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Pre- and Perinatal Risk Factors for Serious Mental Disorders: Ethical Considerations in Prevention and Prediction Efforts

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Abstract

Repeated findings have linked pre- and perinatal risk factors to a variety of mental disorders. Some studies have found large magnitudes of association, suggesting that fetal development represents an important period for understanding neurodevelopmental sequelae. Nevertheless, it remains unclear how best to translate the existing findings into early identification, prevention, and treatment strategies that would be useful for pregnant populations and/or for their offspring. This article will discuss key ethical considerations surrounding the incorporation of findings from studies of the associations between obstetric complications and risk for mental disorders into prevention and prediction efforts.

Key words: Prenatal, perinatal, risk factors, mental disorders

A number of important ethical issues arise when considering a history of obstetric complications (OCs) in the prediction and prevention of serious mental disorders. As we will discuss further below, increasing evidence supports the association between a variety of pre- and perinatal risk factors and offspring psychopathology (Ellman & Cannon, 2008; Ellman & Susser, 2009; Fineberg & Ellman, 2013). For some OCs, the strength of their associations with offspring psychopathology risk exceed those of all but the strongest genetic risk factors (Brown et al., 2004; Brown & Derkits, 2010; Cannon et al., 2000; Harrison, 2015; Walsh et al., 2008). Nevertheless, it remains unclear how best to translate knowledge of the links between OCs and offspring psychopathology into information that would useful to pregnant women. We will discuss some of the notable issues in obstetric complications research, including the high frequency of OCs in the

population, the small risk to individual offspring who have been exposed to OCs, the multiple factors that likely interact with OCs to confer risk, and evidence that informing women of the small risks associated with OCs could confer an even greater risk for the developing fetus.

Obstetric Complications and Risk for Offspring Psychopathology

A variety of definitions have been used to describe OCs; one commonly used definition includes any deviation from normal maternal and/or fetal functioning during the prenatal, labor and delivery, and early neonatal periods (McNeil, Cantor-Graae, & Ismail, 2000). This inclusive definition, which can refer to everything from low birth weight to maternal stress during pregnancy, has led to substantial variation across studies, making results difficult to interpret (Ellman & Cannon, 2008; Ellman & Susser, 2009). This inclusive definition is a legacy of the field's initial explorations into the relationship between early periods of development and risk for mental disorders, which found that, in general, a history of OCs was associated with increased risk for offspring psychopathology (Cannon, Jones, & Murray, 2002; Hultman, Ohman, Cnattingius, Wieselgren, & Lindstrom, 1997). However, the lack of specificity of OCs in early studies, coupled with the high probability that most women will experience at least one OC during their pregnancies, calls into question how useful many of the early findings might be for informing prevention strategies.

More recent studies of the relationship between OCs and risk for psychopathology have used targeted approaches, examining classes of OCs presumed to share underlying mechanisms (e.g., hypoxia or infections) and/or specific maternal biomarkers during pregnancy (e.g., antibodies to specific infections; Ellman & Cannon, 2008; Ellman & Susser, 2009; Fineberg & Ellman, 2013; Mittal, Ellman, & Cannon, 2008). These studies have linked OCs to risk for offspring schizophrenia, depression, bipolar disorder, autism spectrum disorder, and other neurobehavioral difficulties (Brown et al., 2014; Ellman & Cannon, 2008; Ellman & Susser, 2009; Fineberg & Ellman, 2013; Murphy et al., 2017; Parboosing, Bao, Shen, Schaefer, & Brown, 2013; Spann, Sourander, Surcel, Hinkka-Yli-Salomaki, & Brown, 2017). For example, hypoxia-associated OCs, some infections during pregnancy, maternal inflammation during pregnancy, malnutrition (from famine studies), maternal stress during pregnancy, preeclampsia, diabetes, and decreases in fetal growth have all been associated with risk for schizophrenia (Cannon et al., 2002; Ellman & Cannon, 2008; Ellman & Susser, 2009; Fineberg & Ellman, 2013).

