

Are exposure-based cognitive behavioral therapies safe during pregnancy?

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Abstract Anxiety disorders during pregnancy are highly prevalent and associated with serious and enduring consequences for both mother and child. Exposure-based cognitive behavioral (CBT) and behavioral therapies (BT) represent the most empirically supported psychosocial treatments for anxiety disorders in general adult samples. Pregnant women, however, generally have been excluded from this body of research. Evidence that pregnant women inhabit a unique biological context combined with untested assumptions that exposure would unduly stress or harm the fetus have likely prohibited inquiry. This paper seeks to remedy this gap by integrating findings from obstetric, psychiatric, and psychological research to inform central questions regarding exposure-based treatment of anxiety disorders during pregnancy. Based on available evidence, we consider the potential risks and benefits of CBT/BT for anxiety disorders during pregnancy relative to other currently available treatment options. From a multidisciplinary research perspective, we argue that exposure-based therapies are likely to be safe during pregnancy, particularly relative to the alternatives. However, we also highlight critical questions for future research to directly test the

biopsychological impact of exposure-based therapies among pregnant women.

Keywords Anxiety disorders · Cognitive behavioral therapy · Exposure · Pregnancy or antenatal · Safety

Introduction

Increasing attention has been directed towards understanding and treating perinatal mental health disturbances. Most of this attention has focused on perinatal depression and postpartum psychosis. The most commonly occurring category of psychiatric disorders over the lifespan, anxiety disorders (Kessler et al. 2005a), until recently has been almost ignored in the perinatal literature. A small but quickly growing body of research documents the relatively high prevalence of different anxiety disorders during pregnancy and the enduring adverse impact of anxiety disorders on women and their children (see Ross and McLean 2006). Few studies, however, have evaluated treatment options for pregnant women with anxiety disorders.

Cognitive behavioral and behavioral therapies (CBT and BT) are efficacious psychosocial treatments for anxiety disorders with a strong evidence base in general samples (Butler et al. 2006; Hofmann and Smits 2008; Norton and Price 2007). Exposure—deliberate, repeated contact with feared stimuli, memories, images, contexts, and physiological sensations—is a core component of CBT and BT for anxiety disorders. Dozens of studies document that by post-treatment, exposure-based CBT and BTs succeed at reducing or eliminating anxiety symptoms in the majority of adult outpatients with anxiety disorders (Norton and Price 2007). With the exception of one small, nonrandomized study (Lilliecreutz et al. 2010), pregnant women have been generally excluded from this entire body of research. The lack

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of studies examining the safety, feasibility, or efficacy of exposure-based treatments for anxiety disorders during pregnancy represents a critical gap in our knowledge base.

The exclusion of pregnant women from studies of CBT and BT stems most likely from untested assumptions about the maternal and fetal risks of exposure-based treatment. Elevated stress and anxiety during pregnancy (stemming from naturally occurring environmental stressors or psychopathology) carries the burden of transferring risk to the developing fetus (e.g., Buss et al. 2010a; Conde et al. 2010; Dunkel Schetter 2009; Maric et al. 2010; O'Connor et al. 2002b, 2003). This is why *untreated* anxiety disorders during pregnancy are so risky and why research on effective treatments is so important. Exposure itself, however, can be physiologically and psychologically arousing and anxiety provoking in the immediate term, which may provoke similar concerns of harming the mother and fetus.

In addressing such concerns, the degree to which we can generalize about the safety or efficacy of exposure-based treatments from non-pregnant to pregnant women is unclear. Across a number of dimensions, pregnant women reside within a unique biological context relative to the non-pregnant women (and men) on whom exposure-based treatments for anxiety disorders have been empirically tested. For example, activity of the HPA axis looks dramatically different during healthy pregnancy, with cortisol levels soaring to heights that would be disease-indicative in non-pregnant women (Magiakou et al. 1996, 1997; Mastorakos and Ilias 2003). Pregnant women also respond differently than non-pregnant women to acute stress (de Weerth and Buitelaar 2005), with differences varying as a function of pregnancy stage (Entringer et al. 2010). In contemplating the use of exposure-based treatments during pregnancy, the implications of these pregnancy-linked biological changes must be considered.

Finally, the most common treatment for anxiety disorders—pharmacotherapy—carries a wide range of potential risks during pregnancy (e.g., Lattimore et al. 2005; Mintzes and Jureidini 2008), underscoring the need for research on safe and effective alternatives. Benzodiazepines are associated with particularly significant risks (Schmidt et al. 1989; Schweizer and Rickels 1998), even more so during the perinatal period (Dolovich et al. 1998; Wikner et al. 2007). The potential risks and benefits of exposure-based psychotherapies must be considered within a context in which we acknowledge that the main treatment alternative—pharmacotherapy—has been associated with risks to the mother, fetus, and subsequent child.

