gibson *et al*, 2009). Nevertheless there are validation studies reporting good sensitivity and specificity values for the EPDS within comparable study designs and according to DSM-III and ICD-10 criteria (Harris et al, 1989; Jardri et al, 2006). Important to note, our use of the EPDS within a period of 2 weeks postpartum does not provide information on the diagnosis of PPD, which requires the presence of symptoms for at least two weeks. Moreover, heightened EPDS scores in this early postpartum period may still be picking up the tail end of postpartum blues, which itself is a risk factor for the development of PPD. Finally, future studies should clarify, if the association between prepartal OXT and depressive symptoms during the postpartum period remains stable beyond the first two weeks up to several months postpartum and if this relationship holds true for individuals with diagnosed episodes of PPD, as not all women with increased depressive symptoms after delivery develop a full-blown affective disorder.

In summary, our findings suggest that OXT is involved in the etiology of depressive symptoms during pregnancy and needs to be further elaborated in studies assessing neuroendocrinological aspects of PPD. If replicated, the presented results have important clinical relevance. Prepartal identification of subjects at risk for PPD could allow for early preventive interventions and minimize adverse effects for the physiological and psychological wellbeing of mother and child.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Titles and Legends to Figures

Figure 1 Flowchart of study participants.

Figure 2 Graph shows means + standard error of mean of original oxytocin values in the two groups.

Tables

Table 1 Sample and group characteristics and tests for group differences.

	total sample	nPPD group	rPPD group	Test between nPPD and rPPD
	M (SD) / %	*M* (SD) / %	*M* (SD) / %	
	(N = 73)	(n = 59)	(n = 14)	*p*-value
maternal age (years)	31.05 (4.70)	31.22 (4.69)	30.36 (4.88)	.541[a]
income category				.928[b]
low	8.70%	8.90%	7.70%	
average/high	73.90%	73.20%	76.90%	
very high	17.40%	17.90%	15.40%	
pre-pregnancy BMI	22.31 (3.47)	22.10 (3.26)	23.32 (4.40)	.292[a]
parity				
primiparae	74.0%	71.20%	85.70%	
multiparae	26.0%	28.80%	14.30%	
length of gestation (weeks)	39.6 (1.2)	39.7 (1.1)	39.1 (1.4)	.044[a]
birth mode				
ceserean section	23.3%	23.70%	21.40%	
mother is nursing	90.0%	89.7%	92.3%	
infant birth weight (g)	3338.56 (378.44)	3345.93 (359.21)	3307.50 (465.02)	.735[a]
infant sex				
female	46.6%	50.8%	28.6%	
male	53.4%	49.2%	71.4%	

Monthly income categories low = 0-3750 swiss franks, average/high = 3750-11250 swiss franks, very high = above 11250 swiss franks;

nPPD = no risk for Postpartum Depression; rPPD = at risk for Postpartum Depression; BMI = Body-Mass-Index.

[a]*t*-test

[b]χ^2-test

Table 2 Binary logistic regression analysis fort he prediction of being at risk for Postpartal Depression.

	model statistics				predictor statistics			
	χ^2 (df)	P	R^2_{NK}	-2 LL	Wald's X^2 (df)	p	Exp(b)	95% CI for Exp(b)
First analysis	6.195 (1)	.013	0.130	65.169				
plasma oxytocin					5.555 (1)	.018	0.290	0.103 - 0.812
Second analysis	6.497 (2)	.039	0.137	64.867				
plasma oxytocin					5.366 (1)	.210	0.294	0.105 - 0.828
prepartal EPDS score					0.299 (1)	.584	1.254	0.557 - 2.828
Change of model fit compared to first analysis: $\Delta \chi^2$ (1) = 0.302; p = .583								
Third analysis	9.702 (2)	.008	0.200	61.662				
plasma oxytocin					5.250 (1)	.022	0.294	0.103 - 0.838
length of gestation					3.447 (1)	.063	0.931	0.864 - 1.004
Change of model fit compared to first analysis: $\Delta \chi^2$ (1) = 3.507; p = .061								

