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Gestational diabetes: an opportunity to improve long-term health in mothers and children

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Gestational diabetes [A: our style is not to include 'mellitus' and we avoid abbreviating disease names, spelled out throughout, OK?], the most common medical disorder in pregnancy, is defined as glucose intolerance resulting in hyperglycaemia that begins or is first diagnosed in pregnancy [A: we can only keep quotation marks if this definition is a direct quote]. Gestational diabetes is associated with increased pregnancy complications and long-term metabolic risks for the woman and the offspring. However, the current diagnostic and management strategies recommended by national and international guidelines are mainly focused on short-term risks during pregnancy and delivery, except the Carpenter-Coustan criteria, which were based on the risk of future incidence of type 2 diabetes post-gestational diabetes. In this Personal View, first, we summarise the evidence for long-term risk in women with gestational diabetes and their offspring. Second, we suggest that a shift is needed in the thinking about gestational diabetes; moving from the perception of a short-term condition that confers increased risks of large babies to a potentially modifiable long-term condition that contributes to the growing burden of childhood obesity and cardiometabolic disorders in women and the future generation. Third, we propose how the current clinical practice might be improved [A: edits indicated in red throughout, please check if OK or suggest edit]. Finally, we outline and justify priorities for future research.

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See Online for appendix

Introduction

Gestational diabetes is increasingly prevalent and estimated to affect more than 20 million livebirths (about one in six) worldwide. Of these, more than 90% of cases are expected to occur in South and southeast [A: Lancet style] Asia.[1] Gestational diabetes has long been a controversial diagnosis, with variations in the screening procedures and diagnostic criteria between different countries.[2–4] In view of these variations, the term hyperglycaemia in pregnancy has sometimes been used in the definition, which includes gestational diabetes, pre-gestational diabetes (pre-existing type 1 and type 2 diabetes), and overt diabetes diagnosed in pregnancy. Management of women with severe hyperglycaemia improves adverse pregnancy outcomes and has been done for over 10 years.[5] Additionally, management of women with milder degrees of hyperglycaemia could also reduce the rates of gestational hypertension and pre-eclampsia.[6] The well recognised link between maternal glucose concentration and neonatal outcomes attributed to fetal hyperinsulinaemia such as large for gestational age [birthweight >90th centile], neonatal adiposity, and neonatal hypoglycaemia is continuous.[7] Gestational diabetes is perceived to be an acute condition with short-term problems for the mother and her offspring, as glucose intolerance usually reverts back to normal after the pregnancy. In addition to type 2 diabetes, recent studies[8–10] suggest that gestational diabetes is also a risk factor for long-term maternal and offspring cardiometabolic disease. In the knowledge that type 2 diabetes can be prevented by lifestyle intervention and loss of bodyweight between 10% and 15% can result in remission of type 2 diabetes,[11,12] women with gestational diabetes and their families form a key high-risk group, for whom there is a compelling case for targeted intervention.

Screening and diagnosis of gestational diabetes

Although screening procedures and diagnostic criteria vary between countries, gestational diabetes is most typically diagnosed by an oral glucose tolerance test done between 24 weeks and 28 weeks of gestation.[1–4] Studies[13,14] [A: 'recent' deleted as studies from 2001 and 2009] suggest that the onset of gestational diabetes might occur as early as 16–20 weeks, and earlier maternal hyperglycaemia (9–10 weeks)[13] and fetal hyperinsulinaemia (14–20 weeks)[14] are associated with later development of gestational diabetes and a baby deemed large for gestational age. As a result, several ongoing studies are addressing the value of screening, diagnosing, and managing gestational diabetes in early pregnancy.

Screening criteria and glucose thresholds for diagnosing gestational diabetes vary between different countries.[1–4] Screening strategies currently recommended and offered include: universal screening using a two-step strategy (used in USA and Canada);[15,16] selective risk factor screening (used in the UK);[2] and universal screening using a one-step strategy in countries with high-risk and low-medium risk populations.[17–21] Frequently, in many low-resource settings (eg, sub-Saharan Africa), testing is not routinely available partly because the oral glucose tolerance test is cumbersome and labour-intensive.[22] Consequently, the American Diabetes Association and the International Federation of Gynecology and Obstetrics have modified their recommendations to include a single or a two-step strategy according to the local resources.[4,23]

