



The relationship between biological factors (vitamin D, prolactin, oxytocin, thyroid hormones), Pregnancy-Related Anxiety and Maternal-Foetal Attachment

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Abstract

Introduction and Objective. Pregnancy-Related Anxiety (PrA) is a common issue in pregnancy, which is distinctive from Generalized Anxiety Disorder. It has numerous negative outcomes for both mother and child. The aim of this study was to investigate the relationship between vitamin D, thyroid function, prolactin, oxytocin and Pregnancy-Related Anxiety, and to check for any correlations between anxiety levels and maternal-foetal bonding in pregnancy and postpartum.

Materials and method. Seventy pregnant women participated in the study. The relationship was investigated between Pregnancy-Related Anxiety and biological factors and maternal-foetal attachment, using serum levels of vitamin D, TSH, prolactin, oxytocin, and scores of PRAQ-R2, MFAS and MORS questionnaires.

Results. No significant association was found between vitamin D, oxytocin, prolactin, TSH and PrA. Weak positive correlations were found between own appearance subscale of PRAQ-R2 and mothers' perception of giving self subscale in MFAS. A weak positive correlation was also found between PRAQ-R2 and its' subscale concerning own appearance and MORS invasion subscale.

Conclusions. Vitamin D, oxytocin, prolactin and thyroid function are believed to be associated with anxiety disorders. No such association was found. It might suggest that PrA is a distinctive disorder with other pathogenetic factors. Disorders of maternal-foetal attachment may be related to concerns about own appearance in pregnant women; therefore, this issue should be addressed early in pregnancy.

Key words

Pregnancy-Related Anxiety, Oxytocin, Prolactin, Vitamin D, thyroid hormones, TSH, Maternal-Foetal Bonding, Maternal-Foetal Attachment

INTRODUCTION

Pregnancy-Related Anxiety is a syndrome distinctive from Generalised Anxiety Disorder or Panic Disorder [1, 2]. It is defined by three contributing themes: baby concerns, body image concerns and childbirth concerns [3]. It is believed to be a common issue, with a prevalence of 29.6–65%, depending on criteria or tools used [4, 5, 6]. Nonetheless, it is worth noting that even 70% of pregnant women might experience mild anxiety [7]. Most research shows, that anxiety symptoms were observed to be highest in the first trimester, with a downward trajectory in the course of pregnancy. It seems to be stable in the 2nd and 3rd trimesters [8], showing small differences in women regardless of parity [9]. Some researchers have shown that the levels of anxiety are stable throughout the pregnancy [10].

Anxiety during pregnancy was found to cause many adverse effects, both for the mother and the foetus. The consequences include hypertensive disorder in pregnancy [11], postpartum depression [12], decreased likelihood of

breastfeeding [13], and increased chance of caesarean section [14]. Maternal-Foetal attachment seems to be negatively impacted by prenatal anxiety [15]. A large systematic review indicates that prenatal anxiety was linked in a weak to moderate way with disturbances in a relationship between mother and child [16]. As a high cortisol level in women is a birth-inducing factor, prenatal anxiety can cause preterm birth, resulting in low birth weight [17], and poorer condition at birth [18]. PrA can also lead to emotional and behavioural difficulties [19, 20], and impaired brain development [21] in a foetus.

Multiple factors were linked with prenatal anxiety, such as family disharmony [22], previous history of a negative obstetric outcome [23], unplanned pregnancy [23], or lack of social support [24]. Both histories of other psychiatric [25] and medical [26] conditions can account for higher levels of anxiety.

Neurobiological factors were proven to be a causal factor of Generalized Anxiety Disorder [27]. Researchers suggest that PrA may also be caused by various hormonal and neurobiological changes, as outlined below.

Oxytocin (OT) is a neuroendocrine hormone, synthesized in the brain by the paraventricular and the supraoptic nucleus of the thalamus [28]. It was proven to impact mood, pain

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and social activities [29]. Women with lower OT levels were shown to have more depression and anxiety symptoms [30, 31]. The presence of psychosocial stress is associated with higher oxytocin levels [32]. Some evidence suggests that it may also mediate the effect of stress on prenatal depression [32] and prenatal anxiety [29].

