Journal of Affective Disorders 190 (2016) 543–550

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review

Clinical management of perinatal anxiety disorders: A systematic review

C. Marchesi [a,b,c], P. Ossola [a], A. Amerio [a,d,*], B.D. Daniel [b,c], M. Tonna [c], C. De Panfilis [a,b,c]

[a] Department of Neuroscience, Psychiatry Unit, University of Parma, Parma, Italy
[b] Treatment of Affective Disorders in Perinatal Period Unit, University Hospital of Parma, Parma, Italy
[c] Department of Mental Health, Local Healthy Service of Parma, Parma, Italy
[d] Mood Disorders Program, Tufts Medical Center, Boston, MA, USA

ARTICLE INFO

Article history:
Received 7 July 2015
Received in revised form
16 October 2015
Accepted 1 November 2015
Available online 4 November 2015

Keywords:
Anxiety disorders
Perinatal period
Treatment
Antidepressant
Cognitive-behavioural therapy

ABSTRACT

Background: In the last few decades, there has been a growing interest in anxiety disorders (AnxD) in the perinatal period. Although AnxD are diagnosed in 4–39% of pregnant women and in up to 16% of women after delivery, evidence on their clinical management is limited.
Methods: A systematic review was conducted on pharmacological and non-pharmacological treatment of AnxD in the perinatal period. Relevant papers published from January 1st 2015 were identified searching the electronic databases MEDLINE, Embase, PsycINFO and the Cochrane Library.
Results: 18 articles met inclusion criteria. Selected studies supported the use of cognitive-behavioural therapy (CBT) for obsessive–compulsive disorder (OCD), panic disorder (PD) and specific phobia both in pregnancy and postpartum. Selective serotonin reuptake inhibitors (SSRIs) led to significant OCD and PD improvement both in pregnancy and postpartum with no side effects for the babies. In the largest clinical sample to date, 65% of postpartum patients who entered the open-label trial of fluvoxamine (up to 300 mg/day) experienced a 30% or greater decrease in the total score of the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS). During pregnancy, SSRIs and tricyclic antidepressants (TCAs) led to remission of panic symptoms and healthy outcomes for the babies.
Limitations: Study design, mostly case reports, and enrolment of subjects mainly from outpatient specialty units might have limited community-wide generalisability.
Conclusions: Keeping in mind the scantiness and heterogeneity of the available literature, the best interpretation of the available evidence appears to be that CBT should be the first treatment offered to pregnant and breastfeeding women with AnxD. However SSRIs can represent a first line treatment strategy, and not exclusively in cases where AnxD is refractory to CBT.

Contents

* Correspondence to: Department of Neuroscience, Psychiatry Unit, University of Parma, c/o Ospedale Maggiore, Pad. 21 – Braga, Viale A. Gramsci 14, 43126 Parma, Italy.
E-mail addresses: carlo.marchesi@unipr.it (C. Marchesi), paolo.ossola@unipr.it (P. Ossola), andrea.amerio@studenti.unipr.it (A. Amerio), daniel.benjamindaniel@gmail.com (B.D. Daniel), mtonna@ausl.pr.it (M. Tonna), chiara.depanfilis@unipr.it (C. De Panfilis).

http://dx.doi.org/10.1016/j.jad.2015.11.004
0165-0327/

1. Introduction

Even though pregnancy is a period of emotional well-being for most women, one fourth of pregnant women are affected by a mental disorder, with one-twelfth experiencing one of these disorders for the first time (Vesga-Lopez et al., 2008). Over the last few decades, more attention has been focused on anxiety disorders (AnxD), which were more extensively investigated in antenatal period (Goodman and Chenausky, 2014) than in postpartum.

AnxD are diagnosed in 4–39% of pregnant women (Goodman and Chenausky, 2014) and prevalence rates are even higher if comorbid disorders are also considered (Marchesi et al., 2014).

Although prenatal AnxD increase the risk of post-partum depression (Goodman and Chenausky, 2014), their effects on obstetric outcomes are debated. Regarding neonatal/infant outcomes, a low brain-derived neurotrophic factor (BDNF) level in the blood cord; no heart rate response to the mother anxiety; increase cortisol reactivity to stress (not replicated in other two studies) and early attention dysfunction, were found in infants of mothers with prenatal AnxD (Goodman and Chenausky, 2014).

With regard to the post-partum period, AnxD are diagnosed in 16% of women (Vesga-Lopez et al., 2008; Austin et al., 2010; Wenzel et al., 2005; Reck et al., 2008) and up to 50% if comorbid major depression is also taken into account (Austin et al., 2010; Wenzel et al., 2005).

Untreated AnxD increase the risk of postpartum depression (Prenoveau et al., 2013) and have been associated with maternal low self-confidence (Zietlow et al., 2014); early complications in the offspring (e.g. behavioural inhibition, mother–infant interaction problems, insecure attachment), and later adverse child development (Glasheen et al., 2010).

Recent reviews have mostly focused on prevalence rates and clinical presentation of AnxD in pregnant and postpartum women (Goodman and Chenausky, 2014; Ross and McLean, 2006). This is the first systematic review on pharmacological and non-pharmacological treatment approaches of perinatal AnxD.

1.1. Aim of the study

We systematically reviewed the available literature on the treatment of perinatal AnxD and we provide recommendations for clinical management and future research.

2. Materials and methods

We conducted this review according to the methods recommended by the Cochrane Collaboration and documented the process and results in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009; Higgins and Green, 2011).

