

Imperial College London's response to the Department of Health and Social Care's call for evidence on the Women's Health Strategy, June 2021

SUMMARY

- We welcome the government's focus on improving the health and wellbeing of women and girls in the UK. Women's health is a major focus for Imperial's globally recognised research and clinical innovation groups, spanning both women-specific health conditions, such as reproductive and maternal health, and the leading causes of death and disability for women (and men), such as cardiovascular disease (CVD) and mental illness.
- A central premise to our evidence are **the benefits to women's health that will stem from high-quality data on societal trends, on disease incidence, prevention and management, disaggregated by sex and gender**. These data can drive innovation in health and social care and in addressing the wider determinants of health for women.
- Improvements in women's health will substantially benefit wider society through multiple routes. Women represent 51% of the population, provide 70% of unremunerated caring activities, and represent 99% of the routes of transmission of the early developmental determinants of health and disease to the next generation. In addition, women live on average 5 years longer than men
- Progress in these areas is crucial to; **delivering on DHSC priorities¹**, such as the reduction in pre-term birth and stillbirth; **providing equity of access to evidence-based care**, including contraception and CVD treatments; and **ensuring women's experience is at the centre of health policy and provision**.
- Data which truly reflect women's health and experience requires **making the best use of the data collected during routine clinical care, by maximising the involvement of women in research and clinical trials and by designing studies so that they give answers specifically relevant to women**.
- Research into conditions such as cardiovascular disease and common mental illnesses, which are leading causes of death and unhealthy life years in women², could be designed to **give information on risk factors and outcomes which differ in importance and severity in women and men**.
- The COVID-19 pandemic has highlighted the responsiveness and capacity of the UK's clinical research infrastructure. However, women in pregnancy were not recruited in significant numbers to the RECOVERY trial or at all into vaccine trials, leading to uncertainty on treatment and prevention. These **deficits in data and understanding of women's health are evident across all areas of medicine and public services**. Although currently a source of inequity, these also represent **readily realisable opportunities for action through innovations in policy and practice**.

We submit evidence here from the research groups across Imperial College London engaged in improving Women's Health within Themes 3 and 5 of the evidence call. We describe the priority being addressed, the context of the subject area and recommendations which would lead to step-changes in outcomes for women in these areas.

THEME 3: WOMEN'S HEALTH ACROSS THE LIFE COURSE

A woman's health must be considered as a continuum across her life course, spanning adolescence, reproductive years, the menopause and later life health^{3,4}. Factors arising at any stage, even before conception, can impact on health at a later stage in life. Empowering a woman with the information and means to plan her life and spend it in the best possible health is within reach, if evidence-based strategies and interventions can be brought into routine practice.

WOMEN'S REPRODUCTIVE HEALTH

Women spend on average, 30 years of their lives preventing unplanned pregnancy. Unintended pregnancies make up 45% of all pregnancies in England, with nearly 60% of these ending in abortions, and up to half of unintended pregnancies due to incorrect or inconsistent use of contraception. Contraception has an impressive return on investment of £11 for every £1 spent⁵.

Priority: Equity of access to reliable contraception for all women in England through re-designing services around women's lives

Context: Every year in England and Wales, 640,000 women give birth and transition to life with a new baby. Their healthcare in the years after delivering a baby is provided by a disjointed array of primary care, secondary care and community services. Despite the shared goals of these agencies, no single provider is accountable for subsequent unplanned pregnancy, termination of pregnancy or occurrence and recurrence of pregnancy complications including diabetes and hypertension. There is an absence of systems leadership to champion cohesive and consistent postnatal and inter-pregnancy care and women have to seek-out available resources, which are not delivered at the time or place of need, to safeguard their futures.

This is detrimental to both equity of access to reproductive healthcare and for health outcomes in pregnancy and the postnatal period.

Access to contraception after birth Reliable contraception is essential to women's autonomy and is highly cost-effective. Just 12% of women plan to use Implants and Intra-uterine devices (which are 20 times more effective at preventing pregnancy than the pill) after having a baby, but 43% would choose these if they were available before they left hospital⁶. It is possible to conceive from 21 days after delivery and 33-50% of couples resume having sex by 6 weeks after delivery.

