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Pre-Eclampsia and the Developing Brain

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Abstract

Pre-eclampsia is a very common and potentially fatal pregnancy complication faced by millions of pregnant mothers worldwide every year. As well as affecting the mother, though, the disorder has been shown to have a harmful effect on the infant, including a negative influece on foetal brain development. Children born to a pregnancy affected by pre-eclampsia have a higher risk of neurodevelopmental disorders such as autism spectrum disorder, but, truthfully, we don't know why. This article describes the link between pre-eclampsia and foetal neurodevelopment - what we know and what we don't, and how our research is trying to uncover the mechanisms of the relationship between the two. Essentially, we are taking three approaches to this research question: growing neuron-like cells in the lab and modelling pre-eclampsia's effects on them; growing placental cells and stressing them in a way that mimics the placental pathology of pre-eclampsia; and analysing a large dataset from Finland which includes data on neurodevelopment from brain scans. Overall, these three strategies, little by little, are increasing our understanding of the elusive relationship between these two important disorders.

Keywords: pre-eclampsia, autism spectrum disorder, neurodevelopment, placenta.

An Unwelcome Surprise During Pregnancy

Maria is 35 years old and she is eight months pregnant. She has had severe headaches and blurring of her vision for a couple of weeks now, her hands and feet are swollen, she feels sick and has stomach pain that she puts down to indigestion. But she is starting to worry that something may be wrong, concerned more about her baby's health than her own. She goes to her GP who finds that her blood pressure is unusually high, so she is admitted to hospital where she is diagnosed with pre-eclampsia.

"I've never heard of pre-eclampsia before – is it common?"

Actually, yes, it is – in fact more than 10 million women are diagnosed with pre-eclampsia (PE) every year. It is surprising how many people have never heard of the condition, considering

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just how common and potentially serious it is – it affects about 5% of pregnancies and causes an estimated 76,000 maternal deaths every year (that is about the same as the total number of human deaths caused by snakes!). PE is a "hypertensive disorder of pregnancy", which means it involves chronically high blood pressure arising during, and because of, pregnancy. We still do not know exactly what causes PE, and the only cure is delivery of the baby and placenta. If left untreated, the mother can develop serious complications including liver or brain damage, or eclampsia, which is essentially PE with seizures, and often leads to death. Even when the mother recovers, her life-time risk has gone up for type 2 diabetes, kidney disease and cardiovascular disease.

And it is not just the mother who is affected by this serious disorder, but the baby too. It is a delicate process, the construction of a complete human from a tiny ball of cells, and a pre-eclamptic womb is no friendly place to grow up for these first 9 months of your life (or less, if the baby is delivered pre-term, which is often the case in PE). Unsurprisingly, PE is a leading cause of neonatal deaths – half a million every year – and even if the baby survives, just like the mother, they are more likely throughout their life to have high blood pressure, higher BMI, and cardiovascular disease. And we know that PE somehow affects the developing brain too, because children born to a mother with PE are at increased risk of autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and intellectual disability (ID) than their peers. These conditions are known as "neurodevelopmental disorders", which arise when the brain fails to develop along its normal path, and to understand how PE influences the risk of this happening, we must now depart from our talk of PE and instead have a look at the amazingly choreographed performance that is brain development.

Building a Brain

The brain truly is amazing. The seat of all your thoughts, ideas, memories, moods and desires, it controls your, sleep, breathing, eating and drinking, tells your muscles how to move, and creates a sensation of the world around you – it is, essentially, you. But where do brains come from? A weird question, but think about it – at conception you do not have a brain, and at birth you do. And the most amazing part of all is that the brain builds itself. Somehow, over the course of nine months, tens of billions of signal-sending neurons and hundreds of billions more support cells come into being, and create a complex network of tissue that self-folds into that one-kilogram masterpiece inside your head.

This journey starts very early on, only a few weeks into pregnancy, when a few embryonic cells make the decision to become brain-building cells. These cells form a tube, and then divide rapidly for the tube to grow in size. Over time, some of the cells in that tube decide to be neurons, which will then migrate around the brain, guided by signals from their neighbours, to find a specific place where they will stay forever; later on, some others still decide to become support cells and embark on their own journeys. The neurons grow long extensions called neurites, which, like the cells from which they grow, must navigate their way around the neural

tube to find other cells with whom they make connections. These processes, given the technical terms "neurogenesis", "gliogenesis", "migration", "axonal pathfinding" and "synaptogenesis", begin to change the central nervous system's architecture in such a way that, over time, it looks less and less like a tube, and more like a brain. The crucial point underpinning all this is that there is no foreman in control of it all, so each cell must make decisions based on its local environment. If that local environment changes (too much of a certain immune protein or toxin, too little of a certain hormone or nutrient) then the cell might divide too early, migrate to the wrong place, or grow neurites the wrong size and make inappropriate connections. These minor changes add up, sending the brain down a different path than it would normally take, with altering that person's emotional, social, language or intellectual development, and leads them to be diagnosed with a neurodevelopmental disorder.

