Home Office

NON-TECHNICAL SUMMARY

# Improving outcomes in complicated pregnancies

**Project duration**

5 years 0 months

**Project purpose**

- (a) Basic research
- (b) Translational or applied research with one of the following aims:
  - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants
  - (ii) Assessment, detection, regulation or modification of physiological conditions in man, animals or plants

**Key words**

Pregnancy, Fetal growth restriction, Preeclampsia, Placenta, Therapy

| Animal types | Life stages |
|---|---|
| Mice | adult, embryo, neonate, juvenile, pregnant |

## Retrospective assessment

> The Secretary of State has determined that a retrospective assessment of this licence is not required.

# Objectives and benefits

**Description of the projects objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.**

**What's the aim of this project?**

The first aim of this project is to better understand how key risk factors, such as obesity, high blood pressure and advanced maternal age, lead to pregnancy complications and poor health outcomes for mothers and their offspring. Through increasing our understanding of pregnancy complications and their risk factors, we then aim to test whether interventions designed to improve maternal health and/or placental function (a key determinant of a baby's growth) can lead to better outcomes for mothers and their babies, both within the pregnancy itself as well as into later life.

**Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.**

**Why is it important to undertake this work?**

Whilst most pregnancies are healthy and result in good outcomes for mothers and their babies, pregnancy complications remain relatively common. Pregnancy losses, such as miscarriage (loss of a pregnancy before 24 weeks of pregnancy, affecting 15-25% of pregnancies in the UK) and stillbirth (death of a baby after 24 weeks of pregnancy, affecting around 1 in 250 pregnancies in the UK) are devastating outcomes and have far-reaching effects on both physical and mental health.

It is difficult to predict which pregnancies may end in loss, but we do know that poor growth of the baby, also called fetal growth restriction (FGR), is one key risk factor. Preeclampsia (PE) is another pregnancy complication that can increase the risk of pregnancy loss. PE is a serious condition of high blood pressure in pregnancy that can cause problems with the mother's brain, heart, kidney and liver function. If left untreated, it can be life-threatening for mother and baby.

As well as increasing risks during pregnancy, there are life-long increased risks of poor health for mothers who experience these pregnancy complications, and for their babies. Babies who are born small are more likely to develop diabetes and heart disease in later life. In addition, women who have had preeclampsia are at greater risk of developing health problems in later life, including increased risk of heart disease and dementia.

Despite these very serious outcomes, there are currently no effective treatments to prevent fetal growth restriction, preeclampsia or stillbirth, or their long-term consequences. In part this is because we do not fully understand how these conditions arise. The work we will undertake in this project will increase our understanding of how preeclampsia and fetal growth restriction arise, and test whether rational therapeutic interventions can improve pregnancy outcomes as well as long-term maternal and offspring health.

Downloaded: 9:50am, 5 Nov 2024

**What outputs do you think you will see at the end of this project?**

This project will advance our understanding in several key areas of pregnancy and reproductive health. We will generate new knowledge about why women who are older, or who enter pregnancy with high blood pressure or obesity, are more likely to have poor pregnancy outcomes such as pregnancy loss and poor growth of the baby. We will also study the long-term consequences of these higher-risk pregnancies, particularly the consequences of high maternal blood pressure for maternal health in later life, in order to understand what therapeutic strategies might be most useful to improve life-long health in women.

We will present our findings at national and international conferences and publish our research in peer-reviewed publications.

In addition to enhancing our understanding of pregnancy complications associated with specific maternal conditions, we will also test whether we can intervene using treatments either during pregnancy (to prevent or treat pregnancy complications) or in the postnatal period (to improve maternal health following a complicated pregnancy).

By the end of this project, we aim to have generated sufficient data on at least one therapeutic intervention that we think could be used to improve outcomes in pregnant or postnatal women in the future. This information will inform the design of early-phase clinical trials in pregnant women.

**Who or what will benefit from these outputs, and how?**

Short-term benefits: The beneficiaries of the new knowledge generated in this project will include other academics working within the field of reproductive biology, as well as the wider scientific community and the public.

