Arch Womens Ment Health
DOI 10.1007/s00737-012-0308-9

ORIGINAL ARTICLE

Are exposure-based cognitive behavioral therapies safe during pregnancy?

Joanna J. Arch · Sona Dimidjian · Cheryl Chessick

Received: 17 January 2012 / Accepted: 24 August 2012

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

J. J. Arch (✉) · S. Dimidjian
Department of Psychology and Neuroscience,
University of Colorado Boulder,
345 UCB Muenzinger,
Boulder, CO 80309-0345, USA
e-mail: Joanna.Arch@Colorado.edu

S. Dimidjian
e-mail: Sona.Dimidjian@Colorado.edu

C. Chessick
Department of Psychiatry, School of Medicine, Depression Center,
University of Colorado Denver,
Aurora, CO 80045, USA
e-mail: Cheryl.Chessick@ucdenver.edu

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

Published online: 16 September 2012

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., Banhidy 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 (≥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., Banhidy 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) that 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 (McAdrle 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 (McAdrle 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×age of participant)=Max HR; Formula 2: Max HR−(participant's resting HR)=participant's HR reserve; Formula 3: HR reserve×% (from Table 1)+resting HR=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 alterative 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, interceptive 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 interceptive 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.

Acknowledgments This work was supported by the University of Colorado Boulder startup funds to the first author (J.J.A.). We thank Jenn Leiferman, Ph.D., for her helpful suggestions on heart rate exercise safety guidelines during pregnancy.

References

Arch JJ, Eifert GH, Davies C, Plumb JC, Rose RD and Craske MG (2012) Randomized clinical trial of cognitive behavioral therapy versus acceptance and commitment therapy for the treatment of mixed anxiety disorders. *Journal of Consulting and Clinical Psychology*. doi:10.1037/a0028310

Banhidy F, Acs N, Puho E, Czeizel AE (2006) Association between maternal panic disorders and pregnancy complications and delivery outcomes. Eur J Obstet Gynecol Reprod Biol 124: 47–52

Barlow DH (2002) Anxiety and its disorders: The nature and treatment of anxiety and panic, 2nd edn. Guilford, New York

Barlow DH, Craske MG (2007) Mastery of your anxiety and panic workbook, 4th edn. Oxford University Press, New York

Barlow DH, Gorman JM, Shear MK, Woods SW (2000) Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. JAMA 283(19):2529–2536

Beckham JC, Vrana SR, May JG, Gustafson DJ, Smith GR (1990) Emotion processing and fear measurement synchrony as indicators of treatment outcome in fear of flying. J Behav Ther Exp Psychiatry 21(3):153–162

Berntson GG, Quiqley DS, Lozano D (2007) Cardivascular psychophysiology. In: Cacioppo JT, Tassinary LG, Berntson GG (eds) Handbook of psychophysiology, 3rd edn. Cambridge University Press, New York

Blanco C, Heimberg RG, Schneier FR, Fresco DM, Chen H, Turk CL, Liebowitz MR (2010) A placebo-controlled trial of phenelzine, cognitive behavioral group therapy, and their combination for social anxiety disorder. Arch Gen Psychiatry 67 (3):286–295

Bruce SE, Yonkers KA, Otto MW, Eisen JL, Weisberg RB, Pagano M, Keller MB (2005) Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. Am J Psychiatry 162(6):1179–1187

Buss C, Davis EP, Muftuler LT, Head K, Sandman CA (2010) High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6-9 year-old children. Psychoneuroendocrinology 35(1):141–153. doi:10.1016/j.psyneuen.2009.07.010

Butler AC, Chapman JE, Forman EM, Beck AT (2006) The empirical status of cognitive-behavioral therapy: a review of meta-analyses. Clin Psychol Rev 26:17–31

Chen Y-H, Lin H-C, Lee H-C (2010) Pregnancy outcomes among women with panic disorder: do panic attacks during pregnancy matter? J Affect Disord 120(1–3):258–262. doi:10.1016/j.jad.2009.04.025

