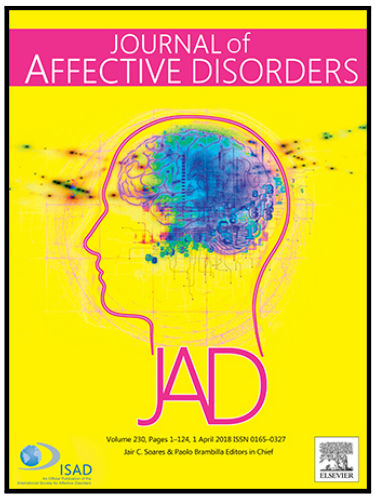

The course of panic disorder during the peripartum period and the risk for adverse child development: A prospective-longitudinal study

Julia Martini , Katja Beesdo-Baum , Susan Garthus-Niegel , Hans-Ulrich Wittchen

PII: S0165-0327(18)32404-2
DOI: https://doi.org/10.1016/j.jad.2020.01.018
Reference: JAD 11467

To appear in: *Journal of Affective Disorders*

Received date: 12 October 2018
Revised date: 20 December 2019
Accepted date: 3 January 2020

Please cite this article as: Julia Martini , Katja Beesdo-Baum , Susan Garthus-Niegel , Hans-Ulrich Wittchen , The course of panic disorder during the peripartum period and the risk for adverse child development: A prospective-longitudinal study, *Journal of Affective Disorders* (2020), doi: https://doi.org/10.1016/j.jad.2020.01.018

Highlights

- Heterogeneous course patterns of PD were observed during the peripartum period.

- PD/panic attacks were commonly observed during the early stages of pregnancy.

- Comorbid PD and MD was the worst condition (impaired bonding, regulatory problems).

The course of panic disorder during the peripartum period and the risk for adverse child development: A prospective-longitudinal study

Julia Martini[a, b] Katja Beesdo-Baum[a, c] , Susan Garthus-Niegel[d, e] & Hans-Ulrich Wittchen[a, f]

[a] Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Germany

[b] Department of Psychiatry & Psychotherapy, Faculty of Medicine of the Technische Universität Dresden, Germany

[c] Behavioral Epidemiology, Technische Universität Dresden, Germany

[d] Institute and Outpatient Clinics of Psychotherapy and Psychosomatic, Faculty of Medicine of the Technische Universität Dresden, Germany

[e] Department of Child Health, Norwegian Institute of Public Health, Oslo, Norway

[f] Department of Psychiatry & Psychotherapy, Ludwig Maximilans Universitaet Munich, Germany

Corresponding author: Julia Martini

Adress: Department of Psychiatry & Psychotherapy, Faculty of Medicine of the Technische Universität Dresden, Fetscherstr. 74, 01307 Dresden, Germany

E-Mail: julia.martini@tu-dresden.de

Tel: +49 (0)351 458 11475

Fax: +49 (0)351 458 4324

Abstract

Background: Panic disorders during pregnancy and after delivery may have detrimental effects for mother and child, but no firm conclusions regarding the course and outcomes peripartum panic disorders can be drawn from previous studies.

Methods: N=306 women were repeatedly interviewed with the Composite International Diagnostic Interview for Women. Social support and partnership quality, gestational outcomes, duration of breastfeeding, regulatory disorders, maternal bonding and parenting style were assessed via medical and maternal reports. Standardized observations of neuropsychological development, infant temperament and attachment were conducted 4 and 16 months after delivery.

Results: Women reported heterogenous courses of panic disorders, and panic disorders /panic attacks were commonly observed during the early stages of pregnancy. Women with peripartum PD

presented with a worse psychosocial situation (e.g. lower social support). Clear behavioral differences (temperament, attachment) in infants of women with panic disorders as compared to women with no anxiety and depression could not be detected in this study, but differences concerning gestational outcomes, duration of breastfeeding, maternal parenting, and bonding as well as regulatory problems in infants were identified.

Limitations: This prospective-longitudinal multi-wave study is restricted by the relative small sizes of the particular groups that limit the power to detect differences between the respective groups.

Conclusions: Heterogenous courses and outcomes of perinatal panic disorders require intensive monitoring of affected mother-infant-dyads who may benefit from early targeted interventions to prevent an escalation of dyadic problems.

Key words: panic disorder; course; pregnancy; postpartum; mother; infant

Introduction

Panic disorder (PD) is one of the most prevalent and disabling psychiatric disorders and prevalence estimates of PD are twice as high in women as in men (Jacobi et al., 2014; Jacobi et al., 2015). The age of onset of PD is typically before or during the reproductive years (according to the meta-analyis by de Lijster et al., 2017: mean age 30.3 years; 95% CI 26.1-34.6 years). Thus, the investigation of the course of PD during the peripartum period and the impact on child development is an important research aim.

Prior studies have shown that the course of peripartum PD is variable and some studies found a decrease or rather low rates of PD, if women become pregnant (Bandelow et al., 2006; George et al., 1987; Hertzberg and Wahlbeck, 1999; Klein et al., 1994; Northcott and Stein, 1994; Villeponteaux et al., 1992). However, worsening or unchanged course patterns of PD during pregnancy have also been reported (Cohen et al., 1994; Cohen et al., 1996; Griez et al., 1995; Wisner et al., 1996). Further evidence suggests heterougeneous course patterns during the postpartum period with an increased risk for a new onset or an exacerbation of PD (Bandelow et al., 2006; Cohen et al., 1994; Cohen et al., 1996; Hertzberg and Wahlbeck, 1999; Sholomskas et al., 1993). Moreover, it has been hypothesized that breastfeeding also affects the course of PD, but studies were inconclusive (Bandelow et al., 2006). Noteworthy, approximately 50% of individuals with PD also suffer from comorbid Major Depression (MD) and prenatal anxiety disorders, such as PD, were specified as prominent risk factors for later depression (Marchesi et al., 2014; Martini et al., 2015; Sutter-Dallay et al., 2004). Therefore pre- and peripartum PD may be associated with significant depressive morbidity. Finally, evidence suggests that psychosocial factors (e.g. marital status, cohabitation with the partner, partnership quality, social support) may be associated with anxiety and depressive disorders during peripartum period (Asselmann et al., 2016b; Asselmann et al., 2016c), but thus far, their role in PD remains unclear.

Panic attacks may lead to exposure of the fetus to stresshormones and some studies suggest that PD is associated with pregnancy and gestational complications and adverse infant development (Acs et al., 2006; Banhidy et al., 2006; Chen et al., 2010; Cohen et al., 1989; Teixeira et al., 1999; Warren et

al., 2006; Yonkers et al., 2017). However, recent research revealed conflicting results on the link between perinatal PD and adverse birth outcomes (e.g., preterm delivery, low birth weight, mode of delivery) (Banhidy et al., 2006; Chen et al., 2010; Yonkers et al., 2017). Interestingly, studies on the familial transmission of anxiety disorders focused especially on families with PD, because children of parents with PD are at risk for multiple anxiety disorders (Rosenbaum et al., 1988; Rosenbaum et al., 1991b). Compared to children of parents without psychopathology, children of parents with PD are more likely to present a temperamental factor called behavioral inhibition (BI, withdrawal in response to novel stimuli and strangers)(Rosenbaum et al., 1988; Rosenbaum et al., 2000; Rosenbaum et al., 1991b) that is considered as a meaningful risk factor for the development of anxiety disorders (Biederman et al., 1993; Rosenbaum et al., 1991a; Turner et al., 1996; van Brakel et al., 2006). However, most previous studies on this issue have focused on infants aged 2 years and older (Fox et al., 2015; Rosenbaum et al., 1988; Rosenbaum et al., 2000). In a recent study on younger children, infants and toddlers of mothers with PD did not show increased reactivity (evidenced to be an early marker of BI) (Fox et al., 2015; Kagan et al., 1998) and BI (Warren et al., 2003).

It is also discussed that children of mothers with anxiety disorders - and PD in particular - may have higher levels of insecure attachment, which is an additional known risk factor for later anxiety disorders (Colonnesi et al., 2011; Drake and Ginsburg, 2012; Kraft et al., 2017; Manassis et al., 1995). However, Warren and colleagues did not show higher rates of insecure attachment in infants of mothers with PD (Warren et al., 2003).

