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THESIS

Panic Disorder during pregnancy: Prevalence, Clinical Features and Predictive Role on Post-Partum Depression.

Results of PND-ReScu Study.

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ABSTRACT

Background:

Anxiety symptoms are frequently reported by pregnant women and are often considered as part of the normal psychic experiences of pregnancy, especially if they are focused on the baby's health or on maternal competencies. Among all anxiety disorders, Panic Disorder (PD) needs to be carefully noted. It has been estimated that 3% to 12% of women experience symptoms related to PD at some time during their childbearing years, including during pregnancy and the postpartum period (Wenzel et al., 2001; Smith et al., 2004).

Although panic symptoms during the perinatal period are typical symptoms reported in the general population, they are often interpreted in the context of the perinatal state and the concerns about the pregnancy and fetus may represent the predominant features (Ross et al., 2006). As others have noted (Austin, 2003; Austin et al; 2005; Glover and O'Connor, 2002), it may be just as important to focus on the detection and treatment of perinatal anxiety, given its significant association with the development of subsequent Post-partum Depression (PPD). Although the role of anxiety disorders on the development of PPD has already been studied in literature, that of individual anxiety disorders has not received specific attention.

Aims:

The aims of this thesis were: 1) to describe prevalence and clinical features of PD of a large non-clinical sample of women recruited at the 3rd month of pregnancy and to compare them with clinical features in a group of non-pregnant women of equivalent age 2) to investigate the role of PD (as family history, previous diagnosis or the occurrence of PD during pregnancy) on the development of PPD 3) to assess the specific role of PD in

predicting probable depression (EPDS>12), minor or major depression (mMD) and false positives (EPDS>12 without mMD) at first month/year after delivery, compared to other anxiety diagnoses.

Methods:

Participants: for the first aim, two samples of women with a diagnosis of PD were recruited; the first sample was composed of 43 pregnant women diagnosed with PD at 3th month of pregnancy, as part of a larger sample (N=1066) of a study conducted at Pisa by the Perinatal Depression-Research and Screening Unit (PND-ReScU). The second, the control group, was composed of 57 non-pregnant female outpatients diagnosed with PD, who presented to the psychiatric outpatient clinics of the same research center. For the second aim, the sample was composed of 600 pregnant women, as part of a larger sample (N=1066) of a study conducted at Pisa by the Perinatal Depression-Research and Screening Unit (PND-ReScU), who completed the assessment at 6th month after delivery; for the third aim, the sample was composed of 500 pregnant women who completed the assessment at the 12^{th} month after delivery.

Instruments:

A diagnosis of Axis I Panic Disorder was carried out with a Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1995) in the group of pregnant women, and with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) in the control group of non-gravid women respectively. The clinical features of Panic Disorder were also evaluated with Panic-Agoraphobic Spectrum–Self-Report (PAS-SR) administered respectively at 6^{th} month post-partum in the sample of pregnant women and at baseline in the control group. Symptoms of maternal depression were assessed using the 10-item Edinburgh Postnatal Depression Scale (Cox et al., 1987). The Post-

partum Depression Predictors Inventory-Revised (PDPI-R) (Beck, 2002) was used to identify the risk factors for PPD. The family history of psychiatric disorders was assessed using the Family History Screen (FHS) (Weissman et al., 2000).

Statistical analysis:

The Chi-square test was used to compare percentages and independent t-tests to compare mean scores. To assess the association between symptoms in the two groups Odds Ratios (Ors) with 95% confidence intervals were performed. Stepwise logistic regression models were performed to determine which panic symptoms were associated with PD in pregnancy. The alpha level was set at 0.05. Logistic regression models were used to estimate the association between PD, family history for PD and PPD. In order to establish the relationship between a specific anxiety disorder and the occurrence of probable depression, mMD and false positives in the postpartum, logistic regression models were performed. Odds Ratios and 95% of confidence intervals were reported. In order to clarify the magnitude of effect size we rescaled the OR in Cohen's d using the γ coefficient (γ= (OR-1)/(OR+1)) (Kraemer and Kupfer, 2006). An effect size of 0.2, 0.5, and 0.8 are "small," "medium," and "large" (Cohen, 1988). Analyses were conducted using SPSS, version 15.

Results:

First research: One hundred and eighty four (17.3%) women had lifetime PD (life-PD), of whom 144 (13.3%) had a previous history of PD and 43 (4%) had current PD (curr-PD). Of the 43 women with current PD (28 (65.1%) with agoraphobia and 15 (34.9%) without agoraphobia), 5 (11.0%) had their first episode during the index pregnancy. As regards comorbidity, pregnant women with curr-PD (25.6%) were about six-fold more likely to have a major depressive episode (OR=5.844; 95% CI:1.513-22.563) than non-gravid

women (5.6%). In the group of pregnant women, the symptoms most represented were: palpitations (90.7%), and shortness of breath (88.4%), choking (79.1%), sweating (74.4%). In the control group of non-pregnant women the symptoms most represented were: palpitations (87.7%), shortness of breath (63.2%), trembling (59.6%), sweating (57.9%). In a stepwise logistic regression a positive association was found between the presence of "*fear of going crazy*" (OR=4.020; 95% CI: 1.188-13.602), "*shortness of breath*" (OR= 9.970; 95% CI: 3.782-26.282) and panic disorder at the 3rd month of pregnancy. The presence of Agoraphobia was significantly higher in gravid women (OR 3.630; 95% CI: 1.557-8.462) than in non-gravid women. Pregnant women reported higher mean scores in the following manic factors of mood spectrum: psychomotor activation (3.923 *vs*. 2.563; t=2.705; p=0.008), creativity (3.461 *vs*. 1.618; t= 3.752; p= 0.000) euphoria (2.128 *vs*. 0.963; t=4.215; p<0.001). No significant differences were found in depressive factors scores in the two groups.

Second research: PD during pregnancy (RR=4.25; 95% CI: 1.48–12.19), a history of PD (RR 2.47; 95% CI: 1.11–5.49) and family history for PD (RR=2.1; 95% CI: 1.06–4.4) predicted PPD after adjusting for lifetime depression and risk factors for PPD.

Third research: After adjustment for risk factors assessed with PDPI-R (RR=3.83; 95% CI: 1.84-7.97), a significant association was found between panic disorder (Adjusted RR=5.27; 95% CI: 2.0-13.91) and social phobia (Adjusted RR=3.80; 95% CI: 1.34-10.46) at the 3rd month of pregnancy and the likelihood of having probable depression at the first month postpartum. After the adjustment for risk factors assessed with PDPI-R (RR=2.74; 95% CI: 1.06-7.07), the predictive role of panic disorder (RR=7.23; 95% CI: 2.31-22.66) and social phobia (RR=6.63; 95% CI: 2.11-20.85) at the 3rd month of pregnancy remained significant in predicting 1st month postpartum mMD. With regard to the one-year period

prevalence, our results show that after adjustment for the established risk factors assessed with PDPI-R (RR=4.66; 95% CI: 2.41-9.02), the only anxiety disorder associated with postpartum depression was panic disorder (Adjusted RR=3.10; 95% CI: 1.16-8.22). OCD (Adjusted RR=8.66; 95% CI: 1.59-47.03) was associated with false positive cases assessed at the 1st month postpartum, while no anxiety disorders were further associated with false positives assessed during the 1st year after childbirth.

Limitations:

First, the response rate is moderately low (49.9%), however it is comparable to that of similar studies that used self-report and structured clinical interviews, in which the observation period spanned from pregnancy to post-partum (Grant et al., 2008; Kitamura et al., 2006). The socio-demographic characteristics of women who refused to participate in the study are not available because data collection was possible only after the informed consent form was signed, as prescribed by the Italian law on privacy; thus we were unable to ascertain if non-responders were mostly of lower socio-economic class and had lower levels of education. Finally demographic characteristics of the two sample (pregnant women and control group) were not homogeneous: pregnant women had higher education levels compared to the control group and were more frequently married or living with the partner.

Conclusions:

Symptoms of panic during pregnancy are typical of panic symptoms of the general population. But symptoms such as "*being afraid of going crazy*" and "*shortness of breath*" are significantly higher in pregnant women with PD compared to the control group, suggesting that these symptoms, particularly "*fear of going crazy*", may be discriminating for discerning panic during pregnancy from panic manifestation of other

periods of life. Furthermore, PD (family history, current PD, history PD) represents an important risk factor for the development of PPD and should be routinely screened in order to develop specific preventive interventions. It is important to underline that the role of a specific anxiety diagnosis in predicting depressive symptoms is related both to outcome definitions and to time of assessment. PD predicted both 1st month PPD than probable depressions. In relation to the 12th month postpartum, the results of this study confirmed the role of Panic Disorder in predicting a diagnoses of minor or major depression even if with a decrease in effect size.

Carrying out antenatal screening of established risk factors and accurate diagnoses of Panic Disorder during pregnancy may help to plan adequate treatment in order to prevent possible postpartum distress outcomes.

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1 Introduction

1.1 Epidemiological Date

Panic disorder is characterized by sudden recurrent and unpredictable panic attacks, associated with persistent worry about the possibility of having future panic attacks (American Psychiatric Association, 2004). Symptoms of panic attacks typically include shortness of breath, heart palpitations, chest pain, dizziness and fear of losing control or dying.

Panic disorder (PD) is one of the most prevalent psychiatric disorders according to the Epidemiological Catchment's Area population survey (Regier et al., 1990). Lifetime prevalence for PD is estimated at 2.25% and in women is double that for men (2% *vs* 1%); the rate of panic disorder with concurrent agoraphobia is even disproportionate: 7.9% for women compared with 3.7% for men (Eaton et al., 1991). Other authors confirm this date with a prevalence of panic disorder two times greater in women than in men (Andrade et al., 1996; Yonkers et al., 1998). The lifetime prevalence rate for panic disorder (3.5%) is even higher in the National Comorbidity Survey (NCS) study than that reported for the ECA study. The lifetime prevalence estimate for panic disorder was also two and a half times greater in women (5.0%) than in men (2.0%) but the 2:1 sex ratio is retained for panic disorder with agoraphobia in the NCS study (Wittchen et al., 1992). In addition to the finding that panic disorder is two to three times more common in women, panic attacks also occur more frequently in women than in men (Keyl and Eaton, 1990); their presence may well elevate the risk for the subsequent occurrence of other psychiatric disorders (Reed and Wittchen, 1998). PD is not only common but is also considered to be a chronic and debilitating illness

associated with significant comorbidity (Yonkers et al., 1998).

It has been estimated that 3% to 12% of women experience symptoms related to PD at some time during their childbearing years, including during pregnancy and the postpartum period (Wenzel et al., 2001; Smith et al., 2004) and according to available data, 11% to 29% of women with PD report the onset during pregnancy (Nonacs and Cohen, 2003). Despite variability in assessment times and procedures, relatively consistent prevalence rates ranging from 1.3% to 2.0% have been reported for panic disorder during the perinatal period (Wenzel et al., 2005; Sutter-Dallay et al., 2004; Smith et al., 2004; Zar et al., 2002; Wenzel et al., 2001). In comparison, the DSM-IV reports lifetime prevalence rates of panic disorder ranging from 1.5% to 3.5% and 1-year prevalence rates of 1.0% to 2.0%, with a typical age at onset ranging from late adolescence to the mid-30s (American Psychiatric Association, 2004).

1.2 Panic Disorder in women

Aside from the variation in prevalence rates, only a few significant differences between men and women with either panic disorder or panic disorder with agoraphobia have been shown (Bekker, 1996; Cameron, 1989). Some studies have found that women who have panic disorder with agoraphobia endorse slightly greater fear (Oei, 1990; Chambless, 1986), although other studies have found that men are more fearful, particularly regarding somatic concerns (Hafner, 1981). In the Edmonton (Canada) population survey (Dick et al., 1994) women with PD had significantly greater levels of phobic avoidance, more reliance on family members as a means to enter fearful situations, and more reports of panic attacks being triggered by leaving home alone or by using public transportation (Dick et al., 1994). Startevic et al. (1998) found that

women with panic disorder were significantly more likely than men to eschew transportation by bus and to avoid unfamiliar places when alone. They also found that women were much more likely than men with panic disorder to report that they needed a companion, especially their spouse or children, to go outside the home. The increased level of dependence may help to explain the consistent finding that women with PD have a greater degree of functional impairment compared with men with PD (Weissman et al., 1997; Starcevic et al., 1998; Turgeon et al., 1998). There is some suggestion that the clinical course and outcome of anxiety disorders, including panic disorder with agoraphobia and panic disorder, differ between men and women. In one naturalistic study of anxiety neurosis (defined according to the Feighner criteria, 1972), women had more symptoms and higher medical care utilization at 4-year follow-up (Noyes et al., 1980). A second observational study found that female sex predicted greater avoidance and panic after 1 year (Maier and Buller, 1988). No sex differences were found in a third study that re-interviewed subjects an average of 3 years after their participation in a treatment study (Noyes et al., 1990). Yonkers et al. (1998) found that women with panic disorder are more likely to re-experience symptoms after gaining remission. Psychosocial substrate contributes to the more chronic course of illness for women with this anxiety disorder. In fact, as noted in previous reviews (Yonkers, 1994; Bekker, 1996), women are more likely to be harm-avoidant and are less likely to expose themselves to fear-inducing situations (Zuckerman et al., 1980). This may decrease the likelihood of therapeutic “auto-exposure” after an initial fear has developed.

1.3 Panic Disorder and the female reproductive cycle.

The dramatic fluctuations in reproductive hormone cycles that occur throughout the female lifecycle appear to have a substantial impact on the clinical course of panic disorder in women. The dramatic decline in estrogen and progesterone levels that characterizes the midluteal phase of the menstrual cycle has been linked to the worsening of anxiety symptoms in general, and panic disorder in particular (Yonkers and Ellison, 1996).