Although mounting evidence supports a link between OCs and a variety of psychiatric conditions, issues emerge when attempting to apply these findings to risk prediction in medical settings. Among these issues is inconsistency of findings across studies, even among studies investigating the same OC-mental-disorder relationship. For instance, one study of herpes infection during pregnancy found a significant relationship with risk for offspring schizophrenia, while another found no relationship (Brown, Schaefer, Quesenberry, Shen, & Susser, 2006; Buka, Cannon, Torrey, Yolken, & Perinatal, 2008). Some of the inconsistency in findings may stem from differences in methods across investigations (e.g., differences in how exposure to infection is quantified and in the gestational timing of blood sample analyses), in addition to the possibility that variability of risk for a specific disorder may be linked to severity of the OC (Brown & Derkits, 2010; Ellman, Yolken, Buka, Torrey, & Cannon, 2009). For instance, one study found associations between maternal influenza B, but not influenza A, infection during pregnancy and risk to offspring childhood cognition (specifically among children who later developed schizophrenia), which suggests that factors associated with the strain of influenza may be key to explaining differences in offspring outcomes (Ellman et al., 2009). This finding raises the possibility that that the severity of an OC, rather than mere exposure, may be critical in determining the degree of disruption in fetal development. Attempts to quantify severity of OCs (as well as variations in maternal responses to OCs) have been relatively lacking in psychopathology research but may provide important clues into future prediction and prevention models.

Another important issue in the study of OC-mental health associations is the lack of clarity as to whether a history of OCs increases risk for specific mental disorders or for symptoms that occur in multiple disorders (Lukkari et al., 2012). Increasingly, studies of broader risk for mental disorders are finding that risk factors, both environmental and genetic, overlap for a variety of serious disorders, which appears to be mirrored by findings in OC literature (Gibson, Alloy, & Ellman, 2016; Gibson, Cooper, Reeves, Anglin, & Ellman, 2017; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Nevertheless, because risk for certain disorders, such as schizophrenia, has been more extensively studied in OC research, the level of specificity of the association between OCs and risk for psychopathology (that is, whether certain pre- and perinatal factors confer risk for certain mental disorders or, more generally, confer risk for symptoms common to multiple disorders) remains largely an open question, thus limiting the utility of this information to inform prediction and prevention efforts.

Individual factors by OC Interactions

Accumulating findings indicate that variation in individual-level maternal factors during pregnancy also may play an important role in determining the level of risk to the developing fetus when an OC occurs. Such evidence includes the finding that many common infections linked to offspring psychopathology (including most strains of influenza) do not cross the placenta, suggesting that disruptions in fetal development may be better explained by fetal exposure to maternal immune responses to infection (and immune responses to other events, e.g., stress), such as increases in proinflammatory cytokines (Fineberg & Ellman, 2013). Further, there is some evidence that OCs interact with genes and genetic risk to confer risk for offspring psychopathology (Clarke, Tanskanen, Huttunen, Whittaker, & Cannon, 2009; Ellman, Huttunen, Lonnqvist, & Cannon, 2007; Forsyth et al., 2013; Mittal et al., 2008; Nicodemus et al., 2008; Ursini et al., 2015). For example, Cannon and colleagues (2008) examined umbilical cord samples from cases who later developed schizophrenia in adulthood and from matched controls in a large, U.S. birth cohort study, finding that cases who had been exposed to hypoxia-associated OCs did not mount a brain-derived neurotrophic factor (BDNF) response to the OC (a neuroprotective response to hypoxia), whereas exposed controls showed elevated BDNF in umbilical cord samples. These results have been interpreted to indicate that the OC alone may not be sufficient to increase risk for schizophrenia, and instead that some interaction between the OC and a lack of neuroprotection (to which the cases appear to have been predisposed) may better explain the increase in offspring risk. Finally, there is evidence that OCs can interact with each other to increase risk for offspring psychopathology, and it may be that examining one OC misses the complex picture of what is occurring prenatally (Fineberg, Ellman, Buka, Yolken, & Cannon, 2013; Murphy et al., 2017). For instance, one study found that maternal infection during pregnancy increased risk for offspring depressive symptoms and that maternal infection significantly interacted with maternal stress during pregnancy (Murphy et al., 2017). Specifically, only mothers who both reported stress and had a second trimester infection had offspring with higher depressive symptoms, indicating that the two OCs had depended upon each other to confer offspring risk. Cumulatively, these findings raise concerns about broadly disseminating information on OC-mental health associations to pregnant women, given that these associations might only pertain to the small portion of women who either have a more severe response to OCs, have co-occurring OCs, and/or carry fetuses who already have an underlying susceptibility to major mental disorders. To effectively inform early intervention/prevention efforts,

OC-psychopathology risk must be considered within the context of a range of other risk factors.