An under-recognised consequence of poor reproductive healthcare for postnatal women is the health impact of a short inter-pregnancy interval. An interval of <1 year between delivery of a baby and next conception is associated with an increase in the risk of pre-term birth and neonatal death⁷, DHSC has set priorities for 25% and 50% reduction respectively by 2025. The direct healthcare UK annual costs for pre-term births is £1.24 billion, largely due to the high cost of neonatal care, with an additional £2.48 billion indirect costs. Pre-term birth carries lifetime adverse impacts on learning, development and health.

Public Health England estimates that post-birth contraception services offer an unparalleled return on investment of £16 for every £1 invested and that NHS costs are recouped within 2 years. New post birth services have sprung up around England during the pandemic to improve access to post-birth contraception, however 78% of these are not commissioned or funded and will shortly have to cease provision.

Recommendations:

- NHS England (NHSE) should roll-out post-birth contraception services on the model of the North-West London regional post-birth contraception service across England.
- Local Authority funding for contraception should be ring-fenced, as the return on investment of £11-16 for every £1 means cuts to contraception provision will cost the taxpayer more than 10 times what is apparently saved in the short term.

Contraception delivered in Primary Care Long-acting reversible contraception is among the most effective contraceptive methods, but uptake remains low even in high-income settings. In 2009/2010, a target-based pay-for-performance scheme in Britain was introduced for primary care physicians to offer advice about LARC methods to a specified proportion of women attending for contraceptive care to improve contraceptive choice.

By 2013/2014, the pay-for-performance scheme resulted in an additional 4.53 LARC prescriptions per 1,000 women (relative increase of 13.4%) more than would have been expected without the scheme. There was a concurrent absolute reduction of -5.31 abortions per 1,000 women, or -38.3% relative reduction. These are profound effects of change in payment which may be applicable in other settings⁸. This incentive is being withdrawn from primary care in Britain so we cannot be certain if the impact could be sustained.

Recommendation: Primary care organisations could consider offering pay-for-performance schemes for long-acting reversible contraception locally. NHSE should consider similar measures in all care settings to improve women's awareness of and access to LARC.

EARLY INDICATORS OF LIFE COURSE HEALTH

Some conditions develop in pregnancy, because changes in the body in pregnancy add to underlying risk factors for disease, revealing those women who are at greater risk of later life conditions. These include pre-eclampsia, which occurs in women at risk of cardiovascular disease in later life and gestational diabetes, which occurs in women at risk of type 2 diabetes in the years after pregnancy.

Priority: Develop interventions to prevent Gestational Diabetes (diabetes which develops in pregnancy) and women's subsequent progression to Type 2 diabetes

Context: Gestational diabetes (GDM) affects 2-18% of pregnancies and is associated with stillbirth, pre-term delivery, big babies, birth trauma, neonatal hypoglycaemia and childhood overweight and obesity. Women with GDM in one pregnancy have a 70% chance of developing it in their future pregnancies.

Women with GDM have 10 times the risk of those not affected by GDM of developing Type-2 Diabetes in the 10 years after delivery⁹. Diabetes care costs the NHS £10 billion a year and this cost will rise: 3.1 million people had diabetes in 2016/17 and by 2035 this is predicted to increase to 4.9 million.

The years after a pregnancy affected by GDM represent a unique period for both preventing recurrence of GDM and preventing Type-2 diabetes in a group of women at high risk of the condition. Women who have had GDM are eligible to enter the NHS Diabetes Prevention Program after developing however no prevention interventions have been shown to be effective for women at risk of GDM.

Recommendation: NIHR should consider a funding call for interventions to prevent Gestational Diabetes and for interventions specifically targeted at women affected by GDM to prevent T2DM.

CANCER

Gynaecological cancers are diagnosed in 21,550 women a year in the UK. Uterine, vulval and cervical cancer have 10-year survival rates of 72%, 67% and 51% respectively, however for ovarian cancer 10-year survival is just 37%.

Priority: Improve the surgical treatment of ovarian cancer for all women in England to improve survival.

Context: A recent trial of ovarian cancer screening in 1,243,282 women concluded that screening was ineffective in reducing mortality from ovarian cancer even though it allowed diagnosis at an earlier stage. The majority of women with ovarian cancer will still present in late stages of the disease and will only have the best of chance of survival if surgery is able to remove all traces of cancer from around the abdomen and pelvis, sometimes including removing bowel, parts of the liver and spleen and sections of the lining of the abdomen over the diaphragm¹⁰. This surgery is highly specialist and is not performed by gynaecologists with the standard training provided in the UK.

