REVIEW ARTICLE

Biologically based treatment approaches to the patient with resistant perinatal depression

Thalia K. Robakis · Katherine Ellie Williams

Abstract This study aims to summarize the current state of knowledge regarding approaches to treatment-resistant depression in pregnancy and the postpartum period and to develop algorithms for ante- and postnatal management in cases of refractory major depression. PubMed, Scopus, Google Scholar, and the Cochrane Library databases were searched without temporal restriction. Search terms included pregnancy and depression, perinatal depression, postnatal depression, treatment resistance and depression, antipsychotics and pregnancy, antidepressants and pregnancy, and mood stabilizers and pregnancy. Abstracts were reviewed for relevance, and further articles were obtained from bibliographic citations. There is a significant subpopulation of patients in pregnancy and postpartum whose depressive symptoms do not respond to first-line treatments. No research studies have focused specifically on this population. Data extracted from studies on women with depressive symptoms in pregnancy suggest that in the absence of evidence on which to base clinical decisions, many are receiving combinations of psychotherapeutic medications that have not been specifically studied for use in pregnancy. Antidepressant use in pregnancy is well studied, but studies specifically addressing the case of the patient who does not respond to first-line treatments are absent. Research in this area is urgently needed. The authors review a number of possible therapeutic approaches to treatment-resistant depression in pregnancy and the postpartum period.

Keywords Treatment-resistant depression · Pregnancy · Antenatal depression · Postpartum depression · Antidepressants

T. K. Robakis (✉) · K. E. Williams
Department of Psychiatry, Stanford University Medical Center,
401 Quarry Road, Stanford, CA 94305, USA
e-mail: trobakis@stanford.edu

Introduction

Depression during the perinatal period is common; in cross-sectional and prospective studies of antenatal and postpartum patients, 8–15 % of women meet criteria for a depressive disorder (Dietz et al. 2007).

Depression in pregnancy is associated with multiple unfavorable pregnancy outcomes. These include reduced prenatal care, inadequate weight gain, and increased substance use (see Marcus 2009 for review), and some studies report higher rates of premature delivery and small for gestational age infants (Davalos et al. 2012).

Depression in the postpartum period is associated with many problems with maternal behavior and interpersonal relations, including difficulty with infant care and other responsibilities (Field 2011), difficulty bonding with the child and establishing breastfeeding in the critical early days, as well as problems within the marital relationship (Paulson and Bazemore 2010). The UK-based Confidential Enquiry into Maternal Deaths study found suicide to be the leading cause of maternal death in the postpartum period (Oates 2003).

Beyond these immediate concerns, perinatal depression may have lasting effects on the child's development (see Brand and Brennan 2009 for review).

Recent research has shown that successful treatment of perinatal depression can lead to improvement in the psychiatric health of the patients' children. Children of mothers whose depression remitted with treatment were found to have improvement in psychiatric symptoms and functioning compared to children of mothers who remained depressed (Wickramaratne et al. 2011; Garber et al. 2011).

Clinical consensus holds that nonpharmacological treatments such as cognitive behavioral or interpersonal psychotherapy are first-line for the pregnant or lactating mother, and often these treatments are successful (Brandon and Freeman 2011; Dennis et al. 2007; Dimidjian and Goodman 2009; Dennis and Hodnett 2007; Cuijpers et al. 2008). However,

little has been written about those cases of severe maternal perinatal depression that remain resistant to psychotherapy and to uncomplicated antidepressant treatments. It is thus at the very point where treatment decisions become most complex and difficult that the clinician encounters a lack of expert guidance. Consequently, the purpose of this paper is to offer guidelines for treatment of the perinatal woman with depression refractory to first-line treatments.

Existing treatment studies and remission rates

How significant is the problem of treatment-resistant depression in pregnancy and postpartum? To answer this question, it is necessary to consider the definition of treatment resistance in the depressed patient. Currently, there is no generally accepted consensus definition (Berlim and Turecki 2007a, b). For the purposes of this review, we will define "treatment resistance" as failure to respond or remit to two trials of appropriate pharmacotherapy, each adequate in dose and period of treatment.

The most complete and informative study of treatment-resistant depression to date, the STAR*D trial, suggested that 8 weeks may be a minimum period of time to allow for a new medication to take effect, and some participants in that trial took as long as 14 consecutive weeks to achieve remission (Warden et al. 2007). In the absence of studies that address minimum treatment periods in pregnant women specifically, we suggest an 8-week minimum treatment period in this population also.

The number of available studies addressing treatment resistance in the perinatal population, and in particular of studies using a pharmacological approach, is surprisingly small. To our knowledge, there is no available work specifically addressing the rates of response to pharmacological treatment in antenatally depressed women (Coverdale et al. 2008). Two naturalistic studies have examined the effects of discontinuation of antidepressant medication during pregnancy. While Cohen et al. (2006) reported relapse rates of 67.7 % in women who discontinued antidepressants in pregnancy, compared to 25.6 % of women who continued medication, Yonkers and colleagues failed to find a difference in relapse rates between groups (Yonkers et al. 2011). Due to ethical concerns, to date, there are no placebo-controlled studies of antenatally depressed women randomized to antidepressant medications (Coverdale et al. 2008); the rates of pharmacological treatment-resistant depression are currently unknown.

Several small medication studies have shown that SSRIs (Stowe et al. 1997; Suri et al. 2001), venlafaxine (Cohen et al. 2001), nefazadone (Suri et al. 2005), bupropion (Nonacs et al. 2005), and paroxetine (Yonkers et al. 2008; Misri et al. 2004) are effective treatments for depression in the postpartum period. However, most of these studies are small (N ranges from 4 to 43) and of very limited duration

(8–12 weeks). The largest pharmacologic studies to date are comparison studies of nortriptyline and sertraline (N=109) (Wisner et al. 2006) and fluoxetine or placebo and CBT (N=87) (Appleby et al. 1997).

