Chapter 11

Anxiety Disorders in Pregnancy and the Postpartum Period

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/52786

1. Introduction

All new mothers are somewhat anxious. Being a mother is a new role, a new job, with a new person in your life and new responsibilities. Anxiety in response to this situation is very common and somewhat adaptive. However, for several reasons, some mothers have excessive worries and experience a severe (and invalidating) level of anxiety in perinatal period. Important gonadal steroid levels modifications have been reported, with as much as a 100-fold variation in serum estrogen levels and a 1000-fold change in serum progesterone levels during pregnancy. These changes can exacerbate such emotional difficulties. Psychological factors may also have an important role to play in the development of anxiety disorders at this time. Often the expectant mother has concerns over the health of the child, the change in lifestyle likely to occur in her own life after the birth of the child (especially if the first child), her own ability to be a good mother, and finances. There are also instances where the pregnancy is unexpected or unwanted, which may further increase stress and anxiety [1].

The postpartum period too is recognized as a time of vulnerability to affective disorders, particularly postpartum depression. In contrast, the prevalence and clinical presentation of anxiety disorders during pregnancy and the postpartum period have received little research attention [2]. In contrast with common belief that pregnancy is a state of well-being with low rates of mental health issues, pregnancy does not protect at all against anxiety and depression [3].

2. Epidemiology and outcomes

There is now a growing realization that many women suffer from either new onset or exacerbation of existing anxiety disorders during perinatal period [4]. Studies of anxiety in pregnancy women show that a significant portion of them are affected [5]. Heron et al., in a large community sample of pregnant women, found that 21% had clinically significant anxiety symptoms and, of these, 64% continued to have anxiety in postpartum [6]. Other studies have also shown higher prevalence rates of anxiety disorders in the postnatal period compared with the general population: 20.4% had an anxiety disorder (approximately two thirds with comorbid depression) and 37.7% of women with a major depressive episode (MDE) had a comorbid anxiety disorder, with a prevalence rate of CIDI diagnosis of 29.2% [7]; 11.1% screened for PAD and 6.1% for PDD, with comorbidity found in 2.1% [8].

Anxiety and depression often occur together, are often present in pregnancy and persist if not treated [9; 10 among others]. These disorders can have a wide range of effects not only for the mother but on the fetus, the infant, partner and other family members (11-13).

Several prospective studies have shown that a prenatal anxiety disorder is one of the strongest risk factors for developing postnatal depression [4;14].

Common themes of severe anxiety during pregnancy include fear of fetal loss or fetal abnormalities. The terrors of parturition have been greatly reduced by analgesia and obstetric care, but pain and injury are still among the fears expressed by over 50% of women. Fear of delivery is often expressed, and other intense fears include those of hemorrhaging to death, or being torn or mutilated. Some women mentioned complication of parturition including maternal death and many are afraid of being alone during delivery [15].

A variety of poor outcomes are associated with anxiety during pregnancy: pre-eclampsia, increased nausea and vomiting, longer sick leave during pregnancy, increased number of visits to obstetrician, spontaneous preterm labor, preterm delivery, low birth weight, low APGAR scores, breastfeeding difficulties, a more difficult labor and delivery with increase of PTSD symptoms related to birth, admission of infant to neonatal care, elective cesarean section (1; 16-18; 19 and 20 for previous reviews).

3. Clinical aspects

The symptoms of anxiety during pregnancy or postpartum might include:

- constant worry;
- nervousness;
- anxiety;
- fatigue;
- restless legs;

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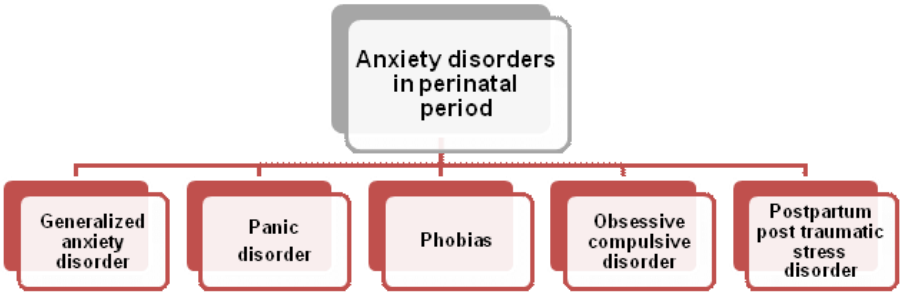
- hypervigilant concerns or attention for the baby;
- extreme lability;
- thoughts of worry regarding the future, or catastrophic events occurring;
- insomnia;
- distractibility and inability to concentrate;
- appetite and sleep disturbance;
- a sense of memory loss;
- physical symptoms like dizziness, hot flashes, vomiting and nausea. [14; 21; 22]

