Abstracts from Invited speakers

Saturday October 6, 2018

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Inflammatory Bowel Disease and Pregnancy
Janneke van der Woude
Erasmus Medical Center, Rotterdam, The Netherlands

Introduction: Inflammatory bowel disease (IBD) is a chronic disease of the gastrointestinal tract that affects men and women in their young and reproductive years of life. Anxieties about potentially harmful medication, the effect of pregnancy on disease, the effect of disease on the fetus and the potential of passing on of disease to offspring are affecting young women with IBD in their choices, resulting in a relatively high 'voluntary' childlessness in this patient group. Management of IBD patients with a pregnancy wish necessitates a pro-active approach. A careful consultation with the parents to be on the effects of maintenance drugs on fertility, disease remission during conception and pregnancy and the outcome of their children is justified in these patients and involves adequate pre-conception counselling.
Fertility in IBD females: Drugs prescribed for the treatment of IBD are not associated with lower fertility rates in IBD females compared to the general population. It is known that if patients are in remission the females are as fertile as the general population (1), however fertility might be reduced in patients with:
-Active Crohn's disease
-Pelvic or abdominal surgery for IBD (e.g. Ileal pouch-anal anastomosis (2-4))
Reasons for this decreased fertility probably include induction of inflammation to the ovaries and fallopian tubes in active Crohn's disease and the occurrence of dyspareunia when there is active perianal disease (5). Further, surgical interventions for IBD may cause tubal adhesions. Patients who have an ileal pouch-anal anastomosis (IPAA), or pouch-surgery, have higher rates of tubal obstruction, hydrosalphinx and destruction of the fimbria, all of which can lower fertility. In the case of an IPAA, patients who underwent a laparoscopic intervention have a lower infertility rate than patients who underwent open surgery (6).
Preconception
Adequate pregnancy counseling in females with IBD begins already early in the disease management. If there is an active pregnancy wish patients should be timely counseled, preferably in the preconception period, as it was shown that this results in less relapses during pregnancy. This is related to drug adherence during pregnancy (7).
Next to discussing the importance of drug adherence, the following factors are advised to discuss during preconception counseling:
-The importance of a sustained remission of, at least, 6 months prior to conception
-The risks of current drugs use and need for drug adjustment
-Life style advise such as cessation of smoking, alcohol use and supplementation of folic acid
-Information about the heredity of IBD
-The effect of drugs on breastmilk
-And the mode of delivery as advised with regards to the disease location
Since disease activity increases the risk of disease relapse during pregnancy and negatively influences fertility it is advised to strive for a (sustained) remission of approximately 6 months prior to conception (5,8). In majority of patients medication is needed to accomplice (sustained) remission and in order to reduce the risk of disease activity during pregnancy appropriate treatment of IBD should be maintained. To increase the adherence and correct usage of IBD drugs during pregnancy, personalized consultation is of great importance. In the next part of this chapter the risks of different IBD drugs will be discussed in more detail. General life style advices are also part of a preconceptional care and include counseling about supplementation of folic acid, cessation of smoking and alcohol use. A major concern, for IBD patients, next to the effects of drugs is the risk of development of IBD in their offspring. Children of parents with IBD have an increased risk of developing IBD. When one parent is affected with IBD the overall risk for their children is 2-13 higher than the general population (9). When both parents are affected the risk becomes much higher, around 30% (10).
Further, mode of delivery and breastfeeding should be discussed during counseling. Active perianal disease is an indication for a cesarean section. Overall mode of delivery is subject to a multidisciplinary approach and primarily decided by an obstetrician on individual basis. The effect of the drugs and their transfer into the mother milk will be discussed in part X.4.
Pregnancy: During pregnancy acute disease flares carry a high risk of adverse maternal and fetal outcome. Disease activity at time of conception and during pregnancy is associated with a higher rate of spontaneous abortion, preterm delivery, thromboembolic events, emergency caesarean section and low birth weight. According to

current European guidelines appropriate treatment of IBD should be maintained in those patients who wish to conceive, in order to reduce the risk of flares during pregnancy (5).
Lactation: In general breastfeeding is supported because there are many advantages for mother and child. Breastfeeding itself is possible for women with IBD and is not associated with a higher chance of disease relapse (11). It is known that IBD women breastfed their baby for a shorter period compared to the general population (12). Reasons for this are concerns about the transfer of drugs into the breastmilk and fatigue of the mother.

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Ischemic Heart Disease and Pregnancy - Results from the ESC Registry Of Pregnancy And Cardiac disease (ROPAC)

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Introduction:
Pregnancy in women with a history of ischemic heart disease (IHD) is increasingly common due to increasing maternal age and higher rates of obesity, smoking, diabetes and hypertension.
Objective:
To describe the maternal and fetal pregnancy outcomes in women with pre-existing and pregnancy-onset IHD.
Methods:
Within the international, prospective ESC Registry Of Pregnancy And Cardiac disease (ROPAC), we describe maternal and fetal outcomes of pregnancy in patients with IHD.
Results:
A total of 117 patients with IHD were included with a mean age of 34.9 years. 88% had pre-existing IHD and 11% experienced a first ischemic event during pregnancy. Pre-pregnancy smoking occurred in 17%, hypertension in 27%, diabetes and heart failure both in 15%, and 13% of patients had a left ventricular ejection fraction of below 40%. Almost half of the patients were using cardiac medication including anticoagulation (49%). There were no cases of maternal mortality, ACS and heart failure during pregnancy occurred in 21% and 7% respectively. Ventricular tachyarrhythmias were seen in 2%. Median pregnancy duration was 38.2 weeks. Mode of delivery was caesarean section (CS) in 65 patients (56%), of which 12 (10%) underwent emergency CS. Preterm birth was seen in 22% and low Apgar scores in 9%. Three babies died within 6 months after delivery (3%), all of whom were born prematurely. Six percent of patients suffered from post-partum hemorrhage. No clinical determinants for ACS during pregnancy or fetal adverse events were found.
Discussion:
Women with IHD tolerate pregnancy relatively well, however, while there were no maternal deaths in our study, 21% of patients suffered from ACS during pregnancy. Fetal adverse outcome was also not uncommon.

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Indirect Causes of Maternal Mortality

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Traditionally, the International Statistical Classification of Diseases has distinguished ‘direct' from ‘indirect' maternal deaths. Within this paradigm, direct deaths are those resulting from obstetric complications, whilst indirect deaths are those resulting from pre-existing disease or non-obstetric disease developing during pregnancy, but aggravated by physiologic effects of pregnancy. Such indirect deaths, for instance, include cancer-related deaths or cardiac deaths in women with pre-existing heart disease.

Compared to direct obstetric deaths, indirect deaths have historically received less attention from health policy makers. Indirect deaths, however, outnumber directs deaths in many high-income countries and are on the rise in many low- and middle-income countries, irrespective of reductions in maternal mortality taking place in many settings. Studies into the incidence of indirect deaths suffer from under-reporting and misclassification, and care for women with non-obstetric disease is often hampered by lack of clarity as to which professional should take responsibility for care and oversight.

There are several reasons as to why the distinction between direct and indirect deaths has become arbitrary and in some ways even counterproductive, leading to continued neglect of indirect causes of death. Examples of such reasons will be given during the presentation. If we change our perspective on maternal mortality and stop making a distinction between direct and indirect mortality, we might actually be able to achieve faster progress in overall maternal mortality reductions. A theme-based approach classifying deaths according to organ system, which is coordinated by obstetricians or obstetric physicians and which involves medical specialists from other relevant disciplines in efforts to improve quality of care, might be a more sensible way forward.

Sunday October 7, 2018

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Generation R Study: an example of transgenerational prospective cohort studies
Sarah Schalekamp-Timmermans, Eric Steegers
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Generation R is a unique population-based prospective cohort study (www.generationr.nl). The infrastructure has been established in 2002 by recruiting the first cohort consisting of n=10.000 pregnant women. These mothers and children are currently participating in our 14 years follow-up visit. In 2017 Generation R launched a new large cohort study: Generation R Next. This study is unique since it aims to study the health and lifestyle of mothers before pregnancy; preconceptionally. Since 2006 over 80 PhD theses and 700 peer-reviewed scientific papers have been published. Generation R represents the perfect example of this year's theme of the ISSHP/ISOM meeting 2018. In our population based pregnancy population we have highlighted the importance of first trimester sFlt-1, PLGF and PAI-2 concentrations in relation to placental function and the risks for preeclampsia and fetal growth restriction. We were among the first to show the importance of fetal sex in placental and maternal adaptation to pregnancy with sexual dimorphic differences in the occurrence of preeclampsia. These studies were accomplished through collaboration within the Global Pregnancy Collaboration (CoLab). Our data collection extends to maternal and child follow-up's after pregnancy which includes women with previous hypertensive pregnancy disorders. We are now conducting a brain MRI study among women who's index pregnancy was complicated by preeclampsia 14 years ago. We previously reported on the altered microvasculature, atherogenic lipid profile, increased left ventricular mass and higher blood pressures in those women 6 years after the pregnancy which eventually lead to an almost seven-fold increased risk for chronic hypertension. This indicates that also mild hypertensive pregnancy disorders pose a risk for cardiovascular disease and therefore these women should be offered long-term cardiovascular follow-up. By this means results from the Generation R Study contribute to the development of strategies for optimizing health and healthcare for pregnant women and their children.

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Disease definitions, medical testing and practice guidelines
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As systematically developed statements to assist professionals and patients in decisions about appropriate health care for specific clinical circumstances, clinical practice guideline have become a widely accepted tool to improve the quality and consistency of care. Since the 1980s, their number has vastly increased, and many rely on solid forms of evidence synthesis.
The development of clinical practice guidelines cannot start without clear descriptions of the "specific clinical circumstances" in which they would apply, and the total body of evidence cannot be interpreted without proper definitions and disease categories.
These definitions are not set in stone. They may change over time, with the availability of new forms of testing, or with advances in our understanding of the development of disease and its management.
We will discuss a number of recent changes in disease definitions by guideline panels, many of which have widened the definition, thereby increasing the number of individuals considered to have the disease. We will also present guidance for modifying the definition of diseases, including a checklist, which was assembled a multidisciplinary, multicontinent working group, including members from the Guidelines International Network, Grading of Recommendations Assessment, Development and Evaluation working group, and the World Health Organisation.

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Maternal mortality in the Netherlands
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Like in many other high-income countries, maternal mortality has become a rare event in the Netherlands. The rarity of the event, which renders anonymization of cases increasingly difficult, combined with an increased focus on data protection, may facilitate under-reporting and hamper measurements of incidence. Moreover, differences in death classification between the Netherlands and, for instance, the United Kingdom make inter-country comparisons problematic. Is the proportion of indirect deaths versus direct deaths in the Netherlands really that much lower compared to the UK, or is it a matter of misclassification or underreporting? And how do we stay vigilant to prevent severe complications that we rarely encounter anymore in clinical practice, but which may have very severe consequences if we fail to manage them correctly?

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Kidney donation and transplantation- consequences for pregnancy
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The number of kidney transplantations (KT) and kidney donations is rising over the years. Pregnancy in KT recipients in increasing, generally pregnancy outcomes are good in kidney transplant recipients, but with high complication rates of hypertension, proteinuria and deterioration of graft function. Several voluntary registries and meta-analyses show on average 36 weeks of pregnancy, with preeclampsia rates of 30% and average birth weight of approximately 2500 grams.
During pregnancy, physiological changes occur in the kidney, in healthy kidneys, glomerular filtration rate (GFR) increases from the first trimester, for more than 50% through an increase of renal blood flow. It is unknown which effect this temporary glomerular hyperfiltration has on long-term graft function. Data of a meta-analysis on this topic will be presented showing that a significant deterioration was seen in short term post-pregnancy graft function in serum creatinine of 0.10 mg/dL [0.02;0.28], p=0.01. No long term deterioration of graft function was seen in this meta-analysis, supporting that pregnancy is safe in KT recipients.
Pregnancy after kidney donation is increasing, but still rare. A recent publication showed that young female kidney donors have a significantly increased chance to develop gestational hypertension or preeclampsia [Garg, NEJM 2015], extending earlier research based on survey data, that showed differences in pregnancy complications, before and after donation. Several factors might potentially contribute to the increased risk for PE after kidney donation, i.e loss of kidney function, post-donation hypertension or loss of renal vasodilator capacity.

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The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice.
Mark Brown[1], Laura Magee[2], Louise Kenny[2], S Ananth Karumanchi[2], Fergus Mccarthy[2], Shigeru Saito[2], David R Hall[2], Charlotte Warren[2], Gloria Adoyi[2], Salisu Ishaku[2]
[1]St George Hospital, Sydney, Australia

This set of recommendations from ISSHP is designed to assist clinicians throughout the world in the recognition and management of the hypertensive disorders of pregnancy; the document includes sections written by those working in low and middle income countries so as to ensure applicability in all parts of the world. Some key points include:
ISSHP does not recommend classifying pre-eclampsia as ‘mild’ or ‘severe’ because the condition may progress rapidly and unpredictably.
Proteinuria is not mandatory for a diagnosis of pre-eclampsia
The HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low platelets) is one (serious) manifestation of pre-eclampsia and not a separate disorder
ISSHP supports first trimester screening for risk of pre-eclampsia when this can be integrated into the local health system, although the cost effectiveness of this approach remains to be established.
ISSHP recommends that women with established strong clinical risk factors for pre-eclampsia (i.e., prior pre-eclampsia, chronic hypertension, pre-gestational diabetes, maternal BMI >30kg/m^2, antiphospholipid syndrome and receipt of assisted reproduction) be treated, ideally before 16 weeks but definitely before 20 weeks, with low dose

aspirin (defined as 75-162 mg/day, as studied in RCTs).
ISSHP recommends at this stage against the routine clinical use of 'rule-in' or 'rule-out' tests (specifically PlGF or sFLT-1/PlGF ratio) for pre-eclampsia
Regardless of the hypertensive disorder of pregnancy, blood pressure requires urgent treatment in a monitored setting when severe (> 160/110 mmHg);
For pre-eclampsia, target diastolic blood pressure is 85 mmHg in the office/clinic (and systolic blood pressure of 110-140 mmHg)
Women with pre-eclampsia who have proteinuria and severe hypertension, or hypertension with neurological signs or symptoms, should receive magnesium sulphate ($MgSO_4$) for convulsion prophylaxis
Annual medical review is advised life-long and all such women should adopt a healthy lifestyle that includes exercise, eating well and aiming for ideal body weight

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ISSHP clinical management guidelines 2018 - applications in LMICs

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The ISSHP clinical management guidelines published in 2018 reflect recommendations based upon evidence combined with expert opinion, to influence good clinical practice. The broad goal was to produce a 'living' pragmatic document, to be updated as more research becomes available. This document acknowledges that in many parts of the world, it will not be possible to adopt all of the recommendations. Consequently, options for management in less-resourced settings are discussed separately in relation to diagnosis, evaluation, and treatment from the antenatal to postnatal period. It is the responsibility of managing physicians to advocate the use of effective interventions whether they practice in well- or under-resourced settings.
The diagnosis and classification of hypertensive disorders of pregnancy are still clinically based. Health systems must reach the entire population with a basic minimum package of care, including at least eight antenatal care contacts with blood pressure and proteinuria testing at each visit. Those with risk factors for pre-eclampsia must receive low dose aspirin and where dietary calcium intake is low, calcium supplements. Clear, level-specific protocols must be developed for the diagnosis, management and referral of pre-eclampsia, and hypertensive diseases of pregnancy, while strategies must be put in place for transport from clinics or primary health care facilities to referral centres.
Antihypertensive agents for treatment of moderate and severe hypertension, and magnesium sulphate to prevent or treat eclampsia must be available at community level centres and clinics so that patients can be stabilised and referred safely. All women with a hypertensive disorder of pregnancy require delivery in a centre that provides emergency obstetric and neonatal care, while women with maternal complications require delivery in a centre capable of providing maternal critical care. Those with pregnancies at the limit of viability require the highest available level of neonatal support.

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Management of Microangiopathic Haemolytic Anaemia in Pregnancy

David Williams
University College London Hospital, London, United Kingdom

Microangiopathic haemolytic anaemia (MAHA) refers to haemolytic anaemia caused by small arteriole endothelial dysfunction. Pregnancy-induced changes to maternal vasculature, coagulation and immunity predispose women to MAHA. Materno-fetal disease follows platelet consumption within microthrombi of arterioles to end-organs and is often organ-specific. The key to successful management is accurate diagnosis.
MAHA and microthrombi within the utero-placental circulation is associated with pre-eclampsia. Childbirth is the cure, but management is supportive until maternal or fetal condition deteriorate, or when fetal maturity is considered sufficient for ex-utero survival.
HELLP syndrome describes the pathological components of MAHA affecting the liver. It presents suddenly with acute hepatic pain and an acute rise in liver transaminases with platelet consumption. HELLP is often associated with placental dysfunction, fetal growth restriction and hypertension. Management is similar to preeclampsia management. Steroids may improve the maternal platelet count and reduce the risk of peripartum bleeding.
MAHA and microthrombi within the brain is suggestive of thrombotic thrombocytopaenic purpura (TTP). Women present with neurological symptoms, headache and seizures. TTP is secondary to low level of metalloproteinase ADAMTS13, which cleaves the endothelial von Willebrand factor and prevents platelet microthrombi. Levels of ADAMTS13 fall during pregnancy such that women with a congenital deficiency, or with autoantibodies against

ADAMTS13, are predisposed to peripartum TTP. Treatment is plasma exchange.
MAHA and microthrombi within the kidneys is suggestive of haemolytic uraemic syndrome (HUS). Pregnant women present with hypertension and acute kidney injury. Treatment of atypical HUS has been transformed by the introduction of Eculizimab that targets a component of the complement system.
Acute fatty liver of pregnancy (AFLP) is a metabolic disorder characterised by a defect in fat metabolism. AFLP presents with multi-organ failure.
This lecture will use a case-based approach to highlight features that discriminate between MAHA and allow implementation of targeted therapies to improve pregnancy outcome.

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Optimizing early identification of women at high risk for cvd
Angela Maas
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Sex-specific factors related to hormonal and reproductive status are known to relate to CVD risk. It is unclear yet, to which extent and within which stage(s) of life these female-specific risk factors are relevant to CVD risk estimation. When considering all age-groups together, reproductive and pregnancy related disorders do not seem to be relevant in 10 years risk estimation. However, when focusing on younger patients (< 55 years) evidence is increasing that assessment of female-specific risk factors may indeed add to identify women at higher risk. This is especially important as young women are considered to be at low risk, until a first premature event has occurred. Reproductive and pregnancy-related factors predispose to earlier signs of endothelial dysfunction, vascular inflammation and atherosclerosis . This especially accounts for women after preeclampsia/HELLP. Coronary artery calcium (CAC) scores, as subclinical signs of atherosclerosis, are higher in women after preeclampsia/HELLP compared to women after normotensive pregnancies. By using the CAC score to risk factor assessment in these women, an important improvement in risk prediction can be achieved. In addition, circulating biomarkers and elevated high sensitive (hs)CRP and hs-Tropinin, may add to better tailor subgroups of women after PE/HELLP who are even more prone to premature CVD event than others.

