Tommy's - Written evidence (PRT0057)

1. Treatments and interventions that can assist in the prediction and prevention of preterm birth

Tests to predict preterm birth

Routine screening for preterm birth in low-risk asymptomatic women and birthing people[1] is not currently recommended by the UK National Screening Committee. Having demonstrated that screening is helpful in high-risk women, we now need to investigate whether similar techniques can be used in all to reduce the risk of preterm birth. Several tests are used to monitor people at risk of preterm birth or who are in suspected preterm labour. Each of these tests has been developed with funding from Tommy's. They are:

- **Transvaginal ultrasound** to measure whether the cervix is shorter than normal. If this is the case, preterm birth is more likely and treatment may be required. This is routinely offered between 16+0 weeks and 24+0 weeks of pregnancy to those at risk of preterm birth and in women with threatened preterm labour.
- **Fetal fibronectin testing**, if labour is imminent, fetal fibronectin may be released into the vagina, where it can be measured using a swab. Fetal fibronectin testing is offered to symptomatic women to determine the likelihood of birth within 48 hours.
- **The QUiPP app**, a decision support tool that uses medical history and fetal fibronectin and/or cervical length to give an individualised risk of having a preterm delivery. While not included in current NICE guidelines, the QUiPP app is already used in clinical practice and an update to the NICE guidelines is expected.

[1] Tommy's acknowledge that not all pregnant people identify as women. Birthing people refers to someone who gives birth, regardless of their gender identity, which may be female, male, nonbinary, or other. Throughout the rest of our evidence, the term pregnant women is used for brevity and is also of relevance to all birthing people.

There are other tests currently in development to help predict preterm birth:

- **Ultrasound to measure the position of the caesarean section scar** during the mid-pregnancy anomaly scan, allowing clinicians to determine if there has been damage to the cervix. Researchers at University College London measured the scar position in women who previously had a full-dilatation caesarean section and found that those whose scar was within or close to the cervix were 7 times more likely to shorten their cervix and deliver preterm in a subsequent pregnancy. This work is being part-funded by Tommy's.
- **Plasma microRNA testing** during the first trimester of pregnancy has been shown to be predictive of preterm birth and cervical shortening.

Treatments and interventions to prevent preterm birth

There are several treatments that are available to those at risk of preterm birth. They are:

- **Smoking cessation interventions** to ensure that the pregnancy is smoke free before 15 weeks; quitting by this stage of pregnancy reduces the risk of preterm birth to that of a non-smoker.
- **Low-dose aspirin** for anyone found to be at increased risk of preterm birth associated with early onset pre-eclampsia and placental insufficiency
- For women with a short cervix (less than 25 mm):
    - **Transvaginal or transabdominal cerclage** (stitch). These are commonly used in asymptomatic, high-risk women with a short cervix. Emergency cerclage is used less commonly in women presenting with painless cervical dilatation, and is currently under evaluation in the CSTICH2 trial. Tommy's researchers led the UK-wide MAVRIC study, which showed that an abdominal stitch (inserted high in the cervix) can

prevent more premature births and save more babies' lives than a stitch inserted through the vagina, when used to treat those who previously had a failed vaginal stitch

- Hormonal treatment with daily **progesterone pessaries**.

For women with diagnosed preterm labour, it is not possible to prevent or significantly delay the birth. Instead, treatment is focused on optimising outcomes for the baby and includes:

- **Tocolysis** to slow down labour when a short-term delay is needed, for example to allow for *in utero* transfer or corticosteroid/magnesium sulphate treatment.
- **Corticosteroid injections** to help with a baby's brain and lung development. The decision about when to administer steroids can be controversial – steroids are most effective when they are given between 24 hours and 1 week before birth.
- **Magnesium sulphate** to reduce the risk of cerebral palsy.
- **Intrapartum antibiotics** to prevent early onset neonatal Group B Streptococcal (GBS) infection.

Treatments and interventions in development:

- **Pravastatin treatment** to prevent preterm birth in women who are at medium-to-high risk of preterm birth. This treatment will be assessed in the placebo-controlled randomised controlled PIONEER trial.