2.1. Information sources and search strategy

Studies were identified by searching the electronic databases MEDLINE, Embase, PsycINFO, and the Cochrane Library. We combined the search strategy of free text terms and exploded MESH headings for the topic of pharmacological and non-pharmacological treatment of AnxD in perinatal period combined as following: (((((pregnan*) OR perinatal) OR breastfeeding[MeSH Terms])) AND ((anxiety[MeSH Terms]) OR anxiety disorder[MeSH Terms])) AND (((treatment) OR therap*) OR pharmacotherap*). The strategy was first developed in MEDLINE and then adapted for use in the other databases (Appendix A). Studies published in English through January 1st, 2015 were included. In addition, further studies were retrieved from the reference listings of relevant articles and consultation with experts in the field.

2.2. Inclusion criteria

2.2.1. Study population and study design

We considered studies that included women with AnxD during perinatal period. All anxiety disorders were considered if diagnostic criteria used were specified. Studies enroling women with OCD were also considered, even though OCD was moved out from AnxD in the DSM5. However, we chose to include OCD in the review because the sequential order of the DSM5 chapters on AnxD and OCD and related disorders, reflects “the close relationship” among them (American Psychiatric Association, 2013). Further, the first-choice treatment of OCD is similar to those of AnxD and therefore the clinical management of OCD during the perinatal period is largely overlapping to that of AnxD.

Participants younger than 18 years of age were also considered.

Among hospital-based studies, inpatients, day-hospital and outpatient subjects were included while emergency care records were excluded as being considered non-representative. All experimental and observational study designs were included. Narrative and systematic reviews, letters to the editor and book chapters were excluded.

2.2.2. Outcome measures

Either pharmacologic, psychotherapeutic and other alternative approaches were considered.

2.2.3. Study selection and data extraction

Identified studies were independently reviewed for eligibility by two authors (AA, PO) in a two-step based process; a first screening was performed based on title and abstract while full texts were retrieved for the second screening. At both stages disagreements by reviewers were resolved by consensus. Data were extracted by two authors (AA, PO) and supervised by a third author (CM) using an *ad-hoc* developed data extraction spreadsheet. The data extraction spreadsheet was piloted on 10 randomly selected papers and modified accordingly.

2.2.4. Quality assessment

The same authors who performed data extraction (AA, PO) independently assessed the quality of selected studies using the checklist developed by Downs and Black both for randomized and non-randomized studies (Downs and Black, 1998). Disagreements by reviewers were resolved by consensus. Table 1 shows the quality assessment total score assigned to each study.

3. Results

One thousand two hundred potential studies were identified from searching the selected databases and listing references of relevant articles. After removing duplicates, 756 articles were retrieved. Studies were screened and selected on the basis of prespecified inclusion and exclusion criteria (Fig. 1). The search identified 18 articles that were included in the systematic review.

Fifteen of the 18 studies (83%) were case reports/case series, and three (17%) open label trials. The study population was more than 25 subjects in only 11% ($n=2$) of the included studies. The majority of the studies were conducted in North America ($n=7$, 39%) and only 3 studies (17%) were conducted in Europe. In all the considered studies diagnosis of anxiety disorders were based on the DSM (Diagnostic and Statistical Manual of Mental Disorders) criteria and were established using validated assessment scales (Table 1).

No study on the treatment of generalised anxiety disorder (GAD), social phobia, post-traumatic stress disorder, and other anxiety disorders in perinatal period fulfilled our inclusion criteria.

3.1. Treatment of anxiety disorders during pregnancy

3.1.1. Non-pharmacological treatment

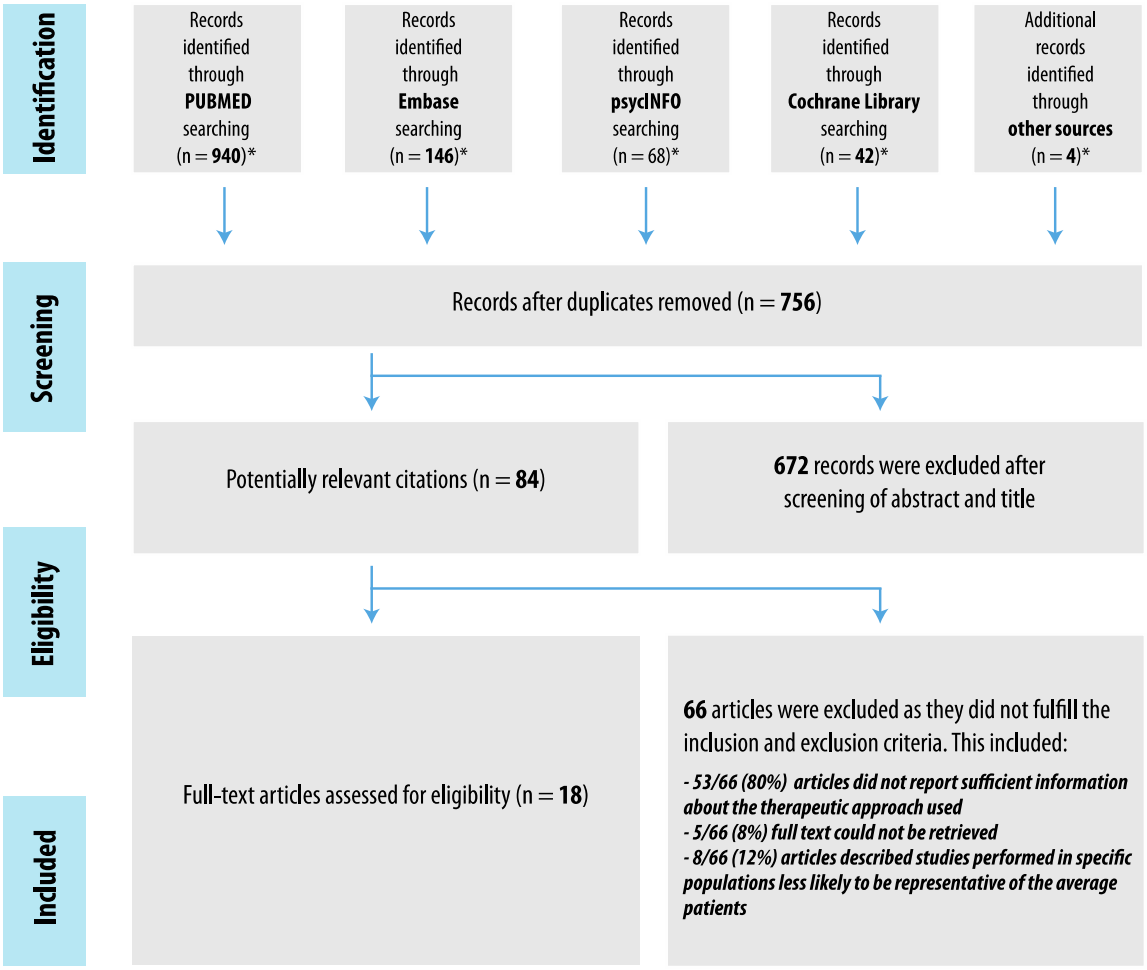
3.1.1.1. Obsessive–compulsive disorder. One case report supported the use of cognitive-behavioural therapy (CBT) for obsessive–compulsive disorder (OCD) during pregnancy (Chelmow and Halfin, 1997) (Table 2). The patient was successfully managed with CBT ("thought-stopping" technique) in combination with frequent visits (every 1–2 weeks) to both her obstetrician and a psychiatrist with special interest in psychiatric disorders in the perinatal period.

