UNIVERSITY OF BIRMINGHAM

Birmingham Health Partners
Collaboration. Innovation. Application.

Safe and Effective Medicines for Use in Pregnancy: **A Call to Action**

By Shaoni Bhattacharya, on behalf of the Birmingham Health Partners Centre for Regulatory Science and Innovation

January 2021

In the UK there are more than

760,000 pregnancies every year

4,000 babies
die due to pregnancy-specific conditions such as preterm birth and pre-eclampsia

~70 mothers
die due to pregnancy-specific conditions such as preterm birth and pre-eclampsia

73%
of drugs given to pregnant women have no safety information

£2.9bn
Preterm birth annual cost to the UK economy

1 Number of new drugs developed for use in pregnancy in over 30 years

For many women, pregnancy is a time of joy and hope. However, throughout a pregnancy there are risks, which can lead to feelings of anxiety, uncertainty and even fear. Some women can develop specific complications during pregnancy, which can affect their own health or the health of their unborn child. Other women may have health issues prior to pregnancy, and effective treatment of these is more challenging due to the complexities of being pregnant.

Tragically, 2.7 million women and children die each year from causes related to pregnancy and childbirth. In the UK, 4,000 lives are lost each year. Many lives could be saved if there are more effective treatment options. In 2017, the UK government pledged to halve perinatal and maternal deaths by 2025. And yet not a single new drug for some of the most serious pregnancy-related conditions has reached patients in more than 30 years. In addition, 98% of the drugs we have to rely on have not been thoroughly tested in pregnancy. Development of new drugs to treat some of the most severe complications of pregnancy is paralysed by complex regulation and fear of litigation.

The UK is one of the best-placed countries in the world to tackle these issues because it has a strong track record of research in pregnancy and has a comprehensive health system which follows individuals from birth until death. This would allow the UK to develop and test new and existing medicines in pregnancy, which would benefit our own population as well as mothers and babies around the world. This report summarises the current situation, recognising the limitations of available data and offering some initial insights into opportunities to create change.

We urge stakeholders to come together – policy-makers, clinicians, women and their families, industry, charities, academics and others – to examine the evidence, discuss the opportunities, and to co-create solutions. At least two women and many more babies will have died from the conditions described here by the time you read this report. Let's work together to change that.


Professor Peter Brocklehurst


Professor Shakila Thangaratinam


Professor Arri Coomarasamy


Professor Katie Morris

Introduction

While many of us benefit from advances and new technologies used in medical drug development, there is one group that has barely made any gains at all: pregnant women.

'Lack of advancement in this area is unacceptably failing women and their families.'

Sarah Stock and Jane Norman writing in F1000Research in 2019

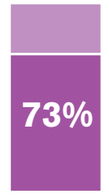
Governments and regulators have encouraged the pharmaceutical industry to branch out in their clinical studies over the last few decades to test new drugs in patients more representative of the general population. This includes extending clinical drug trials to include women, children where appropriate and patients of different ethnicities.

However, pregnant women and their unborn babies remain woefully neglected; deprived of new drugs and reliant in many cases on medicines which have not been thoroughly tested in pregnancy, for example, many drugs used to control high blood pressure. Pregnant women – like everybody else – can get sick. And pregnancy can lead to complications, which may need treatment, and can potentially lead to severe consequences including death for the mother or her unborn child.

For society as a whole, pregnancy complications carry a significant health, economic and social burden. Pre-eclampsia (a condition characterised by high blood pressure in pregnancy) alone kills one woman every six minutes worldwide. In the UK, preterm birth (birth before 37 weeks of pregnancy) costs the economy around £3 billion every year, factoring in long-term disabilities of the surviving children.

This review will present an overview of the current situation for this group, the issues and the available evidence; as well as exploring the barriers and options in better addressing pregnancy and maternal health.

The UK Government's aim is to **reduce maternal** and infant deaths by **50% by 2025**



3 out of 4 women take some medication during pregnancy, but **73%** of drugs have **no safety information** in pregnancy

Only **one new drug** developed for use in pregnancy **in over 30 years**

How are pregnant women underserved?

There's a 'drug drought' for pregnancy, some experts argue. In the last 30 years, only one new drug – atosiban – has been specifically licensed for use in pregnant women in the UK. Licensed in Europe but not the USA, this drug is used to try to prevent birth in women who start labour too early in pregnancy. However, no new drugs have reached pregnant women for other major complications including pre-eclampsia, fetal growth restriction or miscarriage, together responsible for the major burden of death and disability.

In fact, more new drugs may be in development for rare diseases than pregnancy. While 17 drugs for pregnancy complications were actively being developed by the pharmaceutical industry in 2007, 34 were under development for the rare disease amyotrophic lateral sclerosis, which affects four per 100,000 people. The pregnancy-related drug pipeline was just 3% of that for cardiovascular health, which had 660 drugs in active development. Bear in mind that up to 90% of drugs being developed never reach patients, and may take up to ten years and cost over £1 billion to develop even if successful, ie, they are found to be safe, effective and cost-effective.

Consequently, in pregnancy doctors have to rely on older, more established drugs – many of which have never been systematically tested in pregnancy for safety, effectiveness or the right dosage.

