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Associations between nausea and vomiting in pregnancy, disgust sensitivity, and first-trimester maternal serum free β-hCG and PAPP-A

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Abstract

Elevated levels nausea and vomiting in pregnancy (NVP) and disgust sensitivity have been observed in the first trimester and both are thought to have a protective function for the mother and her fetus. Their aetiology is not clear, however, with previous studies attributing elevated NVP and disgust to various factors including endocrine changes, immunological changes, and psychological variables. To date, no study has directly assessed the relationship between disgust and NVP. Here, we prospectively collected two independent samples (S1 and S2; $n_1 = 201$, $n_2 = 391$) of women in the first trimester of pregnancy, who completed the Index of Nausea, Vomiting, and Retching and Disgust Scale-Revised. We also measured free β-human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A) in maternal serum. Our results did not confirm any association between NVP and overall disgust; in addition, they indicate that NVP and disgust may have different proximal causes. Disgust sensitivity was significantly negatively correlated with free β-hCG and (only in S1) with PAPP-A. In contrast, NVP was significantly positively associated with free β-hCG levels and (only in S1) with PAPP-A. While low hCG levels seem to be an important indicator for activation of the behavioral immune system in the first trimester, increased hCG levels play a role in stronger symptoms of NVP, a result consistent with previous studies. Levels of PAPP-A are likely part of a larger network of immunological and endocrine responses and do not appear to provide sufficient information for predicting women's NVP and disgust sensitivity.

Keywords: disgust; NVP; Rhodes index; Compensatory prophylaxis hypothesis; free β-hCG; PAPP-A; parity; anxiety

1. Introduction

The first trimester of pregnancy is accompanied by significant hormonal changes and immunomodulation which reflect developmental and physiological changes occurring in both the mother and embryo. A key hormonal change involves human chorionic gonadotropin (hCG), which is secreted by syncytiotrophoblastic cells of the placenta to stimulate progesterone production by the corpus luteum, essential for pregnancy maintenance. From the moment of embryo implantation, hCG concentration rises exponentially during the first seven weeks, peaks around the 10^{th} gestational week, then gradually declines until delivery (Cole, 2012). Its function seems to be in immunomodulation at the maternal-fetal interface by contributing to maternal immune tolerance against the semiallogeneic embryo (Bansal et al., 2012).

While hCG consists of alpha and beta subunits (Lapthorn et al., 1994), only the latter determines its biological specificity and is used as one of the biochemical markers in first-trimester diagnostic screening of maternal blood. Low hCG levels thus provide information about pregnancy-related disorders and are associated with risk of miscarriage (Goetzl et al., 2004) and reduced fetal growth and birth weight (Barjaktarovic et al., 2017).

A second screening marker is pregnancy-associated plasma protein-A (PAPP-A), a zinc-binding metalloproteinase produced in placental syncytiotrophoblasts. It facilitates activity of the insulin-like growth factor (IGF) family to regulate placental growth and function. Similar to hCG, low levels are associated with negative gestational outcomes, including intrauterine growth restriction (Carbone et al., 2012), abnormal placental size (Fallah Arzpeyma et al., 2021), preeclampsia (Luewan et al., 2018), preterm labor (Pummara et al., 2016) and respiratory distress syndrome (Yakiştiran et al., 2021).

Levels of maternal serum PAPP-A and free β-hCG have also been studied in relation to nausea and vomiting during pregnancy (NVP). NVP occurs most frequently in the first trimester, peaking in the ninth

week of pregnancy (Lacroix et al., 2000). Depending on geographical differences, NVP affects 70-94% of all pregnant women (Gadsby et al., 2021) and has a notably multifactorial aetiology. That hCG may be implicated is suggested by its peak levels coinciding with those of NVP, in the 9^{th} – 12^{th} gestational weeks (Lee and Saha, 2011; Niebyl, 2010), and because elevated levels of free β-hCG (and PAPP-A) are associated with NVP's severest form, hyperemesis gravidarum (HG) (Derbent et al., 2011), which can be fatal for mother and embryo. NVP may also be associated with elevated levels of progesterone and estrogen (Lagiou et al., 2003), maternal androgens (Carlsen et al., 2003), and thyroxin (FT4) (Tan et al., 2002), but with lower thyroid-stimulating hormone (TSH) levels. NVP has also been linked with maternal depression, anxiety and fatigue (Dekkers et al., 2020; Fiurašková et al., 2021).

A possible adaptive function for NVP has been proposed, such that it protects the fetus and mother against potentially harmful substances (Flaxman and Sherman, 2000; Profet, 1992, 1995). Indeed, NVP is frequently associated with avoidance of foods containing potentially toxic abortifacients and teratogens (e.g. alcohol, caffeine, and tobacco), perishable foods such as meat, fish, eggs, and milk (Fiurašková et al., 2021; Flaxman and Sherman, 2000; Pepper and Roberts, 2006), or pungent or bitter vegetables and herbs rich in toxic phytochemicals (Profet, 1992). The proposed adaptive function is supported by the concurrent timing of NVP symptoms with fetal organogenesis, a critical developmental phase.

Similar to NVP, although not restricted to pregnancy, disgust is thought to have a protective function. Disgust is an affective component of the behavioral immune system, involved in changing cognition, affect and behavior in ways that reduces infection risk. According to the Compensatory Prophylaxis Hypothesis (CPH) (Fessler et al., 2005), disgust sensitivity should optimally correspond to the individual's risk of infection, whether mediated by immune status or pathogenic threat. In support of this idea, Fessler et al. (2005) reported that women in the first trimester had higher disgust sensitivity than those in later pregnancy (see also a similar finding by Żelaźniewicz and Pawłovski (2015) in their longitudinal study).