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Controversies in thrombophilia testing & use of newer anticoagulants agents in pregnancy & lactation
Saskia Middeldorp
Amsterdam Medical Center, Amsterdam, The Netherlands

Saskia Middeldorp will first delve into the association between thrombophilia and complications during pregnancy including recurrent miscarriage and fetal loss, pre-eclampsia/eclampsia, intrauterine growth restriction, and placental abruption. These complications are clinical characteristics of the acquired thrombophilia antiphospholipid syndrome. There is also a modest association of some of these complications with inherited thrombophilia, which include factor V Leiden, prothrombin 20210A mutation and deficiencies of the anticoagulant proteins antithrombin, protein C or protein S. Despite absence of evidence in most situations, the use of antithrombotics with the aim to improve pregnancy outcome is widespread. She will review the evidence supporting or refuting the effectiveness of antithrombotics including aspirin and low-molecular-weight heparin in various clinical scenarios.
The second part of the lecture will discuss direct oral anticoagulants (DOACs), also referred to as novel or non-vitamin K antagonist oral anticoagulants (NOACs). These agents are now the recommended drugs of choice for treatment and secondary prevention of venous thromboembolism and atrial fibrillation. These agents are small molecules and hence, pass the placenta. Saskia Middeldorp will discuss the current available data regarding safety of DOACs in pregnancy and lactation, and discuss the management strategies in women who are using DOACs who intend to become pregnant, or have an indication for anticoagulant treatment or prophylaxis in pregnancy.

Monday October 8, 2018

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Maternal and fetal consequences of preeclampsia
Sandra Davidge
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Vascular dysfunction in women with preeclampsia is complex. Placenta-derived circulating factors and/or the maternal response to these factors contribute to vascular endothelial cell dysfunction. Risk factors for preeclampsia include many conditions such as maternal aging, pre-existing hypertension, obesity and diabetes. The heterogeneity of this population, including the diversity of circulating factors such as oxLDL, TNFα, and advanced glycation end products, has contributed to the overall complexity of targeting a specific pathway for therapeutic prevention and/or intervention. Interestingly, these circulating factors are also among the factors known to upregulate and/or activate the lectin-like oxidized LDL receptor-1 (LOX-1). Our laboratory has shown that LOX-1 is increased in the systemic vasculature of women with preeclampsia and contributes to vascular oxidative stress. Moreover, our rat model of reduced uteroplacental perfusion (RUPP), which has preeclampsia-like signs, demonstrates increased LOX-1 expression, increased vascular oxidative stress and ultimately vascular dysfunction. Since LOX-1 has multiple ligands, it may be a point of convergence for many plasma factors known to be elevated in preeclampsia; including placental-derived microparticles; a current area of investigation. Notably, pregnancy has an important influence on both short- and long-term cardiovascular outcomes for women and their offspring. One risk factor for preeclampsia is maternal age, an important factor considering that the age at which women experience their first pregnancy has steadily increased through the decades. We use aged female rats (9.5 months; equivalent to ~35 yr old human), to investigate the impact of maternal aging on later-life maternal and offspring cardiovascular health. Our data show that advanced maternal age worsens postpartum vascular function and that offspring born from aged dams have an altered cardiovascular risk profile that is sex-specific. These data further illustrate pregnancy as a window of opportunity to assess both maternal and offspring future cardiovascular risk.

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Molecular and Functional Long-Term Effects of Preeclampsia on the Cardiovascular System Assessed on a mouse model of severe preeclampsia
Daniel Vaiman, Rajaa Aouache, Francisco Miralles
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Preeclampsia (PE) is a characterized by *de novo* hypertension and proteinuria. Women affected with PE have an increased risk of chronic hypertension and premature cardiovascular disease years later. Mice bearing transgenic fetuses overexpressing the human transcription factor STOX1 (storkhead box1) develop a severe preeclamptic phenotype.
The molecular analysis of long term cardiovascular risks induced by preeclampsia will be studied using our mouse model. We started with 10 eight to ten-months-old mice, 5 had control gestations and 5 preeclamptic gestations 6 to 8 months earlier.
We analyzed heart functional parameters by ultrasonography, in normal and stressed conditions. Then we carried out a transcriptional profile of endothelial cells and hearts of the mice. Fibrosis was evaluated by a histology analysis of the hearts. Finally the cytokine levels in mice plasma will be analyzed on 33 cytokines.
The relative mass of the heart of the preeclamptic mice was increased by 11% ($p=0.017$), with an important fibrosis. Ultrasonography revealed a lesser morphological adaptation to stress. Under dobutamin aortic peak velocity, blood pressure, and right ventricular outflow are significantly increased. The endothelial cells microarray analysis demonstrate that ~3073 transcripts ($p<0.05$) are deregulated in mice affected by PE. Functional clustering works well for the up-regulated transcripts exclusively and revealed significant clustering of genes involved in TNFa signaling, Hypoxia, inflammation, apoptosis, several gene networks centered around interleukin-6, proteoglycan decorin and shc1. We are in the progress of obtaining heart transcriptomics data, as well as brain transcriptomic data.
Our results demonstrate massive quasi-invisible long term effects of preeclampsia, affecting strongly the endothelial cells. Dilatation of hearts and fibrosis indicate a noxious cardiac tissue remodeling in preeclamptic mice. To the best of our knowledge, our study is one of the first to address the molecular effects of preeclampsia in the long term.

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Placental development, blood flow and pre-eclampsia; a role for the endometrium?
Graham Burton
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Placental stress, induced by maternal malperfusion, is believed to be at the epicentre of the pathophysiology of pre-eclampsia, at least for the early-onset sub-type. Deficient remodelling of the spiral arteries has been well documented in the placental bed, with the degree correlating with time of onset of the syndrome. Despite this progress, the cause for the deficiency is still not known. Impaired invasion by the extravillous trophoblast cells essential to the remodelling process has been implicated, as have aberrant interactions between these cells and those of the maternal immune system present in the decidua. Another possibility is that early development of the placenta post-implantation is abnormal, resulting in an impoverished supply of extravillous trophoblast cells. Although this hypothesis has received little attention to date, recent transcriptional analyses have revealed abnormalities in decidualisation in women prior to, and after, pre-eclampsia. Initial growth of the placenta is stimulated by histotroph from the endometrial glands, which contains numerous mitogenic growth factors as well as glucose, lipids and other nutrients. The secretory activity of the glands increases in early pregnancy in response to lactogenic hormones produced by the placenta. However, details of the signalling pathways involved are unknown due to the inaccessibility of the tissues concerned. The recent derivation of endometrial organoids now allows these pathways to be dissected, and prolactin is emerging as a strong stimulant of glandular secretion. Prolactin is secreted by decidual cells, and so may link the transcriptomic data with the supply of extravillous trophoblast cells and deficient arterial remodelling. If the hypothesis were proved correct, the translational impact would be to emphasise the importance of ensuring optimal endometrial function prior to conception. This would have the great advantage of preventing the pre-eclampsia and other placental-related complications at their outset, rather than trying to treat these disorders once established.

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Sexual dimorphism in the placenta
Leslie Myatt
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There is a sexual dimorphism in pregnancy outcomes with male fetuses generally being at higher risk for adverse outcomes. The underlying physiologic mechanisms likely involve sexual dimorphism in placental function given the role of the placenta in directing both maternal metabolic and cardiovascular changes in gestation and fetal growth and development. Gene expression in the human placenta is sexually dimorphic and is affected by maternal inflammatory status, diet and fatty acids in a sex-dependent manner.
We find increased markers of inflammation, hypoxia and apoptotic cell death in the placenta with preeclampsia compared to normotensive pregnancies but with sexual dimorphism as TNFa, Il-6, Il-8, HIF1a, apoptotic markers and DNA binding of the NFkB p65 transcription factor are significantly higher, but the angiogenic marker VEGF significantly lower, in male vs female preeclamptic placentas. Obesity and gestational diabetes are associated with increased placental inflammation and oxidative and nitrative stress, increased miR-210 expression and consequent decreased trophoblast respiration, altered autophagic responses and altered antioxidant defenses, however all of which occur in a sexually dimorphic manner. In trophoblast from a female, but not a male, placenta TNF stimulates the NFkBp50 pathway to increase miR210 expression which in turn depresses mitochondrial respiration. Interestingly miR210 expression is significantly higher in placenta from a female vs a male fetus across all birthweight centiles with the difference being greatest in placentas of large for gestational age fetuses.
The mechanisms of sexual dimorphism in placenta with preeclampsia, obesity or GDM and the range of functional effects remain to be elucidated; however evidence links sex differences to gonadal steroids. Placental levels of aromatase, the rate-limiting enzyme converting androgens to estrogens, are higher in placentas of preeclamptic women with female vs male fetuses and aromatase can be downregulated by TNFα, hypoxia, insulin and leptin, factors which mirror placental conditions with maternal obesity.

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Cardiovascular disease in the mother and offspring after preeclampsia in mice - Protective effects of pravastatin

Guillermina Girardi
King's College London | University of Edinburgh, United Kingdom

Preeclampsia (PE) has been associated with long-term increased risk for cardiovascular disease in women, suggesting that PE is more than an isolated disease of pregnancy. However, it is not known if this increased risk for these long-term diseases is due to factors developed during PE or to prepregnancy renal and cardiovascular risk factors commonly found in women that develop PE.
We investigated if preeclampsia causes long-term cardiovascular consequences after pregnancy for mother and offspring. Using a mouse model in which wild type females with normal prepregnancy health develop PE, we investigated if factors that develop during the preeclamptic pregnancy affect future cardiovascular health of mother and offspring. In the mothers, endothelial dysfunction and hypertension were observed after PE. Furthermore, glomerular injury not only persisted but deteriorated after PE, leading to fibrosis. Left ventricular (LV) remodeling characterized by increased collagen I and MMP-9 deposition and enlarged cardiomyocytes were also detected after PE. Increased LV, internal wall thickness and mass, increased end-diastolic and end-systolic volumes, and increased stroke volume were observed after PE. Increased placenta-derived bioactive factors modulating vascular function, endothelin I and sFlt-1, markers of metabolic disease: leptin and insulin, vasoconstrictor isoprostane-8 and proinflammatory mediators IL-6 and complement C5a were increased in serum during and after a preeclamptic pregnancy. Interestingly, the offspring of PE-mice developed endothelial dysfunction, hypertension and signs of metabolic disease. Increased microglia activation, characterised by increased release of proinflammatory cytokines, was observed in the neonatal brains after PE suggesting neurogenic hypertension. Prevention of placental insufficiency with pravastatin, prevented the cardiovascular complications observed in the mother and offspring. In conclusion, placental-derived factors released during PE has long term health effects on the cardiovascular system of the mother and offspring independently of prepregnancy risk factors. Pravastatin therapy given during PE prevents long term health compromise.

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How does programming work - Animal models of placental dysfunction and their epigenetic outcome

Torsten Plösch
University Medical Center Groningen, Groningen, The Netherlands

An adverse intrauterine environment belongs to the well-known roots of chronic disease in adult life. This is often coined the “Developmental Origins of Health and Disease” (DOHaD) paradigm. One of the key factors transmitting environmental information along the lifespan of an organism is epigenetic programming.
Classical rodent models used in research on the Developmental Origins of Health and Disease are based on dietary interventions during pregnancy. Simulation of human hunger periods by caloric or protein restriction are examples. Similarly, placental dysfunction is often simulated by clamping of the uterine artery, which requires surgical procedures.
I will here compare several novel mouse models of placental dysfunction and their benefits for research. These models are based on the genetic deletion of the transcription factor *TFAP2C* in the placenta, or on a combination of virus-mediated overexpression of sFlt1, with or without low-grade inflammation. The former model leads to growth restriction in the offspring, whereas the latter model is furthermore accompanied by signs of preeclampsia. Interestingly, in both cases also the sex of the offspring matters for the outcome.
These new models, especially when compared to each other, will in future allow us to specifically differentiate between different forms of placental dysfunction, which might contribute to personalized care strategies.

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The role of low-frequency variants in pre-eclampsia: recent findings in a Finnish population

Hannele Laivuori
University of Tampere, Tampere, Finland

The genetic basis of pre-eclampsia and its link with increased lifetime risk of cardiovascular diseases in women with a history of pre-eclampsia and children born from pre-eclamptic pregnancies are incompletely understood. Genetic factors have been shown to account for 55% of the liability of pre-eclampsia with 35% attributed to the maternal genetic effects and 20% to the fetal genetic effects (Cnattingius et al. Am J Med Genet 2004). Genome-wide association screening in offspring from pre-eclamptic pregnancies performed by a collaboration between research groups has already proven a successful approach in finding a common sequence variant near the fms related tyrosine kinase gene (*FLT1)* associated with pre-eclampsia (McGinnis et al. Nat Genet 2017).
The sequencing approach enables identification of both common and rare variants, but is challenging in common complex disorders like pre-eclampsia. An isolated population may offer a major advantage for genetic discovery. In Finland a strong founding bottleneck has been shown to cause enrichment of some low-frequency variants (Lim et al. PLOS Genet 2014). Centrally collected registers with lifelong medical histories can be used together with genetic data to better understand diseases associated with pre-eclampsia. We designed a targeted sequencing study to screen the coding and splicing areas of genes of interest in pre-eclampsia and found maternal low-frequency variants in *FLT1* which may protect from pre-eclampsia (Lokki et al. Hypertension 2017). Using data from health registers we found that the same variants may also protect from heart failure later in life.
Future studies are needed to improve our understanding of the genetic background pre-eclampsia and its links to other diseases. Any new gene discovery will highlight a known pathway or reveal a new biochemical pathway in the pathogenic process leading to pre-eclampsia and may also help in prediction and in identifying individuals with higher risk for later cardiovascular disease.

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InterPregGen: the discovery and validation of genetic variants associated with pre-eclampsia in mothers and babies

Linda Morgan
on behalf of the InterPregGen Consortium, Nottingham, United Kingdom

30 years of molecular genetic studies of common disorders have demonstrated the need for large, well-powered studies to detect genetic variants with individually small effects on disease susceptibility; pre-eclampsia is no exception. InterPregGen is a collaboration between research groups from Europe and Central Asia seeking to identify DNA sequence variants predisposing to pre-eclampsia. The primary approach is meta-analysis of genome-wide association screening (GWAS) data from over 9000 affected mothers, 6500 offspring, and 370,000 control subjects. Variants with evidence of association with pre-eclampsia are followed-up by targeted genotyping in independent sample collections.
In offspring affected by pre-eclampsia there is a highly significant association with a common variant located close to the *FLT1* gene, which encodes Fms-like tyrosine kinase 1 and its soluble isoform sFlt-1 (P=5.38x10^{-11}). The strongest association was in pregnancies with onset of pre-eclampsia after 34 weeks gestation.
Investigation of the maternal genome in pre-eclampsia has highlighted associations with multiple DNA variants which also have confirmed associations with essential hypertension in non-pregnant individuals. In a further 2800 women with non-proteinuric gestational hypertension there is a similar profile of susceptibility variants shared with essential hypertension and pre-eclampsia.
Typical of many common complex disorders, there is no single ‘pre-eclampsia gene’. Current parental or fetal genotype data do not enable prediction of preeclampsia in individual pregnancies. However, the results highlight specific biological pathways responsible for pre-eclampsia’s aetiology. Larger studies are essential to identify additional variants and other pathways affecting pre-eclampsia. The genetic findings justify targeted investigation of *FLT1* regulation in the placenta, and indicate that raised sFlt-1 has a causal role in pre-eclampsia, and is not just a consequence of the disease. Maternal genotyping results confirm a pathophysiological overlap between essential hypertension, gestational hypertension and pre-eclampsia, and emphasise the imperative for long-term cardiovascular monitoring of women with a history of hypertension in pregnancy.

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Immunology of pregnancy and preeclampsia
Ana Claudia Zenclussen
Medical Faculty Otto-von-Guericke University, Magdeburg, Germany

Pregnancy represents a challenge for the maternal immune system; it has to be alert against pathogens while tolerating paternal alloantigens expressed in fetal structures and even present in the maternal circulation. A large body of evidence suggests that cells of the innate immune system are mainly involved in uterine angiogenesis and tissue remodeling, including the remodelling of uterine spiral arteries that are of vital importance for gestation. The adaptive maternal immune system is not only aware of the presence of alloantigens, but actively tolerates them to ensure the survival of the fetus. Our current understanding of pregnancy-related immune mechanisms also includes complex cell-cell interactions not only between immune cells but also between immune cells and the cells of the microenvironment at the feto-maternal interface. In addition, molecules secreted by the conceptus itself, including hormones, are able to modulate the immune system to render it tolerant towards the fetus. Disturbances in the finely modulated immune balance lead to pregnancy complications, including pre-eclampsia.

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Early- and late-onset of pre-eclampsia: how do the maternal circulating biomarkers differ, and why?
Anne Catherine Staff
University of Oslo | Oslo University Hospital, Oslo, Norway

Pre-eclampsia requires the presence of placenta or residual placental compounds (as in postpartum pre-eclampsia), but the relative contribution of maternal predisposing factors versus placental factors to its pathophysiology is not well understood.
The talk will revisit the classical “two-stage model” of pre-eclampsia, as proposed by Redman et al in 1999, where incomplete placentation is the first of two stages of pre-eclampsia, typically of early onset. Maternal “intolerance” of fetal cells and failed uteroplacental spiral artery remodelling has been a proposed pathway for poor placentation, which however involves several mechanisms. The second stage comprises dysfunctional uteroplacental perfusion and placental oxidative stress, followed by secretion of inflammatory factors to the maternal circulation, with ensuing generalized maternal vascular inflammation and pre-eclampsia signs (maternal hypertension and proteinuria).
We have suggested (Redman, Sargent and Staff, Placenta 2013) that the mechanisms leading to a dysfunctional uteroplacental circulation may involve additional mechanisms to poor placentation, and that syncytiotrophoblast (STB) stress, with upregulation of some proteins (as exemplified by “antioangiogenic proteins”) and downregulation of others (exemplified by “proangiogenic proteins”) is the common final pathway. We argue that maternal circulating angiogenic factors are markers of STB stress, not of preeclampsia per se
We have proposed two major forms of placental dysfunction in pre-eclampsia: one extrinsic (poor placentation) and one intrinsic cause (villous overcrowding). Our model explains important differences of early- and late-onset pre-eclampsia, including their relation to maternal circulating placenta-associated proteins used as biomarkers for the syndrome (Redman and Staff, AJOG 2015).
The talk will also argue that there is no condition such as “maternal” pre-eclampsia, as all pre-eclampsia originate in the placenta. We suggest however that maternal factors may contribute two both stages of pre-eclampsia, the first by affecting either placental pathways to STB stress and the latter by amplifying the effects of STB stress on maternal vasculature.