A recent audit of practice in UK centres showed that only 51% of all ovarian cancer patients will ever receive surgery during their anticancer management¹¹. This means that half of the patients will never receive standard of care which is the combination of surgery and chemotherapy. This is largely because some centres consider the level of required as too technically difficult and opt to give chemotherapy alone. Comparing the UK's 37% 10-year survival rate for ovarian cancer with comparable healthcare systems is uncomfortable, 42% in Denmark, 43% in Australia and 46% in Norway.

The Chief Medical Officer recommended in 2015 that the RCOG should ensure that sub-specialist training in gynaecological oncology equips doctors to perform optimal surgery for gynaecological cancers and reduce mortality from ovarian cancer. However, the barriers to delivering optimal surgery go beyond the technical skills of individual surgeons.

Recommendation: NHSE should re-organise the resources and infrastructure of cancer centres in the UK to enable women with more advanced ovarian cancer to have the option of surgery in supra-regional cancer centres, that will specialise in the treatment of advanced stages of the disease. These supra-regional centres should comply with international standard Quality Indicators to support improved outcomes and be accompanied by robust research platforms will be incorporated to any surgical advance. Consideration of women's quality of life under a holistic care umbrella will be an indispensable part of this service improvement.

Priority: Improve diagnostics for gynaecological cancer based on ultrasound

Context: Ovarian cancer remains the leading cause of death from gynaecological cancer in the UK. Differentiating between cancer and a benign ovarian cyst can be challenging. Diagnostic uncertainty in the characterisation of ovarian masses can trigger further investigations and lead to surgical intervention.

Ovarian cysts are common, affecting 14% of women. Surgical management of an ovarian cyst is needed if there are symptoms or if there is a suspicion of cancer. One in ten women in their lifetime will undergo surgery for ovarian cyst, yet the majority will have benign ovarian cysts. Unnecessary surgery has both cost implications for the NHS, but also and more importantly, potentially exposing women to complications, which may compromise their future reproductive potential.

Watchful waiting is safe strategy for women with benign ovarian cysts, due to the low incidence of cyst-related complications, such as ovarian torsion or cyst rupture. Diagnostic confidence in the benign classification of ovarian masses on ultrasound is fundamental to the safe conservative management of ovarian masses.

Ultrasound is used as first-line imaging for suspected ovarian cancer. Ultrasound-based models, such as Simple Rules and Assessment of Different Neoplasia's in the adnexa (ADNEX), have been developed by the International Ovarian Tumour Analysis (IOTA) group to support the classification of ovarian masses¹². The models have been widely validated in the hands of expert and non-expert ultrasound operators yet are still reliant upon the recognition of specific ultrasound features within an ovarian mass.

Machine learning (ML) has already shown great promise within eye and breast screening. The clinical application of ML could improve the diagnosis of benign cysts and ovarian cancer and provide practitioners with an artificial second reader that encodes representations from thousands of scans, more than a specialist sees during their career.

Recommendation: Prioritise funding the development of Machine Learning models to ensure women with suspected ovarian cancer to ensure women receive accurate diagnosis or reassurance and avoid unnecessary surgical intervention for women with benign ovarian masses.

HIV

Women living with HIV in England now have a near-normal life expectancy. However, the pandemic has highlighted how different groups of women still face challenges in accessing essential health services.

Priority: Ensure equity of access to HIV services for women from different ethnic and societal groups and for trans women.

Context: During the pandemic, researchers at Imperial examined the consequences of COVID-19 lockdowns on clinical, virological, and mental health outcomes for BAME women living with HIV and reviewed the needs of this population to optimise HIV care/services.

Studies have shown that women living with HIV are more likely to experience menopausal symptoms than women who do not have HIV, including depression and anxiety. However, because of confusion between menopausal symptoms and potential HIV medication side effects or fear of drug-drug interactions between the latter and HRT, women with HIV are prescribed HRT less frequently than women without HIV. Hence, the relationship between menopause, HIV and HRT use is understudied.

Imperial researchers have also conducted extensive studies in transwomen living with HIV. This is another an understudied population with a 20% higher risk of acquiring HIV and an even higher risk of receiving sub-optimal treatment. A large European study is in progress to investigate outcomes of HIV and barriers to engaging with care in transwomen with HIV. A clinical trial to optimise antiretroviral treatment medication in transwomen living with HIV is also underway.