Estimates of the rate of response to treatment are variable. A recent meta-analysis (Sockol et al. 2011) found four trials of pharmacotherapy for postpartum depression. Remission rates for the intervention groups ranged from 37 to 80 %, and response rates ranged from 43 to 83 %. These numbers suggest that anywhere from a sizable minority to a clear majority of patients do not find significant relief in standard first-line psychopharmacological treatments.

To date, no prospective studies of sequenced treatment for perinatal depression exist. In a retrospective chart reviewing and comparing treatment response in non-postpartum and postpartum depressed patients, Hendrick et al. (2000) reported that 27 % of the postpartum sample required a change in medication in order to achieve response or remission, and 60 % required a combination of more than one antidepressant.

Sockol et al. (2011) also lists ten randomized controlled trials of psychotherapeutic interventions for postnatal depression. Of these, six (Chabrol et al. 2002; Cooper et al. 2003; Honey et al. 2002; Milgrom et al. 2005; Mulcahy et al. 2010; Wiklund et al. 2010) individually established criteria for remission reported the results, which ranged from 59 to 82 % in the intervention groups. While these are encouraging results, they also suggest that there is a significant subpopulation that remains depressed despite such interventions.

To date, there have been no systematic investigations of treatment resistance in perinatally depressed patients. Indeed, in antenatal patients to date, there have been no randomized controlled trials to establish antidepressant efficacy (Coverdale et al. 2008). Hence, the clinical approach is based on a case-by-case evaluation of the known risks of the various medication options versus the projected benefits to the specific patient.

The risks and benefits of the many available psycho-pharmaceuticals in pregnancy and lactation have been covered extensively elsewhere (Byatt et al. 2013; Gentile 2010; Galbally et al. 2010), and we will not repeat this material here. What follows is a discussion of the state of our knowledge with respect to prudent combinations of these medications in situations where monotherapy has proven insufficient.

General guidelines on antidepressants

Due to the lack of studies to inform treatment decisions, the algorithm is similar to that for major depression with non-postpartum onset, with some variations discussed below.

In general, optimal treatment during pregnancy would involve a single medication with an acceptable safety profile and a known history of effectiveness in the particular patient, at the minimum dose which is still effective.

A strategy of cautious dosing is often undertaken by clinicians faced with a need to treat severe depression but a valid concern for medication effects on the fetus. However, undertreatment can represent the worst of both worlds: the fetus is exposed both to the drug and to the effects of the mother's unresolved depressive symptoms (Marcus 2009). Hence, once a decision to treat with medication is made, if results are not seen with a cautious dose, it is appropriate to titrate to an effective one. It should be borne in mind that the effective dose in pregnancy may in fact be higher than the effective dose of the same medication for the same patient prior to pregnancy (Hostetter et al. 2000; Sit et al. 2008; Klier et al. 2007a). As regards dosing, we note here that particularly among pregnant women, undertreatment of depression is frequent and chronic.

One cause of treatment resistance in the perinatal patient may be the changes in antidepressant pharmacokinetics that occur during pregnancy and the postpartum period. Physiologic changes of pregnancy such as increased volume of distribution, decreased concentration of plasma proteins, increased hepatic function, and hormone-induced changes in metabolic enzymes mean that up to 70 % of women treated with antidepressants may need to increase their prepregnancy dose in order to maintain euthymia (Hostetter et al. 2000). During pregnancy, gonadal hormones may induce cytochrome P450 levels (3A4 and 2D6), leading to decreased effective doses of SSRIs (Deligiannidis 2010). Consequently, prior to defining the treatment as "resistant" and augmenting or changing to a new antidepressant, a dose increase would be a logical first step, since monotherapy is always the preferred treatment; e.g. a woman who had previously responded to 20 mg of fluoxetine may need an increase to 30 mg/day in order to achieve remission during pregnancy. In the postpartum period, when gonadal hormone levels decrease, lower doses of SSRI may be needed, and failure to adjust dose may be associated with increased side effects, including anxiety, insomnia, low energy, and cognitive complaints which may be mistaken for treatment resistance.

In the treatment-resistant patient, despite adequate dosage and time allowed to achieve effect, treatment response or remission has not occurred, and the options to either switch treatments or to augment with a second medication or psychotherapy must be considered (Fig. 1). However, prior to initiating any change in treatment strategy, the clinician should be certain that he or she is dealing with true treatment resistance rather than mere inadequacy of dose.

Resistance to treatment in the general patient with depression is best guided by the results of the STAR*D trial (reviewed by Warden et al. 2007). Because there is no equivalent study for the pregnant or postpartum patient, what follows is a discussion of the options in this population based upon a broad review of the existing literature regarding treatment resistance in general.

Major conclusions from the STAR*D results have been summarized by Warden et al. (2007). In particular, the trial found that remission is a preferred outcome. Response without remission resulted in higher rates of relapse over the longer term. However, remission can take time; Warden and colleagues suggest 8 weeks as a minimum time to wait before judging a given treatment ineffective. Some STAR*D participants remitted as late as 14 weeks of treatment.

Another surprising and important finding of the STAR*D trial was that there were few differences in efficacy among medications. Differences in tolerability were more significant and relevant to outcome than any differences in treatment efficacy. In a medication switch, there was no advantage to switching to a medication of a different drug class versus a different medication from the same class. In augmentation trials, all pharmacological augmentors and augmentation with psychotherapy were of approximately equal utility, although liothyronine was better tolerated than lithium, and psychotherapy required a slightly longer time to take effect.