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ELABELA and placental development in pregnancy and preeclampsia
Marie van Dijk
Academic Medical Center, Amsterdam, The Netherlands

The peptide hormone ELABELA (ELA) was discovered in 2013 and found to be essential for zebrafish cardiovascular development through activation of the Apelin receptor (APLNR). In humans, ELA has been found to be expressed in adult kidney and prostate, and in embryonic pluripotent stem cells where it serves as a growth factor, but signals via a yet unidentified second receptor. To further investigate the contribution of ELA to mammalian development ELA knockout mice were generated. The knockout embryos showed clear cardiovascular defects, but also the placentas were affected, which may lead to preeclampsia-like symptoms in ELA knockout mothers. Indeed,

the mice showed significantly increased blood pressure and proteinuria. Remarkably, infusion of synthetic ELA was able to entirely rescue blood pressure, proteinuria, and increase fetal birth weight.
The above findings let to studying ELA in human placentation and preeclampsia (PE). ELA was localized in villous cytotrophoblasts and, as expected for a hormone, in the syncytiotrophoblast layer of first trimester placental tissues. High expression was also observed in invading extravillous trophoblasts. In trophoblast cell lines ELA addition significantly increased the invasive capacity of these cells as measured in transwell invasion assays. In first trimester placental explant cultures ELA changed the morphology of the extravillous outgrowth and decreased trophoblast proliferation. Interestingly, preliminary results suggest that these downstream effects of ELA are not initiated by ELA binding to the Apelin receptor, therefore the second unknown receptor must be considered instead.
Finally, circulating ELA in plasma of healthy and PE pregnancies measured at multiple time points in gestation did not appear to be associated with PE development. However, ELA's peptide properties were found to interfere with the initial measurements done. These technical issues therefore first need to be resolved before definite conclusions can be drawn on the applicability of ELA as potential PE biomarker.

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Integrating basic science with clinical data to inform the design of RCT's for preeclampsia
Stephen Tong
University of Melbourne and Mercy Hospital for Women, Melbourne and heidelberg, Australia

Preeclampsia is associated with increased placental release of anti-angiogenic factors (such as sFlt1 and soluble endoglin) that cause endothelial dysfunction, hypertension and maternal end organ injury. In recent years, our research team have developed a laboratory based drug screening pipeline to identify drugs that 1) decrease placental release of sFlt1 and soluble endoglin 2) decrease endothelial dysfunction in multiple assays and 3) promote vasodilation in whole maternal vessels. We also test an animal model of preeclampsia.
Using this drug screening pipeline in our laboratory we have identified a number of agents that have most - or all - of these properties. They are drugs that are currently used for varying indications and are quite unrelated. They include proton pump inhibitors (used for gastric reflux), metformin (used to treat diabetes), statins (used to treat high cholesterol [we published data validating this concept that was first proposed by others]) sulfasalazine (used for inflammatory bowel disease), resveratrol, and others.
We now currently have a list of drug candidates that may have efficacy in treating or preventing preeclampsia. Importantly, we have progressed to successive RCTs to evaluate whether some of them may indeed be effective in treating preterm preeclampsia (being run in a close collaborative partnership with academics at Tygerberg Hospital). We are also implementing large multi-centre trials to test whether drugs can prevent preeclampsia.
In this presentation, we will discuss our strategic reasoning to decide what order to test these drugs in RCTs, and our approach to designing RCTs. To make these decisions, we have been integrating data from our laboratory studies with clinical reasoning (taking into account any prior published clinical data, pharmacokinetics, known drug side effects, and safety concerns).

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Large randomized trials to reduce the burden of preeclampsia
Peter von Dadelszen
King's College London | St. Thomas' Hospital, London, United Kingdom

In this presentation, we will review the conduct, results and impact of two types of pregnancy hypertension-oriented clinical trials. First we will describe the CHIPS trial that randomised 987 women with non-proteinuric pregnancy hypertension in 95 sites in 16 countries. In the series of CHIPS trial publications there has been a consistent message that tight blood pressure control (target dBP = 85mmHg) offers maternal safety without perinatal harm, and that methyldopa is a reasonable first choice of antihypertensive. Second, we will describe the CLIP trials that recruited 69,445 women in 44 clusters (unit of randomisation) in Mozambique (12 clusters), Pakistan (20 clusters) and India (12 clusters). The results will be summarised and implications of both types of trials and their results for widespread implementation discussed.

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STRIDER: Sildenafil therapy in dismal prognosis early-onset fetal growth restriction - a systematic review with individual participant data
Wessel Ganzevoort[1], Peter von Dadelszen[2], Phil Baker[2], Chirag Kariya[2], Kennth Lim[2], Gluud Christian[2], Zarko Alfirevic[2], Sharp Andrew[2], Katie Groom[2]
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India

In pregnancies complicated by early-onset extreme fetal growth restriction (FGR), there is a high risk of preterm birth and an overall dismal fetal prognosis. The underlying cause is uteroplacental insufficiency. There is ample evidence from in vitro models, and animal models that sildenafil ameliorates this pathological process. Preliminary data in human pregnancies complicated by FGR has also suggested that Sildenafil improves outcomes. A group of international collaborators originating from the Global Obstetrics Network (GONet) launched a joint initiative to fund clinical multicenter studies in research networks in the United Kingdom, The Netherlands, Canada and New Zealand/Australia.

Within each country, stand-alone randomised clinical trials are being or have been conducted within the national network. Synchronization of study design and definitions, central data collection and a pro-active design of a meta-analysis with aggregate data and Individual Participant Data (IPD) have been agreed upon from the start.
The primary outcome for babies is being alive at term gestation without evidence of serious adverse neonatal outcome. An important secondary outcome is age-adequate performance on the two-year Bayley scales of infant and toddler development-III (composite cognitive score and composite motor score). IPD meta-analysis allows meaningful subgroup and sensitivity analyses including assessment of the influence of several patient characteristics: an abnormal serum level of placental growth factor, absent/reversed umbilical arterial end-diastolic flow at commencement of treatment, and other patient characteristics available at baseline such as gestational age and estimated fetal weight.
Conclusion: The concerted effort in the design and conduct of these large international studies provides an efficient use of scarce resources and will optimise speedy resolution of the underlying research questions, in addition to facilitating adequate power for subgroup analyses.

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Trials in low-resource settings: the INFORM study (oral misoprostol versus balloon induction in women with PIH or pre-eclampsia)

Shuchita Mundle, Hillary Bracken, Vaishali Khedikar, Jayashree Mulik, Brian Faragher, Thomas Easterling, Simon Leigh, Paul Granby, Alan Haycox, Mark A Turner, Zarko Alfirevic, Beverly Winikoff, Andrew D. Weeks
India

Between 62,000 and 77,000 women die annually from pre-eclampsia/eclampsia. Prompt delivery, preferably by the vaginal route, is vital for good maternal and neonatal outcomes. Two low cost interventions –low dose oral misoprostol tablets and transcervical Foley catheterisation– are already used in low resource settings. In this open label, parallel randomised study, our objective was to compare their relative risks and benefits

602 women with a live fetus requiring delivery for pre-eclampsia or hypertension were randomly assigned to labour induction with oral misoprostol 25 micrograms every 2 hours (maximum of 12 doses) or a transcervical Foley catheter (size 18 F with 30 ml balloon) which remained until active labour started, the Foley catheter fell out, or 12 hours elapsed. Randomisation was computer-generated with allocation concealment by opaque sequentially numbered sealed envelopes. Induction continued with artificial membrane rupture and oxytocin, administered through a micro-drip gravity infusion set. Fetal monitoring was by intermittent auscultation. The primary outcome was vaginal birth within 24 hours, and trial registration as with ClinicalTrials.gov (NCT01801410).

302 women were allocated to misoprostol and 300 women to Foley catheter; all were analysed. More women in the misoprostol arm had a vaginal birth within 24 hours (57.0% vs. 47.0%; absolute risk difference (RD) 10.0%, with 95%CI 2.0% to 17.9%). Rates of uterine hyperstimulation were very low in both groups (0.7% vs 0.3%; RD 0.3%; -0.8% to 1.5%) and no differences were seen in neonatal morbidity. More women in the misoprostol group would use the same method in the future should they require another induction (82.8% vs. 72.0%; RD 10.8%; 4.2% to 17.4%).

Oral misoprostol 25 micrograms was more effective and more acceptable to women than a transcervical Foley catheter for induction of labour in women requiring delivery because of pre-eclampsia or hypertension.

MRC/DFID/Wellcome Trust Joint Global Health Trials Scheme (ref. G1100686/1).

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LMW heparin and recurrent placenta-mediated pregnancy complications: an individual participant data meta-analysis

Mark Rodger
The Ottawa Hospital and University of Ottawa, Ottawa, Canada

Placenta-mediated pregnancy complications, including pre-eclampsia, placental abruption, birth of a small-for-gestational age infant and late pregnancy loss, are common and cause significant morbidity and mortality. The use of antepartum low-molecular-weight heparin (LMWH) prophylaxis to prevent recurrent placenta-mediated pregnancy complications became common practice despite limited and conflicting evidence supporting its use. Unfortunately, differences in the study design of individual randomized controlled trials have limited comparison across trials. In this talk we will review data from an individual patient data meta-analysis that challenges the role of LMWH in preventing recurrent placenta-mediated pregnancy complications.

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INFLUENCE OF GESTATIONAL AGE AT INITIATION OF ANTIHYPERTENSIVE THERAPY - SECONDARY ANALYSIS OF CHIPS TRIAL DATA

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[2]The South Australian Health and Medical Research Institute, Adelaide, Australia
[3]University of British Columbia, Vancouver, Canada
[4]King's College London | St. Thomas' Hospital, London, United Kingdom
[5]University of Toronto, Toronto, Canada

Introduction: For hypertensive women in the Control of Hypertension In Pregnancy Study (ISRCTN 71416914), we assessed whether the maternal benefits of 'tight' control could be achieved, whilst minimising any potentially negative effect on fetal growth, by delaying initiation of antihypertensive therapy until later in pregnancy.
Objective: In this secondary, exploratory analysis, we examined the relationship between gestational age at randomisation and major CHIPS outcomes (including birthweight <10th centile and preterm birth).
Methods: For the 981 women with non-severe, chronic or gestational hypertension randomised to 'less tight' (target diastolic blood pressure, 100 mmHg) or 'tight' (target 85 mmHg) control, we used mixed effects logistic regression to examine whether effect of 'less tight' (vs. 'tight') control on major outcomes was dependent on gestational age at randomisation, adjusting for baseline factors as in the primary analysis and including an interaction term between gestational age at randomisation and treatment allocation. Gestational age was considered categorically (quartiles) and continuously (linear or quadratic form), and optimal functional form selected to provide best fit to the data based on the Akaike information criterion.
Results: Randomisation before (but not after) 24 weeks' to 'less tight' (vs. 'tight') control was associated with fewer babies with birthweight <10th centile ($p_{interaction}$=0.005), but more preterm birth ($p_{interaction}$=0.043), and no effect on perinatal death or high-level neonatal care >48hr ($p_{interaction}$=0.354). For the mother, 'less tight' (vs. 'tight') control was associated with more severe hypertension at all gestational ages, but particularly so before 28 weeks ($p_{interaction}$=0.076).
Discussion: In women with non-severe, chronic or gestational hypertension, there seems to be no gestational age at which 'less tight' (vs. 'tight') control is the preferred management strategy to optimise maternal or perinatal outcomes.

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Preeclampsia Treatment Strategies: Subtraction vs. Addition

Ravi Thadhani
Massachusetts General Hospital and Harvard Medical School, Boston, United States of America

Preeclampsia can be complicated by end-organ damage, including severe hypertension, cerebral edema, and kidney and liver failure. Impending end-organ damage necessitates immediate delivery, often at the expense of the fetus in cases of preterm preeclampsia. Methods to prolong pregnancy may benefit the fetus, if of course maternal signs and symptoms can be tempered. Towards that end, we have developed a novel method to remove circulating sFlt-1 from maternal circulation in hopes to prolong pregnancy in women presenting with severe preterm preeclampsia. Such a strategy is novel for preeclampsia, but not entirely new in general Obstetrics, since historically and even today pregnant women undergo chronic hemodialysis, and plasma pheresis, during pregnancy for a variety of indications. Implementing such a strategy was stepwise, with a gradual increase in the duration and frequency of apheresis. Care was taken to avoid changes in blood pressure during the treatments, and management of flow rates and anticoagulation had to be modified appropriately. Nevertheless, we have shown that such a strategy has the potential to safely prolong pregnancy, potentially by weeks, in the setting of severe preterm disease. We have also followed women and their offspring now for 3-8 years following treatments, and no adverse events related to the intra-partum interventions were noted. Clinical trials are now underway to examine the utility of both selective and semi-selective removal strategies, and in the coming years we believe such a strategy will be available for women with this devastating condition.

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Preeclampsia and mobile-health technology-based lifestyle interventions to support health and health care

Régine P.M. Steegers
Erasmus MC, University Medical Centre, Rotterdam, The Netherlands

Preeclampsia is a placental-related pregnancy complication largely originating in the first trimester of pregnancy where genetic and environmental factors play a significant role. Periconceptional maternal lifestyle factors are environmental factors that are modifiable and associated with preeclampsia. The overlapping lifestyle factors associated with non-communicable disease are poor nutrition, smoking, and obesity. These factors differ between individuals, populations and high, middle and low income countries. They have in common that their prevalence is high also in the reproductive population, and extremely difficult to change.
Mothers-to-be are most motivated to change lifestyle risk factors when they are aware of the short-term health benefits of having a healthy baby. Given the large potential health return, and relatively low costs and risk of harm, research into potential lifestyle interventions is warranted. One of the recent opportunities is the development of evidence-based and personalized mobile-health technology-based interventions to enhance healthy lifestyles. These interventions should be implemented in patient care to support both parents-to-be as well as healthcare professionals in delivering 'Nutrition and Lifestyle Care'.
In the first part of this presentation an overview will be given of the available evidence on the impact of maternal lifestyle factors on the pathophysiology of placentation. In the second part the usability, feasibility, acceptance and effectiveness of novel mobile-health technology based lifestyle interventions related to pregnancy will be presented.
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PATERNAL CONSEQUENCES OF PREECLAMPSIA

Claire Stramrood
Gelre teaching hospitals, Apeldoorn, The Netherlands

Women experiencing pre-eclampsia or HELLP syndrome are known to be at increased risk of developing mental health conditions such as posttraumatic stress disorder (PTSD) and postpartum depression. While the role of fathers in the etiology and pathophysiology of pre-eclampsia becomes increasingly clear, the effects of pre-eclampsia on the mental wellbeing of fathers is scarcely researched.
A recent meta-analysis on the mental health of fathers demonstrate that 8% of fathers suffers from depression, which is twice the rate of depression in the adult male population. Postpartum posttraumatic stress disorder (PTSD) may also occur in partners. Particularly stressful for fathers in case of severe preeclampsia with preterm birth appears to be the separation from and between mother and child, and starting fatherhood facing existential issues.
Research into the paternal consequences of preeclampsia is scarce and warrants further evaluation. In the meantime, qualitative studies point out the important of supporting partners of women with pre-eclampsia during pregnancy and in the postpartum period: by actively *involving* fathers during the hospitalization and in postnatal care; by *normalizing* the mental health impact of potentially life-threatening conditions such as pre-eclampsia and HELLP syndrome, also on partners; by *monitoring* the wellbeing of fathers postpartum, especially in case of preterm birth and in partners with a history of mental disorders; by *informing* partners of possible mental health consequences; and by *validating* fathers if they report mental health issues or psychiatric symptoms.

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HELLP, from my point of view
Bart-Jan van Unen
The Netherlands

Welcome to my world of HELLP. There are many ways to approach the HELLP syndrome or preeclampsia. In my story I want to share my experiences regarding HELLP syndrome. Not in the sence of absolute truth, but from my point of view. As a man, a husband, a father and as a seemingly helpless spectator. Besides your attention for the patient, the women with HELLP syndrome or women with preeclampsia, I'd like to increase your attention to partners and/or their family. HELLP or preeclampsia is also for them a shocking event. There is an important task for doctors to observe and if necessary to refer to a psychologist With my story I'd like to draw your attention to that.

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Modelling the mechanisms of pre-eclampsia: the bigger picture
Christopher Redman
Oxford University, Oxford, United Kingdom

A good mechanistic model of pre-eclampsia (PE) will not only explain its typical features but all the unusual and perplexing aspects that do not appear to fit. The condition seems to be a relatively simple maternal syndrome with extensive heterogeneity as is typical of complex genetic disorders. But can this all be encompassed within one coherent model?
A working model for many years has been that PE is driven by the placenta, strengthened by the discovery of the trophoblast derived factors (sFlt-1, PlGF) that cause maternal angiogenic and endothelial dysfunction. However another perception has been that of the subtypes - maternal and placental PE. Can the maternal aspects be truly causative or are they better considered as risk features? Early (EOPE) and late (LOPE) onset PE are an alternative way of subtyping. EOPE originates in poor placentation, is more severe, is associated with more fetal growth restriction (FGR) and typical placental pathology. LOPE is less severe with little or no FGR and in many instances no apparent placental pathology. That these different subtypes can be encompassed in one model will be demonstrated.
It has been proposed that pre-eclampsia is primarily a disorder of maternal cardiac dysfunction. This does not mean that the placental model is obsolete. Evidence will be presented that the placental model can not only explain more of the condition than the cardiac model, but also incorporate it.
Is there such an entity as normotensive pre-eclampsia? Can true PE ever resolve with an ongoing pregnancy? How can postpartum disease occur after the placenta has been removed? How do animal models strengthen or undermine the model?
A possible model that addresses these issues will be discussed to attempt to reconcile the overall picture.

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Omics technologies and the future of preeclampsia research and clinical practice
Claire Roberts
University of Adelaide, Adelaide, Australia

Despite the obvious success of human reproduction, pregnancy and childbirth pose significant risk to maternal and infant health. The great obstetrical syndromes have been a scourge for pregnant women and their care-givers continuing to the present day. Our understanding of the aetiology of these syndromes including preeclampsia is incomplete largely due to the fact that there are multiple pathways involved in their pathogenesis. For preeclampsia genetic, nutritional and other environmental factors have been implicated mostly those associated with inflammation, a skewed immune response to "foreign" fetal (paternal) antigens, control of blood pressure and plasma volume expansion, thrombosis, metabolic health, insulin resistance and placental trophoblast invasion and colonization of the uterine spiral arterioles. The challenge is to understand how all of these interact to cause disease. And to determine what to measure to predict risk not just for early onset preeclampsia but also for the much more common but still potentially life threatening preeclampsia at term. The cross talk between fetus, placenta and mother provides clues for new approaches for risk prediction, diagnosis and treatment. Integration of twenty first century omics interrogation of the placenta and maternal blood across gestation may provide tools with which to identify and monitor women and fetuses at risk and permit early intervention and treatments. Casting the net as broadly as

possible enables unbiased identification of novel markers of impending disease. It will likely also inform subsequent diagnostics and treatments. But let's not confine our thinking to one prognostic profile per pregnancy complication. Preeclampsia may be considered to be 2 or more disorders (early onset and term) with different molecular antecedent profiles and potentially different prevention strategies.

