Gastrointestinal symptoms in infants of mothers with a psychiatric history and the role of depression and bonding.

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Abbreviations: GER; Gastroesophageal reflux, GERD; Gastroesophageal reflux disease, PD mothers; mothers with a history of psychiatric disorder I-GERQ-R; Infant Gastroesophageal Reflux Questionnaire Revised , EPDS; Edinburgh Postnatal Depression Scale, PBQ; Postpartum Bonding Questionnaire.

Abstract

Objectives: Gastroesophageal reflux (GER), excessive crying, and constipation are common gastrointestinal symptoms in infancy of multifactorial origin in which psychosocial stress factors play an important role. The aims of this observational study were to investigate the presence of gastrointestinal symptoms in infants of mothers with or without a history of a psychiatric disorder, their association with maternal depressive symptoms, and the possible mediating role of bonding.

Methods: 101 mothers with a history of a psychiatric disorder ("PD mothers") and 60 control mothers were included. Infant gastrointestinal symptoms, maternal depressive symptoms, and mother-infant bonding were assessed using validated questionnaires and diagnostic criteria at 1.5 month postpartum.

Results: The mean total score on the Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R) reported in infants of PD mothers (13.4 SD 5.4) was significantly higher than in infants of control mothers (10.8 SD 5.4; P =.003). No significant differences were found in the presence of excessive crying (modified Wessel's criteria and subjective experience) and constipation (ROME IV criteria) between both groups. Infant GER was associated with maternal depressive symptoms ($P = 0.027$) and bonding problems ($P = <0.001$). Constipation was related to maternal depressive symptoms ($P = 0.045$), and excessive crying (Wessel and subjective criteria) was associated with bonding problems (respectively $P = 0.022$ and $P = 0.002$). The effect of maternal depressive symptomatology on infant GER symptoms and excessive crying was mediated by bonding problems.

Conclusion: Maternal psychiatric history is associated with infant gastrointestinal symptoms, in which mother-infant bonding is a mediating factor.

Keywords: infant, gastrointestinal symptoms, mother infant bonding, maternal depression

What Is Known

- Gastroesophageal reflux (GER), excessive crying, and constipation are gastrointestinal symptoms in infancy in which psychosocial stress plays an important role

- Excessive infant crying is associated with postpartum maternal depression and bonding problems

- Mothers with a psychiatric history are at risk of postpartum depression and bonding problems

What Is New

- There is a higher level of GER symptoms in infants of mothers with a psychiatric history and this is associated with maternal depressive symptoms and bonding problems

- Infant constipation is associated with maternal depressive symptoms

- The effect of maternal depressive symptoms on infant gastroesophageal reflux and excessive crying is mediated by bonding problems

Introduction

Gastroesophageal reflux (GER), excessive crying, and constipation are common gastrointestinal symptoms in infancy (1). These symptoms may occur in up to 50 percent of infants (2), often leading to consultation of a healthcare professional and high costs (3,4). Underlying organic causes are rare and a multifactorial origin is assumed in the majority of cases, among which psychosocial stress factors, such as parenting stress, play an important role.

It is known that mothers with a history of psychiatric disorder often experience more parenting stress and problems with bonding to their infant during the first months postpartum in comparison to mothers without psychiatric problems (5). Additionally, mothers with a history of psychiatric disorder have an increased risk for maternal depression during and after pregnancy (6,7).

Maternal psychiatric diagnosis has been associated with infant gastrointestinal symptoms (8,9). A recent study showed that mothers with a psychiatric disorder were nearly five times more likely to have a baby admitted with complaints of GER in the first year after birth (9). When GER leads to bothersome symptoms, such as growth failure and hematemesis, it is defined as gastroesophageal reflux disease (GERD)(10). Maternal psychopathology is shown to play a role in feeding problems in children with GERD (11). Maternal depression is also associated with excessive crying and infant feeding problems (12-14).

Therefore, we hypothesize that GER, excessive crying and constipation occur more often in infants of mothers with a psychiatric history than in healthy control mothers and that maternal depressive symptoms are associated with more gastrointestinal symptoms in infants.

However, little is known about underlying pathways in the association between maternal psychiatric history and infant gastrointestinal symptoms. Therefore, in the current study we explore if bonding problems are a mediator in the association between maternal depressive symptoms and gastrointestinal symptoms in infants.

Methods

Study design and sample

In this prospective study, data were analyzed from two groups of mother-infant dyads: PD mothers and healthy control mothers. The inclusion criteria for de PD mothers in this study were the actual presence or a history of psychiatric disease.

