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Embryos Starved of Oxygen May Be 'Programmed' for Heart Disease

by Jean Friedman-Rudovsky on 13 February 2012, 5:00 PM

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Early risks. Fetal hypoxia can result from a variety of factors, including a mother living at high altitude, such as this woman in La Paz, Bolivia. Credit: Noah Friedman-Rudovsky

Heart disease has long been ranked the number one cause of death globally. Known as the silent killer, it stalks its prey from conception through adulthood, often striking without warning. A new study suggests that one risk factor may begin even before birth, showing how low oxygen in the womb—or fetal hypoxia—can impair the heart later in life.

Fetal hypoxia can be caused by a variety of factors. Mothers who live at high altitude, smoke, or develop diabetes during pregnancy can starve their embryos of oxygen. When fetal hypoxia is prolonged, the embryo's heart and vessels change: The walls of the heart and aorta grow thicker, and blood vessels may become less responsive to signals to relax, which makes it harder for blood to flow. Previous research had suggested that such adaptations, although they help the unborn baby survive, take their toll in adulthood, increasing the risk of cardiovascular disease.

But it's not clear precisely how this happens. Physiologist Dino Giussani and colleagues at the University of Cambridge in the United Kingdom theorized that hypoxia promotes harm in the womb primarily through stress caused when the low level of oxygen creates an overload of highly reactive molecules known as free radicals.

To test this idea, the team ran an experiment with four groups of pregnant rats: two sets undergoing hypoxic pregnancy and two controls. To create hypoxia, they placed pregnant rats in a chamber that kept their oxygen levels at 13%, rather than the norm of 21%, for the majority of their pregnancy. Some rodents (those in one of the two hypoxia groups and in one of the two control groups) were given vitamin C water daily for its antioxidant effects.

When the pups were born, the researchers noticed dramatic differences between the various groups. Rats born of hypoxic pregnancy with no vitamin C treatment showed increased thickening of the walls of the aorta—up to 170% above normal—and molecular markers of disease, such as an increase in the heart's heat shock proteins, a signal of cardiac oxidative stress. When the pups grew to adulthood, at about 4 months, their hearts pumped consistently harder and faster than normal, which, over the long term is a known predictor of eventual heart failure. The pups also showed obstructions in their large arteries, just as people developing cardiovascular disease do. These changes were not seen in newborn and adult offspring of hypoxic pregnancies treated with vitamin C, the team reports online today in *PLoS ONE*.

Giussani says that the findings show that fetal hypoxia programs both the heart and the circulation in adult life through oxidative stress in the womb. "Although a link between adverse conditions during pregnancy and cardiovascular disease in later life has been established for many years," he says, "what explains this link had remained an enigma."

The research is "fascinating," says physiologist David Barker of the University of Southampton in the United Kingdom and Oregon Health and Science University in Portland, who some consider the father of the fetal origins of adult diseases field, an offshoot of what's known as developmental programming. Much of the emphasis in the past has been on the long-term consequences of nutrition. The work by Giussani's team, he says, "points to the importance of one of the other challenges that the human fetus faces, that is, getting enough oxygen." Adds John Challis of the University of Toronto in Canada, "These are very exciting findings that take us several steps forward. ... Now that we understand the mechanism, we are much closer to being able to intervene." A leading researcher in developmental programming, Challis says this study opens the door to thinking about combating fetal hypoxia in humans with antioxidant therapy.

Giussani agrees that the ultimate goal is to identify a clinical intervention to prevent heart disease. He is quick to add, however, that vitamin C may not be the antioxidant of choice for humans because its effects on human fetal tissue have not been well studied. The next step, he says, is to take the research to the human level, specifically looking at the effect of pregnancy at high altitude —where there's less oxygen in every womb—and heart conditions later in life.

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