Recommendation: Integrated Care Systems should scope local needs to ensure HIV services can deliver comparable health outcomes for those women most at risk of poor access and stigmatisation from HIV.

ABDOMINAL AORTIC ANEURYSM (AAA)

Priority: Improve treatment and survival for women with AAA.

Context: We should not accept the tenet that treating women for AAAs is more problematic as when we do not fully understand how women's aneurysms and healthcare needs differ from those of men. There are no national screening programmes for AAA in women: the prevalence of AAA in women aged 65-75 years is about 4-fold lower than in men and screening programmes would be unlikely to be cost-effective. However, lack of screening and missed opportunity for elective repair leads to a sex-specific disparity in the risk of aneurysm rupture, with women accounting for 1 in 3 ruptures in the UK and Sweden¹³.

Since 1990, there has been a pan-European, rapid decline of age-standardised population mortality from abdominal aortic aneurysm (AAA) for men. However, for women, mortality rates have changed little over time. This suggests that the principal factors responsible for reducing mortality in men, such as smoking cessation or avoidance, screening, widespread use of endovascular repair (EVAR) rather than open repair and better peri-operative care may be less applicable and/or less effective in women.

There is no evidence for the aortic size threshold for intervention in women as women were under-represented in the randomised trials of intervention versus surveillance. However, we know that the rupture rate of small AAA is 4 times higher in women than men.

Recommendation: NIHR should consider a call for dedicated research to improve operative survival for women for AAA repair. Trials investigating outcomes of AAA repair should present sex-specific data.

KIDNEY DISEASE

Priority: Ensure women with kidney disease have timely access to safe and effective contraception, pre-pregnancy planning, fertility treatment and menopause management.

Context: Women with Chronic Kidney disease (CKD) are a microcosm of all the inequity women face in healthcare. CKD causes impaired fertility, increases risk of adverse pregnancy outcomes, makes contraception choice complex, causes premature menopause and is a strong risk factor for cardiovascular disease. Importantly, CKD is more common and more severe in women from minority ethnic backgrounds and those from more socially deprived areas. They face the mental and social stresses of living with a chronic condition, with the threat of end-stage kidney disease (and the need for dialysis or transplantation and a massively increased mortality).

Up to 3% of pregnancies are in women with CKD, often undiagnosed, and 1 in 750 pregnancies is in women with more advanced CKD (stages 3-5). CKD is a risk factor for adverse pregnancy outcomes including preterm delivery, fetal growth restriction and a significant loss of maternal kidney function, and in research led by Imperial brings the possibility of end-stage kidney disease forward by 2-5 years¹⁴. Importantly, there needs to be more consistent follow up of women diagnosed with kidney disease during pregnancy – establishing clear pathways on a regional basis will reduce the risk of missing appropriate long term follow up and improve prevention of end-stage kidney disease.

Recommendations:

- All women with CKD should have access to expert multi-disciplinary obstetric-renal teams (as established at Imperial for the past 26 years) for pre-pregnancy counselling and intrapartum care – in order to ensure optimum pre pregnancy preparation, empower women to make informed choices and provide optimal fetal and maternal monitoring. All pregnancies in women with CKD should be recorded in the national registry - <https://renal.org/rare-renal/patient/pregnancy-and-chronic-kidney-disease-0> (established by a group led from Imperial). Outcomes need to be benchmarked against the standards set out in the NICE assured Renal Association guideline on Pregnancy and Renal Disease¹⁵.
- Use established cohorts (such as those from Imperial's 25-year obstetric renal clinic) to evaluate the health of children born to women with kidney disease; evaluate the benefit of routine neonatal assessment of all babies born to women with CKD and set up a prospective national birth cohort for women affected by CKD and their babies.

THEME 5: RESEARCH, EVIDENCE AND DATA

The rich sources of health data in England, from NHS digital, the ONS and DHSC can be linked with other national datasets, e.g. from child health (UK National Neonatal Research Database) and education and form a valuable, multi-purpose resource which can be harnessed to improve health outcomes, as recognised in the UK National Data Strategy. UK clinical research has been a leading light in the global response to the pandemic and has provided essential data to support our national recovery. We must reassure women in the UK that their health data will be and remain anonymised, used for ethically-approved projects only and not sold on.