PD mothers were all recruited at specialized Psychiatry-Obstetrics-Pediatrics (POP) outpatient clinics from one tertiary referral hospital (Erasmus Medical Center) and six secondary hospitals and two specialized mental health care clinics within the Netherlands. At these POP clinics, pregnant women with a history of psychiatric disorder received a consultation by a multidisciplinary team consisting of a psychiatrist, obstetrician and pediatrician. The presence or history of a psychiatric disorder was clinically assessed during the POP consultation by a clinical psychiatrist with perinatal expertise, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 2000).

Two thirds of the PD mothers were included in one of the secondary hospitals (Antonius Hospital) in a standardized follow-up care program from May 2014 to August 2016. They were asked to participate in this research project and written informed consent was obtained from all participating mothers. Because these participants were not subject to procedures and were not required to follow rules of behaviour, the medical ethical commission deemed that

this study was not subject to the Dutch Medical Research Involving Human Subjects (Act WMO).

One third of the PD mothers and all control mothers were recruited in the context of the INCAS study: a multicenter observational study on maternal parenting capacity and infant development in mothers with a severe mental illness between February 2013 and December 2014. The presence or history of a psychiatric disorder was additionally established using a structured clinical interview administered by a trained interviewer (15). Mothers in the control group were recruited during pregnancy at several midwifery practices in the Netherlands. Mothers were excluded from the control group when the presence of postpartum psychopathology was indicated by a General Severity Index in the clinical range on the Brief Symptom Inventory (BSI) (16,17). When they scored in the clinical range, for example because they did not seek help for their symptoms, they could not be considered as control in the sense of not having a psychiatric disorder. The INCAS study was approved by the Erasmus MC medical research ethics committee and written informed consent was obtained from all participating mothers (NL42662.078012).

For the current study, data regarding infant gastrointestinal symptoms, maternal depression and bonding from PD mothers at 6-7 weeks (6.7 SD1.5) postpartum (n=101) were compared to data from the control group (6.1 weeks SD1.3) (n=60). Mother-infant dyads were excluded from the current analysis if the infant had a gestational age of ≤36 weeks or suffered from a serious medical condition.

Measures

Demographic and background information of the mothers and their infants was gathered by self-report questionnaires.

Infant gastrointestinal symptoms

GER symptoms were assessed by maternal report using the Dutch version of the Infant Gastroesophageal Reflux Questionnaire Revised (I-GERQ-R) (18,19) which consists of 12 items that can be rated either in the yes/no or the Likert scale fashion. The I-GERQ-R is a reliable and valid measure of infant GERD symptoms during the past 7 days. Item scores were summed to obtain a total score for GERD symptoms (range: 0-42). Infant GERD has a cut off level of 16 and both the dichotomized score (present/absent) as well as the total score were used for analysis of infant GER symptoms.

Excessive infant crying was assessed by self-report in one question based on the modified Wessel's criteria (crying more than 3 hours per day during 3 or more days in the last week) (20,21,22). Additionally, a second question on mothers judgment on duration of infants' crying was added, based on the final core outcome set for infant colic (23) ("Do you think your child cries a lot?"). For the current analysis these two items were dichotomized (present / absent). Both outcomes (modified Wessel and subjective experienced excessive crying) were included in the analysis.

The presence of functional constipation was investigated by using 4 questions (≤2 defecations per week; excessive stool retention; painful or hard bowel movements; large fecal mass) based on the ROME IV criteria for infants and toddlers (24). Functional constipation was considered present if at least 2 of these symptoms were reported. These data were only

available for the infants of PD mothers from the INCAS study (n= 34) and for the infants of control mothers (n=60).

Maternal postpartum depressive symptoms and bonding

The Dutch version of the Edinburgh Postnatal Depression Scale (EPDS) was used to assess maternal depressive symptoms (25,26). In this 10-item self-reporting questionnaire a mother reports subjective emotional distress during the past 7 days. All items are rated on a 4-point scale, score range is 0-30 and a higher score indicates more postpartum depressive symptoms.

The Dutch version of the Postpartum Bonding Questionnaire (PBQ) was used to assess problems in the mother-infant relationship (27,28) by self-report. The PBQ includes 25 items rated on a 6-point Likert scale yielding scores on 4 factors: a general factor (scale 1) rejection and pathological anger (scale 2), anxiety about the infant (scale 3) and incipient abuse (scale 4). Item scores were summed up to obtain a total score (range: 0-125). A high score indicates maternal problems with bonding. These data were only available for PD mothers from the INCAS study (n= 34) and for control mothers (n=60).