Long-term implications of gestational diabetes for the mother

Among women with a previous history of gestational diabetes, the lifetime risk of type 2 diabetes might be up to 20 times higher,[8] and nearly 50% of these women will

develop impaired glucose metabolism within 10 years since the gestational diabetes pregnancy.[24,25] After 10–14 years of follow-up, the HAPO study,[25] found that 52% of women with gestational diabetes (defined by the International Association of Diabetes and Pregnancy Study Groups [IADPSG] and the 2013 WHO criteria **[A: please provide reference if available]**) had developed impared glucose metabolism compared with 20% of women that had a normal glucose tolerance range during pregnancy (adjusted OR 3·4–3·6). In addition to the higher risk of diabetes, women with a history of gestational diabetes also display a cluster of cardiovascular disease risk factors such as obesity **[A: BMI ≥30 kg/m²?]**, hypertension, and dyslipidaemia. This finding has translated into large observational cohort studies[8,9,26] showing higher rates of incident ischaemic heart disease independent from the onset of type 2 diabetes.[9] In addition, a recent population-based study[27] from Canada, has shown that women with hyperglycaemia who did not meet the diagnostic thresholds for gestational diabetes still had a higher risk of cardiovascular disease, although some of those women might have met the more stringent criteria by the IADPSG and WHO.

Taken together, these data highlight that gestational diabetes and hyperglycaemia in pregnancy should be treated as a pre-cardiovascular disease state and the management strategy should be to comprehensively identify and systematically treat cardiovascular risk factors beyond the prevention of type 2 diabetes. Although the risk of incident type 2 diabetes is recognised and previous cases of gestational diabetes are incorporated into the QDiabetes-2018 risk prediction algorithm,[28] this risk has not been incorporated into cardiovascular disease **[A: edits in this sentence correct?]** risk calculators. Despite these findings, in the first year after a gestational diabetes pregnancy, only half of women **[A: 50%? Please provide exact percentage and the reference]** in the UK underwent glucose testing and even less had a lipid test. No improvement **[A: no improvement in? Please expand]** was seen in a follow-up study[8] following **[A: change to 'summarised in'?]** the updated National Institute for Health and Care Excellence guidelines. In addition, women who missed post-natal testing seem to be at a higher risk of cardiovascular disease.[29] Although international guidelines recommend testing women **[A: OK?]** for glycaemic status every 1–3 years,[2,4] in practice these women are often missed as they fall between primary and secondary care teams.[8] None of these international guidelines recommend screening for other cardiovascular risk factors. Hence, a clear pathway for identifying and managing women with a previous history of gestational diabetes in the early postnatal period is needed. A simple gestational diabetes recall register or an appointment with a dedicated cardiovascular coordinator might improve the follow-up **[A: of gestational diabetes?]**.[30,31] Incentives for primary care teams could be another approach because many of these women can be managed in the community. This incentive should also incorporate a concerted effort to educate patients and health-care professionals on the future risk of type 2 diabetes and cardiovascular disorders. NICE and international guidelines should be updated to recognise gestational diabetes as a pre-cardiovascular disease.

Panel: **Long-term complications of gestational diabetes**

Complications for the women

- Hypertension[8]
- Type 2 diabetes[8,24,25]
- Vascular dysfunction[33]
- Non-alcoholic fatty liver disease[36,37]
- Dyslipidaemia[8,24,25]
- Chronic inflammation[33,39]
- Chronic kidney disease[42,43]
- Ischaemic heart disease[8,9]

Complications for the offspring

- Childhood obesity[10,25]
- Excess abdominal adiposity[32]
- Metabolic syndrome[34,35]
- Hyperinsulinaemia[38]
- Disordered glucose regulation in adolescents[26]
- Higher blood pressure[40,41]
- Possible early onset of cardiovascular disease[44]
- Possible attention-deficit hyperactivity disorder and autism spectrum disorders[41,45,46]

Long-term implications of gestational diabetes for the offspring

The combination of maternal obesity, excess gestational weight gain, and gestational diabetes contribute to the development of accelerated fetal growth and accumulation of adipose tissue resulting in infants with higher birthweight that are classified as large for gestational age.[7,47–49] In addition, it should be recognised that excess adiposity in the offspring can be independent of birthweight.[50] The effects of an infant being large for gestational age as a result of gestational diabetes extends beyond the immediate concerns of birth injury and neonatal hypoglycaemia; a long-term global concern is the rising rate of childhood obesity.[51–53] Current estimates show that by the age of 2 years, one in ten children have obesity and more than half will have obesity by the age of 35 years.[54] This persistence of obesity into early adulthood is likely to increase the risk of type 2 diabetes and cardiovascular disease. The long-term complications in women and their offspring following gestational diabetes are summarised in panel.