WOMEN'S HEALTH DATA

Data from clinical research and from national datasets data sources could be of even greater utility in delivering national priorities for women's health if they are designed to provide information specific to women and their life course health and made more accessible for research, service improvements and ensuring safety in clinical care. Measures to improve women's participation in research, particularly during pregnancy, are key to providing these crucial data.

Priority: Clinically significant differences have been observed between women and men, yet health research, and thus health policy, continue to be largely sex- and gender-blind.

Context: There is increasing evidence that women and men can differ significantly in how they develop and experience disease. Such differences arise at various stages of a disease – from susceptibility through to diagnosis, progression, treatment and outcomes – as well as at different points in the life course e.g. pregnancy and menopause. This is due to a combination of genetic, epigenetic, hormonal, environmental, social, economic and behavioural factors¹⁶.

Whilst awareness of sex and gender differences in disease is increasing, this is not yet reflected in policies and clinical guidelines, the vast majority of which remain sex- and/or gender-blind. Furthermore, women continue to be underrepresented in clinical studies, and sex and gender comparisons – if done at all – are often afterthoughts, rather than an integral part of study design.

Cardiovascular disease: Coronary heart disease is a leading cause of death amongst women, in the UK and globally. Recent UK data show that the 30-day mortality for women with a myocardial infarction heart attack is twice that of men (5.2% vs

2.3%), even after adjusting for background health factors. In the same study, compared to men, women less frequently received 13 of the 16 quality indicators for acute myocardial infarction. Based on these findings, it was estimated that 8,243 deaths among women could have potentially been avoided if the receipt of guideline-indicated care had been equal between the sexes¹⁷.

There is considerable evidence from the UK and elsewhere that, whilst men are more at risk of developing coronary heart disease, women are more likely to be misdiagnosed and sub-optimally treated^{18,19}. This gender disparity in the receipt of evidence-based treatment has been observed both at the first point of medical contact for incident disease and following a formal diagnosis. For example, women with a *history* of coronary heart disease have been shown to be less likely to be managed according to clinical guidelines compared with similarly affected men.

Some of these gender differences in quality of care will be a downstream effect of the historically sex- and gender-blind guidelines for coronary heart disease management, and as a result should improve following recent changes in these guidelines to be more sex-inclusive. However, of concern is the observation that implicit bias among healthcare professionals exists, which can affect treatment decisions.

Several key coronary heart disease risk factors (e.g. smoking, socioeconomic background and adiposity) have been shown to have a stronger effect on CHD risk in women compared to men. Having diabetes doubled the chance of a future heart attack in men, but tripled the chance in women. Similar findings have been observed for other diseases, including stroke, vascular dementia, and kidney failure. Furthermore, several other key CHD risk factors (e.g. smoking, socioeconomic background and adiposity) have been shown to have a stronger effect on CHD risk in women compared to men.

Dementia: Of the 66,424 deaths registered in 2019 due to dementia and Alzheimer's disease, 23,634 were males (105.1 deaths per 100,000 males) and 42,790 were females (120.1 deaths per 100,000 females). While remarkable advances in dementia research have occurred in the past decade, little attention has been given to sex and gender differences, leading to considerable knowledge gaps in research and a lack of awareness in the research community.

The Society for Women's Health Research Interdisciplinary Network on Alzheimer Disease, comprising of an expert panel of scientists and clinicians, recently published a call to action to dementia researchers providing 12 priority research areas that need to be addressed in sex and gender research in Alzheimer disease. These areas include investigations in survival, risk factors, hormonal influence, co-morbidities, progression of disease, brain development, populations at risk, geographical differences, caregiving and basic and clinical research²⁰.

In summary, to maximise improvements in women's health in the coming years, a new paradigm must be established whereby sex and gender issues are considered at all stages of the research-to-translation pipeline. Failure to do so risks compromising the quality of care and increasing costs due to inappropriate allocation of health resources.

A key part of this shift must be the embedding of sex- and gender-disaggregated data collection, analysis, interpretation and reporting in clinical studies, surveillance systems and Quality and Outcomes Framework (QoF) processes. This will be particularly important, given the ageing population, and the expectation that older women will bear a considerable amount of the disease burden.