2. Existing clinical guidance relating to preterm birth, and how this is implemented

The care that someone receives when they are at risk of preterm birth depends on why they are at risk. Saving Babies' Lives Care Bundle

Version Three (SBLCBv3) provides the most recent guidance on the prediction and prevention of preterm birth, drawing on guidance from the UK Preterm Birth Clinical Network, the British Association of Perinatal Medicine and NICE. The SBLCBv3 emphasises the importance of making birth decisions based on evidence of maternal and/or fetal health issues and influences clinical practice in most UK preterm birth clinics. Key points include:

- Emphasis on reducing spontaneous preterm birth and improving neonatal outcomes through prediction, prevention, and preparation within a strong perinatal team comprising neonatology, obstetrics, and midwifery.
- Establishment of a Preterm Birth Lead Team to oversee implementation of the preterm birth element of SBLCBv3.
- Provision of care for women at risk of preterm birth ideally within preterm birth prevention clinics with midwifery support. These clinics should offer access to risk assessment tests (such as transvaginal cervix scanning and quantitative fetal fibronectin) and potential interventions (such as cervical cerclage and progesterone).
- Ensuring that women have access to evidence-based information, risk assessment tests, and interventions, and can actively participate in decisions regarding their management, even in the absence of preterm birth prevention clinics.
- Ensuring access to supra-regional prevention services within care pathways and networks, including services such as transabdominal cerclage.

3. The ethnic and socioeconomic inequalities seen in relation to preterm birth, and how these could be reduced

Ethnicity has a significant impact on the likelihood of a baby being born too soon. Since data collection began in 2007, Black families in England

and Wales have consistently had higher rates of preterm births, compared to other ethnic groups. Between 2020 and 2021, there was also a notable increase in the rate of preterm birth among Asian families.

Preterm birth creates a harmful cycle, which particularly affects minoritised ethnic groups and socioeconomically deprived families. Our new centre focuses on investigating and addressing these inequities. The five institutions that make up our centre are linked to NHS preterm birth clinics in diverse areas, enabling us to involve women from a variety of backgrounds in our research and helping us to understand why certain groups face higher rates of preterm birth.

The Centre is supporting the UK Preterm Birth Clinical Network which will enable much broader reach into geographically disparate areas to increase the number of people that will benefit from research-based innovations in care.

What is driving this variation?

The drivers of inequalities in pregnancy loss and baby deaths are complex and interrelated. Some ethnic groups are more likely to live in more deprived areas; however, this alone is not sufficient to explain inequalities.

Even after adjusting for the level of deprivation, differences in preterm birth across ethnic groups remain.

Inequalities in pregnancy outcomes and baby loss have been known about for decades.

Explanations include differences in access to and treatment by maternity services, health behaviours, and personal and social contexts. Multiple reports have highlighted the impact of racism and discrimination which some individuals experience when engaging with health services.

Limitations in data and evidence prevent moving beyond diagnosing the problem to taking meaningful actions that will help address inequalities.

Much of the national data are based on aggregated ethnic groups or broad categories of deprivation, which provide limited insights into individuals' lives. More detailed data on factors which could affect pregnancies or access to health services, and intersectional analysis to examine the relationship between these factors, could help inform what is driving inequality and identify potential interventions.

There are also no national targets or long-term funding to reduce inequalities between ethnic groups or areas of deprivation. To meet the Government 2025 target of a 6% preterm birth rate would require much larger reductions among some groups.

The Tommy's National Centre for Preterm Birth Research has projects that aim to dissect out different factors that make women from different backgrounds and some ethnic groups have higher rates of preterm birth. This will include studying biological and social/economic risk factors. This is important because preterm birth is a complex, multifactorial problem that has many different causes, and not all are of relevance for specific individuals.

4. Priority areas for research to prevent preterm birth and improve care for mothers and babies.

Recommendations from Tommy's in collaboration with the Leads of the Tommy's National Research Centre for Preterm Birth: Catherine Williamson (Director), Anna David (UCL Lead, Deputy Director), Phillip Bennett (Imperial Lead) Nigel Simpson (University of Leeds Lead), Andrew Shennan (King's Lead), Steve Thornton (QMUL Lead).

