

Dr Angharad Care - Written evidence (PRT0039)

Background information

1. I am an NIHR academic clinical lecturer at the University of Liverpool, with over 10 years' experience in clinical preterm birth (PTB) prevention research and clinical practice in PTB prevention services currently working at Liverpool Women's Hospital. I am a founding member of the PTB National Clinical Network and co-lead organiser of the first UK national PTB network conference in 2015 and 2024 and have authored multiple chapters on preterm birth prevention. Most recently I have co-authored the largest prospective observational study into preterm prelabour rupture of the membranes (PPROM) less than 23 weeks and associated commentary. These opinions are my own, with contribution from Dr Philip McHale, a Senior Clinical Lecturer in the Department of Public Health and Policy, and a MRC Clinical Fellow, with whom I co-authored a manuscript on mediators of socioeconomic deprivation on preterm birth.

Executive Summary

2. The issues that I wish to highlight are:
 - a. Need for good quality national maternity data collection
 - b. Need for well curated preterm birth prevention clinic research database (PCN database) and associated staffing support to ensure high quality data input.
 - c. Need for appropriate funding for large, national maternity randomised clinical trials, including funding for long term follow up for large national cohorts or RCTs to obtain data on outcomes that matter to parents and families.

- d. Need for appropriate funding of clinical services, with a particular focus on the training and retention of midwifery staff to be able to deliver services focussed on reducing preterm birth in both primary and secondary prevention of preterm birth. (e.g. delivery of continuity of care models)
- e. The role socioeconomic inequalities play in the risk of preterm birth, and how poverty can exacerbate the negative consequences of preterm birth on health and educational outcomes for children. This evidence relates to potential policy points to reduce health inequalities.

Summary of Evidence

3. Data from 4.1 million carefully studied singleton pregnancies from population data from four countries¹ (Czech Republic, New Zealand, Slovenia and Sweden) and California state in the US found that 1) prior preterm birth and 2) pre-eclampsia with onset before term, are the factors that confer the highest risk of preterm birth when present in an individual. However, on a population basis, nulliparity (being a first-time mother) and male gender in the fetus have the largest overall association of having a preterm birth and two-thirds of women who have preterm birth have no apparent risk factors or identifiable mechanism to explain its occurrence (Figure 1). This study is an example of what can be done with good quality country specific individual level patient data in terms of understanding important regional and nationwide specific factors for sPTB, and ultimately where to target public spending. They found factors for preterm birth <37 weeks and <32 weeks vary across gestations and populations, with a higher incidence of preterm birth, in Swedish and US cohorts class II and III obesity (BMI 35-39.9 and 40 or above) were more strongly associated with PTB, however in other countries ethnicity, lower education and advanced maternal

age were more likely to be present in women experiencing PTB < 32 weeks.

4. I believe the barriers to achieving reliable national data in the UK are: 1) the lack of top-down approach to the use of IT systems in the NHS. IT systems vary from hospital to hospital in the UK and even transferring patients within the same region can lead to misunderstandings in history taking and data collection 2) Inconsistencies with the skill mix of people inputting this data and different application of terminology 3) difficulty finding data. 4) lack of quality assurance. As a minimum we require a good quality maternity services dataset or research database to better understand the effects of current interventions.
5. I have been involved in several national audits of practice for preterm birth prevention clinics to try to establish current 'best' practice to treat high risk women with a short cervix on ultrasound scan. These audits published in 2014², 2018³ and 2022⁴ found that vaginal progesterone is being used as a first line treatment in around 20% of preterm birth prevention services, with cervical cerclage (also known as suture or stitch) the most popular choice and some clinicians using a combination of all of them. To try to tease out a "best" of useful "first line" treatment for high-risk women (previous preterm birth and/or short cervix <25mm by 24 weeks) we performed a network meta-analysis⁵ that looked at 61 RCT and 17,273 pregnant women and compared the efficacy of 16 different treatments with placebo or no treatment arm. We used a maternal outcome of PTB < 34 weeks and a neonatal outcome of perinatal death to establish which treatment has the best evidence. i.e. you don't want a treatment that improves time in utero at the expense of a increasing the risk of death once born (e.g. keeping the baby in an infective environment for example). Overall vaginal progesterone was considered to be the treatment of choice and the

recommendation was that future RCTs should be using this therapy as the gold-standard in high-risk women.

