

The Prescient Placenta

The maternal-fetal interface plays important roles in the health of both mother and baby, even after birth.

By Christopher Coe | August 1, 2015



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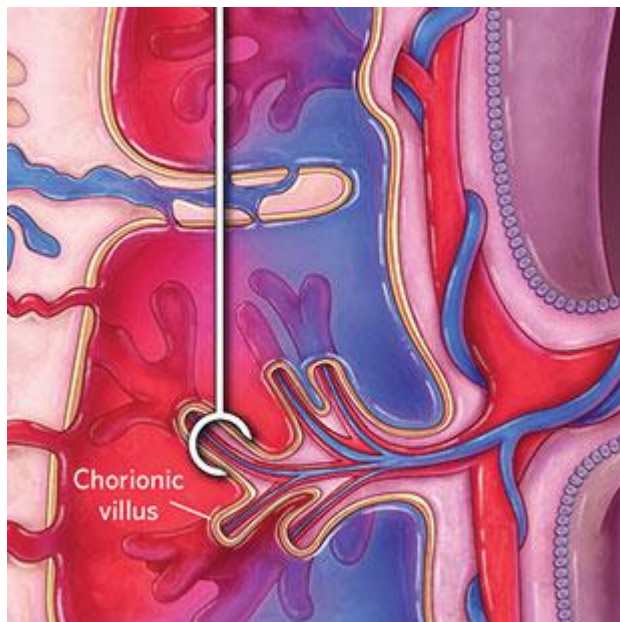
My career has been devoted to studying how early life events affect development, but for many years I focused on infancy and childhood. About 25 years ago, it became clear to me, and to many others, that critical maturational processes were actually initiated well before birth. Understanding how the placenta serves as the maternal-fetal interface is key to gaining additional insight into this critically important period in our lives.

The placenta is a distinctive and defining anatomical characteristic of mammals. Composed primarily of fetal tissue, it is the conduit through which maternally produced nutrients and oxygen enter the fetus and metabolic waste products return to the mother for excretion. It also enables a developing baby to guide pregnancy, from assisting in embryo implantation to helping maintain the gravid state and instructing the mother's body about what is needed for its well-being. Placental signaling can even calibrate the rate of fetal growth and influence the length of the pregnancy.

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Despite its vital importance, the placenta remains underappreciated by many because its relevance and life span are limited to the period before birth. In humans, the placenta and umbilical cord are usually removed quickly after delivery, and in most other mammals the afterbirth is usually consumed by the mother immediately after expulsion from the uterus. To advance our knowledge of placental structure and function, the National Institute of Child Health and Human Development (NICHD) last year launched a major research initiative called [The Human Placenta Project](#) to discover new ways to study, image, and monitor the placenta and to improve pregnancy outcomes.¹ In addition to in vivo research, bioengineering breakthroughs are allowing scientists to use placental cells and synthetic materials to mimic placental diffusion and transport processes in ex vivo microdevices, such as the aptly named placenta-on-a-chip introduced by an international team of researchers this June.² Together, these efforts will increase our understanding of how this responsive organ conveys information about both the external world and in utero conditions to the fetus.

Placental cross-talk



TWO-WAY STREET: The human placenta is the lifeline of the fetus. By bringing the maternal and fetal blood into contact, the placenta receives key nutrients and even delivers antibodies from the mother's immune system to the developing baby. But placental communication is bidirectional, and the fetus also sends messages back to its mother via the organ. Furthermore, the placenta itself becomes a major source of many hormones, such as estrogen, progesterone, and corticotrophin-releasing hormone (CRH).

See full infographic: [JPG](#) © EVAN OTO/SCIENCE SOURCE As a small ball of only 100 cells, the embryo implants in the uterus, with the trophoblast cells that will become the placenta leading the way. Proteins on their surface manipulate maternal leukocytes in the uterine wall, including T cells and natural killer cells, causing them to help engulf the embryo, instead of reject it. Then, as the placental tissues enlarge, trophoblasts recruit maternal monocytes and macrophages to attract and sculpt the maternal blood supply, creating a vascular communication system that will last throughout pregnancy.