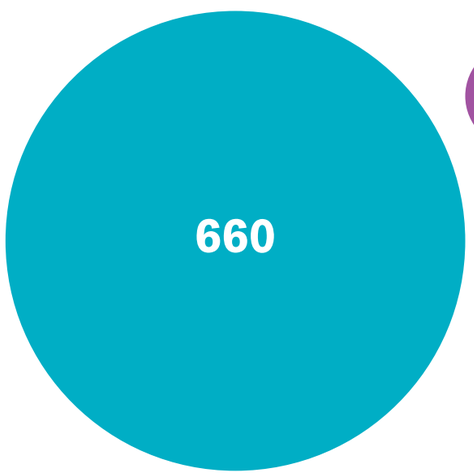
On top of this, of the thousands of drugs being actively developed for other conditions which may affect women who become pregnant, very few are tested directly in pregnant women – which means women may miss out on medical advancements for illnesses they experience during pregnancy, or have to accept the risks of taking medication with unknown side-effects. For example, 98% of the 468 drugs approved in the USA between 1980 and 2000 have no information on the risk of causing birth defects if women take them during pregnancy. And 73% of these new drugs had no safety information for pregnancy.

Medical teams may have to prescribe medicines which are not licensed to be used in pregnancy without adequate information on the drug's effects in pregnancy, or in some cases even when thought unsafe in pregnancy. One UK study in 2010 showed that almost six out of ten drugs prescribed during pregnancy but before birth had warnings from the manufacturer either advising caution in pregnancy or not to take at all. On the other hand, sometimes pregnant women do not receive the medicines they need because of uncertainty or lack of information around a drug's safety.

Research spending on pregnancy is low, while litigation and other care costs of the complications of pregnancy are high. For every £1 the NHS spends on pregnancy care, only 1p is spent on pregnancy research – of which pregnancy drug research will be a fraction.

Pregnancy drug drought

In 2007 **cardiovascular health** had 660 drugs under development...



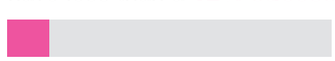
34

...34 were under development for the rare disease **amyotrophic lateral sclerosis**

17

...while only 17 drugs were actively being developed for **pregnancy complications** by the pharmaceutical industry

Even drugs that reach clinical testing have less than a **12% success rate**



Why have we not developed and tested more therapies for pregnant women?

History and fear are powerful factors as to why so few drugs have been developed or tested in pregnant women. The drug thalidomide, used over half a century ago, has cast a long shadow. Originally a treatment for a number of conditions including leprosy, it was proclaimed to be a 'wonder drug' to treat headaches, insomnia and severe morning sickness in pregnant women.

Thalidomide was withdrawn in 1961 after a report linked it to severe birth defects in babies. Up to 10,000 children worldwide are estimated to have been born with severe limb malformations and other congenital defects as a result of thalidomide use in pregnancy. As well as the impact this has on affected families, there have been huge legal battles over compensation, the result being that pharmaceutical regulations were strengthened, with changes to drug development and licensing.

The use of another drug, diethylstilbestrol (DES) in pregnancy changed medical thinking on how embryos and cancer develop. This was given to millions of pregnant women at risk of early miscarriage for decades, but was linked in the 1960s to vaginal and cervical cancers in daughters exposed to the drug while in the womb. The case of DES suggests that long-term follow up – potentially over generations – may be crucial to fully understand the safety of drugs given in pregnancy.

> ***'…experts say that it's crucial to recognise that without research, every pregnant woman who needs to take a medication is doing so blindly.'***
>
> **STAT News article in 2017**

More recently, the UK has almost completely banned the use of sodium valproate in women of childbearing age as it is linked to birth defects, development and learning difficulties in children born to mothers taking the drug while pregnant. Valproate is used to treat epilepsy, bipolar disorder and migraine, and has carried a safety warning that tests in animals had shown that it could cause birth defects since 1974. However, it has been prescribed by clinicians to pregnant women for decades. The UK government, Medicines and Healthcare products Regulatory Agency (MHRA) and the National Institute for Clinical Excellence (NICE) changed their recommendations in 2018, with use of the drug acting as one of the three key case studies examined in a UK safety review 'First Do No Harm' published in July 2020, following extensive patient-led campaigns. Legal action by affected families is ongoing in the UK.

> ***'Possibly the wrong message was taken from the thalidomide episode… Had the drug been tested in very few women in a phase I or phase II clinical trial, the mutagenic effect would most likely have been discovered and the number of babies born with deformities would have been much smaller.'***
>
> **Ruth Macklin writing in The Lancet 2010**

Another reason why so few medicines are tested in clinical trials in pregnant women may be the historical context of women not being included in drug studies at all. Drug safety and effectiveness was extended from animal studies in the 1950s. For example, thalidomide was never tested in women but in chickens, and this did not reveal any birth defect issues.

After the thalidomide disaster came to light, the US regulator, the Food and Drugs Administration (FDA) in 1977 banned women and children from taking part in early phase drug safety trials. This was overturned by legislation in 1993 to include women, however, until recently, those pregnant or breastfeeding were considered a 'vulnerable population' – the idea being that they would be protected from exploitation.

What are the barriers for drug companies?

A huge fear of litigation, especially in the long wake of thalidomide, is a considerable barrier for pharmaceutical companies in testing drugs in pregnant women.

Legal action carries costs, but in the case of potential birth defects caused by the effects of a drug while in the womb, the impact may be lifelong. In the case of DES – which was linked to vaginal and cervical cancers in the daughters of women who took the drug in pregnancy, the impact was multi-generational. A compensation settlement for a baby damaged while in the womb may be high – up to £5 million in the UK. In the US, where juries are involved, this may be as high as US$110 million.

A perceived lack of economic incentives may also be a problem. Pregnancy and pregnancy-related conditions like pre-eclampsia have relatively short-term treatment windows, whereas drug companies make much of their money from drugs treating long-term, chronic conditions. A counter-argument may be that an estimated 210 million women get pregnant every year worldwide, and many will be pregnant more than once – giving a potentially huge untapped market.