As with NVP, the physiological mechanisms related to disgust are not yet fully understood. Some authors have reported a positive correlation between disgust sensitivity and progesterone levels (Fleischman and Fessler, 2011; Żelaźniewicz et al., 2016) which are, in turn, associated with suppression of immune functions. However, Jones et al. (2018) did not find this correlation and neither did two more recent studies, one with a longitudinal design (Stern and Shiramizu, 2022) and the other with a cross-sectional one (Rafiee et al., 2022). In response to the study by Jones et al. (2018), Fleischman and Fessler (2018) argue that disgust responses may still be upregulated to partially compensate for reproductive immunomodulation, but that progesterone either does not drive such changes or interacts with other responsible physiological components. Indeed, the latter suggestion (and thus the CPH) was supported by a recent study (Kaňková et al., 2022) which examined associations between disgust sensitivity and immune indices in early pregnancy. Elevated disgust sensitivity was significantly associated with decreased levels of a wide range of cytokines (e.g. IFN-γ, IL-1β, IL-2 IL-4, TNF-α). These cytokines were also negatively correlated with NVP levels in this study, but the association between cytokines and disgust sensitivity was more robust than their association with NVP.

There are thus clear similarities between NVP and disgust sensitivity: they both tend to peak in the first trimester, may have similar adaptive functions involving fetal protection, and appear to share some potential underlying mechanisms. Moreover, both are positively associated with anxiety in pregnant women (Fiurašková et al., 2021; Olatunji et al., 2007a). Nevertheless, to date, there is a lack of studies that examine both NVP and disgust sensitivity, while at the same time analysing their underlying physiological mechanisms. Here, we aimed to assess the associations between disgust sensitivity and NVP during the first trimester across two independent samples of pregnant women. Based on previous studies, we hypothesised that disgust sensitivity would be positively correlated with NVP. Furthermore, we sought to examine the predictive roles of the two biochemical markers typically measured during first-trimester screening (hCG, PAPP-A) on both disgust sensitivity and NVP symptom severity. We focus on

these two specific markers because elevated levels of free β-hCG were suggested as the main proximate cause of NVP (Forbes, 2002; Lee and Saha, 2011), and both hCG and PAPP-A are associated with HG (Derbent et al., 2011). Moreover, hCG stimulates progesterone production which is often discussed in association with disgust sensitivity. Assuming a positive relationship between NVP and disgust sensitivity, we could expect similar relationships between these biomarkers and both NVP and disgust sensitivity.

2. Methods

In a cross-sectional study, two independent samples were collected in collaboration with the Department of Obstetrics and Gynecology of the General University Hospital in Prague, at the Center of Fetal Medicine and Ultrasound Gynecological Diagnostics. The data collection for this study was planned within a broader project focusing on the effect of oral contraceptive use, within-couple similarity at the major histocompatibility complex, and other factors on human fertility (Fiurašková et al., 2022; Kaňková et al., submitted). The study was approved by the Institutional Review Board of the Faculty of Science, Charles University (Approval No. 2020/07) and by the Ethics Committee of General University Hospital in Prague (No. 384/16; 92/17; 2195/18).

2.1. Participants

We recruited two samples of women in the first trimester of pregnancy. In both samples, we recruited only women with a singleton pregnancy who conceived naturally (no assisted reproduction or hormonal treatment) after. From the final samples, we excluded women with serious chronic or autoimmune diseases (one woman with Crohn's disease in Sample 1 and two women with Crohn's disease, two women with ulcerative colitis and two women with multiple sclerosis in Sample 2). Sample 1 (S1) consisted of 201 women aged 19 to 44 years (mean age = 30.7, SD = 4.3) recruited between November 2017 and November 2019, before the COVID-19 pandemic. Sample 2 (S2) consisted of 391 women aged 20 to 44 years (mean age = 31.7, SD = 4.3) recruited between March 2020 and January 2021, during the COVID-19 pandemic. For more details regarding the samples' characteristics, see Table 1.

Table 1. Characteristics of the samples S1 and S2.

		S1	S2
n		201	391
Age**	Mean (SD)	30.7 (4.3)	31.7 (4.3)
	range	19-44	20-44
Parity*	Primipara, n (%)	126 (62.7%)	208 (53.2%)
	Multipara, n (%)	75 (37.3 %)	183 (46.8%)
	1 child (n)	65	150
	2 children (n)	6	28
	>3 children (n)	4	5
Education level	Elementary school, n (%)	16 (8.0%)	17 (4.4%)
	Secondary school, n (%)	62 (31.2 %)	105 (27.3%)
	University, n (%)	121 (60.8%)	262 (68.2%)
	Missing data, n	2	7
Monthly household income (in thousands CZK)	<30, n (%)	24 (12.6 %)	50 (13.0%)
	31– 45, n (%)	53 (27.7 %)	85 (22.1%)
	46 – 60, n (%)	57 (29.8 %)	116 (30.2%)
	61 – 75, n (%)	28 (14.7 %)	50 (13.0%)
	>76, n (%)	29 (15.2 %)	83 (21.6%)
	Missing data, n	10	7
Residence size (citizens in thousands)	<1, n (%)	21 (10.7 %)	32 (8.3%)
	1-5, n (%)	21 (10.7 %)	34 (8.9%)
	5 – 50, n (%)	33 (16.8 %)	55 (14.3%)
	50 – 500, n (%)	8 (4.1 %)	23 (6.0%)
	>500, n (%)	114 (57.9 %)	240 (62.5%)
	Missing data, n	4	7

The statistical differences between S1 and S2 are marked with an asterisk; *p<0.05, **p<0.01, ***p<0.001.