Specific parenting behaviors (e.g., overcontrol/anger, less emotional warmth/sensitivity) have been linked to higher levels of child anxiety (Drake and Ginsburg, 2012; Rapee, 1997, 2012; Warren et al., 2003), but only few studies investigated parenting behavior in mothers with PD before the infants have developed manifest psychopathology (Warren et al., 2003).

Finally, infant regulatory disorders (e.g., excessive infant crying, feeding, and sleeping disorders) that may be considered as the earliest psychopathological adversities (Hemmi et al., 2011) are quite frequent in infants of mothers with preceeding anxiety disorders (Martini et al., 2017; Petzoldt et al., 2016). Thus, it is important to investigate whether infants of mothers with PD are more prone to particular regulatory disorders.

Overall, no firm conclusions regarding the course of PD in the peripartum period can be drawn from previous studies. The comprehensive investigation of PD during pregnancy and postpartum period requires a multi-wave design considering the lifetime history to distinguish incident and recurrent PD. First results from the Maternal Anxiety in Relation to Infant Development (MARI) study revealed overall decreasing rates of PD during the study period from early pregnancy until 16 months postpartum (Martini et al., 2015; Martini et al., 2009; Martini et al., 2013). This study aims to investigate the course of PD and comorbid MD during the peripartum period in more detail distinguishing incident and recurrent cases and the occurrence of PD during pregnancy and the postpartum period. Moreover, outcomes of women with peripartum PD (PD during pregnancy, PD during postpartum period, incident PD during the peripartum period, recurrent PD during peripartum period, comorbid peripartum PD and MD) will be compared to women with no anxiety and depressive disorders regarding disadvantageous psychosocial factors (e.g. low social support and partnership quality), unfavourable gestational outcomes (e.g. preterm delivery, low birth weight),

and further relevant characteristics (e.g. duration of breastfeeding, infant temperament, infant neuopsychological development, bonding/attachment, parenting, early regulatory disorders).

Material and Methods

Procedure

The prospective-longitudinal Maternal Anxiety in Relation to Infant Development (MARI) Study was conducted among N=306 expectant mothers, sampled from the community in gynecological outpatient settings in Dresden, Germany (study period: 01/2009-09/2012). Participating pregnant women (and their infants) completed up to 7 assessments: T1 (baseline): week 10 to 12 of gestation; T2: week 22 to 24 of gestation; T3: week 35 to 37 of gestation; T4: 10 days postpartum; T5: 2 months postpartum; T6: 4 months postpartum; T7: 16 months postpartum.

Informed consent was obtained from all participants or their legal guardians. The MARI Study was carried out in accordance with the Helsinki Declaration (2013) and was reviewed by the Ethics Committee of the Technische Universität Dresden (No: EK 94042007). More detailed information including objectives, methods, design, and a detailed study flow chart has been published elsewhere (Martini et al., 2013).

Participants

Overall, N=533 pregnant women were approached by the study team in gynecological outpatient settings in Dresden (Germany) and screened for inclusion and exclusion criteria. Fifty women were excluded based on the exclusion criteria, which were as follows: gestational age <12 weeks (n=8), younger than 18 or older than 40 years (n=8), multiple pregnancy (n=2), history of more than 3 spontaneous abortions/(induced) terminations of pregnancy/stillbirths or infant impairment (n=2), invasive fertility treatment (n=9), severe physical disease/microsomnia/skeletal malformation (n=6), substance abuse or heroin substitution during the past 6 months (n=0), severe psychiatric illness (n=2), expectation to leave the area of Dresden (n=6), and insufficient mastery of German language (n=7). Additional 9 women did not participate due to spontaneous abortion before baseline interview (T1), 10 due to lacking consent of partner, 154 due to lacking time, and 4 due to unknown reasons (Martini et al., 2013).
Overall, data of 306 women were eligible for the MARI study. Due to spontaneous abortion/induced termination of pregnancy the participation of n=8 women ended after T1. During the study, n=3 women moved away, n=5 women could not be reached any more by phone, postal and personal contact, n=9 women reported lack of time or interest for further participation, and n=7 women refused contact for follow-up assessment (cumulated dropout rate: 7.9%). Overall, retention rate until 16 months after delivery (T7) was 89.5% (n=274). Some women did not participate at single assessments, e.g. due to preterm delivery, own/infant sickness or lack of time (T2: n=0, T3: n=10, T4: n=2, T5: n=5, T6: n=1, T7: n=7). None of the women who suffered a miscarriage after Baseline-Interview had a lifetime diagnosis of PD.

Measures and Procedures

Maternal PD and MD according to DSM-IV criteria prior to, during and after pregnancy were assessed at each assessment wave (except for T4) using the Computer-Assisted Personal Interview (CAPI) version of the Composite International Diagnostic Interview for Women (CIDI-V) (Martini et al., 2009). The CIDI-V is a modified version of the World Health Organization CIDI (WHO-CIDI) (Kessler and Ustün, 2004) that allows a fully standardized assessment of DSM-IV mental disorders in women

(with specifying ICD-10 codes). Psychometric properties of the CIDI were modest to very good (Reed et al., 1998; Wittchen et al., 1998). The lifetime version was used at baseline (T1) and the interval version at follow-up (T2, T3, T5, T6, T7). Diagnostic interviews were conducted by psychologists having received one week of intensive training and conducted a series of supervised interviews. Interviewers were closely monitored throughout the field period by experienced supervisors (clinical psychologists) (Martini et al., 2015; Martini et al., 2013).

For the purpose of this study, the following PD groups were specified:
- PD prior to, during or after pregnancy (lifetime diagnose of PD cumulated until T7) (PD until T7, N=34)
- PD during pregnancy (at T1, T2 or T3) (PREG, N=22)
- PD during the postpartum period (at T5, T6 or T7) (POST, N=7)
- incident PD during the peripartum period (onset of PD from T1 to T7) (INC, N=11)
- recurrent PD during the peripartum period (recurrence of a lifetime PD from T1 to T7) (REC, N=14)
- comorbid peripartum PD and MD (occurrence of PD and MD from T1 to T7) (PD&MD, N=10)

In addition, based on cumulative lifetime diagnoses of anxiety and depressive disorders (from T1 to T7), the reference group was chosen to be free of anxiety and depressive disorder prior to, during, or after pregnancy (N=92).

Maternal age (in years), marital status ("not married" vs. "married"), cohabitation ("don't live together" vs. "live together"), maternal education ("≤10 years" vs. "≥10 years") and parity ("primiparity" vs. "multiparity") were indicated by mothers using questions that were embedded in the CIDI- V (Martini et al., 2009). Gestational age, preterm delivery (<37+0 week of gestation), infant birth weight and mode of delivery were collected via medical records. Duration of breastfeeding and infant regulatory disorders were examined with a structured diagnostic interview (Baby-DIPS) at T5, T6 and T7 (Schneider and Wolke, 2007). *Excessive infant crying* was defined accoring to the "rule of three" by Wessel and colleagues (1954) as crying for ≥3 hours per day on ≥3 days per week for ≥3 weeks. *Feeding problems* were defined as any feeding problem (from a list of 16 feeding problems), failure-to-thrive, or mothers worrying (a lot or very much) about infant growth over a period of at least 4 weeks. *Sleeping problems* were defined as difficulties in initiating or maintaining sleep for ≥3 nights per week for ≥3 months while the mother was somewhat, a lot, or very much impaired by her infant's sleeping difficulties between 6 and 16 months. Cases that were attributable to a concurrent medical condition were excluded. The Baby-DIPS comprises good to excellent inter-rater reliability (kappa values of lifetime diagnoses k=0.83-0.98) as well as high acceptance rates for interviewers and participants (rated from 0 to 100: mean=88.6±11.0) (Popp et al., 2016). Rates and co-occurence of regulatory problems in the MARI sample were comparable with rates reported by others (Petzoldt et al., 2016).

Social support was assessed at T2 and at T6 using the short form (K-14) of the Social Support Questionnaire (F-SozU) Form A (Fydrich et al., 2009) that contains 14 items. The total score (mean rating of all items) reflects the total level of perceived social support. Reliability and validity have been shown to be very good (Cronbach's $\alpha = 0.94$, retest reliability r=0.96 over a 1-week interval) (Fydrich et al., 2009).