In terms of academic benefits, we will communicate our findings to a broad range of individuals. These include clinical academics who manage women with high-risk pregnancies, and who will gain a deeper understanding of the reasons why certain women are more at risk of different pregnancy complications.

Long-term benefits: The information gained from this project will lead to a better understanding of common pregnancy complications that affect many families worldwide. It may also lead to the development of new drugs or therapeutic approaches to improve pregnancy outcomes and long-term health of patients. If our findings suggest that certain classes of drugs or therapies may be useful in the treatment or prevention of pregnancy complications and their longer-term consequences, this will open up the possibility of developing new or improved drugs.

Ultimately, the work undertaken in this project has the potential to improve population health in the future and will provide essential information to enable us to advance promising therapies towards clinical trials in women at risk of pregnancy complications in the future.

**How will you look to maximise the outputs of this work?**

We will publish our findings in open-access journals and present our research as it progresses in both national and international conferences. We are a highly collaborative research group, and where

appropriate we will share animal tissues generated from this project and data resources with other researchers in the field. We will continue to publish negative findings in a timely manner to try and ensure that other researchers working on similar models or programmes of work may avoid wastage of animals or resources.

In addition to these academic outputs, our research group has an active public engagement strategy. Sharing findings generated from this project with the public is important not only to share exciting progress in this field, but also to educate people about why it is sometimes necessary to use animals in healthcare research. In preparing and delivering school and community education and engagement events, we are also raising the profile of women's health more generally, which is key to ensure that this area of research gets the attention and funding required to make a difference to population health in the future.

**Species and numbers of animals expected to be used**

- Mice: 5050

# Predicted harms

**Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.**

**Explain why you are using these types of animals and your choice of life stages.**

This project will use mice, and predominantly female mice as our primary research questions focus on understanding and treating pregnancy complications. We have chosen to use mice as our research model as we know that the biological pathways involved with a mother's adaptations to pregnancy, as well as early embryo and placental development and later placental function, are very similar between mice and humans.

In order to study the health of the mother and fetus during pregnancy as well as long-term health of the mothers and their offspring beyond pregnancy, we will use animals across a broad range of life stages; from embryonic stages right through until later life. For studies looking at offspring health (both prenatally and postnally) following treatments during pregnancy, we will use both male and female animals, but by necessity the majority of studies in this project will involve female animals.

**Typically, what will be done to an animal used in your project?**

The majority of animals in our project will be pregnant female mice. Typically, female animals with a known risk factor for pregnancy complications such as obesity (here resulting from feeding animals a high-fat diet before they become pregnant), or high blood pressure (here, due to a genetic alteration in the animals), will be mated with males to generate pregnant females. We will study how the pregnancy progresses, measuring the blood pressure of the pregnant females and studying blood flow to the placenta and the baby using ultrasound techniques exactly as would be done in a human pregnancy. One difference however is that we will need to keep animals still whilst we carry out these procedures.

This means that we will need to restrain the mice when we measure their blood pressure, and anaesthetise animals in order to carry out the ultrasound imaging.

As we wish to prevent or treat pregnancy complications or improve long-term health, most animals will also be given a drug or therapy that we think can improve maternal and/or fetal health during the pregnancy or reduce the adverse health outcomes of mothers following a complicated pregnancy. These drugs or therapies may be a dietary supplement or an existing drug that has shown promise either in our non-animal laboratory studies or in the research literature. When it comes to administering treatments, we always try to administer these either in the food or in the drinking water wherever possible, as this is the least disruptive for the animals.

In pregnant animals, we will measure how well fetuses have grown by collecting tissues towards the end of a pregnancy, and in some animals we will study both maternal and offspring health following the birth of the babies from complicated pregnancies that have been treated with drugs or therapies. In this way, we will be able to understand what the long-term impacts of a pregnancy complication and/or a treatment may be.

Wherever possible, we will maintain mice in groups within their cages and they will be given free access to food and water throughout their lives unless we need to remove food for a short period of time to enable us to measure glucose metabolism.