Early life exposures are known to influence long-term health of the offspring, as encompassed by the Developmental Origins of Health and Disease concept **[A: please provide a short explanation to insert here and a reference.]**. Human observational studies have shown an association between exposure to maternal hyperglycaemia, obesity, and disordered glucose regulation in

children and adolescents.[10,38,55] Such conditioning in girls could increase the propensity to gestational diabetes, thus resulting in a vicious cycle of cardiometabolic disorders (figure). Proposed mechanisms derived from studies in animals and humans include altered gene expression through epigenetic mechanisms leading to impaired cellular signalling[56] or disturbances in the development of central fetal pathways controlling appetite and energy balance.[57]

Therefore, solutions are needed to mitigate these fetal programming effects by developing interventions to prevent gestational diabetes among women at risk, and better management of hyperglycaemia is also needed. The approach must include optimisation of cardiometabolic health of the offspring to reduce the risk of childhood and adult obesity and the associated individual and population-level cardiometabolic consequences.

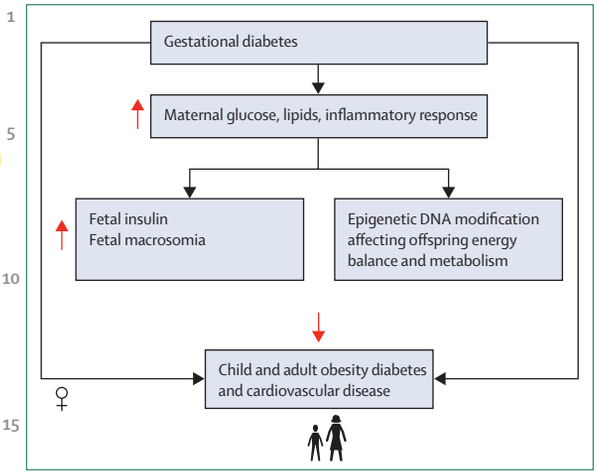

Figure 1: **Developmental programming and gestational diabetes**
Metabolic consequences of maternal gestational diabetes might increase the risk of obesity **[A: BMI ≥30 kg/m²?]**, diabetes, and cardiometabolic disorders in the child and adult, leading to a transgenerational cycle of gestational diabetes and higher cardiometabolic susceptibility.

Preventing gestational diabetes

Meta-analyses of lifestyle intervention studies designed to prevent gestational diabetes showed that interventions can reduce hyperglycaemia, rates of gestational diabetes, gestational weight gain, and caesarean delivery, but without consistently improving perinatal outcomes.[58,59] Similarly, pharmacological interventions have failed to prevent babies being born large for gestational age.[60] However, many multicentre studies did not show a reduction in gestational diabetes, perhaps because participants did not adhere to trial protocols; interventions started too late in pregnancy; women most at risk of gestational diabetes were not targeted (selective screening picks up only 10–15% of women of at risk of gestational diabetes entered in the trials); or a one size fits all approach was used for different ethnic groups.[49] Lifestyle interventions could be effective if selectively targeting the correct risk groups; however, risk assessment is based on clinical risk alone[2,61] and is not sufficiently sensitive. Improving the risk stratification by developing personalised composite risk scores could overcome some of these barriers and allow interventions to be tested in women at the highest risk. Women might adhere to the proposed lifestyle interventions more when they feel that the intervention is personal **[A: correct?]**.