Partnership quality was assessed at T2 and at T6 among all participants who reported to currently have a partner (biological father or not biological father of the child) at the respective assessment

point using the Partnership Questionnaire (PFB) (Hahlweg 1996). The PFB contains 30 items assessing the dimensions quarreling, tenderness, and communication that can be combined to a total score (overall partnership quality). Internal consistency and retest-reliability as well as discriminant and predictive validity of the PFB have been shown to be high (Hahlweg 1996; Rossier et al. 2006).

Early parenting behavior was assessed with the Parenting Attitudes towards Infants and Toddlers (PAIT).The infant version (T6) comprises 20 items (forced-choice) on one factor (loving affection) and the toddler version (T7) contains 30 items (forced-choice) and two factors (loving/affection, rules/structure). The questionnaire comprises good psychometric properties (Martini et al., 2016)

Maternal bonding was assessed with the German Version of the Postpartum Bonding Instrument (PBQ) at T5 (Reck et al., 2006). This self-report questionnaire consists of 25 items assessing impaired bonding, rejection, and anger, anxiety about care and risk of abuse (Brockington et al., 2006). It comprises very good psychometric properties that were confirmed for the German Version (Reck et al., 2006). For this analysis, the scales impaired bonding, as well as rejection/anger was relevant.

Observations of the mothers and their infants were conducted using standardized observation paradigms to assess infants‘ reactivity and BI (Kagan and Snidman, 1991), neuropsychological development (ND) (Petermann and Renziehausen, 2005), and the quality of infant attachment (Ainsworth et al., 1978). Standardized observations were conducted by two female psychologists blinded to the diagnosis of the mother who received two weeks of training. All observations were supervised to ensure a high assessment quality. Observations were recorded by three cameras from different viewpoints. *ND* was assessed at T6 and T7 with the standardized procedure by Petermann and Renziehausen (Petermann and Renziehausen, 2005). The tasks allow for an assessment of developmental deficits in different areas (movement control, fine motor skills, visual perception, exploration behavior, receptive and expressive language, cognitive performance). *Temperament* was measured with the procedures developed by Kagan and colleagues (Kagan, 1994). For the assessment of *infant's reactivity* at T6, the infants sat in a reclining cushioned seat and heard some taped sentences, saw three different colorful mobiles move back and forth, had a cotton swab dipped in dilute butyl alcohol placed under the nostrils, heard a female voice speaking different syllables, and saw a coloured umbrella spread out. During these procedures the mother was out of view of the infant. Videotapes were coded for high motor activity (multiple arm, leg, and back movements) and crying (high percentage of time spent crying) in response to the stimuli. Infants were classified as “high reactive” (high motor activity and crying), “low reactive” (low motor activity and crying) or neither (either high motor activity or low crying amount or the opposite). The assessment of *BI* at T7 involved the presentation of inanimate stimuli to the child (a spinning bingo wheel with noisy objects inside, rotating toys, a puppet show, and sweet and sour tastes). Moreover, strangers (a woman dressed in a white laboratory coat and gas mask and a woman with a black cloth over her head and shoulders) attempted to interact with the child. Videocoding was conducted with the software “Interact” (Mangold) by graduate and postgraduate psychology students who were blinded and had received a training of two weeks for coding the infant's reactivity and BI (Kagan, 1994). The average coding time was 45 minutes for reactivity and BI. At least ten videos were coded during training sessions to yield an adequate observer agreement (kappa >0.8, Cohen 1960) and about 10 % of all videos were randomly selected and reanalysed for quality check to ensure observer agreement with satisfying results (Bakeman et al., 1997).

At T7 mother-infant-dyads participated in the Strange Situation Procedure (Ainsworth et al., 1978), which consisted of eight episodes, including two brief separations and reunions of the infant from/with the mother. Following the procedures described by Ainsworth and colleagues (1978) and Main and Solomon (1990) the attachment group classification was based primarily on the infant's reactions to the mother's return (Ainsworth et al., 1978; Main and Solomon, 1990). Infants who actively greeted and/or sought contact with the mother upon reunion and returned to exploration within 3 minutes were classified as secure (Typ B: secure). Infants who actively averted gaze or avoided or ignored the mother immediately upon reunion (Typ A: avoidant) and infants who sought to reunite with the mother but displayed ineffective proximity and contact-seeking behavior, showing anger and active resistance to contact or prolonged fussiness and persistent low-level distress (Typ C: ambivalent/resistant) were classified as insecure. The average coding time for attachment videos were 60 minutes. Cohen's kappa coefficient for the secure and insecure (avoidant and resistant) attachment classifications was based on 20% of randomly selected and independently scored videotapes of the Strange Situation Test (Murray et al., 1996). Interrater reliability was conducted on 20% of the sample ($\kappa = 1.00$ for ABC classification). Final scores for difficult tapes and coder disagreements were based on consensus (for more information see (Kraft et al., 2017).

Analyses

All analyses were performed using STATA (StataCorp, 2012) to compute descriptive statistics, Chi square tests and t-tests for differences between the above mentioned groups regarding the particular charactersistics. Statistical significance was evaluated two-sided at the 5% level ($p \leq 0.05$). No adjustment for multiple testing was applied, because the individual tests were related to individual hypotheses.

Results

Women with PD until T7 (N=34) did not differ from woment with no anxiety or depressive disorder until T7 (REF, N=92) regarding age (PD until T7: M=28.4, SD=4.3; REF: M=27.7, SD=4.4, t=0.8087, p=0.21) and parity (primiparity: PD until T7: 58.8%, REF: 60.9%, Chi^2= 0.043, p=0.835).

Table 1 presents individual courses of PD and MD during the peripartum period along with selected gestational and offspring outcomes for women who reported incident or recurrent PD during pregnancy and the postpartum period (from T1 until T7). Although PD appeared to be persistent in some women, most participants reported major changes with heterogenous courses and shifts between PD and MD (see columns 5 and 6 of Table 1: "Course of PA, PD, MD during pregnancy (T1-T3) and postpartum (T5-T7) period"). Overall, PDs (or at least panic attacks) were predominantly seen during early and middle pregnancy, and a lower number of PD during the postpartum period was observed. Importantly, the investigated women frequently had a history of additional lifetime anxiety and depressive disorders (see columns 3 and 4, "History of other anxiety or depression diagnoses"). Gestational age and birth weight were in the normal range in most cases, but women with incident PD during pregnancy reported rather short durations of breastfeeding (M=7.0 months, SD=5.3 months) and regulatory disorders were often observed in women with recurrent PD (see columns 7-10 in Table 1: "Gestational age (weeks), Birth weight (gram), Breastfeeding (months), and Regulatory disorder").

Table 2 shows selected sociodemographic and psychosocial characteristics in women of the predefined groups. Significant lower mean values of social support during pregnancy and postpartum period were reported by almost all groups with PD (PD until T7, INC, REC, PREG, POST, PD&MD). Moreover, women with comorbid peripartum PD and MD (PD&MD) reported a significant lower partnership quality during pregnancy and postpartum period and a lower educational level.

Table 3 presents gestational and early offspring outcomes in women of the predefined groups. As compared to women with no anxiety and depressive disorder until T7 (REF) women with PD during pregnancy (PREG) reported significantly less rejection/anger and more loving/affection towards their infants whereas women with postpartum PD (POST) reported significantly impaired bonding and rearing with more rules/structure towards their infants. Moreover, infants of mothers with postpartum PD were born earlier and with a lower birth weight. Women with incident PD during the peripartum period (INC) indicated a shorter duration of breastfeeding and women with recurrent PD during the peripartum period (REC) reported more loving/affection towards their infants and more feeding problems. Women with comorbid peripartum PD and MD (PD&MD) reported more feeding and sleeping problems, rearing with more rules/structure, and impaired bonding and the infants were born with lower birth weight as compared to the reference group.

Discussion

This prospective longitudinal study demonstrated the following: 1) Women reported heterogenous courses of PD and panic attacks were commonly observed during the early stages of pregnancy. 2) Women with PD during peripartum period presented with a worse psychosocial situation (e.g. lower social support and partnership quality) and comorbid peripartum PD and MD was the worst condition. 3) Clear behavioral differences (reactivity, BI, attachment) in infants of women with PD were not observed. 4) However, differences concerning gestational outcomes, duration of breastfeeding, maternal parenting, and bonding as well as regulatory disorders in infants were identified.

