What marsupials taught us about embryo implantation could help women using IVF

July 28 2017, by Oliver Griffith

Credit: Ryan Snyder, CC BY

What do a swollen sprained ankle and a new pregnancy have in common? Believe it or not, they're both closely tied to the body's

inflammation response.

Inflammation is usually the first reaction of the immune system to the presence of injury or infection. It's characterized by local swelling, fever and pain.

Interestingly, inflammation is also key to how a pregnancy begins and ends. It facilitates the implantation of the embryo in the mother's uterus and then eventually the baby's birth. (Inflammation at the time of implantation might be one of the causes of morning sickness.)

But scientists have typically thought of pregnancy as an anti-inflammatory process. The mother's immune system must be suppressed so it doesn't attack and destroy the developing fetus as an unwanted intruder. After all, it contains the father's foreign DNA. Inflammation through the middle of gestation is a major risk to the pregnancy, and can result in miscarriage.

It's been a medical paradox: Why does the body use inflammation to regulate normal physiological processes of pregnancy when it's also one of the biggest threats to the maintenance of pregnancy?

In our research published in the *Proceedings of the National Academy of Sciences*, my collaborators at Yale University and the Eunice Kennedy Shriver National Institute of Child Health and Human Development used an evolutionary perspective to identify why inflammation is used to facilitate implantation in humans. Our close look at opossums could have medical implications for women struggling to conceive, including better success rates using IVF.

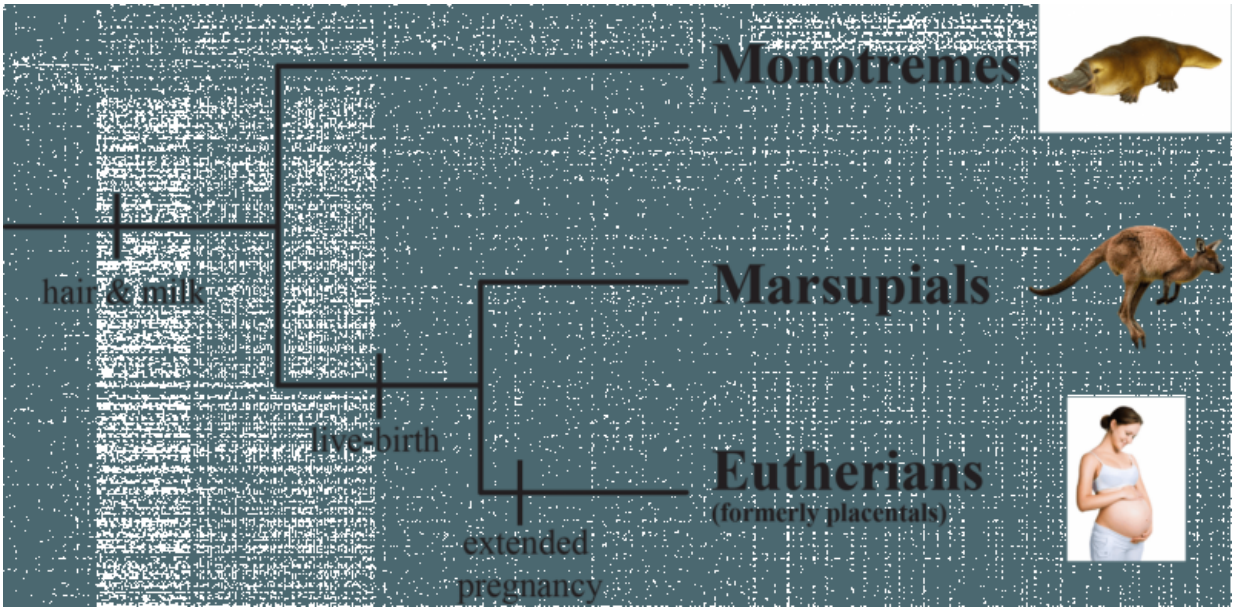
An evolutionary perspective on the paradox

The first mammals on Earth laid eggs. Eventually live birth evolved

more than 160 million years ago in a common ancestor of humans and marsupials.

Marsupial pregnancy shares common features with both egg-laying mammals (monotremes, including the platypus) and eutherian mammals (formerly referred to as placental mammals). Since it's partway between those two, we think marsupial pregnancy likely reflects the reproductive biology of the first live-bearing mammals.

Our research looked at pregnancy in the grey short-tailed opossum as a model for the ancestral condition. Specifically, we wanted to know if they had any hints of inflammation during pregnancy.



Relationship between the major groups of mammals alive today. Monotremes lay eggs. Marsupials give birth to live young but have very short pregnancies, with embryo and maternal tissues separated by an eggshell for most of the time. A short-lived placenta does form, however. Eutherian mammals have an extended pregnancy including a placenta, and give birth to relatively well developed young. Credit: Oliver Griffith, CC BY-ND

Opossum pregnancy is short, lasting only 14 days. For 12 of those days the embryo is separated from the maternal tissue by an eggshell.

To break out of the eggshell, the embryo produces digestive enzymes which essentially dissolve the shell from the inside out. But even once the shell is gone, the embryo continues secreting these enzymes, causing damage to the lining of the uterus.

We found that the loss of the eggshell, and formation of a placenta, coincides with a massive inflammatory reaction by the mother to the presence of the fetus.