**What are the expected impacts and/or adverse effects for the animals during your project?**

The feeding of a high-fat diet to induce obesity in mice, prior to and during pregnancy, can cause animals to develop a greasy coat which can then lead to animals over-grooming, a change from normal behaviour. Similarly, animals housed in a low oxygen environment, to mimic a pregnancy where there is insufficient oxygen delivered to the baby (which can occur at high altitudes and is also thought to be a common mechanism that may occur in obesity, hypertension or in mothers of advanced maternal age), may become more subdued as a result of adapting to lower oxygen levels. The duration of these changes in behaviour, should they happen, are expected to be for the length of the diet or low oxygen exposure; 12-16 weeks or 2 weeks, respectively.

For procedures where we need to restrain or anaesthetise animals in order to measure blood pressure or cardiovascular function/blood flow, animals will experience short-term distress as a result. We do not expect these procedures to induce any lasting harm to any animals.

When sampling blood, we always remove the smallest volume possible for the needs of the experiment, in accordance with NC3Rs best practice. Whilst animals will experience mild and transient discomfort from blood sampling, this is not expected to result in any lasting harm for the animals.

**Expected severity categories and the proportion of animals in each category, per species.**

**What are the expected severities and the proportion of animals in each category (per animal type)?**

For the mice used in this project, we expect:

25% of animals will experience moderate severity, 50% will experience mild severity and 25% will experience sub-threshold severity.

**What will happen to animals used in this project?**

- Killed
- Used in other projects

# Replacement

**State what non-animal alternatives are available in this field, which alternatives you have considered and why they cannot be used for this purpose.**

**Why do you need to use animals to achieve the aim of your project?**

Pregnancy is a particularly complex condition to study as the mother, the baby and the placenta (the organ that supports the growth of the baby) work together to achieve a healthy pregnancy. It is not currently possible to comprehensively study the physiology of pregnancy without using whole animals, although we do conduct our early phase studies (e.g. development of therapeutics) where possible using human tissues and cells to understand some of the more basic aspects of the biology, as outlined below. It is also not possible to test the safety and effectiveness of new treatments for pregnancy diseases in isolated cells or tissues, as these approaches cannot tell us how the drugs/therapies might travel in the body, be transported across the placenta or affect the fetus. For these reasons, we do need to use some animals in order to achieve the aims of this project.

**Which non-animal alternatives did you consider for use in this project?**

Wherever possible, we use cells and human tissues (e.g. placental cell lines, human placental tissue and maternal blood vessels from biopsies taken at Caesarean section) to study aspects of placental development and blood vessel function and to test new potential therapies in the laboratory.  Our research group is also starting to work towards developing organ-on-a-chip technologies for placental transport and other studies, however these approaches are still in the development stages.  Likewise, our clinical collaborators are currently working towards developing in silico human pregnancy modelling approaches. Whilst it is currently too early to replace animals with these emerging technologies, if these models are proven accurate it is likely to lead to a significant reduction in the number of animals used in the future in this field.

**Why were they not suitable?**

There are not currently any non-animal alternatives that adequately model the interacting systems of mother, baby and placenta together. As outlined above, there are models under development, but none of these are sufficiently advanced or validated to replace animals at this point in time.

# Reduction

**Explain how the numbers of animals for this project were determined. Describe steps that have been taken to reduce animal numbers, and principles used to design studies. Describe practices that are used throughout the project to minimise numbers consistent with scientific objectives, if any. These may include e.g. pilot studies, computer modelling, sharing of tissue and reuse.**

**How have you estimated the numbers of animals you will use?**

For the studies described in this project, we have calculated the minimum number of animals required to produce reliable results with effects that are biologically or clinically relevant. We have sought statistical support when calculating the numbers of animals we expect to use in the different studies of this project, using either data from our own experiments where possible, or from the literature, to establish the expected variability of different measurements. Where no previous data are available, we will carry out pilot studies to base future power calculations upon.

The majority of our experiments are designed to compare effects between health and disease (e.g. normal pregnancy versus a pregnancy complicated by PE and/or FGR) and/or to assess whether treatment can improve health outcomes in the animals. We make use of factorial study designs where appropriate, to reduce the total number of animals whilst still generating meaningful data.