2.2. Procedure – data collection

Women in both samples were recruited during the first-trimester ultrasound screening in the 11^{th}-14^{th} gestational week. This takes place approximately two weeks after blood collection (in the 9^{th}-13^{th} gestational week), based on which the levels of first trimester screening biochemical markers (free β-hCG and PAPP-A levels) were determined (see *2.4. Laboratory measurement of free β-hCG and PAPP-A levels*). S1 includes pregnant women who participated in the study with their partners. The inclusion criteria were the willingness of both partners to provide the second blood sample (5 ml; this sample was used for other projects) and to complete a pen-and-paper questionnaire (see *2.3. Questionnaires*). Unlike S1, S2 consists of pregnant women who participated in the study without their partners and only completed the pen-and-paper questionnaire (see *2.3. Questionnaires*), i.e., they did not have to provide the second blood sample for other projects (due to COVID restrictions that were then in place).

All women provided informed consent and had to be over eighteen years of age. They were acquainted with the option of withdrawing from the study at any time without consequence. Their participation was not reimbursed. To ensure anonymity, the questionnaires and levels of free β-hCG and PAPP-A, both obtained by hospital staff, were passed to us marked with alphanumeric codes.

2.3. Questionnaires

All women completed the questionnaires during the first-trimester ultrasound screening in the 11^{th}-14^{th} gestational week (approximately two weeks after blood collection). They completed a background questionnaire, including information about age, history of previous pregnancies, education level, size of residence area, household income, and health data. We also asked women a question about their current health status: Do you have any health problems today (including colds, allergies)? If yes, what are they? Only current health problems related to infection were considered as "yes = 1" (such as different symptoms of common cold, cough, nasopharynx infection), whereas no problems and problems associated with pregnancy itself (e.g. back pain) or chronic problems (e.g. allergies, food intolerances) were coded as a "no = 0". Since the place of recruitment was a maternity hospital, women underwent the

first-trimester ultrasound screening only without serious acute illnesses. The current health problems thus included only mild or fading symptoms of a possible infection.

2.3.1. Nausea and vomiting in pregnancy

The levels of NVP were assessed by the self-report Index of Nausea, Vomiting, and Retching (INVR) (Rhodes and McDaniel, 1999), a widely used instrument for assessing both intra-individual dynamics and inter-individual variation in NVP (Fiurašková et al., 2021). Women rated their individual symptoms, in terms of the strongest form in which they manifested and how often they manifested during the preceding twelve-hour period. It consists of 8 items focusing on the symptoms of nausea and vomiting during an ongoing pregnancy. The items are rated on a 5-point scale ranging from 0 to 4. The overall score (i.e., Rhodes Index) may thus range from 0 to 32, with higher scores indicating stronger symptoms. Participants with incomplete INVR questionnaires (with more than one-fifth of items unanswered) were excluded from the analyses (we excluded four and nine women in S1 and S2, respectively). If one-fifth or fewer responses were missing, we used the average score for the questionnaire to supplement the missing values (we supplemented eight and 13 responses in S1 and S2, respectively). The means of Rhodes index scores and the questionnaire's internal consistencies are shown in Table 2. (Note: The results of analyses did not change statistical significance when all participants with missing data (including those with one-fifth or fewer missing responses) were excluded).

2.3.2. Disgust

Disgust sensitivity was assessed by the Disgust Scale-Revised (DS-R) (Olatunji et al., 2007b) in both samples, and additionally (in S2 only) by the Pathogen domain of the Three Domains of Disgust Scale (TDDS) (Tybur et al., 2009). The mean DS-R/TDDS scores and internal consistencies are shown in Table 2. Because of the very low internal consistency for the Contamination disgust subscale (S1: Cronbach's $\alpha = 0.42$; S2: Cronbach's $\alpha = 0.55$), we reported the results of analyses for this subscale only for the

possibility of comparison with other studies. The results for this subscale will not be discussed or included in the conclusions of the study.

The DS-R (Olatunji et al., 2007b) is a 25-item self-report inventory consisting of three subscales: Core disgust subscale (12 items; disgust elicited by food and animal or bodily products), Animal-reminder disgust subscale (8 items; disgust related to mortality, possible injuries, or body envelope violations), and Contamination disgust subscale (5 items; disgust related to the interpersonal transmission of essences). There are five possible responses to each item ranging from 0 to 4. In the first part of the DS-R (13 items), respondents rate how much they agree with given statements, or how true the statements are about them: "0 = Strongly disagree (very untrue about me), 1 = Mildly disagree (somewhat untrue about me), 2 = Neither agree nor disagree, 3 = Mildly agree (somewhat true about me), 4 = Strongly agree (very true about me)". In the second part of the questionnaire (12 items), the respondents rate how disgusting they would find described experiences: "0 = Not disgusting at all, 1 = Slightly disgusting, 2 = Moderately disgusting, 3 = Very disgusting, 4 = Extremely disgusting". The overall score may range from 0 to 100 (Core subscale from 0 to 48, Animal-reminder subscale 0 to 32, and Contamination subscale 0 to 20). A higher score indicates greater disgust sensitivity. If one-fifth or fewer responses were missing for each subscale, we used the average score of the corresponding subscale to supplement the missing values (we supplemented nine and eight responses in S1 and S2, respectively). Participants with more than one-fifth of items unanswered were excluded from the analyses (n = 2 and n = 3 in S1 and S2, respectively).