The economic model that the pharma industry is based on deters investment in risky, highly regulated, small or short-term markets like pregnancy. This has led to the industry pursuing 'blockbuster' drugs, which can potentially pull in more than US$1 billion a year in sales, at the expense of drug development for conditions that have a smaller market. This includes rare diseases – though in recent years drug companies have moved towards developing drugs for rare diseases, so-called 'orphan drugs', helped by initiatives including the European Medicines Agency's 'Orphan Incentives' scheme. This gives orphan drugs ten years of market exclusivity, allowing the industry a chance to recoup their investment in developing and testing the drug.

Developing drugs and designing clinical trials specifically for pregnant women, plus the toxicity studies needed prior to clinical trials combined with onerous regulatory hurdles, are often considered too complex by drug companies, with the genuine concern they may not pay off economically.

One avenue that pharmaceutical companies could explore is the repurposing of existing drugs used for other purposes, for use in pregnancy. These have the advantages of already having passed many safety and toxicology tests, and can potentially generate huge profits if they are still in patent. However, if such a drug's patent has expired, there is little economic incentive for a company to develop it for pregnancy, or the costs of obtaining a licence for a different use of an established drug may be considered commercially unviable because of the further reproductive toxicology and maternal and fetal tests that might have to be done.

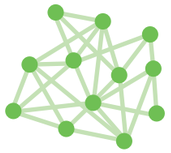
For example, the drug misoprostol was licensed and marketed for stomach ulcers in 1985 and was also shown by many studies to be safe and effective in women for preventing post-partum haemorrhage. Despite this evidence, the company which held its patent did not apply for a licence for this purpose, so it is widely used in pregnancy without having a licence for use.

What are the barriers for drug companies?

Fear of litigation

High drug development costs

Short-term treatment window for pregnancy = low returns



Complex regulation, even for existing drugs

Why do we need medicines for pregnant women and their unborn babies?

Pregnant women fall ill like the rest of the population. They may have pre-existing conditions like asthma, diabetes, epilepsy, depression or other illnesses which may require ongoing medication. Or they may catch infections or develop heart disease or cancer during pregnancy. They may also develop pregnancy-related medical issues that need treatment.

'Pregnancy is not a miracle cure that resolves chronic conditions upon conception. Viruses, bacteria and pathogens do not take a back-seat to gestation. Tumours and epileptic seizures will not wait until a baby is weaned.'

Uppsala Reports article in 2019

Major pregnancy conditions where new drugs could make a huge difference to health – and provide pharma with potential profits – include pre-eclampsia, preterm or premature birth, and fetal growth restriction. In pre-eclampsia, the pregnant woman develops high blood pressure amongst other symptoms, and this can lead to severe complications for mother and baby, including premature birth, restricted fetal growth and even death. Currently, the advice is that women at risk of pre-eclampsia are prescribed low-dose aspirin from 12 weeks of pregnancy. The only current viable major intervention is early delivery of the baby.

Preterm or premature birth is when a baby is born before 37 weeks. It is a major factor in newborn deaths and can lead to long-term disability of surviving children. Fetal growth restriction is when a baby does not achieve its potential for growth, putting the baby at risk of brain damage, respiratory conditions and even death.

How big is the problem of pregnancy-related complications?

Worldwide, the number of deaths and disabilities from pregnancy-related complications is enormous. Maternal and perinatal conditions contribute about 7% of the global burden of disease, according to the World Health Organization. Preterm birth is directly linked to 27% of deaths in newborns worldwide, and in higher-income countries it is associated with 70% of newborn deaths. Globally, about half the deaths in newborn babies can be attributed to being born prematurely. About one-in-ten births worldwide is premature, affecting some 15 million babies a year.

Babies who survive early birth may have long-term complications and disabilities. In the UK, about 60,000 babies are born too early each year. It was estimated in 2009 that preterm birth cost the economy £2.9 billion in a single year, including the long-term costs of associated disabilities, which affect around 28% of preterm births.

Pre-eclampsia can affect up to one-in-ten first time pregnancies, with about one- or two-in-a-hundred women being affected severely. Worldwide, one woman dies every six minutes from pre-eclampsia. It is still very uncommon for women to die from pre-eclampsia in the UK, with one or two deaths a year. However, about 1,000 babies die as a result of pre-eclampsia in the UK every year, usually because they are born too early rather than directly because of the condition.

It is estimated that two in three deaths in women from pre-eclampsia can be avoided.

In the UK, maternal deaths in pregnancy are generally rare, with 9.2 women in every 100,000 dying during or up to six weeks after pregnancy. Heart disease is the leading cause of death during pregnancy, with suicide taking over in the year after birth – reluctance to prescribe or take antidepressants during pregnancy and breastfeeding may be a factor in this. Babies die more frequently than mothers – there are around 4,000 stillbirths and neonatal deaths per year.

It is important to highlight that there are inequalities in maternal health in the UK population. Older women, those from more deprived backgrounds, and Black, Asian and mixed heritage women are more likely to die during or shortly after pregnancy. Black women are five times more likely to die from complications during pregnancy compared with white women.

Of the **210 million births** per year globally

1 in 10 births are premature

Preterm birth is linked to up to 70% of newborn deaths in the developed world

Globally
1 woman dies every 6 minutes
due to pre-eclampsia

2 out of 3
of these deaths are avoidable

1,000 babies
die every year in the UK as a result of pre-eclampsia

60,000 babies
are born too early each year in the UK

Annual costs to the economy as a result of pre-term birth are estimated at £2.9billion

What do pregnant women think?

