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From the Womb into the World: Protecting the Fetal Brain from Maternal Stress During Pregnancy

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Abstract

No other period in a child's life matches the speed of brain development than the first nine months in the womb. Rapid growth goes hand in hand with enormous potential, but also with great vulnerability. This policy-focused review focuses on maternal mental health as a key factor for fetal brain development. Already during pregnancy, the fetal brain wires differently when exposed to maternal stress, and children prenatally exposed to stress have a higher risk of developing neurodevelopmental disorders. Maternal prenatal stress is preventable, treatable, and tractable by policy. Research-based, policy recommends: (1) screening for maternal mental health issues throughout pregnancy, (2) encourage talking about prenatal mental health, (3) evidence-based interventions for pregnant women with mental health issues, (4) avoiding stress-inducing communication towards pregnant women, and (5) stimulating positive postnatal parenting. Investing in healthy pregnancies will improve fetal brain growth, and, ultimately lead to a healthier next generation.

Keywords

prenatal, brain development, fetus, pregnancy, early life adversity

Tweet

Maternal stress, depression, and anxiety are associated with later child behavioral and mental health issues. Investing in maternal mental health during pregnancy will improve healthy fetal brain growth, and, ultimately lead to a happier and healthier next generation.

Highlights

- Maternal stress, depression, and anxiety are associated with later child behavioral and mental health issues;
- Screening for mental health issues during pregnancy, including depression, anxiety, and stress, is recommended;
- Preventive actions should be taken to decrease stigma and encourage talking about prenatal maternal mental health with health care providers;
- There is a need for evidence-based intervention programs for pregnant women with mental health issues;
- Policy should avoid stress-inducing communication towards pregnant women;
- Investing in maternal mental health during pregnancy will improve healthy fetal brain growth, and, ultimately lead to a happier and healthier next generation.

Pregnancy is often viewed as a period of happiness and joy. Mothers are expected to be "glowing" and grateful for the opportunity to bring new life into the world. For a vast number of women, however, this is not the case. Meta-analyses showed that between 18.2% and 24.6% of women reported elevated anxiety symptoms during pregnancy, with higher symptom severity in the third trimester (Dennis et al., 2018). Moreover, about 14.4% of pregnant women in the United State of America reported the use of psychiatric medication during pregnancy (Huybrechts et al., 2013). Similar rates (15%) plague the Netherlands (Browne et al., 2020).

Self-reported percentages likely underestimate the true burden of mental health issues in pregnant women. Most pregnant women meeting the criteria for mental disorders are undiagnosed and untreated (Andersson et al., 2003; Glover, 2014). In one study, only 5.5% of women in need of treatment actually received it (Andersson et al., 2003). Care for the emotional well-being of pregnant women clearly seems to be a neglected part of obstetric medicine (Glover, 2014).

Besides burdening pregnant women, maternal stress during pregnancy can also affect the unborn child (Monk et al., 2019; Van den Bergh et al., 2020). Prenatal exposure

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to maternal anxiety increases risk for child anxiety disorders, attention deficit hyperactivity disorder (ADHD), autism, schizophrenia, behavioral problems, and depression (Lahti et al., 2017; McLean et al., 2018; Szekely et al., 2020; Yamada et al., 2021), also health complications, such as obesity (Burgueño et al., 2020) and infectious disease (Bush et al., 2021). Maternal anxiety and depression during pregnancy may contribute 10%–15% of the attributable load for child emotional and behavioral outcomes (Glover, 2014).

The Fetal Brain and Maternal Stress

The rapidly developing fetal brain may be particularly sensitive to maternal stress during pregnancy (Andersen, 2003; Bock et al., 2015; van den Bergh et al., 2018). Animal research supports this (Bock et al., 2015), as does human research. Neuroimaging *in utero* (rs-fMRI; van den Heuvel & Thomason, 2016) demonstrated that fetal brains exposed to maternal stress wire differently (De Asis-Cruz et al., 2020; Thomason et al., 2021; van den Heuvel et al., 2021) —alterations that may cause behavioral problems and alter neurocognitive functioning after birth (Meredith, 2015; van den Bergh et al., 2018, 2020).