An extended period of inflammation is not compatible with pregnancy, so for a longer pregnancy to evolve (like our own) something needed to change. During the evolution of an extended pregnancy, rather than prevent inflammation during the period of embryo attachment, the body's inflammation response has been repurposed – possibly as a way for the female to respond quickly to the presence of an embryo.

A new use for inflammation

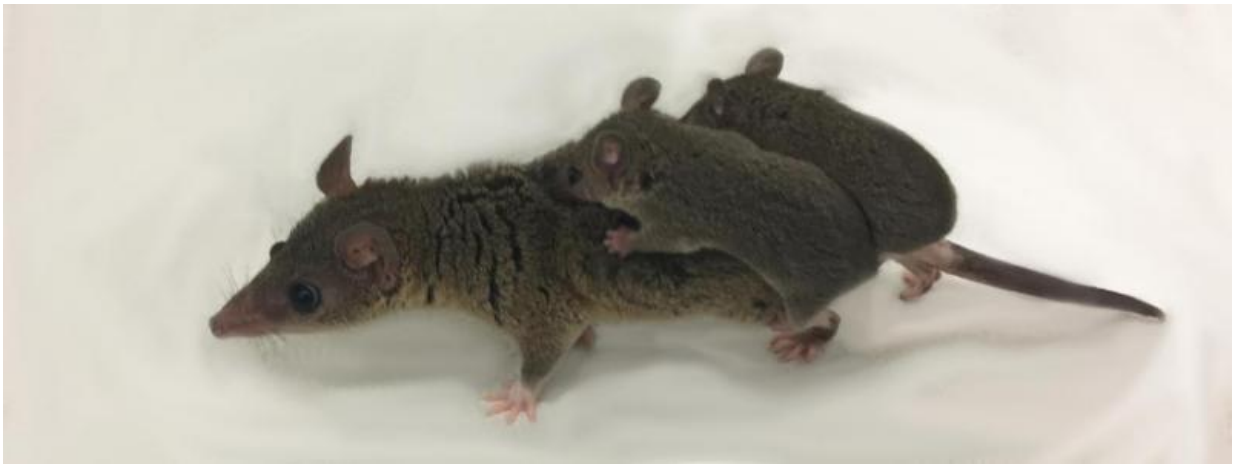
The inflammation that results from maternal-fetal interaction in the opossum provides a clue for why inflammation is used during implantation in eutherian mammals like ourselves.

We suggest that inflammation has been repurposed as a way for the mother and fetus to communicate. Inflammation is one of the first changes that occurs following attachment of the embryo to the uterine wall in women. This inflammation signals to the rest of the uterus to prepare itself for pregnancy.

Rather than evolving a whole new way for the embryo to tell the uterus to get ready for an extended pregnancy, evolution has modified the inflammation response to be a method of communication. Now it's a way for the mother to detect the presence of the embryo, allowing her to support implantation and establish pregnancy.

Once the inflammation gets started in humans, it's readily controlled and the uterus switches to an anti-inflammatory state. We think the ability to make this shift during gestation was a key innovation in eutherian mammals, allowing for an extended pregnancy.

Our findings not only explain the paradox of why inflammation is used to regulate implantation and giving birth, but also provide a paradigm for understanding inflammation as a normal component of pregnancy. It's not only a response to injury – it's become a method of communication.



Grey short-tailed opossums provided a great model for how our own long pregnancies evolved. Credit: Oliver Griffith, CC BY-ND

Evolutionary view could increase IVF success

Historically doctors have thought of implantation as the process of the very early embryo attaching and embedding itself into the uterine wall. From this perspective, it looks like the success of implantation is primarily the embryo's responsibility – that is, how adept is this embryo at attaching and embedding?

With this idea in mind, reproductive technologies have traditionally invested resources into improving embryo viability as a way to facilitate implantation. Researchers have focused less on the mother's receptivity to implantation.

But in reality, implantation is a complex process regulated by both the fetus and the mother.

Our research provides a new framework to think about implantation as an evolved reaction of the mother's body to the presence of a fetus. Now we can start to build a bigger picture of how the molecular changes that support implantation fit together, adding to how researchers have typically relied on their understanding of individual genes and proteins as pieces of the puzzle.

We can now start to understand why doctors have observed for some time that suppressing inflammation (including by taking the anti-inflammatory drug ibuprofen) during implantation decreases the implantation success rate. Also, it might have seemed counterintuitive that scratching the uterus – inducing uterine inflammation – can actually increase implantation success for women. But now we have a new way to understand the job inflammation is doing.

In addition, IVF doctors use several molecular changes to detect a woman's receptivity to implantation in the clinic; we showed that

opossums experience the same molecular changes during embryo attachment. These molecular changes that are vital to both opossum attachment and human implantation must be fundamental to the process – if they occur in both species, they've remained unchanged for more than 160 million years. These processes that have lasted throughout evolution must be essential for reproductive fitness.

Our research allows us to identify important molecules for assessing uterine receptivity and potential drug targets for treating implantation disorders and provides a new way to think about implantation as a modified reaction of the uterus to the presence of a fetus.

More information: Oliver W. Griffith et al. Embryo implantation evolved from an ancestral inflammatory attachment reaction, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1701129114

This article was originally published on The Conversation. Read the original article.

Provided by The Conversation