Queen Mary University of London - Written evidence (PRT0028)

Organisation: We are an inter-disciplinary team of UK clinicians, scientists and engineers with expertise in obstetrics (Anna David, UCL/UCLH), child health (Jonathan Grigg, QMUL), infection (Andrew Prendergast, QMUL/Zimbabwe), epidemiology (Stamatina IIiodromiti, Barts Health NHS Trust), computational modelling (Stefaan Verbruggen, QMUL) and machine learning (Greg Slabaugh DERI/QMUL), working towards understanding how inflammation affects the microstructure of the placenta and fetal membranes leading to preterm birth.

Our aim is to stimulate government to encourage investment in preterm birth / PPROM solutions bringing together experts who will fund inter-disciplinary research in biological and pathological mechanisms, implementation science, pharmaceutical industry and policy.

Clinical importance: In the UK, Preterm premature rupture of the fetal membranes (PPROM) affects 1 in every 13 pregnancies leading to preterm birth. Nationally, the annual NHS costs are £3.9 billion (estimated 2018). A preterm neonatal admission costs around £1,500 daily and when born extremely preterm (less than 28 weeks) has an incremental £94,000 cost at 18 years compared to a term birth due to lifelong disabilities (e.g., cerebral palsy). Over a lifetime, preterm birth costs the NHS an additional £1 billion with most cost incurred in the first few months of life. Currently, there are no clinical solutions to repair the membranes when they rupture spontaneously or after fetal surgery. Approaches to close defects in the membranes with glues or biomaterials have failed clinically and none are in routine use.

Short summary: The integrity of the fetal membranes that surrounds the baby in the womb during pregnancy are vital for normal development. Once the membranes have ruptured or are damaged, they fail to heal leaving a defect until the end of pregnancy. Bacteria may move from the vagina into the womb, causing infection both to the fetus and mother.

This condition is called pre-term premature rupture of the fetal membranes (PPROM) and is a common cause of preterm birth. PPROM also complicates 40% of surgeries that are used to treat abnormalities in the unborn baby. There are currently no clinical solutions to improve healing of the fetal membranes and repair the tissue after fetal surgery or after the membranes rupture spontaneously.

Our research has found a reason for this poor healing response. We found high levels of a protein called connexin 43 (Cx43) in the amniotic membrane around the defect site after fetal surgery. To encourage repair, we developed bioadhesive technology that can provide structural support with good elasticity and strength and has the potential to seal the defect site after implantation. This research was previously funded by Great Ormond Street Hospital Children's charity (17QMU01) and the Rosetrees Trust (M808). We plan to integrate the bioadhesive technology with a clinically approved therapeutic agent that will reduce Cx43 and stimulate repair of the defect. To avoid the need for animal experiments, we will test the mechanical response of the bioadhesives with an inflation device to improve the stretchability and structural properties of the material components by using novel silicone chemistry. This will allow us to repair defects in the membranes after surgery and design best properties for mechanical strength without the need to conduct expensive experiments in animals and to adhere to the national mission for the reduction replacement and refinement of animals in research (NC3Rs).