These findings have important implications for the pregnant patient, who may be more wary of medication combinations than the general psychiatric patient. Multiple medications can have combinatorial effects on fetal development; for example, there is a risk of heart defects when SSRIs are combined with benzodiazepines in pregnancy, although neither drug class is associated with such risk when given alone (Oberlander et al. 2008). Thus, monotherapy whenever possible is the optimal choice for pregnant and lactating patients. If an initial trial of antidepressant fails to produce remission despite adequate dosing and combination with psychotherapy, medication switch is preferable to an addition of a second drug, unless the first drug has had a very significant effect despite falling short of remission.
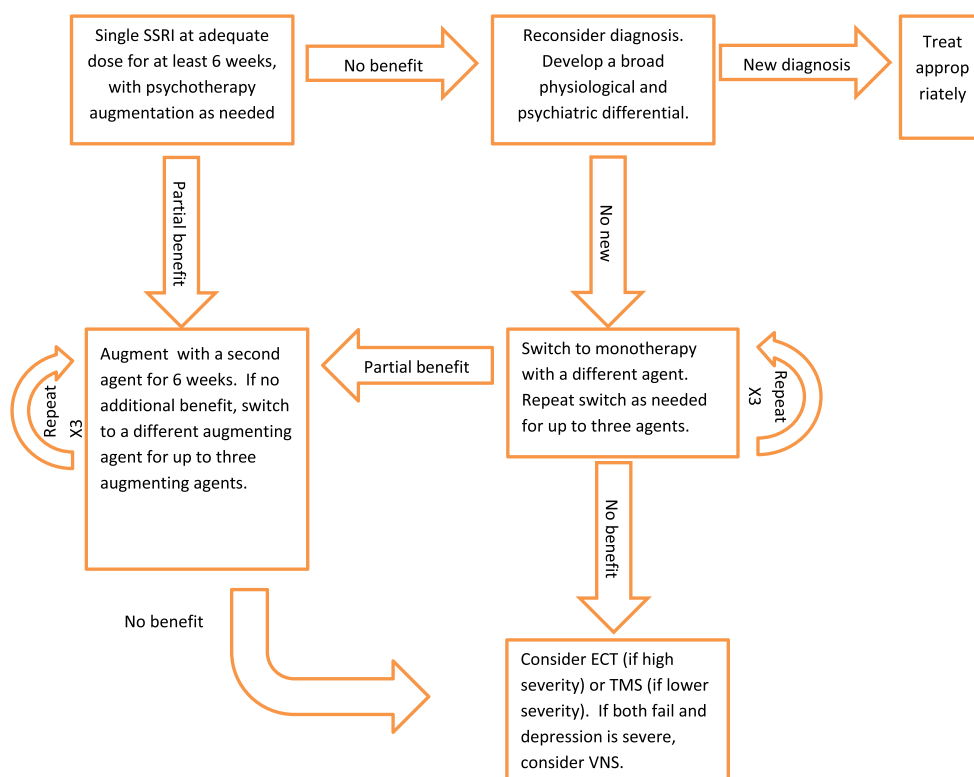
The first choice of drug is one which has an acceptable safety record and a documented history of effectiveness for the specific patient. If such an option is not available, then decisions should be made based on the information that is available regarding both safety of medication options and the patient's previous experiences with medication.

Considerations on combining medications

As a general principle, combinations of medications are more likely to generate unwanted side effects than are single medications. For example, Oberlander et al. (2008) found that a combination of serotonin reuptake inhibitor and benzodiazepine carried twice the risk of major congenital anomalies of treatment with either agent alone.

Although benzodiazepines are not a treatment of choice in depression, and data are sparse regarding use in pregnancy of more commonly used combinations for treatment-resistant depression, it is not unlikely that the principle is true for

Fig. 1 Algorithmic approach to treatment-resistant depression in the perinatal period

```
┌─────────────────────┐   No benefit   ┌─────────────────────┐  New diagnosis  ┌──────────┐
│ Single SSRI at      │ ────────────▶  │ Reconsider diagnosis.│ ───────────────▶│ Treat    │
│ adequate dose for   │                │ Develop a broad      │                 │ approp   │
│ at least 6 weeks,   │                │ physiological and    │                 │ riately  │
│ with psychotherapy  │                │ psychiatric          │                 └──────────┘
│ augmentation as     │                │ differential.        │
│ needed              │                └─────────────────────┘
└─────────────────────┘
         │                                       │
   Partial benefit                             No new
         │                                       │
         ▼                                       ▼
┌─────────────────────┐  Partial benefit ┌─────────────────────┐
│ Augment with a      │ ◀──────────────  │ Switch to           │  Repeat
│ second agent for 6  │                  │ monotherapy with a  │   X3
│ weeks. If no        │   Repeat X3      │ different agent.    │
│ additional benefit, │                  │ Repeat switch as    │
│ switch to a         │                  │ needed for up to    │
│ different augmenting│                  │ three agents.       │
│ agent for up to     │                  └─────────────────────┘
│ three augmenting    │                           │
│ agents.             │                       No benefit
└─────────────────────┘                           │
         │                                         ▼
    No benefit          ┌─────────────────────────────────┐
         └────────────▶ │ Consider ECT (if high severity) │
                        │ or TMS (if lower severity). If  │
                        │ both fail and depression is     │
                        │ severe, consider VNS.           │
                        └─────────────────────────────────┘
```

certain other medication combinations as well. In the absence of data to the contrary, it is prudent to assume that combinations of other classes of medications may also produce combinatorial increased risks.

While the best-case scenario for the depressed patient in pregnancy is the use of a single, well-studied, effective agent, our purpose here is to discuss the situations in which that type of treatment proves insufficient. Thus, we consider cases where the likelihood of harm to the patient or her child or both from ongoing severe mood dysregulation outweighs the estimated likelihood of harm from the use of multiple psychopharmacological agents. Given this situation, we below discuss what is known regarding the use of medication combinations for treatment-resistant depression in pregnancy.

Antidepressants with antipsychotics

Data on combination therapy in pregnant women are absent from the literature, although clearly such therapy is in use clinically (Epstein et al. 2012). Among the 151 pregnant women exposed to antipsychotics in the first trimester in the prospective study by McKenna et al. (2005), 60 were concurrently taking an antidepressant. No specific risks accruing to this population were reported, and the study found few differences in outcome overall either for major malformation or for adverse pregnancy outcome (including spontaneous abortion, stillbirth, and low gestational age at delivery) between its exposure and comparison groups, although the study lacked power to detect moderate increases in risk.