The TDDS (Tybur et al., 2009) is a 21-item self-reported inventory with three domains (Pathogen, Moral, and Sexual). For our study (included additionally only for S2), we used just the 7-item Pathogen domain which is the most relevant for the current investigation and to avoid overload of the participants. Respondents rate the statements from 0 to 6, where 0 = not disgusting at all and 6 = extremely disgusting. The score of the Pathogen domain may thus range from 0 to 42. Because more than one-fifth of items were unanswered, we excluded one woman from the analysis.

(Note: The results of analyses did not change statistical significance when all participants with missing data (including those with one-fifth or fewer missing responses) were excluded).

2.3.3. Anxiety state

The current state of anxiety was measured only in S2. Anxiety symptoms were measured using the 6-item short-form of the state scale of the State-Trait Anxiety Inventory (STAI) (Marteau and Bekker, 1992). For each statement, participants were asked to indicate how they were feeling right now. Each item is rated on a scale of 1 to 4. Total scores can range from 6 to 24, with higher scores indicating higher levels of anxiety. If one-fifth or fewer responses were missing, we used the average score of the corresponding subscale to supplement the missing values (we supplemented one response). Participants with more than one-fifth of unanswered items were excluded from the analyses (n = 7). The mean STAI scores (SD) was 11.7 (3.77) and Cronbach's α for anxiety symptoms was 0.863.

Table 2. Mean scores and internal consistency of DS-R, TDDS and NVPR

		S1	**S2**
Questionnaire completion	n	201	391
(gestational age in days)	Mean (SD)	89.8 (4.0)	89.1 (3.4)
	Range	77-101	76-101
Rhodes index	n	197	382
	Mean (SD)	9.3 (6.6)	8.86 (6.5)
	Median	8.5	8.0
	Range	0-26	0-27
	Cronbach's alpha	0.83	0.83
Overall DS-R score*	n	199	388
	Mean (SD)	50.5 (13.1)	53.0 (15.0)
	Range	12-81	17-95
	Cronbach's alpha	0.79	0.85
Core disgust score	Mean (SD)	26.3 (7.1)	27.4 (7.7)

	Range	7-42	10-48
	Cronbach's alpha	0.66	0.72
Animal-reminder disgust score	Mean (SD)	17.0 (5.8)	17.6 (6.7)
	Range	1-32	0-32
	Cronbach's alpha	0.65	0.76
Contamination disgust score*	Mean (SD)	7.2 (3.2)	8.0 (3.5)
	Range	0-16	0-17
	Cronbach's alpha	0.42	0.55
Pathogen disgust score (domain of TDDS)	n	-	390
	Mean (SD)	-	22.4 (8.0)
	Range	-	4-42
	Cronbach's alpha	-	0.78

The statistical differences between S1 and S2 are marked with an asterisk; *p<0.05, **p<0.01. For more detail, please see a study that addressed this issue (Kaňková et al., submitted).

2.4. Laboratory measurement of free β-hCG and PAPP-A levels

Free β-hCG and PAPP-A levels were extracted from medical records. Both analytes (PAPP-A and free β-hCG) were processed in the central laboratory of the General University Hospital in Prague. The serum was separated within 4 hours of venous blood collection to prevent the breakdown of the total hCG molecule and thus increase the concentration of free β-hCG. The material was then stored at 4-8 °C, and within two days, PAPP-A and free β-hCG were determined by fluorescence immunoassay on Brahms KRYPTOR analyzer (Thermo Fisher Scientific). Absolute values in U/L were converted to MoMs (median multiples) by ASTRAIA software. The central laboratory successfully participates in the External Quality Control programe (EQC UK NEQAS) scheme for these parameters. The mean levels of PAPP-A and free β-hCG for both samples are shown in Table 3.

Table 3. Free β-hCG and PAPP-A levels

		S1	S2
Blood collection* **	n	199	389
(gestational age in days)	Mean (SD)	70.1 (5.2)	72.5 (5.2)
	Range	59-89	63-99
Free β-hCG level*	Mean (SD)	1.32 (0.7)	1.18 (0.7)
(MoM)	Median	1.13	1.02
	Range	0.29-4.52	0.17-4.43
PAPP-A level	Mean (SD)	1.20 (0.7)	1.08 (0.5)
(MoM)	Median	1.05	1.02
	Range	0.28-4.46	0.12-3.12

The statistical differences between S1 and S2 are marked with an asterisk; *p<0.05, **p<0.01, ***p<0.001.

2.5. Statistical analysis

Statistical analyses were performed using Jamovi 1.6.16 (Jamovi, 2021). For all tests, we determined the statistical level of significance as $\alpha = 0.05$. Because of the non-normal distribution of the Rhodes index and both free β-hCG and PAPP-A levels, we used non-parametric tests. The association between disgust sensitivity and NVP was assessed using partial Kendall´s correlation, controlling for maternal age, parity, current health problems and week of pregnancy at the time of completing the questionnaires. We also used partial Kendall´s correlation (again, controlling for maternal age, parity, current health problems, week of pregnancy when completing questionnaire, plus week of pregnancy on the day of blood sampling) to assess the associations between disgust sensitivity or NVP and free β-hCG/PAPP-A levels. We merged the data of both samples and included a binary variable (termed Sample) to investigate potential between-sample effects. Because of many statistically significant differences between S1 and S2 (see Tables 1-3) we also performed the analyses separately for each sample. The raw data are available at https://doi.org/10.6084/m9.figshare.20509353.v1.