Women care about research into medicines they might use during pregnancy. They want to make sure that any medications they take during pregnancy are safe for them and their child. This subject is high on their priority lists. The public rated research into the safety of medicines during pregnancy as the third-highest priority for pregnancy research, behind mental health and birth experiences, in a report by RAND Europe in 2020.

Work by a non-profit organisation, the James Lind Alliance which brings patients, carers and clinicians together to look at research priorities, shows that three of the top ten research priorities for tackling preterm birth focus on treatment and prevention. Likewise, the Alliance's workshop on research priorities on tackling miscarriage also focused on possible interventions including medicines.

Women want more information on drugs in pregnancy. They actively seek advice from doctors, midwives, pharmacists, family, friends and the internet. One UK study in 2016 revealed that almost half the pregnant women it surveyed wanted more information on using medicines during pregnancy.

Pregnant women, in general, will put the health of their unborn children above their own wellbeing. But sometimes this can potentially be harmful to the baby. The same UK study raised concerns that some pregnant women with urinary tract infections would not take medication for fear of causing harm – which could lead to serious complications for both mother and baby.

Both pregnant women and clinicians may overestimate the risk of birth defects with medicine use in pregnancy because of the knowledge gap. This can lead to women not taking crucial medicines they need, for example, for depression or high-blood pressure.

Would pregnant women be willing to participate in clinical drug trials? Speculative views on the theory of participating seem to diverge from real-life recruitment to trials.

'I'd have to really think about it, purely because it's somebody else's life you're putting on the line, not just your own, it's somebody else's future.'

Patient's view from study in Health Expectations in 2020

One 2019 study in Ireland on the views of women taking part in a trial studying a diagnostic test for pre-eclampsia found most were willing for altruistic reasons and felt they were 'paying it forward' in terms of the knowledge gained from them to help women in future pregnancies. They also felt the benefit of an early diagnosis might help their pregnancy. However, the women considered the idea of a medicine being tested in pregnancy as more risky.

Another focus group study with women in the USA, published in 2018, echoed similar views on testing drugs during pregnancy.

However, pregnant women appear willing to participate in drug trials where there is already a risk to their pregnancy. Several large, randomised clinical trials testing drugs in pregnancy have been successfully run by researchers in the UK and recruited many thousands of pregnant women at risk of a serious complication. Notably, these were all funded by public bodies, rather than companies developing new drugs.

Research into medicines safety during pregnancy is a **top 3 priority** for the UK public

50% Want more safety information

Thousands of women already participating in **UK clinical trials**

Previous clinical trials of drugs in pregnancy

The Magpie trial looked at whether magnesium sulphate could benefit women and babies by preventing convulsions in 10,000 women with pre-eclampsia, who were either about to give birth or who had just given birth. The drug seemed to halve pre-eclampsia and probably reduced deaths in mothers, according to the results in 2002. It didn't seem to have any significant side-effects for mothers or babies in the short-term.

The PROMISE trial, led by researchers at the University of Birmingham, sought to validate new approaches to tackling the risks of unexplained miscarriage by comparing the effects of progesterone with placebo in over 800 pregnant women who were at risk. This study, published in 2015, found the drug made no difference – a disappointing result, but one which enabled health professionals to avoid giving unnecessary medication in the hopes of an unproven effect.

What are the pharmaceutical industry's views?

Other than the historical context of the thalidomide tragedy and other cases of drugs used in pregnancy that have later been found to have harmful effects, there is little public documentation on the current views of the industry. Pregnancy-related drug research and clinical trials are notable by their absence.

However, there appears to be some interest from pharma. Private-public initiatives have launched in recent years, such as the EU-funded ConcePTION project to provide better information on the safety of medicines in pregnancy. This launched in April 2019 and is led jointly by Novartis and the University Medical Center Utrecht.

While the Association of the British Pharmaceutical Industry (ABPI) 2019 report on clinical trials and the future of medicine in the UK made no mention of pregnancy research, their 2020 national conference featured keynote presentations on the topic, eliciting significant interest from member organisations who might be willing to partner on such initiatives.

But worries about liability are an ongoing concern. 'Fear is a great motivator', Robert Ternik of Eli Lilly told a US task force meeting discussing the issue in November 2018, according to the American medical news website STAT.

'There is still a perception in the industry of pregnant women being a special population in which you cannot do research.'

Ida Niklson, project co-leader on the ConcePTION initiative and consultant to Novartis in an interview with the Motherhood Collective Impact Programme, February 2020

What potential solutions are being discussed to overcome the barriers?

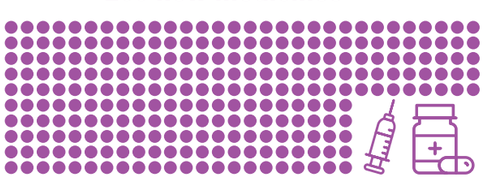
Government, regulators, clinicians and academics, patients and citizens could work collaboratively with drug companies to help progress research into medicines for pregnancy. There are major opportunities for shared approaches in creating financial incentives for investment, attracting international donor agencies, public-private partnerships, addressing regulatory gaps and hurdles, mitigating liability and harnessing new technologies to directly impact the health, safety and wellbeing of pregnant women.

For example, adding patent years to a drug tested for pregnancy could make this financially attractive to pharma. Academics and a US task force which looked at the issue for the US Congress, point to models of drug development for other neglected areas including recent improvements in the drug pipeline for children's medicines. The EU prioritised children's medicine with new rules in 2007. 'Orphan' drug development for rare diseases may also provide another model.