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Mental health consequences of preeclampsia and other pregnancy complications
Susan Ayers
UK

Pre-eclampsia and other complications during pregnancy and birth can be traumatic for some women. Evidence shows that up to a third of women experience birth as traumatic and 4% develop Post-traumatic stress disorder (PTSD) as a result of events during birth. In high-risk groups, such as women with pre-eclampsia, PTSD affects 18.5% of women (Dikmen Yildiz et al., 2017). Symptoms of PTSD include re-experiencing, avoidance, hyper-arousal symptoms and negative cognitions and mood. These symptoms impact on the mother and potentially the mother-infant factors such as breastfeeding. However, the majority of women who experience a difficult or traumatic birth do not develop PTSD. To understand the impact of complications of pregnancy and birth on women's mental health we therefore need to consider individual vulnerability, risk factors during pregnancy and birth, and protective or resilience factors. Two key variables that are important in both risk and resilience are women's prior mental health, and how well they are supported during labour and birth. Positive support from healthcare professionals may both improve birth outcomes and reduce risk of women developing PTSD.

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Mental Health Implications of Surviving Preeclampsia: What we Know, Need to Know & Do
Eleni Tsigas
Preeclampsia Foundation, USA

Reports from survivors of preeclampsia consistently find higher rates of emotional trauma as compared to normotensive pregnancies, even with lower levels of maternal or neonatal morbidity. Postpartum care in most healthcare settings does not address the mental health needs of women and their partners who have survived preeclampsia. This talk with provide a quick overview of the literature, findings from The Preeclampsia Registry and pose future research questions as well as opportunities for clinical care.

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Adverse perinatal outcomes of intrahepatic cholestasis of pregnancy and association with biochemical markers: results of aggregate and independent patient data meta-analyses

Lucy Chappell, Caroline Ovadia, Paul Seed, Alexandros Sklavounos, Jim Thornton, Catherine Williamson
King's College London, United Kingdom

Background
Whilst intrahepatic cholestasis of pregnancy (ICP) is associated with adverse perinatal outcomes, the relationship between specific biochemical markers and individual pregnancy complications has not been established.
Methods
We performed a systematic review of the literature (PubMed, Web of Science, Embase databases from inception to August 2017, selecting studies reporting perinatal outcomes for women with ICP with serum bile acid concentrations reported. Random effects meta-analysis was performed to determine risk of adverse perinatal outcomes. Individual patient data (IPD) were collected to assess associations between biochemical markers and adverse outcomes using logistic and stepwise linear regression (PROSPERO: CRD42017069134).
Findings
22 studies were included in the meta-analysis (5515 ICP cases, 165 081 controls), with IPD from 18 studies (4163 ICP cases). Stillbirth complicated 0.83% ICP and 0.32% control pregnancies (OR 1.46 (0.73 to 2.89)). Stillbirth was associated with maximum total bile acid concentration (ROC AUC 0.80 (0.69 to 0.90)) but not alanine transaminase (ROC AUC 0.46, 95% CI 0.35 to 0.58). Prevalence of stillbirths was 0.20% (0.05-0.50%) with serum total bile acids <40μmol/L, 0.29% (0.08 to 0.74%; hazard ratio 1.55; (0.39 to 6.22, p=0.53)) with total bile acids 40-99μmol/L and 3.08% (1.77 to 4.96%; hazard ratio 17.27 (27 (5.65 to 52.77, p<0.0001)) with total bile acids ≥100μmol/L. Women with ICP had higher odds ratios of preterm birth (OR 3.54, 95%CI 2.72 to 4.62, related to increasing bile acid category.
Interpretation
The risk of stillbirth is increased in women with ICP, but not significantly greater than population rates until serum bile acids ≥100μmol/L. The clear bile acid threshold of 100μmol/L beneath which stillbirth rates were not elevated is a novel and important finding in our study. As most women with ICP have bile acids below this level, they can be reassured, provided repeat bile acid testing is performed.

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EFFECT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) ON POST-OPERATIVE ANALGESIA AFTER CEASEREAN SECTION: RANDOMISED CONTROLLED TRIAL

Angela Makris[1], Charlene Thornton[2], Jane Tooher[2], Geoffrey Brieger[2], Robert Ogle[2], Louisa Sukkar[2], Haider Mannan[2], Annette Robertson[2], Gaksoo Lee[2], Roshika Kumar[2], Ian Douglas[2], Annemarie Hennessy[2]
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Introduction: NSAIDs can cause an elevation in BP but are administered regularly post operatively after caesarean section. The effectiveness of NSAID in this setting was assessed.
Objective: Assess the effectiveness of oral NSAIDs on patient perceived pain compared to placebo in healthy women following caesarean section.
Methods: A multicentre, prospective, stratified randomization (with minimisation), double blind parallel placebo controlled trial was undertaken in 4 Australian metropolitan hospitals. Commencing immediately post operatively after the caesarean section, women received either diclofenac orally, 50mg three times a day with food or placebo for a maximum of 5 days. All women received paracetamol 1g four times a day and had access to a variety of opioid analgesia. The amount of opioid analgesia was converted to morphine to allow for comparisons. A visual analog scale (VAS) assessing the 'usual' amount of pain and the 'worst' pain each day of admission was completed by each participant.
Results: Of 284 women randomised, the results of 270 women were analysed- 136 women in the placebo and 134 in the NSAID group. Women were well matched at baseline. There was no difference in the simple analgesia administered to the NSAID and placebo group (p>0.05). There was a reduction in pain over time in both groups;

however women in the placebo group had higher VAS scores compared to the NSAID group for all days expect Day 5 post-partum (eg Day 1: Placebo 52.6 (95%CI 48.9-56.5) vs NSAID 46.0 (95%CI 42.1-49.9); p=0.008). The placebo group also required greater amounts of narcotic based analgesics.
Discussion: NSAIDs resulted in less patient assessed pain and a reduction in the amount of narcotics administered post caesarean in women with uncomplicated pregnancies.

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Vaginal delivery is safely achieved in pregnancies complicated by spinal cord injury: a retrospective 25-year observational study of pregnancy outcomes in a national spinal injuries centre

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Objective: To assess pregnancy outcomes in women with spinal cord injury.

Design: A retrospective observational study. Setting: National Spinal Injury Centre at Buckinghamshire NHS Trust.

Population: Fifty women with a total of 68 pregnancies were identified. Five patients sustained SCI during pregnancy and the remaining 63 pregnancies were conceived at least one year after SCI, of which 45 pregnancies had a SCI at T10 or above (73%) and 23 pregnancies at T11 or below (27%).

Methods: Retrospective review of the maternity records of all pregnant women with SCI attending Buckinghamshire NHS Trust between 1991 and 2016.

Main Outcome Measures: Maternal demographic data, antenatal complications, method of anaesthetic, intrapartum data (gestation at delivery, onset of labour, mode of delivery, indication for obstetric intervention), neonatal outcomes (low birth weight, stillbirth, neonatal death).

Results: The most common antenatal complications in SCI patients were worsening of spasms (38%) and urinary tract infection (24%). Preterm delivery occurred in 18% of women. Vaginal delivery was achieved in 77% of pregnancies, including 14% instrumental delivery rate and 23% Caesarean delivery rate.

Conclusions: This is the largest reported study of pregnancy outcomes in SCI patients since 1972. Our findings support the current evidence that pregnancy outcomes are generally successful and that vaginal delivery can be safely achieved in the majority of women, independent of the level of SCI.

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Using acylcarnitine screening for identification of newborn fatty acid oxidation disorders (FAOD) from pregnancies complicated by acute fatty liver.

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Introduction: Acute fatty liver of pregnancy (AFLP) is a rare but potentially fatal disease developing in the third trimester and affects 5 per 100,000 pregnancies. Women at risk include primips, those with BMI<20 and twin pregnancies.[1] The underlying pathophysiology in AFLP is poorly understood but has been linked with newborn FAOD with long-chain 3-hydroxyacyl coenzyme-A dehydrogenase deficiency (LCHAD) reported in 1 in 5 babies.[2] Since defective LCHAD enzyme activity leads to accumulation of acylcarnitines species of varying carbon length in the blood, acylcarnitine screening in babies born from AFLP pregnancies may help to pick up cases non-invasively.
Aims: We set up the **S**creening of **A**cylcarnitines of **M**others and **B**abies in **A**FLP (SAMBA) to:
Assess whether acylcarnitine screening from routinely collected national screening programme newborn blood spots is a reliable method to identify FAOD.
Prospectively define the incidence of LCHAD in AFLP pregnancies.
Methods: AFLP was diagnosed using the Swansea criteria.[3] Tandem Mass Spectrometry (MS) API5000 was used to measure free carnitine (C0) and acylcarnitines[C2,C3,C4,C5,C8,C10,C14,C14:1, C16,C16OH,C16:1OH,C18OH,C3DC(DC=dicarboxylic),C4DC (C5OH & methylmalonyl carnitine-isobaric), C5DC(glutaryl) and C6DC] from the newborn screening blood spot cards. DNA analysis was undertaken in stillbirth cases to identify the E474Q mutation reported in 87% of LCHAD cases.

Results: Between 2012-current, 12 women were diagnosed with AFLP and patients presented with nausea, vomiting, headache, malaise and jaundice. 16.6% were twin pregnancies. In 13/14 babies, all measurable hydroxyacylcarnitines (free, short, medium and long-chain) were found to be normal. There was 1 stillbirth (perinatal mortality rate 71.4 per 1000) and DNA analysis was negative for the E474Q mutation.
Conclusions: The application of tandem mass spectrometry has proved to be an effective and non-invasive tool to identify most FAOD. However, in our cohort so far, we have been unable to demonstrate any indication of newborn LCHAD or other FAOD in AFLP cases.

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Charcot Marie Tooth disease in pregnancy.
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Charcot Marie Tooth (CMT) is the most common inherited peripheral neuropathy. It can affect balance, mobility and manual dexterity, all skills that are important in caring for the newborn. Birth registry data from Norway suggests that obstetric complications are increased in CMT (1) but this was not confirmed in a study that included 33 patients (2). The aim of this study was to determine the impact of pregnancy on CMT and to assess how CMT affects pregnancy outcomes.
A retrospective questionnaire was administered to women with CMT attending our service. The questions explored symptoms before, during and after delivery using a CMT Examination Score (CMTES) and obstetric outcomes were recorded.
50 women (89 pregnancies) with CMT were identified. 48% had CMT 1A and the remaining had various subtypes. The average CMTES score was 10.46 +/- 5.9 SD. Symptoms deteriorated in 36% of women during pregnancy. These were fatigue (45%), deterioration in walking (16%), balance (16%), hand function (10%), and falls (8%) and pain (5%). A small number required bilateral walking aids or a wheelchair. 47% of these symptoms resolved after delivery. The mean gestational age at delivery was 39.5 weeks (range 34 -40). Antenatal complications and mode of delivery: spontaneous vaginal (59%), assisted vaginal (13%) and caesarean section (28%) were not different to the general UK population (3).

This data shows a deterioration of symptoms in 36% of cases with subsequent resolution in 47%. In contrast with some studies, the obstetric outcomes do not appear to be different from the general population. This study is on going with the aim of recruiting 100 women with CMT.

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Detection of additional abnormalities or co-morbidities in women with intrahepatic cholestasis of pregnancy
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Introduction: Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-specific liver disease, affecting around0.7% of pregnancies. It is a multifactorial condition with genetic, hormonal and environmental components. ICP is a diagnosis of exclusion, and guidelines often state that clinicians should test for viral and autoimmune causes of raised bile acids and liver transaminases. However, the detection rate for alternative diagnoses or co-morbidities is uncertain in the literature.

Objective: To assess the detection rate of new diagnoses of viral, autoimmune or ultrasonic abnormalities in women presenting with ICP.

Methods: All women with raised bile acid concentrations were identified over a 2-year period between 1 Jan 2016 and 31 Dec 2017 at a maternity unit in London, UK; electronic patients records were searched for additional

investigations, and documentation around diagnoses.
Results: 324 women had a raised bile acid concentration (median 18 (IQR) 13-32 µmol/L) at a median gestation age of 35.1 (IQR 32.0-37.1) weeks' gestation at first presentation. 28.4% were tested for all liver function tests, virology and autoimmune tests. All positive results for hepatitis B surface antigen and hepatitis C IgG were previously known. No new diagnoses of EBV, CMV or hepatitis A were made. From a panel of autoimmune antibody testing, some positive results were found (at varying titres), but none led to a new diagnosis of liver disease. Varying liver (n=26) and gall bladder (n=43) pathology was noted on ultrasound, but none of new clinical significance.

Discussion: In our study cohort, there were no new co-existing abnormalities of clinical significance detected during additional investigations for ICP. Guidelines should review the evidence base and need for comprehensive screening of all women with ICP and consider whether a more targeted approach should be used, based on clinical symptomatology or unusual features.

Cardiology

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Maternal and neonatal outcomes in pregnancies complicated by Marfan syndrome a multi centre retrospective study

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Background
Pregnancies in Marfan's syndrome(MFS) have higher rates of maternal and neonatal complications. However, there are few large studies to evaluate these complications.
Method
Retrospective cohort study of women with MFS managed between 1st January 1998-1st March 2018, from 11 UK centres providing care for women with cardiac disease. Data on livebirths, miscarriages, terminations and maternal cardiac complication was collated. Complications were defined as: aortic dissection, need for cardiac intervention antepartum or up to 6 weeks postpartum and deterioration in left systolic function. Neonatal complications included delivery at <37 weeks and small for gestational age (SGA, birthweight<10th centile). We examined aortic size prior to pregnancy and at least 6 weeks postpartum.
Results
There were 212 pregnancies in 133 women, resulting in 186 livebirths, 17 miscarriages and 9 terminations. Median age at first pregnancy (n=130) was 28.5 years (IQR 23.8–33.0). Only 58% in their 1st pregnancy in whom data was available had documented preconception counselling prior to pregnancy. Excluding three twin pregnancies, median gestation at delivery was 39 weeks, 24 (13.2%) were preterm. The median birthweight centile was 40 (n=153, IQR 16.5–68.5) and 22 (12.1%) deliveries were SGA. Larger aortic root measurements pre-pregnancy were strongly associated with earlier delivery (excluding one case with root diameter =81mm, n=86, p=0.002). In 41% pregnancies women took beta-blockers. Beta blocker use was associated with slightly smaller babies but this was not significant. Four women suffered aortic dissections (one Type A, four Type B all were in the puerperium), four others required root replacement within six weeks of delivery and one at 23 weeks. Three developed left systolic dysfunction during pregnancy. Five women had an increase in aortic diameter >3mm during pregnancy, but overall aortic diameters did not change significantly.
Conclusions
Pregnancy in MFS is high risk for the mother, with favourable neonatal outcomes, yet pre-pregnancy counselling is not universal.

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Birthweight in pregnancies complicated by maternal heart disease

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Objective
To assess the mean and centile birthweight distribution in women with various groups of heart disease compared with controls.
Methods
Data on birthweight and gestational age at birth (≥24 weeks gestation) were collected about women with known heart disease (both congenital and acquired) from seven specialist UK maternity units. Women were assigned to one of 16 groups according to their cardiac lesion. Whenever possible, data on two controls delivering before and after the index cases was also collected. Birth weight percentiles (corrected for gestational age, sex and parity) were calculated using the Aberdeen norms. Using multivariate regression, we also assessed the impact of beta blockers, maternal hypoxemia maternal saturations (<90%) and systemic ventricular function (normal/impaired).
Results
1321 pregnancies in women with heart disease and 2307 controls were studied. All groups of women with heart disease had lower mean centile birthweight than controls, significantly so in 10 groups, the biggest effect being seen in women with Fontan circulation, pulmonary hypertension, prosthetic heart valves, systemic right ventricle, Marfan's syndrome, repaired tetralogy of Fallot, and cardiomyopathy (in that order). Beta blockers, low maternal oxygen saturation, and impaired systemic ventricular function were also associated with significantly lower centile birthweights.Following multivariate regression; mean birthweight with beta blockers was 3116.7g (SD 700.02) cf 3354.7g (SD 539.06) without beta blockers, a difference of 238.1g (p<0.001). Impaired ventricular function was associated with a significantly lower mean birthweight 2559.5g (SD 759.6) vs. 3103.3g (SD 652.4;) p=<0.001), although the effect did not correlate with the severity of the impairment
Conclusion
Our findings identify specific groups of women with heart disease at risk of having a small baby who therefore need close surveillance of fetal growth.

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Current Practices in Maternal Monitoring During Antiarrhythmic Treatment for Fetal SVT: A Scoping Review

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BACKGROUND: In pharmacologic management of fetal supraventricular tachycardia (SVT), antiarrhythmic agents are administered to the pregnant patient serving as a vehicle of transplacental delivery to the fetus. Given that antiarrhythmic therapy can have profound maternal adverse effects, administration of initial loading and dose adjustments should involve deliberate attention to pharmacologic principles with close maternal monitoring for adverse effects. We reviewed current monitoring practices and maternal complications of transplacental antiarrhythmic therapy for fetal SVT.
METHODS: A query of the Embase database for search terms "Fetal" or "Foetal" and "Supraventricular Tachycardia" or "SVT" yielded 93 titles, of which 19 articles detailing the modalities of therapy for Fetal SVT were reviewed.
RESULTS: The 19 articles represented 565 cases of fetal SVT, 111 of which had developed hydrops fetalis. Of these cases, 184 received a course of digoxin alone and 33, 56, and 5 cases received a combination therapy of digoxin with flecainide, sotalol, or amiodarone. Flecainide, Sotalol, and amiodarone were given as monotherapy in 89, 77, and 6 cases, respectively. Maternal monitoring information was available in 15 studies. Investigators performed electrocardiograms (EKGs) at baseline and during follow-up in 12 studies, and monitored electrolytes in five. Two studies reported a mandatory cardiologist consultation for all mothers and two studies considered performing echocardiography in select mothers. Digoxin and flecainide levels were measured in eight and four studies, respectively. Toxicity was reported in 5 patients: two on digoxin monotherapy, two on flecainide monotherapy, and one on combination of digoxin and flecainide.
CONCLUSION: Pharmacologic management of fetal SVT is generally safe for mothers with normal baseline cardiac

assessments and close monitoring of symptoms, EKG, electrolytes, and/or drug levels. Future prospective studies on the treatment of fetal SVT should also include a systematic monitoring strategy for mothers, with consistent reporting of adverse reactions.