3. Results

3.1. Association between NVP and disgust sensitivity

Contrary to expectation, we found no significant correlation between NVP symptom severity and disgust sensitivity, neither in S1 or S2 (partial Kendall´s correlations, controlling for maternal age, parity, current health problems, and length of pregnancy when completing the questionnaires). The analysis of the merged data showed a significant positive correlation between NVP symptom severity and Contamination disgust score (Tau B = 0.059, p= 0.034, Cohen's d=0.19). For more details of analyses, see Table 4.

Table 4. Association between disgust sensitivity and NVP (Rhodes index)

Rhodes index		**S1+S2**	**S1**	**S2**
Overall DS-R score	n	576	195	381
	Tau B	0.029	0.053	0.017
	p	0.299	0.279	0.626
	d	0.09	0.17	0.05
Core disgust score	Tau B	0.053	0.075	0.041
	p	0.060	0.121	0.237
	d	0.17	0.23	0.13
Animal-reminder disgust score	Tau B	-0.035	-0.014	-0.047
	p	0.27	0.773	0.177
	d	0.11	0.04	0.15
Contamination disgust score	Tau B	0.059	0.075	0.047
	p	0.034	0.125	0.174
	d	0.19	0.23	0.15
Pathogen disgust score (TDDS)	n	-	-	382
	Tau B	-	-	0.013
	p	-	-	0.710
	d	-	-	0.04

Partial Kendall's correlation (Tau B) controlling for maternal age, parity, current health problems and length of pregnancy when completing the questionnaires (and also for the variable "sample", in case of merged data), n notifies the sample size, p notifies the level of formal statistical significance, and d notifies Cohen's d effect size

3.2. Association between NVP, disgust sensitivity, free β-hCG, and PAPP-A levels

In the merged dataset, levels of free β-hCG were significantly positively correlated with NVP (Tau B = 0.066, p = 0.019, d = 0.21) and significantly negatively correlated with overall DS-R score (Tau B = -0.078, p = 0.005, d = 0.25) and all of the DS-R subscales (Core: Tau B = -0.072, p = 0.010, d = 0.23; Animal-reminder: Tau B = -0.056, p = 0.043, d = 0.18; Contamination: Tau B = 0.079, p = 0.005, d = 0.25). The analyses showed no statistically significant association between PAPP-A levels and either NVP severity or disgust sensitivity. For more details of analyses, see Table 5.

In S1, the analysis showed no association between free β-hCG levels and NVP. On the other hand, higher levels of PAPP-A were statistically significantly associated with higher NVP (Tau B = 0.114, p = 0.019, d = 0.36). The levels of free β-hCG significantly negatively correlated with overall DS-R score (Tau B = -0.128, p = 0.009, d = 0.41) and the Animal-reminder (Tau B = -0.151, p = 0.002, d = 0.48) DS-R subscale. The correlations between free β-hCG levels and the Core and Contamination disgust subscales were in the same direction, but were not formally significant. Also, lower levels of PAPP-A were statistically significantly associated with a higher overall DS-R score (Tau B = -0.107, p = 0.028, d = 0.34). Related to the DS-R subscales, all scores of disgust subscales were negatively correlated with PAPP-A levels, however no correlation was statistically significant. For more details of analyses, see Table 5.

In S2, the levels of free β-hCG statistically significantly negatively correlated only with the Contamination disgust subscale (Tau B = -0.091, p = 0.008, d = 0.29). The correlations between free β-hCG levels and the overall DS-R score, Core and Animal-reminder disgust subscales, pathogen disgust of TDDS, and NVP were not statistically significant. With relatively small effect size, the associations of free β-hCG levels and pathogen disgust of TDDS (Tau B = -0.064, p = 0.062, d = 0.20) was close to the level of significance. The analyses showed no statistically significant association between PAPP-A levels and either NVP severity or disgust sensitivity. For more details of analyses, see Table 5.

Table 5. Association between NVP/disgust sensitivity and free β-hCG and PAPP-A levels

		S1+S2		S1		S2	
		free β-hCG	**PAPP-A**	**free β-hCG**	**PAPP-A**	**free β-hCG**	**PAPP-A**
Rhodes index	n	575	575	195	195	380	380
(NVP)	Tau B	**0.066**	0.038	0.079	**0.114**	0.054	-0.006
	p	**0.019**	0.171	0.106	**0.019**	0.120	0.872
	d	**0.21**	0.12	0.25	**0.36**	0.17	0.02
Overall DS-R	n	583	583	197	197	386	386
score	Tau B	**-0.078**	-0.051	**-0.128**	**-0.107**	-0.057	-0.022
	p	**0.005**	0.069	**0.009**	**0.028**	0.100	0.520
	d	**0.25**	0.16	**0.41**	**0.34**	0.18	0.07
Core disgust	Tau B	**-0.072**	-0.044	-0.090	-0.083	-0.063	-0.021
	p	**0.010**	0.114	0.063	0.087	0.067	0.535
	d	**0.23**	0.14	0.29	0.27	0.20	0.07
Animal-reminder	Tau B	**-0.056**	-0.032	**-0.151**	-0.078	-0.013	-0.010
disgust	p	**0.043**	0.246	**0.002**	0.110	0.700	0.776
	d	**0.18**	0.10	**0.48**	0.25	0.04	0.03
Contamination	Tau B	**-0.079**	-0.049	-0.068	-0.074	**-0.091**	-0.036
disgust score	p	**0.005**	0.077	0.164	0.125	**0.008**	0.203
	d	**0.25**	0.16	0.22	0.24	**0.29**	0.12
Pathogen disgust	n	-	-	-	-	388	388
score	Tau B	-	-	-	-	-0.064	-0.016
(TDDS)	p	-	-	-	-	0.062	0.648
	d	-	-	-	-	0.20	0.05