Another important caveat is that individual-level factors typically found in large subpopulations of pregnancies also appear to interact with OCs. For instance, higher basal levels of inflammatory cytokines during pregnancy have been found in African American samples, one of several racial/ethnic variations in inflammatory cytokines observed during pregnancy (Giscombe & Lobel, 2005; Rosenberg, Garbers, Lipkind, & Chiasson, 2005; Velez et al., 2008); however, no study (to our knowledge) has examined race as a potential moderator of the association between maternal inflammation during pregnancy and offpsring psychopathology (e.g., schizophrenia), despite racial differences in mental disorder prevalence, such as in schizophrenia (Bresnahan et al., 2007). Additionally, a number of health behaviors and contextual factors, such as disruptions in sleep, stress, and lower socioeconomic status, have been linked to a more pronounced inflammatory response, and to increased susceptibility for infection (Coussons-Read, Okun, & Nettles, 2007; Coussons-Read, Okun, Schmitt, & Giese, 2005; Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006; Morozink, Friedman, Coe, & Ryff, 2010; Okun, Schetter, & Glynn, 2011). Such common individual contextual factors, along with genetic variations that may alter responses in the mother and fetus to OCs, may also interact with OCs to portend risk to the fetus (Rice et al., 2010).

Magnitude of OC Associations

The magnitudes of the associations between OCs and risk for major mental disorders can be quite large when compared to other risk factors for these disorders, with odds ratios ranging from slightly above 1 in some studies to 7 in others. In fact, many of these odds ratios are larger than those found in most genetic association studies of serious mental disorders (Brown et al., 2004; Murphy et al., 2017). However, the meaning of the magnitudes of these associations tend to be translated to the general population and/or to the broader medical community in ways that are at best ineffective and at worst misleading. In low base rate disorders, such as schizophrenia, a basic estimate of the risk to an individual person who has been exposed to a given risk factor can be obtained by multiplying the odds ratio associated with the risk factor (in this case, an OC) by the prevalence rate of the disorder (Davies, Crombie, & Tavakoli, 1998). Practically speaking, this means that if schizophrenia occurs in about 1% of the population and there is a 7.0 odds of developing schizophrenia after being exposed to an OC, then an OC-exposed child would have a 7% likelihood of developing schizophrenia. Of course, we now know that the supposed 1%

prevalence rate of schizophrenia is not as stable as once thought, and that some communities are at higher risk for developing the disorder (Tandon, Keshavan, & Nasrallah, 2008). However, even if we were to incorporate these variations in prevalence rates, the individual risk for an OC-exposed child would remain relatively low (without considering other risk factors). For higher base rate disorders, like depression, the reliability of multiplying the odds ratio by the prevalence rate decreases but still provides a general estimate of risk (Davies et al., 1998).

To determine how best to communicate these findings to pregnant women and obstetric health workers, it is critical to have a clear understanding of what the magnitudes of OC-psychopathology-risk associations mean to the patient. In the media and in peer-reviewed manuscripts that discuss findings related to a variety of OCs (e.g., maternal stress and infection during pregnancy) and offspring outcomes, an explanation of what these findings mean for an individual woman's risk is rarely included (e.g., Shellenbarger, 2010; Velasquez-Manoff, 2015). Even when empirical results are accurately described in popular press articles, effective interpretation of those findings is often absent, and the titles given to the articles are often misleading, e.g., "Why worries about baby are bad for baby" and "Should you bring your unborn baby to work?" (Shellenbarger, 2010; Velasquez-Manoff, 2015). In addition, there is evidence that many medical doctors lack training to interpret statistics from empirical studies, creating the potential for misleading doctor-patient communication about risks specific to a given pregnancy (for review see Ghosh & Ghosh, 2005). The importance of accurate translation of findings is underscored by studies that have linked maternal stress during pregnancy and pregnancy-specific anxiety (e.g., worries about the health of the developing fetus and pregnancy) to adverse birth outcomes, such as decreased gestational age and reduced fetal growth (Dunkel-Schetter, 1998; L. M. Ellman et al., 2008b; Mancuso, Schetter, Rini, Roesch, & Hobel, 2004; Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993). Given the potential for poorly communicated OC-psychopathology-risk findings to prompt unnecessary stress and anxiety in pregnant women, it is unclear whether attempts to educate women about findings in the OC literature are worth the risk of worrying all expectant mothers and, in turn, potentially increasing risk to their pregnancies, especially when elevated OC-related risks are likely to apply to only a small subset of pregnancies.