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Obstetric Outcomes Following Atrial and Arterial Switch Procedures for Transposition of the Great Arteries- a single, tertiary referral centre experience over 20 years

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Complete transposition of the great arteries (TGA) accounts for approximately 5-7% of CHD. Almost all patients with TGA surviving until adulthood have undergone complex, reparative, cardiac surgery, which can complicate physiological adaptation to the demands of pregnancy. The atrial switch procedure (Mustard or Senning procedure) was the first operation to enable survival beyond infancy, as such, pregnancy outcomes have been well described. Cardiac risks of pregnancy include cardiac deterioration, heart failure and arrhythmias. The pregnancy risks include; pre-term delivery (31- 38%) and neonates which are small for gestational age (SGA) (22- 38%). The arterial switch operation (ASO) has now largely superseded the atrial switch procedures, this involves transection and 're-plumbing' of the great arteries to restore near normal anatomy, it follows that adult survivors are now undertaking the challenges of pregnancy.
Our unit is an adult congenital heart disease (ACHD) centre and tertiary level maternal medicine service with over twenty years' experience in the multi-disciplinary team (MDT) management of women with surgically corrected TGA in pregnancy. Here we report and compare obstetric outcomes in women born with TGA, corrected with either an atrial switch procedure or ASO. This is the largest, cohort of pregnancies, with complete obstetric and neonatal outcomes, born to women following an ASO, reported to date and the only comparison of outcomes by procedure.

There were 48 completed pregnancies in 23 women, 19 women who had undergone an atrial switch procedure delivered 38 babies and 4 who had undergone an ASO had 10 babies. We report obstetric and neonatal outcomes for all pregnancies, based upon which we make recommendations for the obstetric care of women with this condition.

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Pregnancy outcome in women with uncorrected single ventricle: A Single center experience from South India.

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Introduction.
Occurrence of single ventricle accounts for 0.5-1.5% of the congenital heart disease in whom survival to adulthood, without surgical intervention, is difficult. Hemodynamic changes during pregnancy poses a challenge, resulting in increased risk of maternal and fetal complications such as heart failure, arrhythmias, miscarriage, low birth weight, complications secondary to premature delivery etc. We report the experience of management of women with single ventricle and compare them with concurrent controls.
Material & Methods
We collected demographic, medical and obstetric details of women with diagnosis of uncorrected single ventricle admitted to a regional tertiary care center in south India during the time period from 2011 to 2017. We also collected the details of 4:1 age matched controls without diagnosis of single ventricle. Outcomes assessed were mode of delivery, maternal mortality, neonatal death and low birth weight. Comparisons were done using Mann-Whitney test or Chi-square test as appropriate
Results
We compared 12 pregnancies in 5 women with uncorrected single ventricle to controls. Two women were on Sildenafil for severe pulmonary hypertension (PAH). Sudden death occurred in a primigravida lady at 26 weeks with Complete AV canal defect with severe PAH following delivery. One patient developed heart failure in third trimester. Cesarean section (12.5% vs 17.5%, p=0.729) were similar. Pre-term delivery (30% vs 5%, p=0.014), low birth weight (50% vs 10%, p=0.002) and perinatal death (25% vs 2.5%, p=0.002) were higher compared to the controls.
Conclusion
Women with single ventricle are at higher risk of maternal or fetal adverse events during pregnancy and peri-partum period. Care under multi-disciplinary team can help optimize the outcome of pregnancy if the women wish to continue pregnancy after thorough counselling.

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A nationwide prospective study of aortic dissection in pregnancy using the UK Obstetric Surveillance System (UKOSS).

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Background: Aortic dissection (AD) in pregnancy is a life-threatening event and 50% of cases in women aged <40 years occur during pregnancy .[1] Patients with AD present with a wide array of symptoms and the condition may be missed and patients treated for other diseases.[2] This study estimated the UK incidence of AD in pregnancy and provided insight into presentation and management practices.

Methods: A national prospective population-based study was undertaken across 229 hospitals over a 2-year period. Participants were diagnosed (a) using suitable imaging (echocardiography, CT or MRI) or (b) at surgery/postmortem.
Results: The estimated UK incidence of AD in pregnancy was 1.31 per 100,000 maternities (95% CI 0.69-1.93 per 100,000) with 17 cases confirmed by diagnostic criteria. The mean [SD] age of women was 32.5[7.2]years. Fourteen cases were due to type-A dissection (involving ascending aorta), the remainder type-B (no involvement of ascending aorta). Nine women died, all of whom with type-A dissection, giving a case fatality rate of 53%.
We compared the UKOSS data for survivors to information available for 21 women with confirmed AD who died (during and just after the UKOSS study period). There were no differences in age, BMI or ethnicity but increased prevalence of pre-existing co-morbidities in women who died. On initial presentation all survivors complained of anterior chest pain (compared to 66% who died). Survivors were more likely to have recorded bilateral BP and pulse readings, prompt imaging (87.5% underwent echocardiography + either CT/MRI aorta). In the survivor group (n=8), 5 women successfully underwent surgical aortic root replacement (for type-A dissection) after appropriate BP control usually β-blockade. 3 were conservatively managed for type-B dissection.
Discussion: AD is a rare but serious illness. Thorough physical examination and prompt imaging with quick access to surgery (type-A) or conservative management (typeB) could prevent mortality from AD.

SLE/Diabetes/Remaining

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Disease flares during pregnancy and postpartum in patients with systemic lupus erythematosus

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Introduction: Prior studies found conflicting results about whether lupus is likely to flare during or after pregnancy. Understanding the effect pregnancy has on disease activity is clinically significant for the patient.

Objective: Using a large cohort of pregnant and non-pregnant women with lupus, we measured the effect of pregnancy on disease flares in systemic lupus erythematosus and estimated modification by hydroxychloroquine (HCQ) use.

Methods: Data were prospectively collected in the Hopkins Lupus Cohort 1987-2015. Women aged 14-45 years with >1 measurement of disease activity were included. The time-varying exposures were classified as pregnancy, postpartum, or non-pregnant/non-postpartum periods. Two postpartum times periods were analyzed: 3 months and 12 months. Flares were defined as change in Physician Global Assessment (PGA) ≥1 from previous visit. A stratified Cox model estimated hazard ratios with bootstrap 95% CIs.

Results: There were 1349 patients, including 398 pregnancies in 304 patients. There was an increased rate of flare during pregnancy (HR: 1.59; 95% CI: 1.27, 1.96), however this effect was modified by HCQ use, with the HR of flares in pregnancy compared to non-pregnant/non-postpartum periods estimated to be 1.83 (95% CI: 1.34, 2.45) for patients with no HCQ use and 1.26 (95% CI: 0.88, 1.69) for patients with HCQ use. The risk of flare was similarly elevated among non-HCQ users in the 3-months postpartum (HR: 1.63; 95% CI: 1.04, 2.39), but not among women taking HCQ (HR: 1.25; 95% CI: 0.71, 1.87). There was no increased risk of flare during the 12-month postpartum period, with no modification by HCQ.

Discussion: Our study supports and extends previous findings that the incidence of flare is increased during pregnancy and within the 3-months postpartum. Continuing HCQ, however, appeared to mitigate the risk of flare during and after pregnancy. No increased rate of flare was observed during a 12-month postpartum period.

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Obstetric Internal Medicine in Spain

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Introduction
Obstetric Medicine is an unrecognised and little known subspecialty in Spain and Europe. Currently in Spain, interactive clinical and academic forums between internists and obstetricians are limited to local or isolated initiatives.
Objective
To gather reliable data about the clinical and academic implication of internists on the care of pregnant women with medical disorders in Spain.
Methods
A web-based survey was sent by email to all members (8000) of the Spanish Society of Internal Medicine in March 2017. Responses were collected for 2 months.
Results
We received 260 responses from 167 hospitals in 43 (of 50) Spanish provinces, and 6 abroad. Overall, 62.93% responders belong to a university hospital. For 74.81% of them internists are the doctors most frequently involved in medical disorders in pregnancy, followed by obstetricians (45.74%) and other medical specialists (43.02%). Around 18.82% have a specific unit/clinic of medical diseases in pregnancy at their hospital. Of those, 8 centres deal with various general disorders, another 8 focus on cardiovascular and hypertensive disorders, and 12 on systemic autoimmune diseases. Nearly 20.39% responders receive more than one referral per week from the Obstetrics department; 18.29% are seen by an internist specialised in the field. Similarly, 12.55% of participants have at least a member in their unit involved in teaching and/or research in the field, whereas 14.84% identifies opportunities for specific training around them. Most of responders (92.55%) do not know any society that focuses on medical complications of pregnancy.
Discussion
Despite the fact that internists are frequently involved in the care of pregnant women with medical disorders in Spain, generally they lack training resources, the specific area is not included in their specialty training program and they rarely participate in research/teaching in that field. Formal colaboration between internists and obstetritians, and structured training activities may still be pertinent.

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Does smoking cessation in pregnancy affect rate of gestational weight gain?

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Objective: To evaluate whether smoking cessation in early pregnancy influences gestational weight gain.
Methods: In this retrospective study smoking status was identified using “tobacco in pregnancy” ICD-9 and ICD-10 codes for term pregnancies with established prenatal care at or before 18 weeks gestation. Data regarding demographics, smoking status prior to and during pregnancy, weights throughout pregnancy, as well as measures of neonatal outcome were recorded. Patients were divided into groups according to smoking status at or before 18 weeks gestation. Although term, given the variability in timing of weight measurements, weight gain was assessed by rate per day. Rate of weight gain was assessed at different intervals representing weight gain in early versus late pregnancy (less than or greater than 28-32 weeks respectively).
Results: Patients were predominantly white (46.6%), average age of 29, with an average pre-pregnancy BMI of 28. For early pregnancy, quitters had a statistically greater rate of weight gain (0.163 lbs/day) compared to smokers (0.133 lbs/day) and compared to nonsmokers (0.110 lbs/day), $p<0.05$. Rate of weight gain in late pregnancy also showed a statistically significant increase for quitters (0.173 lbs/day) compared to smokers (0.131 lbs/day), $p<0.05$. There was no significant difference for neonatal outcomes according to maternal smoking status.
Conclusion: Despite a statistically greater rate of weight gain in patients who quit smoking in early pregnancy compared to continued smokers and non-smokers, neonatal outcomes were similar in all groups. Additional intervention is needed to encourage improved maternal outcomes with smoking cessation in pregnancy.

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Adherence to the Postnatal OGTT in the UAE

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Introduction

Gestational Diabetes (GDM) is a known risk factor for the development of type 2 diabetes. Postnatal Diabetes screening is recommended.
The screening gold standard for this purpose is the 75 gram Oral Glucose Tolerance Test (OGTT) performed at 6-12 weeks postnatal.
The main drawback is patient non-adherence with the test. In our 2014 -2015 study the hospital population demonstrated that only 17 % of patients adhered to the test.

Objectives

Improve patient education regarding GDM with its relevance to Type 2 Diabetes during the Antenatal period
Determine whether education improves compliance with the postnatal OGTT
Calculate the number of abnormal OGTTs

Methods

Two year, prospective study from 1st January 2016 till 31st December 2017. All women diagnosed with GDM in pregnancy were seen by the diabetes educators. Importance of a postnatal OGTT was emphasized.
The physician was instructed to place orders for the 75 gram postnatal OGTT on discharge.
A reminder SMS was sent one day before the OGTT appointment.

Results

The postnatal OGTT adherence became 100%. All patients having an antenatal OGTT in our hospital attended their postnatal OGTT appointement.
Those patients who were diagnosed with GDM elsewhere and subsequently delivered in Corniche Hospital also attended the postnatal OGTT.
The Abnormal OGTTs were 7.7%.
The Diabetes Educators now have focused sessions in the postnatal visit where the OGTT results are discussed and acted upon.

Discussion

The postnatal OGTT remains an important tool in the detection of type 2 diabetes. If used properly it allows:
Early detection of Diabetes allowing early intervention and prevention of future complications.

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Analysis of GDm-Health data: new insights into Gestational Diabetes management

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Aim

Little evidence guides the optimal monitoring and management of blood glucose (BG) in women with gestational diabetes mellitus (GDM). Guidelines are based on population-based thresholds and care is not tailored to the needs of the mother and her baby.
We aim to explore the utility of data analytics for identifying novel outcome predictors in women with GDM based on trends in capillary BG, demographic, clinical and pharmacological data, as captured from a digital BG management system (GDm-health).

Method

We developed a smartphone-assisted BG monitoring system which aims to improve the care of women with GDM. We describe the initial analysis of data from women receiving their care using GDm-health at two NHS Trusts between 2014 and 2018. Patient demographic and contextual data including age, booking weight, height, screening criteria for GDM and results, medication use and timing of initiation, qualitative data on diet and lifestyle, HbA1c and maternal and neonatal outcomes will be analysed and corelated with BG data.

Results

Of 1,661 women with diabetes in pregnancy, 1,446 had GDM. Analysis was performed on data from 876 women

with GDM who had completed a pregnancy. We collected 112,997 readings; (mean 203, SD 181). 36,164 readings were tagged to breakfast, 31,115 to lunch, and 40,316 to evening meal. 5,402 were untagged. 267 of women required pharmacological treatment during their pregnancy with detailed information of dose and timing treatment.
Conclusion
Using large data sets to link BG data with demographic data, therapeutic data, and data on maternal and neonatal outcome will enable new insights to refine targets for BG management during pregnancy; automate decision making around medication commencement and dose adjustment; identify those at most at risk of post-partum hyperglycaemia and identify potential digital biomarkers as predictors of maternal and neonatal outcomes.

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Possibility of corticosteroids to induce premature rapture of membrane in patients with systemic lupus erythematosus
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Introduction: It is mentioned that premature rapture of membrane (PROM) occurs with higher rate in women with systemic lupus erythematosus (SLE) , when compared to general population. Most of women who have SLE need to continue corticosteroids during their pregnancies. The relationships between PROM and corticosteroids are not well known, but a recent report in mice showed that corticosteroids weakened fetal membranes, which induced PROM.
Hypothesis: Here we hypothesize that corticosteroids induce PROM.
Methods: We reviewed all pregnancies delivered after 22 completed weeks' gestation in patients with systemic lupus erythematosus (SLE) who were seen at National Center for Child Health and Development from 2005 to 2016. We sum up the dosage of corticosteroids given during pregnancy, and evaluated the relationship with pregnancy outcomes by univariable analyses.
Results: Forty-eight pregnancies in 48 women were identified. 47 women except one took corticosteroids during their pregnancy. 31 % women received immunosuppressants at the same time. PROM occurred in 11 (22.9 percent). Sum of corticosteroids during the pregnancy was significantly bigger in PROM group than that of non-PROM group (central value (interquartile range)) (2730 (1862, 3570) mg v.s. 1890 (1259, 2590) mg ; p=0.031). Furthermore, the risk of PROM was increased in the frequency with increasing of corticosteroids dose. The amount of corticosteroids at the beginning of pregnancy and immunosuppressants didn't show relationships with PROM. The rate of chorioamnionitis didn't show significant difference between PROM group and non-PROM group.
Discussion: Possibility of risk that the more corticosteroids during pregnancy induce the more PROM was identified, and PROM in our study didn't show relationship with chorioamnionitis. Possibility of corticosteroids to induce PROM in non-infectious etiology is suggested. Further evaluation is needed to seek out for the better management for pregnancies with SLE.

Blood pressure/Cardiology/FGR/Remaining

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Oxidative stress in fetal growth restriction with and without pre-eclampsia
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Introduction
Placental insufficiency, due to impaired spiral artery remodeling, is a feature of fetal growth restriction (FGR) and pre-eclampsia. Both conditions occur isolated, nevertheless, preterm FGR frequently occurs in combination with pre-eclampsia. Placental insufficiency is often related to oxidative stress. Locally and systemically produced reactive oxygen species can oxidize plasma free thiols. Thus, decreased free thiol levels indicate increased systemic oxidative stress.
Objective/Hypothesis
Hence, we expect that plasma free thiol levels are decreased in women with a pregnancy complicated by isolated FGR and pre-eclampsia with FGR as clinical reflection of placental insufficiency and oxidative stress.
Methods
Women with a singleton pregnancy between 24-36 weeks of gestation were included in 2017. A total of twenty four

patients could be included in this pilot study. Patients were assigned to one of the following groups based on pregnancy complications, sequential fetal biometry and Dopplers: isolated FGR(n=9), FGR with pre-eclampsia(n=11) or uncomplicated controls(n=14). Free thiol levels were measured in blood. Placentas were analyzed for signs of placenta insufficiency, such as accelerated maturation, maternal and fetal vascular malperfusion and fetal hypoxia.

Results

Plasma free thiol levels were significantly lower in women with a pregnancy complicated by pre-eclampsia with FGR compared to pregnancies complicated with isolated FGR and uncomplicated pregnancies ($p<0.0001$). Accelerated maturation ($p=0.005$), microscopic infarction ($p=0.003$), distal villous hypoplasia ($p=0.001$), and histopathologic signs for fetal hypoxia ($p=0.05$) dominated in pre-eclampsia with FGR compared to isolated FGR and control placentas. FGR placentas were not histopathologically different from control placentas.

Discussion

Although placental insufficiency applies to both FGR and preeclampsia, oxidative stress is more extensive in pre-eclampsia related FGR compared to isolated FGR and controls. Our histopathologic data suggest that the pathophysiological mechanism in the placenta of FGR in pre-eclamptic women is different from pregnancies complicated with FGR without pre-eclampsia.

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Risk of cardiovascular mortality in women with a history of spontaneous preterm birth: a nationwide cohort study

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Introduction: Data suggest an association between a history of spontaneous preterm birth (sPTB) and cardiovascular disease (CVD) in later life. Therefore, we hypothesized that women with a history of sPTB have a higher cardiovascular mortality (CVM) risk.

Methods: Women who gave birth between 1995 - 2015 (registered in the National Birth Registry) were analyzed for death due to CVD through linkage with the National Death Registry. After excluding women with hypertensive pregnancy disorders and/or intra-uterine growth restriction, CVM for women with sPTB was analyzed prospectively in two different cohorts: including all births per woman and including only the first birth of a woman. Women with a sPTB were compared to women with no preterm birth. Cox-regression models with survival curves were executed.

Results: Of 1,476,048 parous women 6.9% had a history of sPTB. sPTB was associated with a 1.65- fold higher CVM risk (95% CI 1.34 – 2.04). Recurrent sPTB (HR 2.57; 95% CI 1.45 – 4.56) and sPTB under the 32 weeks gestational age (HR 2.59; 95% CI 1.64 – 4.10) were significantly associated with the highest CVM risk.
In the 1,166,476 nulliparous women, 6.4% had a sPTB. sPTB was associated with a 1.38-fold higher risk for CVM (95% CI 1.02 – 1.87). In this cohort the highest CVM risk was also found in women with a sPTB <32 weeks gestational age (HR 3.19; 95% CI 1.84 – 5.56).

Conclusion: These data suggest that sPTB is associated with CVM. The CVM risk is highest in women with recurrent sPTB and sPTB <32 weeks gestation.

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Self-monitoring BP in hypertensive pregnancies: the OPTIMUM-BP pilot study

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IntroductionHypertension affects around 10% pregnancies and is associated with adverse maternal and fetal outcomes. Clinic blood pressure (BP) is typically used to monitor and titrate antihypertensive medication during pregnancy. In the general adult population, antihypertensive titration using self-monitoring improves BP control. This study aimed to evaluate the feasibility of using a self-monitoring BP intervention in pregnant women with hypertension.