Mechanisms: How Does Prenatal Exposure to Maternal Stress Affect the Fetal Brain?

How maternal stress during pregnancy gets "under the skin" of the unborn child, is still largely unknown. Five prominent mechanisms follow (for more information, see Beijers et al., 2014; Jašarević et al., 2015; Rakers et al., 2015; Van den Bergh et al., 2020). Understanding the mechanisms helps develop interventions for maternal stress during pregnancy and its negative impact on the unborn child.

Maternal Stress Hormones

Most often proposed is the maternal stress system (Beijers et al., 2014), releasing multiple hormones, including stress hormones (i.e., cortisol). Maternal and fetal cortisol correlate (Sarkar et al., 2007). Although some exposure to cortisol is essential for normal maturation, excessive levels may alter fetal brain development (Harris & Seckl, 2011; van den Bergh et al., 2018, 2020), ultimately resulting in developmental delays, psychopathology, and health issues later in life. However plausible, systematic review Zijlmans et al. (2015) concluded that cortisol may not be the main underlying mechanism.

The Placenta

The placenta protects the fetus (Shallie & Naicker, 2019). For example, a specific enzyme (i.e., 11β-HSD2) prevents most maternal stress hormones from crossing the placenta (Glover et al., 2009; Wyrwoll et al., 2011). Maternal anxiety may also alter the function of the placenta in other ways, such as via alterations in uterine blood flow, but the evidence is mixed (Kent et al., 2002; Monk, Newport, et al., 2012a; Teixeira et al., 1999). The precise role of the placenta in fetal brain development warrants further investigations (Beijers et al., 2014; O'Donnell et al., 2009). Still, placental functioning could mediate the association between maternal stress during pregnancy and negative child outcomes, such as lower birth weight in girls (Togher et al., 2018), higher stress responses in infants (Jahnke et al., 2021), and ADHD in boys (Shao et al., 2020).

Epigenetics: Changing Gene Expression

Epigenetic modifications are molecular mechanisms that alter gene activity without changing the DNA sequence (Babenko et al., 2015). Prenatal exposure to maternal stress can alter gene expression in multiple tissues, including the fetal brain or the placenta, potentially obstructing normal functioning and development (Babenko et al., 2015; Conradt et al., 2018; Monk, Spicer, et al., 2012b). Epigenetic changes have appeared in children prenatally exposed to maternal anxiety (Cao-Lei et al., 2015, 2021; Hompes et al., 2013; Mulligan et al., 2012; Schroeder et al., 2012), supporting prenatal exposure to maternal anxiety as altering gene expression in the fetus. Furthermore, epigenetic modifications may also alter fetal gene expression in interaction with other mechanisms; for example, via altering placental functioning (Monk, Spicer, et al., 2012b). Reported epigenetic changes of the placenta emerged in mothers suffering from psychological stress (e.g., Capron et al., 2018; Jensen Peña et al., 2012; Lund et al., 2021).

Changed Health Behaviors

When stressed, most people sleep less, eat unhealthy, and exercise less. For pregnant women, these changed health behaviors may negatively affect fetal development (De Weerth, 2018; Monk et al., 2013). Similarly, pregnant women with mental health issues and psychiatric disorders sleep less, sleep worse, and experience more exhaustion (Polo-Kantola et al., 2017; Qiu et al., 2012). Additionally, stressed pregnant women reported higher intake of fatty foods and snacks, a higher intake of micronutrients such as zinc and iron (Hurley et al., 2005), and a lower intake of important vitamins (Lobel et al., 2008). Furthermore, higher pregnancy-related stress is linked to less exercise (Lobel et al., 2008). Depressed women also reported a less active lifestyle during their pregnancy (Teofilo et al., 2014). Although stressed pregnant women alter health behavior and health behaviors alter fetal development (e.g., De Weerth, 2018), not much research has focused on this mechanism (De Weerth, 2018; Monk et al., 2013).