In line with other studies that reported a variable development of PD during the peripartum period (George et al., 1987; Northcott and Stein, 1994; Villeponteaux et al., 1992), heterogenous courses were also seen in this study. Most cases of PD were identified during the early stages of pregnancy and a comparatively low number of women indicated PD after delivery. A particular feature of this investigation was the recruitment of participants already during the first trimester of pregnancy, a period that might have been missed by previous studies. In line with Dannon and colleagues who argued that pregnancy represents a time of high risk for recurrence of PD (Dannon et al., 2006), this study revealed a high occurence of PD in the early stages of pregnancy. The role of estrogen induced panic attacks was recently discussed by Griez and colleagues (Griez et al., 1995) and also other hormonal changes (progesteron, cortisol) may be relevant for the occurence of panic attacks during pregnancy. Furthermore, it can be assumed that pregnancy-related physical changes, the adjustment of the cardiovascular system, and associated internal bodily sensations might serve as interoceptive stimuli that provoke panic attacks during this period (Winkel et al. 2015). However, PD during pregnancy seemed to be rather transient in most cases (see decreasing rates of PD during the study period, Martini et al. 2013, Table 2). In contrast, most women with postpartum PD (4/7) presented a persistent course and indicated PD/panic attacks at least at two of the three assessments after delivery (see Table 1). Overall, the high frequency of PD during pregnancy raises the question about the impact on the developing fetus and child.

In line with earlier findings (Dunkel Schetter and Tanner, 2012; Field et al., 2010; Ibanez et al., 2012), comorbidity of PD and MD was the worst condition regarding the psychosocial situation and adverse maternal and infant outcomes in this study. For example, regulatory disorders and impaired bonding were reported more often reported by women with comorbid peripartum PD and MD as compared to women with no anxiety and depressive disorder. One could assume that those mothers display a higher propensity to anxiety/ psychopathology, which is transmitted to their infants (i.e, intrauterine and/or by rearing) and expressed already during toddlerhood in the offspring (Martini et al. 2016). Early infant diseases and particularly a lower birth weight (immaturity) in infants of mothers with comorbid peripartum PD and MD may serve as an additional aggravating factor in this sequence (Bilgin and Wolke, 2017; Krause et al. 2017).

Moreover, women with PD during peripartum period presented with a worse psychosocial situation (e.g. lower social support and partnership quality), and comorbid peripartum PD and MD was the worst condition. This is in line with former analyses of our work group were we have show that women with comorbid anxiety and depressive disorders prior to pregnancy are at elevated risk for an unfavorable peripartum partnership development (incl. sexual problems) and deficient social support (Asselmann et al., 2016a; Asselmann et al., 2016b, Asselmann et al., 2016 c). Especially women with a

disadvanteageuos psychosocial situation might profit from targeted family interventions or rather partner involvement in psychotherapy (Marchand et al., 2007).

With regard to mother-infant-bonding and rearing, this study showed that the course characteristics of peripartum PD play a diverse role. In line with previous studies, women with postpartum PD and comorbid PD and MD reported more often an impaired bonding, more rejection/anger and rearing with more rules/structure towards their infants (as compared to women with no anxiety and depressive disorder) (Asselmann et al. 2018; Warren et al., 2003). These factors have been linked to higher levels of child anxiety and may be crucial for the familial transmission of anxiety disorders (Drake and Ginsburg, 2012; Rapee, 1997, 2012).

Surprisingly, women with PD during pregnancy and recurrent PD displayed more loving/affection and less rejection/anger towards their infants, respectively. One could speculate that those mothers try to compensate their uncertainity by building a comparatively close relationship to the baby already at this early stage. The finding that infants of mothers with postpartum PD displayed a lower birth weight and were born earlier has to be interpreted with consideration of the temporal sequence. The delivery of an immature infant might provoke uncertainity and anxiety (panic) symptoms in those mothers.

Finally, women with incident PD reported a shorter duration of breastfeeding. Almost every second women from this group reported a shorter period of breastfeeding than the recommended duration of exclusive brestfeeding of 6 months (WHO, 2018). Thus, those women who may have been overwhelmed by the onset of PD during the peripartum period might need assistance in initiating and maintaining breastfeeding.

Overall, the results of this study are in line with the results of Warren and colleagues who showed that infants of mothers with PD did not show more reactivity, BI, or insecure attachment (Warren et al., 2003), as compared to mothers with no PD. But mothers with PD display parenting behaviors (less sensitivity, more anger) that might be associated with early adversities in the infants. Indeed, infants of mothers with (recurrent and comorbid) PD showed more often regulatory problems (Warren et al., 2003), and regulatory disorders can be perceived as early indicators for later psychopathology (Hemmi et al., 2011).

Taken together, the course of maternal PD during peripartum period seems to be relevant with regard to the exposure of the infant to specific parental characteristics (e.g., parenting behaviors) that may be particularly problematic in conjunction with adverse neurodevelopmental vulnerabilities (prematurity, low birth weight) when identifying infants at risk for later psychopathology (Bilgin and Wolke, 2017).

Strenghts and limitations

To our knowledge this is the first study investigating the course of perinatal PD and associated maternal and infant outcomes, simultaneously. Strenghts of this study include the prospective multi-wave design, the consideration of psychosocial factors and the long follow-up period. Using a longitudinal design, this study sucessfully replicated the findings by Warren and colleagues on particular parenting behavior in women with PD and regulatory problems in their infants (Warren et al., 2003). However, this study is restricted by the relative small sizes of the particular groups (e.g.,

only 7 women with PD during the postpartum period) that limit the power to detect differences between the repective groups. Thus, the absence of significant differences between infants of mothers with PD as compared to infants of mothers with no anxiety and depressive disorder regarding inhibited temperament and insecure attachment should not be interpreted as indicative of negative results. Also, it cannot be ruled out, that parents in previous studies by Rosenbaum and colleagues on the association between PD and BI (Rosenbaum et al., 1988; Rosenbaum et al., 2000) had more severe PDs since participants of the present study were recruited from the community. Moreover, Rosenbaum and colleagues investigated older children and behavioral differences in infants of mothers with PD might not appear at such young ages or might only be evident in specific contexts (Warren et al., 2003). Thus, it would have been interesting to examine the differences between the groups in larger samples in more detail. Further prospective studies are warranted to investigate the role of hormonal alterations and other relevant psychosocial factors to explain why PD are twice as frequent in women as in men. It will also be important to include a comprehensive assessment on the history of pharmacological and psychotherapeutic treatment and to examine the role of the paternal figure (e.g. presence or absence of the paternal figure, anamnestic information on paternal anxiety and other mental disorders) on peripartal PD in further studies.

Conclusion

The results of this study highlight the crucial role of adequate diagnostics, psychotherapy, and psychopharmacotherapy during the peripartum period. Primary care providers should assess their patients' psychiatric history to adequately detect PD during peripartum period. A correct diagnosis of peripartum PD is complicated by the clinical overlap of panic and physiological symptoms of pregnancy (e.g., shortness of breath, feeling faint, nausea). A recent review by Marchesi and colleagues revealed that cogntive behavioral therapy and selective serotonin reuptake inhibitors (SSRIs) led to significant improvement of PD in pregnancy and the postpartum period (Marchesi et al., 2016). Guidelines for the treatment of PD and comorbid depressive disorders suggest the consideration of psychosocial and psychotherapeutic interventions, particularly CBT (with partner involvement, Marchand et al. 2007) in lieu of psychopharmacotherapy (APA, 2009 ; Bandelow et al., 2014).

Acknowledgements: Principle investigators are Jun.-Prof. Dr. Julia Martini and Prof. Dr. Hans-Ulrich Wittchen. Core staff members of the project are: Dipl.-Psych. Yvonne Hansche, Dr. Michael Höfler, Dipl.-Psych. Julia Niehoff, Dipl.-Psych. Johanna Petzoldt, Dipl.-Math. Jens Strehle, Dipl.-Psych. Gesine Wieder, Dipl.-Psych. Susanne Winkel and Dipl.-Psych. Julia Wittich.
Advisors/ consultants to the project are: Prof. Dr. Katja Beesdo-Baum, Dr. Franziska Einsle, and PD Dr. Susanne Knappe.

