Healthy pregnancy and prevention of psychosis

Do healthier pregnancies reduce the risk of offspring psychosis? Variants of this question have appeared in recent papers, but with little discussion of how to answer it.

As a starting point, we note that current research on prenatal factors and psychotic disorders is relevant to this question but only addresses it partially and indirectly; that we are not aware of studies that do address it holistically; and that we do not yet know how such studies could be done. We begin by offering a perspective on research on prenatal factors and psychotic disorders. Then we discuss three points that would require consideration before explicitly directing research toward the question at hand.

About 25 years ago, numerous established pregnancy/birth cohorts had already reached adulthood, creating new opportunities for life course investigations[1]. In the US, for example, investigators launched studies of prenatal factors and psychotic disorders that made use of archived prenatal maternal sera in two large pregnancy cohorts. The development and linkage of national electronic registries in Scandinavia and elsewhere further transformed capacity to investigate prenatal factors and psychotic disorders[2]. Studies of prenatal exposures based in "natural experiments" also contributed by mitigating sources of confounding that preclude causal inference in traditional observational designs[3].

We are presently at the cusp of another leap forward, as national registries are being linked to archived biological data[4]; pregnancy cohorts of more than 100,000 births are entering the peak age of risk for psychotic disorders, with prenatal genetic and biological data, and ongoing follow-up[5]; and natural experiments are being conducted which include neuroimaging as well as diagnoses[6].

Relatively strong evidence suggests a role for prenatal infection and nutrition, but prenatal toxic exposures, prenatal stress, and interpregnancy intervals are also viable candidates, to name just a few. New methodologies from epidemiology are increasingly incorporated to strengthen causal inference in these data, meeting challenges such as disentangling the contributions of factors that tend to cluster together due to lifestyle or social conditions. Genomics and population neuroscience are contributing to the converging evidence that prenatal factors matter for psychotic disorders, and yielding insights into mechanisms. We still do not have definitive evidence that a specific modifiable prenatal exposure is a cause of psychotic disorders. There is much room for optimism, however, as new approaches and data bases come to fruition.

As we move closer to definitive results, it becomes important to consider how these results could be incorporated into public health initiatives to promote healthy pregnancy. Some results might yield further evidence for preventive actions already incorporated into healthy pregnancy initiatives, such as recommended vaccinations and nutritional supplements. It seems likely, however, that emerging results will require us to consider public health actions that go beyond these simplest scenarios. Therefore, it would be appropriate in the long-term to adopt a more holistic public health framework for research. For this purpose, three central points would require consideration: What do we mean by a healthier pregnancy? Should we broaden the offspring outcomes beyond psychotic disorders? What could we gain by focusing on the population distribution of relevant prenatal factors that lie on a continuum?

A universally applicable definition of "healthier pregnancy" is elusive, and any particular measure needs justification for purpose and context. From a life course perspective, characteristics of a pregnancy may be beneficial for some offspring health outcomes and harmful for others. Among many examples, pregnancy characteristics that increase birthweight may reduce offspring risk of psychotic disorders but increase offspring risk of pre-menopausal breast cancer[2,7], and advanced paternal age at conception may increase risk of psychotic disorders but lower offspring risk of cardiovascular disease[8]. Moreover, across different contexts, the characteristics and outcomes that need most emphasis will be different.

Neurodevelopmental delays, low cognitive performance, and persistent subclinical psychotic experiences in children are associated with increased risk of subsequent psychotic disorders. These outcomes are manifest earlier and are more common than psychotic disorders; therefore, they are often more amenable to investigation. They have been related to prenatal experiences; however, like for psychotic disorders, the evidence is not definitive. Furthermore, recent work on the structure of psychopathology supports a dimensional transdiagnostic perspective[9]. From this perspective, preventing these earlier outcomes could substantially reduce risk of psychotic disorders, and probably other psychiatric disorders too, and could have more public health significance. By contrast, we may also find that certain prenatal factors are related to a subgroup of frank psychotic disorders and not to these earlier antecedents; hence the need to investigate the breadth of related outcomes.