Several reports suggest that women with panic disorder experience an increase in their anxiety and panic disorder during the midluteal or premenstrual phase of the menstrual cycle (Cameron et al., 1988; Griez et al., 1990). Women with panic disorder are also reported to endorse more severe menstrual symptoms relating to bodily sensations, anxiety sensitivity, state and trait anxiety, fear of body sensations and illness-related concerns compared with control subjects (Sigmon et al., 2000). Pregnancy is characterized by two- to threefold increases in estrogen and a dramatic elevation (80-100X) in progesterone concentration (Altshuler et al., 1998). Estrogen and progesterone may influence mood by interacting with serotonin and norepinephrine neurotransmitter systems implicated in the treatment and pathophysiology of mood and anxiety disorders. Estrogen influences serotonin transporter sites, synthesis, receptor sensitivity, and metabolism of serotonin and decreases monoamine oxidase activity (Chakravorty and Halbreich, 1997; Halbreich, 1997; Seeman, 1997). It also enhances noradrenergic neurotransmission by influencing synthesis, responsiveness of the α2-adrenergic receptor and metabolism of norepinephrine (Etgen and Karkanias, 1994; Halbreich, 1997; Schmidt et al., 1997). Estrogen treatment may effectively treat (Gregoire et al., 1996), or prevent the recurrence (Sichel et al., 1995) of postpartum

depression. Progesterone may have anxiolytic and sedative properties, mediated by benzodiazepine-like action at the GABA receptor-binding site (Paul and Purdy, 1992), but may also lead to dysphoric and mood-destabilizing effects (Buckwalter et al., 1999). No consistent hormonal differences have been found in postpartum women with and without depression (Harris et al., 1994; 1996; Wieck, 1989), suggesting that women with postpartum depression have normal endocrine function, but may have a differential sensitivity to suddenly changing hormonal levels. When a sudden withdrawal of supraphysiologic gonadal steroid levels to a hypogonadal state is simulated, women with a history of postpartum depression develop significant mood symptoms in contrast to women without such history (Bloch et al., 2000). According to Klein's false suffocation alarm theory (Klein, 1993), panic disorder may be due to a deranged suffocation alarm monitor misfiring an evolved suffocation alarm system because panic patients are abnormally sensitive to CO2. During pregnancy, improvement may be explained by a respiration-stimulating effect of progesterone, which leads to hyperventilation and to a decrease in pCO_2. Therefore, according to this theory, pregnancy protects panic patients by increasing the distance of their pCO_2 levels from their thresholds. During the postpartum period, an abrupt progesterone decrease may lead to a sudden absence of its panic-suppressing effect, leading to an increase in panic, similarly to late luteal phase dysphoric disorder. Symptoms of the premenstrual syndrome can be relieved by administration of progesterone (Yonkers et al., 1998). Not only estrogen or progesterone may play a role. Cortisol concentrations also rise during pregnancy to several times their normal values and then slowly return to normal within 15 days of delivery (Harris et al., 1994). Abnormalities of the hypothalamus-pituitary adrenal axis have been reported in patients with panic disorder. Cortisol was elevated

mainly during night-time (Bandelow et al., 1997; 2000) and during panic attacks (Bandelow et al., 2000).

1.4 Course of pre-existing panic disorder during perinatal period

Many women experience pregnancy following the onset of panic disorder and some limited research has described the perinatal course of illness in these women. Although there are conflicting findings, a general pattern of improvement in panic symptoms during pregnancy followed by worsening during the postpartum period has been reported in retrospective studies and case reports (Northcott and Stein, 1994; Klein et al., 1994; George et al., 1987; Cowley et al., 1989). Sholomskas et al. (1993) and Bandelow et al. (2006) found that women who had never been pregnant had significantly more panic manifestations than women who had had at least one pregnancy, suggesting that pregnancy may confer some kind of protection against new-onset panic disorder. Conflicting data exist about the course of panic in pregnancy (Vythilingum, 2008). Most estimates suggest that about half (40-50%) of women with pre-existing panic disorder will have no significant change in their panic symptoms during pregnancy. Pre-existing panic disorder will improve during pregnancy in 30 to 35% of patients and substantially worsen in 20% to 30% of patients during the course of pregnancy (Northcott and Stein, 1994; Cohen et al., 1994), particularly during the last part of pregnancy (Verburg et al., 1994; Griez et al., 1995). George et al. (1987) reported a case series of 3 patients who had improvement in panic symptoms during pregnancy. Cohen et al. (1994) however, collected preliminary data based on a retrospective study of 49 women with pre-gravid PD and reported that the course of PD during pregnancy was variable with a subset of severe cases showing clear relapse.

Hertzberg (1999) analyzed the results from eight reported studies and concluded that 42% experienced improvement in panic disorder during pregnancy, whereas an onset or an exacerbation in panic disorder was reported in 38% of the described pregnancy. Interestingly, women with panic disorder appear unlikely to experience the same outcome (i.e., worsening, improvement or no change) in subsequent pregnancies; that is, the course of panic disorder during successive pregnancies is often markedly different (Northcott and Stein, 1994; Cohen et al., 1994).

However, other evidence (Wisner et al., 1996; Cohen et al., 1994; Cohen et al., 1996) suggests that the most common effect of perinatal status on panic disorder may be no change in symptom severity. For example, one longitudinal study of 22 women with panic disorder and comorbid mood disorder followed over 5 years found that the most common effect of pregnancy on panic symptoms was no change from baseline during pregnancy (31 pregnancies, 69%) (Wisner et al., 1996). However, when change did occur, it was likely to be a decrease in symptoms (12 pregnancies, 27%). Similarly, most women did not experience a change in symptom intensity during the postpartum period (31 pregnancies, 69%). Yet, in the event of change, it tended to be an increase in or onset of symptoms (12 pregnancies, 31%), while one of the women reported a decrease in symptoms during the postpartum period. An interesting finding in this report was that the pattern of change (if any) in panic symptoms was not consistent across gestations for the majority of women who experienced more than 1 pregnancy (9 of 14 women, 64%) (Wisner et al., 1996). The best predictor of symptom change may be pre-gravid symptom severity, with greater severity predicting a worse course (Ross and McLean, 2006).

Although there is conflicting data regarding the relationship between pregnancy and

relapse in PD, there appears to be a consensus in the literature that the postpartum period represents a time of a high risk of relapse for patients with PD (Cohen 1994; 1996). The postpartum period may also associated with an increased risk for the onset of panic disorder. Northcott and Stein (1994) reported that most pregnancies (63%) in their cohort of patients with PD were associated with exacerbation of symptoms in the postpartum period. Sholomskas et al (1993) also demonstrated higher rates of PD onset in the postpartum period. According to available data, 11% to 29% of women with panic disorder report onset during the postpartum period (Sholomskas et al., 1993; Wisner et al., 1996). The mean time of onset was 7.3 weeks postpartum (range 1–12 weeks). Because this rate is significantly greater than the expected age-corrected rate for panic disorder onset in women, it is unlikely to represent a coincidental event (Sholomskas et al., 1993). However, due to the retrospective nature of this study, it is possible that women associated onset of symptoms with childbirth due to its prominence in their memory as a major life event. Controlled research is needed to determine whether the postpartum period is associated with increased risk for new onset of panic disorder (Ross and McLean, 2006).

In patients with pre-existing panic disorder, pregnancy does not appear to increase the likelihood that medication for panic can be successfully discontinued (Cohen et al., 1994). Instead, there is some support for continuing or restarting pharmacotherapy during the latter part of pregnancy in patients with panic disorder who are considered at a high risk for relapse in the postpartum period. Cohen et al. demonstrated that pregnant women with pre-existing panic disorder who receive antipanic medication are significantly less likely to experience a postpartum exacerbation than those who did not receive treatment during pregnancy (Cohen et al., 1994).

The improvement of panic symptoms during pregnancy and worsening of panic symptoms during the postpartum period may be explained by psychosocial influences, hormonal changes and the "*false suffocation alarm hypothesis*" (Bandelow et al., 2006). It can only be speculated how psychosocial factors may be responsible for the bipolar course of panic symptomatology. Improvement during pregnancy may be explained by the mother's looking forward to the birth of the child, while fear of changes in relation to the father, financial problems, an increased workload, or simply reduced sleeping time could be responsible for a deterioration after childbirth. Women who reported stress during pregnancy had a higher risk of panic manifestations (Bandelow et al., 2006). Marital upset and family, health, financial and occupational problems were reported most frequently. However, psychosocial stress factors may not be the only explanation for the postpartum panic phenomenon. For example, normal deliveries had the same high risk of panic manifestations as miscarriages. Moreover, the sudden change from the positive influence of pregnancy to the negative impact of childbirth make another explanation more probable. While environmental influences are mostly present already during pregnancy and a sudden change of these factors after childbirth is unlikely for most women, hormonal changes may serve as a better explanation for the phenomenon. During pregnancy, progesterone and estradiol concentrations rise to a maximum at term, when they are several hundred times higher than during the non-pregnancy period (Martin and Hoffman, 1986). Around 4–5 days after delivery there is a precipitate drop in hormone concentrations (Harris et al., 1994). This coincides with the peak symptoms of "maternity blues". Accordingly, we found an accumulation of new panic manifestations in the first 5 days after childbirth. As panic disorder and depression have many biological features in common (Gregoire et al., 2006),

postpartum panic may have a similar neurobiological basis as postpartum depression (O'Hara et al., 1990; Cox et al., 1993).

1.5 Presentation and predictors of perinatal panic disorder

Panic Disorder is characterized by discrete periods of fear accompanied by physical symptoms such as heart palpitations, flushing and sweating, nausea, dizziness and shortness of breath. These physical symptoms are often also present during pregnancy; an accurate diagnosis of PD in pregnancy is complicated by the fact that there is a significant overlap between the clinical symptoms of PD and physiological symptoms of pregnancy (Weisberg and Paquette, 2002). However, in panic disorder they occur simultaneously, build up to peak intensity within ten minutes and frequently begin "*out-of-the-blue*" or without a clear trigger such as physical exertion. Another important distinction is that in panic disorder, women exhibit fear or concern about these attacks and their implications. They may believe the attacks signal that they are going crazy or having a heart attack (Weisberg and Paquette, 2002). Although panic symptoms during the perinatal period are typical of panic symptoms in the general population, they are often interpreted in the context of the perinatal state; concerns over the pregnancy and fetus may present as the predominant feature. Women during pregnancy may interpret panic attacks as something being wrong with the fetus (Weisberg and Paquette; 2002; Villeponteaux et al., 1992; Northcott and Stein, 1994). In a qualitative, phenomenological study of 6 postpartum women with panic disorder, women reported feeling unable to leave their homes to take their children to groups and activities and worried about the long-term impact of their panic disorder and the resulting isolation on their children (Beck, 1998).

Rates of anxiety disorders detection in primary care settings are typically low (Spitzer, 2000). It is unusual to find a detection of PD in an obstetric setting. One reason may be that panic disorder typically presents in the form of physical symptoms, such as breathing difficulties or tightness in the chest, that can mimic catastrophic illness such as heart attacks or pulmonary emboli. It may be that prenatal health providers are more watchful of serious general medical conditions that affect the mother or the fetus and thus thoroughly evaluate somatic symptoms like shortness of breath and chest pain (Smith et al., 2004).

Although no literature has reported risk factors for or predictors of perinatal panic disorder, there is some evidence from retrospective studies of a relationship between lactation/weaning and panic symptoms. In a report including 43 breastfed babies, weaning of 12 (28%) was associated with exacerbation of panic in the mother (Northcott et al., 1994). In another study of 22 women, 1 participant reported onset of panic at weaning (Villeponteaux et al., 1992). A third study found that 9 out of 16 women who did not breast-feed their babies had panic attacks during the postpartum period, as compared to only 2 out of 17 women who breast-fed (Klein et al., 1994). Six of these women reported onset of panic attacks with weaning. Controlled, prospective studies are needed to determine whether breastfeeding reduces and/or weaning increases, risk for panic disorder (Ross and McLean, 2006).

1.6 Panic Disorder and Depression

Numerous findings have demonstrated high rates of comorbidity between anxiety and depressive disorders (Merikangas et al., 1996; Kessler et al., 1996; Angst, 1996; Lewinsohn et al., 1997). The high comorbidity of panic disorder and major depressive

disorder in individuals has been well documented in epidemiological, clinical, longitudinal and cross-sectional studies in adults and children (Weissman et al., 1993). Kessler et al. (2006) found a lifetime comorbidity between Lifetime Panic Disorder and Major Depressive of 34.7% (OR 2.0; 95% CI: 1.5-2.7), between Panic Disorder and Bipolar I and II of 14.4% (OR 5.4; 95% CI: 3.6-7.9). However, it is unclear if panic disorder and major depressive disorder are distinct or the same disorder, whether one disorder leads to the other or whether the occurrence of both major depressive disorder and panic together in individuals represents a distinct syndrome that is different from either disorder alone (Dube et al., 1986). Secondary depression is common and affects about a third of panic disorder patients (Lesser et al., 1988). Previous studies using both clinical and population-based samples have consistently shown that anxiety disorders typically begin early in life, whereas the onset of depressive disorders generally occurs later during young to middle adulthood (Merikangas et al., 1996; Regier et al., 1998; Schatzberg et al., 1998). Several cross-sectional studies have reported statistically significant associations between primary anxiety disorders and secondary depressive disorders, suggesting that anxiety disorders increase the risk of subsequent depression (Kessler et al., 1996; 1998; 1999). Although recent data from longitudinal studies show that anxiety disorders co-occur with an increased risk of depression (Woodward and Fergusson, 2001; Stein et al., 2001; Goodwin, 2002), little is known about the role of clinical characteristics of anxiety disorders in this association (Wittchen et al., 2000). There is some evidence for a possible key role of panic attacks in the development of psychopathology. For instance, panic attacks are strongly related to the subsequent development of a variety of mental disorders, not just panic disorder and agoraphobia (Reed and Wittchen, 1998). Goodwin and Hamilton (2002) report non-specific relations

between panic attacks and risk of psychiatric morbidity, and other analyses show that panic attacks act as an independent predictor of major depressive disorder among adults in the community, after adjustment for other anxiety comorbidities. In consistence with previous findings (Goodwin, 2001; 2002; Reed and Wittchen, 1998) Bittner et al. (2004) found that among individuals with anxiety disorders, panic attacks were associated with a significantly greater risk for the first onset of major depressive disorders.

Comorbidity between anxiety and depression symptoms is common and has been frequently reported during pregnancy (Field et al., 2003; Heron et al., 2004; Wenzel et al., 2005; Matthey, 2007; Matthey et al., 2003; Littleton et al., 2007; Austin et al., 2007). In a study by Ross et al. (2003), nearly 50% of clinically depressed pregnant and postpartum women had clinically significant comorbid anxiety; and according to Andersson et al. (2006) 20.5% of women who were given a psychiatry diagnosis in the 2nd pregnancy trimester presented comorbid anxiety and depression symptoms. Despite significant comorbidity, the relationship of panic disorder and depression during childbearing has been unexplored.