Statistical analysis

Differences in the prevalence of gastrointestinal symptoms between both groups of infant-mother dyads were tested using regression analysis. Subsequently, we estimated the relationship between maternal depressive symptoms and postpartum bonding problems, and infant gastrointestinal symptoms using linear (reflux) and logistic (excessive crying and functional constipation) regression analysis. We presented regression coefficients and 95% confidence intervals of the unadjusted and fully adjusted analysis (all potential confounding variables).

Finally, we tested whether postpartum maternal bonding problems mediated the relationship between depressive symptomatology of the mother and infant gastrointestinal symptoms. The total score of the I-GERQ-R, excessive crying according to Wessel's criteria, and functional constipation were used as outcome measures. The size and significance of all direct and indirect relationships between depressive symptomatology and gastrointestinal symptoms were estimated using structural equation modelling (SEM). Robust weighted least squares estimation was used to allow the inclusion of continuous and dichotomous variables into the model (29). SEM analysis were conducted using MPlus version 7.4 (30).

Demographic and clinical differences between PD and control mothers and their infants were tested using T-tests and Chi2 tests. Correlations between the infant gastrointestinal symptoms were calculated with spearman's rho correlation tests.

Cases with less than 30% missing data on outcome measures were imputed using series mean. Cases with more than 30% missing data on outcome measures were excluded from the analysis. Data were tested for normal distribution and checked for outliers. Analyses were conducted using SPSS (IBM SPSS statistics 24) unless otherwise specified.

Results

Between February 2013 and July 2016, 678 pregnant women met the criteria of inclusion and exclusion, 205 provided informed consent, of whom 161 women participated until the end of the study. There were 44 patients lost to follow up, 3 mothers in the control group were excluded because of the BSI clinical range, 5 children were excluded because of prematurity and 36 mothers were excluded because the questionnaires were not completed. The 161 infants had a mean age of 6.5 weeks (SD=1.5) and consisted of 44% girls, mean age of their

mothers was 32.1 years (SD=4.6). In the PD group 55% of the mothers had a history of depressive disorder, 28% of anxiety disorder, 5% of a psychotic disorder and 24% of the mothers had a personality disorder, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 2000).

Baseline characteristics of the infants and mothers included are presented in Table 1. PD mothers were significantly more often unemployed, used tobacco more often and reported higher levels of postpartum depressive symptomatology. Infants of PD mothers were less often breast fed and approximately two weeks younger at birth. Additionally, infants of PD mothers were more often admitted to the hospital in the first week postpartum due to routine observation because of maternal medication use.

PD dyads in the INCAS group (n=34) were more often unemployed and reported lower educational levels than the other PD dyads (n=67). Additionally, infants of the PD dyads in the INCAS group showed higher gestational age (M=39.2 weeks; SD=1.9) than infants in the other PD dyads (M=37.2; SD=1.0), and INCAS mothers reported higher levels of depressive symptomatology (M= 10.1; SD=5.9) than other PD mothers (M=6.6; SD=5.4). No differences were observed for the remaining baseline characteristics.

Prevalence of infant gastro-esophageal symptoms

The presence of infant gastrointestinal symptoms is presented in Table 2. The mean total score of I-GERQ-R in infants of PD mothers (*M*=13.4 SD 5.4) was significantly higher than in infants of control mothers (*M*=10.8 SD 5.4).

There were no significant differences between infants of PD mothers and control mothers with regard to the presence of infant GER and excessive crying.

A trend was found towards a higher presence of functional constipation in infants of PD mothers (15%) in comparison to infants of control mothers (3%) ($P = 0.058$).

Relationship between infant gastrointestinal symptoms and maternal postpartum depressive symptoms and bonding problems

As depicted in table 3, a significant positive relationship between infant GER and both maternal depressive symptoms and postpartum bonding problems was found after adjustment for confounders. A significant positive relationship was found between excessive infant crying and postpartum bonding problems and between infant functional constipation and maternal depressive symptoms in both unadjusted and adjusted analyses.

Table 4 shows the results of the path analysis. The effects of maternal depressive symptomatology on infant reflux symptoms and excessive crying were mediated by maternal bonding problems. A direct path between depressive symptomatology and infant reflux symptoms and excessive crying was not found. Functional constipation, on the other hand, was directly impacted by maternal depressive symptomatology, and this association was not mediated by maternal bonding. In line with the results reported in Table 2, the total impact (directly and indirectly through bonding) of maternal depressive symptoms was significant for reflux and functional constipation, but not for excessive crying.

Table 1: Sociodemographic and clinical characteristics of PD mothers and control mothers and their infants (n=161)

Table 2. Prevalence of gastrointestinal symptoms in infants of PD and control mothers.