6. There are, of course, some limitations to the current best data about optimal prevention of preterm birth. The likelihood is that treatments like cerclage and vaginal progesterone all have benefit and potentially harm when used in the wrong patient populations, the correct treatment needs to be targeted to the correct woman. However, without widespread use of a well curated preterm birth prevention clinic database it will be impossible to tease these factors out and clinical trials to try and prove our hypothesis will be almost impossible due to small event rates (i.e. we will need to achieve huge number of participants to detect small improvements on our baseline levels of preterm birth <28 weeks and <34 weeks, as they happen much less frequently even in high risk populations). I fully support the use of the Tommies PCN database achieving NIHR portfolio study status so that research midwifery team support can be given to inputting data as this is a time-consuming task that is at present unrealistic for most PTB clinics that are simply trying to see and treat the patients mandated by Saving Babies Lives v3. Suggested ways forward would be 1) To ensure that we have a suitable national database to allow for investigation of appropriately targeted therapies (2) to continue with the search for alternative biomarkers in blood, amniotic fluid or vaginal secretions to aid our understanding of pathways of action; (3) to explore genetic association studies, a major tool for identifying genes conferring susceptibility to disorders in which both genetic and environmental factors contribute to susceptibility risk; and (4) to understand how to link this new information together to provide individual patient-risk assessment. Performing these studies in the preterm birth prevention clinics to recruit women who have previously had

preterm birth is one strategy to identify candidate clinical biomarkers that may be then tested in a primiparous population.

7. When we looked at local data from Liverpool Women's Hospital attending preterm birth clinics between 2010 and 2012 with a history of PTB or preterm prelabour rupture of membranes (PPROM) < 34 weeks (n=196), 68% (n=134) had a normal cervical length when screened and did not receive prevention treatment, of these 20.9% went on to have a preterm birth <37 weeks with 9% (n=12) delivering before 34 weeks so we know that screening in these population will not work for everyone. Following an IPD published in the Lancet of progesterone in preterm birth prevention it was suggested that progesterone may be useful for high-risk women irrespective of cervical length. From 2018 our clinic at the Liverpool Women's Hospital commenced a policy of vaginal progesterone for all high-risk women from 16 weeks of pregnancy. Using our clinic data recorded on local databases and subsequently the PCN database we found a nearly 50% reduction in preterm births <28 weeks (data being prepared for publication) compared to our screen and treat approach prior to this. This data is insufficient to do anything other than support continued local practice. The nature of small local cohort studies may have magnitudes of error that given a national study may not be replicated. Ideally a randomised controlled trial (RCT) would be performed to establish if this approach is better, however a power calculation is difficult to do as the event rate of preterm birth < 28 weeks is small. It is hard to get an accurate picture of how many high-risk women attending these clinics in the UK deliver < 28 weeks as at present, the uptake with the PCN database is insufficient. Basing a power calculation on PTB rates in a single unit, when there are disparities in socioeconomic status of the populations the hospitals serve may affect the feasibility of a clinical trial. This really underpins the need for, at the

very minimum, a national database to collect cohort information and support for the clinical network to deliver difficult RCTs in this area which will require considerable funding and potentially novel clinical trial design such as cluster randomised controls.

8. For doctors working in preterm birth prevention clinics there are currently no incentives to try and collaborate with neonatal services or even the wider community to try and improve quality of life for children born preterm. Doctors working in preterm birth prevention services currently aim to benchmark their practice against Saving Babies Lives v3. There are currently no incentives or resource to try and provide support to patients in the wider healthcare context including opportunities to educate women with preterm children about interventions to improve education for their children and detection of special educational needs etc. This may be one area to try and empower the patient to drive improvement for their child in the longterm.
9. Consistent socioeconomic inequalities are seen in preterm birth outcomes, with studies internationally demonstrating an almost 50% increased relative risk for mothers from a low socioeconomic background compared to high.⁶ The pathway from socioeconomic status to preterm birth has a number of 'intermediate variables', risks which are affected by socioeconomic status which in turn effects the risk of preterm birth – they 'explain' some of the inequality. For example, pregnant people from a low socioeconomic background are more likely to smoke, which increases the risk of preterm birth. Figure 2 (below) shows some of the factors which act in this way. A systematic review found smoking was the most common risk factor which explained inequalities, explaining around a quarter. Poor mental health and stress, and pre-existing physical health conditions both explain up to a fifth of the inequality.⁷