Table 1
Studies that met inclusion criteria for systematic review.

References	Study design	Country	Study population	Sample size	Diagnosis assessment	Quality*
Pregnancy						
Obsessive–compulsive disorder						
Chelmow and Halfin (1997)	Case report	USA	1 pregnant woman (age 28)	1	DSM-III-R	18/31
Kalra et al. (2005)	Case report	India	1 pregnant woman (age 30)	1	DSM	18/31
Panic disorder						
Gentile (2008)	Case report	Italy	1 pregnant woman (age 27)	1	DSM-IV-TR	18/31
Nascimento et al. (2004)	Case reports	Brasil	2 pregnant women (age 29)	2	DSM-IV	19/31
Robinson et al. (1992)	Case series		3 pregnant women (age ≥ 18)	3	DSM	20/31
Uguz et al. (2013)	Case report	Turkey	1 pregnant woman (age 26)	1	SCID-I, CGI-I; HAM-D; DSM-IV	18/31
Uguz et al. (2014)	Case series	Turkey	16 pregnant women (age range 19–37)	16	SCID-I, CGI; DSM-IV	19/31
Ware and DeVane (1990)	Case reports	USA	2 pregnant women (age ≥ 18)	2	DSM	18/31
Specific phobia						
Lilliecreutz et al. (2010)	Open trial	Sweden	30 pregnant women (mean age 28.5 ± 5.03)	30	IPSA; IPSAV; EPDS; BAI; DSM-IV	24/31
Postpartum						
Obsessive–compulsive disorder						
Arnold (1999)	Open-label trial	USA	3 women (mean age 31.7 ± 6.9)	3	SCID-I, Y-BOCS; DSM-IV	22/31
Challacombe and Salkovskis (2011)	Case series	UK	6 women (age range 25–44)	6	SCID-I, Y-BOCS; DSM-IV	19/31
Christian and Storch (2009)	Case report		1 women (age 26)	1	ADIS, Y-BOCS, OCI-R; DSM-IV	18/31
Hertzberg et al. (1997)	Case report	USA	1 women (age 25)	1	DSM	18/31
Hudak and Wisner (2012)	Case report	USA	1 PPOCD woman (age 32)	1	DSM-IV-TR	18/31
Misri and Milis (2004)	Open-label trial	Canada	14 treatment-resistant OCD women mean age (32.9 ± 4.11)	14	Y-BOCS, CGI; DSM-IV	23/31
Sichel et al. (1993)	Case series	USA	15 women (age ≥ 18)	15	DSM-III-R	19/31
Uguz et al. (2008)	Case series	Turkey	2 treated PPOCD women + 9 controls (mean age 25.18 ± 5.40)	2	SCID-I, Y-BOCS; DSM-IV	19/31
Wisner et al. (1995)	Case series	USA	4 clomipramine-treated breastfeeding women (age ≥ 18)	4	DSM	19/31

OCD: obsessive–compulsive disorder; PPOCD: postpartum-onset obsessive–compulsive disorder; SCID-I: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; Y-BOCS: Yale–Brown Obsessive–Compulsive Scale; ADIS: Anxiety Disorders Interview Schedule; OCI-R: Obsessive Compulsive Inventory–Revised; IPSA: Injection Phobia Scale-Anxiety; IPSAV: Injection Phobia Scale-Avoidance; EPDS: Edinburgh Postnatal Depression Scale; BAI: Beck Anxiety Inventory; CGI: Clinical Global Impressions Scale; CGI-I: Clinical Global Impression-Improvement Scale; HAM-D: Hamilton Rating Scale for Depression; DSM: Diagnostic and Statistical Manual of Mental Disorders.

* Checklist for measuring study quality developed by Downs and Black.



* Search strategy limited to January 2015, English language and human subjects older than 13 years old.

Fig. 1. Flow diagram of papers selected.

3.1.1.2. Panic disorder. One study in the literature supports the use of CBT for panic disorder (PD) during pregnancy and lactation, with good control of anxiety symptoms and clinical remission of PD (Robinson et al., 1992) (Table 2).

3.1.1.3. Specific phobia. An open trial with two group CBT sessions for blood- and injection phobia was conducted on 30 pregnant women that were clinically assessed before and after each group therapy session, as well as three months after delivery (Table 2). The scores on the "Injection Phobia Scale-Anxiety" decreased after each treatment session, and remained stable up to at least 3 months postpartum. CBT seemed also to reduce anxiety and depressive symptoms during pregnancy (Lilliecreutz et al., 2010).