1.7 Risk Factors of Postnatal Depression (PND)

Despite the stereotype that the perinatal phase is a period of happiness, women frequently experience adjustment difficulties and depressive symptoms during pregnancy and in the postpartum period. Reviews and meta-analyses published on postnatal depression (PND) estimate that in Western countries it affects 10% to 15% of women (Beck, 2001; O'Hara and Swain, 1996). Recently, meta-analysis of the Agency for Healthcare Research and Quality estimated that the prevalence of major or minor

depression in pregnancy ranges from 8.5% to 10.0% while in the first postpartum year it ranges from 6.5% to 12.9% (Gaynes et al., 2005). These figures are comparable to those seen in non-childbearing women (O'Hara et al., 1991).

Although every woman is potentially at risk of developing PND, women who present specific risk factors have a significantly increased risk of becoming depressed after delivery. These risk factors are widely studied in literature (Kitamura et al., 1993; Glangeaud-Freudenthal and Boyce, 2003; Robertson et al., 2004) and meta-analyses (Beck, 2001; O'Hara and Swain, 1996) have been carried out to estimate the effect size of each of them. Currently, the known risk factors have been classified, according to their effect size, into three categories: strong-moderate, moderate, and small. The strongest predictors of PND are the experience of depression or anxiety during pregnancy or a previous depressive illness (Ryan et al., 2005; Robertson et al., 2004). In addition to these predictors, life stress and lack of social support have a moderate-severe effect size; psychological factors and marital problems have a moderate effect size, while obstetric factors and socioeconomic status have a small effect size (Robertson et al., 2004). As regards psychiatric risk factors, when anxiety is considered as a dimensional characteristic clinically assessed or measured by a score on a rating scale, the findings in the literature are discrepant. Precursor studies suggested that anxiety during pregnancy increased the risk of PND (Dalton, 1971; Tod, 1964; Heron et al., 2004) while others did not confirm this association (Pitt B., 1968). In a recent study Austin et al. (2007) have demonstrated that women with high antenatal BMWS scores (scale used to assess trait cognitive anxiety) were 2.6 times more likely to have probable PND than those with low scores (Austin et al., 2007). Antenatal anxiety has

been found to be a significant predictor of postnatal depression in three meta-analysis (O'Hara and Swain, 1996; Beck, 2001; Robertson et al., 2004).

Although the role of anxiety symptoms on the development of PND has already been studied in literature (Heron et al., 2004; Sutter-Dallay et al., 2004; Skouteris et al., 2009), the link between anxiety disorders (AD) defined as diagnostic categories and PND has not only received a little specific attention. Moreover, in most of the studies there were methodological limitations such as their small sample sizes and the lack of adjustment for confounding factors. In particular, most studies did not take into account the strong comorbidity between mood disorders and AD, and thus did not explore whether pregnancy AD increases the risk of PND, independently of the existence of pregnancy depression. In a large sample of women Sutter-Dallay (2004) assessed whether pregnancy AD is an independent risk factor for the occurrence of intense postnatal depressive symptoms; these authors found that women presenting with pregnancy AD were four times more likely to present also with postnatal depression at 6 weeks than those without. Further, as literature suggests, no studies have examined the predictive role of a specific diagnosis of anxiety disorder in post-partum depression.

2. AIMS OF THE STUDY

This thesis has three aims:

1) to describe prevalence and clinical features of Panic Disorder of a large non-clinical sample of women recruited at the 3rd month of pregnancy and to compare them with clinical features in a group of non-pregnant women of equivalent age.

2) to investigate the role of PD (as family history, previous diagnosis or the occurrence of PD during pregnancy) on the development of PPD.

3) to assess the specific role of PD in predicting probable depression (EPDS>12), major or minor depression (MMD) and false positives (EPDS>12 without mMD) at first month/year after delivery compared to other anxiety diagnoses.

3. METHOD

3.1 Participants

A sample of pregnant women was recruited as part of a larger study conducted at Pisa in the framework of the Perinatal Research and Screening Unit Study (PND-ReScU). The Perinatal Depression-Research and Screening Unit (PND-ReScU) is based on an ongoing collaboration between the Department of Obstetrics and Gynecology and the Department of Psychiatry, Neurobiology, Pharmacology, and Biotechnologies of the *Azienda Ospedaliera Universitaria Pisana*. The primary aim of the PND-ReScU is to evaluate the effectiveness of screening for early identification and the intervention strategies to reduce mood disorders in the perinatal period. Furthermore, PND-ReScU aims to define a battery of instruments that can be easily administered in a primary prevention set- ting. Women presenting at the obstetrics/gynecology department for the first ultrasound examination (between the 12^{th} and 15^{th} gestational weeks) were recruited for the study. Central to our recruitment plan was a letter to be given to each pregnant woman who came to the local health service to receive a booklet of information prepared by the region of Tuscany that describes various aspects of pregnancy and maternal health. The letter provides a very brief description of perinatal depression and informs the woman of the possibility of participating in a study aimed at evaluating risk factors for this condition. Study recruitment began in February 2004 and ended in March 2007. To be included in the study, a woman had to be between the 12^{th} and the 15^{th} gestational weeks, be willing to sign an informed consent statement and be available to be contacted by phone. Exclusion criteria for the study were age ≤18 years, poor knowledge of the Italian language or other limitations to communication and no fixed residence. The Ethics Committee of the *Azienda Ospedaliera Universitaria Pisana*

approved the study protocol and the assessment procedures. The Committee also required the provision of psychological counseling for women with mild depressive symptomatology and/or for all women who requested it and/or the provision of drug treatment for women with moderate/severe depression, according to international guidelines (U.S. Food and Drug Administration, 1979; American Academy of Pediatrics, 2000). All subjects provided written informed consent to participate in the study after receiving a full description of the study and having an opportunity to ask questions. The Ethics Committee allowed us to collect information only after the informed consent statement was signed, as prescribed by Italian law (art. n. 675 of December 31, 1996) on privacy. Therefore, socio-demographic characteristics of women who refused to participate in the study are not available. The study was funded by a grant from the Italian Ministry of Health.

3.2 Assessment

Several instruments were administered to evaluate a broad range of different aspects related to the perinatal period that might represent potential risk factors for the development of PND. The assessment instruments administered at each time point are listed in Appendix 1 (First et al., 1995; Cox et al., 1987; Beck, 2002; Weissmann et al., 2000; Dell'Osso et al., 2002; Cassano et al., 1997). The schedule of assessment is described in Table 1.

The diagnostic assessment was conducted at baseline using the *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)* (First et al., 1995) by clinicians trained and certified to the use of the interviews when high levels (>0.90) of inter-rater reliability of their diagnoses with the trainer were achieved. All interviewers had long-standing

experience in the administration of standardized interviews. The SCID-I is a semi-structured interview for making the major Axis I DSM-IV diagnoses (American Psychiatric Association, 1994). The SCID encompasses the DSM-IV sections for mood, psychotic, sub-stance use, anxiety, somatoform, eating, and adjustment disorders. Moreover, because the clinical and functional impairment related to depressive symptoms often required a therapeutic intervention, we decided to note the categories of partial remission of major depressive episode, (American Psychiatric Association, 1994) which includes women who had a recent major depressive episode and who currently had residual symptoms, and minor depression (Jardri et al., 2006). The diagnosis of minor depression proposed in the appendix to the DSM-IV (American Psychiatric Association, 1994) requires the presence of 2 to 4 criteria of depression, lasting for at least 2 weeks, excluding individuals with a previous history of MDD (American Psychiatric Association, 1994). For the purpose of this study, we included in this category women who currently met the criteria for the diagnosis of minor depression and who fully remitted from a past episode of major depression, excluding the possibility that this episode was a residual phase of a major depressive episode. Symptoms of maternal depression were assessed using the 10-item *Edinburgh Postnatal Depression Scale* (Cox et al., 1987). Originally designed as a screening instrument for postnatal depression, the EPDS has since been validated for use during pregnancy (Murray and Cox, 1990). The EPDS (see Appendix 1) is a 10-item self-report scale designed as a screening instrument for postnatal depression but has also been validated in non-postnatal women (Cox et al., 1987). Each item is scored on a four-point scale (0–3), the minimum and maximum scores being 0 and 30, respectively. Five of the items explore dysphoric mood, two explore anxiety and three assess guilt and suicidal

thoughts. The total is calculated by summing up the item scores. A score of 13 and above is used to identify probable cases with a sensitivity of 86% and a specificity of 78% (Cox et al., 1987). The scale does not provide a clinical diagnosis of depression, but a score above 13 is widely used to indicate the presence of probable depressive disorder. The EPDS rates the intensity of depressive symptoms present over the previous 7 days. A cut-off score of 13 has been found to identify most seriously depressed women, although in case of a score of 9 or more, clinical assessment has been recommended (Cox et al., 1983). In 1992, the EPDS was translated into Italian and was found to have good psychometric properties (Carpiniello et al., 1997). When women exceeded the threshold score (total scores ≥13) of EPDS, suggesting the probable presence of depression, we have re-administered section A of SCID to confirm the diagnosis of depressive disorders. Scores on EPDS item 3, "*blamed myself unnecessarily*", item 4, "*anxious or worried for no good reason*", and item 5, "*scared or panicky for no very good reason*", were extracted for further analysis. These items were clustered as "Anxiety EPDS". Scores on EPDS item 1, "*I have been able to laugh and see the funny side of things*", item 2, "*I have looked forward with enjoyment to things*", and item 8, "*I have felt sad or miserable*", were extracted for further analysis. These items were clustered as "Depression EPDS".

Information on socio-economic status was drawn from the *Postpartum Depression Predictors Inventory-Revised* (PDPI-R) (Beck, 2002), which is a self-report instrument designed to identify the risk factors for postpartum depression. The PDPI-R categorizes socio-economic status on 3 levels: -low, medium, and high, without providing anchor points related to the income per year. The 13 PDPI-R factors are (1) marital status, (2) socio- economic status, (3) self-esteem, (4) prenatal depression, (5) prenatal anxiety, (6)

unwanted/unplanned pregnancy, (7) history of previous depression, (8) social support, (9) marital dissatisfaction, (10) life stress, (11) childcare stress, (12) infant temperament, and (13) maternity blues. The first 10 predictors comprise the prenatal version of the PDPI-R. The last 3 risk factors are specific to the postpartum period. The total score on the prenatal version of the PDPI-R ranges between 0 and 32, while the PDPI-R Full Version (Prenatal plus Postpartum Versions) is used after delivery and includes all 10 factors of the Prenatal Version plus three additional risk factors: childcare stress, infant temperament and maternity blues. The total score of the Full Version ranges between 0 and 39 (Beck et al., 2006). The higher the score, the more risk factors for PPD a subject has. A previous study (Oppo et al., 2009) found that at the 3rd month of pregnancy women who crossed the threshold of 4 had a greater likelihood of having postpartum depression. All the described instruments proved to have good reliability and validity.

The family history of psychiatric disorders was assessed using the *Family History Screen* (FHS) (Weissman et al., 2000). The FHS is used to assess the presence of 15 psychiatric disorders and suicidal behavior in first-degree relatives. The validity of this instrument against best-estimate diagnosis based on direct interview of probands and relatives has been demonstrated for major depression, anxiety disorders, substance use disorder and suicide attempts (Weissman et al., 2000).

The lifetime experience of panic-agoraphobic spectrum symptoms was assessed using the *Panic-Agoraphobic Spectrum–Self-Report* (PAS-SR) at 6th month post-partum. The term “panic-agoraphobic spectrum” (Cassano et al., 1997; 1998) refers to a broad array of features associated with DSM-IV panic disorder, including typical and atypical manifestations of core panic symptoms (such as panic-like somatic symptoms, anxious

expectation, and agoraphobia), as well as a range of related temperamental or behavioral features (categorized as separation anxiety, stress sensitivity, medication sensitivity, illness-related phobias and reassurance seeking). The PAS-SR, a 114 - item self-report scale, assesses the lifetime experience of panic-agoraphobic symptoms and features across eight domains, including (1) Separation sensitivity; (2) Typical and atypical panic-like symptoms; (3) Stress sensitivity; (4) Medication and substance sensitivity; (5) Typical and atypical agoraphobia; (6) Anxious expectation; (7) Illness phobia and hypochondria; (8) Reassurance orientation. The interview version of this measure has been shown to have excellent psychometric properties and the 8 panic-agoraphobic spectrum sub-scales have been shown to display a strong pattern of convergent and discriminate validity with existing panic and anxiety assessment measures across multiple diagnostic groups and control subjects who were never psychiatrically ill (Shear et al., 2001). The self-report version of this instrument has been shown to agree very well (intraclass correlation coefficient = 0.94) with the interview version (Shear et al., 2001). In receiver-operating characteristic curve analyses, a cut-off score of 35 was determined to best distinguish between psychiatric outpatients with and without clinically significant lifetime panic spectrum features (Frank et al., 2000).

By means of factor analysis of a tetrachoric correlation matrix conducted on PAS-SR, 10 factors were extracted, accounting overall for 66.3% of the variance (Rucci et al., 2009). Items were organized by factors, then ordered by decreasing magnitude of loadings within factors. The factors have been labelled as follows:

Panic symptoms. This factor includes DSM criteria for panic attack with the highest loadings on "*heart pounding, racing, or skipping*" and "*shortness of breath*" "*trembling or shaking*".

Agoraphobia. This factor describes DSM criteria for agoraphobia with loadings on "*nervous when in a crowded place*" or "*avoided (or feeling nervous) when in an open place like a town square or a wide street*".

Claustrophobia. This factor includes feelings of restriction or entrapment when "*wearing high-necked shirts, ties, or tight-fitting clothes because they made you feel trapped*" or "*wearing seatbelts*" and avoidance of situations that evoke fears of suffocation such as swimming under water or vomiting.

Separation anxiety. This factor describes anxiety symptoms associated with separation from loved ones or from home, with loadings on "*it was very difficult for you to be alone or without a loved one, either at home or in other places*" or "*anxiety when you were separated, or anticipated separation, from home or loved ones (for example, if you went to stay with a relative or someplace else)".*

Fear of losing control. This factor includes symptoms of fear of losing control, with highest loadings on "*fear of losing your mind or losing control*" or "*feeling confused or numb*" and symptoms of depersonalization and de-realisation "*felt cut off from yourself or from parts of your body*", "*felt that things around you were no longer familiar but unreal and strange*".

Drug sensitivity and phobia. This factor explores excessive worrying about the possible side effects of medication, with loadings on "*taking a prescribed medication because it might cause you permanent brain damage*" or "*taking prescribed medications because you thought they might harm you or that you were overly sensitive to side effects or allergic*".

