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Silent Struggle: A New Theory of Pregnancy

By CARL ZIMMER

Pregnancy can be the most wonderful experience life has to offer. But it can also be dangerous. Around the world, an estimated 529,000 women a year die during pregnancy or childbirth. Ten million suffer injuries, infection or disability.

To David Haig, an evolutionary biologist at Harvard, these grim statistics raise a profound puzzle about pregnancy.

"Pregnancy is absolutely central to reproduction, and yet pregnancy doesn't seem to work very well," he said. "If you think about the heart or the kidney, they're wonderful bits of engineering that work day in and day out for years and years. But pregnancy is associated with all sorts of medical problems. What's the difference?"

The difference is that the heart and the kidney belong to a single individual, while pregnancy is a two-person operation. And this operation does not run in perfect harmony. Instead, Dr. Haig argues, a mother and her unborn child engage in an unconscious struggle over the nutrients she will provide it.

Dr. Haig's theory has been gaining support in recent years, as scientists examine the various ways pregnancy can go wrong.

His theory also explains a baffling feature of developing fetuses: the copies of some genes are shut down, depending on which parent they come from. Dr. Haig has also argued that the same evolutionary conflicts can linger on after birth and even influence the adult brain. New research has offered support to this idea as well. By understanding these hidden struggles, scientists may be able to better understand psychological disorders like depression and autism.

As a biologist fresh out of graduate school in the late 1980's, Dr. Haig decided to look at pregnancy from an evolutionary point of view. As his guide, he used the work of Robert Trivers, an evolutionary biologist at Rutgers University.

In the 1970's, Dr. Trivers argued that families create an evolutionary conflict. Natural selection should favor parents who can successfully raise the most offspring. For that strategy to work, they can't put too many resources into any one child. But the child's chances for reproductive success will increase as its care and feeding increase. Theoretically, Dr. Trivers argued, natural selection could favor genes that help children get more resources from their parents than the parents want to give.

As Dr. Haig considered the case of pregnancy, it seemed like the perfect arena for this sort of conflict. A child develops in intimate contact with its mother. Its development in the womb is crucial to its long-term health. So it was plausible that nature would favor genes that allowed fetuses to draw more

resources from their mothers.

A fetus does not sit passively in its mother's womb and wait to be fed. Its placenta aggressively sprouts blood vessels that invade its mother's tissues to extract nutrients.

Meanwhile, Dr. Haig argued, natural selection should favor mothers who could restrain these incursions, and manage to have several surviving offspring carrying on their genes. He envisioned pregnancy as a tug of war. Each side pulls hard, and yet a flag tied to the middle of the rope barely moves.

"We tend to think of genes as parts of a machine working together," Dr. Haig said. "But in the realm of genetic conflict, the cooperation breaks down."

In a 1993 paper, Dr. Haig first predicted that many complications of pregnancy would turn out to be produced by this conflict. One of the most common complications is pre-eclampsia, in which women experience dangerously high blood pressure late in pregnancy. For decades scientists have puzzled over pre-eclampsia, which occurs in about 6 percent of pregnancies.

Dr. Haig proposed that pre-eclampsia was just an extreme form of a strategy used by all fetuses. The fetuses somehow raised the blood pressure of their mothers so as to drive more blood into the relatively low-pressure placenta. Dr. Haig suggested that pre-eclampsia would be associated with some substance that fetuses injected into their mothers' bloodstreams. Pre-eclampsia happened when fetuses injected too much of the stuff, perhaps if they were having trouble getting enough nourishment.

In the past few years, Ananth Karumanchi of Harvard Medical School and his colleagues have gathered evidence that suggests Dr. Haig was right. They have found that women with pre-eclampsia had unusually high levels of a protein called soluble fms-like tyrosine kinase 1, or sFlt1 for short.

Other labs have replicated their results. Dr. Karumanchi's group has done additional work that indicates that this protein interferes with the mother's ability to repair minor damage to her blood vessels. As that damage builds up, so does her blood pressure. And as Dr. Haig predicted, the protein is produced by the fetus, not the mother.

"When I first came across David Haig's hypothesis, it was absolutely cool," said Dr. Karumanchi. "And it made me feel like I might be on the right track."

Dr. Haig is now collaborating with Dr. Karumanchi and his Harvard Medical School colleagues to understand more about how exactly sFlt1 may cause pre-eclampsia. They describe their research in the latest issue of Current Topics in Developmental Biology.

Dr. Haig also made some predictions about the sorts of maternal defenses that have evolved. One of the most intriguing strategies he proposed was for mothers to shut down some of the genes in their own children.

This strategy takes advantage of the fact that most of the genes we carry come in pairs. We inherit one copy from our mother and one from our father. In most cases, these pairs of genes behave identically. But in the past 15 years, scientists have identified more than 70 pairs of genes in which the copy from one parent never makes a protein. In some cases, a parent's gene is silenced only in one organ.