Research shows that there are some risk factors that may predispose some women to anxiety disorders in perinatal period that include:

- family history of anxiety disorders;
- personal history of depression or anxiety
- thyroid imbalance;
- low socioeconomic status;
- unplanned or unwanted pregnancy;
- child care stress;
- personal characteristics like guilt-prone, perfectionistic, feeling unable to achieve, low self-esteem. [23].

Intense postnatal anxiety impairs maternal functioning, causes significant distress and may seriously disturb mother-infant interaction, with consequences raging from maternal neglect and failure to thrive to infanticide [4].

Anxiety disorders can take different forms in perinatal period:



4. Generalized Anxiety Disorder (GAD)

There are few data on the epidemiology of GAD during pregnancy and postnatally. Wenzel et al. found that 4.4% of women in their study met diagnostic criteria for GAD and that over 30% reported subsyndromal symptoms [1, 32].

Sixty-five percent of patients with current GAD report comorbid disorders (most commonly depression, panic disorder, and agoraphobia). GAD, persistent and excessive worry of more than 6 months duration, may be more common in postnatal women than in the general population [23].

Pregnant women with GAD experience excessive worries about a number of life domains along with various physical symptoms such as tension headaches, muscle aches, irritability and poor concentration. Pregnancy itself is associated with role changes, health concerns for the fetus and bodily changes and may form the content of these worries. Diagnosing GAD poses special challenges in pregnancy, since it is normal to have a degree of worry and anxiety in this period of women's life [4].

There are no data on the course of pre-existing GAD in pregnancy. A large-scale community prospective study of around 8,300 women (based on the Avon Longitudinal Study of Parent and Child), which measured anxiety symptoms during pregnancy and postpartum period (from 18 weeks gestation to 8 months postnatally), found while 14.6% scored above threshold at 18 weeks gestation and 8% scored above threshold at 8 weeks postnatally, with 2.4% *de novo* presentation [24].

GAD main symptoms are:

- anxiety;
- apprehensive expectation;
- nervousness;
- fatigue;
- excessive, intrusive and persistent worries;
- a pervasive feeling of apprehension or dread;
- inability to tolerate uncertainty;
- difficulty concentrating or focusing on things;
- muscle tension;
- sleep disturbance;
- feeling edgy, restless, or jumpy;
- stomach problems, nausea, diarrhea.

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5. Panic disorder

Panic disorder is an anxiety disorder characterized by recurring severe panic attacks, for at least one month. A panic attack may be a one-time occurrence, but many people experience repeated episodes.

Due to the physiological changes of pregnancy a woman may be at increased risk of onset or recurrence of panic disorder.

Physiological symptoms such as fear and autonomic arousal symptoms like shortness of breath, pounding heart and dizziness may be misinterpreted in catastrophic ways in relation to the pregnancy [3].

However, recent data suggest that pregnancy may confer some kind of protection against this disturb. In contrast the early postpartum period is reported to be a time of increased vulnerability to panic disorder, with figures ranging from 0.5% to 1.5% at 6 week postpartum [5]. In 1988, Metz and Sichel described panic disorder presenting for the first time in the early postpartum period. They showed that panic disorder affects approximately 10% of postpartum women [cited in 21]. Other important authors described cases of panic disorder presenting for the first time in the postnatal period [4 among others].

Wisner, Peindl and Hanusa, in 1996, found that 11% to 29% percent of women with panic disorder reported an onset during the postpartum period and women with a history of mild panic symptoms have experienced worsening of these symptoms in postpartum period (within the first 2 or 3 weeks and eventually being accompanied by depressive symptoms) [25].

Premenstrual hormonal changes may play a role in panic disorder, which would implicate the role of ovarian hormones in vulnerability to anxiety and panic in the postpartum period [4, 26].