Funding: This work is funded by the Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Germany and supported in part by the Lundbeck Institute Skodsborg, Denmark. Parts of the field work were additionally supported by the Friends and Sponsors (Gesellschaft der Freunde und Förderer) of the Technische Universität Dresden.

References

Acs, N., Bánhidy, F., Horváth-Puhó, E., Czeizel, A.E., 2006. Maternal panic disorder and congenital abnormalities: A population-based case-control study. Birth Defects Research 76, 253-261.

Ainsworth, M.S., Blehar, M.C., Waters, E., Wall, S., 1978. Patterns of attachment: A psychological study of the strange situation. Lawrence Erlbaum Associates, Hillsdale.

APA, 2009 Practice Guidelines for the treatment of panic disorders.

Asselmann E., Hoyer., J., Wittchen, H.-U., Martini J., (2016a) Sexual problems during pregnancy and after delivery among women with and without anxiety and depressive disorders prior to pregnancy: A prospective-longitudinal study. Journal of Sexual Medicine, 13, 1 95-104.

Asselmann, E., Wittchen, H.-U., Petzoldt, J., Martini, J. (2016b) Peripartum changes in partnership quality among women with and without anxiety and depressive disorders prior to pregnancy: a prospective-longitudinal study. Archives of Womens Mental Health 19, 2, 281-290.

Asselmann, E., Wittchen, H.-U., Petzoldt, J., Martini, J. (2016c) Peripartum changes in social support among women with and without anxiety and depressive disorders prior to pregnancy: a prospective-longitudinal study. Archives of Womens Mental Health 19, 6, 943-952.

Asselmann, E., Venz, J., Wittchen, H.-U., Martini, J. (2018) Maternal anxiety and depressive disorders prior to, during and after pregnancy and infant interaction behaviors during the Face-to-Face Still Face Paradigm at 4 months postpartum: A prospective-longitudinal study. Early Human Development, 122, 45-53.

Bakeman, R., Quera, V., McArthur, D., Robinson, B.F., 1997. Detecting sequential patterns and determining their reliability with fallible observers. Psychological Methods 2, 357-370.

Bandelow, B., Sojka, F., Broocks, A., Hajak, G., Bleich, S., Ruther, E., 2006. Panic disorder during pregnancy and postpartum period. European Psychiatry 21, 495-500.

Bandelow, B., Wiltink, J., Alpers, G.W., Benecke, C., Deckert, J., Eckhardt-Henn, A., Ehrig, C., Engel, E., Falkai, P., Geiser, F., Gerlach, A.L., Harfst, T., Hau, S., Joraschky, P., Kellner, M., Köllner, V., Kopp, I., Langs, G., Lichte, T., Liebeck, H., Matzat, J., Reitt, M., Rüddel, H.P., Rudolf, S., Schick, G., Schweiger, U., Simon, R., Springer, A., Staats, H., Ströhle, A., Ströhm, W.W., B., Watzke, B., Wedekind, D., Zottl, C., Zwanzger, P., Beutel, M.E., 2014. Deutsche S3-Leitlinie Behandlung von Angststörungen.

Banhidy, F., Acs, N., Puho, E., Czeizel, A.E., 2006. Association between maternal panic disorders and pregnancy complications and delivery outcomes. European Journal of Obstetrics & Gynecology and Reproductive Biology 124, 47-52.

Biederman, J., Rosenbaum, J.F., Bolducmurphy, E.A., Faraone, S.V., Chaloff, J., Hirshfeld, D.R., Kagan, J., 1993. A 3-year-follow-up of children with and without Behavioral-Inhibition. Journal of the American Academy of Child and Adolsecent Psychiatry 32, 814-821.

Bilgin, A., Wolke, D., 2017. Development of comorbid crying, sleeping, feeding problems across infancy: Neurodevelopmental vulnerability and parenting. Early Human Development 109, 37-43.

Brockington, I.F., Fraser, C., Wilson, D., 2006. The postpartum bonding questionnaire: A validation. Archives of Womens Mental Health 9, 233-242.

Chen, Y.H., Lin, H.C., Lee, H.C., 2010. Pregnancy outcomes among women with panic disorder - Do panic attacks during pregnancy matter? Journal of Affective Disorders 120, 258-262.

Cohen, L.S., Rosenbaum, J.F., Heller, V.L., 1989. Panic attack-associated placental abruption: A case report. Journal of Clinical Psychiatry 50, 266-267.

Cohen, L.S., Sichel, D.A., Dimmock, J.A., Rosenbaum, J.F., 1994. Impact of pregnancy on panic disorder - A case series. Journal of Clinical Psychiatry 55, 284-288.

Cohen, L.S., Sichel, D.A., Faraone, S.V., Robertson, L.M., Dimmock, J.A., Rosenbaum, J.F., 1996. Course of panic disorder during pregnancy and the puerperium: A preliminary study. Biological Psychiatry 39, 950-954

Colonnesi, C., Draijer, E.M., Jan, J.M., Stams, G., Van der Bruggen, C.O., Bögels, S.M., Noom, M.J., 2011. The relation between insecure attachment and child anxiety: A meta-analytic review. Journal of Clinical Child and Adolescent Psychology 40, 630-645.

Dannon, P.N., Iancu, I., Lowengrub, K., Grunhaus, L., Kotler, M., 2006. Recurrence of panic disorder during pregnancy: A 7-year naturalistic follow-up study. Clinical Neuropharmacology 29, 132-137.

de Lijster, J.M., Dierckx, B., Utens, E.M.W.J., Verhulst, F.C., Zieldorff, C., Dieleman, G.C., Legerstee, J.S., 2017. The age of onset of anxiety disorders: A meta-analysis. The Canadian Journal of Psychiatry 62, 237-246.

Drake, K.L., Ginsburg, G.S., 2012. Family factors in the development, treatment, and prevention of childhood anxiety disorders. Clinical Child and Family Psychology Review 15, 144-162.

Dunkel Schetter, C., Tanner, L., 2012. Anxiety, depression and stress in pregnancy: Implications for mothers, children, research, and practice. Current Opinion in Psychiatry 25, 141-148.

Field, T., Diego, M., Hernandez-Reif, M., Figueiredo, B., Deeds, O., Ascencio, A., Schanberg, S., Kuhn, C., 2010. Comorbid depression and anxiety effects on pregnancy and neonatal outcome. Infant Behavior & Development 33, 23-29.

Fydrich, T., Sommer, G., Tydecks, S., Brähler, E., 2009. Fragebogen zur sozialen Unterstützung (F-SozU): Normierung der Kurzform (K-14) Social Support Questionnaire (F-SozU): Standardization of short form (K-14). Zeitschrift für Medizinische Psychologie 18, 43–48.

Fox, N.A., Snidman, N., Haas, S.A., Degnan, K.A., Kagan, J., 2015. The relation between reactivity at 4 months and Behavioral Inhibition in the second year: Replication across three independent samples. Infancy 20, 98-114.

George, D.T., Ladenheim, J.A., Nutt, D.J., 1987. Effect of pregnancy on panic attacks. American Journal of Psychiatry 144, 1078-1079.

Griez, E.J.L., Hauzer, R., Meijer, J., 1995. Pregnancy and estrogen-induced panic. American Journal of Psychiatry 152, 1688-1688.

Hahlweg K (1996) Fragebogen zur Partnerschaftsdiagnostik. Hogrefe, Goettingen

Hemmi, M.H., Wolke, D., Schneider, S., 2011. Associations between problems with crying, sleeping and/or feeding in infancy and long-term behavioural outcomes in childhood: A meta-analysis. Archives of Diseases in Childhood 96, 622-629.

Hertzberg, T., Wahlbeck, K., 1999. The impact of pregnancy and puerperium on panic disorder: A review. Journal of Psychosomatic Obstetrics and Gynecology 20, 59-64.

Ibanez, G., Charles, M.A., Forhan, A., Magnin, G., Thiebaugeorges, O., Kaminski, M., Saurel-Cubizolles, M.J., 2012. Depression and anxiety in women during pregnancy and neonatal outcome: Data from the EDEN mother-child cohort. Early Human Development 88, 643-649.