3.1.2. Pharmacological treatment

3.1.2.1. Obsessive–compulsive disorder. One case report supported the use of fluoxetine for OCD during pregnancy (Table 2). Contaminating obsessions and washing compulsions started at the beginning of the pregnancy and the patient took fluoxetine (up to 60 mg/day) until the last month of gestation with no side effects for the baby (e.g. birth weight, gestational age, Apgar scores, cyanosis, respiratory distress, and tachypnea). Complete remission of obsessive–compulsive symptoms was reported in the following year (Kalra et al., 2005).

3.1.2.2. Panic disorder. With regard to selective serotonin reuptake inhibitors (SSRIs), few case reports support the use of citalopram (Uguz, 2013) and escitalopram (Gentile, 2008) for PD during pregnancy (Table 2). Two pregnant women with PD, who underwent citalopram (20 mg/day) and escitalopram (40 mg/day) treatments, respectively, presented good control of anxiety symptoms and healthy outcomes for the child. Furthermore, adding mirtazapine to the SSRIs treatment, the patient reported a dramatic decrease in nausea, insomnia and appetite loss without any neonatal complication in the baby (Uguz, 2013).

With regard to tricyclic antidepressants (TCAs), PD patients treated with nortryptiline (Nascimento et al., 2004) and imipramine (Uguz et al., 2014; Ware and DeVane, 1990) benefited from pharmacotherapy, reporting remission of panic symptoms. In the largest clinical sample to date, based on the Clinical Global Impression-Improvement Scale (CGI-I), 75% of pregnant women responded to low doses of imipramine (10–40 mg/day) with a statistically significant reduction of the mean number of panic attacks per week from 12.9 to 2.7 before and after the treatment, respectively (Uguz et al., 2014) (Table 2).

3.2. Treatment of anxiety disorders during postpartum

3.2.1. Non-pharmacological treatment

3.2.1.1. Obsessive–compulsive disorder. Two case reports supported the use of CBT, alone or in combination of pharmacotherapy (SSRIs),

Table 2
Intervention and results of selected studies.

References	Intervention	Results
Pregnancy		
Obsessive–compulsive disorder		
Chelmow and Halfin (1997)	CBT sessions ("thought-stopping" technique)	OCD successfully managed with CBT in combination with frequent visits (every 1–2 weeks) to both her obstetrician and her psychiatrist.
Kalra et al. (2005)	Fluoxetine (up to 60 mg/day), 3rd–8th month of gestation	Healthy infant. No OCS at one-year follow up.
Panic disorder		
Gentile (2008)	Escitalopram (40 mg/day) and alprazolam (1.5 mg/day)	Decrease in panic symptoms; healthy infant.
Nascimento et al. (2004)	Nortryptiline (75 mg/day and 100 mg/day, respectively)	Complete remission of panic symptoms
Robinson et al. (1992)	CBT sessions	Decrease in panic symptoms.
Uguz et al. (2013)	Citalopram (20 mg/day) and mirtazapine (7.5 mg/day)	Decrease in nausea, insomnia and appetite loss; good control of panic symptoms; healthy infant.
Uguz et al. (2014)	Imipramine (10–40 mg/day)	Decrease in the mean number of panic attacks per week before and after the treatment.
Ware and DeVane (1990)	Imipramine low doses	Decrease in panic symptoms.
Specific phobia		
Lilliecreutz et al. (2010)	2 CBT session group	Decrease in the scores of the IPSA during pregnancy and postpartum (up to at least 3 months); good control of anxiety and depressive symptoms.
Postpartum		
Obsessive–compulsive disorder		
Arnold (1999)	Fluvoxamine (up to 300 mg/day)	2 of the 3 patients experienced a positive response ($\downarrow \geq 30\%$ in the Y-BOCS total score).
Challacombe and Salkovskis (2011)	CBT sessions (12 h/2 weeks; up to 3 follow-up sessions offered at monthly intervals)	Clinical benefits reported in terms of own symptoms and in parenting in general.
Christian and Storch (2009)	CBT sessions	Clinical remission of OCD
Hertzberg et al. (1997)	Clomipramine (100 mg/day)	Decrease in OCS
Hudak and Wisner (2012)	Citalopram (80 mg/day); psychoeducation sessions; exposure with response prevention therapy	Decrease in OCS
Misri and Milis (2004)	Quetiapine augmentation of SSRIs or SNRIs	Decrease in OCS in 11 treatment-resistant OCD women (reduction of 59.6% in the Y-BOCS score). Sedation was the most commonly reported side effect.
Sichel et al. (1993)	Fluoxetine, cloipramine, desipramine (or a combination of this drugs)	Decrease in OCS in all 15 patients. At 1-year follow-up, 12 patients had elected to remain on pharmacotherapy because of the presence of residual obsessions.
Uguz et al. (2008)	Sertraline (150 mg/day)	Clinical remission of OCD and decrease in OCS in the 2 patients treated with sertraline, respectively.
Wisner et al. (1995)	Clomipramine (75–125 mg/day)	No adverse clinical effects were observed in the infants; good control of OCS

OCD: obsessive–compulsive disorder; OCS: obsessive–compulsive symptoms; CBT: cognitive behaviour therapy; m-ECT: modified-electroconvulsive therapy; IPSA: Injection Phobia Scale-Anxiety; Y-BOCS: Yale–Brown Obsessive–Compulsive Scale; SSRIs: selective serotonin reuptake inhibitors; SNRIs: Serotonin–norepinephrine reuptake inhibitors; AD: antidepressant; Differences statistically significant ($p < 0.05$).

with significant benefits in terms of obsessive–compulsive symptoms and parenting in general (Challacombe and Salkovskis, 2011; Christian and Storch, 2009) (Table 2). In particular, for one woman, eight sessions of CBT induced the clinical remission of postpartum OCD (Christian and Storch, 2009).