In 1998 Beck conducted a phenomenological study to describe the experiences of the women with panic, in the postpartum period. Through interviews with mothers diagnosed with postpartum panic disorder, the author found six emerging themes describing the essence of the mother's experience:

- theme 1: the terrifying physical and emotional components of panic paralyzed women, leaving them feeling totally out of control;
- theme 2: during panic attacks, women's cognitive functioning abruptly diminished, whereas between these attacks women experienced a more insidious decrease in their cognitive functioning;
- theme 3: during the panic attack, women feverishly struggled to maintain their composure, leading to exhaustion;
- theme 4: because of the terrifying nature of panic, preventing further panic attacks was paramount in the lives of the women;

- theme 5: as a result of recurring panic attacks, negative changes in women's lifestyles ensued lowering their self-esteem and leaving them to bear the burden of disappointing not only themselves but also their families;
- theme 6: mothers were haunted by the prospect that their panic could have residual effect on themselves and their families.

Anticipatory anxiety about future attacks and consequences of these on the fetus can be significantly disabling. The symptoms of panic disorder in perinatal period my worse and some women becoming agoraphobic and socially isolated [23].

Panic disorder main symptoms are:

- shortness of breath or hyperventilation;
- palpitations, pounding heart, or accelerated heart rate;
- trembling or shaking;
- chest pain or discomfort;
- sweating;
- feeling unreal or detached from your surroundings;
- choking feeling
- nausea or abdominal distress;
- feeling dizzy, light-headed, or faint;
- numbness or tingling sensations;
- hot or cold flashes;
- fear of dying, losing control, or going crazy;
- paresthesias (numbness or tingling sensations). [3;4;27].

6. Phobias

"Fear" is the normal response to a genuine danger. Phobia is an irrational fear of an object or a situation leading to avoidance. It is an abnormally fearful response to a danger that is imagined or is irrationally exaggerated. People can develop phobic reactions to animals (e.g., spiders), activities (e.g., flying), or social situations (e.g., eating in public or simply being in a public environment).There is no literature on the exact prevalence and impact of specific phobias such as social phobia or agoraphobia during pregnancy. But there are two specific types of phobia that has been discussed in relation to pregnancy and child birth: tokophobia (intense fear of childbirth) and the phobia for the infant.

Tokophobia can lead to woman avoiding pregnancy, terminating pregnancy of a very much wanted baby or demanding caesarean section in subsequent pregnancies. It has been classified

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as: primary in a nulliparous woman, secondary if the woman has had previous traumatic deliveries or secondary to depressive illness or post-traumatic stress disorder (PTSD) during pregnancy. The prevalence of serious fear of childbirth was 5.5% in women. Is very important to consider factors influencing this fear:

- history of sexual or physical abuse;
- a traumatic gynecological examination;
- previous experience of childbirth and related anxiety;
- myths about labor and childbirth. [3;21]

Fear of childbirth may also be a symptom of PTSD associated with childbirth.

Phobia for the infant: a mother with infant-focused anxiety may develop a phobia for the infant. Brockington [28] describes the fear of cot death and says that a cause of severe chronic anxiety in the puerperium is fear of sudden infant death syndrome. They are mothers who will not let their infants sleep, for fear they stop breathing and other who waken them to see if they are alive. These mothers experience severe insomnia, because of the need to lie awake listening to the baby's breathing; they may check the infant 20-30 times every night.

Symptoms of a phobia include the following:

- feelings of panic, dread, horror, or terror;
- a persistent and overwhelming fear of the object or situation;
- recognition that the fear goes beyond normal boundaries and the actual threat of danger;
- reactions that are automatic and uncontrollable, practically taking over the person's thoughts;
- rapid heartbeat
- shortness of breath;
- trembling;
- an overwhelming desire to flee the situation, all the physical reactions associated with extreme fear;
- extreme measures taken to avoid the feared object or situation [27].