Table 3. Relationship between maternal postpartum depressive symptoms (EPDS) and postpartum bonding problems (PBQ) and infant gastrointestinal symptoms.

Table 4 Path model: standardized direct and indirect effects and standard error of maternal postpartum depressive symptoms and bonding problems on infant gastrointestinal symptoms.

Discussion

This study shows a higher reported mean reflux score in infants of mothers with a history of a psychiatric disorder (PD), irrespective of the presence of actual depressive symptoms, than in infants of control mothers. The overall presence of excessive infant crying and constipation did not significantly differ between groups, although a trend was seen towards a higher prevalence of functional constipation in the PD group. Furthermore an association was found with maternal depressive symptoms and both infant GER and constipation and not with excessive infant crying. Lastly, maternal depressive symptoms were mediated by maternal bonding in their association with infant reflux symptoms and excessive crying.

Our results are in line with three small studies showing an association between maternal depression and GER (11,31,32). In two Australian studies including 27 and 100 infants with diagnosis of "infant distress syndrome" severe enough to warrant admission, there was a high percentage of infant GER (44% and 36%) and clinical levels of major depressive disorder in their mothers (48% and 39%). Nevertheless, the clinical impression that infant reflux

appeared to be associated with maternal anxiety and depression could not be confirmed in these studies (31,32). As case control study by Karacetin (11) found significantly higher depression and anxiety scores in 39 mothers of children with GERD versus a matched control group.

Several hypotheses exist concerning the association between maternal depression and GER. First, it is possible that depressed mothers misinterpret normal infant signals and infant facial expressions (8,33,34), leading to suspicion of GER and subsequently health care professional visits and infant medication. Second, the reverse causation hypothesis is that maternal psychopathology is not a risk factor for reflux symptoms, but that infant gastrointestinal symptoms could result in the development or exacerbation of maternal psychopathology, for example through negative infant-mother interaction patterns (35,36). This hypothesis is supported by the mediating role of bonding we found in the association between maternal depression and infant GER symptoms and excessive crying. More insight into the causal mechanism underlying this association could improve treatment in clinical practice.

Unexpectedly, we found no significant association between excessive infant crying, defined by both modified Wessel criteria and maternal depression which is in contrast with abundant literature showing maternal postpartum depression to be correlated, and even a consequence of, excessive infant crying (13,37). We speculate that the main reason for this finding is that our study was underpowered; a post hoc analysis showed that our sample size was able to significantly detect medium sized differences (Cohen's delta: 0.5 and OR of 1.8), with a significance level of 0.05 and power of 0.80.

Although functional constipation was reported five times more often by PD mothers (15%) than in the control group (3%), this difference was not statistically significant, possibly due to the small number of women in the PD group who filled out the constipation questionnaire. However, this finding is in line with a study by Krause (33) in which no association between reported infant constipation and maternal anxiety and/or depression prior and during pregnancy was shown. It should be noted, however, that Rome criteria were not used to diagnose functional constipation. Larger studies with validated questionnaires may shed more light on the possible association between infantile constipation and depression in mothers.

A limitation of our study is that we did not correct for functional gastrointestinal symptoms in the mothers as there is transference of functional symptoms between parents and children, which might interact as a confounder between maternal depressive symptoms and GER (38). Another potential confounder is the use of medication in the group of infants with gastrointestinal disorders; in the Netherlands however, effective over-the counter medication for functional gastrointestinal symptoms in infants is unavailable and the prescription of reflux medication to infants has dropped significantly due to a more stringent national guideline.

The findings in our study have several implications for clinical practice. First, obstetricians should consider offering pregnant women with a (history of) psychiatric disorder preventive strategies, like a "surviving crying" package which has been shown to significantly reduce depression and anxiety in parents and reduce crying of the baby by increasing parental confidence and parental sleep (39). Moreover, it is important that physicians are aware of the mental wellbeing of mothers who visit their practice with an infant with gastrointestinal symptoms. They should be encouraged to ask about feelings of depression and bonding in

order to gain insights in possible negative cycles in which maternal and infant problems could exacerbate each other (40).

In conclusion, infants of mothers with a psychiatric disorder are at an increased risk for developing gastro intestinal symptoms, which are related to maternal postpartum depressive symptoms and bonding problems. The underlying mechanisms of transference seem to differ depending on the specific gastro-intestinal symptom. It is of importance that health care professionals take the maternal psychiatric history and maternal actual wellbeing in account when treating their infants with gastrointestinal symptoms, and refer to mental health professionals if necessary.