Clark DM, Salkovskis PM, Hackmann A, Middleton H, Anastasiades P, Gelder M (1994) A comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder. Br J Psychiatry 164(6):759–769

Clark DM, Ehlers A, McManus F, Hackmann A, Fennell M, Campbell H, Louis B (2003) Cognitive therapy versus fluoxetine in generalized social phobia: a randomized placebo-controlled trial. J Consult Clin Psychol 71(6):1058–1067. doi:10.1037/0022-006x.71.6.1058

Conde A, Figueiredo B, Tendais I, Teixeira C, Costa R, Pacheco A, Nogueira R (2010) Mother's anxiety and depression and associated risk factors during early pregnancy: effects on fetal growth and activity at 20 weeks of gestation. J Psychosom Obstet Gynecol 31(2):70–82. doi:10.3109/01674821003681464

Craske MG (1999) Anxiety disorders: Psychological approaches to theory and treatment. Westview, Boulder

Craske MG (2003) *Origins of phobias and anxiety disorders: Why more women than men?* Elsevier Ltd., Oxford

Craske MG, Barlow DH (2007) Mastery of your anxiety and panic: Therapist guide, 4th edn. Oxford University Press, New York

Craske MG, Maidenberg E, Bystritsky A (1995) Brief cognitive-behavioral versus nondirective therapy for panic disorder. J Behav Ther Exp Psychiatry 26(2):113–120

Craske MG, Roy-Byrne P, Stein MB, Sullivan G, Hazlett-Stevens H, Bystritsky A, Sherbourne C (2006a) CBT intensity and outcome for panic disorder in a primary care setting. Behav Ther 37 (2):112–119. doi:10.1016/j.beth.2005.05.003

Craske MG, Roy-Byrne P, Stein MB, Sullivan G, Hazlett-Stevens H, Bystritsky A, Sherbourne C (2006b) CBT intensity and outcome for panic disorder in a primary care setting. Behav Ther 37:112–119

Craske MG, Kircanski K, Zelikowsky M, Mystkowski J, Chowdhury N, Baker A (2008) Optimizing inhibitory learning during exposure therapy. Behav Res Ther 46(1):5–27. doi:10.1016/j.brat.2007.10.003

Craske MG, Stein MB, Sullivan G, Sherbourne C, Bystritsky A, Rose RD, Roy-Byrne P (2011) Disorder-specific impact of coordinated anxiety learning and management treatment for anxiety disorders in primary care. Arch Gen Psychiatry 68(4):378–387. doi:10.1001/archgenpsychiatry.2011.25

Croen LA, Grether JK, Yoshida CK, Odouli R, Hendrick V (2011) Antidepressant use during pregnancy and childhood autism spectrum disorders. Arch Gen Psychiatry 68(11):1104–12. doi:10.1001/archgenpsychiatry.2011.73

de Beurs E, van Balkom AJLM, Van Dyck R, Lange A (1999) Long-term outcome of pharmacological and psychological treatment for panic disorder with agoraphobia: a 1-year naturalistic follow-up. Acta Psychiatr Scand 99(1):59–67. doi:10.1111/j.1600-0447.1999.tb05385.x

de Weerth, C., & Buitelaar, J. K. (2005). Physiological stress reactivity in human pregnancy—a review. *Neuroscience and Biobehavioral Reviews. Special Issue: Prenatal Programming of Behavior, Physiology And Cognition, 29*(2), 295-312. doi:10.1016/j.neubiorev.2004.10.005

DeSilva P, Rachman S (1984) Does escape behaviour strengthen agoraphic avoidance—a preliminary study. Behav Res Ther 22(87–91)

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. doi:10.1176/appi.ajp.2007.06111893

Dolovich LR, Addis A, Vaillancourt JM, Power JD, Koren G, Einarson TR (1998) Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. BMJ 317(7162):839–843

Dunkel Schetter C (2009) Stress processes in pregnancy and pretern birth. Curr Dir Psychol Sci 18(4):205–209

Entringer S, Buss C, Shirtcliff EA, Cammack AL, Yim IS, Chicz-DeMet A, Wadhwa PD (2010) Attenuation of maternal psychophysiological stress responses and the maternal cortisol awakening response over the course of human pregnancy. Stress: Int J Biol Stress 13(3):258–268. doi:10.3109/10253890903349501