Among the 571 women taking antipsychotics in pregnancy studied by Reis and Kallen (2008), 172 were concomitantly exposed to antidepressants (of which 101 cases used SSRIs). This study found slight increases in a risk for major malformation, preterm birth, and low birth weight with antipsychotic use. While the authors noted that associations with preterm birth and low birth weight have been described with SSRIs, they did not offer any specific discussion of the group of women who received this combination.

Among the 22 women taking antipsychotics in pregnancy studied by Johnson et al. (2012), 17 were concomitantly taking antidepressants. In this study, the negative effects of antidepressants on neuromotor development did not reach a statistical significance after control for covariates. The sample size was too small to draw conclusions regarding neuromotor outcomes after use of antipsychotics with or without antidepressants.

The best studied antidepressant–antipsychotic combination is olanzapine with fluoxetine, which is FDA approved for treatment-resistant depression and available commercially in combination. There is research consensus that combination therapy is more effective for treatment-resistant depression than monotherapy with either drug. Short-term safety and tolerability assessments suggest that while some measures (such as total increase in body weight and increase in serum glucose concentration) are similar to treatment with olanzapine alone, others (including serum triglycerides and prolactin concentration) are more severe in patients receiving combined therapy (reviewed in Bobo and Shelton 2009).

However, long-term safety and tolerability assessments in the general population are still lacking.

At this juncture, although many women have been exposed concurrently to antidepressants and antipsychotics in pregnancy, a systematic investigation of the safety of this practice has yet to be conducted. As yet, no specific outcomes (adverse or otherwise) have been reported in the literature, and there is thus no evidence for a combinatorial increase in adverse effects. It is reasonable to regard the adverse effect profiles as additive in the absence of evidence for such combinatorial effects.

Mood stabilizers with antipsychotics

At present, there have been no studies targeted to discover whether adverse effects can be specifically attributed to the combination of an antipsychotic with a mood stabilizer. Although in the available studies of antipsychotics, teratogenicity is more heavily concentrated among cases where polydrug therapy, and specifically polytherapy with anticonvulsants, was used (Coppola et al. 2007; Reis and Kallen 2008), it is difficult to separate the known teratogenic effect of the anticonvulsant from any additional risk conferred by cotherapy with the antipsychotic. Untangling this issue would require a targeted prospective study with a large number of participants; such a study has yet to be produced. Some insights may be gleaned into an examination of the cases of polydrug therapy included within larger studies of psychotropic medications in pregnancy.

In the study of antipsychotic use in pregnancy by Reis and Kallen, 23 women were concurrently taking an anticonvulsant and an antipsychotic. Three of these women gave birth to offspring with malformations: two major (trisomy 18, mother taking haloperidol and phenytoin; and ventricular septal defect, mother taking zuclopenthixol and valproic acid) and one minor (unstable hip, mother taking haloperidol, levopromazine, and carbamazepine). All three of these mothers were taking anticonvulsants with known teratogenic potential, and from this small number of cases, it is impossible to tell whether the combination with an antipsychotic augments this risk.

In the study by McKenna et al. (2005), 18 women combined an antipsychotic with an anticonvulsant (13 took valproate; 4, carbamazepine; 3, lamotrigine; and 1 each, gabapentin and topiramate). No major malformations were reported among any of these pregnancies.

Thus, what can be said regarding the combination of an antipsychotic with an anticonvulsant in pregnancy is that this type of therapy is already in use clinically, and while malformation rates appear to be increased as would be expected based on the anticonvulsant alone, the majority of pregnancies do not have an easily observable adverse outcome.

Antidepressants with mood stabilizers

Although the combination of an antidepressant and mood stabilizer is a ubiquitous one given the prevalence of bipolar depressive episodes and the dearth of options for monotherapy, there have been no studies targeted towards disentangling the effects of combination therapy in the pregnant patient. Paradoxically, since studies on anticonvulsants and antidepressants individually are able to recruit larger numbers of patients than those examining the less commonly used antipsychotics, it is more feasible to exclude patients receiving polypharmacy, and thus, these patients are largely missing from the datasets.

At this juncture, although there are reasonably good data regarding outcomes with most antidepressants and anticonvulsants when used separately, there is no way to judge what distinct effects might arise from their use in combination.

Hormonal approaches to the perinatal patient with treatment-resistant depression

During pregnancy and postpartum, estrogen and progesterone levels change dramatically from the prepartum state, yet to date, most studies have not found a direct relationship between gonadal hormone levels and perinatal depressive symptoms (Bloch et al. 2003; Chatzicharalampous et al. 2011). A number of theories have been proposed describing more complex relationships between endocrine factors and depressive symptoms in the peripartum (see Klier et al. 2007b for review). However, all such theories remain in the experimental stages, and as such are not of great use as a guide to the clinician.

There is a relationship between premenstrual dysphoric symptoms and risk for peripartum depression, suggesting an underlying, as yet unclarified sensitivity to changes in gonadal hormones in at least a subgroup of women with peripartum mood disturbances (Schmidt et al. 1998; Sugawara et al. 1997). For women who are breastfeeding, the hormonal milieu will be one of relatively low estrogen and high prolactin. While most studies have not found that breastfeeding is associated with depression, and in fact, several studies have reported a negative correlation of postpartum depression with breastfeeding, for some women, a low estrogen environment may be associated with increased anxiety or depression, and the hormonal milieu of lactational amenorrhea should be considered in all cases of treatment-resistant perinatal depression. While administration of progesterone has not been shown to be effective in the prevention or treatment of postpartum depression (Dennis and Hodnett 2007), estradiol augmentation of antidepressants has been found to be superior to placebo in at least two studies (Ahokas et al. 2001; Gregoire et al. 1996) and should be considered as a treatment option in women for whom steroid hormones are not contraindicated (Moses-Kolko et al. 2009).