Prolactin (PRL) plays a role in the regulation of the hypothalamic-pituitary-adrenal axis (HPA axis), thereby modulating anxiety-like behaviours. Studies show a correlation between a high PRL levels and psychological distress [33]. On the other hand, some research suggests that it may suppress anxiety-like behaviour in pregnant women, and maintain normal maternal behaviour in an anxiogenic situation [34].

Similarly, thyroid function is influenced by the HPA axis. Due to the adaptive changes of the HPA axis in pregnancy, thyroid function may be impaired [35]. Moreover, thyroid hormones modulate the serotonergic system and plasma serotonin levels correlate with free triiodothyronine (FT3) and free thyroxine (FT4) [36]. Pregnant women with higher anxiety scores measured by the GAD7 questionnaire had higher concentrations of thyroid stimulating hormone (TSH) and lower concentrations of serum FT3 and FT4. These correlations were also present in euthyroid women [35].

Vitamin D is a valid regulator of gene expression of multiple cellular functions [37]. It promotes neurotransmission, neurogenesis, amyloid clearance and synaptogenesis, and prevents neuronal death [38]. Calcitriol activates the synthesis of tryptophan hydroxylase 2 (TPH-2) in the brain and therefore is linked with the production of serotonin [39]. Pregnant women with lower vitamin D levels were shown to may have higher anxiety scores [40].

Given the burden of PrA, it important that it is diagnosed and treated early in the course of the pregnancy. Nonetheless, research shows that awareness of such a condition is low among healthcare workers [41, 42]. Also, there are no formal screening protocols worldwide [43]. Even despite the growing interest in anxiety disorders in pregnancy, research in this field is still scarce [44]; for example, a large systematic review identified only one paper investigating the relationship between prenatal anxiety and vitamin D level [45].

OBJECTIVE

The aim of the study was to:

- a) investigate the relationship between vitamin D, thyroid function, prolactin, oxytocin and Pregnancy-Related Anxiety;
- b) check for any correlations between anxiety levels and maternal-foetal bonding in pregnancy and postpartum.

It was hypothesised that higher levels of anxiety in pregnant women were associated with lower vitamin D concentration, lower oxytocin level, lower prolactin level and higher TSH. It was also hypothesised that higher PrA scores were linked to impaired maternal-foetal bonding.

MATERIALS AND METHOD

Sample. Data was collected in 2020 – 2022 from patients in the ‘Mama i Ja’ (‘Mummy and Me’) private maternity clinic

in Wrocław, Poland. All patients attending the clinic who matched the inclusion criteria were invited to participate in the study. They received a printed leaflet with study information from their Ob-Gyn during a medical appointment. The information packet included questionnaires and a voucher for free blood tests. It also included consent forms to participate in the study. The selected sample consisted of 70 pregnant women who gave their consent for participation.

The inclusion criteria were: speaking Polish, being 28–34 weeks pregnant, written informed consent. The exclusion criteria were: having a high-risk pregnancy, having any previous psychiatric history, age under 18-years-old. It was decided to include only patients who were 28–34 weeks pregnant, as anxiety symptoms seem to be more stable in this period among pregnant women, regardless of parity.

A mixed method design was used, including a cross-sectional design to investigate the relationship between the biological factors, PrA and Maternal-Foetal attachment in pregnancy, and a prospective cohort study design to investigate the relationship between the above- mentioned with Maternal-Foetal attachment after childbirth.

The study was approved by the Ethical Committee of the Medical University in Wrocław (Approval No. KB-621/2020).