Medical reassurance. This factor describes the need for reassurance from professionals, with loadings on "*Have you ever made repeated requests for special diagnostic*

procedures (for example, an angiogram or gastroscopy) even though your doctor didn't recommend it?" or "*Have you ever asked for medical lab tests even when your doctor didn't recommend them?".*

Rescue object. This factor includes the need of some patients to take objects with them such as an umbrella, a hat or a bottle of water to reduce anxiety.

Loss sensitivity. This factor describes having more difficulty than the average person in adjusting to the end of a relationship with a friend or a lover or the end of a psychotherapy.

Reassurance from family members. This factor describes the need for reassurance from family members or friends with loadings on "*did you ever seek help from your parents, spouse, friends, or neighbours because of these symptoms?*" or "*did you ever feel that you needed to be comforted and reassured by your friends and family?".*

The lifetime experience of mood spectrum symptoms was assessed using the *Mood Spectrum Self-Report Questionnaire, lifetime version (MOODS-SR-LT)* (Dell'Osso et al., 2002). The MOODS-SR assesses lifetime (LT) symptoms, traits and lifestyles associated with mood disorders, as well as "*temperamental*" features related to mood dysregulation. The instrument consists of 161 items coded as present or absent for one or more periods of at least 3-5 days during the subject's lifetime. Items are organized into 3 manic-hypomanic and 3 depressive domains, as well as a section that assesses disturbance in rhythmicity and vegetative functions, yielding a total of seven domains. For the present study, at T0, T1 and T2 assessments, we omitted items inquiring about symptoms experienced when pregnant, because all study subjects are pregnant. At subsequent evaluations, subjects endorsed all the items. The cut-off score is 22 both for the depressive domain and for the manic-hypomanic domain. By means of factor

analysis of a tetrachoric correlation coefficients conducted on depressive component of MOODS-SR, six-factors were identified (Cassano et al., 2009).

The factors have been labelled as follows:

Factor 1. *Depressive mood.* This factor includes a number of symptoms and temperamental features that span depressed mood, loss of interests and loneliness, with principal loadings on "*persistently sad or empty, blue or down in the dumps*", "*serious, introverted or gloomy*", "*lost interest in hobbies or sport*", "*purposeless, as if everything had lost its significance*", "*lonely*", "*deeply annoyed*" and "*difficulty making new friends*".

Factor 2. Psychomotor retardation. This factor includes psychomotor retardation in different areas of daily activities, physical weakness and tiredness, with principal loadings on "slowed down", "passive, sluggish", "difficulty starting to do anything", "speech or thinking seemed slowed down", "fatigued, weak, or tired for the smallest task", "trouble getting out of bed in the morning" and "your housework deteriorated".

Factor 3. Suicidality. This factor includes items related with suicidal ideation, plans and attempts, with principal loadings on "suicide attempt", "want to die or hurt yourself", "specific plan to hurt or kill yourself", "suicide attempt requiring medical attention" and "wishing not to wake up in the morning".

Factor 4. Drug/illness related depression. This factor describes the tendency to feel depressed when ill or after having taken substances, with principal loading on "depressed when stopping any of these substances" and "depressed when drinking lots of alcohol or using substances".

Factor 5. Psychotic features. This factor includes paranoid thoughts and psychotic symptoms, with principal loading on “you felt surrounded by hostility, as if everybody was against you”, “everyone was talking about you” and “others were causing all of your problems”.

Factor 6. Neurovegetative symptoms. This factor includes a number of items that describe problems with sleep, appetite and sexual function, with principal loadings on “repeatedly wake up in the middle of the night and had difficulty falling sleep” and “less sexually active”.

By means of factor analysis of a tetrachoric correlation coefficients conducted on conducted on manic component of MOODS-SR, nine-factors were extracted (Cassano et all., 2009).

The factors have been labelled as follows:

Factor 1. Psychomotor Activation. This factor includes a number of symptoms that span flight of ideas, increased energy levels and activity, with principal loadings on “too many thoughts at once”, “racing thoughts”, “constantly active”, “shifting interests” and vigorous.

Factor 2. Creativity. This factor includes features of artistic creativity and sensitivity, with principal loading on “very artistic and creative”, “bursts of inspiration or creativity”, “sensitive to the forms and harmony in nature” and “mentally very sharp, brilliant and clever”.

Factor 3. Mixed Instability. This factor includes sexual promiscuity, alcohol related mood changes and irritability, frequently changing job, residences, friends and hobbies with principal loading on “changed sexual partners”, “tended to ignore everyday rules

and social etiquette", "more interested in sex" and "irritable or elevated mood when you were abusing alcohol".

Factor 4. Sociability/Extraversion. This factor includes features of optimism, sociability and extraversion, with principal loading on "always intense romantic life", "confidence, enthusiasm and energy", "warm, extroverted and sociable" and "intense romantic life".

Factor 5. Spirituality/Mysticism/Psychoticism: This factor includes ecstatic experiences and psychotic symptoms of mania, with principal loading on "unusually spiritual or mystical", "mystical experiences or visions", "direct access to the truth", "ESP" and "hearing inspiring voices".

Factor 6. Mixed Irritability. This factor includes irritability associated with the use of medications and with medical illnesses, with principal loadings on "irritable or elevated mood when you had a medical problem such as a flu or a cold" and "irritable or elevated mood when you took medications".

Factor 7. Inflated Self-esteem. This factor describes excessive self-esteem, with principal loading on "always right, incapable of making mistakes" and "thinking you could make decisions for others".

Factor 8. Euphoria. This factor is aligned to the symptoms of mood elevation with loadings on "making puns or plays on words", "high sense of humor", "making a lot of jokes", "enthusiastic for the smallest thing" and "persistently good or high".

Factor 9. Wastefulness/Recklessness. This factor describes the tendency to spend more money than one can afford and risk-taking behaviors such as driving recklessly, with principal loading on "gave lots of presents, even when you really couldn't afford them", "pleasurable and easy to buy things", and "spending too much money; driving recklessly".

4. Research 1. To describe prevalence and clinical features of Panic Disorder of a large non-clinical sample of women recruited at the 3rd month of pregnancy and to compare with non pregnant women's sample.

4.1 Methods

4.1.1. Subjects

Two samples of women with a diagnosis of Panic Disorder were recruited: the first sample was composed of 43 pregnant women as part of a larger sample of a study conducted at Pisa by the Perinatal Depression-Research and Screening Unit (PND-ReScU); the second, the control group, was composed of 57 non-pregnant female outpatients diagnosed with PD, who presented to the psychiatric outpatient clinics of the same research center. There was no statistically significant difference in the age of the two groups. Regarding the group of pregnant women, of the 2,598 women who were asked to participate in the study, 399 (13.5%) did not meet inclusion criteria and 61 (2.3%) miscarried before the baseline assessment. A total of 1,072 (50.1%) refused to participate for various reasons including lack of time, lack of interest in the study protocol, the convictions that they would never become depressed or resistance on the part of the partner. Of those eligible (N=2138), 1,066 (49.9%) signed an informed consent to participate in the study.

4.1.2 Instruments

A diagnosis of Axis I Panic Disorder was carried out with a Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1995) in group of pregnant women, with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) in the

control group of non-gravid women respectively. The clinical features of Panic Disorder were also evaluated with Panic-Agoraphobic Spectrum–Self-Report (PAS-SR), administered respectively at 6th month post-partum in the sample of pregnant women and at baseline in the control group. The lifetime experience of mood spectrum symptoms was assessed using the Mood – Spectrum – Self-Report (MOOD-SR), lifetime version, administered respectively at 3rd month post-partum in the sample of pregnant women and at baseline in the control group.

It was possible to compare and analyze symptoms of Panic Disorder evaluated with two different scales (SCID and MINI) because the 13 symptoms of panic perfectly matched in the two interview.

4.1.3 Statistical analysis

Data are presented as means (standard deviations), or percentages. The Chi-square test was used to compare percentages and the independent t-test to compare mean scores. To assess the association between symptoms in the two groups Odds Ratios (Ors) with 95% confidence intervals were performed. Stepwise logistic regression models were performed to determine which panic symptoms were associated with PD in pregnancy. The alpha level was set at 0.05.

Analyses were conducted using SPSS, version 15.

4.2 Results

4.2.1 Demographic characteristics of the sample study

Demographic characteristics of pregnant women are provided in Table 2. Mean age was 32.3 years (SD = 3.9), a large majority (89.9%) had at least 13 years of education, 92% (N

= 981) were married or living with the partner, 82.8% were employed, 96.2% were living in urban or sub- urban areas, and 90.8% had a medium socio-economic status. One third of women (N = 360) had 1 or more children.

Demographic characteristics of the control group of pregnant women are provided in Table 3. 44.6% (N=25) had at least 13 years of education, 44.6% (N=25) were single, 48,2% were employed. Fisher's exact test was performed to compare demographic characteristics in the two groups; there was no statistical significant differences in the employment status (Fisher's exact test: p=0.368). There was statistical significant differences in the marital status ((Fisher's exact test: p<0.001) and in the education level (Fisher's exact test: p<0.001).

4.2.2 Prevalence of panic disorder at the third month of pregnancy.

One hundred and eighty four (17.3%) women had lifetime PD (life-PD), of whom 144 (13.3%) had a previous history of PD and 43 (4%) had current PD (curr-PD). Of the 43 women with current PD (28 (65.1%) with agoraphobia and 15 (34.9%) without agoraphobia), 5 (11.0%) had their first episode during the index pregnancy (Table 4). As regards comorbidity, pregnant women with curr-PD (25.6%) were about six-fold more likely to have a major depressive episode at the 3rd month of pregnancy (OR=5.844; 95% CI: 1.513-22.563) than non-gravid women (5.6%).

4.2.3 Clinical features of PD in pregnant women and controls.

Symptoms of pregnant women with a diagnosis of Current Panic Disorder (N=43) were compared with symptoms of the control group of women with Panic Disorder.

The symptoms of Panic Disorder of both groups were reported in Graph.1.

In the group of pregnant women, the symptoms most represented were: palpitations (90.7%), shortness of breath (88.4%), choking (79.1%) and sweating (74.4%) In the control group of non-pregnant women the symptoms most represented were: palpitations (87.7%), shortness of breath (63.2%), trembling (59.6%) and sweating (57.9%).

Symptoms significantly higher in pregnant women with PD compared with the control group were: fear of going crazy (OR 10.803; 95% CI: 4.235-27.555), shortness of breath (OR 4.433; 95% CI: 1.511-13.010), choking (OR 3.913; 95% CI: 1.591-9.621), depersonalization and derealization (OR 3.218; 95% CI: 1.376-7.523), flushes (OR 2.870; 95% CI: 1.233-6.684), and tingling (OR 2.446; 95% CI: 1.065-5.618).

Finally, in order to identify which symptoms were significantly associated with panic disorder in pregnancy, a stepwise logistic regression model was performed. In this model, a positive association was found between the presence of "being afraid of going crazy" (OR=4.020; 95% CI: 1.188-13.602), "shortness of breath" (OR= 9.970; 95% CI: 3.782-26.282) and panic disorder at the 3rd month of pregnancy.

The presence of Agoraphobia was significantly higher in gravid women (OR 3.630; 95% CI: 1.557-8.462) than in non-gravid women. Agoraphobia rates of both groups were reported in Graph.2.

In addition, clinical features of panic disorder were investigated with the lifetime version of the PAS-SR questionnaire. The total score and the factors of the PAS-SR were similar in the two groups (Table 5).

A T-Test was performed to compare mood spectrum scores in the two groups. Pregnant women reported higher mean scores in the following manic factors of mood spectrum: psychomotor activation (3.923 vs. 2.563; t=2.705; p=0.008), creativity (3.461

vs. 1.618; t= 3.752; p= 0.000) euphoria (2.128 vs. 0.963; t=4.215; p<0.001) (Table 6). No significant differences were found in depressive factors scores in the two groups (Table 7).

4.3 Discussion

Anxiety symptoms are frequently reported by pregnant women and are often considered as part of the normal psychic experiences of pregnancy, especially if they are focused on the baby's health or on maternal competencies. Of all anxiety disorders, PD needs to be carefully noted. In fact, a gender effect has been demonstrated for PD, affecting predominantly women (ratio male–female: 1.0–2.3) (Kessler et al., 2006). PD most commonly manifests onset from late adolescence to the mid-30s; therefore it is likely that a significant number of women suffering from a PD will experience a pregnancy during the course of their illness. Therefore, PD is associated with high rates of psychiatric comorbidity, especially with major depression (Lesser et al.,1988) and, notably, PD patients with comorbid depression usually display greater symptom severity (Andrade et al., 1994), poorer response to both psychotherapeutic (Feske et al., 1998, Frank et al., 2000) and pharmacological treatments (Frank et al., 2000; Grunhaus et al., 1994), compared to PD patients without comorbidity.

It has been estimated that 3% to 12% of women experience symptoms related to PD at some time during their childbearing years, including during pregnancy and the postpartum period (Wenzel et al., 2001; Smith et al., 2004). There are a few studies reporting the prevalence of PD in pregnant women. In the sample of pregnant women of the present study a higher lifetime prevalence of PD (17.3%) was found than in women in the Italian general population (2.2%) (de Girolamo et al., 2006); these results

may be explained by the high sensitivity to reassurance typical of panic patients that might have led to a selection bias, thereby increasing the response rate of these women. On the other hand, the SCID was administered by trained and certified psychiatrists; this might determine a higher level of diagnostic accuracy and skill in discriminating between diagnoses (i.e., panic disorder vs. agoraphobia). The current prevalence of panic disorder (4%), even if higher than that reported by Andersson et al. (2003) (0.2%) and by the MATQUID (2004) (1.4%), was in line with the prevalence reported by Smith et al. (2004) (2%) and Spitzer et al. (2000) (3%) in the validation study of the Primary Care Evaluation of Mental Disorders (PRIME-MD) in obstetric-gynecological patients. In a controlled study of Nigerian women in late pregnancy (Adewuya et al., 2006), investigators showed a rate of 5.2% of PD. In consonance with prior investigation data (Nonacs and Cohen, 2003), in this study 5 (11.0%) women had their index episode during pregnancy.