Timing of screening

There is also growing evidence that gestational diabetes testing should be done earlier in the pregnancy. Many international guidelines recommend early pregnancy screening for undiagnosed diabetes using the standard criteria.[4] However, other guidelines advise against plasma glucose or HbA_{1c} testing early in the pregnancy, even to rule out pre-existing type 2 diabetes, because of the scarcity in cost-effectiveness studies.[2] Data have shown that fetal overgrowth is already present when gestational diabetes is diagnosed by an oral glucose tolerance test at 28 weeks of gestation, and at 20 weeks in women who are overweight and obese.[62] In India, elevated fetal adiposity has been shown before the diagnosis of gestational diabetes in women who did not have prediabetes or type 2 diabetes in early pregnancy (ruled out by fasting glucose).[63] Babies from these women had higher adiposity but did not have an elevated birthweight, the so-called thin-fat phenotype.[49,63] Although the IADPSG and WHO recommend to diagnose gestational diabetes in early pregnancy using the same diagnostic threshold that is used at 24–28 weeks (ie, fasting plasma glucose ≥5·1 mmol/L), many clinicians have not followed this recommendation because of insufficient interventional evidence, clinical capacity, and concerns about increasing medicalisation during pregnancy. An ongoing randomised controlled trial identifies women **[A: at risk of gestational diabetes?]** using an oral glucose tolerance test early in the pregnancy (<20 weeks) and will inform whether early intervention can improve pregnancy outcomes.[64] We propose the need for routine detection of undiagnosed pre-existing type 2 diabetes at the antenatal appointment to ensure that women with more severe hyperglycaemia do not remain undiagnosed until 24–28 weeks of gestation. In addition, we recommend an earlier oral glucose tolerance test at 24 weeks of gestation, especially among women who have obesity **[A: BMI ≥30 kg/m² ?]**.

Personalised composite risk score screening

To optimise the benefits of an antenatal intervention, the diagnosis of gestational diabetes needs to be made more closely related to the outcome **[A: unclear sentence, please clarify.]**. Prospective observational data have shown that the relationship between maternal glucose and large for gestational age infants is continuous, with no clear inflection point of risk.[7] Many guidelines use simple risk scoring to identify women who will develop

impaired glucose tolerance, rather than complications related to gestational diabetes on the basis of the following criteria: a BMI of 30 kg/m² or more, having a macrosomic baby weighing 4·5 kg or more, a previous diagnosis of gestational diabetes, having a first-degree relative with diabetes, being from a minority ethnic group with a family history and high prevalence of diabetes, having polycystic ovarian syndrome, and being aged 30 years and older. The US Department of Health also advises a simple yes or no risk scoring to decide on who should be tested (age ≥25 years).[61] These strategies do not recognise differential risk among ethnic groups (such as South Asian)[65] or relative risk contribution by different predictors (eg, BMI, age, fasting, and post-prandial hyperglycaemia) for outcomes (gestational diabetes or its complications)—eg, the competing risks model approach in pre-eclampsia.[66]

The current screening strategy does not reflect the pathogenesis of gestational diabetes which is most likely heterogeneous. Genome-wide association studies have identified candidate genetic variants which are similar between type 2 diabetes and gestational diabetes. Outside pregnancy, defects in insulin secretion (~30%) or insulin sensitivity (~50%) have been identified in women with previous hyperglycaemia during pregnancy.[67] In turn, these defects might also differentially contribute to the adverse effects because of irregular adipocytokines, fatty acids, triglycerides, or HDL,[67,68] and other unknown factors. Thus, emphasising the need to develop and evaluate personalised risk scores for diagnosis and management of gestational diabetes[69–71] to identify women who would benefit from continued monitoring and intervention. A recent study[72] highlighted the benefit of using machine learning to accurately predict gestational diabetes and implement prevention strategies for those at higher risk. Although the data are encouraging, the applicability is limited to women with a comprehensive health record of a previous pregnancy and the availability of glucose challenge test results. Targeting resources to those most in need is a pragmatic approach, and would likely be supported by women; however, health systems struggle with the demands of gestational diabetes diagnosis and management **[A: edit for clarity, OK?]**, particularly in low-income and middle-income countries (LMICs).[19,22]

Any new screening strategy needs to improve outcomes if implemented. **[A: statement here was obvious, sentence deleted. OK?]** Although randomised trials show that the management of gestational diabetes does not increase[5] or reduce the likelihood of a caesarean birth,[5,6] implementation in the real word setting resulted in two times higher rates of labour induction and a caesarean birth.[73,74]

Finally, a contextualised approach is probably required. Studies are limited on the cost-effectiveness of gestational diabetes screening strategies and diagnostic criteria;[75–77] however, universal screening for gestational diabetes would be cost-effective in the UK, only if the purpose was to prevent type 2 diabetes.[75] Instead of global recommendations on cost-effectiveness, population-based local recommendations should be considered[78,79] because cost-effectiveness will depend not only on the prevalence of gestational diabetes and core short-term outcomes,[80–82] but also on the population and setting dependent long-term outcomes for women and their offspring.