MethodsPregnant women with hypertensive disease were enrolled between December 2015 and December 2017 across four UK sites and randomised 2:1 to BP self-monitoring or usual care. Women attended up to 3 antenatal study visits and postnatal follow-up at 6 weeks. Self-monitoring involved daily BP measurements, recording these in

a study diary or via mobile-phone based telemonitoring.
Results87 women with chronic hypertension were randomised (56 BP self-monitoring; 31 usual care), representing 65% of those screened and eligible. Eight women declined to join the study (3 for anxiety around self-monitoring and five as they wished to continue self-initiated BP monitoring). Average monthly recruitment ranged from 2.2 to 3.6 participants per site. 98% (n=85) women completed the study.
There were 2 terminations and one early miscarriage. For women who continued monitoring beyond 24 weeks' gestation [n=82], 28% (n=23) developed superimposed pre-eclampsia, 22% (n=18) of babies were delivered before 37 weeks' gestation and 11% (n=9) of birthweights were <10th centile. There was one stillbirth (25 weeks' gestation and one neonatal death (after delivery at 24 weeks' gestation). Full details of outcomes by trial allocation will be presented.
ConclusionsSelf-monitoring of hypertension in pregnancy is feasible with good recruitment and retention within the study. The high incidence of maternal and perinatal adverse outcomes may reflect the risks associated with chronic hypertension. These results support a larger trial evaluating the effect of blood pressure self-monitoring on definitive maternal and fetal outcomes.

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A Comparative Study of Two Immunoassays of Placental Growth Factor
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Objective: To compare the results obtained from use of two commercially available immunoassays of maternal placental growth factor (PlGF) in a multiple pregnancy cohort
Methods: Results obtained using the Triage® PlGF Test (Alere) were compared against those from the Quantikine® ELISA PlGF kit (R&D Systems). A Spearmans rho correlation co-efficient was used to check for correlation between the two scores. Data were then categorised into normal and abnormal according to a cut off of <100 pg/ml, previously defined by the PELCIAN study. Concordance between the results of the two immunoassays were examined using chi-square tests.
Results: 200 biobanked plasma samples were analysed for levels of circulating PLGF. These samples had been obtained from women, at various gestational ages, in multiple pregnancy. A strong, positive correlation ($r = 0.89$, $n = 200$, $p < 0.001$) was seen between the PlGF results from the two assays. However, univariate analysis found that the ELISA was significantly less likely to identify samples as abnormal compared to the Triage test (3.9%, n=10 v 22.9%, n=59; $p < 0.001$).
Discussion: Although the two assays correlate well, there is a significant difference in the actual PlGF values obtained. This is likely due to measurement of differing isoforms of PlGF in each assay. The ELISA kits may be detecting PlGF-2 & PlGF-3 while PlGF-4 remains untested**.** This highlights the importance of developing a unique reference range for any commercial PlGF test before introducing it into the clinical setting.

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Hypertensive disorders in pregnancy as a predictor of cardiovascular disease in a Sri Lankan population
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Introduction
Women with a history of hypertensive disorders are known to be at greater risk of developing subsequent hypertension and cardiovascular disease in Caucasians. Deaths due to cardiovascular disease is a leading cause of mortality and morbidity in South Asia. We undertook this study to look at the association between hypertension in pregnancy and cardiovascular disease and its risk factors in later life in a Sri Lankan population that represents the south Asian community.
Methodolgy
This study was part of a large community-based investigation on non-communicable diseases, the Ragama Health Study (RHS) conducted in 2014. The study was conducted in the Ragama Medical Officer of Health (MOH) administrative area from January to September 2014. The householders list of each GN division was used for stratified sampling and the population aged 35–64 years was identified. 986 consenting women who had experienced giving birth to at least one child were recruited to this study.
Results
Women with a history of hypertensive disorders during pregnancy had a significantly higher risk (OR 3.31) of having hypertension and metabolic syndrome (OR 2.75) compared to women without such a history. There was also a 1.7

fold risk of having type 2 diabetes mellitus, 2.82 fold risk of having a stroke and a 2 fold risk of having a diagnosis of ischeamic heart disease.

Conclusions

This is the first study that has looked at the association between hypertensive disorders in pregnancy and development of cardiovascular risk factors in a South Asian population. A history of hypertensive disorder in pregnancy was found to greatly increase this risk. Women with a history of hypertensive disorder need to be regularly monitored following pregnancy, in order to detect the emergence and modify cardiovascular risk factors in a timely manner.

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Reducing Excessive Laboratory Investigations for Preeclampsia: A Quality Improvement Project

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Objectives: Pregnant women suspected of having preeclampsia receive laboratory workup for diagnosis and surveillance. However, many investigations are ordered from past protocols currently deemed inappropriate- with considerable healthcare cost and the potential for iatrogenic harm. This quality improvement (QI) project aimed to reduce unnecessary patient blood draws and healthcare costs.
Methods: QI tools were used to analyze the workup process on the labour and delivery, triage, and antepartum wards of a tertiary care centre. Healthcare providers were surveyed regarding laboratory ordering practices to identify problems, which was corroborated with 20 inpatient chart reviews. Laboratory usage and costs were analyzed pre- and post-intervention. An algorithm for ordering preeclampsia investigations was developed by a multidisciplinary team, implemented, posted on wards, and pocket aide distributed to residents. Practitioners were invited to educational seminars to support adoption, and posters raised awareness of the issue. Post-intervention surveys and chart reviews were conducted, and interventions refined.
Results: Survey data indicated most providers ordered broad panels of investigations, rarely re-evaluated frequency, and were unaware of laboratory costs. A majority of respondents acknowledged that some investigations did not affect patient management and based these decisions on institutional convention. Baseline data showed 10,462 investigations were ordered ($69,350) (Jan-Apr, 2017). Post-intervention data (Sept 2017- April 2018) revealed a 39% reduction in investigation cost ($6851/month), particularly those of low clinical utility including D-dimer (69%) and urea (71%). Weekly data show the post-intervention reduction in excessive laboratory investigations were sustained and stable.
Discussion: This simple and inexpensive intervention reduced overall laboratory investigations for preeclampsia, particularly those of low clinical utility. This resulted in annualized savings of $89060 (39%). However, institutional ordering conventions are a significant barrier to change and some providers are resistant. Ongoing efforts to quantify balancing measures will safeguard against delayed diagnosis or treatment of preeclampsia.

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Maternal mortality: how can lifes be saved

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The massive problem of preeclampsia in indonesia: in need of a redesigned national health care system

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Objectives: Preeclampsia is a global maternal health burden due to its high maternal mortality and morbidity, especially in low income countries like Indonesia. The present national multicenter study was conducted to evaluate the characteristics and outcomes of preeclampsia in Indonesia, that has never been published before.
Methods: This is a one year (2016) retrospective multicenter study of all preeclampsia cases in seven tertiary referral centers in Indonesia: Medan, Bandung, Semarang, Solo, Surabaya, Bali, and Manado.
Results: Among the total 1232 preeclampsia (PE) cases registered, late-onset preeclampsia (>34 weeks) was the most common PE phenotype; 54% compared with 48% early-onset PE. Many of the preeclamptic women had known risk factors for preeclampsia, including anemia (26%), obesity (10%), and chronic hypertension (8%). Maternal mortality was quite high (2.2%). Maternal complications were dominated by HELLP syndrome (9.8%) and pulmonary edema (6.5%). About 11.9% of the mother required ICU admssion. Most of our patients underwent cesarean section (52.8%). Perinatal mortality rate was 12%. The most frequent perinatal complication was asphyxia (27%). 11% of these newborn needed NICU admission.
Discussion: In contrast to most Western countries, the rate of preterm PE and pulmonary edema in Indonesia seems much higher than published. The new format of our national health coverage (BPJS) does often not cover the real cost of hospital treatment. The true hospital costs is in more than 93% of preeclampsia patients exceeding the BPJS funding, and the excess costs must be borne solely by the hospital. As such PE represents also a major financial problem for the already struggling public hospitals in Indonesia.
Conclusion: Preeclampsia stands out as a massive health care problem in Indonesia. Improving quality and consistency of antenatal care and a complete redesign of the national health care insurance system will be the pivotal steps forward to reduce its terrible impact.

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Prevalence of eclampsia in low-resource countries: Secondary analysis of a pragmatic stepped wedge cluster randomised controlled trial.

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Introduction: In 2015, approximately 42,400 women died as a result of hypertensive disorders worldwide, over 99% of which occured in low and middle-income countries (LMIC). The majority of prevalence data is based on small observational studies or modelled data.
Objective: To describe the prevalence of eclampsia in LMIC.
Methods: This is a secondary analysis of stepped-wedge randomised controlled trial undertaken in ten clusters across Africa, India and Haiti between April 2016 and November 2017. Cluster level consent was obtained therefore all women presenting for maternity care were eligible. Eclampsia data was prospectively collected from routine data

sources and active case finding.
Results: A total of 2692 women experienced eclampsia and there were 536,233 deliveries across 287 facilities. Prevalence of eclampsia was 0.5% but varied between sites (Table 1). 45% of women experienced their first fit in the community, with 24% occurring in clinic and 31% in hospital. Magnesium availability differed between clusters (Table 1) but availability within clusters did not significantly fluctuate over time (rate of change 0.2 (-0.1 to 0.6) p=0.21). On average, 33% of eclampsia occurred in women under 20 years old, this varied from 10% in Addis Ababa, Ethiopia to 51% in Zomba, Malawi. 60% occurred in women aged 20-34 and 7% occurred in women aged 35 or older.
Discussion: Prevalence of eclampsia, and distribution with age, varies between countries. More than 50% of eclampsia occurs in facilities despite magnesium sulphate being widely available.

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Difference in difference analysis of task-shifting with community health extension workers to manage hypertensive disorders in pregnancy in Nigeria
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INTRODUCTION: In Nigeria, though the task-shifting policy recognizes community health extension workers (CHEWs) to administer a loading dose of magnesium sulphate in severe pre-eclampsia/eclampsia prior to referral, it is silent on whether CHEWs should administer anti-hypertensive drugs for the associated hypertension.
OBJECTIVE: This study tests the feasibility and acceptability of CHEWs managing hypertension in HDPs at Primary Care level.
METHODS: A cross-sectional survey (*baseline n=72 and endline n=73*) carried out in 40 selected facilities, stratified into intervention and comparison arms (n=20/ study arm). CHEWs in intervention arm received training, job aids and mentoring on how to identify and manage HDPs with alpha methyldopa and were monitored for one year. The comparison received no training. Structured interviews using pre-tested questionnaires were conducted before and after the intervention. A difference-in-difference (DID) analysis was conducted using SPSS version 20.
RESULTS: There was significant increase in CHEWs' ability to define hypertension correctly (DID=33.3%,p=0.009), describe how to manage blood pressure (DID=13.8%,p=0.000) and grade the hypertension as mild, moderate or severe (DID=60%,p=0.000). CHEWs in the intervention arm were more likely to know when to introduce and stop anti-hypertensives (DID=69.3%,p=0.000; DID=48.9%,p=0.000, respectively), and were more likely to classify HDPs into chronic hypertension (DID=35%,p=0.024), gestational hypertension (DID=18.2%,p=0.054), pre-eclampsia (DID=10.2%,p=0.073), severe pre-eclampsia (DID=39.6%,p=0.000) and eclampsia (DID=20.1%,p=0.804). CHEWs in the intervention arm were more likely to prescribe an antihypertensive (DID=42.2%,p=-0.095) and mostly prescribed (DID=20.6%,p=0.03) methyldopa compared to their counterparts in the comparison arm. Antihypertensives were mainly procured through the open market. Incidence of anti-hypertensives stock-outs were frequent.
DISCUSSION: CHEWs gained and retained knowledge and skills in the diagnosis and management of HDPs-associated hypertension. If this is combined with regular availability of commodities, care for women with HDPs at PHC level could improve remarkably.

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A national surveillance approach to monitor incidence of eclampsia in the Netherlands: the Netherlands Obstetric Surveillance System (NethOSS)
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Introduction: In 2004-2006, the incidence of eclampsia was more than twice as high in the Netherlands as compared to the United Kingdom. Since this comparison of these nationwide collected data, many efforts have been made to decrease the incidence of eclampsia and its related complications.
Objective: To determine the current incidence of eclampsia in the Netherlands and the impact of management changes ten years after the previous nationwide assessment.
Methods: Cases of eclampsia were prospectively collected using the newly established Netherlands Obstetric Surveillance System (NethOSS) in all hospitals with a maternity unit in the Netherlands. Complete casefile copies for 2013-2016 were used for comparative analysis of individual level data with the previous cohort (2004-2006).
Results: The monthly card return rate was 97%; 88 women with eclampsia were identified. Incidence decreased from 6.2 / 10 000 in 2004-2006 to 1.8 / 10 000 deliveries (RR 0.28, 95% CI 0.22 – 0.36). We observed an increase in the use of antihypertensive medication (61/82 versus 35/216; RR 18.4, 95% CI 9.74 – 34.70) and magnesium

sulfate (82/82 versus 201/216; RR 1.08, 95% CI 1.04 – 1.12). In the current registration, target blood pressure was achieved after a median of 145 minutes (IQR 74-322) in case of severe hypertension. There was a decrease in perinatal mortality from 3.0 / 100 000 in 2004-2006 to 0.2 per 100 000 deliveries (RR 0.08, 95% CI 0.01 – 0.60). Maternal death occurred in one woman compared to three in the previous registration.
Discussion: This study demonstrates a considerable reduction in the incidence of eclampsia and illustrates the potential success of management strategies suggested by emerging evidence in recent years. At the same time, there is a possibility for further reduction in incidence by introducing specific algorithms for a goal-directed management approach and stricter adherence to guidelines.

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Birth outcomes with early-and late-onset sign/symptoms of preeclampsia/eclampsia: a cross-sectional postpartum study in Bangladesh
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Introduction: Early-onset of preeclampsia/eclampsia (EO-PE/E) before 34 weeks of gestation and late-onset of preeclampsia/eclampsia (LO-PE/E) after 34 weeks are associated with negative maternal and fetal health outcomes.
Objective: We examined birth outcomes of women admitted to the maternity unit before and after 34 weeks.
Methods: A total of 146 PE/E women were admitted to a tertiary hospital in Bangladesh between November 2017-March 2018; 40 women admitted before 34 weeks and 106 women after 34 weeks gestation. Descriptive statistics and logistic regression were used to examine birth outcomes of women admitted.
Results: Significantly more women admitted before 34 weeks were older (>=35 year) than those admitted after 34 weeks (15.0% vs. 7.0%, p<0.05). More, women (84%) admitted after 34 weeks needed a cesarean section compared to women admitted before 34 weeks (40%) (p<0.001). Neonates born to women admitted before 34 weeks pregnancy had significantly lower birth weight (<1500 gm) (23.5% vs. 1.0%, p<0.001), more neonatal complications (65.0% vs. 24.0%, p<0.001), and higher fetal death (53.0% vs. 6.0%) as compared to neonates born to women who admitted after 34 weeks gestation. Women with EO-PE/E had significantly increased odds for fetal deaths (Adjusted Odds Ratio (AOR):20.2, 95 % Confidence Interval (CI): 6.95-58.4, P<0.001) compared to women who had the LO-PE/E and onwards**.** Furthermore, only 13.3% and 14.1% of 115 SPE/E women had administrated injection Magnesium Sulphate ($MgS0_4$) loading dose before and after 34 weeks from outside hospital (p<0.01); 75% babies died in women with SPE/E before 34 weeks and 8% died compared to women admitted after 34 weeks (P<0.001).
Discussion: Women admitted in the hospital with EO-PE/E had significantly worse birth outcomes compared to women who had admitted with LO-PE/E. Further follow-up of these women will help us to understand more details of postpartum health complications of mothers and babies.

Nephrology

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Progression from isolated proteinuria to severe preeclampsia - does severity of proteinuria matter?
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Introduction
The majority of women with preeclampsia have increased proteinuria. However, the 2013 Task Force on Hypertension in Pregnancy suggested that the degree of proteinuria is no longer a severe feature of preeclampsia due to a minimal correlation between proteinuria levels and pregnancy outcome. This change has brought about even more uncertainty regarding the clinical significance of isolated proteinuria in the development of pre-eclampsia.
Objective
To investigate the association between the severity of isolated proteinuria and later development of severe preeclampsia and other placental mediated complications.
Methods
Pregnant women with new onset proteinuria levels exceeding 300 mg in 24-hour urine collection, who were referred to our institution between 2014 and 2017 were approached. Exclusion criteria included immediate diagnosis of preeclampsia, chronic renal disease or chronic hypertension. 104 women met inclusion criteria and were followed throughout pregnancy and until after delivery.

Results
Overall, 29 of 104 (28%) women developed severe preeclampsia. The rate of severe preeclampsia was significantly higher in women with proteinuria ≥3 g\24h (57.1%) compared to women with proteinuria < 3g\24h (20.1%), ($p<0.001$). Proteinuria ≥3 g\24h remained a significant risk factor for severe preeclampsia after controlling for maternal and gestational age, BMI and twin gestations. Additionally, women with proteinuria ≥3 g\24h were significantly more prone to developing HELLP syndrome (28.6%), compared to women with proteinuria levels <3 g\24h (10.8%), ($p<0.05$). The mean gestational age at delivery of women who developed severe preeclampsia was 34.2±2 for women with ≥3g\24h, versus 36.4±1 for women with < 3g\24h, ($p<0.01$). The median time interval (days) between the diagnosis of proteinuria and presentation of severe preeclampsia was not significantly different between women with ≥3g\24h (15) and < 3g\24h (17).
Discussion
Isolated proteinuria > 3g\24his a significant risk factor for severe preeclampsia and HELLP syndrome with a rapid and earlier progression to clinical disease.

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Differential effects of RAAS inhibition, sympatheticinhibition and low sodium diet on blood pressure in women with a history of preeclampsia
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Introduction: Current guidelines for prevention of cardiovascular disease after preeclampsia lack sufficient evidence to recommend a particular blood pressure lowering strategy.
Objective: To investigate the most effective blood pressure lowering strategy in women with a history of preeclampsia with postpartum (borderline) hypertension.
Methods: Randomized, four-way, double-blind, crossover study in 8 women with a history of preeclampsia with diastolic blood pressure >80 mmHg and/or systolic blood pressure >120 mmHg (PALM-study, NTR4590). In each woman the effects of 8 weeks of renin-angiotensin-aldosterone system (RAAS) inhibition (losartan 100mg), sympatheticinhibition (moxonidine 0.4mg), low sodium diet (50mmol NaCl/24 hour) and placebo on 24-hour blood pressure were determined. Nocturnal dipping was assessed as non-dipping is associated with increased cardiovascular risk. Data were analyzed using linear mixed models with subject*visit as random factor.
Results: No significant effect of blood pressure lowering strategy was observed on 24-hour blood pressure, although a trend towards lower mean arterial blood pressure was observed on losartan (92 ± 7mmHg) and low sodium diet (94 ± 14 mmHg) compared to placebo (97±13 mmHg) and moxonidine (98 ± 13 mmHg). Nocturnal dipping of mean arterial blood pressure did significantly differ ($p_{strategy}= 0.03$), with increased dipping on low sodium diet (-18 ± 9 mmHg, $p=0.01$) and losartan (-18 ± 5 mmHg, $p<0.01$), compared to placebo (-13 ± 3 mmHg) and moxonidine (-6 ± 6 mmHg). On moxonidine compliance was lowest and one patient needed to terminate the treatment prematurely because of side-effects.
Discussion: Equal beneficial effects of RAAS inhibition and low sodium diet were observed on 24-hour blood pressure, especially on nocturnal dipping, in women with a history of preeclampsia. These findings fit with the previously reported increased salt-sensitivity and disturbances in RAAS after preeclampsia.

