INTERIM REPORT

Harris-Wellbeing Preterm Birth Research Centre

1 April 2019 – 31 March 2020

The Harris-Wellbeing Preterm Birth Research Centre (referred to as the Harris-Wellbeing Centre for the purpose of this report) was founded in 2015. The funding (£1 million, for a 5 year period) was awarded by the charity Wellbeing of Women in a national competition. The award stipulated that no further funding will be available beyond 2020 (i.e., that the centre should be self-sustainable by this time and will keep the name and the status for another 5 years minimum). The Harris-Wellbeing Centre has been granted a no cost extension for a period of 12 months with a revised end date of 31/03/2021.

Preterm birth is the single biggest cause of neonatal morbidity and mortality in the UK and worldwide. The central hypothesis of our research centre is that preterm birth has a wide range of causes, which if present in a particular configuration will contribute to preterm birth. To improve understanding of the contributions of these factors to preterm birth we use a multidisciplinary approach to the management of clinical research within our centre, this includes pan-omic analyses, systems biology and research synthesis to bridge the gaps between molecular mechanisms, physiology and therapeutics. ***Our overarching aim is to use personalised medicine to deliver targeted preventative strategies by sophisticated stratification of pregnant populations***.

Four work packages are currently underway (for the period 1 April 2015 to 31 March 2021) details are as follows:

1) Biomarkers of preterm birth

The central component within this thread has been a biomarkers of preterm birth cohort study. We have been very fortunate to have 298 women with previous preterm birth (under 34 weeks) and 270 women with previous healthy pregnancies take part in this work. These women have all now had their babies, we have collected all the necessary data and are within the final analysis stages of the project.

The final analysis stage is focusing on linking detailed pregnancy outcome data to the results obtained from blood and vaginal secretions samples to assess how the data interact, and whether or not there are any indicators that can predict, and prevent, preterm birth in a better way.

We have completed metabolomics analysis from high risk women and healthy controls (Juhi Gupta, Harris-Wellbeing of Women Fellow, 3rd year PhD). The metabolites that were found to be significant are phenylalanine (reported in previous PTB literature), creatinine and glucarate. Some unknown peaks are currently under investigation using **triangular analysis** (GWAS - metabolomics – transcriptomics), which may help to reveal correlations between “unknown” metabolites and transcripts. Given that we measured the transcriptome and metabolome changes at two time points (16 and 20 weeks), by integrating these two data-types we will identify metabolites and their interactions that have functional relevance. We will use our data, data from literature and publically accessible databases to identify a metabolite-gene/transcript relationship.

Our pilot **integrative analysis** (GWAS, metabolomics, transcriptomics, proteomics) formed the key part of Angharad Care’ Thesis (Harris-Wellbeing of Women Fellow) December 2019. This work has demonstrated that even in a small number of well phenotyped individuals our current machine learning approach is feasible and multi-omic data integration with clinical outcomes is possible. We plan to expand our pilot using data on all women with a complete multi-omic data sets.

An initial finding from the pilot component of the biomarkers of preterm birth study was that a gene involved in selenium metabolism may be associated with preterm birth. This was particularly exciting because it mirrored a similar finding Professor Mouglia's group in Cincinnati. We were able to collaborate with Professor Mouglia's group to measure serum selenium levels in our cohort, and correlate these with both the genetic data and the risk of recurrent preterm birth. We found that women who have preterm birth do have slightly lower levels of selenium, but the contribution of selenium to recurrent preterm birth in this cohort appears modest. This analysis is currently in preparation for a manuscript.

The vaginal microbiota component of our biomarkers study is part of the 'second wave' of vaginal microbiota and preterm birth work (first 'wave' 2014-2019), and we are progressing this field by focusing in detail on the work of previous studies, to confirm which associations are (and are not) reproducible in our women at high risk of preterm birth. We have found that a higher 'bacterial load' (more microbes) is associated with recurrent early preterm birth. We have also confirmed links between some specific microbes that have been associated with preterm birth in other cohorts. This work has been presented orally at the UK National Preterm Birth Conference, as a poster at the Annual Academic Association of RCOG meeting, and is currently being prepared for manuscript submission. We have also assessed the utility of the clinically available high vaginal swabs for women at high risk of preterm birth within the biomarkers study. Lucy Button, who was a medical student with our team in 2019, presented this work orally at the UK Preterm Birth Conference, and won first prize for the best presentation of the day.