In the context of strong efficacy among general populations, a dearth of data during pregnancy, and limited alternative treatment options, an in-depth, empirically informed reflection on the role of exposure-based treatments for anxiety disorders during pregnancy is critical. In this review,

we ask, Relative to available treatment options, what are the risks and benefits of exposure-based treatments for antenatal anxiety disorders?¹ We thus weigh the potential risks and benefits during pregnancy of exposure-based CBT and BT—the most successful psychosocial treatments for anxiety disorders outside of pregnancy. First, we briefly review the risks of untreated anxiety disorders during pregnancy, considering on what basis we should treat anxiety disorders *during* pregnancy rather than withhold treatment until after birth. Second, we review the most common evidence-based pharmacotherapy and psychotherapy treatment options for anxiety disorders and their application during pregnancy. Third, we review evidence on the intensity of physiological and psychological arousal during exposure with an eye towards examining safety, and consider how the unique biological context of pregnancy may impact physiological exposure responses. Finally, we outline an agenda for future research and consider potential implications for clinical service delivery.

Risks associated with anxiety disorders during pregnancy

Anxiety disorders represent the most prevalent category of psychiatric disorders in the general population, with 1-year prevalence rates of 18.1 % (Kessler et al. 2005b). Further, anxiety disorders overall are nearly twice as prevalent among women than men (Craske 2003; Kessler et al. 2005a). Pregnancy generally does not serve a protective function with respect to anxiety disorders; in fact, pregnancy is associated with new onset for several anxiety disorders (panic disorder, obsessive compulsive disorder, and generalized anxiety disorder; see Ross and McLean 2006 for review). Thus, women enter pregnancy with high baseline rates of anxiety disorders simply because they are women, and pregnancy appears to confer unique additional risks for some of the anxiety disorders.

Anxiety disorders and elevated anxiety during pregnancy have been associated with a range of negative sequelae for mother and child. All but one study on the consequences of individual anxiety disorders during pregnancy found that they are linked to negative maternal, birth, or fetal/child outcomes, including preterm birth, small-for-gestational-age infants, and risky maternal health behaviors (e.g., Banhidhy et al. 2006; Chen et al. 2010; Morland et al. 2007). Further, a history or presence during pregnancy of *any* anxiety disorder serves as an independent risk factor for the development of postpartum depression (Martini et al.

¹ The term “antenatal anxiety disorders” is used as shorthand throughout to indicate “anxiety disorders that occur during antenatal periods”. This non-technical term is not meant to imply that anxiety disorders that occur during antenatal periods differ (except in timing) from anxiety disorders that occur outside of antenatal periods.

2010). Still more alarmingly, elevated levels of antenatal anxiety (anxiety disorders were not assessed) have been associated with negative and enduring child consequences including lower grey matter density (Buss et al. 2010b) and a range of serious behavioral and emotional problems (O'Connor et al. 2002b, 2003; van den Bergh and Marcoen 2004; van den Bergh et al. 2005a, 2006, 2008) that appear independent of postpartum depression (O'Connor et al. 2002a).

Potential mechanisms linking antenatal anxiety disorders and elevated anxiety to poor birth and offspring outcomes include HPA axis dysfunction (Dunkel Schetter 2009; van den Bergh et al. 2005b) and anxiety-linked changes in uterine blood flow (Teixeira et al. 1999). Although research has yet to consistently confirm these biological mechanisms, particularly for uterine blood flow (see Kinsella and Monk 2009), significant associations between maternal plasma and amniotic cortisol levels have been found, especially among women with higher anxiety levels (see Sarkar et al. 2008). Specifically, the *correlation* between amniotic and maternal cortisol levels was significantly stronger among mothers with higher anxiety levels (while awaiting amniocentesis), though absolute amniotic cortisol levels were not higher. The authors concluded that maternal anxiety may alter cortisol-related placental function (Sarkar et al. 2008). If uterine blood flow is confirmed as a mechanism linking maternal anxiety to child outcomes, noradrenaline release via sympathetic-adrenal medullary (SAM) activation has been proposed as a likely transmitting mechanism (Kinsella and Monk 2009; Teixeira et al. 1999). In summary, for reasons that likely involve HPA, SAM, and placental dysfunction but are not fully understood, anxiety disorders and elevated anxiety during pregnancy present serious, independent, and enduring risks to both mother and child.

The fetal programming implications of elevated anxiety and anxiety disorders during pregnancy pose a strong argument for treating anxiety disorders *before* or *during* pregnancy rather than waiting until postpartum, when anxiety-linked biological changes in utero may have already caused adverse consequences for the developing fetus. Correlations between maternal and amniotic cortisol levels grow increasingly robust during the second half of pregnancy (Sarkar et al. 2008), suggesting advantage for intervening as early as possible during pregnancy. Many women, however, do not interface with the medical system until several months into gestation, which suggests the public health imperative of identifying treatments that can be safely and effectively implemented throughout pregnancy.

Treatment options: pharmacotherapy and psychotherapy

Despite a strong public health imperative to investigate safe, effective treatments for pregnant women, little data are

available to inform the effectiveness of interventions for anxiety disorders during pregnancy (see Ross and McLean 2006). Further, we know very little about patterns of care for anxiety disorders among pregnant women. Using benchmarks provided by care patterns for anxiety disorders in general primary care samples (Stein et al. 2004) and for antenatal depression (Dietz et al. 2007), it is likely that pharmacological treatment is the most frequent intervention provided for pregnant women with anxiety disorders. For antenatal anxiety disorders, however, risk-benefit decisions about pharmacological options can be particularly difficult because of the potential risks of fetal exposure to medication and the frequent need for more than one medication in the context of the limited information available to guide pregnant women and their treatment providers.