R^2_{NK} = Nagelkerke R^2; -2 LL = -2 Log Likelihood (deviance); χ^2 = Chi-Square; EPDS = Edinburgh Postnatal Depression Scale.
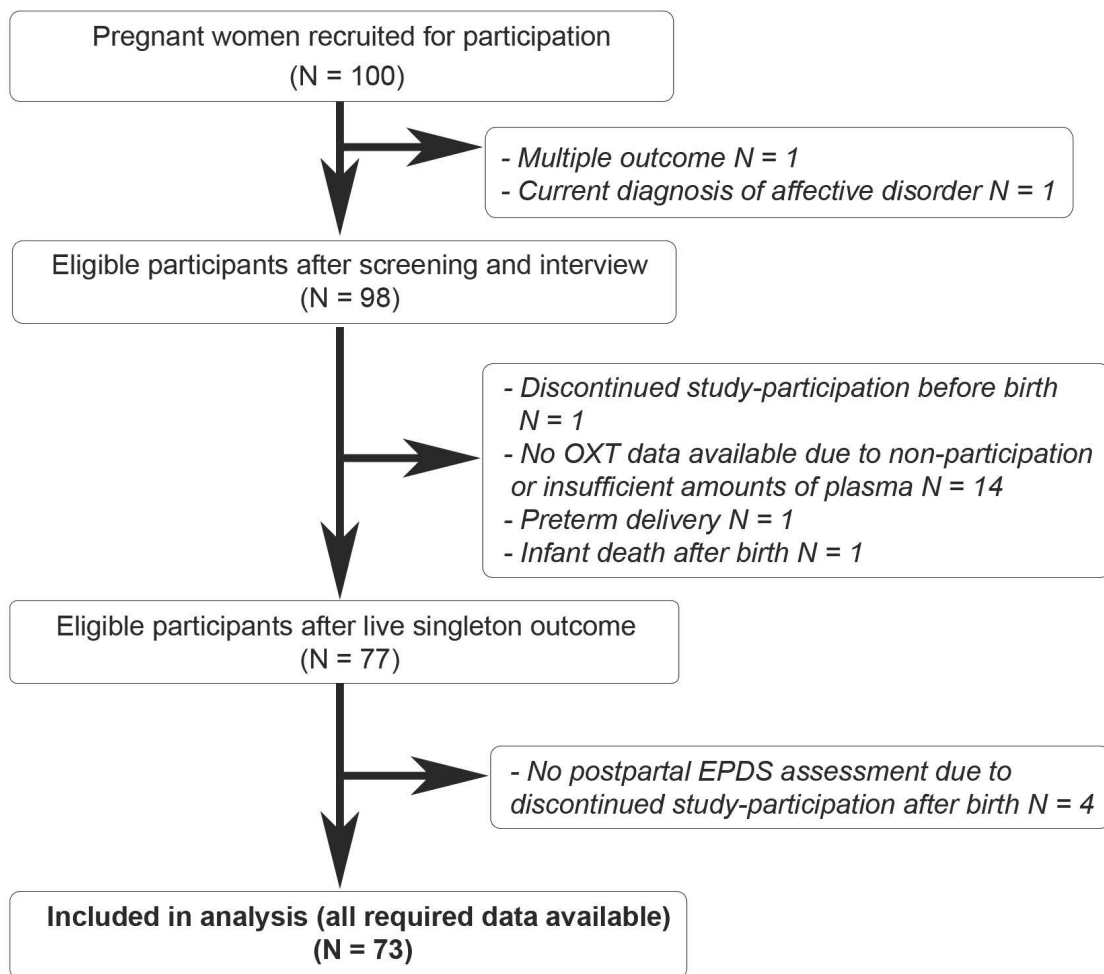