Our status as the Harris-Wellbeing Centre has given us the momentum and authority to adopt research findings quickly. In November 2018 a Cochrane review recommended omega 3 supplementation for preterm birth prevention; this was the best evidence for a new preterm birth prevention therapy for over a decade. We introduced supplementation in Liverpool Women's Hospital in January 2019. We were able to use stored samples from participants involved in our biomarkers of preterm birth research to assess levels of omega 3 in the blood in women at high, and low risk of preterm birth in the UK. This analysis was performed in collaboration with researchers from the University of Adelaide, Australia. We have found that women in our cohort have low plasma levels of omega 3, whether at high or low risk of preterm birth. This would suggest that our cohort may benefit from omega 3 supplementation. Surprisingly we found no association between plasma omega 3 level and chance of recurrent preterm birth. This could be because omega 3 levels are 'overpowered' by alternative factors in these women, or the contribution of omega 3 to recurrent preterm birth is smaller than we are able to detect. This is important because it suggests that supplementation may not be equally beneficial in all cohorts. This work has been submitted as a manuscript for publication.

2) Muscles - Researchers continue to explore the timing and dosage of different drugs applied to uterine tissues as well as explore how the uterine environment (pH, levels of oxygen) affects their actions. We will be submitting a paper on our findings from a study exploring the effects of combining different drugs on contractions soon. Other work has included a gene study to explore differences in the womb of women carrying twins to those carrying just one (singleton) baby. The results of the study showed there was very little difference between singleton and twin pregnancies except for between preterm singletons and term twins where there is likely to be the most difference in the amount of stretch on the uterus. The work was published in PloS One early this year. Other work which is progressing well is investigating how different hormones work at the cellular level on the uterus and an invited review on this was published recently. We are planning further publications from this work.

3) Evaluating different preventative strategies by research synthesis - The final delivery for work package 3 is the publication of the network meta-analysis. Statisticians are currently working on results for both networks to be included in this publication. The review will include over 100 randomised clinical trials to summarise evidence for treatments for women with high risk of preterm birth due to short cervix or prior history of preterm birth (Network 1) or women at risk of preterm birth due to the presence of asymptomatic vaginal infections such as bacterial vaginosis (Network 2).

With our review of preterm birth guidelines (BJOG), the overview of treatments to prevent preterm birth (Cochrane Library), and now with the network meta-analysis (NMA) rankings of prevention strategies, we have certainly evaluated all of the available evidence to prevent spontaneous preterm birth. Our Cochrane overview has an Altmetric score of 196, which is in the top 5% of all outputs scored by Altmetric. The overview was mentioned by 261 tweeters and was the subject of a blog. The overview has also been cited in 11 publications. We expect the NMA will have an equally significant impact to inform women and health professionals of the relative benefits of current treatments to prevent preterm birth. In particular, there is little recent synthesis on vaginal infections, a known contributor to spontaneous preterm birth.

Systematic reviews of interventions provide the evidence base for guidelines, such as those written by the World Health Organisation. In this respect, evidence synthesis has a direct impact on outcomes for millions of women around the world by providing clinical trial evidence for health care decisions.

We also wish to highlight an example of an exceptional value for money from work package 3. In July 2019 we hosted a 3 hour workshop together with the UK Data Service, to improve researchers' and public knowledge of the importance of sharing clinical trial data. Many researchers do not know how to enable secure sharing of their clinical trial data, wasting valuable resource that could answer pressing clinical questions. 50 members of the clinical research community and interested public attended the event at the Liverpool Women's Hospital. This collaboration resulted of our NIHR-funded Cochrane pilot grant, written by Harris-Wellbeing Centre team members Ms. Medley and Professor Alfirevic. Data-sharing is a critical component of clinical science going forward, and the Harris-Wellbeing Centre is at the vanguard when showing support for these kinds of initiatives.

4) Drug delivery - Dr Andrew Sharp and Dr Sarah Arrowsmith, along with Dr Tom McDonald from the University of Liverpool's Chemistry department have submitted an application to Rosetrees Trust to continue this work. The team want to study different nanomedicine formulations of indomethacin to find more effective treatments, as well as look more closely as its actions in the cells of the uterus to gain a better understanding of how these nanomedicines work. To make the medicine safer, they also plan to add a targeting marker to deliver it directly to the uterus and avoid it crossing the placenta and reaching the baby. They anticipate that these new formulations would offer a safer and more effective treatment for preterm labour.