7. Obsessive–Compulsive Disorder (OCD)

Obsessive-compulsive disorder is a relatively common psychiatric disorder with lifetime prevalence rate of 0.8% to 3.2% in the community. It is an important health problem, because it leads to an impairment in the quality of life and functional status and to disabilities in occupational and social areas. Epidemiological studies show that OCD is more frequent in

females compared to males. The mean age of onset of this disorder includes the childbearing years in women. Women with postpartum onset OCD often experience obsessions about harming their baby, they may avoid their infants due to their fear of acting on such thoughts. For this reason, their symptoms often impair their ability to care their infants. This situation may give rise to depressive symptoms [29-30].

The prevalence of OCD during pregnancy has been reported in the range of 0.2% to 5.2% in the literature, the relatively consistent rates among the studies are between 1% to 3%. Obsessive-compulsive symptoms are more frequently seen in pregnant women [29; 31].

The prevalence of OCD in postpartum period has been reported within wide range of 0.7% to 9.0%, and obsessive-compulsive symptoms were described in 14% to 63.5% of postpartum women [15; 32; 33; 34].

There are several case reports showing that pregnancy and postpartum period are associated with the onset of OCD more frequently than other life events [29].

The etiology of postpartum onset OCD is unknown. The acute onset may be due to the dramatic, rapid fall in the female hormones estrogen and progesterone, resulting in a dysregulation of serotonin, which than interacts with any predisposition to mental disorder. Another hypothesis regarding etiology, may be the rapid increase in oxytocin to a high level near the end of pregnancy and during postpartum, which may trigger an exacerbation or the onset of OCD [4].

In literature there are few studies analyzing risk factors for pregnancy induced OCD.

The main risk factors associated with pregnancy onset OCD are:

- primiparity;
- second or third trimester of gestation;
- number of gestations and live birth;
- miscarriage;
- gestational complication;
- positive family history of OCD. [29].

Compared to pregnancy onset OCD, the studies described above illustrate with more details the factors associated with postpartum onset OCD.

The main risk factors associated with pregnancy onset OCD are:

- primiparity (6.57% vs 1.81% multiparous ones);
- the first 4 weeks of postnatal period;
- higher levels of anxiety;
- obsessive-compulsive personality disorder;
- avoidant personality disorder;

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- personal history of major depression;
- the existence of OCD related dysfunctional belief. [29-30].

Symptoms of perinatal OCD can include:

- obsessions, also called intrusive thoughts, which are persistent, repetitive thoughts or mental images related to the baby;
- compulsions, where the woman may do certain things over and over again to reduce her fears and obsessions;
- fear of being left alone with the infant;
- hypervigilance in protecting the infant;
- loss of appetite;
- tremendous guilt and shame;
- horrified by these things. [21; see also www.ppmdsupport.com]

Obsessions are defined as:

1. recurrent and persistent thoughts, impulses, or images that are experienced at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress;
2. the thoughts, impulses, or images are not simply excessive worries about real-life problems;
3. the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action;
4. the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion) [27].

Compulsions are defined as:

1. repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly;
2. the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive [27].

Compared with non-postpartum onset OCD, aggressive obsessions exhibit a tendency to be seen more frequently seen in postpartum onset OCD, and the most common obsessions were contamination and aggressive obsessions. Many authors noted that the aggressive obsessions had 9 times more chances of occurring in a postpartum woman with OCD than in a healthy postpartum woman. The aggressive obsessions mostly include fear of harming the baby [29,

33]. In some instances, sufferers report obsessions having to do with accidental harm, while in others the obsessions involve unwanted thoughts or ideas of intentionally harming the newborn. Some examples of the kinds of postpartum obsessions are as follows:

- the idea that the baby could die while sleeping (S.I.D.S);
- the thought of dropping the baby from a high place;
- the thought of putting the baby in the microwave;
- an image of the baby dead;
- thoughts of the baby choking and not being able to save him;
- unwanted impulses to shake the baby to see what would happen;
- thoughts of yelling at the baby;
- thoughts of poking the baby in the soft spot in her head (fontanel);
- thought of stabbing the baby;
- thoughts of drowning the baby during a bath. [29; 33 see also www.ocfoundation.org/EO_Postpartum.aspx;].

Other women have contamination obsessions that are often focused on the baby:

- microorganisms;
- chemicals or dirt contaminations via her hand or the baby's bottles or foods. [30].

Compared with obsessions, the studies has less frequently focused on compulsive symptoms after the childbirth.

The most common compulsions are:

- cleaning/washing;
- checking.