Scientists do not fully understand this process, known as genomic imprinting. They suspect that it is made possible by chemical handles called methyl groups that are attached to units of DNA. Some handles may turn off genes in sperm and egg cells. The genes then remain shut off after a sperm fertilizes an egg.

Only a few of these genes have been carefully studied to understand how they work. But the evidence so far is consistent with Dr. Haig's theory. One of the most striking examples is a gene called insulin growth factor 2 (Igf2). Produced only in fetal cells, it stimulates rapid growth. Normally, only the father's copy is active. To understand the gene's function, scientists disabled the father's copy in the placenta of fetal mice. The mice were born weighing 40 percent below average. Perhaps the mother's copy of Igf2 is silent because turning it off helps slow the growth of a fetus.

On the other hand, mice carry another gene called Igf2r that interferes with the growth-spurring activity of Igf2. This may be another maternal defense gene. In the case of Igf2r, it is the father's gene that is silent, perhaps as a way for fathers to speed up the growth of their offspring. If the mother's copy of this second gene is disabled, mouse pups are born 125 percent heavier than average.

A number of other imprinted genes speed and slow the growth of fetuses in a similar fashion, providing more support for Dr. Haig's theory. And in recent years, some medical disorders in humans have been tied to these imprinted genes. Beckwith-Wiedemann syndrome, for example, causes children to grow oversize organs that are prone to developing tumors. Some cases of the disorder have been tied to a mutation that replaces a mother's silent copy of Igf2 with an extra copy of the father's.

"Both of the copies come from the father, and you get double the amount of Igf2, " said Dr. Haig. The extra Igf2 appeared to cause a fetus to grow too quickly, leading to the syndrome.

Dr. Haig's work is now widely hailed for making sense of imprinted genes. "Molecular biologists had it worked out in exquisite detail, but they had no idea why it existed," said Kyle Summers, a biologist at East Carolina State University. "Haig just comes in and says, 'I know why this is happening,' and explained it."

Dr. Haig has recently been exploring his theory's implications for life after birth. "I think it can influence all sorts of social behaviors," he said.

Scientists have found that some genes are imprinted in the brain after birth, and in some cases even in adulthood. "Imprinted genes and behavior are the new frontier," said Dr. Lawrence Wilkinson of the University of Cambridge. In a paper to be published in The Philosophical Transactions of the Royal Society of London, Dr. Wilkinson and his colleagues argue that the evidence on imprinted brain genes — preliminary as it is — fits with Dr. Haig's theory. They call it "the most robust evolutionary hypothesis for genomic imprinting."

One major source of conflict after birth is how much a mother will feed any individual offspring. A baby mammal is more likely to thrive if it can get more milk from its mother. But nursing demands a lot of energy from mothers that could be used for other things, like bearing and nursing more offspring.

It turns out that a number of imprinted genes are active in the brain, where they might influence how babies behaved toward their mothers. One strong candidate for that role in mice is a gene known as GnasXI. Normally the mother's copy of the gene is silent. If the father's copy is not working, mouse pups are weak sucklers. They draw so little milk that by 9 days old, they are a quarter of the weight of

normal mice. Switching off the father's copy of GnasXI may be putting a brake on the aggressive nursing of their pups.

Some genes continue to be imprinted in the brain even in healthy adults. Dr. Haig has proposed that the evolution of these genes has been shaped by the groups in which mammals live.

In many mammal species, females tend to stay in the groups where they are born and males leave. As a result, females tend to share more genes with other members of their group than males. A conflict may emerge between maternal and paternal genes over how the members of the group should act. Maternal genes may favor behavior that benefits the group. Paternal genes may favor behavior that benefits the individual.

"You have to think about resources in a different way," Dr. Wilkinson said. "Instead of thinking about foodstuffs, you have to think about social resources. Your mom and dad want different things from your behavior."

Dr. Wilkinson and his colleagues are beginning to identify genes that may play this role. One, known as Nesp55, is active in mouse brains. The father's copy of the gene is silent. Dr. Wilkinson and his colleagues found that disabling the mother's Nesp55 gene makes mice less likely to explore a new environment. Normally, the mother's copy of Nesp55 may encourage the mice to take more risks on behalf of the group, whether that risk involves looking for food or defending the group. "It's a possibility, but it needs to be proved," said Dr. Wilkinson.

Dr. Wilkinson suspects that conflict between imprinted brain genes may add to the risk for mental disorders, from autism to depression. Because one copy of each of these genes is silenced, they may be more vulnerable. "If you ask me, do I think that imprinted genes are likely in the next 10 years to crop up as mechanisms in mental disorders, I'd say yes," he said.

Dr. Haig has enjoyed watching his theory mature and inspire other scientists. But he has also had to cope with a fair amount of hate mail. It comes from across the political spectrum, from abortion opponents to feminists who accuse him of trying to force patriarchy into biology.

"People seem to think, 'He must have a political agenda,' " Dr. Haig said. "But I'm not talking at all about conscious behaviors. I'm just interested in these mechanisms and why they evolved."