Recommendations:

- NIHR should, where possible and appropriate, stipulate that funded studies should be powered to show outcomes by sex and gender.
- NHS Digital should ensure that routine clinical data and surveillance systems, where possible and appropriate, analyse and report data disaggregated by sex and gender

Priority: Improve the safety of treatments in pregnancy through increasing the involvement of women in clinical trials

Context: The longstanding approach of pharmaceutical companies, sponsors and ethics committee has been to "protect" women and their unborn children by excluding not only pregnant and lactating women from clinical trials but also women of child-bearing potential unless they agree to double contraception. The consequence is that for many conditions the safety and indeed even the correct dosing of therapies during pregnancy is unknown for years after licencing.

An example of this is in HIV infection where not only is treatment essential for maternal health but also to prevent mother-to-child transmission in utero peripartum and, through breast-feeding, post-partum. As part of an action

supported by IMPAACT, an HIV clinical trials network, and the WHO we are contributing to the drive to change the clinical research and licencing mindset to that of protecting women and their children through active participation in clinical trials. This means not only recruiting pregnant women into phase 2 and phase 3 clinical trials but ensuring that data that would otherwise be lost, is retained, by allowing women to continue in clinical trials if they do become pregnant²¹.

Another example is kidney disease, where conditions such as Lupus Nephritis disproportionately affect women. Ensuring trials are accessible, pragmatic and engage the women most at risk is especially true in conditions such as Lupus Nephritis - most patients are women of childbearing age, predominantly from non-white ethnic backgrounds; nearly all trials exclude women contemplating pregnancy and breastfeeding (mostly due to safety concerns with new drugs). Additionally, these trials not only tend to be very burdensome in terms of visits and blood tests but also come with a recommendation of a 2-year delay before trying to have a baby. These issues unsurprisingly deter women from participating, especially if their kidney function is deteriorating and they do not want to postpone pregnancy for so long. Whilst trials need to address safety, they need to have more flexible timelines and recognise the social and economic barriers to participation.

Recommendation: a series of workshops leading to the publication of expert guidance, from all parties, including regulators, involved in therapeutic and prophylactic intervention studies on the participation of pregnant women in clinical trials.

Priority: Use the data collected as part of women's routine care to support maternity service improvement, improve maternal safety and involve women in pregnancy in clinical trials

Context: The UK has a wealth of data on outcomes and treatments in pregnancy and breastfeeding, but much of it is fragmented across different datasets according to the care setting, outcome and UK nation it relates to. There are gaps in the available data with some variables either missing completely or poorly recorded and there are opportunities to optimise data collection and access to support the continual improvement of maternity services and outcomes and involve women in pregnancy in clinical research and trials.

The NHS Digital Maternity Services Dataset has collected UK data from 2015²². The data from this is not research ready but could, in combination with other datasets, feed into a high-quality national maternity research dataset, on the model of the UK National Neonatal Research Database (UKNNRD)²³.

Imperial College has convened a collaboration with HDR-UK, NHS digital and academic institutions across the UK and provided initial funding to establish a UK National Maternity Research Dataset as part of a Women and Children's data hub. The end-goal of this would be to use the data collected routinely in maternity care to improve services, maternity safety and deliver clinical trials for women in pregnancy.

Over time, this database can be linked to other data sets to establish how pre-pregnancy health impacts pregnancy outcomes, how pregnancy outcomes influence women's later life health and that of their child and to develop a national, multi-purpose data resource for women's health.

Recommendation: DHSC should support HDR-UK to form a Women's Health data hub, linking national and relevant regional and local datasets to drive improvement of women's health.

NATIONAL PRIORITIES FOR MATERNITY CARE

The DHSC has set out national priorities to reduce pre-term birth from 8% to 6% and reduce stillbirth by 50% by 2025. Other conditions, such as diabetes and cardiovascular disease, may become evident in young women going through pregnancy (and then resolve) decades before they develop type 2 diabetes and cardiovascular disease.

Priority: Reduce pre-term birth and the estimated £3.72 billion societal costs associated with each annual cohort of pre-term births in the UK.

Context: 8% of babies are born pre-term, before 37 weeks, and experience a range of impacts on their health, learning and development which can last a lifetime. Each year there are around 15 million preterm births across the world – and it is responsible for 1.1 million infant deaths.