Some compulsions were related to the baby:

- avoiding kitchen knives;
- not bathing the infant;
- staying physically isolated from the baby;
- checking the breathing or baby's body;
- excessive or ritualized washing or cleaning. [29; 33].

The important thing is that women with postpartum onset OCD, compared to psychotic women, have relatively good insight, do not exhibit psychotic features, don't want to harm the baby, recognize that thoughts/images are unhealthy and take step to protect the baby [32-34].

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Less attention has been focused on the clinical characteristics of OCD in pregnancy [35]. Few reports suggest that contamination obsessions and cleaning/washing compulsions may be seen more frequently compared to other symptoms. Moreover, symmetry obsessions and checking compulsions are frequently observed in pregnant women. Aggressive and contamination obsessions in some pregnant women may be related to the fetus and some pregnant women experience thoughts of harming their unborn child. Often OCD is comorbid with other psychiatric disorders, in particular with major depression. Comorbid depression developed simultaneously or within 2 to 3 weeks after the onset of OCD. There are no studies that reported literature examining comorbid disorders in pregnant women with OCD [29; 34].

When undiagnosed and untreated, postpartum OCD can cause extreme distress in the mother and can also influence the type of care an infant receives, family relationships and interactions [30; 4].

These women run the risk of maternal-infant attachment difficulties [21].

8. Postpartum Post–Traumatic Stress Disorder (PTSD)

The term post-traumatic stress disorder (PTSD) refers to a disorder that can occur following the experience or witnessing of life-threatening events. We usually recognize events like terrorist incidents, serious accidents, or violent personal assaults as being capable of causing such trauma, so, it has proved difficult for people to understand that a "natural" process like childbirth can also be traumatizing. The fact is that a traumatic event can actually be any experience which involves the threat of death or serious injury to an individual or another person close to them (e.g. their baby). A person must then respond with intense fear, helplessness or horror for a diagnosis of PTSD to be made. The reported prevalence of diagnosed PTSD caused by childbirth ranges from 2-3% to 25% in the postpartum women [23].

Research into this field is limited and, to date, it has largely focused on the importance of the type of delivery a woman has undergone. However, recent studies have begun to look at the significance of women's perceptions of their birth experience. Then, it is now generally accepted that PTSD can be a consequence of a traumatic birth experience and important studies demonstrate that women did in fact suffer this type of traumatic stress after birth (see for more infos at www.birthtraumaassociation.org.uk). This type of PTSD are called postpartum post-traumatic stress disorder (PP PTSD) or post natal PTSD (PN PTSD) or "birth trauma".

Most often, this illness is caused by a real or perceived trauma during delivery or postpartum. These traumas could include:

- prolapsed cord;
- unplanned Caesarian section;
- cardiac arrest;

- postpartum hemorrhage;
- induction;
- use of vacuum extractor or forceps to deliver the baby;
- rapid delivery;
- severe toxemia;
- manual removal of placenta;
- premature birth;
- separation from infant in NICU;
- feelings of powerlessness, poor communication and/or lack of support and reassurance during the delivery. [26; 36; see also www.ppmdsupport.com].

Most significant risk factors for postpartum PTSD are therefore the following:

- domestic violence;
- history of sex trauma (e.g. sexual abuse, rape);
- previous adverse reproductive events (e.g. ectopic pregnancy, miscarriage, stillbirth);
- history of mental health problem;
- migration;
- mode of delivery;
- fear for their own safety or that of their child;
- lack of control;
- the attitudes of staff;
- inadequate pain relief;
- poor social support;
- previous traumatic events. [3,5,21, 27; 36; 37 see also www.birthtraumaassociation.org.uk].

A person who has been diagnosed with PTSD will find their normal life interrupted in many ways by a strong and powerful set of emotions and feelings over which they have no control.

Symptoms may start soon after childbirth or they could be delayed for months, and may persist for a long time and resulting in other problems such as depression [see for more infos at www.ppmsupport.com].