Priorities for clinical practice

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Although it is not possible to review all the gaps in evidence, we summarise urgent priorities for clinical practice and research, and justify the rationale behind each recommendation. First, HbA_{1c} or fasting plasma glucose should be measured in early pregnancy to identify undiagnosed pre-diabetes and type 2 diabetes, and to improve short-term and long-term outcomes. Although recommended by many guidelines, this practice is not routinely done in LMICs and in many high-income countries. Identifying women with severe hyperglycaemia in early pregnancy allows more time to intervene with diet, lifestyle, and medication to improve their pregnancy outcomes.

Second, reporting of gestational diabetes in the maternity data systems should be compulsory. Although the recording of data has improved in primary care systems, the transfer of information by maternity systems to primary care remains inadequate. Improving the accuracy of coding by including ethnicity and other key variables would enable development of a national register for gestational diabetes which could be linked to data on the offspring. This register would inform cardiometabolic prevention programmes for women and their children.

Third, postnatal care pathways for women with a previous diagnosis of gestational diabetes should be developed, prioritising these women to national diabetes prevention programmes. Several countries including the UK, Australia, and USA are setting up national diabetes prevention programmes. To expand these programmes, considerable resources are required for LMICs. Prioritising women with a previous history of gestational diabetes will be cost-effective, enabling better preparation for subsequent pregnancies and prevention of type 2 diabetes and cardiovascular disease. We suggest that all women with gestational diabetes should have a postnatal check at around 12 weeks after giving birth. This check could coincide with a child health check or a vaccination schedule. In addition to the postnatal measurement of HbA_{1c}, a comprehensive cardiovascular assessment should be done for risk factors such as blood pressure, smoking history, and lipid management; and should be recorded and appropriately managed.

Finally, pathways need to be developed for children born to women with gestational diabetes. Childhood obesity is rapidly rising worldwide, and the double-burden of stunting and obesity is also increasing in LMICs. To

prevent childhood obesity, the intervention has to happen at age XX years **[A: please provide age range?]**. Health visitors and other health-care professionals could be trained to provide families with advice on healthy lifestyle interventions from the birth of the first child **[A: correct?]**.

Priorities for research

First, the use of risk scores in early pregnancy should be developed and examined for risk stratification of gestational diabetes and its complications, particularly in LMICs. Current screening strategies for detection and management of gestational diabetes are suboptimal. The prevalence of gestational diabetes detected by selective screening is only around 10–20% and the remaining 80–90% of women are negative **[A: please provide reference.]**. Nearly half **[A: you mentioned half previously, deleted the 'third'. Please provide reference.]** of all women with gestational diabetes are not assigned to the risk group and are not screened for gestational diabetes,[1] which increases the risk of stillbirth.[83,84] Obese women with a negative oral glucose tolerance test and higher HbA_{1c} (≥5·7%; ≥39mmol/mol) during childbirth have a higher metabolic risk 4 years post-partum and their infants have a higher risk of obesity compared with women in whom gestational diabetes has been treated.[85] Current gestational diabetes screening strategies have a glucocentric approach and novel or cardiovascular risk factors (eg, triglycerides, adiponectin) are not taken into account. Lifelong consequences of fetal exposure to hyperglycaemia (and other factors) could have already developed by the time of screening. More than 90% of gestational diabetes and 80% of maternal and infant mortality occurs in LMICs. Evidence is still inadequate in these populations at high-risk, although ongoing studies (NCT03005600) might provide answers.[64] Developing accurate, population-specific, and personalised composite risk scores has the potential to address these concerns.

Second, it should be explored whether early pregnancy screening and intervention improves cardiometabolic outcomes for the offspring, in the short-term and longer-term. There is little evidence that treating mild early pregnancy fasting hyperglycaemia reduces adverse outcomes in the short-term. Studies on short-term and long-term outcomes are needed, with a focus on the potential benefits and harms of early intervention. Several risk prediction models have been proposed but need to be tested and validated in different populations.