Babies who survive an early birth often face serious and lifelong health problems, including chronic physical and mental non-communicable diseases e.g. lung disease, vision and hearing impairment, cerebral palsy, and learning disabilities.

The DHSC has set a priority of reducing pre-term birth from 8 to 6% by 2025¹. The causes of pre-term birth are varied and progress has been made to reduce complications such as pre-eclampsia which lead to doctors recommending early delivery by starting labour or by caesarean section.

However, the cause of pre-term labour, which starts spontaneously and accounts for a significant proportion of pre-term births, remain unclear. The March of Dimes Prematurity Research Center at Imperial College London is leading in establishing the role of infection in spontaneous pre-term labour and the differences between women in their immune responses to infection. Differences in the microbiomes (bacteria that normally live in the body) between women who go on to have pre-term deliveries have been identified as key²⁴ and a trial is underway at Imperial College to test whether modifying the microbiome can prevent pre-term birth.

Recommendation: Research into the causes of spontaneous pre-term labour and indicated pre-term birth (necessitated by e.g. risk of severe maternal illness or of stillbirth) should be supported and their findings translated into national guidance and clinical practice as an urgent priority

Priority: Reduce stillbirth and its devastating impact on families

Context: At present, national efforts to reduce stillbirth have focussed on detecting babies which are small for their stage in pregnancy and delivering them, often before they are 'term' or mature. Pre-term birth, as described above, has significant impact on the lifelong health of the baby. As such, the present national priorities to both reduce pre-term birth and stillbirth are in tension.

We need to better understand the differences between pregnancies where the fetus is pathologically small (fetal growth restriction) and requires early delivery as opposed to those where the baby is small but healthy. Correctly identifying the women with the highest risk of stillbirth will prevent unnecessary, early delivery in those at low risk of stillbirth.

The TRUFFLE 2 trial, <https://www.truffle-study.org/>, funded by NIHR at Imperial College and across a network of 52 European maternity centres, seeks to determine the best way to look after babies which have fetal growth restriction. Studies alongside the main trial will test how best to differentiate those which are small but healthy (and can be monitored until labour starts) and those which will become unwell and would benefit from early delivery.

Recommendation: NHSE's Saving Babies Lives Care Bundle 2 should remain under review to incorporate ongoing clinical research to reduce stillbirth whilst not increasing pre-term birth. It should be evaluated with a National Maternity Research Database (as described above).

Priority: Improve Mental health following early pregnancy loss in women and partners

Context: Early pregnancy loss is common, in the UK alone there are approximately 260,000 early pregnancy losses each year. The psychological sequelae of such a loss represents a major public health problem that requires immediate action.

The PEIEPE Study at Imperial College showed that 1 in 3 women suffer with mental health disorders including post-traumatic stress disorder (PTSD), anxiety and depression 1 month following early pregnancy loss (miscarriage and ectopic pregnancy) which can persist long term in as many as 1 in 6²⁷. Mental health of partners is also negatively affected. Although the psychological impact on partners may not be as severe, research shows that partners often feel marginalised and are more likely to engage in compensatory behaviours (alcohol and substance use).

Untreated, mental health disorder such as PTSD are unlikely to resolve, evidence from other traumas shows 1 in 3 people with PTSD continue to have symptoms for as long as 30 years. The wider health, social and economic impacts are well documented and include; physical health problems, psychological co-morbidities, relationship breakdown, difficulties in the work place, unemployment and increased maternal and fetal risks in future pregnancies.

Currently there is no routine provision of mental health support, screening or treatment after an early pregnancy loss. Access to mental health services relies on women or their partners recognizing their mental health problems and feeling empowered to seek help through primary care, charities or peer support groups. Many feel unable to seek support as they might with other traumas, due to the cultural taboo, shame, guilt and self-blame surrounding early pregnancy loss.

Recommendations:

- Research into mental health screening, support and treatment following early pregnancy loss should be prioritised with the findings being urgently translated into national guidance and clinical practice.
- Access to mental health support and services for women and their partners following early pregnancy loss should be made more accessible.

Priority: Reduce the impact of mental illness and stress on women in pregnancy and their children

Context: 1 in 5 women are affected by mental illness during and after pregnancy, suicide is a leading cause of death in the year after pregnancy. Evidence suggests that there can be an increased risk to the future child if the mother feels stressed, or has experienced early trauma and it is therefore important to think and help beyond diagnosis²⁵.