Jacobi, F., Hofler, M., Siegert, J., Mack, S., Gerschler, A., Scholl, L., Busch, M.A., Hapke, U., Maske, U., Seiffert, I., Gaebel, W., Maier, W., Wagner, M., Zielasek, J., Wittchen, H.-U., 2014. Twelve-month prevalence, comorbidity and correlates of mental disorders in Germany: The Mental Health Module of the German Health Interview and Examination Survey for Adults (DEGS1-MH). International Journal of Methods in Psychiatric Research 23, 304-319.

Jacobi, F., Höfler, M., Strehle, J., Mack, S., Gerschler, A., Scholl, L., Busch, M.A., Hapke, U., Maske, U., Seiffert, I., Gaebel, W., Maier, W., Wagner, M., Zielasek, J., Wittchen, H.-U., 2015. Twelve-months prevalence of mental disorders in the German Health Interview and Examination Survey for Adults - Mental Health Module (DEGS1-MH): A methodological addendum and correction. International Journal of Methods in Psychiatric Research 24, 305-313.

Kagan, J., 1994. Galen's prophecy: Temperament in human nature. Basic Books, New York.

Kagan, J., Snidman, N., 1991. Infant predictors of inhibited and unihibited profiles. Psychological Science 2, 40-44.

Kagan, J., Snidman, N., Arcus, D., 1998. Childhood derivatives of high and low reactivity in infancy. Child Development 69, 1483-1493.

Kessler, R.C., Ustün, T.B., 2004. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). International Journal of Methods in Psychiatric Research 13, 93-121.

Klein, D.F., Skrobala, A.M., Garfmkel, R.S., 1994. Preliminary look at the effects of pregnancy on the course of panic disorder. Anxiety 1, 227-232.

Kraft, A., Knappe, S., Petrowski, K., Petzoldt, J., Martini, J., 2017. Maternal bonding and infant attachment in women with and without social phobia. Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie 45, 49-57.

Krause, L., Einsle, F., Petzoldt, J., Wittchen, H.-U., Martini, J. (2017) The role of maternal anxiety and depressive disorders prior to and during pregnancy and perinatal psychopathological symptoms for early infant diseases and drug administration. Early Human Development, 109, 7-14.

Main, M., Solomon, J., 1990. Procedures for identifying infants as disorganized/ disoriented during the Ainsworth Strange Situation., In: Greenberg, M.T., Cicchetti, D., Cummings, M. (Eds.), Attachment in the preschool years: Theory, research, and intervention. University of Chicago Press, Chicago, pp. 121–160.

Manassis, K., Bradley, S., Goldberg, S., Hood, J., Swinson, R.P., 1995. Behavioural inhibition, attachment and anxiety in children of mothers with anxiety disorders. Canadian Journal of Psychiatry 40, 87-92.

Marchand, A., Todorov, C., Borgeat, F., Pelland, M. E. (2007) Effectiveness of a brief cognitive behavioural therapy for panic disorder with agoraphobia and the impact of partner involvement. Behavioral and Cognitive Psychotherapy, 35, 5, 613-629.

Marchesi, C., Ampollini, P., Paraggio, C., Giaracuni, G., Ossola, P., De Panfilis, C., Tonna, M., Viviani, D., 2014. Risk factors for panic disorder in pregnancy: A cohort study. Journal of Affective Disorders 156, 134-138.

Marchesi, C., Ossola, P., Amerio, A., Daniel, B.D., Tonna, M., De Panfilis, C., 2016. Clinical management of perinatal anxiety disorders: A systematic review. Journal of Affective Disorders 190, 543-550.

Martini, J., Asselmann, E., Einsle, F., Strehle, J., Wittchen, H.-U. (2016) DisordersA prospective-longitudinal study on the association of anxietydisorders prior to pregnancy and pregnancy- and child-related fears. Journal of Anxiety Disorders, 40, 58-66.

Martini, J., Petzoldt, J., Einsle, F., Beesdo-Baum, K., Hofler, M., Wittchen, H.-U., 2015. Risk factors and course patterns of anxiety and depressive disorders during pregnancy and after delivery: A prospective-longitudinal study. Journal of Affective Disorders 175, 385-395.

Martini, J., Petzoldt, J., Knappe, S., Garthus-Niegel, S., Asselmann, E., Wittchen, H.-U., 2017. Infant, maternal, and familial predictors and correlates of regulatory problems in early infancy: The differential role of infant temperament and maternal anxiety and depression. Early Human Development 115, 23-31.

Martini, J., Wittchen, H.-U., Soares, C.N., Rieder, A., Steiner, M., 2009. New women-specific diagnostic modules: the Composite International Diagnostic Interview for Women (CIDI-VENUS). Archives of Womens Mental Health 12, 281-289.

Martini, J., Wittich, J., Petzoldt, J., Winkel, S., Einsle, F., Siegert, J., Hofler, M., Beesdo-Baum, K., Wittchen, H.-U., 2013. Maternal anxiety disorders prior to conception, psychopathology during pregnancy and early infants' development: A prospective-longitudinal study. Archives of Womens Mental Health 16, 549-560.

Martini, J., Wittich, J., Taubert, L., Strobel, A., 2016. Fragebogen zu Erziehungseinstellungen im Säuglingsalter und im Kleinkindalter [Parenting Attitudes towards Infants and Toddlers,PAIT], In: Mall, V., Freiedmann, A. (Eds.), Frühe Hilfen in der Pädiatrie: Bedarf erkennen - intervenieren - vernetzen. Springer, Berlin, pp. 268-273.

Murray, L., Fiori-Cowley, A., Hooper, R., Cooper, P., 1996. The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. Child Development 67, 2512-2526.

Northcott, C.J., Stein, M.B., 1994. Panic disorder in pregnancy. 55, 539-542.

Petermann, F., Renziehausen, A., 2005. Neuropsychologisches Entwicklungsscreening (NES). Huber, Bern.

Petzoldt, J., Wittchen, H.-U., Einsle, F., Martini, J., 2016. Maternal anxiety versus depressive disorders: Specific relations to infants' crying, feeding and sleeping problems. Child Care Health and Development 42, 231-245.

Popp, L., Fuths, S., Seehagen, S., Bolten, M., Gross-Hemmi, M., Wolke, D., Schneider, S., 2016. Inter-rater reliability and acceptance of the structured diagnostic interview for regulatory problems in infancy. Child and Adolescent Psychiatry and Mental Health 10.

