

Published in *Cosmos Magazine*, 30 January 2019

## **Excess insulin is toxic to placental cells, study finds**

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While investigating possible causes of unexplained pregnancy loss, US researchers have discovered that insulin is toxic to first trimester placental cells.

It has long been known that women with insulin resistance have higher rates of pregnancy loss, according to the study's senior author, Zev Williams, Director of Columbia University Fertility Center in New York.

However, the culprit was thought to be glucose; "that if you have high glucose then somehow that causes the pregnancy loss," Williams says.

"What we found though, which was really surprising, is that insulin itself is actually directly toxic to the early placenta."

The findings are reported in a [paper](#) published in the journal *Fertility and Sterility*.

Although the study was conducted *in vitro* – in test tubes – insulin levels were matched to those found in women with insulin resistance. One reason the findings were unexpected is that insulin is a growth factor.

"If I take a liver cell or a skin cell or a muscle cell, and I grow those cells in the presence of insulin, those cells love it – they grow better," explains Williams.

"The only cell that we found that actually has this effect are the cells from the first trimester placenta."

Further tests revealed that the effect of insulin on placental cells mimics therapeutic doses of chemotherapy on normal cells, causing DNA damage and cell death.

When they grew the cells in the presence of metformin – a drug widely used to manage blood sugar levels in people with diabetes – with the same insulin levels that were toxic, the insulin's damaging effects were completely blocked.

"So what's encouraging about the data and the findings, is it doesn't just point out a cause for pregnancy loss, but it immediately offers an opportunity to intervene," Williams says.

The first path of intervention, he adds, would be a low carbohydrate, low sugar diet, to prevent sugar spikes that trigger excess insulin being released by the pancreas to keep blood glucose levels down.

On the heels of this discovery, Williams' team started testing insulin levels along with blood glucose in women who had experienced unexplained miscarriages. They found that some women with normal glucose levels were making "sky high" levels of insulin to maintain those blood sugar levels.

After following a low carbohydrate, low sugar diet, and taking metformin, their subsequent pregnancies were normal.

"So if we're able to replicate this in large clinical trials, it would suggest that the way we've been screening patients may be wrong," Williams says. "We've been screening by measuring sugar levels, but what we might need to be doing is actually measuring the insulin levels."

The [placenta](#), Williams says, is "this incredible structure that has to function like the lungs, the kidneys, the liver; it's an immune system, it's its own endocrine organ, and it has this incredibly complex, intricate role in early pregnancy."

Importantly, it's also very good at taking oxygen and nutrients from the mother.

Williams' working hypothesis is that because calories have typically been restricted throughout the bulk of history, the placenta is tuned to extract as much sugar from the mother as possible to meet the baby's needs.

"In our current diet there's no lack of calories, and there's no lack of ready supply of glucose and carbohydrates. But the placenta isn't really adapted to living in the nutrition environment we live in today.

"The signal for the placenta to extract nutrition is when there is insulin present in the mother. So the placenta has an overly robust reaction to it – it's like it's got a faucet turned all the way up. At least that's our current thinking on this."

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