Several different types of prenatal stress for the mother have been shown to increase the risk of emotional, behavioural and cognitive problems for the child, and to play a causal role. Such stress in the mother includes her worry about the outcome of her pregnancy, her exposure to a raised level of daily hassles, to a natural or manmade disaster, and to emotional cruelty or other forms of domestic abuse by her partner.

It may be appropriate for health professionals caring for pregnant women to explore aspects of their mental well-being which may be a source of stress. How is the relationship with the partner? Did they suffer from early abuse or other adverse childhood experiences? Do they have specific anxieties about the outcome of their pregnancy? Have they been exposed to any other major stresses or problems with money or housing? These are not questions usually explored and arise from the wider determinants of health.

Recommendation: Services to ameliorate common sources of stress in pregnancy could be made more accessible to women in pregnancy, such as health education, financial advice and English for Speakers of Other Language Lessons.

Priority: Improve safety and reduce unnecessary intervention in women with early pregnancy complications

Context: A limited set of biomarkers (blood tests) are available to predict complications in late pregnancy, however early pregnancy care management is reliant on hormone levels and ultrasound which have changed little in the last few decades and are used inconsistently in early pregnancy units across the UK.

If a pregnancy cannot be located in the uterus on ultrasound, it may be an ectopic pregnancy (outside the uterus) which can cause heavy bleeding and are potentially life threatening. Termed pregnancies of unknown location (PUL), these account for 8-42% of all early pregnancies and clinical management currently relies on beta human chorionic gonadotrophin (bhCG), with or without progesterone, used variably nationally either in isolation, as part of a ratio or within various risk prediction models pending a final diagnosis of ectopic or intra-uterine pregnancy. The most precise form of PUL risk and outcome prediction is achieved using the externally validated 'M6 model', which includes progesterone, bhCG and the bhCG ratio, which picks up 96% of ectopic pregnancies²⁶. Use of this model was recommended as part of RCOG COVID-19 guidance but has not been implemented in all early pregnancy units.

Unfortunately, even with optimal use of current biomarkers, some ectopic pregnancies (8-16% of all PUL, 1% total incidence) are missed, leading to significant morbidity and mortality. Additionally, there are currently no biomarkers available that can accurately predict miscarriage, which affects 25% of pregnancies.

Research is ongoing to replace or supplement the current pool of limited biomarkers to further improve objective, early diagnosis, potentially reducing the need for admission to hospital and unnecessary interventions.

Actions: All early pregnancy units should implement the M6 PUL risk prediction model, which has been developed, implemented and externally validated in a multicentre population, in order to improve safety for women with ectopic pregnancy and reduce unnecessary intervention for women with PUL.

INNOVATION AND ENTERPRISE IN WOMEN'S HEALTH

FemTech is fast becoming a significant sub-sector of the tech industry. Previously relating to companies that focus on issues around reproductive health, the sector has now grown to serve a range of health and wellness needs for women (and people who experience similar health issues) through software, diagnostics, products and tech-enabled health services.

Priority: Support the integration of proven technology and innovation into NHS care for women

Context: Imperial in conjunction with research partners is supporting Hackathons with a strong emphasis on cross-cultural collaboration and virtual team working, supported by industry leader panels and global mentors. Participating students are incentivised with their guaranteed retention of Intellectual Property developed at these events. A key focus for the hackathons is Women's Health with the goals of improving the lives of women by tackling issues in sexual health, menstruation and period care products, fertility and birth control and the menopause.

Imperial researchers have collaborated with industry with funding from an Innovate UK grant to develop the The 'Caretmedical' app, <http://caretmedical.net/index.html> . The app uses specially designed algorithms that link mother

and previous baby characteristics to national and international guidelines and highlights these both for the woman ("health profile") and for the professional ("medical dashboard"). This means that recommendations for management are contextual and person specific rather than generic.

Such recommendations have been shown to improve the quality of maternity care. There are currently more than 200 pregnancy apps available, but all of these are generic, which means that the information they give is not (or hardly at all) specifically tailored to the characteristics of the individual woman and requires the woman herself to decide which information is relevant to her. In the Caretek app, only information specifically relevant to the individual woman is shown.

Recommendation: DHSC should consider strategies to support the FemTech sector in delivering collaborative innovation within the NHS and improving the personalisation of health advice provided to women in pregnancy.

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