Rapee, R.M., 1997. Potential role of childrearing practices in the development of anxiety and depression. Clinical Psychology Review 17, 47-67.
Rapee, R.M., 2012. Family factors in the development and management of anxiety disorders. Clinical Child and Family Psychology Review 15, 69-80.
Reck, C., Klier, C.M., Pabst, K., Stehle, E., Steffenelli, U., Struben, K., Backenstrass, M., 2006. The German version of the Postpartum Bonding Instrument: Psychometric properties and association with postpartum depression. Archives of Womens Mental Health 9, 265-271.
Reed, V., Gander, F., Pfister, H., Steiger, A., Sonntag, H., Trenkwalder, C., Sonntag, A., Hundt, W., Wittchen, H.-U., 1998. To what degree does the Composite International Diagnostic Interview (CIDI) correctly identify DSM-IV disorders? Testing validity issues in a clinical sample. International Journal of Methods in Psychiatric Research 7, 142-155.
Rosenbaum, J.F., Biederman, J., Gersten, M., Hirshfeld, D.R., Meminger, S.R., Herman, J.B., Kagan, J., Rossier, J., Rigozzi, C., Charvoz, L., Bodenmann, G. (2006) Marital satisfaction: Psychometric properties of the PFB and comparison with the DAS. Swiss Journal of Psychology 65:55–63
Reznick, J.S., Snidman, N., 1988. Behavioral inhibition in children of parents with panic disorder and agoraphobia. A controlled study. Archives of General Psychiatry 45, 463-470.
Rosenbaum, J.F., Biederman, J., Hirshfeld-Becker, D.R., Kagan, J., Snidman, N., Friedman, D., Nineberg, A., Gallery, D.J., Faraone, S.V., 2000. A controlled study of behavioral inhibition in children of parents with panic disorder and depression. American Journal of Psychiatry 157, 2002-2010.
Rosenbaum, J.F., Biederman, J., Hirshfeld, D.R., Bolduc, E.A., Chaloff, J., 1991a. Behavioral-Inhibition in children - A possbile precursor to panic disorders or social phobia. Journal of Clinical Psychiatry 52, 5-9.
Rosenbaum, J.F., Biederman, J., Hirshfeld, D.R., Bolduc, E.A., Faraone, S.V., Kagan, J., Snidman, N., Reznick, J.S., 1991b. Further evidence of an association between behavioral inhibition and anxiety disorders: Results from a family study of children from a non-clinical sample. Journal of Psychiatric Research 25, 49-65.
Schneider, S., Wolke, D., 2007. Diagnostisches Interview zur Erfassung von Regulationsstörungen im Säuglings-und Kleinkindalter (Baby-DIPS). Universität Basel, Basel.
Sholomskas, D.E., Wickamaratne, P.J., Dogolo, L., Obrien, D.W., Leaf, P.J., Woods, S.W., 1993. Postpartum onset of panic disorder - A coincidental event. Journal of Clinical Psychiatry 54, 476-480.
StataCorp, 2012. Stata Statistical Software: release 12.1.College Station, TX: Stata Corporation.
Sutter-Dallay, A.L., Giaconne-Marcesche, V., Glatigny-Dallay, E., Verdoux, H., 2004. Women with anxiety disorders during pregnancy are at increased risk of intense postnatal depressive symptoms: A prospective survey of the MATQUID cohort. European Psychiatry 19, 459-463.
Teixeira, J.M., Fisk, N.M., Glover, V., 1999. Association between maternal anxiety in pregnancy and increased uterine artery resistance index: Cohort based study. British Medical Journal 318, 153-157.
Turner, S., Beidel, D.C., Wolff, P.L., 1996. Is Behavioral Inhibition related to the anxiety disorders. Clinical Psychology Review 16, 157-172.
van Brakel, A.M.L., Muris, P., Bögels, S.M., Thomassen, C., 2006. A multifactorial model for the etiology of anxiety in nonclinical adolescents: Main and interactive effects of Behavioral Inhibition, attachment and parental rearing. Journal of Child and Family Studies 15, 5, 568-578.
Villeponteaux, V.A., Lydiard, R.B., Laraia, M.T., Stuart, G.W., Ballender, J.C., 1992. The effects of pregnancy on preexisting panic disorder. Journal of Clinical Psychiatry 53, 201-203.
Warren, S.L., Gunnar, M.R., Kagan, J., Anders, T.F., Simmens, S.J., Rones, M., Wease, S., Aron, E., Dahl, R.E., Sroufe, L.A., 2003. Maternal panic disorder: Infant temperament, neurophysiology, and parenting behaviors. Journal of the American Academy of Child and Adolsecent Psychiatry 42, 814-825.
Warren, S.L., Racu, C., Gregg, V., Simmens, S.J., 2006. Maternal panic disorder: Infant prematurity and low birth weight. Journal of Anxiety Disorders 20, 342-352.
WHO, 2018. WHO fact sheet: Infant and young child feeding.
Wisner, K.L., Peindl, K.S., Hanusa, B.H., 1996. Effects of childbearing on the natural history of panic disorder with comorbid mood disorder. Journal of Affective Disorders 41, 173-180.

Winkel, S., Einsle, F., Pieper, L., Höfler, M., Wittchen, H.-U. Martini, J. (2015) Associations of anxiety disorders, depressive disorders and body weight with hypertension during pregnancy. Archives of Womens Mental Health, 18, 3, 473-483.

Wittchen, H.-U., Lachner, G., Wunderlich, U., Pfister, H., 1998. Test-retest reliability of the computerized DSM-IV version of the Munich-Composite International Diagnostic Interview (M-CIDI). Social Psychiatry and Psychiatric Epidemiology 33, 568-578.

Yonkers, K.A., Gilstad-Hayden, K., Forray, A., Lipkind, H.S., 2017. Association of panic disorder, generalized anxiety disorder, and benzodiazepine treatment during pregnancy with risk of adverse birth outcomes. JAMA Psychiatry 74, 1145-1152.

Appendix A. Supplementary material

Research data for this article

Due to the sensitive nature of the questions asked in this study and the personal observations with the mothers and their infants, survey respondents were assured raw data would remain confidential and would not be shared.

Table 1: Individual courses of Panic Disorder (PD) and Major Depression (MD) during the peripartum period in women with incident (N=11) and recurrent PD (N=14) along with gestational and offspring outcomes

AoO	History of PD (w/ wo Agoraphobia)	History of anxiety or depression diagnoses		Course of PA, PD, MD during pregnancy (T1-T3)	and postpartum (T5-T7) period	Gestational age (weeks)
INC: Incident PD in peripartum period (N=11)						
26		F40.1, F41.1, F43.1	F32	T1:MD, T2:PD, T3: PD	T7:PD,MD	39
23				T2:PD		40
31		F40.1		T1:PD, T2:PD		40
28		F40.2, F41.1	F33	T2:PD		38
26		F40.2, F43.1	F33	T2:PD		40
32		F40.2, F41.1, F43.1	F33	T1:PA, T2:PD		41
37				T2:PD		39
38			F33	T2:PD	T7:PA	38
26			F33		T7:PD, MD	36
26		F41.1, F43.1		T3:PD	T6:MD, T7:MD	37
32		F40.2			T5:PD,MD	41
REC: Recurrent PD in peripartum period (N=14)						
25	F40.01 (22)	F40.1, F40.2	F32	T2:PD		39
28	F40.01 (14)	F41.1, F43.1	F33	T2:PD,MD	T5: MD,T7:MD	41
31	F41.0 (3)	F40.2		T1:PD		40
34	F40.01 (29)		F32	T2:PD	T5:PA, T7: PD	38
28	F41.0 (23)		F32	T2:PD		39
30	F40.01 (20)		F32	T2:PD		no
25	F40.01 (20)			T2:PD		40
19	F40.01 (3)		F33	T1:PD, T2:PA		41
30	F40.01 (21)	F40.1, F40.2, F41.1	F33	T1:PD, T2:MD		40
21	F40.01 (21)	F40.1, F40.2	F33	T1:PD,MD, T2:PA, T3: MD	T5: PD, MD, T6: MD, T7: PA,MD	39
30	F41.0 (27)	F40.1, F40.2	F34.1	T1:PD, T2:PA,	T7:MD	40
29	F40.01 (17)	F40.2, F41.1, F43.1	F33	T1:PD,MD, T2:PA, T3:PA	T5:PA, T7: PD	39
31	F40.01 (17)	F43.1		T2:PD		38
23	F40.01 (22)	F40.1, F40.2, F41.1, F42.8, F43.1	F33	T2:PA, T3:PA,MD	T5:PD,MD, T7:PA	37

Note: PD: Panic Disorder, PA: Panic Attacks, MD: Major Depression Episode, AoO: Age of Onset, T1: first trimester of pregnancy, T2: second trimester of pregnancy, T3: third trimester of pregnancy, T5: 2 months postpartum, T6: 2-4 months postpartum, T7: 4-16 months postpartum, no: no information available, CRY: excessive infant crying, FEED: feeding disorder, SLEEP: sleeping disorder; light-grey background: PD during pregnancy (T1-T3, N=22); dark-grey background: postpartum (T5-T7, N=7).