3.2.2. Pharmacological treatment

3.2.2.1. Obsessive–compulsive disorder. Studies included in the review supported the use of SSRIs (citalopram, sertraline, fluoxetine, fluvoxamine) (Arnold, 1999; Hudak and Wisner, 2012; Sichel et al., 1993; Uguz et al., 2008) and TCAs (clomipramine, desipramine) (Sichel et al., 1993; Wisner et al., 1995; Hertzberg et al., 1997) with statistically significant symptom improvement (Table 2). In particular, in the largest clinical sample to date, 65% of the patients who entered the open-label trial of fluvoxamine (up to 300 mg/day) experienced a 30% or greater decrease in the total score on the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) (Arnold, 1999).

With regard to alternative therapeutic approaches, Misri and colleagues conducted an open-label trial to investigate the efficacy of twelve-week quetiapine augmentation of SSRIs or serotonin–norepinephrine reuptake inhibitors (SNRIs) in resistant OCD in the postpartum period (Misri and Milis, 2004). They reported a statistically significant reduction in obsessive–compulsive symptoms between baseline and end point (Table 2).

4. Discussion

Studies included in this review supported the use of CBT for OCD, PD and specific phobia both in pregnancy and postpartum. SSRIs led to significant OCD and PD improvement both in pregnancy and postpartum with no side effects for the babies. In the largest clinical sample to date, 65% of postpartum patients who entered the open-label trial of fluvoxamine (up to 300 mg/day) experienced a 30% or greater decrease in the total score of the Y-BOCS. During pregnancy, SSRIs and TCAs led to remission of panic symptoms and healthy outcomes for the babies.

During pregnancy, guidelines for the treatment of OCD, PD, GAD, agoraphobia, and social phobia suggest the consideration of psychosocial and psychotherapeutic interventions, particularly CBT, in lieu of pharmacotherapy (American Psychiatric Association, 2007, 2009). Pharmacotherapy may be indicated for pregnant women with refractory anxiety disorders.

As confirmed by this review, scant and heterogeneous data are available on treatment strategies of AnxD in perinatal period, but, given the current guideline recommendations and available scientific evidence, some observations can be made.

4.1. Clinical practice suggestions for the treatment of pregnant women

Psychotherapy, particularly CBT, should be the first line treatment of AnxD in pregnant women due to its efficacy and safety. Limitations for the use of CBT are the availability of experienced therapists, the severity of the disorder and the need to perform "homework" or to confront feared situations.

Although, according to the guidelines, pharmacotherapy may

be indicated in pregnant women with refractory AnxD, in the last decade, the use of a SSRI compound in pregnancy is widespread in clinical practice. In fact, as demonstrated by data collected by the Swedish and Danish Medical Birth Registers, and by The USA Medicaid database (Reis and Kallen, 2010; Huybrechts et al., 2014; Jimenez-Solem et al., 2013), nearly all the available SSRI compounds are largely prescribed in pregnant women (14,979 women in Sweden, 35,414 in Denmark and 46,144 in USA), even within the first trimester of pregnancy (5123 women in Sweden, 15,403 in Denmark and 46,144 in USA), at a time when the drugs may exert their possibly teratogenic effect.

In these populations, which did not involve only depressed women, the risk of any major malformation (a malformation that severely impaired function or that needed a surgical correction of the affected organ) and particularly of any cardiac malformation did not increase in women treated with SSRIs (OR 0.87; CI 95% 0.76–1.01 and 1.06; CI 95% 0.93–1.22, respectively) (Reis and Kallen, 2010; Huybrechts et al., 2014). Similarly, no substantial increase was found in the overall prevalence of cardiac birth defects among infants exposed to SSRIs or venlafaxine in a large cohort study (Furu et al., 2015) and a recent bayesian analysis of previous reports found an increased risk of birth defects only for paroxetine or fluoxetine early in pregnancy.

Nevertheless, in Swedish Register (Reis and Kallen, 2010) an increased risk of cardiac defects (mainly atrial or ventricular septum defects) (OR=1.66; CI 95% 1.09–2.53) was observed in infants of women exposed to paroxetine (but not to other SSRI compounds) during the first trimester of pregnancy. This finding was not confirmed (OR=0.94; CI 95% 0.73–1.21) in a recent study involving 11,126 women who were treated with paroxetine in the first trimester (Huybrechts et al., 2014). Finally, the risk of cardiac and other malformations did not increase with the use of high doses of SSRIs (Jimenez-Solem et al., 2013).

A recent meta-analysis suggests that SSRIs exposure during pregnancy increased the risk of low birth weight (<2500 gr) (RR=1.48; 95%CI 1.22–1.79) and preterm birth (<37 weeks gestation) (RR=1.74; 95% CI 1.52–2.00). These effects were more pronounced in depressed women than in anxious women (Huang et al., 2014). These findings confirm the data of a previous meta-analysis, which found an increased risk for low birth weight (RR=1.49; 95% CI, 1.25–1.77) and for preterm birth (RR=1.39; 95% CI, 1.19–1.61) in the new-borns of mothers with untreated depressive disorders during pregnancy (Grote et al., 2010). Finally, a case-control study, involving women with depressive or anxiety disorders, found an increased risk for preterm birth (OR=5.07, 95% CI=1.34–19.23), but not for low birth weight, in new-borns exposed to high doses of SSRIs (Roca et al., 2011).