Targeted programmes with funding and a prioritisation process for off-label drugs (which companies have no financial incentive to study) have helped in children's drug development. Regulators could also make it a requirement for new drug submissions to include trial data on safety in pregnant women in order to gain market approval. In the UK, there has been discussion around launching an 'Obstetric Investigational Plan', following on from the success of Paediatric Investigational Plans in the UK and Europe.

Targeted programmes can drive rapid innovation:

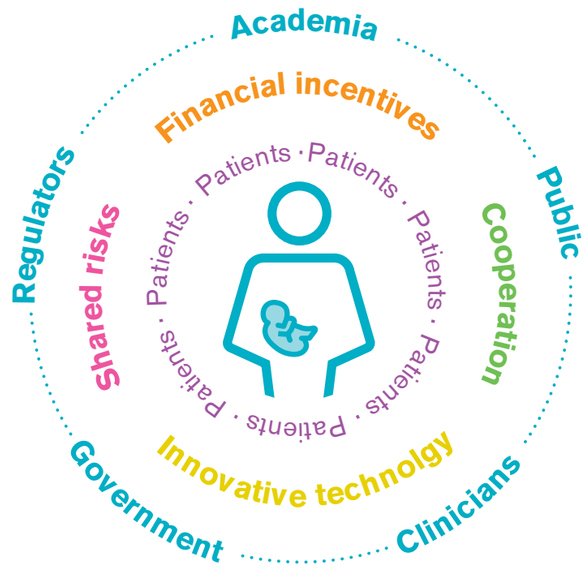
EU prioritised children's medicine with new rules in 2007 leading to **260 new medicines**



On the other hand, ways to 'de-risk' research into pregnancy drugs might help assuage the drug industry's huge fear of litigation. For example, the US pregnancy task force discussed a federally funded compensation scheme to protect companies, based on the US Vaccine Injury Compensation Program.

Harnessing new and innovative technologies could help provide new lab models for testing in a pre-clinical setting to mitigate risks and fears around safety and toxicity before moving on to trials in pregnant women. For example, using 'organ-on-a-chip' experiments where a chip simulates the responses of an organ to drugs. Advances in computing and data analysis may also help to minimise risks and more quickly and robustly identify promising candidates for further development.

Potential approaches will require careful consideration, public support and ethical approval. Using pregnant animals to test drugs are of limited value as human pregnancy is unlike that of any animal, but another suggestion is that instead, we could harness human embryonic stem cells for lab testing of products. Additionally, human samples from terminations of pregnancy could be used, although this would require building significant public dialogue and trust.



How Europe helped develop its children's medicines

The proportion of clinical trials in children increased over 50% after the EU brought in new regulations to stimulate drug development for children in 2007. Only 8.25% of all clinical trials in the EU were in children in 2007 – this grew to 12.4% by 2016. The European Paediatric Regulation has led to 260 new medicines or indications for children since the rules came into force. Under this, companies applying for new market authorisations, or licences for their drugs must have results from a 'Paediatric Investigational Plan' (unless inappropriate for this age group). As a financial incentive, companies with a successful plan are rewarded with a six-month patent extension.

Why act now?

While in the past the rationale behind not including pregnant women in clinical drug trials may have come from an ethical standpoint of 'first do no harm', the thinking on this may be changing. Many now argue that it is unethical not to include pregnant women in drug research.

3 out of 4 women take some medication during pregnancy, but...

73%

of drugs have no safety information in pregnancy

10%

of drugs are classified as "high-risk"

1 Only **1 new drug** has been developed in the last 30 years specifically for use in pregnancy

There is a growing awareness and momentum internationally that pregnant women are being deprived of modern medicines and should be included in drug testing. Both the USA and Europe have made considerable moves towards this in recent years.

The US regulator, the Food and Drugs Administration, has issued two sets of draft guidance on how to study drugs in pregnant and breastfeeding women. This follows on from recommendations in 2018 by a federal task force convened to investigate the lack of research in this group of patients. In the USA, there appears to be some pressure from academics, patients and the public for more research.

In Europe, there are initiatives underway to improve drug safety knowledge in pregnancy, including research partnerships with the pharmaceutical industry. The UK's own National Institute for Health Research also has a focus on improving reproductive health. However, these positive intentions have not yet led to a meaningful change in the number of drugs being developed for, or tested in, pregnancy.

Another reason to act now is that pregnant women in many developed countries like the UK are becoming more 'medically complex' as a patient group. Women are generally having babies at a later age than in the past, which increases their risk of certain pregnancy conditions like pre-eclampsia. Older expectant mothers may also be more likely to have chronic conditions like diabetes, which need treatment.

Whether properly safety tested or not, pregnant women take a lot of therapeutic drugs, and this has been growing over recent decades. Widespread 'off-label use' is a concern, with three out of four pregnant women taking at least one medicine for which there is no good safety data. One UK hospital study in 2010 showed that one-in-ten prescriptions given to its antenatal patients off-label was for a medicine considered high-risk.

Tackling the 'knowledge gap' and lack of properly tested medicines for pregnant women may also be important if the UK is to reach its goal of halving perinatal deaths in babies by 2025. And globally, improving maternal, newborn and child health, and reducing inequalities is crucial if we want to achieve the UN's Sustainable Development Goal 3 on Good Health and Wellbeing.

There may be a real opportunity now to save lives and improve the health of mothers and children. Every year, 216 women die for every 100,000 babies born. The World Health Organization says three-quarters of these deaths are preventable. It aims to cut this to 70 deaths for every 100,000 babies born by 2030.