Neurostimulatory approaches to the perinatal patient
with treatment-resistant depression

Given the rapidity of recent advances in neurostimulatory treatments for psychiatric disease, there is to date no publication that summarizes the guidelines on these new treatments with regard to the perinatal patient. We will thus offer one here.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is the most well established of the neurostimulatory methods, having been in clinical use since 1937. Two large literature-based case series of ECT use in pregnancy exist: Miller (1994), a description of 300 cases, and Anderson and Reti (2009), covering 339 cases. The former found 28 instances of likely ECT-related complications, including transient benign fetal arrhythmias, mild vaginal bleeding, abdominal pain, and self-limited uterine contractions. Several more serious concerns including stillbirth, neonatal death, and congenital malformations were described, however, all were thought due to factors unrelated to the ECT. The latter case series described 18 cases of ECT-related complications in the mothers (including status epilepticus, preterm labor, vaginal bleeding, and placental abruption) and 20 cases in the fetuses, most typically arrhythmias. There was also a single case of fetal death, which was thought due to status epilepticus in the mother. The literature also contains scattered case reports of serious fetal complications including CNS infarction, fetal ascites, and spontaneous abortion (Balki et al. 2006; Pinette et al. 2007; Echevarria Moreno et al. 1998; Gilot et al. 1999).

These data overall suggest a number needed to harm of something over 10, which compares very favorably to antidepressant medications.

Only three studies have looked at the long-term effects of children whose mothers received ECT while pregnant. Two found no negative effects among 16 and 15 children respectively, while the other described cognitive deficiencies in 2 of 8 children in the series (Forssman 1955; Smith 1956; Impastato et al. 1964).

Overall, the decision to commence ECT must be based on an extensive discussion with the individual patient and careful consideration of her particular needs and circumstances. Overall, if the depression is severe, resistant, and requires rapid treatment, ECT is an excellent option in the peripartum patient.

Vagal nerve stimulation

Vagal nerve stimulation is a relatively recent addition to the arsenal of treatments for depression. Initially developed for treatment of seizure disorders, in 2005, vagus nerve stimulation (VNS) received FDA approval for an additional indication "for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments" (US Food and Drug Administration 2008).

The effectiveness of VNS for depression compares extremely well to that of traditional pharmaceutical antidepressants (Rush et al. 2000; Nahas et al. 2005; George et al. 2005; Sackeim et al. 2001), and it is an attractive option for the pregnant patient because it lacks the systemic effects of pharmaceutical treatments. However, there are few available accounts of VNS use in pregnant women. A report by Husain et al. (2005) discusses the case of a woman who became pregnant after 2 years of VNS use for depression. VNS was continued throughout a pregnancy, with no adverse effects reported for the mother or the child, who was 2 years old at the time of publication. A small pilot study of 24 rabbits (Danielsson and Lister 2009; conducted by Cyberonics, the makers of the VNS devices) found no effect of VNS on fertility, teratogenicity, or neonatal morbidity.

There is also a single case report available on VNS in pregnancy for the treatment of epilepsy (Houser et al. 2010). In this case, the stimulator was implanted approximately 2 months prior to conception. The pregnancy was complicated by mild preeclampsia, and the delivery by uterine atony and postpartum hemorrhage. These complications were not obviously related to the VNS, and the infant was healthy.

The most significant risks of the VNS are incurred by the initial surgery required to place the stimulator. A recent review of such risks (Fahy 2010) lists bradycardia with, in rare cases, progression to asystole, surgical trauma resulting in airway compromise, and possible vocal cord dysfunction as among the most notable risks of the procedure. Standard risks of general anesthesia and surgical invasion such as aspiration, excessive bleeding, and infection also apply. Fahy also discusses evidence that ongoing stimulation may precipitate or worsen existing sleep apneas.

Thus, the decision to continue VNS in a woman who becomes pregnant with a stimulator in place is a relatively clear one, especially if benefits of the treatment have already become obvious. However, given the known additional risks of surgery in pregnant women (including preterm labor, thrombotic events, hypotension with decreased placental perfusion, difficult airway, and others), it is considered best practice to delay all nonemergent surgeries until after parturition. In the case of a pregnant woman with highly refractory depression who otherwise met the indications for VNS implantation, the decision as to whether the potential benefit of the stimulator outweighed the risks associated with the surgery would be best made on an individual basis after an extensive consultation with the surgical, anesthetic, and obstetric teams.

Transcranial magnetic stimulation

The clinical efficacy of transcranial magnetic stimulation compares poorly to that of ECT (Fink 2011; Rasmussen 2011). However, its efficacy is similar to that of antidepressant medications (Rasmussen 2011); it is currently FDA approved for patients who have failed at least one antidepressant, and it is of special interest in the pregnant population because it is significantly less invasive than the other available neurostimulatory approaches, ECT and VNS.

A pilot study of transcranial magnetic stimulation (TMS) treatment (Kim et al. 2011) in ten pregnant women with depression reported that the procedure was generally well tolerated and that seven of ten subjects responded (defined as a >50 % decrease in HDRS-17 scores). Three subjects achieved remission (defined as HDRS-17 less than 8). Treatment resistance was not a requirement for admission into the study, and four of them were taking antidepressants concurrently with TMS.

Several case reports and small case series (Zhang and Hu 2009; Zhang et al. 2010; Klirova et al. 2008) also report good tolerability of TMS in pregnant women with depression. Gahr et al. (2011) report successful ECT treatment of a pregnant patient who had previous nonresponse to TMS. Garcia and colleagues report remission in eight of nine women treated with rTMS for postpartum depression (Garcia et al. 2010).

Overall, TMS is a viable option for the pregnant or postpartum patient with depression. Although its clinical efficacy does not compare well to that of ECT or VNS, it is significantly less invasive than either and avoids the systemic effects of pharmaceutical therapies. Although it would be optimal to have more data in hand on TMS and the pregnant patient, and specifically on long-term developmental outcomes, the available information at least suggests that the procedure is generally well tolerated. From a safety perspective, TMS is a reasonable choice, although, especially for the patient with refractory depression, it should be understood that TMS is not likely to represent a panacea.

Directions for future research

Although randomized pharmaceutical trials with pregnant women are ethically problematic and thus are unlikely to be conducted, there are several other lines of feasible and important research that would be extremely helpful to perinatal psychiatrists.

