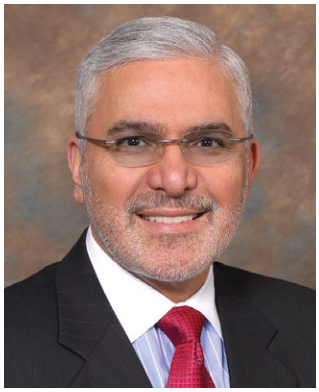

Henry A. Nasrallah, MD
Editor-in-Chief

For couples seeking to conceive, offer advice on reducing the risk of schizophrenia in their child

A couple who wants to have a child recently approached me because they were worried about the husband's family history of schizophrenia.

I explained to them that schizophrenia is a neurodevelopmental syndrome that comprises hundreds of different disorders of genetic or non-genetic etiology, all of which share a similar psychotic phenotype. Although the various genetic causes of schizophrenia are difficult to prevent—but may be prevented in the future with epigenetic techniques—the many non-genetic (environmental) pathways to schizophrenia can be avoided to significantly reduce the incidence of schizophrenia by 40% to 50%, according to some estimates.

I will share what I told this couple, because even couples without any family history of psychosis may have a child who develops schizophrenia because of a variety of environmental risk factors.

Many non-genetic (environmental) pathways to schizophrenia can be avoided to significantly reduce the incidence of this disorder

Genetic risk factors

One-half of the 20,000 genes in the 23 chromosomes of the human genome participate in constructing and sculpting the extremely intricate and complex human brain. There are many ways that genetic factors can increase the risk of schizophrenia,[1] and only some are transmitted by parents:

Risk genes. More than 30 risk genes have been identified as heritable in schizophrenia. They are spread over many chromosomes and more are likely to be discovered. Most of those risk genes regulate glutamate—not dopamine—pathways, and each increases the risk by 2% to 4%.

Copy number variations (CNVs) are produced via meiosis mishaps, where 1 or 3 alleles of certain genes are formed instead of the usual 2. A high frequency of CNVs have been found in schizophrenia compared with the general population—but also are found in autism and bipolar disorders—and are believed to disrupt brain development in various ways.

De novo mutations. Recent studies on large samples of people with schizophrenia (50,000 to 100,000) uncovered a much higher rate of mutations (some code for proteins while others are nonsense mutations that code for nothing). Obviously, these mutations led to anomalous neurodevelopment.

There are hundreds, maybe thousands, of genetic subtypes within the schizophrenia syndrome. Advances in epigenetics, which allow silencing of culprit genes or overexpression of protective genes, one day may enable psychiatric geneticists to prevent schizophrenia in fetuses at risk.

continued

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From the Editor

Non-genetic risk factors

Just as with the genetic pathogenic heterogeneity, the schizophrenia syndrome can be caused by numerous environmental adverse events,[2] many of which can be avoided, including:

Older paternal age (>45) at time of conception doubles or triples the risk of schizophrenia[3] as well as autism and bipolar disorder. Aging sperm are associated with a higher rate of DNA fragmentation and genetic mutations.

Prenatal complications, especially during the second trimester when CNS development takes place. These adverse prenatal events skew fetal brain development to produce psychosis in adulthood and can be minimized with optimal prenatal care, which sadly is lacking among the poor. These include:

- Vaginal infections before pregnancy,[4] such as herpes simplex virus, can cause fetal brain inflammation and increased risk of schizophrenia.
- Infections during pregnancy—whether bacterial, viral, or protozoan (*Toxoplasma gondii*)—have been shown to significantly increase the risk of schizophrenia in offspring.[5] An increase in serum C-reactive protein during pregnancy also is a biomarker of increased risk.
- Poor diet, especially starvation, can double or triple the risk of schizophrenia.
- Vitamin deficiency, especially folate and vitamin D, are critical for normal brain development.[6] Vitamin D is vital to mitigate neuroinflammation.
- Smoking before and during pregnancy.[4]
- Medical illness during pregnancy, especially gestational diabetes, increases the risk of schizophrenia in the fetus by 800%.[7]
- Severe stress during pregnancy, such as the death of the spouse, doubles the risk of schizophrenia.[2]
- Schizophrenia risk is 400% to 500% higher among those born and raised in an urban area, compared with a rural area.[8]
- Babies born in northern latitudes, such as in Sweden, Norway, or Canada, have a 10-fold risk of schizophrenia in adulthood compared with babies born near the equator.[6] This has been attributed to lack of sunshine and the risk of severe vitamin D deficiency in northern latitudes.
- High maternal body mass index during the first trimester[7] increases the child's risk of schizophrenia.
- Low number of prenatal visits is associated with higher risk of schizophrenia.
- Obstetric complications that cause hypoxia and a low Apgar score after birth increase the risk of schizophrenia. This includes long labor, cord around the neck, meconium spillage into the amniotic fluid, and mechanical injury with forceps delivery.
- Infection in the newborn shortly after birth.