Once linked with the mother's circulatory system, the placenta begins to secrete hormones that will actively stimulate and synergize with the mother's endocrine system to maintain her gravid state. This signaling also influences the mother's physiology so as to engender an ideal

environment for the baby's development. For example, if the fetal compartment becomes hypoxic, vasodilation of maternal arteries can increase the fetus's supply of oxygenated blood.

The placenta is also able to regulate how much maternal hormone reaches the baby. During the first half of human gestation, while the fetal adrenal glands are very small, most of the cortisol in the fetus's circulation comes from the mother. But as the adrenals grow, the placenta produces an enzyme, called 11 β -hydroxysteroid dehydrogenase (11 β -HSD), which converts some maternal cortisol to cortisone, a less-active form of corticosteroid. Similarly, the placenta regulates hormone interactions that start on the fetal side and affect the mother. As pregnancy progresses, dehydroepiandrosterone (DHEA) released from the fetal adrenal glands is used by the placenta as a substrate to produce estrogen. Released into maternal circulation, this estrogen has many functions, including acting with maternal prolactin to get breast tissue ready to produce milk. In fact, during the latter months of pregnancy, the majority of the estrogen and progesterone in a woman's blood comes from the placenta, with relatively little secreted by her ovaries.

Placental communication also has a significant role in priming the immune system of the fetus, training it to tolerate certain stimuli and thereby preventing harmful reactions. In this way, the maturing white blood cells of the fetus learn not to attack the small number of maternal lymphocytes that, because of the proximity of the maternal and fetal blood vessels, inadvertently cross into fetal circulation.

While the placentas of all mammalian species secrete hormones and help train the fetal immune system, the placentas of primates have some unique functions. For example, only the placentas of monkeys, apes, and humans have the ability to synthesize corticotrophin-releasing hormone (CRH). In nonpregnant individuals, CRH is secreted by the hypothalamus to stimulate the pituitary and adrenal glands. But from the middle to the end of pregnancy, the placenta of higher primates also produces CRH. As CRH levels increase, the hormone helps to regulate fetal adrenal function. CRH is also one of several priming signals that will initiate labor. Thus, if placental CRH release gets too high during the third trimester, it can precipitate premature birth. (See "[Why So Soon?](#)," *The Scientist*, May 2013.)

Another distinctive feature of the primate placenta is that it can actively transfer maternal antibodies to the fetus. All mammalian mothers provide protective antibodies to their offspring, but many animals such as cows, horses, and pigs deliver these antibodies largely after birth in breast milk. In contrast, the placenta of higher primates expresses a receptor for immunoglobulin of the G subtype (IgG), the mother's memory antibody against viruses and bacteria to which she has been exposed. The placenta binds IgG antibodies circulating in the maternal bloodstream and transfers them to the fetus, typically at an accelerated pace during the final weeks of pregnancy. When our research group quantified maternal antibody levels in the blood of newborn rhesus monkeys and chimpanzees, we found them to be equivalent to that of an adult.³ In humans, this placental IgG transfer is even more active: infants are usually born with concentrations of blood antibody that are twice that of their mothers. These prenatally acquired antibodies provide the infant with three to six months of immune protection after delivery, eliminating the immediate need for the infant to generate new antibodies.

Given the intimate relationship between placental signaling and fetal health, it should come as no surprise that disruptions to this essential line of communication between mother and

baby can lead to serious problems, such as a miscarriage or lifelong impairments in the child. It is known that some allergens, certain food proteins, environmental pollution, and cigarette smoke crossing the placenta can initiate immune biases, which increase the risk for allergies and asthma in children. Researchers are also discovering that a number of neurodevelopmental conditions, including autism spectrum disorders, may be initiated in utero. Many of these prenatal programming effects are likely mediated by alterations in placental physiology and function. Currently, laboratories around the world are investigating how the placenta contributes to the fetal blueprint that governs later development and health.