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Obstetric and renal outcomes of pregnant women with chronic kidney disease (CKD) stages 3-5.
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Introduction
Quantification of risks of pregnancy in women with impaired kidney function (CKD stages 3-5) is limited by cohort size and historical data. This contemporary cohort is the largest available to date.

Methods
Women with CKD stages 3-5 (eGFR<60ml/min/1.73m^2) were identified from six UK centres (2003-2016). Outcomes analysed included gestation, mode of delivery, birthweight, neonatal intensive care and maternal renal function. Statistical analysis was Fisher's exact test for binary data, Mann-Whitney test for continuous data, and non-parametric Spearman correlation. Risk ratios were derived by comparing with an unselected UK obstetric cohort 2004-2012 (n=53,917).
Results
222 women with stage 3-5 CKD (38% stage 3a, 44% stage 3b, 18% stages 4-5) were recruited. Live birth rate was high (98%). In women with stage 3-5 CKD vs general obstetric cohort, there was an increased risk of preterm delivery <37 weeks (54% vs 7%, RR=8.4, p=<0.0001), low birthweight <2500g (49% vs 7%, RR=7.3, p=<0.0001), Caesarean delivery (59% vs 28%, RR=2.1, p=<0.0001), and need for neonatal intensive care (35% vs 6%, RR=6.1, p=<0.0001). A lower pre-pregnancy eGFR was associated with earlier gestation at delivery (p=<0.001) and a lower birth weight centile (p=0.003). A failure of the serum creatinine to fall in early (10-16 weeks) pregnancy was associated with earlier gestation at delivery (p=0.002), lower birth weight centile (p=0.01) and loss of maternal renal function at 1 year post-partum (p=<0.001).

Conclusions
All women with CKD 3-5 have a high risk of adverse obstetric outcomes, which should inform pre-pregnancy counselling. The absence of a fall in serum creatinine in early pregnancy may represent insufficient 'renal reserve'. This leads to the hypothesis that pathological hyperfiltration during pregnancy contributes to adverse pregnancy outcomes and a post-partum decline in maternal renal function.

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EFFECT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) ON BLOOD PRESSURE IN THE POST-PARTUM PERIOD: A RANDOMISED CONTROLLED TRIAL
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Introduction: NSAIDs can cause an elevation in blood pressure (BP) in women outside of pregnancy when taken acutely and chronically. It is unclear if NSAIDs have a similar effect on BP in women with uncomplicated pregnancies.
Objective: Assess the effect on blood pressure (BP) of oral NSAIDs compared to placebo in healthy women following caesarean section.
Methods: A multicentre, prospective, stratified randomization (with minimisation), double blind parallel placebo controlled trial was undertaken in 4 Australian metropolitan hospitals. Commencing immediately post operatively after the caesarean section, women received either diclofenac orally, 50mg three times a day with food or placebo for a maximum of 5 days. BP was measured by ambulatory BP measurement as well as ward based BP. Women with HDPs during pregnancy and unable to tolerate opioids were excluded. Data was analysed with STATAv14.
Results: A total of 284 women were randomised and the results of 270 women were analysed- 136 women in the placebo and 134 in the NSAID group. Women were well matched at baseline. The use of NSAIDs statistically but not clinically significantly reduced the ABPM measured systolic BP compared to placebo -2.2mmHg (95%CI -4.4mmHg to -0.1mmHg; p=0.04) over the 5 days post-partum. The diastolic BP was also lower in the NSAID group compared to placebo -1.5mmHg (95%CI -2.8mmHg to -0.14mmHg; p=0.03). No women required treatment for hypertension as assessed by usual clinical practice.
Discussion: NSAIDs do not elevate blood pressure after term caesarean in women with uncomplicated pregnancies.

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Preeclampsia, HELLP-syndrome after kidney transplantation.
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Preeclampsia (PE) and HELLP -syndrome often complicates pregnancies after maternal kidney transplantation. Moreover, women who become pregnant after renal transplantation are at higher risk of any TMA(thrombotic

microangiopathy)-disorders.
OBJECTIVE:
We aimed to assess frequency of TMA, PE, HELLP –syndrome and negative obstetric outcomes, kidney function decline during the pregnancy.
METHODS:
An retrospective single-center cohort study 01/2014- 12/2017: 19 patients with renal allograft, 29 ± 4.35 years old (24-39). Renal function at conception and after delivery, pregnancy outcomes, clinical and laboratory parameters were collected from women who were pregnant after renal transplantation and had transplant and obstetric care.
RESULTS:
10 of 19(52,6%) have had laboratory signs of TMA during pregnancy –gr.1. All of them had normal levels of calcineurin inhibitor concentration. Symptoms of TMA were wavy, alternating with spontaneous improvement and were not regarded as manifestations of a possible PE in 6 (sFlt-1 were normal). 4 of 19 (21.3%) had full HELLP-syndrome. Without TMA 9/19- gr.2. Only patients with HELLP or PE had elevated sFlt-1/PlGF ratio. There were no “pure” PE(without signs of partial HELLP). In patients without signs of TMA, the sFlt-1 / PlGF ratio did not exceed the 4.95. Anemia was detected in all patients, but the signs of TMA showed anemia more pronounced. Thrombocytopenia was noted only in patients with signs of TMA. GFR was significantly reduced in all patients with signs of TMA.
CONCLUSION: Signs of TMA during pregnancy after kidney transplantation have had every second woman. Pregnancy outcomes were worse in TMA, newborns had lower Apgar scores, growth and birth weights. Pregnancy after kidney transplantation is independent risk factor of the development of HELLP syndrome, rather than “pure” PE. Patients with TMA demonstrate the most pronounced impairment of kidney function and an unfavorable outcome of pregnancy.

Cardiology

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Aberrant corpus luteum number as a contributor to altered maternal vascular health in early pregnancy and preeclampsia risk after assisted reproduction

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Introduction: Pregnancies conceived after utilization of assisted reproductive technologies (ART) are associated with an increased risk for preeclampsia. The pathophysiologic reasons are mainly unknown.
Objective: We sought to determine if a non-physiologic hormonal milieu influenced by the number of corpora lutea (CL) and the mode of conception affects maternal vascular health in early pregnancy.
Methods: Blood pressure, endothelial function, circulating endothelial progenitor cell numbers (CPCs), lipid levels, and CL hormones were compared in a prospective cohort of women at 11 to 14 weeks’ gestation by number of CL and mode of conception (N=57): 0 CL (programmed frozen embryo transfer (FET), N=18); 1 CL (spontaneous pregnancy after infertility [N=16] and modified natural cycle FET [N=12]); or > 3 CL associated with *in-vitro* fertilization [N=11].
Results: Women with 0 or > 3 CL lacked the drop in mean arterial blood pressure compared to women with 1 CL (P=0.05; P=0.05). Reactive Hyperemia Index (RHI) was impaired in patients lacking a CL compared to women with 1 CL (P=0.04). Baseline pulse wave amplitude (BPWA) was higher in subjects with > 3 CL compared to 1 CL (P=0.01) or zero (P=0.01). Suppression of CL development in FET cycles was associated with a lower RHI compared with FETs in a natural cycle (P=0.03). The number of angiogenic and non-angiogenic CPCs was lower in the absence of a CL in FETs (P=0.02 and P=0.04). Relaxin levels correlated with the number of angiogenic CPCs (r=0.31; P=0.03).
Discussion: Maternal vascular health in early pregnancy is altered in women with aberrant numbers of CL (0 or >3), and might represent insufficient cardiovascular adaption leading to an increased risk of preeclampsia.

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Maternal cardiovascular changes secondary to sildenafil intake in pregnancies complicated by severe fetal growth restriction: STRIDER trial

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Background
Fetal growth restriction (FGR) is associated with maternal cardiovascular changes. Sildenafil, a phosphodiesterase type 5 inhibitor, potentiates the actions of nitric oxide and could alter maternal haemodynamics. The main aim of this study was to investigate the effect of sildenafil on maternal haemodynamics in pregnancies complicated by severe early-onset FGR.
METHODS
In this multicentre, placebo-controlled trial, we randomly assigned 135 women with singleton pregnancies and severe early-onset FGR (defined as a combination of estimated fetal weight or abdominal circumference below 10th centile and absent/reversed end diastolic flow in the umbilical artery on Doppler velocimetry diagnosed between 22^{+0}-29^{+6} weeks' gestation) to either sildenafil 25mg three times daily or placebo until 32^{+0} weeks' gestation or delivery. The maternal blood pressure (BP), heart rate (HR), augmentation index, pulse wave velocity (PWV), cardiac output, stroke volume (SV) and total peripheral resistance were recorded before, one hour after, and 48-72 hours post-randomisation, and postnatally.
RESULTS

Sildenafil increased maternal HR by 4bpm more than placebo did [5bpm (95%CI:1,12) vs 1 (-5,8);P=0.004] and reduced systolic BP by 1mmHg more than placebo [-4mmHg (-9,1) vs -3mmHg (-8,5);P=0.048]. Even after adjusting for maternal BP, sildenafil reduced aortic PWV by 0.6 m/sec more than placebo [-0.90m/sec (-1.31,-0.51) vs -0.26 (-0.75,0.59);P=0.001]. Sildenafil was associated with a non-significant decrease in the SV index [-5.5m/m^2/beat (-11,-0.5) vs 0 (-0.5,4);P=0.056].

CONCLUSIONS
Sildenafil increases HR, reduces BP and reduces arterial stiffness in pregnancies complicated by FGR. These changes are modest and their clinical impact on mother and baby, both short- and long-term, remains uncertain.

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The P4 study: Blood pressure 6 months and 2 years after Pre-eclampsia

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Introduction
Women who have had pre-eclampsia (PE) have increased risk for future hypertension and cardiovascular disease; however, what defines normal blood pressure (BP) for healthy young non-pregnant women is unclear.
Objective
To determine: a) the normal BP range for healthy young women who have had a normal pregnancy (NP); b) the percentage of women with prior PE with BPs above this range.
Methods
The prospective P4 study examines BP, cardiovascular function and risk, mental health and paediatric assessment following PE and NP at 6 months, 2 yrs. and 5 yrs. post-partum. We measured routine sphygmomanometry BP, central BP (CBP) with applanation tonometry, and 24 hr. ambulatory BP (ABPM) at 6 months (NP=245, PE=76) and, in the same women, at 2 years (NP=66, PE=27) post-partum.
Results
At 6 months PE women had higher: 1) routine BP (112/71 vs. 104/66 mmHg, p<0.001); 2) central BP (105/74 vs. 97/68 mmHg, p=0.002); 3) ABPM (114/71 vs. 107/67mmHg, p<0.001) than NP women. The upper normal BP at 6 months was 122/79 mmHg for routine BP ('traditional' = 140/90 mmHg), 115/81 mmHg for central BP ('traditional' =

120 mmHg systolic) and 120/77 mmHg for ABPM ('traditional' = 130/80 mmHg).
Between group differences persisted at 2 years post-partum; there were no changes in any BP parameter ***within*** groups between 6 months and 2 years.
Clinicians using traditional values would have considered up to 3% as hypertensive by routine BP, 8% by Central BP and 17% by ABPM; using these new limits hypertension detection rates were 15,13 and 20% respectively at 6 months and 22, 32 and 17% at 2 years.
Discussion
These new normal BP limits for defining hypertension in young women are lower than those used in the general community; using these values defines more formerly PE women as hypertensive than using traditional cut-off BP levels.

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Multiple Pregnancy Significantly Impairs Maternal Vascular Function Postpartum
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Introduction: Cardiovascular disease (CVD) is significantly increased among women with previous adverse pregnancy outcomes, particularly preeclampsia. Data suggest that the increased risk of CVD among women with pregnancy hypertension such as preeclampsia is driven primarily by shared common risk factors that precede pregnancy. However, paradoxically data also indicate that a history of multiple uncomplicated pregnancies alone is associated with an increased risk of future CVD compared to never pregnant women.
Objective The focus of this project was to begin to investigate the effect of pregnancy itself on future maternal vascular function.
Methods: Female apoE$^{-/-}$ mice were bred 1, 2 or 3 times and compared to age matched (10 months of age) female virgin apoE$^{-/-}$ mice (n=8-9/ group). Blood pressure was measured by tail cuff. Endothelial-dependent and independent vascular function of mesenteric arteries was assessed using an isometric myograph.
Results: Plasma cholesterol levels were similarly elevated in all apoE$^{-/-}$ mice. Blood pressure was significantly elevated in the mice bred 3x (138±29/94±13) compared to virgin mice (118±12/83±10 mmHg, $p<0.01$). Contractile response and tension to phenylephrine was not different between arteries from virgin and 1, 2, or 3x prior pregnant apoE$^{-/-}$ mice. Methacholine-induced endothelial-dependent relaxation was significantly blunted in arteries from 2 and 3x prior pregnant mice (62±5 and 60±7%, respectively) compared to 1x prior pregnant (77±8%) and virgin mice (83±9%, $p<0.001$). Endothelial-dependent relaxation was not different between arteries in the presence of the nitric oxide synthase inhibitor L-NAME. Similarly, endothelial-independent relaxation in response to nitroprusside was not different between virgin and prior pregnant mice.
Discussion: Compared to virgin apoE$^{-/-}$ female mice, similarly aged mice with multiple previous pregnancies have higher blood pressure and blunted endothelial-dependent relaxation. These data support epidemiologic data identifying an association between prior pregnancy (multiple) and increased risk of future maternal heart disease.
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Preeclampsia and premature cardiovascular disease in a large UK pregnancy cohort
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Introduction
Preeclampsia affects 3-5% of pregnancies, manifesting as hypertension and proteinuria in the second half of pregnancy. Recent research has highlighted an association between preeclampsia and subsequent cardiovascular disease (CVD).
Aims
To investigate the association between preeclampsia and other hypertensive disorders of pregnancy and subsequent CVD in a large dataset with sufficient granularity on endpoints.

Methods
A UK cohort of 1.9 million completed pregnancies and preeclampsia events (N=33,344) was compiled from a larger linked dataset of primary and secondary care records, including 12 CVD endpoints. Outcomes were defined using the CALIBER resource (https://www.caliberresearch.org/portal). Cox models were used to quantify the association between preeclampsia and CVD and were adjusted for maternal age, ethnicity, pre-pregnancy hypertension, and socioeconomic status.
Results
Having one or more pregnancies affected by preeclampsia doubled a woman's risk of any subsequent CVD event (hazard ratio (HR) for any stroke event:1.94 (1.58-2.41), total N=1,698; HR for any cardiac event:2.08 (1.99-2.18), total N=51,008). Adjustment for diagnosis of hypertension between end of pregnancy and first CVD event attenuated associations slightly (stroke HR:1.74 (1.41-2.16); cardiac HR:1.94 (1.85-2.03)). Mean (SD) age at start of follow-up in our pregnancy cohort was 28.48 (6.15) years and at first event among women was 34.67 (8.17) years, compared to 56.46 (20.33) for the whole female linked records dataset.
Conclusion
Our study identified a significant association between preeclampsia and premature CVD events, many of which occur below the UK national CVD screening age of 40 years. As adjustment for post-pregnancy hypertension attenuates but does not eradicate the association, this implies that some, although not all, of the effect of preeclampsia on early life CVD is mediated via hypertension. Our data suggest that preeclampsia should be incorporated into national screening tools to identify women at risk of early life CVD events and interventions implemented to reduce CVD risk.

Thrombosis and treatment

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Effect of Aspirin on Soluble Fms-Like Tyrosine Kinase-1 Levels and Placental Growth Factor in Women With Suspected or Confirmed Preeclampsia

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Background: Patients with preeclampsia display elevated placenta-derived sFlt-1 (soluble Fms-like tyrosine kinase-1) and decreased placental growth factor (PlGF) levels. Low-dose aspirin use is recommended for the prevention of preeclampsia in high-risk women, although its exact pathogenic mechanism remains unknown. Preclinical studies have shown that aspirin decreases sFlt-1 secretion in vitro. Our aim is to investigate whether aspirin use affects sFlt-1 and PlGF in women with confirmed or suspected preeclampsia.

Methods. A prospective cohort study was conducted involving 430 women. Of these women, 45 took aspirin for 10 to 32 (median 23) days before sFlt-1 and PlGF measurement. Measurements were only made once at study entry, between weeks 20 and 41 (median 33) weeks.

Results. Women using aspirin at study entry were compared to either all women not using aspirin, or given that sFlt-1 and PlGF alter with advancing gestation, to gestational age-matched women not using aspirin. We aimed at obtaining 2 gestational age-matched non-users for each individual drug user. Aspirin use tended to lower sFlt-1/PlGF ratio ($p = 0.05$), but this trend was mitigated when matched with gestational age-matched controls ($p > 0.05$). With regard to other drugs affecting sFlt-1, PPI use was associated with lower sFlt-1 levels both when compared with all non-PPI users and with 80 gestational age-matched controls. No sFlt-1/PlGF factor alterations were observed in women using ferrous fumarate or macrogol while, and as expected, women using antihypertensive medication displayed higher sFlt-1 levels and lower PlGF levels. The PPI use-associated decrease in sFlt-1 was independent of the application of aspirin or antihypertensive drugs. Rates of pregnancy complications for aspirin users were not different from non-aspirin users.

Discussion Treatment with aspirin does not associate with lower sFlt-1 or altered PlGF levels. Larger studies are required to further elucidate the pathogenic role of aspirin in the prevention of preeclampsia.

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Acetylsalicylic acid for inhibition of platelet aggregation during pregnancy.

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Introduction
Acetylsalicylic acid (ASA) is used as prevention against several obstetric complications. The efficacy of ASA on inhibition of platelet aggregation is well-known, but the effective dose of ASA during pregnancy is under debate.

Objective/hypothesis
We hypothesized that the inhibition of platelet aggregation by ASA is similar during the three trimesters of pregnancy.

Methods
Platelet aggregation was studied in women with recurrent miscarriage treated with ASA 75 mg (group A, n=176) or placebo (group B, n=177) and in healthy women with normal pregnancy (group C, n= 79).
Platelet aggregation was detrmined with multiple elctrode impedance aggregometry (Multiplate, ASPI test, Roche Diagnostics International Ltd, Switzerland) before conception, during the three trimesters of pregnancy and postpartum.