Preterm birth is a complex, multifactorial disorder with biological, environmental and social determinants. When considering priority areas of research it is important to note the different underlying causes of preterm birth as the research focus will vary depending upon the reason for preterm birth.

Spontaneous preterm birth:

Considerable progress has been made in studies of pregnancies that are identified as being at high-risk of spontaneous preterm birth, e.g. women with short cervix where either progesterone or cervical cerclage are used. However, this subgroup represents a minority of pregnancies affected by spontaneous preterm birth.

There is now increasing recognition that placental insufficiency, fetal growth restriction and pre-eclampsia are associated with an increased risk of spontaneous preterm birth, probably due to inflammatory processes driving softening of the cervix, preterm prelabour rupture of the membranes and ensuing preterm labour.

Current research suggests that trauma to the internal cervical os or cervix itself compromises cervical function. This is concerning as there is increasing avoidance of instrumental birth (eg forceps, vacuum) and resort to Caesarean section. Research is establishing the optimal strategies for identification and prevention in this subgroup of women.

There has been limited progress at prediction and prevention of spontaneous preterm birth for the majority of pregnancies where there are no apparent risk factors. Research studies have identified microbiome signatures consistent with preterm birth risk, and genomic studies have identified gene candidates in women of European ancestry, but there have been no well powered genomic studies of women from different ethnic groups. Emerging data indicate that microRNA markers may predict pregnancies at risk of preterm birth. Future research will enable evaluation of prediction algorithms that incorporate Informative biomarkers and clinical parameters in large cohorts of diverse groups of pregnant individuals.

To understand the aetiology of complex disorders it is important to perform large-scale studies with greater sample numbers than can be

collected by a single research group, emphasising the importance of collaboration between research groups. Thus, it is important to incentivise researchers to not work in a siloed manner. The approach to phenotyping must also be rigorous to enable an individualised approach to risk assessment. Prioritisation of research that delineates individual risk factors for spontaneous preterm birth in subgroups of pregnant women within the diverse antenatal population of the UK (and internationally) will enable accurate targeting of interventions.

A precision medicine approach will enable the development of individualised interventions that are more likely to be effective for specific sub-groups of high-risk women.

Iatrogenic preterm birth:

Iatrogenic preterm birth is often associated with gestational disorders, e.g. pre-eclampsia or fetal growth restriction, multifetal pregnancy or maternal diseases. For this disparate group of pregnant women, decisions about the timing of birth will vary depending upon the underlying disorder. Therefore, research projects that focus on specific conditions and causes are more likely to enable the development and implementation of effective interventions. Historically pregnant women have been excluded from clinical trials and therefore very few new therapies have been developed and studied in women with gestational disorders, and similarly there has been a reluctance to research the impact and safety of drugs to control maternal medical disorders.

Many of the routine requirements to perform clinical trials are not available or difficult to deliver in pregnancy. This is, in part due to insufficient understanding of the natural history of gestational diseases, and inadequate predictive tests. Development of accurate tests and robust inclusion/exclusion criteria would enable trials to better focus on those most at risk of preterm birth.

Industry and academic researchers currently struggle to find insurance for clinical trials involving pregnant participants, and likewise insurers struggle to assess the risks of these studies given so few are conducted and so few have resulted in any litigation. As insurers have to rely on limited information to assess risk, their premiums may be disproportionate to the compensation limits they can offer. In the meantime, studies demonstrate that patients are keen and willing to participate in trials of medication in pregnancy.

Both patients and healthcare providers consider that the optimal primary outcome measures for clinical trials of therapeutics in pregnancy are maternal and neonatal outcomes, commonly at two years of age when it is possible to assess neurodevelopmental delay. There are no good short term indications of infant outcomes that can be used as surrogates, meaning that such trials are lengthy, expensive and subject to participant drop-out.