Leading delivery of shared global ambitions:

WHO:
'*75% of worldwide deaths of pregnant women are avoidable*'

UK Government aim:
50% reduction in UK maternal and infant deaths by 2025

UN Sustainable Development Goal 3 GOOD HEALTH AND WELL-BEING

Why the UK?

The UK is ideally placed to test new and repurposed drugs in pregnant women. We are already well-established in running clinical trials in pregnant women, with more such trials than most other countries. And our integrated healthcare systems – particularly our world-leading NHS – means that the UK can provide long-term follow-up of women and children. This would make the UK an ideal testbed.

What is more, other long-term outcomes such as educational attainment, which may manifest only after many years, can also be tracked thanks to our longitudinal record systems. For example, the Health Data Research UK initiative, set up in 2017, links routine data including health, education and criminal justice data. It enables innovators across the NHS, universities, charities and private companies to work together to understand and utilise the benefits of integrated health data from existing records and new sources such as wearable technologies, and has already delivered new research in pregnancy.

There is also a strong economic case for developing pregnancy drugs in the UK. Clinical research is worth more than £2.7 billion a year in England alone, according to a 2019 report by the ABPI on clinical trials and the future of medicines. In it, the pharma industry recognises the expertise and value of the NHS, but makes no mention of pregnancy.

The industry organisation also notes that uncertainty around Brexit may undermine the UK's attractiveness for clinical research. It urges that it will be 'critical' for the UK government to deploy innovative research programmes after the UK leaves the EU. Our recent report on the UK's approach to regulation and innovation in health care identified that novel regulatory frameworks around the use of medications in pregnancy was a key area for exploration in this context, supported by both the ABPI and the government's new Regulatory Horizons Council.

The UK's current pregnancy research spend of about £51 million a year – a fraction of which will be drug research – is dwarfed by the pregnancy-related litigation costs of £2.5 billion in 2018–19 alone to the NHS, as well as the long-term cost to the NHS and education systems of managing disability.

'The NHS has massive potential as a driver for global investment, with our health service offering a great opportunity to trial new medicines and vaccines, with its wealth of expertise and access to health data.'

Association of the British Pharmaceutical Industry report in 2019

ORACLE II: how long-term study in the UK revealed cerebral palsy risks

The UK offers a world-class system for following-up patients' health, well-being and even educational attainment long-term. The ORACLE II study, which compared two antibiotic treatments and placebo in preventing spontaneous preterm birth, found more children had cerebral palsy at age seven if they had received antibiotics while in utero, with one – erythromycin – being associated with greater functional impairment in children at this age. Neither treatment was better than placebo for preterm birth. The study also looked at educational attainment by analysing SATS exams taken by UK children at age seven.

Summary

The lack of understanding of which drugs can be safely used in pregnancy plus the lack of new drug development in pregnant women is a major global public health issue. Women and their babies are being denied the benefits of modern medicine – they are dying for lack of research. Worldwide, three-out-of-four women who die during pregnancy and birth could be saved. Two-out-of-three pregnant women dying as a result of pre-eclampsia could be saved. And some 15 million babies worldwide are born too early each year leading to death and disability.

This is not a problem that we can ignore at home.

There are around 4,000 stillbirths and neonatal deaths in the UK every year. Maternal deaths are not as common, but are still unacceptably high. Pregnancy complications cost the economy billions of pounds annually in direct and long-term care, and litigation around perceived failings of care is of the same scale. We occupy an incredibly opportune and fortunate position in our ability to tackle these issues – but have not yet taken any steps to do so.

The toll of inaction is as huge as modern medicine's capacity to act, and to act now.

This is an issue which deserves consideration from policy-makers and vocal support from all of us. There are very real practical, policy and psychological barriers to achieving change – but none that cannot be overcome through collaboration.

With discussion and collaborative effort between government, regulators, researchers and communities of women and their families, and the pharmaceutical industry, we can stop excluding women and their babies from the modern world and give them access to the medicines they deserve.

References

Action on Pre-eclampsia. Homepage: **https://action-on-pre-eclampsia.org.uk**

Action on Pre-eclampsia. 'Q & A'. **https://action-on-pre-eclampsia.org.uk/public-area/questions-answers/#1464629876065-9a90b258-3faa**

Adam MP, Polifka JE, Friedman JM: Evolving knowledge of the teratogenicity of medications in human pregnancy. *Am J Med Genet C Semin Med Genet*. 2011; 157C(3): 175–82.

Association of the British Pharmaceutical Industry. 'Clinical trials: How the UK is researching the medicines of the future.' Autumn 2019. **www.abpi.org.uk/media/7607/rmi-0128-0919-clinical-trials-report.pdf**

Barron, Danielle. 'Bridging the knowledge gap for pregnant and breastfeeding women.' *Motherhood Collective Impact Programme*. February 2020. **https://motherhoodcollectiveimpact.org/bridging-the-knowledge-gap-for-pregnant-and-breastfeeding-women**

Bhattacharya, Shaoni. 'Taking drug trials to the limit'. *New Scientist*. March 2011. **www.newscientist.com/article/mg20928042-300-taking-drug-trials-to-the-limit**

Brocklehurst, Peter. *Personal communication*. 9/9/20, 23/9/20 and 24/9/20.

Brocklehurst, Peter. 'What Can We Do to Improve Maternal and Child Outcomes?' Presentation to Increasing Trust in Biopharmaceutical Industry Research conference, February 2020.

Chappell, Lucy C. and Anna L. David. 2016. 'Improving the Pipeline for Developing and Testing Pharmacological Treatments in Pregnancy.' *PLOS Medicine* 13 (11): e1002161 **https://doi.org/10.1371/journal.pmed.1002161**

ConcePTION project. 'ConcePTION press release.' May 2019. **www.imi-conception.eu/news-details/?news_id=463**. Accessed 10/9/20.