Farchione TJ, Fairholme CP, Ellard KK, Boisseau CL, Thompson-Hollands J, Carl JR, Barlow DH (2012) Unified protocol for transdiagnostic treatment of emotional disorders: a randomized controlled trial. Behav Ther 43(3):666–678

Feske U, Chambless DL (1995) Cognitive behavioral versus exposure only treatment for social phobia: a meta-analysis. Behav Ther 26:695–720

Foa EB, Kozak MJ (1986) Emotional processing of fear: exposure to corrective information. Psychol Bull 99:20–35

Foa EB, Zoellner LA, Feeny NC, Hembree EA, Alvarez-Conrad J (2002) Does imaginal exposure exacerbate PTSD symptoms? J Consult Clin Psychol 70(4):1022–1028. doi:10.1037/0022-006x.70.4.1022

Foa EB, Huppert JD, Cahill SP (2006) Emotional processing theory: An update. In: Rothbaum BO (ed) Pathological anxiety: Emotional processing in etiology and treatment. Guilford, New York, pp 3–24

Gloster AT, Wittchen H-U, Einsle F, Lang T, Helbig-Lang S, Fydrich T, Arolt V (2011) Psychological treatment for panic disorder with agoraphobia: a randomized controlled trial to examine the role of therapist-guided exposure in situ in CBT. J Consult Clin Psychol 79(3):406–420. doi:10.1037/a0023584

Grayson JB, Foa EB, Steketee G (1982) Habituation during exposure treatment: distraction vs attention-focusing. Behav Res Ther 20:323–328

Grey S, Sartory G, Rachman S (1979) Synchronous and desynchronous changes during fear reduction. Behav Res Ther 17(2):137–147. doi:10.1016/0005-7967(79)90022-6

Grey S, Rachman S, Sartory G (1981) Return of fear: the role of inhibition. Behav Res Ther 19(2):135–143. doi:10.1016/0005-7967(81)90037-1

Haug TT, Blomhoff S, Hellstrom K, Holme I, Humble M, Madsbu HP, Wold JE (2003) Exposure therapy and sertraline in social phobia: 1-year follow-up of a randomised controlled trial. Br J Psychiatry 182:312–318

Hemels ME, Einarson A, Koren G, Lanctot KL, Einarson TR (2005) Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis. Ann Pharmacother 39(5):803–809. doi:10.1345/aph.1E547

Hofmann SG (2008) Common misconceptions about cognitive mediation of treatment change: a commentary to Longmore and Worrell (2007). Clin Psychol Rev 28:67–70

Hofmann SG, Smits JAJ (2008) Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. J Clin Psychiatry 69(4):621–632

Hunter S, Robson SC (1992) Adaptation of the maternal heart in pregnancy. Br Hear J 68:540–543

Jaycox LH, Foa EB, Morral AR (1998) Influence of emotional engagement and habituation on exposure therapy for PTSD. J Consult Clin Psychol 66(1):185–192. doi:10.1037/0022-006x.66.1.185

Kallen B, Olausson PO (2008) Maternal use of selective serotonin re-uptake inhibitors and persistent pulmonary hypertension of the newborn. Pharmacoepidemiol Drug Saf 17(8):801–806. doi:10.1002/pds.1570

Kammerer M, Adams D, Castelberg BB, Glover V (2002) Pregnant women become insensitive to cold stress. BMC Pregnancy Childbirth 2(1):8

Kessler RC, Berglund P, Demler O, Jin R, Walters EE (2005a) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey replication. Arch Gen Psychiatry 62(6):593–602

Kessler RC, Chiu WT, Demler O, Walters EE (2005b) Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey replication. Arch Gen Psychiatry 62(6):617–627

Kinsella MT, Monk C (2009) Impact of maternal stress, depression and anxiety on fetal neurobehavioral development. Clin Obstet Gynecol 52(3):425–440