Let's come back now to PE. While the disease is unfolding in the mother, and her baby's brain is busy constructing itself, something about PE is affecting neurodevelopmental processes in such a way that when we look at the population of children born to a healthy or a pre-eclamptic pregnancy, we see that the children exposed to PE have a 30-35% higher chance of being diagnosed with ASD, ADHD or ID. But how exactly it affects the developing brain – well, that's another matter. The short answer is we just don't know, but the not-so-short and not-so-defeatist answer is that we can look at the research that is out there and use this information to guide our own experiments to find out more. That is where our research comes in.

Where Do We Begin to Look for Answers?

There is a lot more going on in PE than just high blood pressure, including much that we do not fully understand yet, and we think that some of these other physiological changes can affect brain development. To understand what is happening in the foetal brain in PE, we are taking a few different approaches.

You cannot exactly peer into someone's brain as it develops, but you can grow neuron-like cells in a plate and peer easily into that. So that is what we do – we grow neuron-like cells and watch them as they develop; as they stretch, grow, respire, migrate, connect; we let them do what they do inside a developing brain, and we measure everything as it happens (Fig. 1A). Half these cells are given something to mimic PE (certain proteins, for example, or serum from women with PE), while the other half gets the equivalent from a healthy pregnancy, and we compare the results. Neurons are not exactly brains, but they are the functional units and protagonists of the brain, and these experiments are giving us some really interesting insights into what PE does to neuronal development. What we have found so far is that the serum from women with PE causes cells to use more oxygen and grow longer neurites than they normally would in a healthy pregnancy, and that this happens because women with PE have higher levels of an immune protein that affects neurons.

Although the exact cause of PE is still up for debate, we do know it has something to do

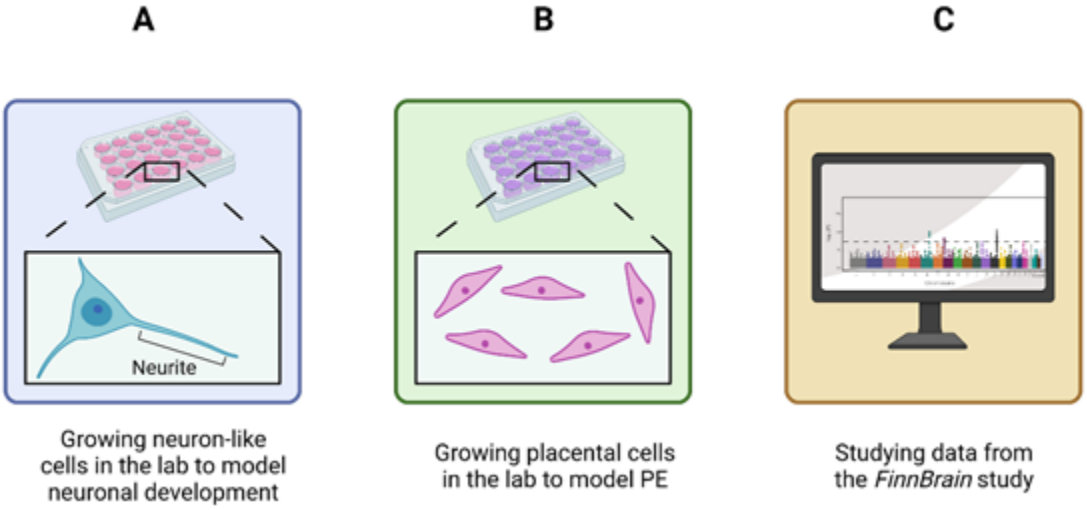


Figure 1: Approaches taken in the lab to study the relationship between PE and foetal neurodevelopment. Figure made by author using Biorender.com.

with that enigmatic organ that some people like to eat – yes, the placenta. Your placenta (if you have one) is a truly amazing organ – it's not just a barrier between the mother and baby, and certainly not just superfluous afterbirth. The placenta plays an active role in guiding pregnancy and foetal development – which, of course, includes neurodevelopment. In PE, after failing to establish itself properly in the very early stages of pregnancy, the placenta becomes highly stressed, and sends signals to the mother and baby to perpetuate the disease. It is thought not to be a coincidence that once the placenta has been delivered, and it can no longer send stress signals to the motherś body, the disorder subsides. This is crucial, because it means that whatever it is about PE that affects the baby's brain, it almost certainly involves the placenta in some way or another. So, scientists love the placenta, not because it is so delicious, but because it is a window into what went on during that woman's pregnancy and it can tell you so much about foetal development.

To study this in the lab, we have set up a model of a pre-eclamptic placenta, by taking a type of placental cell called cytotrophoblasts, and stressing them in such a way that mimics what actually happens in PE (Fig. 1B). Of course it is never possible to model things perfectly, but what we have already shown is that these cells are highly stressed, they do not migrate or divide so well, and they secrete altered protein levels – and this is exactly what's seen in the placenta of women with PE. To mirror this work with placenta cells, we're also taking tiny samples from the actual placenta of women with or without PE, and looking at whether its functions that control brain development are impaired. Just like in our placenta cell model, the real PE placenta has higher immune signalling and releases different protein levels that could affect neurons. Now that we are confident in our PE placenta model, the next stage is to take what the cells secrete and apply it to developing neuron-like cells, just like we did with the serum, and record what happens. The purpose of these experiments, then, is to study how

PE-like placenta cells release different molecules that influence neuron development.