First, safety evaluations of selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), which have emerged as the first-line pharmacotherapy treatment for most anxiety disorders, are mixed during pregnancy and often suffer from weak methodology (Lattimore et al. 2005; Misri and Kendrick 2007; Yonkers et al. 2009). Possible risks of spontaneous abortion (Hemels et al. 2005), low birth weight (Oberlander et al. 2006), preterm birth (Wisner et al. 2009), congenital heart defects when combining with a benzodiazepine (Oberlander et al. 2008), newborn respiratory distress (Oberlander et al. 2006), persistent pulmonary hypertension (Kallen and Olausson 2008), and serotonergic overstimulation and withdrawal syndromes (Lattimore et al. 2005) have led to calls for caution (Mintzes and Jureidini 2008). Preliminary data also suggests a possible link between SSRI use during pregnancy and risk of autism among offspring (Croen et al. 2011), although replication is needed. Moreover, of the antenatal SSRI and SNRI studies that do exist, relatively few focus on anxiety disorders. Thus, we know far less about the safety or efficacy of SSRIs and SNRIs for treating antenatal anxiety disorders than we do for antenatal depression.

Second, benzodiazepines are commonly used to treat anxiety disorders; however, this class of medication carries particularly high levels of risk among general samples. The potential for misuse and addiction, anxiety rebound, and difficulties tapering and eliminating use of benzodiazepines have been well documented in the psychiatric literature (Schmidt et al. 1989; Schweizer and Rickels 1998). Specifically during pregnancy, benzodiazepine use has been associated with a range of negative birth outcomes, including preterm birth, low birth weight, and possibly higher rates of pylorostenosis and alimentary track atresia following third trimester use (Wikner et al. 2007). An early meta-analysis on potential associations between benzodiazepine use and congenital malformations found mixed results (Dolovich et al. 1998), again warranting caution. In summary,

broad evidence suggests that fetal risks involved in pharmacotherapy cannot be ignored (Misri and Kendrick 2007).

The potential risks of pharmacotherapy raise the question of whether medications represent the most efficacious or desired treatment option for anxiety disorders during pregnancy. Although we lack efficacy data from pregnant samples, we can draw upon relevant data from non-pregnant samples. Randomized clinical trials comparing psychotropic medications to exposure-based CBT for anxiety disorders often show that CBT results in equivalent (de Beurs et al. 1999; Mitte 2005) or better long-term outcomes than medications, particularly after both treatments are discontinued (Barlow et al. 2000; Clark et al. 1994, 2003; Klosko et al. 1990; see Roshanaei-Moghaddam et al. 2011). Furthermore, studies on the combination of medication and CBT for anxiety disorders suggest little advantage of combined treatment versus CBT alone (see Otto et al. 2005 for review). In fact, some studies have documented worse long-term outcomes when medication is added to CBT for social phobia (Haug et al. 2003) or panic disorder (Barlow et al. 2000; Otto et al. 1996). Moreover, CBT benefits endure for at least several years following successful treatment (see Butler et al. 2006 for review), which for pregnant women could translate into maintenance of treatment gains through the critical perinatal and early infant periods, and potentially through future pregnancies. Thus, a recent exception notwithstanding (Blanco et al. 2010), CBT alone, rather than medication or combined treatment, appears to represent the most efficacious intervention for anxiety disorders over the long term.

Pregnant women also appear to prefer non-pharmacologic treatment for anxiety disorders. Our data show that the vast majority ($\geq 75\%$) of pregnant women, including those reporting high anxiety, prefer psychotherapy alone to pharmacotherapy or combination therapy for anxiety (Arch JJ, Cognitive behavioral therapy and pharmacotherapy for anxiety: predictors of treatment preference among pregnant and non-pregnant women, unpublished). Further, pregnant women indicate greater willingness to do exposure-based CBT than pharmacotherapy by a large effect size. These data are consistent with studies of non-pregnant samples. For example, in a large sample of anxiety disorder patients in primary care, significantly more patients selected CBT or combined treatment than medication-only treatment (Roy-Byrne et al. 2010). Anxiety disorder patients also exhibit lower attrition in CBT relative to pharmacotherapy (Barlow et al. 2000; Mitte 2005), suggesting that CBT is better tolerated than medication among adults in general.

The available evidence, therefore, strongly suggests that pregnant women are likely to prefer non-pharmacological approaches to anxiety disorder treatment, a choice that is supported by the efficacy studies comparing medication to CBT. Such non-pharmacological approaches have been

widely implemented in diverse treatment settings including medical clinics (Roy-Byrne et al. 2010), creating the important possibility for pregnant women to fulfill medical and mental health care needs in a single location. Further, CBT treatments are often relatively brief (e.g., Craske et al. 1995; Neuner et al. 2004), meeting the needs of pregnant women with limited time and, in advanced pregnancy, mobility.