In late pregnancy, the administration of SSRIs exposes the new-borns to the following two risks:

1. increased risk of poor neonatal adaptation syndrome (OR 5.07; CI 95% 3.25–7.90). This affects up to 30% of new-borns and is generally transient, being only very occasionally severe enough to require treatment (Grigoriadis et al., 2013). This risk is prevented if the mother maintained the SSRIs after delivery (see breastfeeding);
2. increased risk of persistent pulmonary hypertension (OR 2.5; CI 95% 1.32–4.73) (Grigoriadis et al., 2014). Although statistically significant, clinically, the absolute risk of persistent pulmonary hypertension in the new-born remained low, as 2.9–3.5 per 1000 infants exposed to SSRIs in late pregnancy developed this condition (Grigoriadis et al., 2014). As such, the Food and Drug Administration " does not find sufficient evidence to conclude that SSRIs use in pregnancy causes persistent pulmonary hypertension in the new-born" (*Drug Safety Communication, 12.14.2011*).

Concerning the cognitive, psychomotor and behavioural effects of the in-utero exposure to SSRIs on new-borns, a recent study demonstrated in depressed mothers no impact on cognitive and behavioural development, while a minimal effect (within the normal range) was found on psychomotor functioning in the first year (Santucci et al., 2014). A recent review found that in-utero exposure to SSRIs has an effect on later cognitive and behavioural development but no effect on early development (Hermansen and Melinder, 2014). However, it remains to be determined whether the effects on child development found after SSRIs treatment in pregnant women are only due to the SSRIs exposure or if the underlying depression is also involved (Olivier et al., 2014).

The use of benzodiazepines (BDZ) is not recommended during pregnancy (Iqbal et al., 2002), particularly in the first trimester due to the risk of cleft lip/palate, even though the absolute risk is low (Bellantuono et al., 2013), and in late pregnancy for the occurrence of a withdrawal syndrome or a "floppy baby syndrome" in BDZ dependent new-borns.

In conclusion, concerning the pharmacological treatment of pregnant women, the safety profile of the SSRIs used during pregnancy, even in the first trimester, based on the findings of the recent large meta-analyses, is reassuring. However, we suggest prescribing sertraline and citalopram particularly, which are the safer and better studied SSRIs for use during pregnancy.

4.2. Clinical practice suggestions for the treatment of breastfeeding women

Some authors suggested that in the postpartum, there is no reason that the treatment of AnxD should differ from AnxD outside the perinatal period (Abramowitz et al., 2003). This suggestion is safely applicable for both psychotherapy, which should be the first line treatment of AnxD in breastfeeding women, and also for pharmacotherapy. In fact, the available data concerning the effects of exposure of breastfeeding infants to a SSRI drug are reassuring, and breastfeeding should not be generally discouraged in women using SSRIs.

A recent review (Rowe et al., 2015) demonstrated that in breastfeeding mothers the transfer of sertraline, fluvoxamine, and paroxetine into human milk is low and uptake by the infant is even lower. Thus far, no or minimal untoward effects have been reported following the use of these three compounds in breastfeeding mothers. Sertraline is overwhelmingly favoured, as more than 50 mother–infant pairs have been evaluated, and milk and infant plasma levels are low to undetectable. In breastfeeding, fluoxetine and citalopram should not be the drugs of first choice, because the long plasma half-life of the former and the detectable plasma level in new-borns for the latter may cause adverse effects in infants (Rowe et al., 2015).

Concerning BDZ, in a prospective study only 2 (1.6%) infants (2–24 months old) of 124 women taking BDZ (52% lorazepam, 18% clonazepam and 15% midazolam) were found to have central nervous system depression (Kelly et al., 2012). If these agents are used, choose a product with a short half-life and use the lowest effective dose for the shortest duration to minimise exposure.

5. Limitations

The main limitation of included studies is sample size, as documented by the quality assessment scores. Only four studies (22%) were assigned a score equal or greater than 20/31 on the Downs and Black quality scale (Downs and Black, 1998) (Table 1). The majority of the selected studies are case reports (83%, 15/18) with only three clinical trials (17%). Study design and enrolment of subjects mainly from outpatient specialty units might have limited

community-wide generalisability.

Another limitation is the inclusion of papers published only in English. The the four papers included in the Other Sources section, were retrieved from the grey literature (i.e. through the internet and among the references of the potentially relevant studies), nonetheless this search has not been systematic and could results in a further bias of a review (Mahood et al., 2014). Considering the limited number of studies; the broad scope of diagnosis; types of treatment included and the diversity of study designs (including both case studies and clinical trials), the conclusions extracted cannot be easily generalised.

The main strength of this study is that it is the first systematic review of this topic, and thus includes the entire available body of scientific evidence. Further, in all included original studies the diagnosis of AnxD were consistently based on the DSM criteria and were established by trained investigators using validated assessment scales mainly with interrater reliability.

Competing interests

Dr. Marchesi, Dr. Ossola, Dr. Amerio, Dr. Daniel, Dr. Tonna, and Dr. De Panfilis report no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Contributors

Authors CM, PO, AA, and BDD designed the study and wrote the protocol. Studies were identified and independently reviewed for eligibility by two authors (AA, PO) in a two-step based process. Data were extracted by two authors (AA, PO) and supervised by a third author (CM) using an ad-hoc developed data extraction spreadsheet. The same authors who performed data extraction (AA, PO) independently assessed the quality of selected studies using the checklist developed by Downs and Black both for randomized and non-randomized studies. Authors CM, PO, AA, BDD, MT, CDP wrote the first draft of the manuscript. Our manuscript has been approved by all authors.