Klosko JS, Barlow DH, Tassinari R, Cerny JA (1990) A comparison of alprazolam and behavior therapy in treatment of panic disorder. J Consult Clin Psychol 58(1):77–84. doi:10.1037/0022-006x.58.1.77

Lang AJ, Craske MG (2000) Manipulations of exposure-based therapy to reduce return of fear: a replication. Behav Res Ther 38(1):1–12

Lang PJ, Melamed BG, Hart J (1970) A psychophysiological analysis of fear modification using an automated desensitization procedure. J Abnorm Psychol 76(2):220–234. doi:10.1037/h0029875

Lattimore KA, Donn SM, Kaciroti N, Kempber AR, Neal CR, Vazquez DM (2005) Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and effects on the fetus and newborn: a meta-analysis. J Perinatol 25:595–604

Lilliecreutz C, Josefsson A, Sydsjo G (2010) An open trial with cognitive behavioral therapy for blood- and injection phobia in pregnant women—a group intervention program. Arch Women's Mental Health 13:259–265

Longmore RJ, Worrell M (2007) Do we need to challenge thoughts in cognitive behavioral therapy? Clin Psychol Rev 27:173–187

Magiakou MA, Mastorakos G, Rabin D, Margioris AN, Dubbert B, Calogero AE, Chrousos GP (1996) The maternal hypothalamic-pituitary-adrenal axis in the third trimester of human pregnancy. Clin Endocrinol 44(4):419–428

Magiakou MA, Mastorakos G, Webster E, Chrousos GP (1997) The hypothalamic-pituitary-adrenal axis and the female reproductive system. Annals NY Acad Sci 816:42–56

Maric NP, Dunjic B, Stojiljkovic DJ, Britvic D, Jasovic-Gasic M (2010) Prenatal stress during the 1999 bombing associated with lower birth weight: a study of 3,815 births from Belgrade. Arch Women's Mental Health 13(1):83–89. doi:10.1007/s00737-009-0099-9

Martini J, Knappe S, Beesdo-Baum K, Lieb R, Wittchen H-U (2010) Anxiety disorders before birth and self-perceived distress during pregnancy: associations with maternal depression and obstetric, neonatal and early childhood outcomes. Early Human Dev 86(5):305–310. doi:10.1016/j.earlhumdev.2010.04.004

Mastorakos G, Ilias I (2003) Maternal and fetal hypothalamic-pituitary-adrenal axes during pregnancy and postpartum. Ann N Y Acad Sci 997:136–149

Matthews KA, Rodin J (1992) Pregnancy alters blood pressure responses to psychological and physical challenge. Psychophysiology 29:232–240

McAdrle WD, Katch FI, Katch VL (eds) (1991) Exercise physiology: Energy, nutrition, and human performance, 3rd edn. Lea & Febiger, Malvern

Mintzes, B., & Jureidini, J. (2008). Should paroxetine be used to treat depression during pregnancy? The American Journal of Psychiatry 165(11): doi:10.1176/appi.ajp.2008.08040573

Misri S, Kendrick K (2007) Treatment of perinatal mood and anxiety disorders: a review. Canadian J Psychiatry/La Revue canadienne de psychiatrie 52(8):489–498

Mitte K (2005) Meta-analysis of cognitive-behavioral treatments for generalized anxiety disorder: a comparison with pharmacotherapy. Psychol Bull 131(5):785–795

Morland L, Goebert D, Onoye J, Frattarelli L, Derauf C, Herbst M, Friedman M (2007) Posttraumatic stress disorder and pregnancy

health: preliminary update and implications. Psychosom: J Consultation Liaison Psychiatry 48(4):304–308. doi:10.1176/appi.psy.48.4.304

Moser JS, Cahill SP, Foa EB (2010) Evidence for poorer outcome in patients with severe negative trauma-related cognitions receiving prolonged exposure plus cognitive restructuring: implications for treatment matching in posttraumatic stress disorder. J Nerv Ment Dis 198(1):72–75

Neuner F, Schauer M, Klaschik C (2004) A comparison of narrative exposure therapy, supportive counseling, and psychoeducation for treating post-traumatic stress disorder in an African refugee settlement. J Consult Clin Psychol 72(579–587)