CBT is typically provided over 8–16 sessions, although CBT for panic disorder can result in substantial improvement in as few as four to five sessions (Craske et al. 1995, 2006a), and a single prolonged exposure session for specific phobia demonstrates effectiveness (Ost 1989). CBT and BT for anxiety disorders both begin with psychoeducation about the nature of fear and anxiety, including normative sympathetic nervous system responding. Next, patients self-monitor their symptoms to identify antecedents and responses to anxiety episodes. In CBT, cognitive restructuring, also known as logical empiricism, helps patients to identify their stream of anxiety-filled thoughts, using logical reasoning to empirically test the content of anxiety-filled thoughts (“I will die of a panic attack”) against the reality of their own life experience (“I have had 100 panic attacks and have never died from one”). Cognitive restructuring can lead to behavioral experimentation, in which patients test dominant anxious thoughts (“If I leave my house, I will have a panic attack and die”) by enacting the feared behavior and observing whether the feared event occurs (“I left my house and felt anxious but I didn’t die”). Both CBT and BT for anxiety disorders utilize repeated exposure to feared contexts, images, memories, stimuli, and internal sensations. Exposure can occur *in vivo* (confronting feared external stimuli in real time), interoceptively (inducing feared internal bodily sensations, usually related to panic), and imaginably (visualizing the feared stimuli or event). *In vivo* exposures for panic disorder with agoraphobia might involve traveling increasing distances outside of a geographic “safety zone,” interoceptive exposures might involve hyperventilation and spinning to invoke panic-like sensations, and imaginal exposure might involve invoking a feared image of having a panic attack alone in a location where help was unavailable.

Although CBT for anxiety disorders has been tested and delivered primarily as a multi-component treatment package, the evidence suggests that exposure is the necessary if not sufficient component. Exposure by itself represents an effective treatment for anxiety disorders (Craske 1999; Feske and Chambless 1995; Longmore and Worrell 2007). The addition of the cognitive component of CBT generally does not increase the efficacy of exposure therapy alone, suggesting that cognitive restructuring is unnecessary (Feske and Chambless 1995; Longmore and Worrell 2007), although the debate continues (Hofmann 2008). A recent study on severe PTSD showed that contrary to expectations, the addition of cognitive components to

exposure therapy resulted in *worse* outcomes than exposure therapy alone (Moser et al. 2010). Similarly, a large study of CBT for panic disorder demonstrated that strong utilization of the *non*-exposure components of CBT resulted in *worse* outcomes (Craske et al. 2006b). A large trial of CBT for panic disorder with agoraphobia (Gloster et al. 2011) showed that exposure evidenced a dose–response effect in reducing subsequent agoraphobic avoidance. Similarly, a PTSD study demonstrated that symptoms did not improve significantly until *after* imaginal exposure to the worst traumatic memory was initiated (Nishith et al. 2002). In summary, extant evidence suggests that exposure is a powerful, if not the most powerful, component of CBT for anxiety disorders. If we aim to offer pregnant women the most effective psychotherapy for anxiety disorders, we must consider the possibility of utilizing exposure.

Potential negative effects of exposure: do they exist? If so, when, for how long, and at what intensity?

Weighing the possible risks and benefits of exposure for anxiety disorders during pregnancy demands a careful examination of the time course of such risks and benefits. Extant studies of exposure therapy (in non-pregnant samples), however, rarely address issues of safety or negative consequences directly (for exceptions, see Foa et al. 2002; Olatunji et al. 2009). Although investigating safety is not their intended focus, studies on within- and between-session habituation—reductions in fear responding during exposure to feared stimuli—can inform safety considerations. In reviewing habituation studies with an eye towards safety, we consider two questions: First, what are the immediate psychological and physiological sequelae that take place during exposure to feared stimuli? Second, what is the time course of response to exposure? Specifically, how long does it take for patients to benefit from exposure-based anxiety disorder treatments, and what is the risk of symptom exacerbation following exposure onset? For purposes of examining these questions, we define within-session habituation studies as representing the *immediate* effects of exposure and between-session habituation studies as representing the *short-term* effects of exposure. To our knowledge, not a single study has examined these processes during exposure in pregnant women. Data from non-pregnant samples are reviewed as a starting point for developing guidelines for clinical practice and future research with pregnant women.

1. What are the immediate negative effects?

Many studies on within-session habituation—the immediate sequelae of exposure—were conducted early in the development of exposure therapy. We summarize the studies that provided physiological data on the ongoing exposure

response. These studies found moderately elevated heart rate (of 80–130 beats per minute [bpm]) and skin conductance (levels or fluctuations) for the first 4–20 min of exposure followed by rapid physiological habituation (Beckham et al. 1990; Grey et al. 1981; Lang et al. 1970; Watson et al. 1972). Such studies have focused primarily on patients with specific phobias; only a few have addressed other anxiety disorders. For example, during an intensive 90-min exposure to “contaminated” objects, patients with OCD evidenced only moderate physiological and self-reported arousal (Grayson et al. 1982), a finding that counters stereotypes of prolonged in vivo exposure as highly intense.