An ironclad connection

My own research focuses on another important aspect of placental function: iron transfer. The transferrin receptor, located in the outermost cell layer of the placenta's chorionic villi, shuttles maternal iron into the fetal blood supply. (See [illustration](#).) In monkeys and humans, about 50 percent of the iron that a baby will need for postnatal growth must be acquired in this way before birth. The remaining iron allotment will come in breast milk during nursing. But when the prenatal endowment is low, the lactating mother does not have a compensatory mechanism to increase iron concentrations in her milk.

By tracking iron levels of infant monkeys up to one year of age, my colleagues and I showed that neonatal iron status was a strong predictor of the risk for anemia.⁴ To track placental iron transfer at the source, less common isotopic forms of iron, such as ⁵⁷Fe and ⁵⁸Fe, can be given safely to a pregnant female or infant.⁵ When these are administered intravenously to or consumed orally by a pregnant woman or monkey, it is possible to quantify how much of the iron isotope becomes incorporated into the red blood cells (RBCs) of the fetus after the iron crosses the placenta. For months after birth, residual traces of this maternally-derived iron can be detected in the infant's RBCs. In ongoing research with monkeys, we found that the iron isotope transferred by the placenta was recycled after birth, allowing the infant to conserve and continue to benefit from the prenatally acquired iron.

A healthy diet during pregnancy and quality prenatal care are important for ensuring sufficient fetal iron levels, but there is also a less obvious intervention that involves the placenta.

Cord blood collected from human infants at delivery can also yield valuable information about their iron status. In collaboration with [Pamela Kling](#), a neonatologist at the University of Wisconsin, our team found that maternal obesity and large weight gains of more than 45 pounds during pregnancy can interfere with the transfer and storage of iron in the fetus.^{6,7} This fetal iron deficiency was magnified if an overweight woman progressed to gestational diabetes, because she was then prone to birthing a particularly large infant, who used up more of the iron transferred by the placenta. Other researchers have shown that the placenta cannot sufficiently upregulate the expression of transferrin receptors in a diabetic pregnancy to compensate for the fetal iron deficiency. Like infant monkeys with low iron levels, iron-deficient human infants are more prone to become anemic by one year of age, and their iron status should be checked by six months of age, rather than at the normal well-baby visit at one year.

A healthy diet during pregnancy and quality prenatal care are important for ensuring sufficient fetal iron levels, but there is also a less obvious intervention that involves the placenta, and takes advantage of its final functions at delivery. Both immediately and for a

few minutes after the placenta is passed from the mother, a large amount of blood is transferred to the neonate. It is essentially a transfusion that can reach volumes of 80–100 mL, a meaningful volume for a newborn infant who has just 300 to 500 mL of blood in his or her whole body. During the usual hospital delivery, much of this blood transfer from the placenta is prevented when the doctor clamps the cord, but we and others have shown that allowing this transfer can benefit babies.⁸ Specifically, the iron present in the hemoglobin of the transferred RBCs can later be scavenged by the infant's macrophages and recycled as the RBCs senesce. For preterm infants, there also appear to be other collateral benefits of a short delay in cord clamping, including a reduced risk for hemorrhage in the fluid-filled areas of the brain, a major cause of brain damage and cerebral palsy in premature infants.