There is one last thing we are doing too, as part of a collaboration with researchers at the University of Turku (UTU) in Finland. UTU runs the FinnBrain study, which is one of the biggest and best of its kind: starting in 2010, they enrolled 4,000 pregnant women in the south of Finland as part of a massive cohort aimed at finding out more about how maternal stress, inflammation and other pregnancy-related factors affect the child's brain development. They have been following these children, who are now approaching 12 years of age, ever since birth with brain scans and neuropsychological tests, amassing an incredible amount of data and, as you can imagine, this data is the perfect place to look if you want to learn how pregnancy conditions affect the developing brain. So, working with these clinicians and scientists, we will be diving deep into this powerful dataset to analyse all sorts of maternal factors from stress and inflammation to hormone signalling and, using brain scan data, how these are related to the structural development of the children's brains (Fig. 1C). While our work with cells is useful and informative, this neuroimaging element of our work makes things even more clinically relevant by studying real people. This project is just getting underway, so watch this space!

Putting It All Together

So, what can Maria, recently diagnosed with PE, expect for her baby's brain development? Well, what we know so far is that whatever that child's pre-existing risk was for developing a neurodevelopmental disorder, it has now gone up by 30-35%. We know that PE will be very severe on her body and will affect developmental processes in her baby, including in the baby's brain, and that this in some cases will have no discernible effect, but in others will be enough to tip the scales and send the brain's development on a trajectory that leads to a neurodevelopmental disorder. What our research is adding to this is that the changes to the mother's immune system in PE can have very specific effects on neuronal development, that immune signalling is altered in the placenta of women with PE, and that it is possible to model the conditions of the PE placenta at a single-cell level in the lab (Fig. 2). With this behind us, our ongoing and upcoming experiments will look at how PE-like placental secretions affect neuronal development, and how maternal factors, such as immune changes, affect brain development in real children.

But why should you care about any of this – how is it meaningful? A question every scientist dreads, but nonetheless one of the most important questions for us to ask. Put simply, if we can find out how PE adversely affects brain development, then maybe we could prevent this. Women at elevated risk of developing PE, or who, like Maria, have recently been diagnosed, could be started on lifestyle or pharmacological interventions that would protect her baby's brain – much the same way that women today are advised to supplement with folic acid to prevent neural tube defects like spina bifida in their child. It might also tell us something about PE or neurodevelopmental disorders more generally, and ultimately lead to improvements in the health and wellbeing of the mother and child.

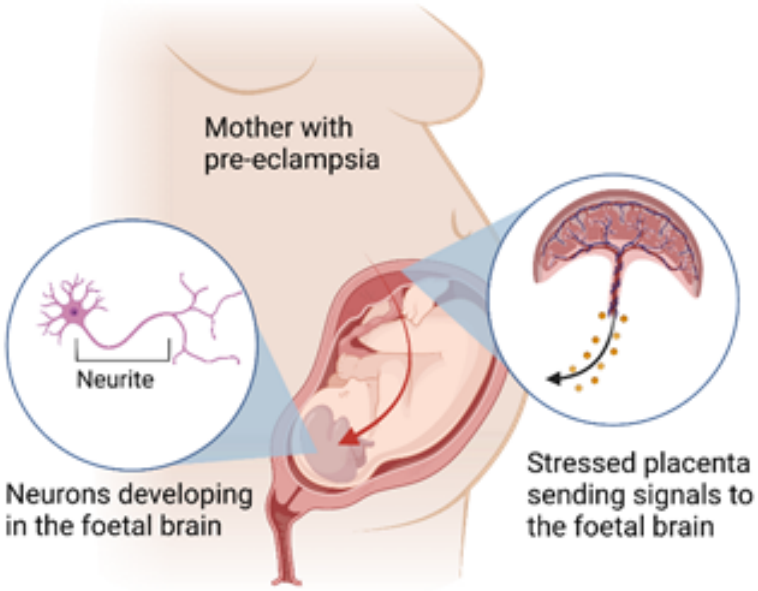


Figure 2: PE influencing neuron development in the foetal brain. Figure made by author using Biorender.com.

A scientific endeavour to understand and prevent neurodevelopmental disorders before they arise is by no means an attempt to disregard or delegitimize the many amazing people today for whom their autism or ADHD is an integral part of their identity and being. It truly is wonderful that society is beginning to acknowledge and celebrate neurodiversity, and that there are so many people with ASD and ADHD who are healthy, active members of society, for whom 'disorder' is not an appropriate word. But we must also remember to see the less functional end of the spectrum, to remember that as many as half of autistic people will never speak, and that a significant proportion have limited opportunities in life with no prospect of independent living, and the profound emotional impact this has on them and their families. And if PE increases how often this happens, then it is at least worth trying to figure out how. The more we know, the better informed and better armed we are to improve our decisions and improve our health.

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Declaration of Interests

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