Third, alternatives to the oral glucose tolerance test such as novel biomarkers or continuous glucose monitoring should be used as the diagnostic test for gestational diabetes. Oral glucose tolerance tests are difficult to perform, have poor reproducibility, and are being discontinued for a diabetes diagnosis beyond pregnancy. The role of emerging biomarkers and continuous glucose monitoring, which measure direct fetal exposure to maternal glycaemia, offer an alternative solution to identify mothers and infants at risk for complications from gestational diabetes. Any alternative solution should be cost-effective and available in LMICs.

Fourth, management strategies for gestational diabetes should be personalised and informed by the pathogenesis for those at risk of complications. Approximately 20% of women with gestational diabetes have adverse pregnancy outcomes and with effective intervention, this percentage can be halved. Thus, most cases of untreated gestational diabetes do not result in adverse outcomes during pregnancy.[5–7] **[A: sentence deleted here because risk identification has been mentioned in the text many times]**

Fifth, postnatal personalised risk stratification should be developed for type 2 diabetes and the associated cluster of cardiovascular risk factors should be identified to inform future monitoring of HbA_{1c}, blood pressure, and serum lipids. Research suggests that women with gestational diabetes are at higher risk of incident type 2 diabetes and develop cardiovascular disease at a younger age. Personalised and population-specific cardiovascular risk stratification will inform future monitoring and prevention strategies for these women with potential for better adherence in the postnatal period.

Sixth, the barriers and facilitators should be understood to improve postnatal evaluation of glycaemic and cardiovascular risk status in women with a previous history of gestational diabetes. Studies that can provide insights and postnatal evaluation of cardiovascular risk and strategies for improving these barriers are required. Community health workers who visit and assess the children could play a role. Similarly, vaccination programmes could incorporate health checks for women with gestational diabetes. The accuracy of point of care devices for measuring HbA_{1c} and lipid profiles have improved and could be used for routine cardiovascular risk evaluation in community care settings.

Lastly, health economics should be incorporated into a wider range of screening and management trials. Models of cost-effectiveness that incorporate long-term effects on

Search strategy and selection criteria

References for this Personal View were identified through searches on PubMed for articles published from Jan Day, 1981, to Jan Day, 2020, **[A1: Please update dates to search strategy to more recent, as your article will be published in the September issue of the journal and thus searching to just Jan 2020 makes the article seem outdated. A2: please provide the exact dates]** by using the terms: "gestational diabetes mellitus", "hyperglycaemia in pregnancy", "long-term complications", "cardiovascular disorders", "offspring", "childhood obesity", and "childhood complications". Relevant articles resulting from these searches and relevant references cited in these articles were reviewed. Articles published in English were included. To keep references to a minimum, some of the original articles cited in systematic reviews were not included.

the mother and child and facilitate transferability of results between countries should also be developed. Clinical and cost-effectiveness priorities are essential to inform policy makers worldwide, which will enable countries to decide on what interventions are suitable. Replicating studies in all populations is not feasible, especially the long-term effects. Therefore, transferability across similar populations will enable evidence-based guidance for many LMICs.

Conclusion

In summary, gestational diabetes provides a unique opportunity to identify women and babies at increased long-term risk of obesity, type 2 diabetes, and cardiovascular disease. Although short-term outcomes in gestational diabetes should remain a part of the research agenda, the focus needs to shift towards an earlier and more personalised diagnosis including preventive care and the future health of women with a history of gestational diabetes.

Contributors

PS and the Diabetes in Pregnancy Working Group of the Maternal Medicine Clinical Study Group, Royal College of Obstetricians and Gynaecologist, are a group of academics, clinicians, and policy makers. **[A: the deleted text here is not needed in the contributors section] [A: deleted text here, not needed, OK?]** PS and the following members of the Working Group conceptualised this Review; Laura A Magee, Matthew A Coleman, Peter von Dadelszen, Fiona Denison, Richard Holt, Robert S Lindsay, Lucy MacKillop, Claire L Meek, Helen R Murphy, Dharmintra Pasupathy, Lucilla Poston, Rebecca M Reynolds, Eleanor Scott, and Sara L White. **[A: PS is the only author on the by-line, names written out, correct?]** All Working Group member names can be found in the appendix. PS wrote the initial draft. All members of the Working Group edited and revised the manuscript and approved the final version.

Declaration of interests

We declare no competing interests.

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[A: reference 86 deleted as it is an ongoing trial, trial number given within text instead, OK?]