Cascade Models of Obstetric Complications

As far as the mechanisms by which OCs confer risk for offspring psychopathology, it remains

unclear whether OCs are directly associated with the subsequent development of psychopathology or, rather, trigger a cascade of developmental sequelae in which OCs are one of several incremental factors that contribute to eventual development of mental health problems. Current research, which has addressed this question predominantly in animal models, provides support for the idea that prenatal immune activation may act as a neurodevelopmental disease 'primer,' leading to alterations in immune functioning that can exert damaging effects on the brain throughout development (Fineberg & Ellman, 2013; Meyer, 2013). Some evidence in humans supports the possibility that OCs may lead to subtle developmental difficulties that alter the offspring's interactions with the environment and indirectly contribute to onset of psychopathology. For example, some findings suggest that fetal exposure to infection may lead to premorbid deficits in cognitive functioning among children who later develop schizophrenia (Ellman, Yolken, Buka, Torrey, & Cannon, 2009). Other studies have found greater social maladjustment among children who later develop psychosis (Done, Crow, Johnstone, & Sacker, 1994). It is possible that these premorbid cognitive and social problems in childhood interact over time with contextual factors, such as peer influences and familial context, to increase risk for psychopathology through numerous pathways.

In particular, peer victimization, especially if chronic or severe, has been associated with psychotic symptoms in adolescence (Schreier et al., 2009) and with the potential for increased risk of psychosis in adults (Lataster et al., 2006). It is possible that premorbid disturbances in childhood may predispose children to peer victimization and contribute to increased risk for later psychopathology. For example, one recent study found that individuals exposed to childhood victimization had pervasive impairments in cognitive functions and that these cognitive deficits were largely explained by pre-existing cognitive vulnerabilities that predated exposure to victimization (Danese et al., 2017). Such findings lend support to the idea that OCs may contribute to increased susceptibility to victimization through cognitive impairments that begin before experiences of childhood victimization. This hypothesis is also in keeping with research suggesting that victims of bullying are more likely to display social deficits compared to non-victimized, same-aged peers (Hawker & Boulton, 2000). However, few studies have examined the role of these contextual factors in relation to other genetic and environmental contributors to subsequent psychopathology. Further investigation of such contextual factors is warranted, given that these factors are viable targets for intervention and logical opportunities to interrupt the "cascade" of events contributing to risk for later psychopathology. School-based anti-bullying programs offer a unique avenue for intervention, as

they have been shown to have moderate effects on peer victimization (Lee, Kim, & Kim, 2015). Prevention efforts such as these may be more fruitful than efforts designed to maximize maternal health during pregnancy. Although continued advances in prenatal care will justifiably remain an important focus, OCs during pregnancy may be, to an extent, unavoidable given how commonly they occur (Centers for Disease Control and Prevention, 2016).

Conclusions

The findings outlined above describe a complicated picture of the use of OC research in prediction and prevention of major mental disorders. Although the magnitudes of the associations between OCs and risk for mental disorders are relatively large compared to other identifiable risk factors, the risk for an individual woman and her baby is fairly small. Further, the dissemination of findings about OCs and offspring mental health could potentially increase the likelihood of pregnancy-specific anxiety and stress during pregnancy, both of which have been associated with adverse birth outcomes (Dunkel-Schetter, 1998; Ellman et al., 2008a; Mancuso et al., 2004; Wadhwa et al., 1993). A push to develop more comprehensive models of who is actually at risk for subsequent mental disorders following exposure to an OC is warranted and could provide important clues for early intervention strategies. Such models should incorporate individual-level variables that we know interact with OCs, such as maternal and fetal genetic variations, maternal stress during pregnancy, maternal health risk behaviors (e.g., substance use, sleep patterns, etc.), maternal/fetal ethnic/racial information, and other maternal demographic factors. In the meantime, alternate prevention strategies could be used (that do not rely on effective risk communication) to potentially reduce the psychopathology associated with OCs by, for instance, implementing public health programs that expand the use of best practices for treating infections during pregnancy, and increasing the availability of pre- and postnatal psychological resources (e.g., stress reduction-based programs) that aid in general pre- and postnatal health. Finally, the effectiveness of prevention and intervention strategies at a variety of developmental periods would be greatly enhanced by the development of algorithms that incorporate OCs, maternal individual level variables, childhood developmental outcomes, and contextual factors.

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