Partial Kendall's correlation (Tau B) controlling for maternal age, parity, current health problems and both lengths of pregnancy when blood sampling and completing the questionnaires (and also for the variable "sample", in case of merged data), n notifies the sample size, p notifies the level of formal statistical significance, and d notifies Cohen's d effect size

3.3. The effect of parity on the association between NVP, disgust sensitivity, free β-hCG, and PAPP-A levels

The analyses of the merged data controlled for maternal age showed no statistically significant effect of parity on both NVP severity (n = 579, Tau B = 0.022, p = 0.438) and disgust sensitivity (overall DS-R score: $F_{1,584} = 1.21$, p = 0.271; Core: $F_{1,584} = 0.002$, p = 0.961; Animal-reminder: $F_{1,584} = 2.60$, p = 0.107; Contamination: $F_{1,584} = 2.29$, p = 0.130). However, primiparas had significant higher free β-hCG (n = 588, Tau B = -0.089, p = 0.001) and PAPP-A levels (n = 588, Tau B = -0.080, p = 0.004). Based on these results, and because there was a significant difference in the representation of primiparas between S1 and S2 (see Table 1), we performed all analyses of the merged data (S1+S2) separately for primiparous and multiparous women.

We found no statistically significant association between NVP severity and disgust sensitivity (overall DS-R score: Tau B = 0.016, p = 0.664; Core: Tau B = 0.036, p = 0.335; Animal-reminder: Tau B = -0.046, p = 0.223; Contamination: Tau B = 0.057, p = 0.125) in 324 primiparous women. We also found no statistically significant association between NVP severity and disgust sensitivity (overall DS-R score: Tau B = 0.054, p = 0.209; Core: Tau B = 0.078, p = 0.066; Animal-reminder: Tau B = -0.018, p = 0.675; Contamination: Tau B = 0.073, p = 0.087) in 252 multiparous women.

The analyses of the association between NVP/disgust sensitivity and free β-hCG and PAPP-A levels separately for primiparous and multiparous women showed more statistically significant effect in primiparous women. In these women the levels of free β-hCG significantly positively correlated with NVP (Tau B = 0.082, p = 0.028) and significantly negatively correlated with overall DS-R score (Tau B = -0.075, p = 0.044). In primiparous women, the levels of PAPP-A also significantly negatively correlated with the overall DS-R score (Tau B = -0.090, p = 0.016) and the Core disgust subscale (Tau B = -0.083, p = 0.026). In multiparous women, we found a significant correlation only for free β-hCG levels and the Contamination disgust subscale (Tau B = -0.099, p = 0.020). For more details of analyses, see Table 6.

Table 6. Association between NVP/disgust sensitivity and free β-hCG and PAPP-A levels separately for primiparous and multiparous women

		S1+S2 Primiparas		S1+S2 Multiparas	
		free β-hCG	**PAPP-A**	**free β-hCG**	**PAPP-A**
Rhodes index	n	324	324	251	251
(NVP)	Tau B	**0.082**	0.007	0.041	0.074
	p	**0.028**	0.845	0.341	0.083
	d	**0.26**	0.02	0.13	0.24
Overall DS-R	n	329	329	254	254
score	Tau B	**-0.075**	**-0.090**	-0.067	-0.006
	p	**0.044**	**0.016**	0.118	0.882
	d	**0.24**	**0.29**	0.22	0.02
Core disgust	Tau B	-0.069	**-0.083**	-0.054	0.002
	p	0.065	**0.026**	0.204	0.967
	d	0.22	**0.27**	0.17	0.01
Animal-reminder	Tau B	-0.052	-0.066	-0.044	0.006
disgust	p	0.164	0.077	0.296	0.887
	d	0.17	0.21	0.14	0.02
Contamination	Tau B	-0.054	-0.046	**-0.099**	-0.054
disgust score	p	0.144	0.212	**0.020**	0.205
	d	0.17	0.15	**0.32**	0.17
Pathogen disgust	n	206	206	182	182
score	Tau B	-0.026	-0.011	-0.096	-0.026
(TDDS)	p	0.584	0.819	0.058	0.608
(only S1)	d	0.08	0.04	0.31	0.08

Partial Kendall's correlation (Tau B) controlling for maternal age, current health problems, "sample" and both lengths of pregnancy when blood sampling and completing the questionnaires, n notifies the sample size, p notifies the level of formal statistical significance, and d notifies Cohen's d effect size

3.4. The effect of anxiety on the association between NVP, disgust sensitivity, free β-hCG, and PAPP-A levels

Because both NVP and disgust sensitivity are positively associated with anxiety in pregnant women (Fiurašková et al., 2021; Olatunji et al., 2007a), we also assessed the effect of anxiety on the association between NVP, disgust sensitivity, free β-hCG, and PAPP-A levels in sample 2 (when the anxiety questionnaire was administered). The analyses showed no statistically significant correlation between the anxiety state and both NVP severity and disgust sensitivity (for all scores DS-R and TDDS). We also found no statistically significant correlation between anxiety and both free β-hCG, and PAPP-A levels. When we added the variable of state anxiety as a control variable into the main analyses of S2, the results were unchanged. Again, levels of free β-hCG were statistically significantly negatively correlated only with the Contamination disgust subscale (Tau B = -0.089, p = 0.010, d = 0.28).