Postnatal Parenting

Many mothers stressed, anxious, or depressed during birth will develop postnatal mental health issues after birth (e.g., Grant et al., 2008; Heron et al., 2004; Sutter-Dallay et al., 2004). In turn, these mental health issues can negatively affect maternal parenting and mother–infant interaction quality (e.g., Hakanen et al., 2019; Ierardi et al., 2019; MacMillan et al., 2021). Prenatal and postnatal stress can have separate, potentially additive effects (Grant et al., 2009).

Women's brains change during pregnancy, likely preparing them to become better mothers (Barba-Müller et al., 2018; Gholampour et al., 2020; Hoekzema et al., 2016; Kim et al., 2010). However, in women stressed during pregnancy, the brain seems to respond less accurately to infant signals. For example, the brains of mothers with depression and anxiety were less responsive to happy infant faces (Arteche et al., 2011).

Policy Recommendations: What Can We Do About It?

Screen for Maternal Mental Health Issues Throughout Pregnancy

Any relevant policy must identify those women suffering or at risk (Austin, 2004; Trussell et al., 2018), yet screening is rare and often focused on postpartum depression only. Screening should start early and persist, to capture varied trajectories throughout prenatal and early postnatal years (Boekhorst et al., 2019; Korja et al., 2018).

A successful screening tool needs to be brief (< 5 min), easy to score (Trussell et al., 2018), ideally *before* a prenatal visit, and effectively translated (Shrestha et al., 2016). Practitioners should respond to mother's elevated symptoms immediately during the visit (Trussell et al., 2018).

Decrease Stigma and Talk About Prenatal Maternal Mental Health

Self-disclosure can be difficult for women due to experienced stigma of mental health issues and cultural norms about how women should feel during pregnancy. For instance, over 70% of women did not self-disclose symptoms of anxiety and depression because they regarded their feelings as a natural part of pregnancy (Browne et al., 2020). The main reason for women to self-disclose their symptoms was because their midwife asked about their mental health, whereas the main reason *not* to self-disclose was because their midwife did not ask about mental health issues (Browne et al., 2020). Mothers experiencing mental health issues during pregnancy indicated midwives as key to self-disclose and to facilitate uptake of treatment (Viveiros & Darling, 2018). Thus, midwifes and gynecologists break barriers for self-disclosure and should be well-trained to talk about mental health issues with their patients.

Nevertheless, midwifes and other health practitioners experience obstacles in referring their patients to effective treatment, especially at the beginning of the care-accessing process (Viveiros & Darling, 2019). For instance, midwifes reported that they are unaware of referral pathways and community resources or that these services are often unapproachable for various reasons (e.g., broken referral, not enough time to contact services, restrictive eligibility criteria). In one study, more than 50% of midwifes were unable to identify any services for their patients (Stanley et al., 2006). Indeed, to date, no clear protocols exist for referring women with mental health issues during pregnancy in most clinical settings (Glover et al., 2018). Additionally, many midwives reported that they felt insecure about bringing up mental health support because they either were afraid of insulting or shaming the mother or felt they lacked knowledge and skills to do so (Viveiros & Darling, 2019).

Other primary care providers, such as obstetricians, pediatricians, and family medicine practitioners reported similar barriers and lack of skills and training (Leiferman et al., 2008). In the same study, > 90% of the primary care providers expressed willingness to learn more about ways to enhance mental wellbeing in their patients. They preferred online education (CME/CEU) and clear guidelines as a method for receiving new information and training. Taken together, policy should focus on training primary care providers to talk openly about mental health issues, decrease the stigma, and support them with clear referral protocols.

Offer Evidence-Based Interventions for Pregnant Women's Mental Health

After identifying pregnant women at risk or already suffering from prenatal mental health problems, providing effective services promptly is key. Preferably, the interventions should start as early as possible to relieve the mother's suffering and to protect the fetal brain most effectively. Nevertheless, interventions in late pregnancy are likely to still be beneficial (Glover, 2014). Preventive interventions for women *at risk* could even start before pregnancy, focusing on self-care, such as sleep quality, regular exercise, and balanced dietary intake (Hurley et al., 2005). Social support and partner involvement also buffer against developing mental health issues during pregnancy (Boekhorst et al., 2019; Hughes et al., 2020; Takács et al., 2021).