Nishith P, Resick PA, Griffin MG (2002) Pattern of change in prolonged exposure and cognitive-processing therapy for female rape victims with posttraumatic stress disorder. J Consult Clin Psychol 70(4):880–886. doi:10.1037/0022-006x.70.4.880

Norton PJ, Price EC (2007) A meta-analytic review of adult cognitive-behavioral treatment outcome across the anxiety disorders. J Nerv Ment Dis 195:521–531

Norton PJ, Hayes-Skelton SA, Klenck SC (2011) What happens in session does not stay in session: changes within exposures predict subsequent improvement and dropout. J Anxiety Disord 25 (5):654–660. doi:10.1016/j.janxdis.2011.02.006

Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C (2006) Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. Arch Gen Psychiatry 63(8):898–906. doi:10.1001/archpsyc.63.8.898

Oberlander TF, Warburton W, Misri S, Riggs W, Aghajanian J, Hertzman C (2008) Major congenital malformations following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using population-based health data. Birth Defects Res B Dev Reprod Toxicol 83(1):68–76. doi:10.1002/bdrb.20144

O'Connor TG, Heron J, Glover V (2002a) Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. [Peer Reviewed]. J Am Acad Child Adolesc Psychiatr 41(12):1470–1477. doi:10.1097/00004583-200212000-00019

O'Connor TG, Heron J, Golding J, Beveridge M, Glover V (2002b) Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years: report from the Avon Longitudinal Study of Parents and Children. Br J Psychiatry 180(6):502–508. doi:10.1192/bjp.180.6.502

O'Connor TG, Heron J, Golding J, Glover V (2003) Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. J Child Psychol Psychiatry 44 (7):1025–1036. doi:10.1111/1469-7610.00187

Olatunji BO, Deacon BJ, Abramowitz JS (2009) The cruelest cure? Ethical issues in the implementation of exposure-based treatments. Cogn Behav Pract 16:172–180

Oliver NS, Page AC (2003) Fear reduction during in vivo exposure to blood-injection stimuli: distraction vs. attentional focus. Br J Clin Psychol 42(1):13–25. doi:10.1348/014466503762841986

Ost LG (1989) One-session treatment for specific phobias. Behav Res Ther 27(1):1–7

Otto MW, Pollack MH, Sabatino SA (1996) Maintenance of remission following cognitive behavior therapy for panic disorder: possible deleterious effects of concurrent medication treatment. Behav Ther 27(3):473–482. doi:10.1016/s0005-7894(96)80028-1

Otto MW, Smits AJJ, Reese HE (2005) Combined psychotherapy and pharmacotherapy for mood and anxiety disorders in adults: review and analysis. Clin Psychol Sci Pract 12:72–86

Rachman S, Lopatka C (1988) Return of fear: underlearning and overlearning. Behav Res Ther 26(2):99–104

Rachman S, Craske M, Tallman K, Solyom C (1986) Does escape behavior strengthen agoraphobic avoidance? A replication. Behav Ther 17(4):366–384. doi:10.1016/s0005-7894(86)80069-7

Roshanaei-Moghaddam B, Pauly MC, Atkins DC, Baldwin SA, Stein MB, Roy-Byrne P (2011) Relative effects of CBT and pharmacotherapy in depression versus anxiety: is medication somewhat better for depression, and CBT somewhat better for anxiety? Depress Anxiety 28:560–567

Ross LE, McLean LM (2006) Anxiety disorders during pregnancy and the postpartum period: a systematic review. J Clin Psychiatry 67 (8):1285–1298

Rowe MK, Craske MG (1998a) Effects of an expanding-spaced vs massed exposure schedule on fear reduction and return of fear. Behav Res Ther 36(7–8):701–717

Rowe MK, Craske MG (1998b) Effects of varied-stimulus exposure training on fear reduction and return of fear. Behav Res Ther 36 (7–8):719–734

Roy-Byrne PP, Craske MG, Sullivan G, Rose RD, Edlund MJ, Lang A, Stein MB (2010) Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized controlled trial. JAMA 19(303):1921–1928