A large observational study of rates of response to antidepressant treatment in pregnant and postpartum women would be helpful. An observational study of changes in dosing requirements for antidepressants across the trimesters of pregnancy and the postpartum period would also prove an essential guide to clinicians managing depression in pregnant women.

Further study on the effects of drug combining is urgently needed. Evidently, multiple psychotropic medications are being used in combination by thousands of pregnant women, and yet there has been very little systematic investigation of the results of such drug combinations. A registry or large observational study that specifically aimed to study outcomes from combinations of two or more psychotropic medications in pregnancy would be invaluable.

Additional studies on less prevalent but potentially promising approaches, including estradiol augmentation and TMS, to define response rates and adverse effects, are also greatly needed.

Conclusions

Depressive disorders in the perinatal population are a significant problem, with serious implications for the long-term well-being of mothers and their children. The literature is lacking in studies that specifically address treatment-resistant depression in the perinatal population.

When faced with the treatment-resistant patient, it is up to the clinician to balance the needs of the individual patient with the unfortunately often partial and incomplete data on the compatibility of the various available treatments with pregnancy and lactation. Too often, faced with these incomplete data, conservative clinicians will lean towards undertreatment. However, for a number of treatments that have historically been avoided in this population, it is becoming clear that the possible negative effects are less severe than may have been thought in the past and may not always be absolutely contraindicated, depending on the severity and degree of treatment resistance of the individual case.

Further research is urgently needed, both to delineate the scope of the problem of insufficient treatment response in depressed perinatal women and to define more fully the risks and benefits of the available treatment alternatives.

References

Ahokas A, Kaukoranta J, Wahlbeck K, Aito M (2001) Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17beta-estradiol: a preliminary study. J Clin Psychiatry 62(5):332–336

Anderson EL, Reti IM (2009) ECT in pregnancy: a review of the literature from 1941 to 2007. Psychosomatic Medicine 71(2):235–242

Appleby L, Warner R, Whitton A, Faragher B (1997) A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression. BMJ 314(7085):932–936

Balki M, Castro C, Ananthanarayan C (2006) Status epilepticus after electroconvulsive therapy in a pregnant patient. Int J Obstet Anesth 15(4):325–328

Berlim MT, Turecki G (2007a) Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. Can J Psychiatr Revue Canadienne De Psychiatrie 52(1):46–54

Berlim MT, Turecki G (2007b) What is the meaning of treatment resistant/refractory major depression (TRD)? A systematic review of current randomized trials. Eur Neuropsychopharmacol 17(11):696–707

Bloch M, Daly RC, Rubinow DR (2003) Endocrine factors in the etiology of postpartum depression. Comprehensive Psychiatry 44(3):234–246

Bobo WV, Shelton RC (2009) Fluoxetine and olanzapine combination therapy in treatment-resistant major depression: review of efficacy and safety data. Expert Opin Pharmacother 10(13):2145–2159

Brand SR, Brennan PA (2009) Impact of antenatal and postpartum maternal mental illness: how are the children? Clin Obstet Gynecol 52(3):441–455

Brandon AR, Freeman MP (2011) When she says "no" to medication: psychotherapy for antepartum depression. Current Psychiatry Reports 13(6):459–466

Byatt N, Deligiannidis KM, Freeman MP (2013) Antidepressant use in pregnancy: a critical review focused on risks and controversies. Acta Psychiatr Scand 127(2):94–114

Chabrol H, Teissedre F, Saint-Jean M, Teisseyre N, Roge B, Mullet E (2002) Prevention and treatment of post-partum depression: a controlled randomized study on women at risk. Psychol Med 32(6):1039–1047

Chatzicharalampous C, Rizos D, Pliatsika P, Leonardou A, Hasiakos D, Zervas I et al (2011) Reproductive hormones and postpartum mood disturbances in Greek women. Gynecol Endocrinol 27(8):543–550

Cohen LS, Viguera AC, Bouffard SM, Nonacs RM, Morabito C, Collins MH et al (2001) Venlafaxine in the treatment of postpartum depression. J Clin Psychiatr 62(8):592–596

Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC et al (2006) Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 295(5):499–507

Cooper PJ, Murray L, Wilson A, Romaniuk H (2003) Controlled trial of the short- and long-term effect of psychological treatment of post-partum depression. I. Impact on maternal mood. Br J Psychiatry 182:412–419

Coppola D, Russo LJ, Kwarta RF Jr, Varughese R, Schmider J (2007) Evaluating the postmarketing experience of risperidone use during pregnancy: pregnancy and neonatal outcomes. Drug Saf 30(3):247–264

Coverdale JH, McCullough LB, Chervenak FA (2008) The ethics of randomized placebo-controlled trials of antidepressants with pregnant women: a systematic review. Obstet Gynecol 112(6):1361–1368

Cuijpers P, Brannmark JG, van Straten A (2008) Psychological treatment of postpartum depression: a meta-analysis. J Clin Psychol 64(1):103–118

Danielsson I, Lister L (2009) A pilot study of the teratogenicity of vagus nerve stimulation in a rabbit model. Brain Stimulation 2(1):41–49

Davalos DB, Yadon CA, Tregellas HC (2012) Untreated prenatal maternal depression and the potential risks to offspring: a review. Archives of Women's Mental Health 15(1):1–14

Deligiannidis KM (2010) Therapeutic drug monitoring in pregnant and postpartum women: recommendations for SSRIs, lamotrigine, and lithium. J Clin Psychiatr 71(5):649–650

Dennis CL, Hodnett E (2007) Psychosocial and psychological interventions for treating postpartum depression. Cochrane Database of Systematic Reviews (4):CD006116

Dennis CL, Ross LE, Grigoriadis S (2007) Psychosocial and psychological interventions for treating antenatal depression. Cochrane Database of Systematic Reviews (3):CD006309

Dietz PM, Williams SB, Callaghan WM, Bachman DJ, Whitlock EP, Hornbrook MC (2007) Clinically identified maternal depression before, during, and after pregnancies ending in live births. Am J Psychiatry 164(10):1515–1520