Appendix A. MEDLINE search strategy

SET	MEDLINE
1	Pregnan*
2	Perinatal
3	*Breastfeeding*
4	Sets 1–3 were combined with “OR”
5	*Anxiety*
6	*Anxiety disorder*
7	Sets 5–6 were combined with “OR”
8	Treatment
9	Therap*
10	Pharmacotherap*
11	Sets 8–10 were combined with “OR”
12	Sets 4, 7 and 11 were combined with “AND”
13	Set 12 was limited to January 2015, Humans, English language, Adolescent: 13–18 years, Adult: 19+ years

Words written in *italic* were used as MeSH headings, the others were used as free text.

References

Abramowitz, J.S., Schwartz, S.A., Moore, K.M., Luenzmann, K.R., 2003. Obsessive–compulsive symptoms in pregnancy and the puerperium: a review of the literature. J. Anxiety Disord. 17, 461–478.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). American Psychiatric Pub, USA.

American Psychiatric Association, 2007. Practice guideline for the treatment of patients with obsessive-compulsive disorder. American Psychiatric Association, Arlington, VA.

American Psychiatric Association, 2009. Practice guideline for the treatment of patients with panic disorder, Second ed. American Psychiatric Association, Arlington, VA.

Arnold, L.M., 1999. A Case Series of Women With Postpartum-Onset Obsessive–Compulsive Disorder. J. Clin. Psychiatry 1, 103–108.

Austin, M.P., Hadzi-Pavlovic, D., Priest, S.R., Reilly, N., Wilhelm, K., Saint, K., Parker, G., 2010. Depressive and anxiety disorders in the postpartum period: how prevalent are they and can we improve their detection? Arch. Women's Ment. Health 13, 395–401.

Bellantuono, C., Tofani, S., Di Sciascio, G., Santone, G., 2013. Benzodiazepine exposure in pregnancy and risk of major malformations: a critical overview. Gen. Hosp. Psychiatry 35, 3–8.

Challacombe, F.L., Salkovskis, P.M., 2011. Intensive cognitive-behavioural treatment for women with postnatal obsessive-compulsive disorder: a consecutive case series. Behav. Res. Ther. 49, 422–426.

Chelmow, D., Halfin, V.P., 1997. Pregnancy complicated by obsessive–compulsive disorder. J. Matern. Fetal Med. 6, 31–34.

Christian, L.M., Storch, E.A., 2009. Cognitive behavioral treatment of postpartum onset: obsessive compulsive disorder with ag- gressive obsessions. Clin. Case Stud. 8, 72–83.

Downs, S.H., Black, N., 1998. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J. Epidemiol. Community Health 52 (6), 377–384.

Furu, K., Kieler, H., Haglund, B., Engeland, A., Selmer, R., Stephansson, O., Valdimarsdottir, U.A., Zoega, H., Artama, M., Gissler, M., Malm, H., Nørgaard, M., 2015. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. BMJ 350, h1798. http://dx.doi.org/10.1136/bmj.h1798.

Gentile, S., 2008. Use of escitalopram during pregnancy: navigating towards international guidelines and the real world. Clin. Drug. Investig. 28 (11), 735–739.

Glasheen, C., Richardson, G.A., Fabio, A., 2010. A systematic review of the effects of postnatal maternal anxiety on children. Arch. Women's Ment. Health 13, 61–74.