Instruments. The participants were asked to complete the first part of the study at 28–34 weeks pregnant. They were asked to complete a survey that consisted of:

- a) a socio-demographic questionnaire, including age, place of residence, marital status, education, and relevant medical history, including history of gestational diabetes, and age of pregnancy.
- b) Pregnancy-Related Anxiety Questionnaire–Revised 2 (PRAQ-R2) [46] created by Huizink et al. This is a short, 10-item questionnaire, useful for screening pregnant women for Pregnancy-Related Anxiety. It is validated for use independently of parity. The questionnaire covers three dimensions of PrA: fear of giving birth, fear of bearing a handicapped child, and worry about own appearance. The authors of this questionnaire did not identify the cut-off point for the diagnosis of PrA. A Polish adaptation was used in the current study which was proven to have good validity and reliability [47].
- c) The Maternal-Foetal Attachment Scale (MFAS) [48] – a 24-item scale which measures the construct of maternal-foetal attachment during pregnancy. It identifies several aspects of the relationship between a mother and her unborn child: differentiation of self from the foetus, interaction with the foetus, attributing characteristics and intentions to the foetus, giving of self, role-taking and nesting. The cut-off point was not identified by the authors of the questionnaire. In the current study, a Polish adaption by Bielewska-Batorowicz was used [49].

Patients also had a blood sample taken to measure serum vitamin D, TSH and prolactin levels. The tests were conducted in a private laboratory in Wrocław. Samples were frozen, and subsequently tested for oxytocin level and glucose levels in the laboratory at Wrocław Medical University.

Following birth, patients were e-mailed a link to the MORS-SF questionnaire and asked to complete it online. Mothers’ Object Relations Scales Short-form (MORS-SF) is a 14-item questionnaire used to assess mothers’ perception of

their infants: emotional warmth-coldness (subscale MORS-warmth) and the invasion-withdrawal of the infant (subscale MORS-invasion). Higher scores of MORS-warmth indicate warm affection towards the child, and higher levels of MORS-invasion – a perception of the infant's invasion in the mother's life. In MORS-warmth a score lower than 20 may indicate grounds for possible concern, and 11 or less should indicate concern. As per MORS-invasion, a score higher than 12 may indicate grounds for possible concern, and results higher than 16 should indicate concern. The authors found that this instrument has good validity and reliability [50]. The Polish version is available on the questionnaire's website.

Analysis. To answer the research questions, statistical analyzes were carried out using the IBM SPSS Statistics 27 package. Pearson correlation analysis was performed. The level of significance was considered to be $p = 0.05$. The Pearson correlation was calculated to check associations between the level of vitamin D, oxytocin, prolactin and thyroid hormones and the occurrence of PrA, measured as the result of PRAQ-R2 and its subscales.

To verify the second hypothesis, which states that a higher level of anxiety during pregnancy, determined using the PRAQ-R2 questionnaire, negatively affects the mother-child relationship, both during pregnancy and after birth, using the Pearson correlation it was checked whether the results for the PRAQ-R2 questionnaire (and its subscales) correlated with the results of the Maternal-Fetal Attachment Scale questionnaire (and its subscales).

Finally, it was checked whether there was an independent effect of vitamin D, oxytocin, prolactin, and TSH levels on the mother's attachment to the fetus/child. For this purpose, an analysis using the Spearman correlation was performed.

In the last step, it was checked which variables were correlated with the age and week of pregnancy.

RESULTS

Sample. Seventy women completed the first survey, of whom 59 attended blood tests. Of these, 55 samples were tested for oxytocin and glucose level (4 samples were not suitable for testing due to the small amount of the material). All participants completed the MORS-SF questionnaire after the delivery.

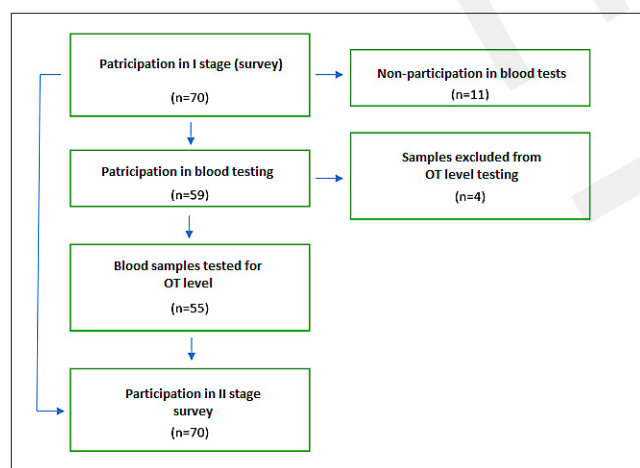


Diagram 1. Flow diagram.