Thus, fear in non-pregnant patients undergoing exposure treatment generally habituated quickly, that is, physiological arousal and self-reported fear declined rapidly while facing anxiety-provoking stimuli and contexts. Further, initial reported anxiety and heart rate (HR) levels at the start of exposure were often only moderately high, countering the assumption that exposure is by definition extremely intense. More data are needed about anxiety disorders other than specific phobia and, of course, about exposure effects during pregnancy. In addition, within-session habituation studies focus on self-reported fear and physiological measures of heart rate and occasionally skin conductance. While these are important starting points and offer ease of measurement, other physiological systems that are sensitive to arousal but rarely measured may also be affected by exposure, including HPA, vascular, and possibly immune functioning. Extant studies therefore provide an important yet partial window into the immediate sequelae of exposure-based treatments.

Although no studies have examined the immediate effects of exposure during pregnancy, studies on laboratory stressors during pregnancy may inform hypotheses regarding exposure effects. A comprehensive review of over one dozen studies (de Weerth and Buitelaar 2005) concluded that pregnant women (relative to non-pregnant women) show *dampened* physiological responding to acute stress provocation on measures such as heart rate, blood pressure, and cortisol (e.g., Kammerer et al. 2002; Matthews and Rodin 1992). Although most studies focused on women in the third trimester of gestation and some lacked a non-pregnant control group, the evidence for diminished physiological reactivity was relatively consistent (de Weerth and Buitelaar 2005).

Acute stressors studied during pregnancy (thermal heat, cold pressor, loud noise, stroop color, and mental arithmetic) are similar to exposures for anxiety disorders—both intend to produce anxiety or stress responses of a similarly limited duration. If we conceptualize exposure to feared stimuli as an acute stressor, pregnancy—at least late pregnancy—is likely to result in diminished physiological reactivity to exposure. If true, then the reactivity seen in non-pregnant samples should define the “maximum intensity” of

reactivity across both pregnant and non-pregnant samples. Considering the complex and inconsistent relationship between maternal and fetal stress responses (see Kinsella and Monk 2009), elevated cardiovascular load during pregnancy (Hunter and Robson 1992), and evidence that maternal anxiety moderates the relationship between maternal and amniotic cortisol levels (Sarkar et al. 2008), however, this hypothesis may not capture the intricacy of the relevant response systems. Exposure-based treatments, moreover, differ from acute stress studies in that they involve *repeated* engagement with arousing stimuli. Research is needed to test this “maximum intensity” hypothesis directly and to explore how the unique biological context of pregnancy interacts with exposure across different gestational periods.

On a related point, one could argue that lowered acute stress reactivity during pregnancy will diminish the *efficacy* of exposure therapy by lowering initial fear activation—a hypothesized necessary feature of successful exposure (Foa et al. 2006; Foa and Kozak 1986). In that initial fear activation does not consistently predict exposure treatment outcomes (Craske et al. 2008), however, diminished acute stress reactivity may not lead to diminished exposure efficacy.

In summary, additional investigations are recommended before exposure can be implemented broadly for pregnant women. In addition to testing the immediate effects of exposure in pregnant women via traditional measures of self-report, HR, and skin conductance, broader, time-sensitive physiological measures of HPA functioning (e.g., salivary cortisol), sympathetic functioning (e.g., catecholamines), vascular responding (e.g., blood pressure), and immune response (e.g., short-term shifts in inflammatory or healing markers) are recommended to advance our understanding of what occurs during and immediately after exposure—and to address the range of concerns regarding potential risks of exposure during pregnancy. Further, it is important to assess whether the short-term or cumulative effects of exposure over multiple sessions are more harmful than the immediate effects.

2. What are the short-term negative effects?

Regarding between-session habituation—conceptualized herein as the short-term effects of exposure—we ask, For how many exposure sessions do patients remain physiologically and psychologically aroused, at least at the beginning of session? As reviewed by Craske et al. (2008), many but not all individuals with anxiety disorders show reductions in physiological (e.g., heart rate and sometimes skin conductance) and psychological (e.g., subjective fear ratings) responses *across* exposure sessions (e.g., Jaycox et al. 1998; Oliver and Page 2003)—diminished responding to feared stimuli encountered repeatedly at different time points. Varying the location and intensity of stimuli

encountered during exposure can slow habituation rates (Lang and Craske 2000; Rowe and Craske 1998b). Nonetheless, treatment outcomes are excellent, and habituation still occurs.

The type of anxiety disorder and related exposure content also may influence the time course of habituation. Only two known studies—both among chronic PTSD patients—have examined session-by-session symptom fluctuations during exposure therapy with an eye towards evaluating potential adverse effects. Prolonged exposure treatment for PTSD is “often considered the most aversive application of exposure therapy” (Olatunji et al. 2009, p. 174), providing a “worst case scenario” for possible adverse effects of exposure therapy. The two PTSD studies demonstrated a paradox: Symptoms did not improve until imaginal exposure to the worst traumatic memory was initiated, but initiating imaginal exposure sometimes caused a transient worsening of symptoms (Foa et al. 2002; Nishith et al. 2002). Temporary symptom exacerbation in one study (Foa et al. 2002), however, was evident in only one quarter of PTSD patients, endured only 1 to 3 weeks, and did not impede successful treatment outcomes. In the other study (Nishith et al. 2002), re-experiencing symptoms increased slightly for 1 week following exposure onset, and diminished sharply thereafter. In summary, these two studies—both on prolonged exposure—showed that the magnitude of initial worsening (among the minority who initially worsened) was relative small, transient, and did not impede treatment outcomes. We can thus conclude that even prolonged exposure for PTSD does not pose short- or long-term risks to patients.