Comorbidity between anxiety and depression symptoms is common and has been frequently reported during pregnancy (Field et al., 2003; Heron et al., 2004; Wenzel et al., 2005; Matthey, 2007; Matthey et al., 2003; Littleton et al., 2007; Austin et al., 2007). In a study by Ross et al. (2003), nearly 50% of clinically depressed pregnant and postpartum women had clinically significant comorbid anxiety; and according to Andersson et al. (2006) 20.5% of women who were given a psychiatric diagnosis in the 2nd pregnancy trimester presented comorbid anxiety and depression symptoms.

In this study, twenty-five pregnant women (25.6%) had a current comorbidity between depressive and panic disorder. Pregnant women with current PD were about six-fold more likely to have a major depressive episode at the 3rd month of pregnancy (OR=5.844; 95% CI: 1.513-22.563) compared to non-gravid women.

Panic Disorder is characterized by paroxysmal and recurrent attacks in which intense fear is accompanied by an array of physical and psychological symptoms. Palpitations, tachycardia, dyspnea, dizziness and trembling are the most frequent and significant symptoms reported by patients with PD (Startevic et al., 1993). Physical symptoms such as heart palpitations, flushing and sweating, nausea, dizziness and shortness of breath are often present during pregnancy (Weisberg and Paquette; 2002); an accurate diagnosis of PD in pregnancy is complicated by the fact that there is significant overlap between the clinical symptoms of PD and the physiological symptoms of pregnancy. However in PD, panic symptoms occur simultaneously, build to peak intensity within ten minutes and frequently begin "*out-of-the-blue*" or without a clear trigger such as physical exertion (Weisberg and Paquette, 2002). Another important distinction is that in panic disorder women exhibit fear or concern about these attacks and their implications. For instance, women may believe that the attacks are a signal that they are going crazy or having a heart attack (Weisberg and Paquette; 2002).

Furthermore, although panic symptoms during the perinatal period are typical symptoms reported in the general population, they are often interpreted in the context of the perinatal state and concerns about the pregnancy and fetus may represent the predominant features (Ross et al., 2006).

One strength of this study was to describe symptoms in pregnant women with a diagnosis of current panic disorder and to compare with a control group of non-pregnant women, using structured diagnostic interviews. To date, only a few studies have assessed clinical features of PD (Weisberg and Paquette, 2002): for example, Guler et al. (2008) have investigated the severity of PD with the Panic Agoraphobia Scale (PAS) but not the clinical features of PD. Therefore, few studies have included an

appropriate non-perinatal control group.

This is the first study that has systematically described symptoms of PD in gravid women and that has compared clinical features of PD between gravid and non-gravid woman, using structured diagnostic interviews. According to the literature (Weisberg and Paquette, 2002), the results of this study suggested that symptoms of panic during pregnancy reflected those typically reported by the general population. Specifically, the panic symptoms most represented in the gravid women group were: palpitations (90.7%), shortness of breath (88.4%), choking (79.1%), sweating (74.4%), flushes (72.1%). However, symptoms such as being afraid of going crazy (OR 10.803; 95% CI: 4.235-27.555), shortness of breath (OR 4.433; 95% CI: 1.511-13.010), choking (OR 3.913; 95% CI: 1.591-9.621), depersonalization/derealization (OR 3.218; 95% CI: 1.376-7.523), flushes (OR 2.870; 95% CI: 1.233-6.684), tingling (OR 2.446; 95% CI: 1.065-5.618) were significantly higher in pregnant women with PD compared to the control group. In particular, the symptom "*being afraid of going crazy*" is associated with the highest odds ratio; this finding could suggest a possible key role of this symptom in identifying a specific panic phenotype connected to pregnancy. Further investigations are warranted to clarify the potential utility of this result in clinical practice and in neurobiological studies.

According to the literature, "*fear of going crazy*" is the symptom that has most often been associated with psychosensorial symptoms of depersonalization and derealization (Bandelow et al., 1996; Briggs et al., 1993; De Beurs et al., 1994) in the general population. Cassano et al. (1989) suggested that PD subjects with derealization may represent a more severe subgroup of patients (an earlier age of onset of panic disorder, greater avoidance behavior, more comorbidity with depressive symptoms). Moreover,

Segui et al., (2000) found similar results in a large sample of PD with depersonalization; Miller et al. (1994) found that panic disorder patients with derealization featuring in their attacks were more likely to have depression.

Thus, the relevance of symptoms such as derealization/depersonalization and fear of going crazy in pregnant women with PD may suggest that panic in pregnancy is particularly severe. Furthermore, it can be hypothesized that "*depersonalization*" symptoms in pregnant women with PD may be due to coping deficit related to the gravid state that may lead to a feeling of "*a sense of unreality and detachment from themselves*".

In this study, agoraphobia was significantly higher in gravid women compared to non-gravid women (OR 3.630; 95% CI: 1.557-8.462). Our results were not in line with those of Guler et al. (2008) which showed that agoraphobia was similar in pregnant women and in controls. However, this inconsistency in the results might be due to the fact that Guler et al. had a small sample size and also to cultural differences. Panic symptoms in pregnant women are often interpreted in the context of the perinatal state, and concerns about the pregnancy and the fetus may represent the predominant features (Ross et al., 2006). Bearing this in mind, also "*agoraphobia*" may be interpreted in the context of the perinatal state; the higher level of agoraphobia reported by pregnant women compared to controls may be explained by the additional concerns they have related to their gravid state. While non-pregnant women with agoraphobia seem to be afraid of having a panic attack for the implications on their own health, pregnant women would seem to be worried also for the fetus; this additional concern may go further in explaining the increase of agoraphobic behavior in pregnant women in comparison with controls.

T-Tests were performed to compare mood spectrum scores in two samples of women with PD. While no significant differences were found in depressive mood spectrum scores in the two samples, pregnant women reported higher mean scores in the following manic factors: psychomotor activation (3.923 *vs* 2.563; t student=2.705; p=0.008), creativity (3.461 *vs* 1.618; t student= 3.752; p=0.000), euphoria (2.128 *vs* 0.963; t student=4.215; p=0.000).

In non-puerperal states, experiencing hypomanic symptoms has been linked with an increased likelihood of taking part in risk behaviors; increased lifetime suicidality; poor response to antidepressants; increased social behavior, creativity/expressiveness and episodic improvements in motivational functioning (Heron et al., 2009). There has been little investigation of milder manic states in the perinatal period (Heron et al., 2009). The implications of experiencing manic symptoms of mood spectrum in the perinatal period require further investigation. Hypomanic symptoms often only come to clinical attention because they are associated with a high risk of subsequent depression or because they escalate into more severe manic symptoms. Women who develop severe episodes in bipolar affective puerperal psychosis report experiencing mild hypomanic symptoms in the early postpartum period (Heron et al., 2007; 2008).

In this study, the finding that pregnant women with PD reported higher mean scores in manic factors such as psychomotor activation, creativity, euphoria, compared to non-pregnant women (particularly at the first trimester of pregnancy) can be explained by the mother's looking forward to the arrival of the child that might determine some changes in energy levels, mood state, etc.

These results need to be considered while keeping in mind the following limitations. First, these findings should be confirmed by further prospective studies, including a

larger sample size. Secondly, demographic characteristics of the two groups were not homogeneous: pregnant women had higher education levels compared to the control group and were more frequently married or living with the partner.

Thirdly, in comparison with pregnant women lower depression comorbidity in the control group may be due to a selection bias; in fact the control group was composed of non-pregnant female outpatients who presented to specific surgery for diagnosis and treatment of DP. Moreover, the lack of a specific measure of severity of PD has allowed us to make only clinical observations about panic symptoms severity. Another limitation of this study is that the derealization and depersonalization symptoms have been investigated by the same item of the SCID/MINI; this did not allow us to understand which of these two symptoms was more represented during pregnancy. As such due to the small sample size of women with manic factor, we were unable to carry out more detailed analyses to assess the stability of manic factor rates across three trimesters of pregnancy, to assess clinical features of post-partum depression in women with manic factors during pregnancy as compared to those without manic factors.

5. Research 2) To investigate the role of PD (as family history, previous diagnosis or the occurrence of PD during pregnancy) on the development of PPD.

5.1 Methods

5.1.1 Subjects

Of the 2,598 women who were asked to participate in the study, 399 (13.5%) did not meet inclusion criteria and 61 (2.3%) miscarried before the baseline assessment. A total of 1,072 (50.1%) refused to participate for various reasons including lack of time, lack of interest in the study protocol, the convictions that they would never become depressed or resistance on the part of the partner. Of those eligible (N=2138), 1,066 (49.9%) signed an informed consent to participate in the study. For the present aim, the analyses were conducted on the 600 women who completed the assessment at 6th month after delivery (FIG.1)

5.1.2 Instruments

A diagnosis of Axis I Panic Disorder was carried out with a Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1995). The family history of psychiatric disorders was assessed using the Family History Screen (FHS) (Weissman et al., 2000). The Post-partum Depression Predictors Inventory-Revised (PDPI-R) (Beck, 2002) was administered to identify the risk factors for PPD. Depressive symptoms were assessed at the 1st, 3rd and 6th month after delivery using the 10-item Edinburgh Postnatal Depression Scale (Cox et al., 1987). When women exceeded the threshold score (≥13) of EPDS, the Mood module of SCID was

administered to distinguish between false positives and women who met criteria for minor or major depression (mMD).

5.1.3 Statistical Analyses

Data are presented as means (standard deviations), or percentages. The Chi-square test was used to compare percentages and the t-test to compare mean scores. Logistic regression models were used to determine whether PD predicted mMD above and beyond the established risk factors assessed with PDPI-R. Because the association between PD and mMD may be confounded by previous and current depression and several risk factors, we included both previous and current episodes of MD and PDPI-R total score in the model to control for their effect. The alpha level was set at 0.05. Analyses were conducted using SPSS, version 15.

5.2 Results

5.2.1 Demographic characteristics of the sample study

Demographic characteristics of participants are provided in Table 2. The 600 women who completed the 6^{th} month follow-up did not differ from those who did not complete the follow-up on marital status, socio-economic status, employment, living area, parity and presence of PD at baseline. They were 1 year older (32.7±3.7 *vs*. 31.7±4.1; p<0.001) and had a higher education level (92.6% *vs*. 88.5% p=0.02).

5.2.2 Comorbidity with mMD at the 3rd month of pregnancy

One hundred and eighty four (17.3%) women had lifetime PD (life-PD), of whom 144 (13.3%) had a previous history of PD and 43 (4%) had current PD (curr-PD). Of the 43 women with a curr-PD, 18 (41.9%) had an mMD episode in comorbidity and 6 (14%) had a comorbidity with other anxiety disorder at study entry. Women with curr-PD were about ten-fold more likely to have mMD at the 3rd month of pregnancy (OR=9.2; 95% CI: 4.8–17.7). Of the 144 women with a previous history of PD, 28 (21.6%) had an mMD episode at study entry; a previous history of PD was associated with a three-fold higher risk of having mMD at the 3rd month of pregnancy (OR=3.24; 95% CI: 2.0–5.3).

5.2.3 Association with history and current PD with post-partum depression

Overall 40 (6.7%) women had mMD in the post-partum period. Of the 24 women with curr-PD who completed the follow-up assessment, 6 (25%) had an mMD in the post-partum period. Curr-PD during pregnancy was associated with a significantly higher risk of developing mMD in the postpartum (RR=5.8; 95% CI: 2.2–15.8) (Graph.3) Adjusting for the PDPI-R and for history and current major depression, the risk slightly decreased, but it remained statistically significant (RR=4.25; 95% CI: 1.48–12.19). Comorbidity with other anxiety disorders at baseline was not associated with mMD. A previous history of PD was associated with the risk of developing mMD in the post-partum (RR=3.1; 95% CI: 1.5–6.7) and this risk remained significant even after adjustment for the established risk factors (PDPI-R) and for previous and current depression (RR 2.47; 95% CI: 1.11–5.49) (Graph.3).

5.2.4 Association with family history for DP with post-partum depression

The predictive role of family history for psychiatric disorders on development of PPD was analyzed; only family history for PD was associated with an increased risk of developing mMD in the post-partum (RR=2.35; 95% CI: 1.2–4.6). After adjusting for risk factors (PDPI-R) and the presence of curr-PD as well as a previous and current depression, women with a family history for PD were also at higher risk for PPD (RR=2.1; 95% CI: 1.06–4.4) (Graph.3).

5. 3 Discussion

In recent decades, a large number of psychiatric, psychosocial and obstetrical risk factors for postnatal depression (PND) have been identified (Kumar and Robson, 1984; O'Hara and Swain, 1996; Verdoux et al., 2002). Among psychiatric risk factors, the best documented to date is a personal or family history of mood disorder, with an increased risk especially marked in women with pregnancy depression (O'Hara and Swain, 1996). The results of this study revealed that anxiety symptoms should not be too hastily considered as a normal adaptive process to pregnancy, but should be further investigated to exclude the presence of a PD diagnosis, given its significant association with the development of subsequent PND (Sutter-Dallay et al., 2004). As literature suggests, no studies have examined the predictive role of a specific diagnosis of anxiety disorder in post-partum depression, although previous studies have evaluated the predictive role of anxiety symptoms (Austin et al., 2007) and anxiety disorders in general (Sutter-Dallay et al., 2004). This the first study that has evaluated the predictive role of PD on the development of PND. The results of this research suggest that PD as present in the patient's history or in the family history is

an independent risk factor for PND. Women with PD have significantly greater risk of developing PND than those without PD and women with PD during the early phase of pregnancy are 4.2 times more likely to have PND than those without PD, even after controlling for the risk factors for PPD (Beck, 2002) or the presence of previous or current depression. Moreover, these findings point out that women who had both a previous history of PD and a family history for PD are, respectively, 2.5 and 2.1 times more likely to develop PPD, independently of lifetime comorbidity of mMD and the presence of risk factors for PND (Beck, 2002).

The complex relationships between anxiety and depression have been explored in clinical and epidemiological samples (De Graaf et al., 2003; Levine et al., 2001; Merikangas et al., 2003). In accordance with previous findings, the present study suggests that a continuum of risk may exist between pregnant women and subjects from the general population with regard to the comorbid association between anxiety and depressive disorders. The specificity of the postnatal period compared to other periods of the lifecycle may be related to a possible acceleration of the risk of transition from AD to depression under the influence of the various psychosocial and biological stressors prevalent in the perinatal period. In other words, the link between anxiety and depression may be quantitatively, but not qualitatively, different in perinatal periods compared to other stages of the life (Sutter-Dallay et al., 2004).