General symptoms of postpartum PTSD might include:

- anxiety and panic attack;
- intrusive re-experiencing of a past traumatic event;

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- recurrent intrusive memories;
- flashbacks or nightmares;
- avoidance of stimuli associated with the event, including thoughts, feelings, people, places and details of the event;
- persistent increased arousal (irritability, outbursts of anger, difficulty sleeping an concentrating, hypervigilance, exaggerated startle response);
- reduced consciences status;
- feeling a sense of unreality and detachment;
- depressive symptoms;
- fear of sexual intimacy;
- restricted range of affect;
- sense of a foreshortened future. [21,23; 35 see also www.ppmsupport.com and www.birth-traumaassociation.org.uk].

It is important to understand that, following a traumatic event, sufferers of PTSD are left with a world view which has been altered profoundly and which often leaves them deeply afraid and anxious. The world is no longer considered to be a safe place and it can be difficult to trust the very individuals (health care professionals) who are supposed to be there to help. For those who develop PTSD, the future may look bleak as they struggle to liberate themselves from the images of the trauma they have endured. This can be particularly hard for women with 'birth trauma' because they often suffer these problems at a time when everyone expects them to be happy and positive. As a result, they often end up feeling guilty and this lowers self-esteem [36; 37; see for more info at www.ppmsupport.com].

If untreated, PTSD is associated with increased physical morbidity, subsequent psychiatric illness, accidental and non-accidental death. It may also have the following consequence:

- depression;
- suicide risk;
- an increased incidence of alcohol and other substance abuse;
- profound problems for a woman's relationship with her baby, problems with breast feeding and bonding;
- sexual avoidance;
- tokophobia (fear of childbirth);
- requests for otherwise unnecessary elective caesarean sections in subsequent pregnancies;
- over-vigilance and anxiety about a child's health;
- the impact on a woman's family

- avoidance of future medical care. [4; 36 see also www.ppmsupport.com].

9. Pharmacological and non-pharmacological treatments

Hereafter a short summary of the most commonly proposed treatment of anxiety in pregnancy and postpartum period, bearing in mind that pharmacological approaches, especially in pregnancy but also in breastfeeding period, are to be used with caution, collaborating with gynecologists, and weighting risks and benefits with greater attention than in "normal" patients; and bearing in mind, too, that until now there is a lack of evidence for the effectiveness of psychological therapies for anxiety disorder during the perinatal period (even if it is reasonable to consider that anxiety in pregnancy and postpartum differs little from the same disorders among non-pregnant women in both their presentation and course, and reasonably in the efficacy of its treatment).

Bear also in mind that there are some concerns about diagnostic criteria of anxiety disorders (and of depression, too) in pregnancy, as outlined in Matthey and Ross-Hamid [34] and McGuiness and al. [35], and these might be limitations in the correct use of medications in this period.

Psychological treatments

A detailed description of all the psychotherapies available for treating anxiety is beyond the scope of this chapter [see 24 and 36 for further details], anyway the most recent evidences are very well described elsewhere in this book . It is however useful to remind that cognitive-behavioral therapies are, at now, the golden standard based on efficacy and efficiency results compared to other form of psychological interventions. These therapies can be tailored on the client with more adequacy than other more structured (and ideologically based) form of psychotherapies, and can be of adequately short duration and time-sparing (in front of the time-consuming "job" of being mother, a short and time-sparing approach is desirable). Relaxation techniques are a specific application of CBT, are specifically symptom oriented, and can be proposed as the sole intervention for mild form of anxiety. CBT and relaxation can be exerted in groups, favouring indirect group support.

Interpersonal psychotherapy has gained a growing success, but its efficacy in anxiety problems is still questionable, lacking clinical evidence of efficacy, whereas its efficacy in depression is confirmed.

Psychodynamic psychotherapies, too, have questionable efficacy on anxious problems and require more commitment and time (and money too).

Pharmacological treatments

This section will describe the most frequently used pharmacological treatments to counteract anxiety and the most widely accepted evidences with regard to safety in pregnancy and post partum period.

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Benzodiazepines

Earlier studies suggesting an increase in orofacial cleft defects following in utero exposure to benzodiazepines are counteracted by a recent large prospective study founding no significant association with such (or other) birth defects, although benzodiazepines are associated with negative obstetric outcomes like poor Apgar score at birth, tendency to preterm birth and low birth weight [38].