The mean age of the participants was 32 years old (SD=4.53; range 20–41), with 26 living in a rural area, 16 in a town < 80,000 inhabitants, 3 in a town with 80,000–300,000 inhabitants, and 25 participants in a large city. Two participants were single, 49 were married, and 19 identified themselves as cohabiting. One participant had a primary level of education, 3 had secondary level education, 20 had high school level education, and 46 had graduated from a university.

Table 1. Demographic characteristics of the sample

Variable		
No. of participants	70	
Age	20–41 years old. (Mean = 32. SD = 4.53)	
Place of residence	Rural area	26 (37%)
	Town < 80.000	16 (23%)
	Town 80.000–300.000	3 (4%)
	City > 300.000	25 (36%)
Civil state	Cohabiting	88 (28%)
	Married	223 (71%)
	Not in a relationship	5 (2%)
Education	Primary level	1 (1%)
	Secondary level	3 (4%)
	High school level	20 (29%)
	University	46 (66%)

The mean PRAQ-R2 result was 25.56 (SD=7.26); mean MFAS result – 94.67 (SD=9.36); mean MORS-invasion result – 9.43 (SD=3.82), and MORS-warmth – 26.84 (SD=3.53); mean oxytocin level – 804 pg/ml (SD=547 pg/ml, range – 182–3812 pg/ml).

For MORS-warmth, 3 participants obtained results below 20 points (indicating grounds for possible concern) and none scored below 11. In MORS-invasion, 4 participants scored over 12 (indicating grounds for possible concern), and 2 participants scored over 17 points (indicating concern).

Correlations between levels of oxytocin, vitamin D, prolactin and TSH and PrA. Analysis showed that there was no association between the level of vitamins D, prolactin, oxytocin or TSH, and the overall PRAQ-R2 score or its subscales (fear of giving birth, worries about bearing a handicapped child, concern about own appearance) (Tab. 2).

Table 2. Correlation between level of vitamin D, prolactin, oxytocin and TSH, and PRAQ-R2 and its subscales

Variable		Vitamin D [ng/ml]	Oxytocin [ng/ml]	Prolactin [ng/ml]	TSH [ng/ml]
PRAQ-R2	Pearson's correlation	0.01	-0.14	0.15	-0.09
	p	0.952	0.320	0.253	0.520
	N	59	55	59	59
fear of giving birth	Pearson's correlation	-0.12	-0.03	0.18	-0.05
	p	0.350	0.858	0.178	0.703
	N	59	55	59	59
worries about bearing a handicapped child	Pearson's correlation	-0.02	-0.14	0.09	-0.01
	p	0.885	0.300	0.497	0.970
	N	59	55	59	59
concern about own appearance	Pearson's correlation	0.17	-0.12	0.07	-0.16
	p	0.195	0.403	0.592	0.232
	N	59	55	59	59

Table 3. Correlation between level of anxiety and results of MFAS and its' podscales

Variable		MFAS	role-taking and nesting	differentiation of self from foetus	interaction with the foetus	attributing characteristics and intentions to the foetus	giving of self
PRAQ-R2	Pearson's correlation	-0.03	-0.02	-0.05	-0.02	-0.02	0.01
	p	0.807	0.898	0.661	0.851	0.838	0.938
fear of giving birth	Pearson's correlation	0.09	0.06	0.06	-0.04	0.08	0.13
	p	0.459	0.614	0.648	0.76	0.493	0.28
worries about bearing a handicapped child	Pearson's correlation	-0.07	-0.01	-0.13	-0.05	-0.11	0.07
	p	0.557	0.91	0.279	0.668	0.372	0.569
concern about own appearance	Pearson's correlation	-0.06	-0.09	0.01	0.06	0.02	-0.23
	p	0.614	0.482	0.951	0.612	0.888	0.06

Correlations between PrA and maternal-foetal attachment.