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Table 1: Sociodemographic and clinical characteristics of PD mothers and control mothers and their infants (n=161)

	PD group (n=101)	Control group (n=60)	Test
Mother			
Age (mean [SD[a]])	31.9 (4.7)	32.4 (4.8)	T(158)=0.97; *P*=0.561
Dutch ethnicity	90.7%	85.0%	Chi^2(1)=1.03; *P*=0.311
Educational level (%Post vocational)[b]	36.1%	50.8%	Chi^2(1)=3.06; *P*=0.080
Employment (%Yes)	63.1%	80.0%	Chi^2(1)=4.78; ***P=0.029***
Tobacco use during pregnancy	23.3%	8.5%	Chi2(1)=5.36; ***P=0.021***
EPDS[c] (Mean; SD)	7.8 (5.7)	3.2 (3.3)	T(156)=-5.57; ***P<0.001***
Infant			
Age (weeks) (mean [SD])	6.7 (1.5)	6.1 (1.3)	T(157)=-2.35; ***P=0.020***
Primiparous	56.4%	43.9%	Chi^2(1)=2.31; *P*=0.129
Sex (% male)	58.4%	53.3%	Chi^2(1)=.40; *P*=0.529
Breast feeding >50% of intake	37.3%	66.3%	Chi^2(1)=12.57; ***P<0.001***
Gestational age at birth in weeks (mean [SD])	37.9 (1.6)	39.8 (1.4)	T(158)=7.80; ***P<0.001***
SGA[d] <p10	5.0%	6.8%	Chi^2(1)=0.24; *P*=0.628
Hospital admission in first week	21.4%	5.0%	Chi^2(1)=7.80; ***P=0.005***

[a] SD = standard deviation. [b]Secondary vocational education and academic education. [c]EPDS= Edinburgh Postnatal Depression Scale. [d]SGA= small for gestational age.

Table 2. Prevalence of gastrointestinal symptoms in infants of PD and control mothers.

	Infants of PD mothers (N=101)	Infants of control mothers (N=60)	Regression coefficient
Reflux *GER* (% [n / ntotal])	28 (27/97)	18 (10/57)	OR: 1.8(0.8-4.1); *P*=0.152
IGERQ-R^a total (mean [SD])	13.4 (5.4)	10.8 (5.4)	β: 0.2 (0.9-4.3); ***P*=0.003**
Excessive crying *Modified Wessel's* (% [n / ntotal])	6 (6/98)	14 (8/59)	OR: 0.4 (0.1-1.3); *P*=0.122
Subjective (% [n / ntotal])	18 (17/96)	12 (7/60)	OR: 1.6 (0.6-4.2); *P*=0.312
Functional constipation^b (% [n / ntotal])	15 (5/33)	3 (1/60)	OR: 5.2 (0.95-28.4); *P*=0.058

a. IGERQ-R = Infant Gastroesophageal Reflux Questionnaire Revised. b:Only data available from INCAS study.

Table 3. Relationship between maternal postpartum depressive symptoms (EPDS) and postpartum bonding problems (PBQ) and infant gastrointestinal symptoms.

	EPDS Regression coefficient (95% C.I.) Unadjusted	EPDS Regression coefficient (95% C.I.) Fully adjusted[a]	PBQ Regression coefficient (95% C.I.) Unadjusted	PBQ Regression coefficient (95% C.I.) Fully adjusted[a]
Reflux - *IGER-Q*	β: 0.26 (0.10-0.41); *P*=0.001	0.21 (0.02-0.40); *P*=0.027	β:0.27 (0.16-0.38); *P*<0.001	0.27 (0.15-0.39); *P*<0.001
Excessive crying *Modified Wessel's*	OR: 1.07 (0.98-1.17); *P*=0.111	1.05 (0.92-1.95); *P*=0.472	OR: 1.07 (1.00-1.15); *P*=0.038	1.12 (1.02-1.24); *P*=0.022
Subjective	OR: 1.09 (1.01-1.18); *P*=0.029	1.07 (0.96-1.20); *P*=0.226	OR: 1.13 (1.05-1.22); *P*=0.002	1.21 (1.07-1.36); *P*=0.002
Functional constipation[b]	OR: 1.16 (1.04-1.31); *P*=0.010	1.31 (1.01-1.71) ; *P*=0.045	OR: 1.04 (0.97-1.12); *P*=0.266	1.05 (0.95-1.17); *P*=0.349

[a] Adjusted for age infant at visit, gestational age at birth, infant admission in 1st week, breast feeding, employment status mother, smoking during pregnancy
[b] Only data available from INCAS study