**What steps did you take during the experimental design phase to reduce the number of animals being used in this project?**

In planning for this project, we have attended experimental design training courses and have consulted several times with local statisticians to ensure that we are using statistical methods that maximise efficiency in our study designs.

**What measures, apart from good experimental design, will you use to optimise the number of animals you plan to use in your project?**

For all studies investigating a new animal model (e.g. a new animal model of PE or FGR described in the scientific literature) we make use of pilot studies in a small number of animals to ensure that the model exhibits the specific features we wish to model in our hands before proceeding to any treatment studies. This is to ensure that the data from all animals used thereafter is translationally relevant.

When conducting studies to understand the effects of treatments across different groups, we use experimental designs that are as efficient as possible to conduct our studies (e.g. factorial study design).

We ensure that tissues taken from animals used in this project are used across as many projects as possible, and where appropriate try to share tissue between researchers from our own group as well as other groups with similar interests.

# Refinement

**Give examples of the specific measures (e.g., increased monitoring, post-operative care, pain management, training of animals) to be taken, in relation to the procedures, to minimise welfare costs (harms) to the animals. Describe the mechanisms in place to take up emerging refinement techniques during the lifetime of the project.**

**Which animal models and methods will you use during this project? Explain why these models and methods cause the least pain, suffering, distress, or lasting harm to the animals.**

Mice are the most appropriate model for use in our pregnancy studies, being mammalian, exhibiting similar pregnancy-induced physiological adaptations and having a placental structure and function similar to that of humans.

In terms of our experimental methods, animals are housed in groups wherever possible. Drugs or therapies are delivered in the least invasive way, via the diet or drinking water wherever possible. Any procedures to study a physiological function in an intact animal are done so non-invasively where possible (e.g. ultrasound imaging) or under non-recovery conditions (e.g. terminal anaesthesia for placental transport studies) to minimise harm to the animals. Where this is not possible, for example glucose tolerance testing, we use microsampling to minimise the volume of blood taken.

**Why can’t you use animals that are less sentient?**

In order to understand mammalian pregnancy and develop treatments that can ultimately be translated into humans, we need to use a mammalian species, with the mouse being the most appropriate and least sentient species for this work.

We will study effects of pregnancy complications and new treatments on developing fetuses at early gestational ages (i.e. at immature life stages) in some of our studies. However, in order to study the effects of these treatments on the pregnant female and to understand the long-term effects of these treatments, we must study adult animals.

**How will you refine the procedures you're using to minimise the welfare costs (harms) for the animals?**

Any animal undergoing an intervention (e.g. administration of a new treatment to a pregnant mouse) will be monitored by researchers for the duration of the treatment period, with increased monitoring during the initial days to ensure there is no change in food or fluid intake. Likewise, animals exposed to hypoxia will have increased monitoring during the period of incubation.

For blood pressure measurements, animals will be habituated to the restraint tubes before measurements are made to minimise the stress of the procedure and improve the reliability of results. For studies where blood pressure will be measured during pregnancy, animals will be habituated before the animals become pregnant.

If any animals undergo recovery surgery for the purposes of implanting a drug delivery device (minipump), then we will ensure animals are given both pre- and post-operative analgesia and undergo increased monitoring until they have made a full recovery.

Downloaded: 9:50am, 5 Nov 2024

**What published best practice guidance will you follow to ensure experiments are conducted in the most refined way?**

Our research studies are planned and conducted in accordance with the PREPARE and ARRIVE guidelines to try and ensure that the research we produce is as reliable and reproducible as possible. We are also committed to publishing both positive and negative findings, and have an established track record of doing so.

Researchers working on this project will engage with continued professional development; all researchers will undertake training in experimental design (e.g. as delivered annually by the animal facility) as part of their training within the research group.

**How will you stay informed about advances in the 3Rs, and implement these advances effectively, during the project?**

Through our institution we receive monthly newsletters where the latest developments from the NC3Rs are communicated to all researchers.  We will make use of the 3R's assessment tools throughout the lifecycle of this project, to ensure that any new advances that we can apply to our research are implemented.

Downloaded: 9:50am, 5 Nov 2024