Finally because few pregnancy therapeutics intervention trials are undertaken, there are insufficient numbers of experienced obstetric and midwifery healthcare providers to develop protocols, apply for funding and deliver on clinical trials. Research should be encouraged into the safety and efficacy of drugs that can improve the outcomes of maternal disorders as well as preterm birth, as for many this will also reduce rates of iatrogenic, or maternal disease-associated preterm birth.

<u>It is important to listen to the voice of people with lived experience when deciding research priorities</u>.

The James Lind Alliance recommended research priorities for preterm birth; the top research priority was "Which treatments (including diagnostic tests) are most effective to predict or prevent preterm birth?"

Other prioritised research questions included parental counselling before a preterm birth, the value of first trimester screening, prevention and

treatment of Group B streptococcus, preterm prelabour rupture of the membranes (PPROM), transvaginal scanning to detect and treat short cervix and imaging the placenta. Using the JLA recommendations, in the context of what has been achieved by preterm birth researchers to date, research priorities for preterm birth can be divided into three themes:

i) research to explain causes of preterm birth

ii) design and evaluate new interventions

iii) ways to support people who have been affected by PTB to improve psychological, medical, economic and neurocognitive impacts of PTB

These themes underpin the portfolio of research project being pursued in the Tommy's National Research Centre for Preterm Birth. Once research findings have been generated it is essential to also invest in Implementation Science research to ensure that robust research findings impact clinical practice. Similarly, policy research and health economics should be integrated alongside clinical research projects to enhance implementation of research findings to improve outcomes in a timely manner. The Tommy's National Research Centre for Preterm Birth is working with the King's Policy Institute to ensure that policy makers are involved with the Centre's research from the beginning of each project. In the first year of the Centre a Policy Lab will be run in collaboration with the team at the King's Policy Institute. A wide range of stakeholders will be invited with expertise in research, policy, and implementation science to ensure the Centre's research is endorsed by them and is set-up to deliver implementable policy from the outset.

Additional issues of relevance to research efficiency

Another issue that needs to be addressed is research bureaucracy and regulation. While this is not specific to preterm birth research, there are

considerable bureaucratic hurdles that limit the pace at which basic science and translational research can progress. It will be important to address this to maximise efficiency and improve outcomes for all patients including those affected by preterm birth.

Appendix 1

1. The importance of translating research-based evidence into changes in policy and practice

Tommy's has a strategy to ensure that findings from our research centres are translated into recommendations for policy makers, and improved care and practice, as quickly as possible. We believe this is an essential role for us to play, working with others, and supports the wider system to make change.

As the largest UK charity funder of pregnancy research, we lead ground-breaking research through our centres, to identify the causes of pregnancy complications and baby loss, working with researchers, health care professionals and communities. We then use the evidence to campaign and advocate for change, helping to transform the way front-line care and support are delivered.

A recent example relates to the PRISM clinical trial, which took place at our National Centre for Miscarriage Research. The trial found that progesterone should be prescribed to women experiencing bleeding in early pregnancy, when they have previously had a miscarriage, to prevent miscarriage. We worked to ensure the findings were included in NICE miscarriage care guidelines.

Professor Arri Coomarasamy, Director of Tommy's National Centre for Miscarriage Research at the University of Birmingham, said:

"The miscarriage care guidelines from NICE include a very welcome change, after many years researching the use of progesterone and working to make treatment more accessible.

"Our research has shown that progesterone is a robust and effective treatment option, which could prevent 8,450 miscarriages a year in the UK – but we know it's not yet reaching everyone who might benefit. This recommendation from NICE is an important step in tackling the current variation in miscarriage services across the country and preventing these losses wherever possible."

We will adopt a similar approach through our new National Centre for Preterm Birth Research, including through a Policy Lab later this year, which will ensure we are thinking about how to bring our research recommendations to clinical practice at the start of the research process, so families can benefit from the best care as quickly as possible.

There are other ways that Tommy's is collaborating with other organisations in the maternity sector to help inform policy makers and make change as quickly as possible.