A large sample size and the use of a structured clinical interview represent major strengths of this study that may have important practical and theoretical implications. In fact, on one hand these findings clearly point out that PD, as a past history or even as a family history, need to be routinely screened in pregnant women

to identify those at risk of developing PND. On the other hand, they further support a relationship between PD and hormones among female patients. During pregnancy, in accordance with the false suffocation alarm theory (Klein, 1993), the increased plasma levels of progesterone that stimulate respiration and the consequent decrease of partial pressure of carbon dioxide ($PaCO_2$) may have a protective effect on DP. However, conclusive studies of this area are lacking, although they are urgently needed to clarify the neurobiology of PD during pregnancy and its link with PND. Moreover, it is possible that the increasing of perceived social support may reassure the women with a history of PD.

The results of this study had several limitations. First, the response rate is moderately low (49.9%), however it is comparable to that of similar studies that used self-report and structured clinical interviews, in which the observation period spanned from pregnancy to post-partum (Grant et al., 2008; Kitamura et al., 2006). Secondly, the percentage of women with at least a high school diploma (89.9%) is significantly higher than the percentage in women delivering in Tuscany (66.8%) (*Agenzia Regionale Sanità Toscana, 2006*). Moreover, to confirm or to exclude a diagnosis of mMD the Mood section of the SCID was administered at each follow-up visit to women exceeding the EPDS threshold of 12. The use of this cut-off may lead to an underestimation of some cases, since some women with minor depression may have EPDS scores of around 10, thus we cannot establish exactly the number of false negatives. Finally, the homogeneous socio-economic status of the sample, including predominantly employed women with a medium socio-economic status can affect the external validity of our results.

6. Third Research. To assess the specific role of DP in predicting probable depression (EPDS>12), major or minor depression (MMD) and false positives (EPDS>12 without mMD) at first month/year after delivery.

6.1 Methods

6.1.1 Subjects

Of the 2,598 women who were asked to participate in the study, 399 (13.5%) did not meet inclusion criteria and 61 (2.3%) miscarried before the baseline assessment. A total of 1,072 (50.1%) refused to participate for various reasons including lack of time, lack of interest in the study protocol, the convictions that they would never become depressed or resistance on the part of the partner. Of those eligible (N=2138), 1,066 (49.9%) signed an informed consent to participate in the study.

For the present aim, the analyses were conducted on the 500 women who completed the assessment at the 12th month after delivery (FIG.1). During the follow-up 566 participants dropped out (53.1%). Socio-demographic and clinical characteristics between the 566 women who dropped out and those who completed the 12th month follow-up assessment (n=500) were compared: no significant differences were detected on marital status, socio-economic status, educational level, living area and parity. Women who dropped out were significantly younger (31.8±4.1 *vs*. 32.8 ±3.8; t=3.82; p <0.001), and more frequently unemployed (8.6% *vs*. 4.5%; chi-square=7.01; p=0.008). Furthermore, the frequency of anxiety disorders (AD) and the overall risk factors assessed with the PDPI-R were compared at baseline between the two groups. No significant differences were found on AD between women who dropped out and women who completed the follow up, with the

exception of specific phobia: namely, women with a diagnosis of specific phobia dropped out in a greater percentage (63.2% *vs*. 52.9%, chi-square=5.19; p=0.023). Women who dropped out had a higher PDPI total score than women who completed the 12th month follow-up assessment (4.1±3.6 *vs*. 3.4±3.1; t=-3.8; p<0.01).

6.1.2 Definition of "Postpartum depressions"

In this study three different conceptualizations of postpartum depression assessed in a two-step process were used: probable depression, mMD and false positives (FIG. 2)

1st step: Identification of probable depression

The severity of depressive symptoms was assessed using the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al. 1987). In the present study, the threshold of 12 was used to define probable depression, in line with the EPDS original study (Cox et al., 1987) that used RDC criteria as the gold standard (Spitzer et al., 1978). This threshold has been confirmed by other authors and recently by Matthey and colleagues (2006).

2nd step: Identification of Minor or Major Depressive Episode (mMD) and false positives.

Participants exceeding the EPDS cut-off score were interviewed by 6 psychiatrists and psychologists trained and certified to the use of Structured Clinical Interview for DSM-IV Disorders (SCID-I) (First et al., 1995) to confirm the diagnosis of mMD. Women who had probable depression but who did not meet criteria for mMD were coded as false positives.

6.1.3 Instruments & timing of assessment

The timing of assessment for the predictors and the timing of assessment for the outcome measures are reported in FIG.1. At study entry, anxiety disorder diagnoses were assessed by a psychiatrist or a psychologist with the SCID (First et al., 1995) and two self-report measures were completed (EPDS and PDPI-R). The Post-partum Depression Predictors Inventory-Revised (PDPI-R) (Beck 2002) was used to identify the risk factors for PPD. The EPDS (Cox et al., 1986) was further administered at five different times: at the 1st, the 3rd, the 6th, the 9th, and at the 12th month after childbirth. When the EPDS score was >12, the mood section of the SCID was administered by a trained psychiatrist or psychologist in order to determine whether the subject met DSM-IV criteria for mMD or was a false positive. For the purpose of this study, both the 1st month postpartum point prevalence and the 12th month period prevalence (calculated as the percentage of women with depression at any time during postpartum) were used as the gold standard.

6.1.4 Statistical analyses

Data are presented as means and percentages. The differences between categorical variables were calculated using the chi-square or McNemar test, while the differences between continuous variables were calculated using the independent t test. In order to establish the relationship between a specific anxiety disorder and the occurrence of probable depression, mMD and false positives in the postpartum, logistic regression models were performed. Furthermore, the relationship between anxiety disorders and the occurrence of different outcome measures in the postpartum were analysed using a stepwise logistic regression model.

Odds Ratios and 95% of confidence intervals were reported. In order to clarify the magnitude of effect size we rescaled the OR in Cohen's d using the γ coefficient (γ= (OR-1)/(OR+1)) (Kraemer and Kupfer, 2006). An effect size of 0.2, 0.5, and 0.8 are "small," "medium," and "large" (Cohen, 1988). Analyses were conducted using SPSS, version 15.

6.2 Results

6.2.1 Postpartum depressions

At the 1st endpoint (1st month postpartum), of the 751 women who completed the 1st month postpartum assessment, 41 (5.5%) had probable depression (EPDS total score of 13 or more). In 58.5% (N=24) of the cases of probable depression (N=41), a diagnosis of minor or major depression (mMD) was confirmed, and the prevalence of mMD at the 1st month postpartum was 3.2%: the difference observed in prevalence rates estimated with EPDS (5.5%) and with an interview-based method was statistically significant (McNemar=4.65, p=0.031). 41.5% of the probable depressions were false positives; however, the EPDS total score (17.8±3.0 *vs*. 16.2±3.6; t=1.49, p=0.14), EPDS anxiety factor (6.7±1.5 *vs.* 6.5±1.5; t=0.37, p=0.71), and EPDS depression factor (11.1±2.3 *vs*. 9.7±2.8; t=1.72; p=0.09) did not differ between mMD and false positives. Regarding the functional impairment, mMD and false positives had a similar mean total score on the WSAS (20.0±8.8 *vs*. 19.9 *vs*. 9.5; t-test=0.041; p=0.97). Furthermore, the percentage of women who received treatment (pharmacological or psychological support or combined treatment) was similar in mMD and false positives (50.0% *vs*. 41.2%, chi-square=0.31, p=0.58).

At the 2nd endpoint (12th month postpartum), of the 500 women who completed the

study, 89 (17.8%) had probable depression, of whom 49 (55.1%) had a major or a minor depressive episode. Therefore, the one-year period prevalence of "postpartum depression", defined as the diagnosis of minor or major depression, decreased from 17.8% (89/500) to 9.8% (49/500).

The difference observed in the one-year prevalence rates of postpartum depression estimated with the EPDS (17.8%) and the SCID (9.8%) was statistically significant (McNemar=13.45, p<0.001). 44.9% of the probable depressions detected during the 1st year postpartum were false positives. The EPDS total score was higher in mMD than in false positives (17.6±3.3 *vs*. 15.3±3.0; t=3.18, p=0.002); furthermore, the EPDS depression factor was higher in mMD than in false positives (11.1±2.8 *vs*. 9.3±2.3; t=3.06, p=0.003), while the EPDS anxiety factor (6.5±1.6 *vs*. 6.0±1.8; t=1.31, p=0.19) and the functional impairment (21.3±7.7 *vs*. 17.8±8.5; t=1.95, p=0.06) was not.

6.2.2 Anxiety Disorders as predictors of "postpartum depression".

Outcome: probable depression (EPDS score >12)

The relationships between anxiety disorders during pregnancy and probable depression assessed with the EPDS were examined using logistic regression models. First, 1st month point prevalence was used, then we performed the analysis using 1-year period prevalence as a dependent variable. To determine whether having any anxiety disorder or a specific anxiety disorder during pregnancy was associated with probable depression, univariate logistic regression models were performed; the results are reported in Table 8.

In order to identify which anxiety disorders were significantly associated with

probable depression, the stepwise logistic regression model was fitted. After adjustment for risk factors assessed with PDPI-R (RR=3.83; 95% CI: 1.84-7.97), a significant association was found between panic disorder (Adjusted RR=5.27; 95% CI: 2.0-13.91) and social phobia (Adjusted RR=3.80; 95% CI: 1.34-10.46), while the OCD, that was significant before adjustment for PDPI-R, was no longer associated with probable depression at the 1st month after childbirth. Using one-year period prevalence as an outcome measure, the stepwise logistic regression model was fitted to assess which anxiety disorders were significantly associated with probable depression. A positive association was found between the presence of PTSD (Adjusted RR=12.2; 95% CI: 1.10-135.85) and the greater likelihood of developing an mMD, while the GAD, that was significant before adjustment for PDPI-R, was no longer associated with probable depression during the 1st year postpartum.

Outcome: minor or major depressive episode (mMD)

As for the above, we used both 1st month point prevalence and one-year period prevalence as outcome measures. To determine the relationship between the presence of each current anxiety diagnosis at the 3rd month of pregnancy and the likelihood of having mMD at the first month postpartum, univariate logistic regression models were performed. Table 8 reports the relative risk (RR) for each anxiety disorder in predicting mMD. In order to identify which anxiety disorders were significantly associated with probable depression, the stepwise logistic regression model was fitted. After the adjustment for risk factors assessed with PDPI-R (RR=2.74; 95% CI: 1.06-7.07), the predictive role of panic disorder (RR=7.23; 95% CI: 2.31-22.66) and social phobia (RR=6.63; 95% CI: 2.11-20.85) remained

significant in predicting 1st month postpartum mMD.

With regard to the one-year period prevalence, our results show that after adjustment for the established risk factors assessed with PDPI-R (RR=4.66; 95% CI: 2.41-9.02), the only anxiety disorder associated with postpartum depression was panic disorder (Adjusted RR=3.10; 95% CI: 1.16-8.22).

6.2.3 The issue of false positive (EPDS score >12 without a diagnosis of mMD)

41.5% (N=17) at the 1st month postpartum, and 44.9% (N=40) during the 1st year after childbirth of the probable depressions were false positives. We evaluated whether a diagnosis of any anxiety disorder during pregnancy was associated with false positive cases detected with the EPDS (>12) and not confirmed with the SCID. The results showed that, after adjustment for confounders, a diagnosis of any anxiety disorder predicted false positive cases only at the 1st month after childbirth (Adjusted RR=2.78; 95% CI= 1.03-7.49), but not during the first year postpartum (Adjusted RR=1.30; 95% CI= 0.53-3.22) Table 8 reports the relative risk (RR) both for any anxiety disorder and for each anxiety disorder in predicting false positives.

Finally, we performed two stepwise logistic regression models to evaluate the role of anxiety disorders in predicting both 1st month and one-year false positive cases and we controlled for the effect of the confounders. Our results showed that only Obsessive Compulsive Disorder (OCD) (Adjusted RR=8.66; 95% CI: 1.59-47.03) was associated with false positive cases assessed at the 1st month postpartum, while no anxiety disorders were further associated with false positives assessed during the 1st year after childbirth.

6.2.4 Effect sizes of anxiety disorders in predicting postpartum depressions

The magnitude (ES) of the relationships between different anxiety diagnoses and different conceptualizations of postpartum depression were computed for those diagnoses that were significantly associated with the three outcomes in the adjusted models using Cohen's d. Panic Disorder had the largest effect size in predicting both mMD (Cohen's d=0.87) and probable depression (Cohen's d=0.82) at the 1st month postpartum, while this effect slightly decreased during the first year postpartum (Cohen's d=0.71). Social Phobia had a large effect size and a medium effect size in predicting mMD (Cohen's d=0.86) and probable depression (Cohen's d=0.77) at the 1st month postpartum, respectively. Obsessive Compulsive Disorder had a large effect size (Cohen's d=0.89) in predicting false positive cases detected with the EPDS (>12) and not confirmed with the SCID. Furthermore, Post Traumatic Stress Disorder had a large effect size (Cohen's d=0.92) in predicting probable depression during the first year postpartum. Finally, the association between established risk factors assessed with the PDPI-R and the postpartum distress outcomes in the six adjusted models that we performed vary from 0.67 and 0.85 (Cohen's d), indicating overall effect sizes from medium to large.

6.3 Discussion

Literature suggests that anxiety is a feature of perinatal depression (Hendrick et al., 2000; Ross et al., 2003) and that, in the perinatal period, anxiety symptoms are usually conceptualized and measured in depression rating scales such as the EPDS (Cox et al., 1986). Concerning the EPDS, although the instrument was conceptualised to detect probable cases of depression, authors reported that the instrument has

both a depression factor and an anxiety factor (Browers et al., 2001; Philipps et al., 2009). Therefore, also false positives might present clinically relevant symptoms that need treatment. There is growing recognition that in current usage "postpartum depression" (PPD) is an umbrella term that includes a heterogeneous group of conditions with features of both depression and anxiety, underlying the need for a new definition of the PPD construct itself. Thus, both the construct and the prevalence estimates of PPD are strictly related to the instrument used to assess it. In the light of these methodological issues, it could be hypothesized that different, specific risk factors might play a different role in predicting different "postpartum depressions".