Dimidjian S, Goodman S (2009) Nonpharmacologic intervention and prevention strategies for depression during pregnancy and the postpartum. Clin Obstet Gynecol 52(3):498–515

Echevarria Moreno M, Martin Munoz J, Sanchez Valderrabanos J, Vazquez Gutierrez T (1998) Electroconvulsive therapy in the first trimester of pregnancy. The Journal of ECT 14(4):251–254

Epstein RA, Bobo WV, Shelton RC, Arbogast PG, Morrow JA, Wang W et al (2012) Increasing use of atypical antipsychotics and anticonvulsants during pregnancy. Pharmacoepidemiol Drug Saf. doi:10.1002/pds.3366

Fahy BG (2010) Intraoperative and perioperative complications with a vagus nerve stimulation device. J Clin Anesth 22(3):213–222

Field T (2011) Prenatal depression effects on early development: a review. Infant Behav Dev 34(1):1–14

Fink M (2011) Transcranial magnetic stimulation is not a replacement for electroconvulsive therapy in depressive mood disorders. The Journal of ECT 27(1):3–4

Forssman H (1955) Follow-up study of sixteen children whose mothers were given electric convulsive therapy during gestation. Acta Psychiatrica Et Neurologica Scandinavica 30(3):437–441

Gahr M, Blacha C, Connemann BJ, Freudenmann RW, Schonfeldt-Lecuona C (2011) Successful treatment of major depression with electroconvulsive therapy in a pregnant patient with previous non-response to prefrontal rTMS. Pharmacopsychiatry 45(2):79–80

Galbally M, Roberts M, Buist A (2010) Mood stabilizers in pregnancy: a systematic review. Aust New Zeal J Psychiatr 44(11):967–977

Garber J, Ciesla JA, McCauley E, Diamond G, Schloredt KA (2011) Remission of depression in parents: links to healthy functioning in their children. Child Development 82(1):226–243

Garcia KS, Flynn P, Pierce KJ, Caudle M (2010) Repetitive transcranial magnetic stimulation treats postpartum depression. Brain Stimulation 3(1):36–41

Gentile S (2010) Antipsychotic therapy during early and late pregnancy. A systematic review. Schizophr Bull 36(3):518–544

George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM et al (2005) A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry 58(5):364–373

Gilot B, Gonzalez D, Bournazeau JA, Barriere A, Van Lieferinghen P (1999) Case report: electroconvulsive therapy during pregnancy (electroconvulsivotherapie au troisieme trimestre de grossesse: a propos d'un cas). L'Encephale 25(6):590–594

Gregoire AJ, Kumar R, Everitt B, Henderson AF, Studd JW (1996) Transdermal oestrogen for treatment of severe postnatal depression. Lancet 347(9006):930–933

Hendrick V, Altshuler L, Strouse T, Grosser S (2000) Postpartum and nonpostpartum depression: differences in presentation and response to pharmacologic treatment. Depress Anxiety 11(2):66–72

Honey KL, Bennett P, Morgan M (2002) A brief psycho-educational group intervention for postnatal depression. Br J Clin Psychol 41(Pt 4):405–409

Hostetter A, Stowe ZN, Strader JR Jr, McLaughlin E, Llewellyn A (2000) Dose of selective serotonin uptake inhibitors across pregnancy: clinical implications. Depression and Anxiety 11(2):51–57

Houser MV, Hennessy MD, Howard BC (2010) Vagal nerve stimulator use during pregnancy for treatment of refractory seizure disorder. Obstet Gynecol 115(2 Pt 2):417–419

Husain MM, Stegman D, Trevino K (2005) Pregnancy and delivery while receiving vagus nerve stimulation for the treatment of major depression: a case report. Annals of General Psychiatry 4:16

Impastato DJ, Gabriel AR, Lardaro HH (1964) Electric and insulin shock therapy during pregnancy. Diseases of the Nervous System 25:542–546

Johnson KC, Laprairie JL, Brennan PA, Stowe ZN, Newport DJ (2012) Prenatal antipsychotic exposure and neuromotor performance during infancy. Arch Gen Psychiatry 69(8):787–94

Kim DR, Epperson N, Pare E, Gonzalez JM, Parry S, Thase ME et al (2011) An open label pilot study of transcranial magnetic stimulation for pregnant women with major depressive disorder. Journal of Women's Health 20(2):255–261

Klier CM, Mossaheb N, Saria A, Schloegelhofer M, Zernig G (2007a)
Pharmacokinetics and elimination of quetiapine, venlafaxine, and traz-
odone during pregnancy and postpartum. J Clin Psychopharmacol
27(6):720–722

Klier CM, Muzik M, Dervic K, Mossaheb N, Benesch T, Ulm B et al
(2007b) The role of estrogen and progesterone in depression after
birth. J Psychiatr Res 41(3–4):273–279

Klirova M, Novak T, Kopecek M, Mohr P, Strunzova V (2008) Repetitive
transcranial magnetic stimulation (rTMS) in major depressive epi-
sode during pregnancy. Neuro Endocrinology Letters 29(1):69–70

Marcus SM (2009) Depression during pregnancy: rates, risks and
consequences—Motherisk update 2008. Can J Clin Pharmacol
16(1):e15–22

McKenna K, Koren G, Tetelbaum M, Wilton L, Shakir S, Diav-Citrin O
et al (2005) Pregnancy outcome of women using atypical antipsy-
chotic drugs: a prospective comparative study. The J of Clin
Psychiatry 66(4):444–9, quiz 546

Milgrom J, Negri LM, Gemmill AW, McNeil M, Martin PR (2005) A
randomized controlled trial of psychological interventions for
postnatal depression. Br J Clin Psychol 44(Pt 4):529–542

Miller LJ (1994) Use of electroconvulsive therapy during pregnancy.
Hospital & Community Psychiatry 45(5):444–450

