

CAF/26/109 - Proton Pump Inhibitor Use in Very Premature Infants: Determining Their Impact on Microbial Colonisation and Potential Clinical Outcomes

Over 500 babies are born very prematurely (before 32 weeks gestation) every year in Scotland. These babies require weeks of specialist care in neonatal units before they are discharged home. Despite this, a significant portion of these infants die before discharge (39 died in Scotland in 2024) or go on to develop serious complications.

Traditional drug trials are difficult to conduct in preterm babies for a variety of reasons. This means that there is often less evidence to guide treatment in premature babies than there would be for older children or adults.

Until it was withdrawn in 2019, a stomach acid reducer called ranitidine was regularly used in premature babies. There was evidence that ranitidine was linked to serious complications in very small babies such as necrotising enterocolitis (a condition leading to inflammation and death of baby's intestinal tissue) and serious infections. These are significant causes of death and disability in premature babies.

Since 2019, there has been a large increase in the use of another stomach acid reducing medication called omeprazole. This is from a class of medicines called "proton pump inhibitors" (PPIs). These are thought to be a stronger acid-reducing medicine than ranitidine. It is usually prescribed with the aim of protecting the lining of the stomach or for reducing reflux symptoms. There is, however, little evidence that it is effective for this in preterm babies. Despite the similarities to ranitidine, there have been no studies to see if omeprazole use brings the same risk of serious complications as ranitidine.

Using routinely collected data from Scottish neonatal units we will look at both the benefits and risks of omeprazole, including changes to rates of serious infection, necrotising enterocolitis and death.

Early life PPI use is also associated with increased risks of allergies, infections and even childhood cancers. One possible cause of these risks is by changes in the microbiome (a term used to describe the collection of microbes living both in and on us). Since PPIs work by reducing the acidity of stomach acid, they may allow more bacteria to travel through the stomach into the intestines or and change the living conditions for bacteria throughout the gut. In adults and older children this change in stomach acidity has been shown to significantly alter the microbiome.

Babies are particularly vulnerable to microbiome disruption: the gut goes from having no bacteria just before birth to developing a diverse microbiome over the first weeks and months of life, achieving "adult-type" microbiome by the age of 3. Despite this,

the effects of early life PPI use on the developing microbiome of very preterm babies has not been studied. Doing so is critical in ensuring we are not causing harm in a vulnerable population and to better understand a critical period of microbiome development.

By taking weekly poo samples and mouth swabs from very preterm babies admitted to Ninewells Neonatal Unit, we will describe the microbiome and how it changes over time in those treated with omeprazole and compare this to those who are not. To look at longer-term microbiome changes, we will also recruit a group of healthy babies and will compare their microbiome at 6 and 12 months with our premature group.

Finally, to facilitate further studies on the development of the microbiome in babies, we will ask families to help us understand their thinking on this subject and how they would like studies to be designed in this area. This will help us develop the most family-friendly research opportunities in the future.