Analysis showed that at the level of statistical tendency, a negative, weak relationship can be observed between the variable: concern about own appearance in PRAQ-R2 and giving of self in MFAS. For the remaining variables, no association between the level of anxiety and the MFAS questionnaire and its subscales could be demonstrated (Tab. 3).

The analysis showed that at the level of statistical tendency, a negative, weak relationship can be observed between MORS-invasion and the result for the PRAQ-R2 questionnaire and its subscale: concern about own appearance. For the remaining variables, the analysis showed that there was no association between the level of anxiety measured with the PRAQ-R2 and the results for the MORS-warmth and MORS-invasion questionnaires (Tab. 4).

Table 4. Correlation between anxiety level and results of MORS-warmth and MORS-invasion

Variable		MORS-warm	thMORS-invasion
PRAQ-R2	Pearson's correlation	0.05	-0.23
	p	0.693	0.06
fear of giving birth	Pearson's correlation	0.06	-0.10
	p	0.644	0.404
worries about bearing a handicapped child	Pearson's correlation	0.01	-0.18
	p	0.936	0.133
concern about own appearance	Pearson's correlation	0.05	-0.20
	p	0.668	0.092

Correlation between level of vitamin D, oxytocin, prolactin and TSH and maternal-foetal attachment. Analysis showed that the relationship between the level of the mother's attachment to the child and the measured physiological variables could not be demonstrated.

The analysis showed that at the statistical trend level, a positive, weak, correlation between the glucose level and the result for MORS-warmth could be observed (Tab. 5).

Correlation between socio-demographic factors and anxiety level, and maternal-foetal attachment. Analysis showed that a significant, weak and negative correlation can be observed between the result for the scale of taking a parental role and the age of the patient, and a positive, moderate and positive correlation between the result for the scale of treating the child as a separate being and the week of pregnancy (Tab. 6)

Table 5. Correlation between TSH, prolactin, oxytocin, vitamin D and maternal-foetal attachment score

		TSH [uIU/ml]	Prolactin [ng/ml]	Vitamin D [ng/ml]	Oxytocin [ng/ml]
MFAS	Pearson's correlation	-0.04	-0.14	0.09	0.17
	p	0.771	0.295	0.48	0.228
	N	59	59	59	55
MORS warmth	Pearson's correlation	0.21	0.02	-0.12	-0.16
	p	0.113	0.863	0.371	0.248
	N	59	59	59	55
MORS invasion	Pearson's correlation	0.23	0.03	0.09	-0.08
	p	0.076	0.823	0.481	0.574
	N	59	59	59	55

Table 6. Correlation between age and age of pregnancy and PRAQ-R2, MFAS and MORS results

Variable		Age	Age of pregnancy
PRAQ	Pearson's correlation	0.1	0.01
	p	0.436	0.433
fear of giving birth	Pearson's correlation	0.02	0.20
	p	0.843	0.101
worries about bearing a handicapped child	Pearson's correlation	0.18	0.01
	p	0.126	0.905
concern about own appearance	Pearson's correlation	-0.07	0.02
	p	0.578	0.877
MFAS	Pearson's correlation	-0.17	0.15
	p	0.161	0.227
Role-taking	Pearson's correlation	-.237*	0.056
	p	0.048	0.65
Differentiation of self from the foetus	Pearson's correlation	-0.16	.336**
	p	0.175	0.005
Interaction with the foetus	Pearson's correlation	-0.03	0.05
	p	0.797	0.68
Attributing characteristics and intentions to the foetus	Pearson's correlation	-0.19	0.09
	p	0.109	0.463
Giving of self	Pearson's correlation	0.06	0.03
	p	0.612	0.8
MORS warm	Pearson's correlation	0.05	0.16
	p	0.711	0.18
MORS inv	Pearson's correlation	0.02	0.06
	p	0.86	0.632