10. Work we have done in Liverpool⁸ and in Wales suggest the explanation of inequalities by risk factors occur mostly through smoking. However, even when we remove the effects of these risk, there are still significant inequalities in the risk of preterm birth. This suggests action on the risk factors for preterm birth, particularly smoking, in pregnant people from deprived background, will potentially be effective in reducing inequalities in the rates of preterm birth. However, direct action on poverty is still required.
11. Evidence suggests that negative consequences of preterm birth on cognitive and mental health outcomes is exacerbated by low socioeconomic status. Action is needed to support babies born preterm, particularly for disadvantaged families, to improve educational attainment and mental health.⁹⁻¹¹

Figures

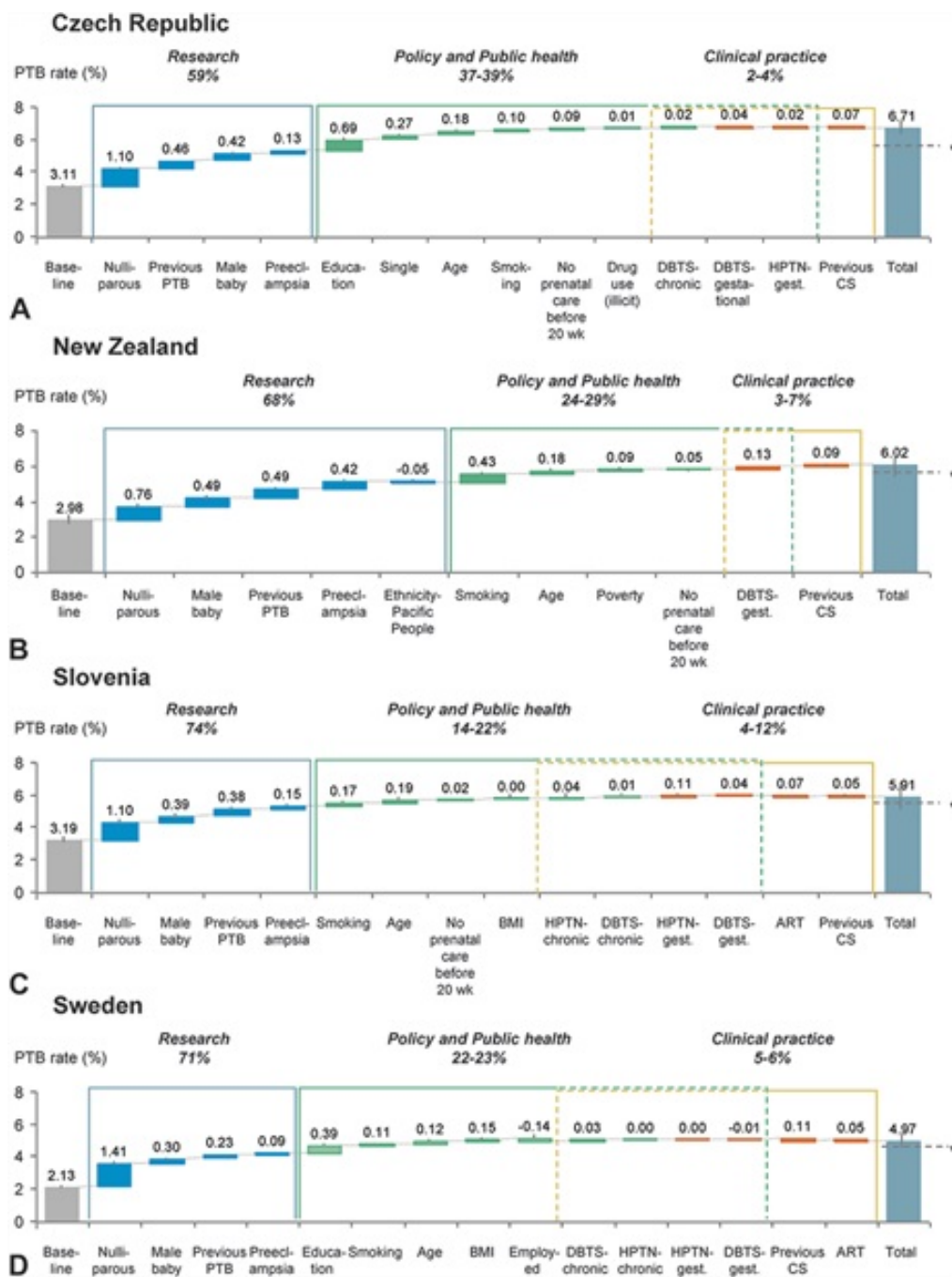


Figure 1 Estimated contribution of risk factors on population singleton preterm birth rate and opportunities for various stratified interventions shown in waterfall format. From Martin, James N. Jr MD; D'Alton, Mary MD; Jacobsson, Bo MD; Norman, Jane E. MD. In Pursuit of Progress Toward Effective Preterm Birth Reduction.

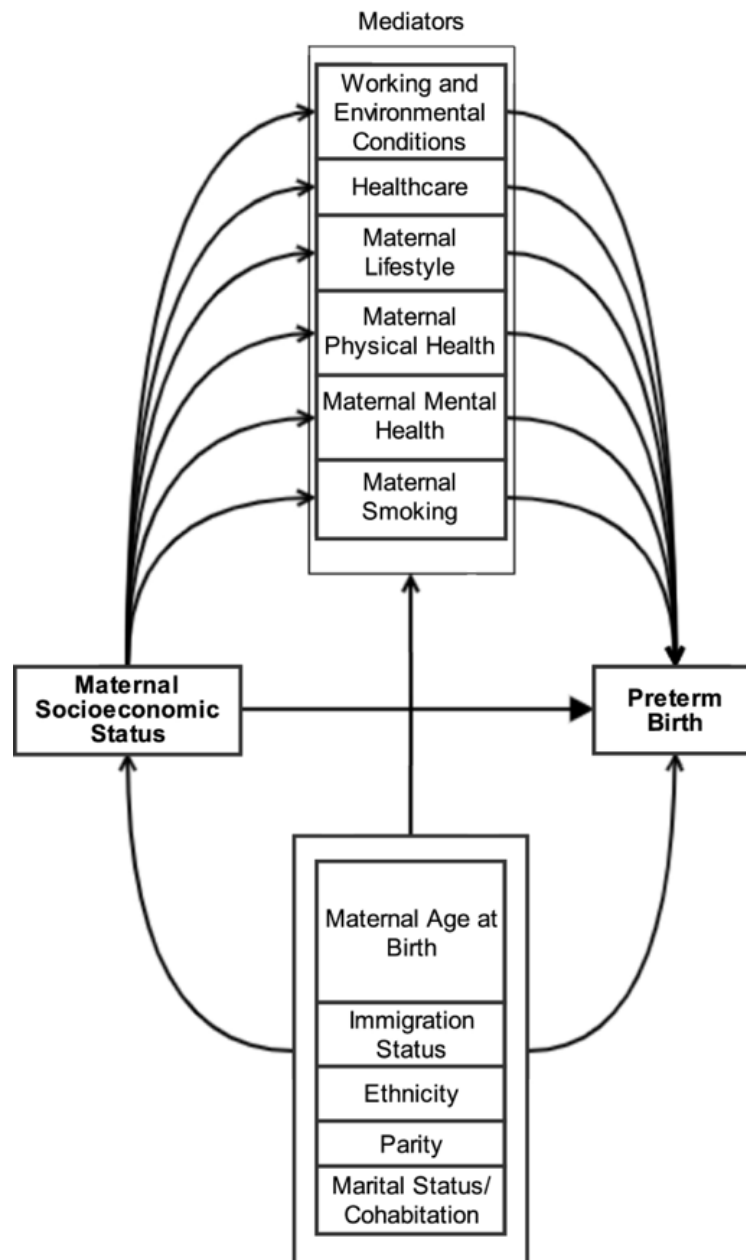


Figure 2 Mediators of Maternal Socioeconomic Status on Preterm Birth. From McHale P, Maudsley G, Pennington A, Schlüter DK, Barr B, Paranjothy S, et al. Mediators of socioeconomic inequalities in preterm birth: a systematic review. BMC Public Health. 2022 Jun 7;22(1):1134.

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