Studies of within- and between-session habituation are useful for our purpose of exploring questions of safety. However, the evidence linking within- and between-session habituation to successful exposure therapy *outcomes* is fairly weak and inconsistent (see Craske et al. 2008). For example, a phobic patient approaching a feared spider will likely see substantial reductions in heart rate and skin conductance after 5–20 min of continuous exposure, but these reductions do not consistently predict long-term improvement. On the basis of such findings, Craske et al. (2008) argue for an alternative approach that promotes repeated surges of arousal elicited throughout exposure, thus providing continuous new learning experiences that disconfirm patient's catastrophic expectancies. Provoking repeated upsurges in arousal means that patients remain physiologically and psychologically aroused for more extended periods—a potentially undesirable situation for pregnant women. Recent data suggests, moreover, that lower within-session habituation during the first exposure session (as would result from deliberately provoked repeated surges of arousal) predicts treatment attrition (Norton et al. 2011), another undesirable outcome. A gentler, graduated exposure

model likely represents a more appropriate model for conducting exposure during pregnancy. On the other hand, findings from the Foa et al. (2002) PTSD study are consistent with broader evidence demonstrating that when fear fails to habituate (or only minimally habituates) within or between exposure sessions, patients still stand a good chance of improving from treatment (see Craske et al. 2008; e.g., Grey et al. 1979; Jaycox et al. 1998; Lang and Craske 2000; Rachman and Lopatka 1988) and sometimes show more lasting improvement than patients whose fear habituates more fully (Rowe and Craske 1998a, b). One could argue, therefore, that even when fear minimally habituates during treatment, long-term fear reduction offsets short-term physiological arousal even within the context of pregnancy. Direct testing is clearly needed.

Recommendations for research and clinical practice

There is a striking paucity of research on the use of exposure-based treatment for anxiety disorders among pregnant women, despite the fact that it is the most widely supported intervention among general populations. Pregnant women have been systematically excluded from such research, seemingly due to untested hypotheses about potential adverse effects on the mother and fetus. Reversing this trend is critical. Prior to embarking on future research or clinical practice, however, it is important to consider whether the potential risks of exposure-based treatment during pregnancy may be so high as to preclude such steps. We think that this is unlikely for two reasons. First, studies in non-pregnant patients indicate that exposure typically results in rapid reductions of anxiety and fear; for PTSD, mild symptom exacerbation, if it occurs at all, is transient and does not impede treatment success (Foa et al. 2002; Nishith et al. 2002). Second, as noted, the stress context of pregnancy differs dramatically from that of non-pregnancy, with pregnant women displaying dampened responses to acute stressors (de Weerth and Buitelaar 2005). We therefore hypothesized that physiological and psychological reactivity to exposure during pregnancy can be predicted to remain within mild to moderate levels. In contrast, *untreated* anxiety disorders are highly chronic (Bruce et al. 2005; Yonkers et al. 2003), characterized by sustained elevated anxiety or panic attacks (Barlow 2002), and linked to enduring negative outcomes for mother and child (e.g., Banhidly et al. 2006). We conclude, therefore, that exposure-based treatments for antenatal anxiety disorders are likely to pose far less risk than untreated anxiety disorders.

Research To better understand the impact of exposure during pregnancy and address safety concerns, at least two lines

of research are needed to build on what we know about exposure in non-pregnant patients, and to directly assess the use of exposure-based treatments for pregnant women with anxiety disorders. First, we need controlled laboratory research on the immediate and short-term effects of exposure among pregnant women. To understand the extent to which exposure causes physiological change consistent with a profile of stress, we need to assess maternal HPA and sympathetic nervous system responses before, during, and after exposure treatment sessions. This line of inquiry would facilitate addressing whether relevant outputs linked to these systems—maternal cortisol, catecholamines, salivary alpha amylase, skin conductance, heart rate/heart rate variability, respiration, blood pressure, and fetal heart rate/heart rate variability—are elevated during exposure and if so, at what intensity and duration. We should inquire how such HPA and sympathetic responses differ by exposure length, focus, and intensity, and by fetal gestational and maternal age. To establish a basis for comparison, we need to compare responses in pregnant women to those of non-pregnant women. To help ensure safe levels of arousal during exposure, we can use objective criteria for safe levels of physiological arousal during pregnancy, such as the HR criteria we propose below.