Next phase

Since our inception in 2015 our centre has widened its scope and as well as targeting spontaneous preterm birth we are now applying personalised medicine to pregnancy complications that lead to medically indicated preterm births such as growth restriction and preeclampsia.

The Harris-Wellbeing Centre has been instrumental in raising the profile of preterm birth research in the UK over recent years. We have led and hosted the first Annual UK Preterm Birth Research Conference in 2015 and been involved in the delivery of subsequent conferences and events since this time. Our research team of clinical academics, physiologists, statisticians and research management staff based within the University of Liverpool has been actively engaged in shaping both the research and clinical agenda related to preterm birth prevention, both nationally and internationally.

Several clinical academics are members of the UK preterm birth clinical network which has been instrumental in the UK government's pledge to reduce the rate of preterm birth from 8% to 6% by 2025. Internationally, Professor Alfirevic has fostered links with high-profile organisations including March of Dimes and the Patient Centred Outcome Research Institute (PCORI) from the U.S.

The Harris-Wellbeing Centre is committed to ensuring synergy between patients and research and has an established Patient and Public Involvement/Engagement Group 'Liverpool Babies' who contribute to the ongoing cycle of clinical research development, management, delivery and dissemination. As part of the University of Liverpool's response to COVID-19, the Liverpool Babies group have been instrumental in the design of a new research study COVID-PREP 'Pregnancy Testing Programme'. The study will determine the proportion of women booking in their first trimester of pregnancy (n=16,000) who have positive SARS-CoV-2 serology and determine the risk on maternal and neonatal outcomes. The Liverpool Babies PPIE group recently completed an on-line survey which was also made available on social media. We received over 300 completed surveys of which over 90% supported the research idea.

The Harris-Wellbeing Centre's portfolio has seen rapid growth since it began in 2015 including successfully securing funding from various competitive national funding streams including NIHR HTA, EME and RfPB, Wellcome Trust and Wellbeing of Women. The Harris-Wellbeing Centre adopts a collaborative approach to the development and delivery of its' central aim.

In June 2019 we successfully obtained a project grant from Wellbeing of Women for a UKOSS (UK Obstetric Surveillance System) study into extremely (16^{+0}-22^{+6} weeks gestation) preterm prelabour rupture of the membranes (EPPROM), and UKOSS approval to perform the study. This study started collecting data in September 2019 and will run for 1 year. This is currently continuing through the COVID-19 pandemic, although this decision might alter. This work will form the largest cohort of EPPROM cases and will allow us to provide important prognostic information to women and clinicians faced with this harrowing situation.

The Harris-Wellbeing Centre has maximised opportunities to successfully establish and develop links within the University of Liverpool and in collaboration with partner academic institutions, NHS organisations, charities and industry. Examples of this are detailed below with further information available upon request.

Approximately one third of medically indicated preterm births are performed for suspected fetal growth restriction. The Harris-Wellbeing Centre is central to the delivery of a number of clinical research studies related to fetal growth restriction in single (PLANES, STRIDER) and multiple pregnancies (FERN). We are also studying the pharmacokinetics of treatment given to mothers to prevent early onset neonatal Group B Streptococcal Infections (PKPD Study), a complication which disproportionately affects preterm neonates.

The Harris-Wellbeing Centre will be central in the set up and delivery of a newly funded longitudinal birth cohort of mothers, fathers and their first-born infants (triad design), called Children Growing up in Liverpool (C-GULL). C-GULL is an exciting new programme of research that will establish a large contemporary birth cohort of 10,000 first-born babies and their parents. C-GULL will be the first birth-cohort to launch in the UK in almost 20 years and it will offer an unprecedented opportunity to the global scientific community to study the early life origins of a range of health outcomes. C-GULL is funded by the Wellcome Trust, the Liverpool City Region Combined Authority and the University of Liverpool. This programme of research will provide the platform to deliver a programme of research that has the potential to impact all themes recognised in the University's Research and Impact Action Plan. It will facilitate Institutional collaborations in existing areas of excellence as well as develop new partnerships regionally, nationally and internationally.

PUBLICATIONS (01/04/2019-31/03/2020)

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