Misri S, Reebye P, Corral M, Milis L (2004) The use of paroxetine and
cognitive-behavioral therapy in postpartum depression and anxiety:
a randomized controlled trial. J Clin Psychiatry 65(9):1236–1241

Moses-Kolko EL, Berga SL, Kalro B, Sit DK, Wisner KL (2009)
Transdermal estradiol for postpartum depression: a promising
treatment option. Clin Obstet Gynecol 52(3):516–529

Mulcahy R, Reay RE, Wilkinson RB, Owen C (2010) A randomised
control trial for the effectiveness of group interpersonal psycho-
therapy for postnatal depression. Archives of Women's Mental
Health 13(2):125–139

Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby
SH et al (2005) Two-year outcome of vagus nerve stimulation
(VNS) for treatment of major depressive episodes. J Clin
Psychiatry 66(9):1097–1104

Nonacs RM, Soares CN, Viguera AC, Pearson K, Poitras JR, Cohen LS
(2005) Bupropion SR for the treatment of postpartum depression:
a pilot study. Int J Neuropsychopharmacol 8(3):445–449

Oates M (2003) Perinatal psychiatric disorders: a leading cause of mater-
nal morbidity and mortality. British Medical Bulletin 67:219–229

Oberlander TF, Warburton W, Misri S, Riggs W, Aghajanian J,
Hertzman C (2008) Major congenital malformations following
prenatal exposure to serotonin reuptake inhibitors and benzodiaz-
epines using population-based health data. Birth Defects Res B
Dev Reprod Toxicol 83(1):68–76

Paulson JF, Bazemore SD (2010) Prenatal and postpartum depression in
fathers and its association with maternal depression: a meta-
analysis. JAMA 303(19):1961–1969

Pinette MG, Santarpio C, Wax JR, Blackstone J (2007) Electroconvulsive
therapy in pregnancy. Obstet Gynecol 110(2 Pt 2):465–466

Rasmussen KG (2011) Some considerations in choosing electroconvul-
sive therapy versus transcranial magnetic stimulation for depres-
sion. J ECT 27(1):51–54

Reis M, Kallen B (2008) Maternal use of antipsychotics in early pregnancy
and delivery outcome. J Clin Psychopharmacol 28(3):279–288

Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C
et al (2000) Vagus nerve stimulation (VNS) for treatment-resistant
depressions: a multicenter study. Biol Psychiatry 47(4):276–286

Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas
Z et al (2001) Vagus nerve stimulation (VNS) for treatment-
resistant depression: efficacy, side effects, and predictors of out-
come. Neuropsychopharmacology 25(5):713–728

Schmidt PJ, Nieman LK, Danaceau MA, Adams LF, Rubinow DR
(1998) Differential behavioral effects of gonadal steroids in wom-
en with and in those without premenstrual syndrome. N Engl J
Med 338(4):209–216

Sit DK, Perel JM, Helsel JC, Wisner KL (2008) Changes in antidepres-
sant metabolism and dosing across pregnancy and early postpar-
tum. J Clin Psychiatry 69(4):652–658

Smith S (1956) The use of electroplexy (E.C.T.) in psychiatric syn-
dromes complicating pregnancy. J Ment Sci 102(429):796–800

Sockol LE, Epperson CN, Barber JP (2011) A meta-analysis of treat-
ments for perinatal depression. Clin Psychol Rev 31(5):839–849

Stowe ZN, Owens MJ, Landry JC, Kilts CD, Ely T, Llewellyn A et al
(1997) Sertraline and desmethylsertraline in human breast milk
and nursing infants. Am J Psychiatry 154(9):1255–1260

Sugawara M, Toda MA, Shima S, Mukai T, Sakakura K, Kitamura T
(1997) Premenstrual mood changes and maternal mental health in
pregnancy and the postpartum period. J Clin Psychol 53(3):225–232

Suri R, Burt VK, Altshuler LL, Zuckerbrow-Miller J, Fairbanks L
(2001) Fluvoxamine for postpartum depression. Am J Psychiatry
158(10):1739–1740

Suri R, Burt VK, Altshuler LL (2005) Nefazodone for the treatment of
postpartum depression. Archives of Women's Mental Health
8(1):55–56

US Food and Drug Administration (2008) VNS therapy system,
premarket approval: supplement. http://www.accessdata.fda.gov/
scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p970003s050.
Accessed 28 June 2013

Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR (2007) The
STAR*D project results: a comprehensive review of findings.
Current Psychiatry Reports 9(6):449–459

Wickramaratne P, Gameroff MJ, Pilowsky DJ, Hughes CW, Garber J,
Malloy E et al (2011) Children of depressed mothers 1 year after
remission of maternal depression: findings from the STAR*D-
child study. Am J Psychiatry 168(6):593–602

Wiklund I, Mohlkert P, Edman G (2010) Evaluation of a brief cognitive
intervention in patients with signs of postnatal depression: a ran-
domized controlled trial. Acta Obstetricia Et Gynecologica
Scandinavica 89(8):1100–1104

Wisner KL, Hanusa BH, Perel JM, Peindl KS, Piontek CM, Sit DK et al
(2006) Postpartum depression: a randomized trial of sertraline
versus nortriptyline. J Clin Psychopharmacol 26(4):353–360

Yonkers KA, Lin H, Howell HB, Heath AC, Cohen LS (2008)
Pharmacologic treatment of postpartum women with new-onset
major depressive disorder: a randomized controlled trial with
paroxetine. J Clin Psychiatry 69(4):659–665

Yonkers KA, Gotman N, Smith MV, Forray A, Belanger K, Brunetto WL
et al (2011) Does antidepressant use attenuate the risk of a major
depressive episode in pregnancy? Epidemiology 22(6):848–854

Zhang D, Hu Z (2009) RTMS may be a good choice for pregnant
women with depression. Archives of Women's Mental Health
12(3):189–190

Zhang X, Liu K, Sun J, Zheng Z (2010) Safety and feasibility of
repetitive transcranial magnetic stimulation (rTMS) as a treatment
for major depression during pregnancy. Archives of Women's
Mental Health 13(4):369–370