Second, we need to conduct randomized clinical trials of exposure-based CBT and BT across a broad range of anxiety disorders during pregnancy. The recent report by Lilliecreutz et al. (2010) provides an important model for future research. In the only exposure-based treatment study of an anxiety disorder during pregnancy, Lilliecreutz et al. (2010) treated 30 pregnant women with blood-injury-injection phobia in an open trial. Treatment consisted of two group sessions of prolonged exposure to lancets, needles, catheters, syringes, and to receiving injections, finger pricks, vein punctures, and catheter placements. The treatment group showed large significant reductions from pre- to post-sessions on phobic anxiety—particularly during the second treatment session when the most intense *in vivo* exposures were conducted. At postpartum follow-up, the treatment group maintained or improved upon gains, whereas the untreated control group showed little to no change. This study reported no adverse events and full (100 %) patient retention. In summary, the results of this groundbreaking study indicate that pregnant women benefitted significantly from an exposure-based treatment for blood-injury-injection phobia without any detectable adverse effects. In that blood-injury-injection phobia involves a different physiological mechanism (vasovagal/parasympathetic surge) than other anxiety disorders, data now are needed on the other anxiety disorders. To maximize research and recruitment efficiency during pregnancy, we could assess exposure-based treatment across *heterogeneous* anxiety disorder patients, as recent studies using unified treatment

protocols (Farchione et al. 2012) or single-treatment manuals with disorder-specific branching mechanisms (Arch et al. 2012; Craske et al. 2011) have done successfully.

Future RCTs can build on the pioneering work of Lilliecreutz et al. (2010) by integrating minimally invasive, real-time measures of physiological and subjective responding into exposure treatment studies, thereby facilitating a broader understanding of immediate and short-term exposure effects for the mother and fetus. By gathering an extensive array of data, we can confidently apply and modify (if needed) exposure-based therapy for anxiety disorders during pregnancy and assess the extent to which we subsequently improve maternal, birth, and child outcomes.

Clinical practice As research advances, many pregnant women are likely to be interested in the option of exposure-based treatments in clinical practice settings. Thus, it is also important to consider possible implications for clinical service delivery. We offer two primary recommendations: the use of heart rate-based exercise guidelines and the option of possible exposure modifications to increase physical tolerability.

First, heart rate-based exercise guidelines during pregnancy offer an avenue for assessing exposure safety during pregnancy. Although contributions from multiple physiological systems can complicate interpretation (Berntson et al. 2007), heart rate is a useful index of physiological arousal in that it is easy and inexpensive to monitor continuously during exposure and has been evaluated in the antenatal exercise literature (McArdle et al. 1991). Heart rate thus represents a reasonable starting point from which to consider parameters for exposure-related arousal during pregnancy.

Based on exercise guidelines during pregnancy (McArdle et al. 1991), heart rate safety parameters accounting for differences in age, body mass index, and fitness levels can be developed for use during pregnancy. Although we have not yet tested these guidelines in the context of exposure-based therapy, we offer them as an example of an empirically based approach to developing physiological safety parameters for conducting exposure (or other arousing interventions) during pregnancy. The guidelines are based on resting HR upon morning waking, which accounts for pregnancy trimester-related physiological changes. Average resting HR can be inserted into the formulas below to determine an individualized maximum HR parameter:—Formula 1: $206.9 - (0.67 \times \text{age of participant}) = \text{Max HR}$; Formula 2: $\text{Max HR} - (\text{participant's resting HR}) = \text{participant's HR reserve}$; Formula 3: $\text{HR reserve} \times \% \text{ (from Table 1)} + \text{resting HR} = \text{maximum HR safety parameter}$. In cases in which the individual has two or more conditions (e.g., sedentary and obese), the most conservative percentage should be applied.

Table 1 Individualized heart rate (HR) maximum percentage

Condition	Max HR (%)
Sedentary	65–75
Conditioned exerciser	85
Pre-pregnancy BMI, 25–29.99 kg/m ²	65–75
Pre-pregnancy BMI, 30+ kg/m ²	65

For a 38-year-old, obese (at pre-pregnancy) pregnant woman with a high resting HR (100 bpm)—a patient for whom the most conservative HR parameters apply—the maximum HR parameter would be 153 bpm. Maximum HR during exposures in non-pregnant samples tended to peak at 80 to 95 bpm—far below this parameter. Heart rate notably increases during pregnancy (Hunter and Robson 1992); for example, basal HR after the first trimester is comparable to HR during exposure in non-pregnant samples. At least initially, therefore, utilizing HR safety parameters could prove an important step in establishing the range of normal response to exposure during pregnancy and determining whether they tend to remain within the typical range for non-pregnant patients. Occasionally, patients in previous studies have shown HRs during exposure that exceeded this maximum HR parameter (e.g., Watson et al. 1972). If HR exceeds the individualized safety parameter during an exposure, we would recommend implementing sitting rest procedures until HR returns to well below maximum range, and then reentering the exposure. Previous research has suggested that exiting exposure during maximum anxiety is not detrimental (DeSilva and Rachman 1984; Rachman et al. 1986), particularly if patients return to the exposure shortly thereafter, so this approach should not confound the extinction or inhibitory learning process. As noted, however, rest procedures are likely to be rarely needed. Of course, pregnant women with complications or health conditions that make physical arousal risky—rule outs that also are common in exposure-based treatment studies in general populations that exclude patients with respiratory or pulmonary conditions (e.g., Arch et al. 2012)—would require special adaptations or alternative treatments. In addition, care must be taken not to reinforce interoceptive vigilance in anxious patients by using HR parameters. For example, the HR monitor should be discrete and readable in session only by the therapist (not patient), and the therapist should remain calm and confident so as not to reinforce patients' anxiety regarding interoceptive sensations.