Unfortunately, providing effective intervention has many barriers. First, only few evidence-based programs for pregnant women with (higher risk for) mental health issues exist (Glover et al., 2018). While numerous programs are developed, few underwent rigorous scientific investigation in well-controlled large randomized controlled trials (RCTs). A promising program dedicated to perinatal mental health issues is,

among others, the Mindfulness-based Childbirth and Parenting (MBCP) program—a fully manualized childbirth preparation program adapted from Mindfulness-based Stress Reduction (Duncan & Shaddix, 2015). Recent RCT studies and qualitative studies so far support the effectiveness of this program in decreasing prenatal depression, stress, and anxiety and its acceptability in pregnant women and their partners (Lönnberg et al., 2018, 2020). Still, larger RCTs are necessary, as is testing these programs in different cultural contexts.

Access to these services is another issue. Women living in rural and underserved areas could encounter physical problems with accessing health care programs, such as lack of transport (Trussell et al., 2018). Online treatment services could form a solution here, but private internet access is an issue. Also, translating face-to-face programs into online formats requires great care and fresh validation; online versions might well be less effective (Boekhorst et al., 2021). Providing online services, especially unguided, might not be the best solution, even though easy and cheap.

Financial access is another barrier since many pregnant women with high stress, anxiety, and depression do not have insurance that covers mental healthfully or at all (Trussell et al., 2018). Minority and underserved women are more often lacking properly insurance and at higher risk for experiencing mental health issues during pregnancy (Gavin et al., 2011). Many midwives reported "insurance constraints" as a major barrier for effective referral (Viveiros & Darling, 2019). One solution would provide free prenatal mental health services.

Avoid Stress-Inducing Communication Towards Pregnant Women

Pregnant women are not responsible for negative outcomes of their unborn child due to their own stress or mental disorder. Pregnant women are already bombarded with advice on what not to do, eat, or feel by family, friends, media, and community. A whole list of foods and health practices already incur societal disapproval, such as smoking or drinking alcohol. For pregnant women already struggling, health care providers' advice can be overwhelming and discouraging.

Effective training of health care providers, increased time during visits, and more continuous care could tackle this issue. Midwives reported time constraints as a major barrier for properly discussing mental health problems with their patients (Viveiros & Darling, 2019). Continued care, from the same professionals during pregnancy and at birth, can build a relationship safe for discussing mental health issues (Simcock et al., 2018; Viveiros & Darling, 2018).

Stimulate Positive Postnatal Parenting

Positive parenting after birth ("*postnatal moderation*") can offset the negative effects of prenatal exposure to maternal depression or anxiety. Children exposed to elevated maternal distress during pregnancy did not display negative outcomes (decreased cognitive functioning and higher negative emotionality) if they received high-quality caregiving from their mother after birth (Grande et al., 2021). Secure attachment of the child to its mother and maternal sensitivity toward the child also protected the child from negative influences of maternal mental health issues during pregnancy (Bergman et al., 2008; Grant et al., 2010). This has major implications for policy since it suggests that investing in positive parenting in the early postnatal period can improve outcomes for children of mothers with prenatal mental health issues.

Conclusion

To provide children with the best start possible, invest in the emotional wellbeing of their mothers during and after pregnancy. (This is also good for the mother.) The child brain wires differently when prenatally exposed to maternal psychological stress; children born of mothers that experienced high levels of prenatal stress have a higher risk of neurodevelopmental disorders, such as autism, ADHD, and mood disorders. Fortunately, maternal mental health issues during pregnancy are preventable and treatable and, thus, targetable by policy. This policy-focused review provided several recommendations to improve maternal mental health during pregnancy. Investing in healthy pregnancies will improve fetal brain growth and, ultimately, lead to a healthier next generation.

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