Coomarasamy Arri, Williams H. Truchanowicz E. Seed P.T. Small R. Quenby S. Gupta P. Dawood F. Koot Y.E. Bender Atik R. *et al*. 'A randomized trial of progesterone in women with recurrent miscarriages.' *N. Eng. J. Med*. 2015;373:2141-8.DOI: 10.1056/NEJMoa1504927

Eichler HG, Abadie E, Baker M, Rasi G. Fifty years after thalidomide; what role for drug regulators? *Br J Clin Pharmacol* 2012; 74: 731–3.

European Federation of Pharmaceutical Industries and Associations. 'Stimulating the development of new medicines for children.' **www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/stimulating-the-development-of-new-medicines-for-children**. Accessed 24/9/20.

European Medicines Agency. 'EMA Regulatory Science to 2025: Strategic reflection.' 2020. **www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf**

European Medicines Agency. 'Orphan Incentives'. **www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/orphan-incentives**

European Medicines Agency. 'Paediatric Investigation Plans.' **www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans** Accessed 25/9/20.

European Medicines Agency. 'Rewards and incentives for paediatric medicines.' **www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/rewards-incentives-paediatric-medicines**. Accessed 25/9/20.

Fisk NM, Atun R: Market failure and the poverty of new drugs in maternal health. *PLoS Med*. 2008; 5(1): e22.

Flenady V, Reinebrant HE, Liley HG, Tambimuttu EG, Papatsonis DNM. 'Oxytocin receptor antagonists for inhibiting preterm labour.' *Cochrane Database of Systematic Reviews* 2014, Issue 6. Art. No.: CD004452. DOI: 10.1002/14651858.CD004452.pub3

Food and Drug Administration (US). FDA Press Release. Statement from Principal Deputy Commissioner Amy Abernethy, M.D., Ph.D., and Janet Woodcock, M.D., director of FDA's Center for Drug Evaluation and Research, on policies designed to capture more data to better understand effects of prescription drugs in pregnant and nursing women. May 2019. **www.fda.gov/news-events/press-announcements/statement-principal-deputy-commissioner-amy-abernethy-md-phd-and-janet-woodcock-md-director-fdas**

Gov.UK. 'Valproate medicines (Epilim ▼, Depakote ▼): contraindicated in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met.' **www.gov.uk/drug-safety-update/valproate-medicines-epilim-depakote-contraindicated-in-women-and-girls-of-childbearing-potential-unless-conditions-of-pregnancy-prevention-programme-are-met**. Accessed 28/9/20.

Graham, Jennifer. 'Pregnant women are largely left out of drug research. Should this change?' *Deseret News*. October 2019. **www.deseret.com/2018/10/20/20656577/pregnant-women-are-largely-left-out-of-drug-research-should-this-change**

Hardy, Janet R., Brian P. Leaderer, Theodore R. Holford, Gillian C. Hall, and Michael B. Bracken. 2006. 'Safety of medications prescribed before and during early pregnancy in a cohort of 81 975 Mothers from the UK General Practice Research Database.' *Pharmacoepidemiology and Drug Safety* 15 (8): 555–64. As of 25 September 2020: **https://doi.org/10.1002/pds.1269**

Hayes-Ryan, Deirdre, Sarah Meaney, Caroline Nolan, Keelin O'Donoghue. 'An exploration of women's experience of taking part in a randomized controlled trial of a diagnostic test during pregnancy: A qualitative study.' *Health Expectations*. 2020; 23 (1): 75-83. **https://doi.org/10.1111/hex.12969**

Health Data Research UK. 'Health Data Research UK Approach.' **www.hdruk.ac.uk/what-is-health-data-research/health-data-research-uk-approach**. Accessed 25/9/20.

Herring, Christopher, Aine McManus and Andrew Weeks. 2010. 'Off-label prescribing during pregnancy in the UK: an analysis of 18,000 prescriptions in Liverpool Women's Hospital.' *International Journal of Pharmacy Practice* 18 (4): 226–29. As of 25 September 2020: **https://onlinelibrary.wiley.com/doi/abs/10.1211/ijpp.18.04.0007**

Hoover, Robert N. *et al*. 'Adverse Health Outcomes in Women Exposed In Utero to Diethylstilbestrol.' *N. Engl. J. Med*. 365(14), 1304–1314, **https://doi.org/10.1056/NEJMoa1013961** (2011).

Independent Medicines and Medical Devices Safety Review. 'First Do No Harm.' July 2020. **www.immdsreview.org.uk/downloads/IMMDSReview_Web.pdf**

James Lind Alliance Priority Setting Partnership. 'Miscarriage Top 10'. **www.jla.nihr.ac.uk/priority-setting-partnerships/miscarriage/top-10-priorities.htm**

James Lind Alliance Priority Setting Partnership. 'Preterm Birth Top 10.' **www.jla.nihr.ac.uk/priority-setting-partnerships/preterm-birth/top-10-priorities**

Kaye, Dan Kabonge. 'The moral imperative to approve pregnant women's participation in randomized clinical trials for pregnancy and newborn complications.' *Philosophy, ethics, and humanities in medicine*: PEHM vol. 14,1 11. 6 Sep. 2019, doi:10.1186/s13010-019-0081-8.