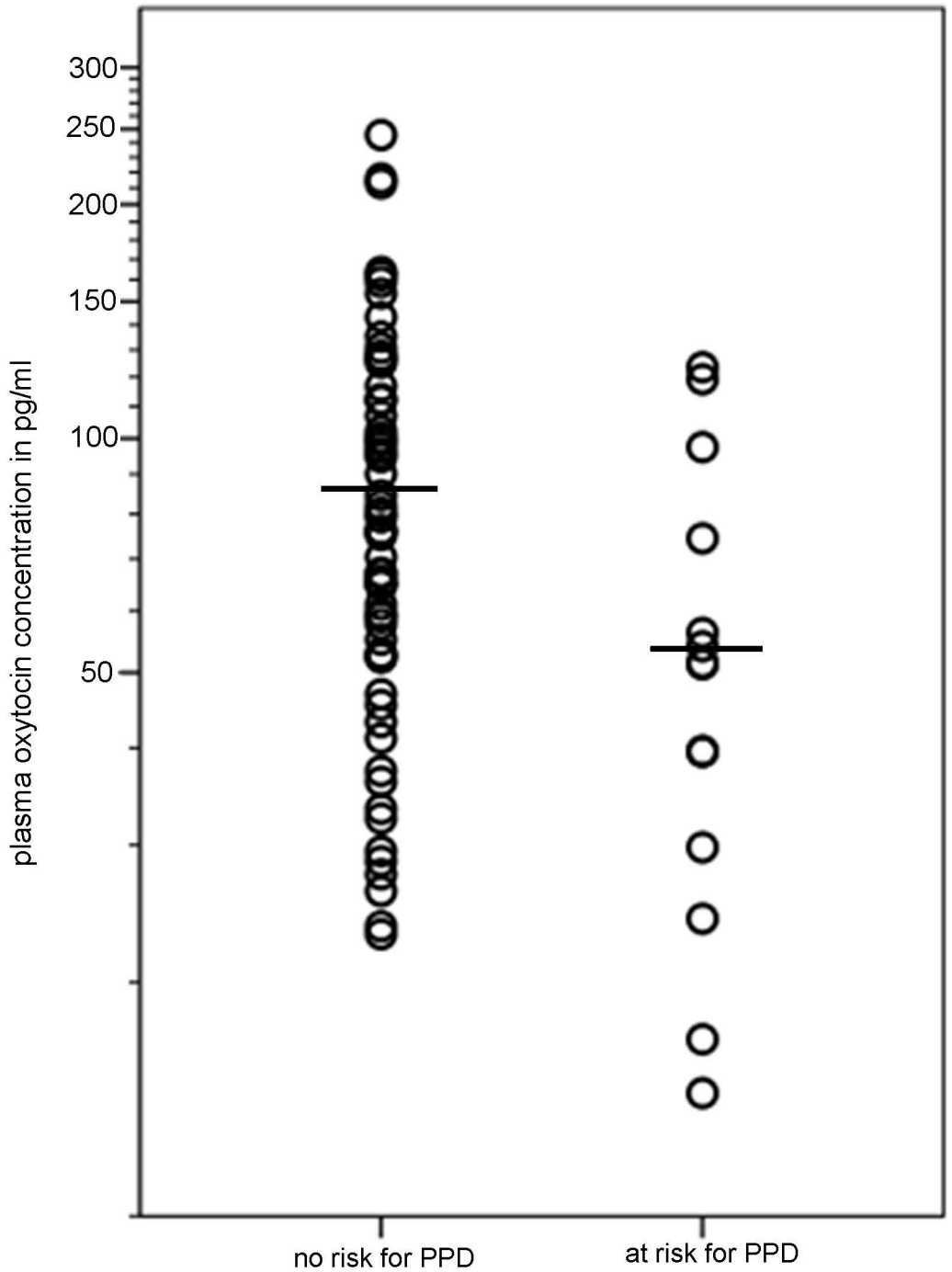**Figure 1** Flowchart of study participants.

Figure 2 Graph shows individual oxytocin concentrations in the two groups and group means. Oxytocin values are shown on a logarithmic scale.