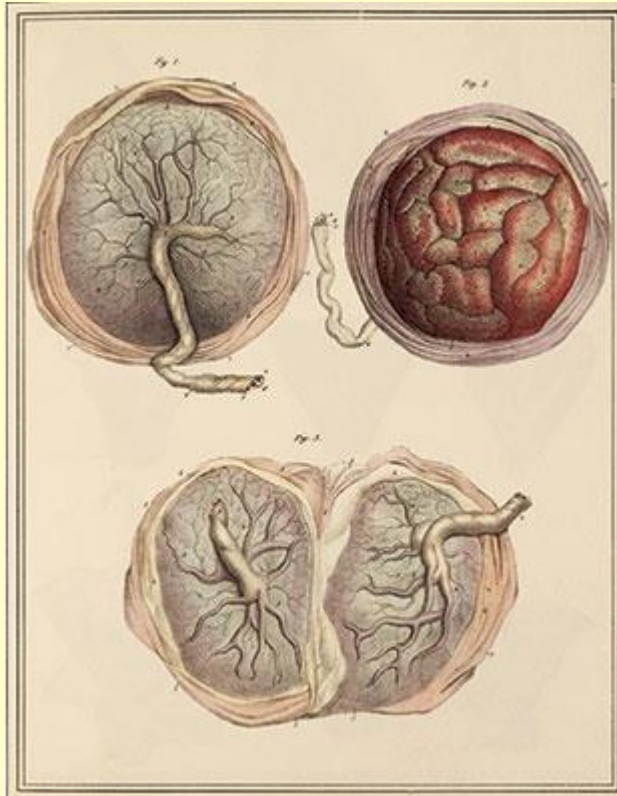
In animals, the placenta has one other final, sacrificial act that benefits both the mother and newly born infant. Most female animals will consume the placenta after it has passed at delivery. This behavior, called placentophagia, exists in all nonhuman primates, even the folivorous species that normally consume only leaves and fruit. In addition to assisting in separating the placenta and umbilical cord from the infant, this behavior is also thought to help establish the mother-infant relationship. While the exact biochemical signals remain unknown, the placenta contains hormones and neurotransmitters that likely help initiate maternal care and bonding. A monkey infant delivered by C-section and cleaned by the veterinarian before being returned to its mother is much less likely to be accepted by her. Birthing the infant and consuming the placenta seem to be potent factors in promoting solicitous care by the new mother and making the infant appear more attractive.

Respect the placenta

From the first moments of implantation to the provision of extra blood after delivery, the placenta is essential to fetal survival and infant well-being. While we are only just beginning to unravel the diverse secrets of the placenta, including how it first came into existence in our early mammalian ancestors (see “The Evolution of the Placenta” below), one thing is clear: the placenta must strike a delicate balance, buffering the fetus from external insults while conveying nutrients and information about the world and the mother's state of health.

Given the vital, life-sustaining role of the placenta, perhaps it is not surprising that some cultures view the organ as integral to who we are, and believe that it should be saved after birth. In some cases, the placenta is stored in special vessels or ritually buried, allowing people to be reunited with it at the end of their lives. Even from the perspective of biology, we should be in awe of how effectively the placenta nourishes and nurtures us during its brief life span. It prepares us to enter the world and even helps in the decision about when the time is right to make that critical leap.

THE EVOLUTION OF THE PLACENTA



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The placenta is a defining feature of living mammals. But 200 million years ago, the first warm-blooded mammals still laid eggs, like the modern platypus. In the late 1990s, researchers discovered that the capacity to fuse embryonic and fetal tissues into a placenta was initially achieved by integrating genetic material from ancient retroviruses into the mammalian genome (*Phil Trans R Soc B*, 368:20120507, 2013). The immune-suppressive actions of those genes continue to allow the modern placenta to exert its immunomodulatory effects on the uterine endometrium. That function became increasingly important as the placenta of primates evolved to penetrate more deeply into the uterus, becoming closer to the maternal blood supply and thus increasing exposure of the mother's immune system to fetal cells and proteins.

Across live-bearing species in the animal kingdom, the placenta has evolved a number of different shapes and depths of penetration (*PNAS*, 103:3203-08, 2006). In ancestral primates, a tissue barrier provided a more-defined separation between the maternal and fetal blood supply. Modern prosimians still have such a barrier. But one of the anatomical traits distinguishing monkeys, apes, and humans is the hemochorial placenta, which penetrates deeply into the uterine wall and establishes a more intimate interface between the mother and her fetus. This placental connection, and the lengthening of gestation, set the stage for more-prolonged nursing and care after birth. In this way, the intimate mother-child relationship embodied by the placenta presages the parental one that will subsequently emerge.

Christopher Coe is a professor at the University of Wisconsin–Madison and director of the Harlow Center for Biological Psychology. He has published more than 240 papers on early development and maternal-fetal and mother-infant relationships in animals and people.

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