Table 2: Sociodemographic and psychosocial characteristics of women with incident, recurrent, pregnancy, and postpartum Panic Disorder (PD) and comorbid peripartum PD and Major Depression (MD)

	REF: no A or D until T7 (N=92)	**PD until T7 (N=34)**	**INC (N=11)**	**REC (N=14)**	**PREG (N=22)**	**POST (N=7)**
Age (M, SD)	27.7 (4.4)	28.4 (4.3)	29.6 (4.9)	27.4 (4.3)	28.5 (4.6)	27.3 (4.7)
Educational status						
lower education (≤10 years)	23 (25.0)	14 (41.2)	5 (45.5)	7 (50.0)	10 (45.5)	4 (57.1)
higher education (>10 years)	69 (75.0)	20 (58.8)	6 (54.6)	7 (50.0)	12 (54.6)	3 (42.9)
Marital status						
not married	60 (65.2)	20 (58.8)	7 (63.6)	10 (71.4)	14 (63.6)	6 (85.7)
married	32 (34.8)	14 (41.2)	4 (36.4)	4 (28.6)	8 (36.4)	1 (14.3)
Cohabitation						
don't live together	6 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
live together	86 (93.5)	34 (100.0)	11 (100.0)	14 (100.0)	22 (100.0)	7 (100.0)
Partnership quality during pregnancy (PFB, T2) (M, SD)	73.4 (10.2)	72.1 (12.3)	73.0 (6.6)	69.6 (15.3)	71.6 (12.9)	74.3 (7.4)
Partnership quality during postpartum period (PFB, T6) (M, SD)	69.4 (11.3)	67.3 (14.6)	69.1 (8.5)	61.1 (15.5)	64.6 (14.3)	65.2 (8.5)
Social support during pregnancy (F-Sozu, T2) (M, SD)	4.5 (0.4)	4.3 (0.6)	4.2 (0.5)	4.3 (0.6)	4.3 (0.5)	3.8 (0.5)
Social support during postpartum period (F-Sozu, T6) (M, SD)	4.5 (0.4)	4.1 (0.8)	4.0 (0.7)	4.0 (1.0)	4.0 (0.9)	3.7 (1.1)

Note: REF: no anxiety and depressive disorder until T7, PD until T7: any panic disorder during the peripartum period, INC: incident panic disorder in the peripartum period, REC: recurrent panic disorder in the peripartum period, PREG: panic disorder in pregnancy, POST: panic disorder in the postpartum period, PD&MD: comorbid panic disorder and major depression in the peripartum period, PFB: Partnership Questionnaire, F-Sozu: Social Support Questionnaire (F-SozU), N: number, % percentage, M: mean, SD: standard deviation, Chi^2: Chi-sqaure, t: t-test, p: p-value, * signifi

Table 3: Gynecological characteristics and pregnancy outcomes in women with incident, recurrent, pregnancy, and postpartum Panic Disorder (PD) and comorbid peripartum PD and Major Depression (MD)

	REF: no A or D until T7 (N=92)	PD until T7 (N=34)	INC (N=11)	REC (N=14)	PREG (N=22)	POST (N=7)	PD&MD (N=10)	Group differences
Parity								
primiparity	56 (60.9)	20 (58.8)	6 (54.6)	10 (71.4)	13 (59.1)	4 (57.1)	6 (60.0)	
multiparity	36 (39.1)	14 (41.2)	5 (45.5)	4 (28.6)	9 (40.9)	3 (42.9)	4 (40.0)	
Gestational age (M, SD)	39.5 (1.5)	39.4 (1.3)	39.0 (1.6)	39.3 (1.2)	39.3	38.4 (1.6)	38.9 (1.7)	POST vs REF: t=1.803, p=0.037
Preterm delivery (<37+0)	5 (6.0)	1 (3.0)	1 (9.1)	0 (0.0)	0 (0.0)	1 (14.3)	1 (10.0)	
Birth weight (M, SD)	3381.2 (449.1)	3381.5 (467.3)	3213.2 (568.3)	3361.5 (397.9)	3361.7 (472.9)	3011.4 (315.9	3118.0 (325.5)	POST vs REF: t=2.129, p=0.018 PD&MD vs. REF: t=1.793, p=0.038
Mode of delivery								
Spontaneous delivery	68 (81.9)	23 (69.7)	8 (72.7)	11 (84.6)	17 (80.9)	6 (85.7)	19 (79.2)	
C-section	10 (12.1)	8 (24.2)	3 (27.3)	1 (7.7)	3 (14.3)	1 (14.3)	4 (16.7)	
Operative vaginal delivery	5 (6.0)	2 (6.1)	0 (0.0)	1 (7.7)	1 (4.8)	0 (0.0)	1 (4.2)	
Duration of breastfeeding (in months) (M, SD)	10.0 (4.4)	9.9 (4.7)	7.0 (5.3)	10.8 (4.3)	10.2 (4.6)	8.3 (5.7)	8.2 (5.0)	INZ vs REF: t=1.811, p=0.037
Excessive crying (N/%)	6/83 (7.2)	4/33 (12.1)	2/11 (18.2)	1/13 (7.7)	2/21 (9.5)	1/7 (14.3)	2/10 (2.0)	-
Feeding problems (N/%)	21/83 (25.3)	16/33 (48.5)	4/11 (36.4)	7/13 (53.9)	9/21 (42.9)	4/7 (57.1)	7/10 (70.0)	REC vs REF: Chi^2=4.433, p=0.035 PD&MD vs REF: Chi^2=8.474, p=0.004
Sleeping problems (N/%)	9/83 (10.8)	8/33 (24.2)	2/11 (18.2)	3/13 (23.1)	5/21 (23.8)	0/7 (0)	4/10 (40.0)	PD until T7 vs. REF: Chi^2=5.006, p=0.025 PD&MD vs REF: Chi^2=6.310, p=0.012
Maternal loving/affection (PAIT, T6) (M, SD)	9.1 (2.1)	9.5 (2.2)	8.3 (3.0)	10.2 (1.3)	9.9 (1.7)	8.3 (3.4)	8.5 (3.2)	REC vs REF: t=1.69, p=0.046
Maternal loving/affection (PAIT, T7) (M, SD)	8.9 (1.8)	9.6 (1.8)	9.4 (2.6)	9.7 (1.6)	10.0 (1.5)	8.8 (2.9)	8.4 (2.6)	PREG vs REF: t=2.18, p=0.016
Maternal rules/structure (PAIT, T7) (M, SD)	4.7 (1.5)	4.8 (1.6)	5.1 (2.0)	5.1 (1.5)	4.7 (1.5)	6.5 (1.5)	6.1 (1.6)	POST vs REF: t=2.93, p=0.002 PD&MD vs REF: t=2.519, p=0.007
Neuropsychological development (T6) (M, SD)	11.6 (0.8)	11.5 (1.0)	11.1 (1.7)	11.8 (0.5)	11.7 (0.59)	11.1 (1.9)	11.3 (1.7)	-
Neuropsychological development (T7) (M, SD)	13.3 (1.8)	13.3 (1.8)	13.25 (1.3)	13.3 (2.3)	13.2 (2.0)	14.0 (1.4)	13.0 (2.5)	-
Highly reactive (T6) (N/%)	9/76 (11.8)	4/28 (14.3)	2/9 (22.2)	1/12 (14.3)	3/18 (16.7)	1/7 (14.3)	1/9 (11.1)	-
Lowly reactive (T6) (N/%)	36/76 (47.4)	14/28 (50.0)	3/9 (33.3)	7/12 (57.3)	8/18 (44.4)	4/7 (57.1)	5/9 (55.6)	-
Behavioral inhibition (T7) (N/%)	34/77 (44.2)	12/29 (41.4)	4/8 (50.0)	4/13 (30.8)	6/18 (33.3)	2/7 (28.6)	5/10 (50.0)	-
Maternal impaired bonding (PBQ, T5) N/%)	4.5 (4.0)	5.0 (5.6)	5.3 (7.0)	4.3 (4.6)	3.3 (3.8)	9.1 (8.6)	8.11 (7.8)	POST vs REF t=2.652, p=0.0047 PD&MD vs REF: t=2.318, p=0.011
Maternal rejection/anger (PBQ, T5) (N/%)	1.5 (2.0)	1.6 (2.8)	2.1 (3.7)	0.7 (1.4)	0.65 (13)	3.1 (4.3)	2.6 (3.9)	PREG vs REF: t=1.780, p=0.039 POST vs REF: t=1.928, p=0.029
Bonding: secure (N/%)	49/75 (65.3)	16/28 (57.1)	3/8 (37.5)	9/12 (75.0)	12/17 (70.6)	3/7 (42.9)	4/10 (40.0)	-

Note: REF: no anxiety and depressive disorder until T7, PD until T7: any panic disorder during the peripartum period, INC: incident panic disorder in the peripartum period, REC: recurrent panic disorder in the peripartum period, PREG: panic disorder in pregnancy, POST: panic disorder in the postpartum period, PD&MD: comorbid panic disorder and major depression in the peripartum period, PAIT: Parenting Attitudes towards Infants and Toddlers , PBQ: Postpartum Bonding Questionnaire, N: number, % percentage, M: mean, SD: standard deviation, Chi^2: Chi-sqaure, t: t-test, p: p-value