Second, although it is premature to hypothesize that arousal-related modifications to exposure therapy are necessary during pregnancy, it is important to consider the different but related issue of physical tolerability and whether modifications are required for pregnant women to tolerate

exposure interventions. We suggest that pregnancy is not likely to pose physical tolerability limitations for imaginal or most in vivo exposure procedures, for example, imagining previous traumas in PTSD or practicing public speaking in social phobia. On the other hand, interoceptive exposure, in which internal bodily sensations associated with fear are deliberately induced, may pose some tolerability challenges during pregnancy. Interoceptive exposure is central to CBT treatment of panic disorder (Craske and Barlow 2007) and sometimes is utilized in the treatment of other anxiety disorders as well (e.g., Tuerk et al. 2009). Nausea, indigestion/heartburn, dizziness, shortness of breath, and other common pregnancy-related discomforts, as well as movement restriction due to robust fetal size in late pregnancy, may pose challenges to implementing standard interoceptive exposure procedures. Many of the physiological sensations deliberately provoked during interoceptive exposure—dizziness, shortness of breath, heat, fullness of stomach, mild nausea, loss of balance, fatigue, and feeling “out of it” (Barlow and Craske 2007)—are naturally induced (though usually to a lesser degree) by pregnancy. Pregnancy may exacerbate the intensity with which women experience interoceptive exposure sensations due to the fact that at baseline, many pregnant women experience a mild version of these sensations already. This assertion is speculative but worth

pondering in light of possible pregnancy-related safety considerations.

To guard against exacerbating pregnancy-related discomforts to the point of severe nausea, vomiting, or other potential adverse effects, in Table 2, we suggest potential pregnancy-related modifications of common interoceptive exposures.

We offer these suggestions tentatively and speculatively—lacking data, we do not know whether such modifications will prove necessary or helpful. The suggested modifications are offered because they demonstrate how readily exposures could be modified for application during pregnancy, if needed, without prohibiting or restricting use of exposure therapy during this period more generally.

Summary

In considering whether exposure-based treatments for anxiety disorders are likely to be safe during pregnancy, we integrated a wide range of findings from obstetrics, psychiatry, and psychology. Extant findings converge on the notion that exposure is likely to be safe during pregnancy, particularly in comparison to pharmacotherapy or untreated anxiety disorders. However, direct investigation is clearly needed. In

Table 2 Standard exposures to feared bodily sensations (interoceptive exposures) and potential pregnancy-related modifications

Interoceptive exposure	Standard instructions ^a	Purpose	Potential pregnancy modifications
Spinning	Spin while standing or sitting in an office chair for up to 1–3 min	Induces dizziness, lightheadedness	Spin in chair (to prevent falling); only perform if not nauseous at baseline
Head lifting	Place head between knees for 30 s and then suddenly lift it	Induces lightheadedness	Perform only if not nauseous at baseline and if fetal size does not inhibit
Straw breathing	Occlude nose and breath through a large or small straw for up to 2 min	Induces feelings of shortness of breath or air hunger	Perform only if mother does not suffer shortness of breath generally
Breath holding	Hold breath as if underwater for as long as you are able	Induces a sense of breathlessness and suffocation	Stop if fetal or maternal HR exceed safety parameters; do not hold for extended periods (e.g., more than 30 s)
Body tension	Tense whole body without causing any pain for up to 1 min	Induces muscle weakness, tension, and trembling	Avoid tensing abdominal area
Climbing steps fast walking/jogging	Run or climb steps for several minutes, lifting knees as high as possible	Raises heart rate, induces shortness of breath	Perform by walking quickly in place (to prevent falling)
Hyperventilating	Take one deep breath every 2 s for up to 3 min	Induces unreality, shortness of breath, tingling, cold or hot feelings, dizziness, and other symptoms	Stop if maternal HR exceed safety parameters
Wearing nose plugs	Breath through mouth while wearing swimming nose plugs or holding nose for up to several minutes	Induces a sense of suffocation	Stop if maternal HR exceeds safety parameter
Wearing tight scarves or ties	Wear around neck for as long as can be tolerated	Induces a sense of tightness around the throat	Stop if maternal HR exceeds safety parameter
Staring at light bulb or venetian blinds	Stare for 30 s, and then look away quickly	Induces visual symptoms common in panic attacks	None apparent
Starting at self in mirror	Stare for 2+min, without looking away	Induces sensations of unreality/derealization	None apparent

^a Per Craske and Barlow protocols for panic disorder (Craske unpublished; Craske and Barlow 2007)

outlining an agenda to guide future research in this area, we aim to promote systematic investigation of how to safely and effectively treat anxiety disorders during pregnancy. Given the high prevalence, limited treatment alternatives, and enduring negative consequences of anxiety disorders during pregnancy, addressing this critical knowledge gap holds the potential to benefit generations of women and their children.

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