Kenyon, Sara, Pike, K Jones, DR, Brocklehurst, P, Marlow, N, Salt, A *et al*. 'Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial.' Lancet, 372 (2008),1319-1327. **https://doi.org/10.1016/S0140-6736(08)61203-9**

Liu KA, Mager NAD. 'Women's involvement in clinical trials: historical perspective and future implications.' *Pharm. Pract.* 2016;14(1):708. doi: 10.18549/PharmPract.2016.01.708. **www.ncbi.nlm.nih.gov/pmc/articles/PMC4800017**

Lynch MM, Squiers LB, Kosa KM, Dolina S, Read JG, Broussard CS, Frey MT, Polen KN, Lind JN, Gilboa SM, Biermann J. Making decisions about medication use during pregnancy: Implications for communication strategies. *Maternal and Child Health Journal*. 2018;22(1):92–100. doi: 10.1007/s10995-017-2358-0.

Macklin, Ruth. 'Enrolling pregnant women in biomedical research.' *Lancet* 2010; 375 (9715), 632-633. **https://doi.org/10.1016/S0140-6736(10)60257-7**

Mangham, Lindsay J., Stavros Petrou, Lex W. Doyle, Elizabeth S. Draper and Neil Marlow. 2009. 'The Cost of Preterm Birth Throughout Childhood in England and Wales.' *Pediatrics* 123 (2): e312–27. As of 25 September: **https://doi.org/10.1542/peds.2008-1827**

Mayo Clinic. 'Pre-eclampsia'. **www.mayoclinic.org/diseases-conditions/preeclampsia/symptoms-causes/syc-20355745**

MBRRACE-UK: Saving Lives, Improving Mothers' Care. 'Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2015–17.' Nov 2019.

MBRRACE-UK Perinatal Mortality Surveillance report for births in 2017. 'MBRRACE-UK Perinatal Mortality Surveillance Report for Births in 2017'. October 2019. **www.npeu.ox.ac.uk/assets/downloads/mbrrace-uk/reports/MBRRACE-UK%20Perinatal%20Mortality%20Surveillance%20Report%20for%20Births%20in%202017%20-%20FINAL%20Revised.pdf**

McKiever, M., Frey, H. & Costantine, M.M. 'Challenges in conducting clinical research studies in pregnant women.' J Pharmacokinet Pharmacodyn 47, 287–293 (2020). **https://doi.org/10.1007/s10928-020-09687-z**

Medley N, Vogel JP, Care A, Alfirevic Z. 'Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews.' *Cochrane Database Syst. Rev*. 2018;11:CD012505 Published online 2018 Nov 14. doi: 10.1002/14651858.CD012505.pub2

Michalowska Howells, Bozena. 'Sodium valproate – hoping for support and answers for families affected by Foetal Valproate Syndrome'. Leigh Day website blog, March 2020. **www.leighday.co.uk/Blog/March-2020/Sodium-valproate-hoping-for-support-and-answers**. Accessed 17/9/20.

Morris, Katie. 'Unmet Clinical Needs in Pregnancy.' Presentation to Increasing Trust in Biopharmaceutical Industry Research conference, February 2020.

National Institute for Health Research. Reproductive Health. **www.nihr.ac.uk/explore-nihr/specialties/reproductive-health.htm**

National Institutes of Health (US). 'Task force on research specific to pregnant women and lactating women: Report to Secretary, Health and Human Services, Congress.' September 2018. **www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf**

Postnote, UK Parliamentary Office of Science and Technology. 'Children's Medicines.' July 2006. No. 266. **www.parliament.uk/globalassets/documents/post/postpn266.pdf**

RAND Europe. 'Pregnancy Research Review: Policy Report'. 2020
Ross, Gerard. 'Ending the Pregnant Pause.' Uppsala Reports Issue 81, p 16-21. October 2019. **https://view.publitas.com/uppsala-monitoring-centre/uppsala-reports-81/page/16-17?utm_source=newsletter&utm_medium=email&utm_campaign=UR81&utm_content=UR81_newsletter**. Accessed 10/9/20.

Royal College of Obstetricians and Gynaecologists. 'Developing New Pharmaceutical Treatments for Obstetric Conditions'. Scientific Impact Paper No.50. May 2015.

Second Wave Initiative, UNC Center for Bioethics. **https://bioethics.unc.edu/second-wave-initiative**. Accessed 11/9/20.

Stock SJ and Norman JE. *F1000Research* 2019, Medicines in pregnancy [version 1; peer review: 3 approved] 8(F1000 Faculty Rev): 911 **https://doi.org/10.12688/f1000research.17535.1**

The Magpie Trial Group. 'Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised, placebo-controlled trial.' *Lancet*. 2002; 359: 1877-1890. **https://doi.org/10.1016/S0140-6736(02)08778-0**

The Thalidomide Trust. 'About Thalidomide'. **www.thalidomidetrust.org/about-us/about-thalidomide**. Accessed 17/9/20.

Thielking, Megan. 'Women need answers on drug use during pregnancy. Here's how to improve research'. *STAT News*, 5 Dec 2017. **www.statnews.com/2017/12/05/clinical-trials-pregnant-women**. Accessed 11/9/20.

Twigg MJ, Lupattelli A, Nordeng H. 'Women's beliefs about medication use during their pregnancy: a UK perspective.' *Int J Clin Pharm*. 2016;38(4):968–976. doi: 10.1007/s11096-016-0322-5.

Widnes SF, Schjøtt J. 'Risk perception regarding drug use in pregnancy.' *Am J Obstet Gynecol*. 2017; 216(4): 375–8.

UNIVERSITY OF BIRMINGHAM
Edgbaston, Birmingham,
B15 2TT, United Kingdom
www.birmingham.ac.uk

Infographic consultancy: ***nigelhawtin.com***

Designed and printed by

UNIVERSITY OF BIRMINGHAM | creativemedia