Nevertheless, benzodiazepines use in pregnancy has still contrasting evidences about safety for the newborn, due to methodological limits in the studies (not consideration of the consequences of maternal illness on fetus, familiar history of malformations, and so on) [39-40], even if the more recent data, considering a more wide spectrum of variables and a better quality in the design of the studies, seem to uphold the global safety of these molecules [41-42] except for anal atresia associated with lorazepam use in the I trimester [40] and for low weight at birth and preterm birth [43].

Regarding to the use of benzodiazepines in the III trimester of pregnancy and peripartum period, a floppy infant syndrome has been described, and also a transient slowing of growth (a complete normalization is however reached in the first year of life) [39,44].

There are some evidences pointing out the at now not yet clear balance risks / benefits of the use of benzodiazepines in pregnancy, especially with alprazolam [45].

According to available studies [45 amongst all], some indications on the use of benzodiazepines during pregnancy are the following:

- 'short-acting' benzodiazepines should be preferred and then can be used safely during pregnancy and breastfeeding if they are only used for a short period (less than 4 weeks)
- use the lowest dose, shorter treatment period, more fractioned dose (to avoid plasma peaks) as possible
- avoid multiprescriptions
- the use of 'long-acting' benzodiazepines should be avoided, in order to avoid accumulation reaction.
- use only benzodiazepines with safety records of long period

Antidepressants

There is a growing number of large prospective studies on **SSRI** in pregnancy and postnatal period, most of the evidence going against an association between any particular selective serotonin reuptake inhibitor (SSRI) and birth defects [48-53]. However some data evidenced an association between SSRI use and negative obstetric outcome like mild degrees of preterm birth and low birth weight [47; 54-56], and there are adverse neonatal outcomes reports including mild degrees of poor neonatal adaptation (neonatal withdrawal syndrome) following SSRI exposure [47,54,56-57], all of them transient. Fluoxetine is associated with a slight increase of negative obstetric outcomes but not of malformations after I trimester exposition [57], the study being supported by Lilly.

An increase of spontaneous abortions has been reported in some studies, even if not statistically significant [59-61].

In particular, these problems are evident using paroxetine. As for benzodiazepine studies, however, these studies suffer of methodological limitations [62-65] and sampling problems [63-64, 66-68,69-70].

Citalopram and escitalopram are associated with a slight increase of spontaneous abortions, comparable with any other antidepressant, and not significant low weight at birth but no increase of malformations [60, 70].

A link between neonatal persistent pulmonary hypertension and late exposure to SSRIs has initially been suggested [71-74] but not confirmed in following studies [75-78], even if some doubts already emerged [79]. An association between paroxetine exposure (especially in the I trimester) and infant cardiovascular malformations has recently been reported [50; 68, 80-83], even if a recent meta-analysis [84] and a large cohort study [85] found no significant association. Despite these results, and having other more "sure" SSRI, it is better and precautionary not to prescribe paroxetine as first line treatment.

There is limited evidence on the use of **SNRIs**, with most available evidence concerning venlafaxine, showing a lack of significative association with an increased risk of major birth defects [46, 50, 59], but a mild association with 'neonatal withdrawal syndrome' [85], neonatal seizures [86] and low weight at birth [87], and transient (resolving in less than 1 week) behavioral signs, but there was also an increase of use of tobacco and alcohol in treated women [88].

Mirtazapine has associated with an increase of spontaneous abortions but not with any increase of malformations [89]. The same results are for **bupropione** [90], **nefazodone** and **trazodone** [91]

Side effects of in utero exposure to **TCAs** are similar to those of SSRIs (i.e. premature delivery, low birth weight, neonatal distress, respiratory problems, hypoglycemia, cyanosis, jitteriness, convulsions, decreased Apgar score and the need for special-care nurseries) but have been reported to be more severe [80-81, 92].

Duration of treatments with antidepressants is not associated with teratogenic risk [93], as well as with gestation period of exposition [94].

Antipsychotics

In relation to antipsychotics, to be avoided as first line treatment of anxiety but useful in certain resistant subtypes of GAD, there are sparse evidence of non significant association with any birth defect, both for first generation antipsychotics [95-96] and for new generation antipsychotics [97-98]. First- and second-generation antipsychotics however have been associated with obesity in pregnancy [97] and high or low birth weight [98-99].