Characteristics of a pregnancy may be related to psychotic disorders on a continuum. A large study found that lower birthweight was associated with increased risk of psychotic disorders, but across a broad continuum, implying that a shift in the entire distribution of birthweight (or the causal factor it represents) in the population might do more for prevention of psychotic disorders than reducing the number of low birthweight babies[2]. Furthermore, across the continuum of birthweight, lower birthweight was associated with all treated psychiatric disorders, not only with psychotic disorders. Caution is needed, however, because the relationship of prenatal factor and outcome may not be linear, but rather J-shaped or U-shaped.

We suggest that, alongside the currently dominant approach to research on prenatal factors and psychotic disorders, it could

be useful to set the stage for a more holistic program of research on healthy pregnancy and prevention of psychosis. We have highlighted three central questions that could be amenable to research and might be significant for public health interventions. We should bear in mind, however, that the results of such research may offer guidance, but may not provide unequivocal answers.

Finally, we note that, with few exceptions[3], studies of prenatal factors and psychotic disorders have been done in high-income countries. This makes it difficult to generalize any holistic framework to lower-resource settings, where maternal exposures and conditions affecting pregnancy are different, and access to prenatal care is more limited. Interventions may need to be integrated into broadly conceived programs, such as the Maternal Health Thematic Fund[10]; and we may need to consider, for example, whether reducing maternal mortality and obstetric fistulas could result in less childhood trauma and thereby benefit offspring neurodevelopment. A global approach to healthy pregnancy and psychosis will depend upon the expansion of research to diverse low- and middle-income country settings.

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Serotonin, psychedelics and psychiatry

Serotonin is a key neuromodulator known to be involved in brain development, perception, cognition, and mood. However, unlike as with dopamine for example, a compelling unified theory of brain serotonin function has not yet been established. This is likely due to the exceptional complexity of the serotonin system, with its 14+ receptors, over twice the number identified for any of the other major neuromodulator systems[1].

Serotonin has been implicated in several major psychiatric disorders, and most obviously in depression. Chronic medication with selective serotonin reuptake inhibitors (SSRIs) remains the dominant treatment for unipolar depression, and SSRI prescription rates have been increasing year-on-year at record levels. Such widespread SSRI use has not noticeably impacted on depression prevalence, however, and questions continue to be asked about the safety, efficacy and general philosophy of chronic pharmacotherapy.

Historically, psychiatry has been a divided house, with the psychodynamic model dominating the first half of the 20th century, and the biomedical model ever since. It is natural for early perspectives within nascent disciplines to overshoot in confidence before maturing and moderating over time. Such has been the case with psychodynamic psychology for example, and there are reasons to suspect that something similar may be happening in relation to the pharmacological model.

This subtle shift in perspective is especially evident in contemporary serotonin and depression research. Until recently, it was not unusual to hear patients, doctors and even psychiatrists speak with presumed authority about how deficient serotonin functioning is causal of depression, offering solace in the view that "serotonin is to blame". As with genetic determinism, one should be mindful of the emotional function of such explanations – especially in psychiatry, the most personal of medical disciplines.

So what is the relationship between serotonin and depression? A fair (but unsatisfactory) answer to this question is that "it is complex". Not wishing to sit on the fence, however, a more constructive statement is that there is increasing evidence that serotonergic processes play a critical role in mediating an individual's sensitivity to context[2]. For example, within the last decade, seminal work has been done to demonstrate how genetic variation within[3] and pharmacological manipulations of[4] the serotonergic system interact significantly with environmental factors to determine outcomes in mental health. The natural implication is that the pure pharmacological model can explain only part of the mental health picture.

What, then, is the alternative? By implication, we should be looking for a hybrid model, a middle-way, that combines the precision, potency and cost-effectiveness of biomedicine with the depth of insight and roundedness of psychology. There is already evidence that SSRIs, in combination with evidence-based psychotherapies, offer (marginally) superior efficacy over either treatment alone[5] – but should our search stop here?