4. Discussion

In this study based on two independent samples, we assessed the association between nausea and vomiting in pregnancy, disgust sensitivity and two biochemical markers (free β-hCG and PAPP-A) in women in the first trimester of pregnancy. We found no association between disgust sensitivity and NVP (except for the positive correlation of NVP and the Contamination disgust subscale with very low internal consistency). In both samples assessed together, NVP was significantly and positively correlated, and disgust sensitivity was significantly and negatively correlated, with the levels of free β-hCG. In these merged samples, the associations between PAPP-A levels and both NVP and disgust sensitivity were not significant. However, some results differed between samples. In S1, a higher NVP score was significantly associated with higher levels of PAPP-A, but in S2, we did not observe a significant association. The total DS-R score was significantly negatively correlated with free β-hCG and PAPP-A levels only in S1, the sample collected before the COVID-19 pandemic. Most of the observed effects were significant only for primiparous but not for multiparous women. We found no changes in results after adding anxiety state as a controlling variable into the main analyses in S2, in which state anxiety was measured.

Our results did not confirm our hypothesis that NVP is positively associated with disgust sensitivity. This could be due to the time when these variables were measured. Women completed the questionnaires between the 11th and 14th gestational weeks, on average in the 13th week. The strongest symptoms of NVP are typically observed around the 9th gestational week (Niebyl, 2010; Suhaid et al., 2022). On the other hand, disgust sensitivity related to items such as spoiled food or bodily secretions increased with advancing pregnancy between the 9th and 14th gestational weeks (Kaňková et al., 2022). It is, therefore, possible that the end of the first trimester is not the optimal period for measuring this association. However, our results discussed below indicate relative independence and specific physiological mechanisms responsible for increasing of the NVP and disgust sensitivity. We can also speculate that the correlation itself will only be demonstrable for some specific manifestations of NVP and disgust sensitivity, perhaps related to specific similarities such as an aversion to some foods or an ongoing anxiety disorder (Andersson et al., 2004; Dekkers et al., 2020; Olatunji et al., 2007a). Finally, it needs to be noted that there is a possibility that NVP does not have an adaptive function. Instead, it could be a by-product of the genetic conflict that occurs between the mother and embryo (e.g. Forbes, 2002), in which case it would not be necessarily related to disgust sensitivity. This could be a possible explanation, considering that NVP and disgust sensitivity correlate differently with hCG levels in our data.

We also tested how free β-hCG and PAPP-A levels influence the intensity of NVP. In both samples, we reported a positive correlation (with a small effect size) between free β-hCG levels and NVP, which was statistically significant when we analysed data from S1 and S2 together. This result is in line with previous studies suggesting that free β-hCG is the main proximate cause of NVP (Forbes, 2002; Lee and Saha, 2011). Recently, Suhaid et al. (2022) reported that pregnant women with severe degrees of emesis gravidarum had higher levels of free β-hCG than women with normal pregnancies. However, in a review including 35 studies on NVP and hCG (Niemeijer et al., 2014), 18 studies found a significant relationship between elevated hCG levels and NVP or HG, three studies showed lower hCG levels in women with these symptoms, and 13 studies revealed no such significant correlation – for these reasons, we are cautious in using one-tailed tests. Although the effect of hCG on NVP is still not known for certain, two

main mechanisms are discussed. The first includes the influence of hCG on stimulation in the upper gastrointestinal tract, causing distension in this part, leading to an increase of gastric acid secretion and accumulation of fluid in the intestinal lumen, which triggers emesis gravidarum (Gomes et al., 2018). The second mechanism relates to the stimulation of thyroid function due to the structural similarity of hCG and thyroid-stimulating hormone (TSH). Indeed, the peak of hCG levels, between the 8th to 14th gestational week, correlates with a decrease in TSH levels, while still observing an increase in free thyroxine (T4) levels (Glinoer et al., 1990). Goodwin et al. (1992) then showed a significant positive association between the level of thyroid stimulation and the severity of vomiting.

The positive association between PAPP-A and NVP observed in S1 has also been found by Derbent et al. (2011). Women with HG had higher maternal serum PAPP-A levels in the first trimester compared to normal pregnancies. In pregnancies with HG, low antioxidant enzyme activities (Güney et al., 2007) and increased oxidant stress (Aksoy et al., 2009) compared to normal pregnancies have been reported. Therefore, Derbent et al. (2011) speculate that increased oxidative stress and decreased antioxidant activity in HG could be the reason for induced PAPP-A expression.