DISCUSSION

The first hypothesis in the current study was that vitamin D, oxytocin, prolactin and thyroid function are correlated with the level of Pregnancy-Related Anxiety, measured by PRAQ-R2. The results obtained show that there is no link between these factors and the presence of PrA. Similarly, Ma et al. [29] did not find any link between the level of oxytocin and prenatal anxiety, and pointed out that this may be due to the rapid changes in oxytocin levels in pregnancy. The results in the current study show a large inter-individual difference in oxytocin levels, with values ranging from 182–3812 pg/ml. One paper describes similar differences in their sample [51], while another study shows that the method of measurement may affect the results, as oxytocin levels measured without the extraction were much higher (more than 100x higher) than oxytocin levels measured following extraction [52]. This is a subject that should be researched further by serial tests of oxytocin levels, possibly in a more homogenous group.

The obtained results in the current study indicate that there is no link between Pregnancy-Related Anxiety and serum levels of vitamin D. Nonetheless, a large systematic review identified only one paper researching anxiety levels in pregnancy and vitamin D level [45]. Vitamin D is an important regulator of gene expression in a broad range of cerebral functions, and its receptor is abundant in brain tissue. As vitamin D is postulated to contribute to mental health issues along with the HPA axis [37], the link between vitamin D deficiency and PrA needs to be examined further.

The second hypothesis was that Pregnancy-Related Anxiety is related to the attachment of a mother to her child. It was found that there might be some correlation between the mother's concern about own appearance and her perception of giving self. Moreover, a weak correlation was found between the mother's concern about own appearance and the MORS-invasion subscale. This may indicate that women who worry about their appearance during pregnancy, especially have a higher perception of subordination to the needs of the foetus during pregnancy, and further feeling of the child's invasion into the mother's life. Previous research indicated that higher anxiety was correlated with worse quality of maternal-foetal attachment [15].

The authors believe that it is worth noting that only one paper [52] used the pregnancy-specific questionnaires to measure anxiety levels' relationship with prolactin, oxytocin, TSH or vitamin D. Even though there are several papers suggesting that there is a link between anxiety disorders in pregnant women and these biological factors, the results of the current study might indicate that these factors are related to anxiety levels in pregnancy, but not to Pregnancy-Related Anxiety, which is a distinctive disorder. The authors wish to point out the necessity to conduct further studies to research the causality between the above-mentioned biological factors and Pregnancy-Related Anxiety (but measured by tools designed specifically for the purpose).

As Pregnancy-Related Anxiety is a frequent disorder with multiple and complex consequences, it is important to identify its pathogenesis. PrA is a relatively new concept, lacking much necessary research. Many papers assume that it might have a similar pathogenesis to other anxiety disorders, which may be comorbid with pregnancy. Nonetheless, researchers highlight the differences between PrA and other anxiety disorders [46]. Therefore, the authors of the current study

highlight the need to treat it distinctively in further research.

Furthermore, the authors highlight the importance of addressing concern about own appearance as a factor that might impact maternal-foetal attachment. We believe that psycho-education and social support (including engagement in community groups and social programmes) might improve further mothers' perception of their own appearance, thereby helping with their bonding with a child.

CONCLUSION

Pregnancy-Related Anxiety is a common disorder which has several consequences for the mother and her child. It is an disorder distinct from other anxiety disorders that may present in pregnancy. No correlation was found between vitamin D, prolactin, oxytocin and thyroid function, and PrA. These factors may be related to other anxiety disorders in pregnancy, but not to PrA. The maternal-foetal attachment might be impacted by the mother's perception of own appearance, hence this needs to be addressed at the early stages of pregnancy.

Limitations of the study. The study group was relatively small and heterogeneous. The participants who took part might differ from the population of pregnant women who did not participate in the study. It is believed that the participants would have more interest in mental health issues overall than the non-participants, since they contributed their time to take part in the study. Furthermore, the study included only pregnant women from Poland. Hence the results might not be generalisable to pregnant women in different countries. Moreover, it was noted that the cross-sectional design was a limitation of the study. The number of participants in the second stage of the study was relatively small for the cohort design.

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