For example, in 2021, Sands and Tommy's formed a Joint Policy Unit. The unit aims to work towards halving the number of UK baby deaths by ensuring decision makers have access to up-to-date information, and that maternity policy is informed by robust evidence. The unit was formed to reduce duplication, since both organisations are looking to achieve similar influencing objectives.

Tommy's and Sands co-lead the Maternity Consortium, a group of organisations brought together with funding from the VCSE Health & Wellbeing Alliance. The aim of the group is to use collective expertise to reduce health inequalities for families through the pregnancy journey from pre-conception and through the first year of life.

2. The evidence base for Tommy's pregnancy information and campaigns.

A key part of our strategy to change outcomes is to translate research-based evidence into reliable information for the public. Tommy's has held

an accreditation for production of high quality health information since 2011. We were one of the first organisations accredited (and passing annual assessments) through the NHS Information Standard, which is now the PIF Tick quality mark, run by the Patient Information Forum (PIF).

All patient information produced by Tommy's is governed by our Information Production Policy (IPP), which meets the PIF Tick criteria. The Tommy's IPP describes how we produce accurate, accessible, trustworthy content for our users, ensuring that:

- information is created using a consistent and documented process
- staff receive ongoing training and support
- resources meet a genuine need
- information is based on reliable, up-to-date evidence which is communicated clearly
- users are involved in the development of information
- information is written to meet health and digital literacy, language and accessibility needs of the target audience
- information is clearly communicated, easy to access and navigate
- there is a clear process for users to provide feedback
- information is promoted to maximise reach
- the impact of information is measured.

This process governs the lifecycle of more than 600 information products that we maintain at Tommys to support women and birthing people, and their families, through every stage of their pregnancy journey.

One of the ways Tommy's distributes health information is via our campaigns. One such campaign was the Sleep on Side campaign, which ran in 2017. This encouraged pregnant women to sleep on their side in their third trimester to reduce their risk of stillbirth. The distribution of this information was a recommendation of the MiNESS study (details below).

The patient information developed for the Sleep on Side campaign was produced with a steering committee that included representatives from NHSE, RCM, Sands, Action Medical Research, NCT, IHV, Kicks Count, Cure Kids, PHE (now OHID) and the International Stillbirth Alliance.

Clinical oversight was provided by:

- Professor Alex Heazell, Professor of Obstetrics and Honorary Consultant Obstetrician, Manchester University NHS Foundation Trust (MFT)
- Professor Jane Sandall, Professor of Social Science and Women's Health, King's College London
- Professor Lesley McCowan, Head of Department, Sub- specialist in Maternal Fetal Medicine, Department of Obstetrics and Gynaecology, University of Auckland
- Professor Viv Bennett CBE, Chief Public Health Nurse, Office for Health Improvement and Disparities (OHID), formerly PHE
- Dr Tomasina Stacey, Senior Lecturer and PhD Coordinator (Division of Methodologies), King's College London

Evidence for patient information produced as part of the Sleep on Side campaign

The evidence for the link between going to sleep position and stillbirth is robust. There have been 6 studies into maternal sleep position during pregnancy and risk of stillbirth.

The first was by Stacey et al[1] in 2011. This study, from New Zealand, found an association between maternal supine sleep position during pregnancy and an increased risk of stillbirth. Similar findings have been observed in other studies with similar methodologies and similar effect sizes conducted in high-income countries (HICs), Sydney[2] , New Zealand[3] and the UK[4].

As a result, going-to-sleep on the side positions from 28 weeks of pregnancy are now recommended in Australia, New Zealand and the United Kingdom and have been targeted through stillbirth prevention campaigns.

There have also been 2 systematic reviews—a 2018 scoping review by Warland et al[5]. and a 2019 individual participant data (IPD) meta-analysis by Cronin et al[6]. that have evaluated the impact of maternal sleep on fetal outcomes. Both reviews also found an association between supine sleep position and stillbirth.

In 2021 a NICE evidence review committee concluded that it was of sufficient quality to recommend advising women of the likely link between supine sleep position and stillbirth in an update to the Antenatal Care guidelines NG201.

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