We also found significant negative correlations between free β-hCG levels and disgust sensitivity (the total DS-R score and each of the subscales) in analyses of merged data. When the two samples were analysed separately, there were significant negative correlations between both free β-hCG and PAPP-A levels and disgust sensitivity (the total DS-R score) in S1 but not in S2. Because lower levels of both free β-hCG and PAPP-A are associated with negative outcomes related to pregnancy (see Introduction), the observed negative correlation between these markers and disgust sensitivity could be explained as an increased need to protect a potentially "more vulnerable" fetus. hCG seems to be important for immunomodulation related to tolerance of a semi-allogeneic embryo (Schumacher et al., 2013). This hormone is essential in early pregnancy because of its positive effect on the increase of regulatory T-cells, especially IL-1β levels (Furcron et al., 2016). Elevated disgust sensitivity in the first trimester of

pregnancy was also associated with decreased levels of cytokines including e.g. IFN-γ, IL-1β, IL-2 IL-4, IL-7, IL-17A, and TNF-α (Kaňková et al., 2022). Our results, therefore, indicate that lower free β-hCG levels could be associated with insufficient immune activity in early pregnancy and play an important role in the mechanism that then causes elevated disgust sensitivity during this sensitive period in women's lives.

While a significant negative association between free β-hCG levels and disgust sensitivity was confirmed in both samples (before and during the pandemic) analysed separately, as well as in the analysis of the merged data while controlling for "sample", the correlation between PAPP-A levels and disgust sensitivity was significant only in the sample collected before the pandemic (S1). Free β-hCG, therefore, seems to be a more important marker of the activity of the behavioural immune system, specifically elevated disgust sensitivity, than PAPP-A. In times of high pathogenic risk in the environment, such as the COVID-19 pandemic, when disgust sensitivity was shown to be higher overall (Kaňková et al., submitted; Miłkowska et al., 2021), PAPP-A apparently does not play any role in the regulation of disgust sensitivity during early pregnancy.

The inconsistent results in both samples related to PAPP-A levels were also observed for NVP. Our findings show that while higher levels of PAPP-A were positively correlated with NVP in S1, no significant relationship between these variables was revealed in S2. Moreover, we showed no significant effect of PAPP-A levels on NVP in the analyses of the merged data. This could indicate either of three possible explanations. The first is that the significant correlations in S1 simply occurred by chance. A second explanation might be an association between PAPP-A levels and the COVID-19 pandemic, during which we collected data from S2. Indeed, Sanchez et al. (2021) found that levels of PAPP-A increased in early infection with SARS-CoV-2. On the other hand, no women had an acute COVID-19 infection in S2, because women had to be healthy for a preventive examination at the hospital. Also, we observed no differences in PAPP-A levels between S1 and S2 (see Table 3). Lastly, differences in results could also be

related to a significantly higher proportion of primiparas in S1 and significantly older women in S2. However, even this explanation seems to be less likely, because age and parity were included as control variables in all analyses.

The analyses performed separately for primiparous and multiparous women showed that the levels of free β-hCG were significantly positively correlated with NVP, and both free β-hCG and PAPP-A levels were significantly negatively correlated with disgust sensitivity, only in primiparous women. That we did not observe similar results in multiparas indicates that there could be other factors that affect (maybe even in different directions) the studied associations in multiparous women (e.g. number of previous pregnancies, age of previous children, breastfeeding, etc.). Moreover, we also found that primiparas had significantly higher free β-hCG and PAPP-A levels compared to multiparas, which is in line with previous observations (e.g. Järvelä et al., 2012).

Limitations

The limitation of both studies is the interval between questionnaire completion and blood collection for the measurement of biochemical markers. On average, women completed the questionnaire 2-3 weeks later than their blood was taken. In our results, therefore, the current state of the organism (NVP or disgust sensitivity) does not directly correspond to the actual levels of the measured markers. On the other hand, we may expect relative differences between participants in either form of measure to remain somewhat stable over this interval. Furthermore, our data certainly allow us to conclude how the levels of these markers measured in the 10^{th} week of pregnancy predict disgust sensitivity and NVP in the 13^{th} week of pregnancy. Especially for NVP, this could be helpful in the context of the more severe manifestations of NVP that persist in the second and third trimesters.

Another limitation of the study is the period of data collection in S2, which took place during the COVID-19 pandemic. In fact, higher disgust sensitivity was observed in pregnant women during the COVID-19

pandemic compared to the pre-pandemic period (Kaňková et al., submitted), while NVP levels were not affected by the pandemic in the same study. For this reason, results from S1 may reflect more accurately the true inter-relationships between the studied variables.

5. Conclusion

Although there were many reasons to expect a positive relationship between NVP and disgust sensitivity in early pregnancy, our results did not support this hypothesis. Moreover, we have shown that both phenomena may likely have different proximal causes, even though the primary goal of NVP and disgust sensitivity appears similar: to protect the organism from toxins and pathogens, respectively. In the context of first-trimester biochemical markers, hCG appears to be an important indicator regulating behavioral immune system activation: decreased hCG levels around the 10^{th} gestational week predicted higher disgust sensitivity at the end of the first trimester. On the other hand, we observed the opposite pattern for NVP, with higher hCG levels predicting more severe NVP. The same was true for PAPP-A levels and both NVP and disgust sensitivity, but only in S1, suggesting that PAPP-A is probably part of a larger network of immunological and endocrine responses and does not by itself provide sufficient information to predict future development of NVP and disgust sensitivity.

Declaration of competing interest

The authors declare that they have no conflicts of interests.

Data availability

Open data are provided at https://doi.org/10.6084/m9.figshare.20509353.v1.

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