Postpartum and breastfeeding

In relation to breastfeeding, current evidences suggest that SSRIs [51, 100-102] and benzodiazepines with short half-lives [102] are transferred in only low concentrations to breast

http://dx.doi.org/10.5772/52786

milk. During lactation, benzodiazepine use is not associated with adverse events in newborns [102]. Regarding the use of benzodiazepines during breastfeeding, the little informations available derive from a low number of studies, but the data are converging to a relative safety in their use, even if their use needs some cautions since neonatal metabolism and global clearance is very slow, and benzodiazepines in the long term tend to accumulate [103-104].

A recent review on antidepressants use during breastfeeding period showed an acceptable safety using SSRI and nortryptiline, a cautious use of fluoxetine, and suggesting doxepine and nefazodone to be avoided [105], even if a recent review on antidepressants and breastfeeding suggests as first choice, due to their low degree of excretion into human milk, sertraline, paroxetine and fluvoxamine, not recommending (for their long half life) citalopram escitalopram and fluoxetine [103]. For a complete review about limits and methodological problems in available studies on breastfeeding and use of psychiatric drugs see in particular Llewellin and Stowe [106], Fortinguerra et al. [103] and Moretti [104].

Final considerations about psychopharmacological treatments

As previously described, therefore, there are some (even if acceptable) risks associated with the use of psychotropic medications in this delicate period, but the clinician – GP, psychiatrist, gynecologist (and the mother, and her relatives) have to bear in mind that it should not be assumed that it is always better to avoid medication. Untreated mental health disorders in this period, as seen before, can significantly (and sometimes dramatically) affect the physical and/or mental wellbeing of the woman, the fetus/infant, and significant other(s) and family [24,107-109] (see Table 2 for a summary). So, a careful evaluation of risks (comprehending the naturalistic prevalence and incidence of birth defects - the background risk of birth defects in the general population is between 2% and 4% - compared to the, often low, increase linked to treatments) and benefits has to be carried on, in order to reach a real informed consent of the woman and her significant others to an adequate pharmacological treatment of the most invalidating form of anxiety disorders.

When prescribing a medication for a woman with a mental health disorder who is planning a pregnancy, pregnant or breastfeeding, the following recommendations, even if not new (2007) have to be followed [24]:

- choose medications with lower risk profiles for the mother and the fetus or infant;
- start low and increase slow to the lowest effective dose for the shortest time needed for treatment;
- monotherapy better than combination treatment;
- consider additional precautions for preterm, low birth weight or sick infants
- adequate monitoring of relapse, and discontinuation/withdrawal symptoms

TREATMENT	IN PREGNANCY AND IN POSTPARTUM PERIOD
NON-PHARMACOLOGICAL TREATMENTS	a. Psychoeducational interventions b. Psychotherapy • Cognitive-behavioral therapy (CBT) • Interpersonal therapy (IPT) • Psychodynamic therapy • Mother-infant psychotherapy c. Psychological support d. Progressive muscle relaxation
PHARMACOLOGICAL TREATMENTS	a. Anxyolitics b. Antidepressant c. Antipsychotics
COMBINED TREATMENT	An integrated approach where pharmacological treatment and psychotherapy work together is the best therapeutic intervention to achieve the most successful recovery from symptoms

(from: Beyondblue, 2011) [36].

Table 1.

Fetal/obstetrical outcomes	• Preterm delivery, prolongation of gestation • Lower birth weight, fetal distress • Spontaneous abortion higher risk • Pre-eclampia higher risk • Labour complications
Neonatal outcomes	• Neonatal maladaptation • Higher risk of admission in neonatal ICU • Lower Apgar • Growth retardation, slowed mental development • Behavioral disturbances
Child development	• Maternal-fetal / maternal-infant bonding disturbances • Affect disregulations (tantrums) • Alterations in the development of cognitive, relational, behavioral domains • Higher risk of separation anxiety and disorganized attachment styles • Higher impulsivity and lower QI at 14-15 yrs
Risk to mother	• Poor nutrition and impaired self care • Non compliance to medical advices • Worsening of comorbid medical illnesses • Increased use of substances (tobacco, alcool, drugs) • Postpartum psychiatric complications • Impact of family members

Table 2. Untreated anxiety and aoutcomes (adapted from 107-109)

http://dx.doi.org/10.5772/52786

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