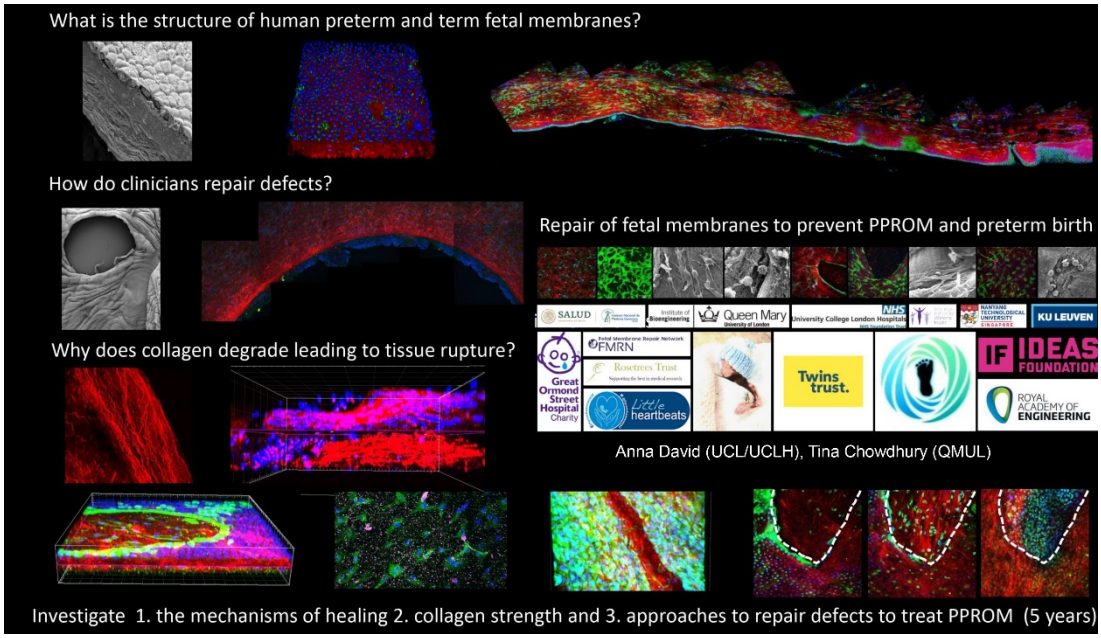
If we can prevent PPROM for just a few weeks, our approach could prevent the life-long medical conditions and disabilities associated with preterm birth. The findings from our work will also provide insights into the mechanisms of why women rupture their membranes spontaneously and greatly improve women's health in the UK (https://www.little-heartbeats.org.uk/) and around the world (https://twinstrust.org).

Reason for submitting evidence:

- Air pollution is an important cause of preterm birth but is under investigated. There is emerging evidence that exposure to air pollution during pregnancy is associated with preterm birth. Air pollution results mainly from the combustion of fossil fuels or industrial emissions and has become a major global public health issue for people in all age groups. The relationship between breathing in air pollution during pregnancy and a higher risk of preterm birth is well established. We have detected black carbon particles in placenta macrophages and decidua trophoblasts of Term placentas collected from pregnant women living in London. In our pilot study, we also found carbon particles in fetal membrane cells similar to the work by the Belgium and Aberdeen team who confirmed particles in trophoblasts. They also found evidence of black carbon particles in the liver, lungs and brains of fetuses from electively terminated and healthy progressing pregnancies, demonstrating translocation to the placenta and fetal circulation system. The inflammatory mechanisms induced by carbon particles from diesel exhaust cars are unknown. There is an urgent need to better understand the effects of air pollution on the molecular mechanisms in gestational fetal membranes as they will have significant implications for policies that protect child health and pregnancy in the UK, particularly during the **net-zero transition**.
- We need **significant investment** to investigate the biological and pathological **mechanisms** to repair membranes. Our goal is to develop a human model of the placenta and membranes, to evaluate tissue strength, structure and the healing response *in vitro*. By understanding the interactions, we will develop complementary *in silico* and machine learning models that will be linked with population-level data on feto-maternal health from birth cohort studies conducted in the UK. However, this area of inter-disciplinary research is under-funded and if we are going to identify

risk factors and potential pathway interventions for PPROM and preterm birth, we need significant investment in R&D. Ultimately, our model will provide a shareable tool to support design of novel population-level interventions for preterm birth and improve mother and child health outcomes.

- Whilst we have established a bioengineering technology to repair preterm membranes *in vitro*, we have no understanding of how the approach works clinically to close the defect and prevent rupture. Our long-term goal will be to develop clinical interventions such as the bioadhesive technology to prevent PPROM and explore a pregnant woman's risk of preterm rupture to prevent preterm birth.



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