The third aim of this study was to evaluate the role of anxiety diagnoses, in particular of PD, during pregnancy, as predictors of different conceptualizations of postpartum depression (probable depression, mMD, false positives). Overall, anxiety in pregnancy was associated with a substantially increased likelihood of postnatal distress outcomes, even after controlling for established risk factors assessed with PDPI-R. One of the main findings of this study was that different anxiety diagnoses had a specific predictive role on the different conceptualization of postnatal distress and that, in general, the effect size of a predictor decreased from the 1st month to the 12th month postpartum. Regarding the 1st month postpartum, results indicated that after adjustment for potential confounders assessed with PDPI-R, while PD and Social Phobia predicted both a diagnosis of minor or major depression and a high depressive symptomatology conceptualized as an EPDS score above 12 (probable depression), a diagnosis of OCD predicted false positive cases that were detected as probable depression with the EPDS, but not subsequently confirmed with the SCID.

Panic Disorder and Social Phobia had a greater effect size in predicting 1st month PPD than probable depressions.

In relation to the 12th month postpartum, the results of this study confirmed the role of Panic Disorder in predicting a diagnoses of minor or major depression even if with a decrease in effect size. The role of PTSD in increasing the likelihood of having high scores during the 1st year postpartum has to be viewed with caution. In general, although results are consistent with the literature that reveal the role anxiety disorders and symptoms have in the development of PPD (Heron et al., 2004; Sutter-Dallay et al., 2004; Skouteris et al., 2009), it is important to underline that the role of a specific anxiety diagnosis in predicting depressive symptoms is related both to outcome definitions and to time of assessment.

There are some limitations that should be taken into account in interpreting the findings in the present study. First, as women participated on a voluntary basis, the study was not carried out on an epidemiological sample and this may have favored the inclusion of women. Secondly, the socio-demographic characteristics of women who refused to participate in the study are not available because data collection was possible only after the informed consent form was signed, as prescribed by the Italian law on privacy; thus we were unable to ascertain if non-responders were mostly of lower socio-economic class and had lower levels of education. A third limitation was that over half of the participants (53.1%) did not complete the follow-up. Moreover, while some anxiety diagnoses such as Panic Disorder, GAD, and Social Phobia are frequent, OCD and PTSD are quite uncommon; thus, the association between this specific anxiety diagnosis with postpartum depressive symptomatology should be taken with caution. In particular, looking at the confidence intervals it can

be seen that the effect of PTSD might vary from small to large, thus this specific result requires careful interpretation.

7. Conclusion

Many of the physiological sensations that occur during pregnancy closely resemble anxiety symptoms; thus, these disorders may be masked in pregnant women. For this reason it is essential that treatment providers in obstetric offices, primary care settings, and mental health clinics be attuned to the signs of anxiety disorders (Weisberg and Paquette, 2002). Moreover, it is important to differentiate between manageable antenatal anxiety occurring as part of the life transition to parenthood which is amenable to extra support and information and more debilitating antenatal anxiety conditions that require specific assessment and treatment by a mental health professional (Adewuya et al., 2006). Our findings suggest that panic symptoms in pregnant women are typical panic symptoms reported by the general population. Moreover, symptoms such as "*fear of going crazy*", "*shortness of breath*" are significantly more represented in pregnant women with panic disorder than in the control group, suggesting that these symptoms, particularly "*fear of going crazy*" are likely to improve the screening and identification of women who experience panic during pregnancy. According to the results of this study, pregnant women with panic disorder seem to present higher depersonalization, agoraphobia, depression comorbidity and manic mood factors than the control group; these findings might suggest that severity of panic symptoms will be particularly pronounced in pregnant women as compared with non-pregnant women. As others have noted (Austin, 2003; Austin et al., 2005; Glover and O'Connor, 2002), it may be just as important to

focus on the detection and treatment of perinatal anxiety, given its significant association with the development of subsequent postnatal depression. The findings of this study suggest that Panic Disorder represents an important risk factor for the development of post-partum depression and patients should be routinely screened in order to develop specific preventive interventions. Interestingly, both personal and family history for Panic Disorder are independent risk factors, suggesting that the neurobiology of Panic Disorder may be strictly interlinked with that of post-partum depression. Finally, it is important to underline that the role of specific anxiety diagnosis such as panic disorder in predicting post-partum depressive symptoms is related both to outcome definitions and to the time of assessment and that, in general, the effect size of a predictor decreased from the 1st month to the 12th month postpartum. Panic Disorder had a greater effect size in predicting 1st month post-partum depression than probable depressions. In relation to the 12th month postpartum, the results of this study confirmed the role of Panic Disorder in predicting a diagnoses of minor or major depression, even if with a decrease in effect size. Pregnancy may be an ideal time for intervention, to mitigate the mother's suffering and to reduce the long-term consequences of an untreated mental disorder. Carrying out antenatal screening of established risk factors and accurate diagnoses of Panic Disorder during pregnancy may help to plan adequate treatment in order to prevent possible postpartum distress outcomes. Further studies are needed to replicate our findings and to clarify the neurobiology of Panic Disorder during pregnancy and its link with Post-Partum Depression in order to identify a specific subgroup of women warranting special attention.

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Tab. 1 Schedule of Assessment.

	PREGNANCY			POSTPARTUM			
	T0 (3rd mo.)	T1 (6th mo.)	T2 (8th mo.)	T3 (1st mo.)	T4 (3th mo.)	T5 (6th mo.)	T6 (9th mo.)	T7 (12th mo.)
Informed consent	X							
Clinical evaluation	X							
Demographic profile	X							
SCID-I	X	X*	X*	X*	X*	X*	X*	X*
FHS	X							
PDPI-R	X	X	X	X	X	X	X	X
MOODS-SR LF	X							
MOODS-SR LM	X	X	X	X	X	X	X	X
PAS-SR-LF	X							
OBS-SR LF	X							
ABS-SR	X							
EPDS	X	X	X	X	X	X	X	X
WSAS	X	X	X	X	X	X	X	X
STAI-Y	X	X	X	X	X	X	X	X

Tab.2 Socio-demographic characteristics of the sample of pregnant women.

	Baseline (N=1066)	**6 th month follow-up (N=600)**
Demographic characteristics		
Age (mean+SD)	32.27+3.95	32.7+3.74
Marital Status N(%)		
Single	47(4.4)	24(4.0)
Married/cohabiting	981(92)	551(91,8)
Separed/divorced	30(2.8)	20(3.4)
Widowed	2(0.2)	2(0.3)
Missing	6(0.6)	3(0.5)
Employment status N(%)		
Student	22(2.1)	10(1.7)
Unemployed	70(6.6)	30(5.0)
Employed	883(82.8)	510(85.0)
Housewife	60(5.6)	34(5.7)
Other	17(1.6)	8(1.3)
Missing	14(1.3)	8(1.3)
Education level (N%)		
Primary school	3(0.3)	1(0.2)
Secondary School	94(8.8)	43(7.2)
Hight school (completed)	511(48.0)	279(46.5)
University degree	447(41.9)	273(45.4)
Missing	11(1.0)	4(0.7)
Socioeconomic Status N(%)		
Low	34(3.2)	16(2.7)
Medium	968(90.8)	556(92.7)
High	19(1.8)	9(1.5)
Missing	45(4.2)	19(3.2)
Living area N(%)		
Urban	534(50.1)	302(50.3)
Suburban	491(46.1)	282(47.0)
Rural	26(2.4)	10(1.7)
Missing	15(1.4)	6(1.0)
First pregnancy N(%)		
Yes	704(66.0)	406(67.7)
No	360(33.8)	192(32.0)
Missing	2(0.2)	2(0.3)

Tab.3 Socio-demographic characteristics of the control group.

Demographic characteristics	Baseline (N=56)
Marital Status N(%)	
Single	25(44.6)
Married/cohabiting	20(35.7)
Separed/divorced	4(7.1)
Missing	7 (12.5)
Employment status N(%)	
Student	14(25.0)
Unemployed	1(1.8)
Employed	27(48.2)
Housewife	7(12.5)
Missing	7(12.5)
Education level (N%)	
Primary school	2 (3.6)
Secondary School	17(30.4)
Hight school (completed)	25(44.6)
University degree	5(8.9)
Missing	7(12.5)

Tab.4 Clinical Characteristics of the Sample of Pregnant women.

Clinical Characteristics	Baseline (N=1066)	6th month follow-up (N=600)
Lifetime panic dIsorder N(%)	187 (17.5%)	101 (16.8%)
Current panic disorder N(%)	43 (4.0%)	24 (4%)
History of panic disorder N(%)	144 (13.5%)	77 (12.8%)

Tab. 5 PAS-SR factors in the two samples: pregnant women and controls.

Factor	Pregnant women Mean (SD)	Controls Mean (SD)	T-Tests;p
Panic	10.80 (4.29)	10.89 (4.23)	-0.094; 0.926
Agoraphobia	7.08(4.50)	7.58 (5.13)	-0.475; 0.636
Claustrophobia	3.02 (2.46)	3.56 (2.65)	0.969; 0.335
Separation Anxiety	4.25 (2.86)	5.12 (3.01)	-1.385; 0.169
Fear Control	4.00 (3.23)	4.12 (2.47)	-0.212; 0,833
Drug Phobia	4.13 (2.52)	4.32 (2.56)	-0.345; 0,731
Medical reassurance	1,22 (1.51)	1,58 (1.91)	-0.950; 0.345
Rescue ob	0.88 (0.74)	0.96 (0.94)	-0,400; 0,690
Loss sensitivity	1.16 (0.91)	1.45 (1.06)	-1,331; 0,187
Reassurance relatives	2.58 (0.76)	2.21 (0.97)	1.892; 0.62

Tab. 6 T-Test. MOOD-SR Manic factors in the two samples: pregnant women and controls.

Manic Factor	Pregnant Women Mean (SD)	Controls Mean (SD)	T-Tests; p
Psychomotor Activation	3.92 (2.71)	2.56 (2.14)	**2.705; 0,008**
Creativity	3.46 (2.67)	1.61 (2.08)	**3.752; 0.001**
Mixed Instability	0.74 (1.27)	0.61 (0.91)	0.557; 0,579
Sociability/Extraversion	1.97 (1.88)	1.27 (1.62)	1.929; 0,057
Spirituality/ Mysticism/ Psychoticism	0,25 (0.54)	0,23 (0.54)	0,176; 0,861
Myxed Irritability	2,10 (1.56)	2,23 (1.56)	-,408; 0,684
Inflated Selfsteem	0.84 (1.06)	0.72 (0.89)	0.587; 0,558
Euphoria	2,12 (1.39)	0.96 (1.26)	**4,215; 0,001**
Wastefulness/Recklessness	1,17 (1.12)	0.83 0.99)	1,531; 0,130

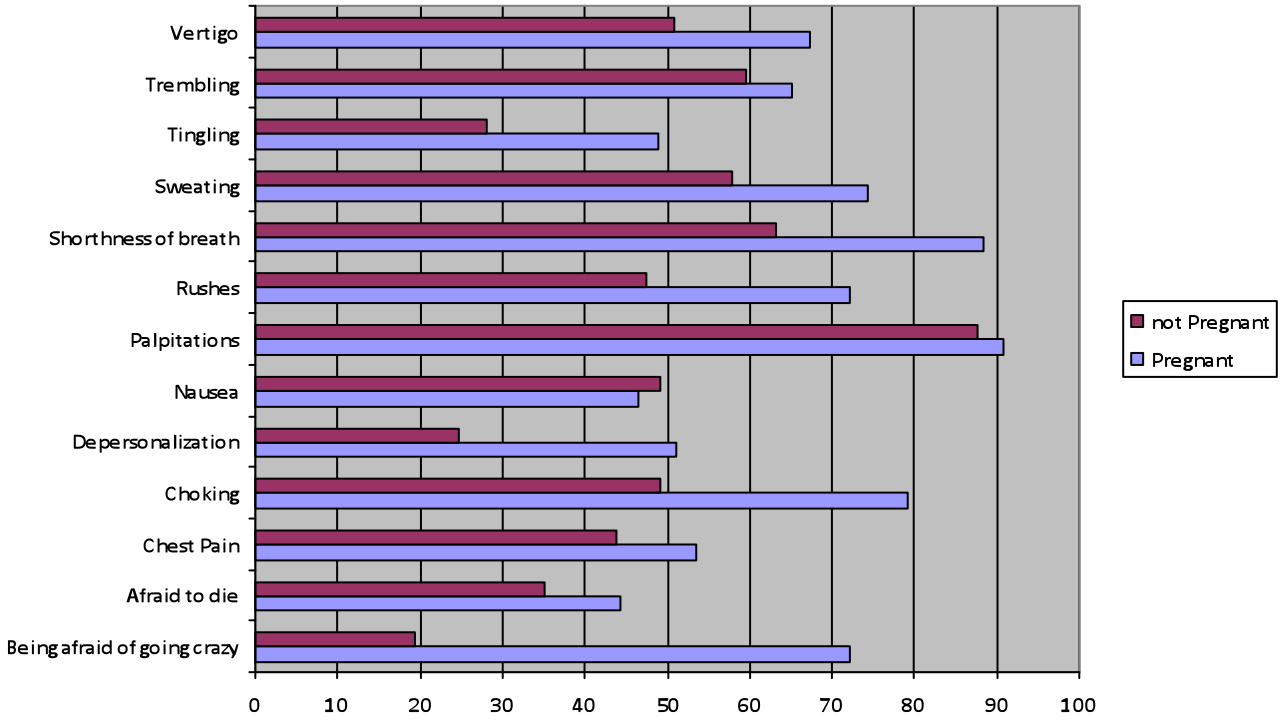
Tab. 7 T-Test. MOOD-SR Depressive factors in the two samples: pregnant women and controls.