Goodman, J.H., Chenausky, K.L., Freeman, M.P., 2014. Anxiety disorders during

pregnancy: a systematic review. J. Clin. Psychiatry 75, 1153–1184.
Grigoriadis, S., VonderPorten, E.H., Mamisashvili, L., Eady, A., Tomlinson, G., Dennis, C.L., Koren, G., Steiner, M., Mousmanis, P., Cheung, A., Ross, L.E., 2013. The effect of prenatal antidepressant exposure on neonatal adaptation: a systematic review and meta-analysis. J. Clin. Psychiatry 74, 309–320.
Grigoriadis, S., Vonderporten, E.H., Mamisashvili, L., Tomlinson, G., Dennis, C.L., Koren, G., Steiner, M., Mousmanis, P., Cheung, A., Ross, L.E., 2014. Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and meta-analysis. BMJ 348, 6932.
Grote, N.K., Bridge, J.A., Gavin, A.R., Melville, J.L., Iyengar, S., Katon, W.J., 2010. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch. Gen. Psychiatry 67, 1012–1024.
Hermansen, T.K., Melinder, A., 2014. Prenatal SSRI exposure: effects on later child development. Child. Neuropsychol. 4, 1–27.
Hertzberg, T., Leo, R.J., Kim, K.Y., 1997. Recurrent obsessive–compulsive disorder associated with pregnancy and childbirth. Psychosomatics 38, 386–388.
Higgins, J., Green, S. 2011. Cochrane handbook for systematic reviews of interventions, version 5.1.0.: The Cochrane Collaboration.
Huang, H., Coleman, S., Bridge, J.A., Yonkers, K., Katon, W., 2014. A meta-analysis of the relationship between antidepressant use in pregnancy and the risk of preterm birth and low birth weight. Gen. Hosp. Psychiatry 36, 13–18.
Hudak, R., Wisner, K.L., 2012. Diagnosis and treatment of postpartum obsessions and compulsions that involve infant harm. Am. J. Psychiatry 169, 360–363.
Huybrechts, K.F., Palmsten, K., Avorn, J., Cohen, L.S., Holmes, L.B., Franklin, J.M., Mogun, H., Levin, R., Kowal, M., Setoguchi, S., Hernández-Díaz, S., 2014. Antidepressant use in pregnancy and the risk of cardiac defects. N. Engl. J. Med. 370, 2397–2407.
Iqbal, M.M., Sobhan, T., Ryals, T., 2002. Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. Psychiatr. Serv. 53, 39–49.
Jimenez-Solem, E., Andersen, J.T., Petersen, M., Broedbaek, K., Andersen, N.L., Torp-Pedersen, C., Poulsen, H.E., 2013. Prevalence of antidepressant use during pregnancy in Denmark, a nation-wide cohort study. PLoS One 8, 63034.
Kalra, H., Tandon, R., Trivedi, J.K., Janca, A., 2005. Pregnancy-induced obsessive compulsive disorder: a case report. Ann. Gen. Psychiatry 4, 12.
Kelly, L.E., Poon, S., Madadi, P., Koren, G., 2012. Neonatal benzodiazepines exposure during breastfeeding. J. Pediatr. 161, 448–451.
Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P., Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339, b2700.
Lilliecreutz, C., Josefsson, A., Sydsjo, G., 2010. An open trial with cognitive behavioral therapy for blood- and injection phobia in pregnant women – a group intervention program. Arch. Women's Ment. Health 13, 259–265.
Mahood, Q., Eerd, D.V., Irvin, E., 2014. Searching for grey literature for systematic reviews: challenges and benefits. Res. Synth. Methods 5, 221–234.
Marchesi, C., Ampollini, P., Paraggio, C., Giaracuni, G., Ossola, P., De Panfilis, C., Tonna, M., Viviani, D., 2014. Risk factors for panic disorder in pregnancy: a cohort study. J. Affect. Disord. 156, 134–138.
Misri, S., Milis, L., 2004. Obsessive–compulsive disorder in the postpartum: open-label trial of quetiapine augmentation. J. Clin. Psychopharmacol. 24, 624–627.
Nascimento, I., Lopes, F.L., Valenca, A.M., Mezzasalma, M.A., Nardi, A.E., 2004. [Panic disorder and pregnancy]. Rev. Bras. Psiquiatr. 26, 211–212.
Olivier, J.D., Akerud, H., Sundstrom Poromaa, I., 2014. Antenatal depression and antidepressants during pregnancy: unraveling the complex interactions for the offspring. Eur. J. Pharmacol. [Epub ahead of print]
Prenoveau, J., Craske, M., Counsell, N., West, V., Davies, B., Cooper, P., Rapa, E., Stein, A., 2013. Postpartum GAD is a risk factor for postpartum MDD: the course and longitudinal relationships of postpartum GAD and MDD. Depress. Anxiety 30, 506–514.
Reck, C., Struben, K., Backenstrass, M., Stefenelli, U., Reinig, K., Fuchs, T., Sohn, C., Mundt, C., 2008. Prevalence, onset and comorbidity of postpartum anxiety and depressive disorders. Acta Psychiatr. Scand. 118, 459–468.
Reis, M., Kallen, B., 2010. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. Psychol. Med. 40, 1723–1733.
Robinson, L., Walker, J.R., Anderson, D., 1992. Cognitive-behavioural treatment of panic disorder during pregnancy and lactation. Can. J. Psychiatry 37, 623–626.
Roca, A., Garcia-Esteve, L., Imaz, M.L., Torres, A., Hernandez, S., Botet, F., Gelabert, E., Subirà, S., Plaza, A., Valdés, M., Martin-Santos, R., 2011. Obstetrical and neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitors: the relevance of dose. J. Affect. Disord. 135, 208–215.
Ross, L.E., McLean, L.M., 2006. Anxiety disorders during pregnancy and the postpartum period: a systematic review. J. Clin. Psychiatry 67, 1285–1298.
Rowe, H., Baker, T., Hale, T.W., 2015. Maternal medication, drug use, and breastfeeding. Child. Adolesc. Psychiatr. Clin. N. Am. 24, 1–20.
Santucci, A.K., Singer, L.T., Wisniewski, S.R., Luther, J.F., Eng, H.F., Dills, J.L., Sit, D.K., Hanusa, B.H., Wisner, K.L., 2014. Impact of prenatal exposure to serotonin reuptake inhibitors or maternal major depressive disorder on infant developmental outcomes. J. Clin. Psychiatry 75, 1088–1095.
Sichel, D.A., Cohen, L.S., Dimmock, J.A., Rosenbaum, J.F., 1993. Postpartum obsessive compulsive disorder: a case series. J. Clin. Psychiatry 54, 156–159.
Uguz, F., Kaya, N., Sahingoz, M., Cilli, A.S., Akman, C., 2008. One year follow-up of postpartum-onset obsessive–compulsive disorder: a case series. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 1091–1092.
Uguz, F., Sahingoz, M., Gungor, B., Askin, R., 2014. Low-dose imipramine for treatment of panic disorder during pregnancy: a retrospective chart review. J. Clin. Psychopharmacol. 34, 513–515.
Uguz, F., 2013. Low-dose mirtazapine added to selective serotonin reuptake inhibitors in pregnant women with major depression or panic disorder including symptoms of severe nausea, insomnia and decreased appetite: three cases. J. Matern. Fetal Neonatal Med. 26, 1066–1068.
Vesga-Lopez, O., Blanco, C., Keyes, K., Olfson, M., Grant, B.F., Hasin, D.S., 2008. Psychiatric disorders in pregnant and postpartum women in the United States. Arch. Gen. Psychiatry 65, 805–815.
Ware, M.R., DeVane, C.L., 1990. Imipramine treatment of panic disorder during pregnancy. J. Clin. Psychiatry 51, 482–484.
Wenzel, A., Haugen, E.N., Jackson, L.C., Brendle, J.R., 2005. Anxiety symptoms and disorders at eight weeks postpartum. J. Anxiety Disord. 19, 295–311.
Wisner, K.L., Perel, J.M., Foglia, J.P., 1995. Serum clomipramine and metabolite levels in four nursing mother-infant pairs. J. Clin. Psychiatry 56, 17–20.
Zietlow, A.L., Schluter, M.K., Nonnenmacher, N., Muller, M., Reck, C., 2014. Maternal self-confidence postpartum and at pre-school age: the role of depression, anxiety disorders, maternal attachment insecurity. Matern. Child. Health J. 18, 1873–1880.