Sarkar P, Bergman K, O'Connor TG, Glover V (2008) Maternal antenatal anxiety and amniotic fluid cortisol and testosterone: possible implications for foetal programming. J Neuroendocrinol 20 (4):489–496. doi:10.1111/j.1365-2826.2008.01659.x

Schmidt LG, Grohmann R, Muller-Oerlinghausen B, Otto MW, Ruther E, Wolf B (1989) Prevalence of benzodiazepine abuse and dependence in psychiatric in-patients with different nosology. An assessment of hospital-based drug surveillance data. Br J Psychiatry 154:839–843

Schweizer E, Rickels K (1998) Benzodiazepine dependence and withdrawal: a review of the syndrome and its clinical management. Acta Psychiatr Scand 393:95–101

Stein MB, Sherbourne CD, Craske MG, Means-Christensen A, Bystritsky A, Katon W, Roy-Byrne PP (2004) Quality of care for primary care patients with anxiety disorders. Am J Psychiatry 161(12):2230–2237

Teixeira JM, Fisk NM, Glover V (1999) Association between maternal anxiety in pregnancy and increased uterine artery resistance index: cohort based study. BMJ 318(7177):153–157

Tuerk PW, Grubaugh AL, Hamner MB, Foa EB (2009) Diagnosis and treatment of PTSD-related compulsive checking behaviors in veterans of the Iraq War: the influence of military context on the expression of PTSD symptom. Am J Psychiatry 166:762–767

van den Bergh BR, Marcoen A (2004) High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year-olds. Child Dev 75(4):1085–1097. doi:10.1111/j.1467-8624.2004.00727.x

van den Bergh BR, Mennes M, Oosterlaan J, Stevens V, Stiers P, Marcoen A, Lagae L (2005a) High antenatal maternal anxiety is related to impulsivity during performance on cognitive tasks in 14- and 15-year-olds. Neurosci Biobehav Rev 29(2):259–269. doi:10.1016/j.neubiorev.2004.10.010

van den Bergh BR, Mulder EJH, Mennes M, Glover V (2005b) Antenatal maternal anxiety and stress and the neurobiological development of the fetus and child: links and possible mechanisms. A review. Neurosci Biobehav Rev 29(2):237–258

van den Bergh BR, Mennes M, Stevens V, van der Meere J, Borger N, Stiers P, Lagae L (2006) ADHD deficit as measured in adolescent boys with a continuous performance task is related to antenatal maternal anxiety. Pediatr Res 59(1):78–82. doi:10.1203/01.pdr.0000191143.75673.52

van den Bergh BR, Van Calster B, Smits T, Van Huffel S, Lagae L (2008) Antenatal maternal anxiety is related to HPA-axis dysregulation and self-reported depressive symptoms in adolescence: a prospective study on the fetal origins of depressed mood.

Neuropsychopharmacology 33(3):536–545. doi:10.1038/sj.npp.1301450

Watson JP, Gaind R, Marks IM (1972) Physiological habituation to continuous phobic stimulation. Behav Res Ther 10(3):269–278. doi:10.1016/0005-7967(72)90043-5

Wikner BN, Stiller CO, Bergman U, Asker C, Kallen B (2007) Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. Pharmacoepidemiol Drug Saf 16(11):1203–1210. doi:10.1002/pds.1457

Wisner KL, Sit DK, Hanusa BH, Moses-Kolko EL, Bogen DL, Hunker DF, Singer LT (2009) Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. Am J Psychiatry 166(5):557–566. doi:10.1176/appi.ajp.2008.08081170

Yonkers KA, Bruce SE, Dyck IR, Keller MB (2003) Chronicity, relapse, and illness—course of panic disorder, social phobia, and generalized anxiety disorder: findings in men and women from 8 years of follow-up. Depress Anxiety 17(3):173–179

Yonkers KA, Wisner KL, Stewart DE, Oberlander TF, Dell DL, Stotland N, Lockwood C (2009) The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Gen Hosp Psychiatry 31(5):403–413. doi:10.1016/j.genhosppsych.2009.04.003