Depressive Factor	Pregnant Women Mean (SD)	Controls Mean (SD)	T-Tests; p
Depressive Mood	8.12 (6.42)	8.41 (5.88)	-,227; 0.821
Psychomotor retardation	4.69 (4.50)	5.96 (4.15)	-1.411; 0.162
Suicidality	0.69 (1.21)	0.43 (0.89)	1.174; 0.244
Drug illness related depression	0.74 (1.06)	0.65 (0.96)	0.421; 0.675
Neurovegetative symptoms	3.33 (2.99)	3.98 (2.17)	-1.217; 0.227
Psychotic symptoms	2.07 (1.84)	1.60 (1.39)	1.429; 0.157

Tab. 8 Predictive role of Specific Anxiety Disorders on Probable Depression, mMD and false positives

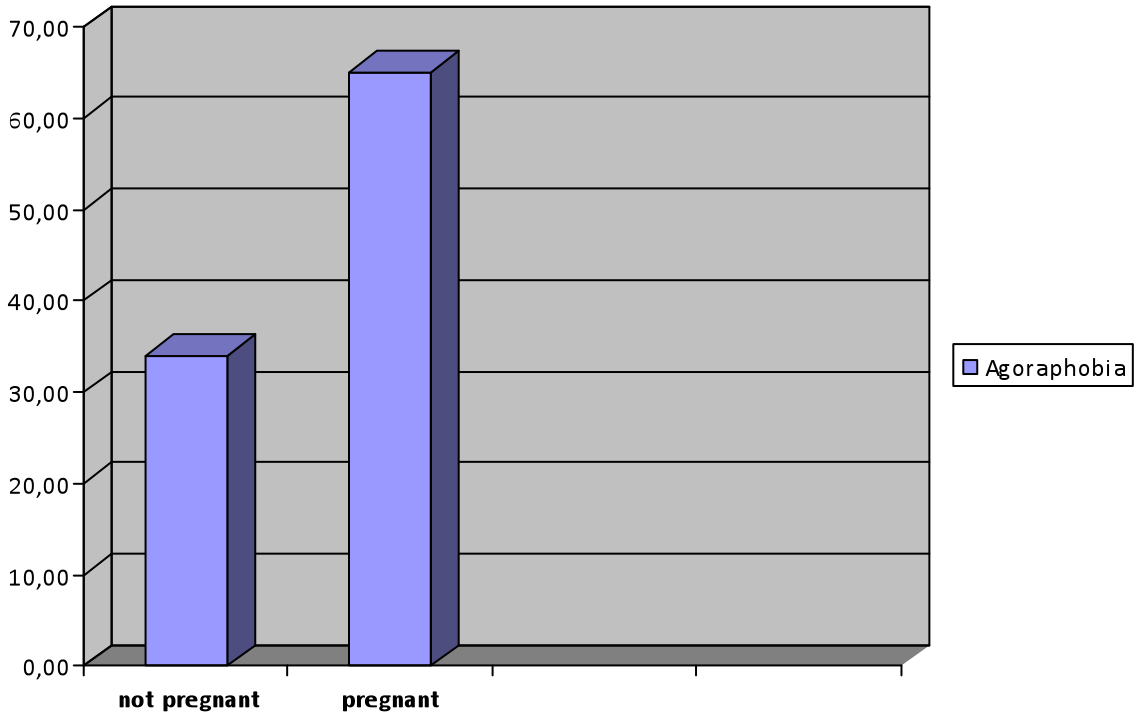
DSM IV anxiety disorders	1st month PPD (EPDS>12) RR (95%CI)	1st month PPD (mMD) RR (95%CI)	1st month false positive RR (95%CI)	12th month PPD (EPDS>12) RR (95%CI)	12th month PPD (mMD) RR (95%CI)	12th month false positive RR (95%CI)
PDPI-R	**3.83 (1.87-7.97)**	**2.74(1.06-7.07)**	**5.45(1.7-17.09)**	4.9(2.9-8.18)	4.66(2.41-9.02)	6.3(2.6-15.4)
PANIC DISORDER	**5.27 (2.0-13.91)**	**7.23 (2.31-22.66)**	NS	**NS**	**3.10 (1.16-8.22)**	NS
AGORAPHOBIA	NS		NS	NS	NS	NS
SOCIAL PHOBIA	**3.80 (1.34-10.46)**	**6.63(2.11-20.85)**	NS	**NS**	**NS**	NS
SPECIFIC PHOBIA	NS		NS	NS	NS	NS
OCD	**NS**		**8.66 (1.59-47.03)**	**NS**	NS	**NS**
PTSD	NS		**NS**	**12.2 (1.10-135.85)**	**NS**	**NS**
GAD	**NS**		**NS**	**NS**	NS	**NS**

Graph 1. Panic Symptoms in the two groups (pregnant and not pregnant women).



*p<0.05
**p<0.0.1
***p<0.001

Graph. 2 Agoraphobia in the two groups.



Graph. 3 Panic Current, History of Panic, Family History of Panic: Relative Risk (RR) of developing mMD in the post-partum.

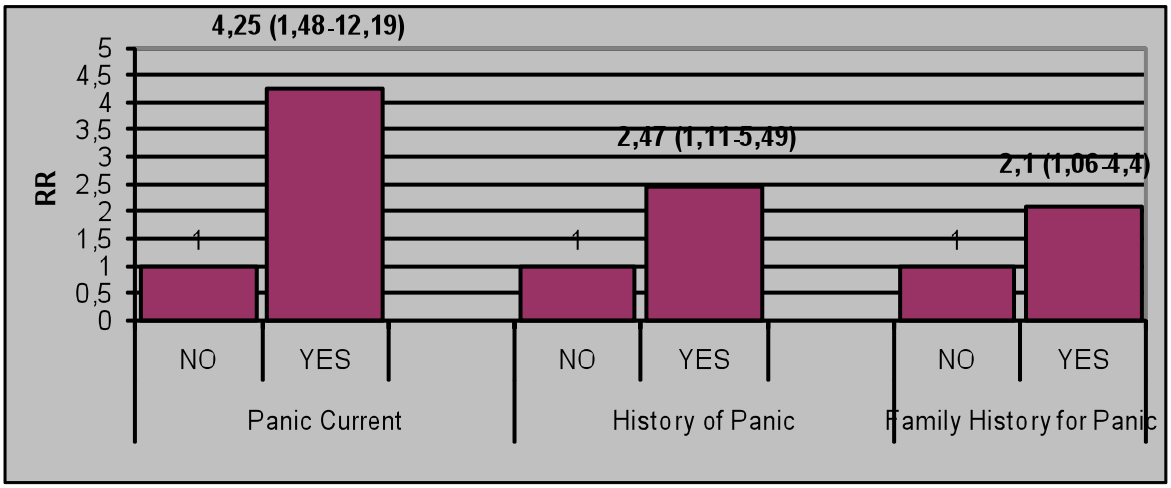


Fig.1

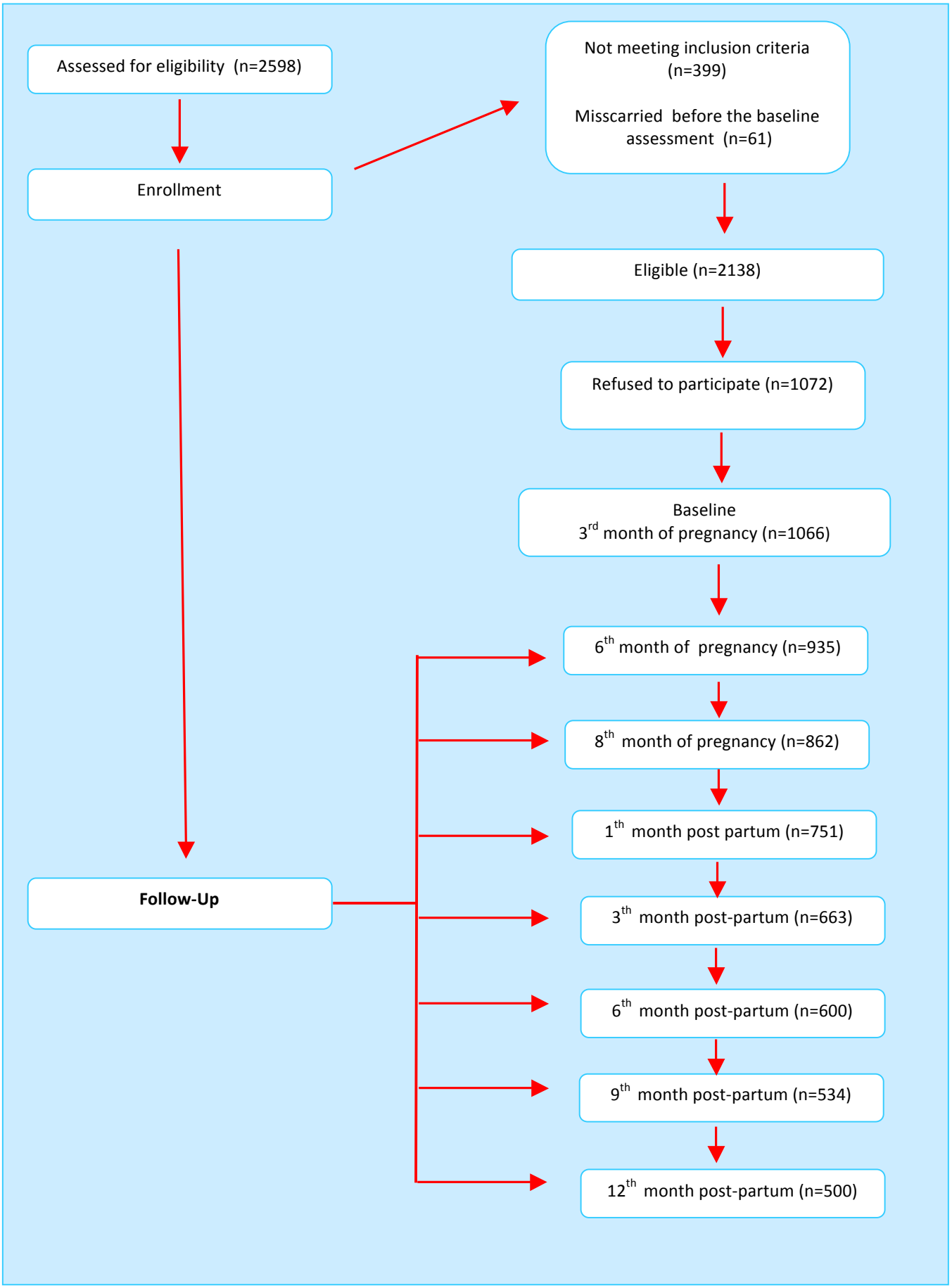
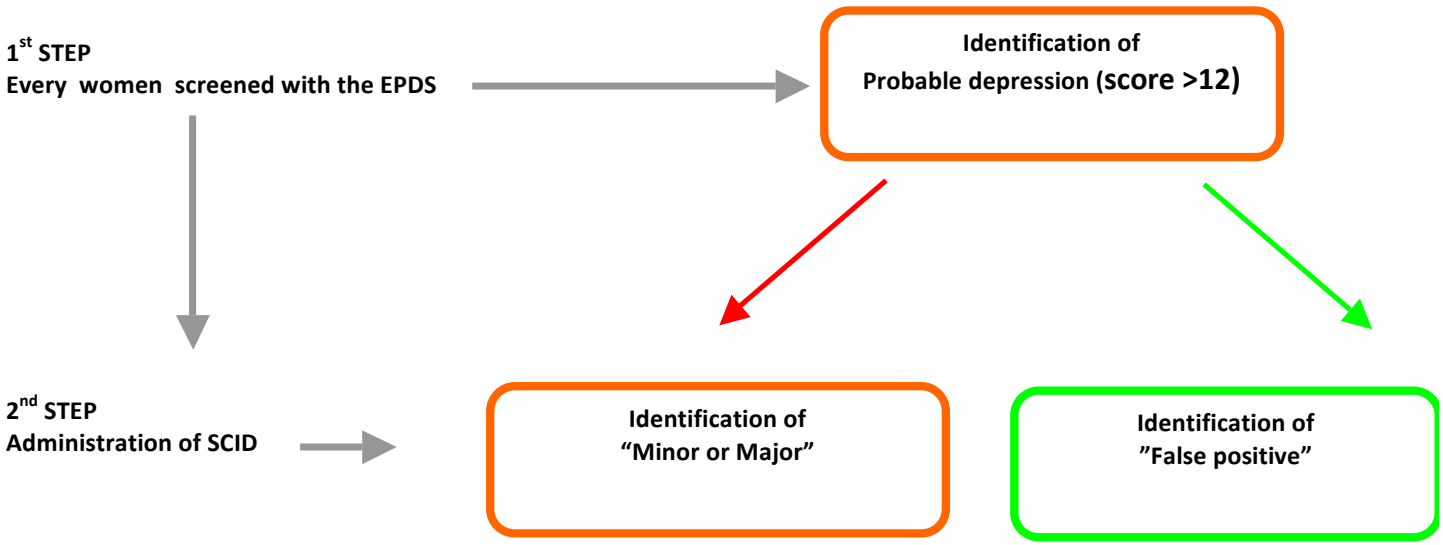

Assessed for eligibility (n=2598)
Not meeting inclusion criteria (n=399)
Misscarried before the baseline assessment (n=61)
Enrollment
Eligible (n=2138)
Refused to participate (n=1072)
Baseline
3rd month of pregnancy (n=1066)
6th month of pregnancy (n=935)
8th month of pregnancy (n=862)
1th month post partum (n=751)
Follow-Up
3th month post-partum (n=663)
6th month post-partum (n=600)
9th month post-partum (n=534)
12th month post-partum (n=500)

FIG. 2 Procedure of outcomes definition: Probable depression; mMD and false positives.



Appendix 1

Instruments

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1995)

Semi-structured interview for making the major Axis I DSM-IV diagnoses (American Psychiatric Association; 1994). The SCID encompasses the DSM-IV sections for mood, psychotic, sub-stance use, anxiety, somatoform, eating, and adjustment disorders.

Edinburgh Post-natal Depression Scale (EPDS) (Cox et al., 1987)

Ten-item self-report scale, specifically designed to screen for postnatal depression in community samples (Cox et al, 1987), but also validated for use during pregnancy (Murray & Cox, 1990).

Post-partum Depression Predictors Inventory-Revised (PDPI-R) (Beck, 2002)

Instrument that explores 13 risk factors for the development of postpartum depression: the higher the score, the more risk factors a subject has for post-partum depression.

Family History Screen (FHS) (Weissmann et al., 2000)

Instrument that evaluate the familial burden of psychiatric disorders, assessing the presence of 15 psychiatric disorders and suicidal behaviour in first-degree relatives.

Mood Spectrum Self-Report Questionnaire, lifetime version (MOODS-SR-LT) (Dell'Osso et al., 2002)

Instrument that assesses symptoms, traits and lifestyles associated with mood disorders, as well as "temperamental" features related to mood dysregulation; items are organized into 3 manic-hypomanic and 3 depressive domains, as well as a section that assesses disturbance in rhythmicity and vegetative functions, yielding a total of seven domains.

Panic-Agoraphobic Spectrum Self-Report Questionnaire, lifetime version (PAS-SR-LT) (Cassano et al., 1997)

Instrument that consists of 114 items exploring panic-agoraphobic experiences that the subject may have had at any time during their life; in particular: separation sensitivity, typical and atypical panic-like symptoms and agoraphobia, stress sensitivity, medication and substance sensitivity, anxious expectation, illness phobia and hypochondriasis and reassurance orientation.