Severe physical or sexual abuse before age 5 is associated with increased risk of schizophrenia in adulthood.[2] This may be because of stress-induced epigenetic mechanisms (silencing or overexpressing certain genes).

Migration has been shown to increase the risk of schizophrenia by 3 to 5 fold. The exact reason is unclear, but it could be a combination of social stress, exposure to new types of germs, less sunshine, and even a different diet.

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From the Editor
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The advice offered here can also reduce a child's risk of autism, bipolar disorder, mental retardation, and attention-deficit/hyperactivity disorder

My advice to the couple? Get a good obstetrician well before conception; get the mother immunized against infections; eat a lot of fish (omega-3 fatty acids); take adequate doses of folate and vitamin D, perhaps even choline[9]; avoid smoking before and during pregnancy; adopt a healthy, balanced diet; avoid excessive weight gain and/or gestational diabetes; avoid contact with people with infections; avoid exposure to cat feces (toxoplasmosis); schedule frequent prenatal visits; and hope for a smooth and uneventful delivery and a newborn with an Apgar score of 9 or 10. All this will greatly reduce the non-genetic risks of schizophrenia, but is unlikely to modify the genetic risks. However, it has been shown that a combination of both genetic and non-genetic risk factors is associated with a more severe form of schizophrenia.[10]

Optimal prenatal and postnatal care can be helpful for couples with a family history of schizophrenia (without moving to deliver their baby in a rural village near the equator). However, if their child starts using marijuana during adolescence, all bets are off. The risk of schizophrenia and serious cortical tissue loss increases dramatically when a carrier of risk genes use *Cannabis*. But that's another editorial, to be read by clinicians in states where marijuana has been (foolishly, I believe) legalized.

Henry A. Nasrallah, MD
Editor-in-Chief

References

1. Rodriguez-Murillo L, Gogos JA, Karayiorgou M. The genetic architecture of schizophrenia: new mutations and emerging paradigms. Annu Rev Med. 2012;63:63-80.
2. van Os J, Kenis G, Rutten BP. The environment and schizophrenia. Nature. 2010;468(7321):203-212.
3. Brown AS, Schefer CA, Wyatt RJ, et al. Paternal age and risk of schizophrenia in adult offspring. Am J Psychiatry. 2002;159(9):1528-1533.
4. Betts KS, Williams GM, Najman JM, et al. Maternal prenatal infection, early susceptibility to illness and adult psychotic experiences: a birth cohort study. Schizophr Res. 2014;156(2-3):161-167.
5. Brown AS, Derkits EJ. Prental infection and schizophrenia: a review of epidemiologic and translational studies. Am J Psychiatry. 2010;167(3):261-280.
6. Kinney DK, Teixeira P, Hsu D, et al. Relation of schizophrenia prevalence to latitude, climate, fish consumption, infant mortality, and skin color: a role for prenatal vitamin d deficiency and infections? Schizophr Bull. 2009;35(3):582-595.
7. Kawai M, Minabe Y, Takagai S, et al. Poor maternal care and high maternal body mass index in pregnancy as a risk factor for schizophrenia in offspring. Acta Psychiatry Scand. 2004;110(4):257-263.
8. Kelly BD, O'Callaghan E, Waddington JL, et al. Schizophrenia and the city: a review of literature and prospective study of psychosis and urbanicity in Ireland. Schizophr Res. 2010;116(1):75-89.
9. Ross RG, Hunter SK, McCarthy L, et al. Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. Am J Psychiatry. 2013; 170(3):290-298.
10. Maynard TM, Sikich L, Lieberman JA, et al. Neural development, cell-cell signaling, and the "two-hit" hypothesis of schizophrenia. Schizophr Bull. 2001;27(3):457-476.