Results
Mean values (SD) of the ASPI test before conception, available in groups A and B were 68.7U (25.7) and 75.1U (27.7), (p=0.026).
Platelet aggregation was markedly inhibited during pregnancy, but the inhibition decreased over the trimesters in group A. The ASPI tests were 12.8U (9.3), 19.2U (16.7) and 26.5U (23.1) in gestational weeks 13, 30 and 36 ($p<0.001$ for all comparisons with baseline). Outliers at the three sampling periods during pregnancy are likely to be non-responders to ASA.
The women treated with placebo and the healthy pregnant women presented only minor decrease in platelet aggregation during pregnancy. There were no differences between group B and C and no changes over time in these groups.

Discussion
Inhibition of platelet aggregation by ASA decreased as pregnancy continued. This can be a result of changes in plasma volume and increased turn-over of platelets. It is likely that the ASA dose has to be increased if the same inhibition of platelet aggregation by ASA is to be achieved during all three trimesters.

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Aspirin prescribing in pregnancy: Are we doing it?

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Introduction
The NICE guidelines on hypertension in pregnancy recommend the use of aspirin to reduce the chance of gestational hypertensive disease in those with risk factors. If there are two or more moderate or any major risk factors present then aspirin 75mg should be offered from 12-weeks gestation. There is little published evidence on the number of women eligible for aspirin or the number who are actually offered aspirin in early pregnancy.
Objective
To assess the number of women eligible for aspirin and the rates of aspirin prescription in a large London hospital.
Methods
The maternity data collection system (BadgerNet, Clevermed Ltd) records of 1000 consecutive pregnant women who delivered in 2016 at a central London teaching hospital were reviewed. Their eligibility for aspirin was assessed using the NICE guideline: Hypertension in pregnancy 2013. The clinical notes of those with moderate or major risk factors were then reviewed to assess for aspirin prescription in those who were eligible and pregnancy outcomes including the development of gestational hypertensive disease.
Results
116 (11.6%) women were eligible for aspirin; 56 had two or more moderate risk factors and 60 had major risk factors. In 49 (42%) women, there was no indication from the notes that aspirin was considered. 78% of those with major risk factors were offered aspirin. 14 out of 19 women with essential hypertension and 18 out of 27 with

previous gestational hypertensive disease were offered aspirin. Only 36% of women with multiple moderate risk factors were prescribed aspirin.

Discussion

About 12% of women delivering at a central London hospital were eligible for aspirin. Current rates of aspirin prescribing are sub-optimal, especially in patients with multiple moderate risk factors and those with previous gestational hypertensive disease. Familiarity with the NICE criteria for aspirin is essential to ensure improvement in aspirin prescription.

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Preclinical assessment of new generation antiplatelet therapies to prevent preeclampsia

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Key pathophysiological steps in preeclampsia include 1) placental oxidative stress, 2) elevated sFlt1 and 3) endothelial dysfunction. While the antiplatelet drug aspirin has shown potential to prevent preeclampsia, its effectiveness remains limited. New generation antiplatelet drugs (Clopidogrel, Prasugrel and Ticagrelor) have distinct properties beyond antiplatelet actions (inflammation and endothelial dysfunction), thus may be more effective to prevent preeclampsia. We examined whether new generation antiplatelet drugs are better than aspirin at countering various pathophysiological steps in models of preeclampsia.

Methods: Primary human cytotrophoblast, placental explants and endothelial cells (HUVEC and uterine microvascular (UtMVs)) were treated with increasing doses of Clopidogrel, Prasugrel, Ticagrelor or Aspirin (0-100μM). Endothelial dysfunction was induced and antiplatelet agents were added. Functional assays measured the adherence of primary human monocytes to stimulated endothelial cells. Media and cell lysates were collected to assess 1) ROS production, 2) antioxidant response element signaling pathways, 3) production of vasoactive mediators, 4) production of sFlt1, PlGF and pro-inflammatory mediators and 4) markers of endothelial dysfunction.

Results: New generation antiplatelet agents induced nuclear Nrf2 translocation (antioxidant transcription factor), increased antioxidant gene expression (HO-1, NQO1 and GCLC). Consistently reactive oxygen species (ROS) production was reduced with new generation antiplatelet treatment. Furthermore the new generation antiplatelets potently reduced sFlt1 secretion from preeclamptic placental explants, and importantly they also increased PlGF mRNA expression. Antiplatelet agents rescued endothelial dysfunction, mitigating monocyte-endothelial adhesion, and reduced VCAM1 and ET-1 expression (both mRNA and protein) and enhanced eNOS activity. Aspirin however had no beneficial effects in our in vitro/ex vivo models of preeclampsia.

Conclusions: In contrast to aspirin, new generation antiplatelets potently upregulate antioxidant defences, reduce ROS formation, decrease sFlt1 secretion, enhance activity of vasoactive mediators and counter endothelial dysfunction in human models of preeclampsia. Given they are classified as category B/C drugs, they represent exciting candidate therapies to prevent preeclampsia.

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Attenuation of Angiotensin II-Induced Preeclamptic Symptoms by Recombinant Thrombomodulin in Mice - a novel therapeutic approach for preeclampsia

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Introduction: Placental dysfunction and disturbance of systemic endothelial function in the mother is involved in the pathetiology of preeclampsia (PE). According to the recent reports, recombinant thrombomodulin (rTM), an anticoagulant clinically used as a treatment for disseminated intravascular coagulation, plays a protective role to diminish endothelial damage under variety of pathological situations.

Objective: To examine the efficacy of rTM administration in PE developed by angiotensin II (AngII) infusion in pregnant mice.

Methods: Pregnant mice were continuously infused with Angâ…¡ for 7 days from pc 10 to 17 using the osmotic mini pump. rTM was administered intraperitoneally for 4 days from pc 13 to 16. In the control group, saline was administered instead of rTM during the same period. Blood pressure (BP) was monitored daily. Blood and urine samples were collected before and after rTM or saline injection. On pc 17, the mice were sacrificed to check the fetal growth and the placental status.

Results: Continuous infusion of Ang II induced the symptoms mimicking human PE. Significant elevation of BP was

confirmed from day 3 after starting Ang II infusion. Occurrence of proteinuria on pc 17 was limited to Angâ…¡ infused pregnant mice. Angâ…¡ infusion caused growth restriction to the fetuses. Administration of rTM significantly attenuated all three symptoms of PE.
Discussion: rTM attenuated Ang II-induced PE symptoms in the mouse model. Our findings suggest that rTM could be a novel approach for the tretment of PE.

PRE-EMPT

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Pre-pregnancy and early pregnancy calcium supplementation in women at high risk of pre-eclampsia: a randomized, placebo controlled trial
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Background: Reducing the death toll from hypertensive disorders of pregnancy is a global priority. Low dietary calcium may account for the high prevalence of pre-eclampsia/eclampsia in low-income countries. Calcium supplementation in the second half of pregnancy reduces the severe consequences of pre-eclampsia but the effect of calcium supplementation before and in early pregnancy, when pre-eclampsia is thought to evolve, has not been assessed.
Methods: We conducted a multi-country randomised, double-blinded placebo-controlled trial to determine the effect of calcium supplementation before and in early pregnancy in sites in South Africa, Zimbabwe and Argentina over a six-year period. Participants with previous pre-eclampsia or eclampsia received 500 mg elemental calcium or placebo daily from enrolment before pregnancy until 20 weeks' gestation. All participants received unblinded calcium 1·5g daily after 20 weeks' gestation.
Findings: Baseline data were well matched. Almost half the women became pregnant. Pre-eclampsia was reduced by 20% with calcium (not statistically significant). Pregnancy loss and/or pre-eclampsia was reduced by 18% (borderline significance). Diastolic blood pressure was significantly reduced at both 20 and 32 weeks' gestation. There were no other statistically significant differences.
Interpretation: Reduced pregnancy loss and/or pre-eclampsia, and persistently lower diastolic blood pressure at 32 weeks despite high dose calcium supplementation to all participants from 20 weeks' gestation suggests a persistent effect of calcium supplementation before and in early pregnancy on the genesis of pre-eclampsia. Public health strategies to promote adequate calcium intake may reduce pregnancy loss and/or pre-eclampsia, among many other general health benefits.

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Oral antihypertensive treatment of severe hypertension in pregnancy - a randomized trial of 3 regimens
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INTRODUCTION: Management of severe hypertension in pregnancy requires prompt treatment – most commonly with intravenous medications. This strategy presents significant barriers to care, particularly in low resource environments.
OBJECTIVE: To compare the effectiveness of three oral antihypertensive regimens in pregnant women with severe hypertension.
METHODS: In an open-labeled trial in two hospitals in Nagpur, India, (NCT01912677), pregnant women ≥28 weeks' gestation with sBP ≥160mmHg or dBP ≥110mmHg were randomized to: (1) nifedipine 10mg orally repeated hourly up to 2 additional doses for sBP >155mmHg or dBP >105mmHg, (2) labetalol 200mg orally repeated hourly for 2 additional doses as above, or (3) methyldopa 1000mg as a single dose. The primary outcome was achieving a sBP 120-150mmHg and dBP 70-100mHg at 6h without an adverse outcome or fetal compromise.
RESULTS: 894 women were randomized: nifedipine (n=298), 83.2% achieved primary outcome, (0.7% required additional drugs); labetalol (n=295), 77.3% achieved primary outcome, (3.1% required additional drugs); methyldopa (n=301), 76.4% achieved primary outcome, (18.3% required additional drugs), (NvsMD p=0.04)X^2, (LvsMD p=0.08), X^2, (NvsL p=0.07)X^2. Without use of additional drugs, nifedipine and labetalol were superior to methyldopa, (P<0.001)X^2. Nifedipine was associated with maternal tachycardia, (p<0.001)X^2, persistence of headache,

(p=0.005)X^2, and a greater likelihood of neonatal admission to the NICU, (NvsMD p=0.01)X^2, (LvsMD p=0.6), X^2, (NvsL p=0.06)X^2. $MgSO_4$ use was limited, 11.7%. The eclampsia rate was 0.1%. There were no maternal deaths or ICU admissions. 96% of infants were born alive; 95% of live-born were alive at discharge.
DISCUSSION: Each regimen achieved some success. As a single agent, nifedipine and labetalol were superior to methyldopa. A structured approach of measuring BP and intervention with oral medications in a high risk environment achieved low rates of maternal and neonatal complications despite some differences in BP control across groups. This was achieved with a low rate of $MgSO_4$ utilization.

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Community Level Interventions for Pre-eclampsia (CLIP) in India: a cluster randomised controlled trial
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Background
In India, hypertensive disorders of pregnancy cause approximately 7.1% of maternal deaths. Task-sharing pregnancy hypertension-oriented care to community healthcare providers may protect against adverse pregnancy outcomes.
Objective
To reduce by 20%, one or more of: maternal death/morbidity, stillbirth, or neonatal death/morbidity in the intervention arm.
Methods
The India Community Level Interventions for Pre-eclampsia (CLIP) cluster randomised controlled trial took place in 12 clusters in Belagavi and Bagalkote, Karnataka (NCT01911494). The CLIP intervention (6 clusters) consisted of community engagement, mobile health-guided home-based pregnancy and postpartum care, initiation of life-saving therapies ($MgSO_4$ or methyldopa) and referral to facility, as appropriate. Data were collected by population-based survey based on the Global Network Maternal and Newborn Health Registry. Treatment effect was estimated by multilevel logistic regression, adjusting for baseline cluster- and individual-level characteristics of prognostic significance. A priori defined secondary analyses included evaluation of temporal and dose-dependent treatment effects.
Results
Of 14,777 women recruited (7,833 intervention; 6,944 control), none were lost to follow-up. The primary outcome did not differ between trial arms (1,249 women, 15.85% vs.1,172, 16.88%, respectively; adjusted odds ratio [aOR] 0.93, 95% confidence interval [0.73-1.18], p=0.62). In both arms, an estimated reduction in the odds of primary outcome of 1.0% per quarter was observed (OR= 0.99, 95% CI [0.99-1.00], p=0.02). In intervention clusters, the temporal trend-adjusted outcome rate decreased by 8.0% (aOR 0.92 [0.91-0.95], p<0.001) for each study visit beyond six visits.
Discussion
The CLIP intervention failed to show a difference in maternal and perinatal mortality/morbidity between arms. However, a significant temporal reduction in adverse outcomes was achieved in both trial arms, particularly maternal morbidity; possibly related to data monitoring-based continuous quality improvement. Receipt of more than six CLIP visits was associated with fewer adverse outcomes, suggesting a possible threshold of intervention that must be delivered to achieve positive health outcomes.

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Community Level Interventions for Pre-eclampsia (CLIP) in Pakistan: a cluster randomised controlled trial
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Background
In Pakistan, an important contributor to maternal, fetal, and neonatal mortality is pregnancy hypertension. Its early detection and initial management may be amenable to task-sharing by Lady Health Workers (LHWs).
Objective
To reduce by 20%, one or more of: maternal death/morbidity, stillbirth, or neonatal death/morbidity in the intervention clusters.
Methods
The Pakistan Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised control trial (NCT01911494) recruited pregnant women in 20 union councils (clusters) in Sindh Province. The CLIP intervention (10 clusters) consisted of community engagement and LHW-provided mobile health-guided clinical assessment and initial treatment ($MgSO_4$ or methyldopa, as appropriate), and referral by LHWs to facility for further management. Data were collected by quarterly household survey. Treatment effect was estimated by multi-level logistic regression modeling, adjusting for baseline cluster- and individual-level variables of prognostic significance. A priori defined secondary analyses included evaluation of temporal and dose-dependent treatment effects.
Results
Of 39,444 women recruited (20,264 women intervention, 19,180 control), losses to follow-up were 3·7% and 4·5%, respectively. The primary outcome did not differ between arms (N=5381 women, 26·6% vs. N=4195, 21·9%); adjusted odds ratio (aOR) 1·20, 95% confidence interval (CI) [0·84-1 72]. In both arms, an estimated reduction in the odds of primary outcome of 7.0% per quarter was observed (OR=0.93, 95% CI 0.93,0.94, p<0.001). In the intervention arm, the temporal trend-adjusted primary outcome rate decreased by 8.0% (aOR=0.92 [0.90-0.95], p<0.001) for each CLIP visit beyond three.
Discussion
While there was no difference in the primary outcome in intervention vs. control clusters, outcomes improved over time in all clusters, particularly maternal morbidity; suggesting that quarterly household surveillance served as an intervention. Receipt of more than three CLIP visits was associated with fewer adverse outcomes, suggesting a possible threshold of intervention that must be delivered to achieve positive health outcomes.

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Community Level Interventions for Pre-eclampsia (CLIP) in Mozambique: a cluster randomised controlled trial

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Background
Hypertensive disorders of pregnancy (HDP) contribute to 35.8% of maternal mortality in Mozambique. Community-level early detection and initial management of HDP by agentes polivalentes elementares (APEs) could prevent adverse pregnancy events.
Objective
To reduce by 20%, one or more of: maternal death/morbidity, stillbirth, or neonatal death/morbidity in intervention clusters.
Methods
The Mozambique Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised controlled trial (NCT01911494) recruited pregnant women in 12 administrative posts (clusters) in Maputo and Gaza Provinces. The CLIP intervention (6 clusters) consisted of community engagement, APEs-led mobile health-guided clinical assessment and initial treatment ($MgSO_4$ or methyldopa), and referral to facility, as appropriate. Data were collected in all clusters by six-monthly household surveillance. Treatment effect was estimated by multilevel logistic regression adjusting for baseline cluster- and individual-level factors of prognostic significance. A priori-defined secondary analyses included evaluation of temporal and dose-dependent treatment effects.
Results
Of 15,224 pregnancies (7980 intervention, 7244 control), losses to follow-up were 1.9% and 2.7%, respectively. The primary outcome did not differ between intervention and control clusters (1387, 17.4% vs. 1289, 17.8%; adjusted odds ratio [aOR] 1.34, 95% confidence interval [CI] [0.71-2.51]; p=0.36). In both arms, the odds of primary outcome decreased by an estimated 8.0% every quarter (OR=0.92, 95% CI [0.93-0.94], p<0.001). In intervention clusters, the primary outcome rate decreased by 9.0% (OR=0.91, 95% CI [0.88-0.94], p<0.001) for each CLIP visit beyond three.
Discussion
Overall, the CLIP primary outcome did not differ between arms. However, the rate decreased significantly in both

intervention and control clusters over time, in particular maternal morbidity, raising the possibility that household surveillance may be an effective intervention. More than three CLIP visits was associated with a fewer adverse outcomes (partially mediated by access to care), suggesting a possible threshold of intervention that must be delivered to achieve positive health outcomes.

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The incidence of pregnancy hypertension in the Community Level Interventions for Pre-eclampsia (CLIP) trials - population-level data from Mozambique, Nigeria, India and Pakistan

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Background: Most estimates of pregnancy hypertension incidence in less-developed countries are from hospital-based cross-sectional surveys and are likely too high.
Objective: We aimed to estimate population-based rates in intervention clusters of the CLIP cluster trials (NCT01911494).
Methods: In study regions, all pregnant women were eligible and identified in their homes or local primary health centres (2013-17). In intervention clusters, trained community health care workers (CHWs) provided supplementary hypertension-oriented care that included standardised blood pressure (BP) measurement using the validated CRADLE device. Hypertension was BP≥140/90mmHg (≥2 measurements). Based on gestational age at presentation, hypertension was chronic (<20 weeks) or gestational (≥20 weeks). Pre-eclampsia was gestational hypertension with ≥1+ proteinuria or one/more relevant maternal symptom, sign, or fetal manifestation. This analysis includes women in intervention clusters who were delivered by trial end. Chi-squared was used to compare hypertension rates between countries (p<0.05 significant).
Results: Most women (N=43,189 in 27 intervention clusters) received at least one CHW-measured BP and were delivered by trial end. Pregnancy hypertension incidence was significantly lower in Pakistan (9.3%) than India (10.4%), Mozambique (11.0%), or Nigeria (10.1%) (p<0.007). Most hypertension was diastolic only (46.5% India, 72.6% Pakistan, 61.1% Mozambique, and 63.2% Nigeria). Chronic hypertension was more common in Africa (2.2% Mozambique, 2.6% Nigeria) than South Asia (1.1% India, 1.5% Pakistan) (p=0.001). At first presentation with elevated BP, gestational hypertension was most common, particular in Mozambique (8.3%) compared with India (6.9%), Pakistan (6.5%) or Nigeria (7.1%) (p<0.001); pre-eclampsia was most common in India (3.8%), followed by Nigeria (3.0%), Pakistan (2.4%), Mozambique (2.3%) (p<0.001). Rarely did formerly normotensive women present with eclampsia (1/5410 (0.02%) India, 3/7112 (0.04%) Nigeria).
Discussion: Pregnancy hypertension incidence and type are similar in less- and more-developed settings. Most women present with gestational hypertension which is amenable to surveillance and timed delivery aimed at decreasing mortality and morbidity.

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Proteinuria among women in the CLIP Trials

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Background
The WHO recommends blood pressure (BP) and proteinuria measurement at each antenatal care (ANC) visit, but the value of proteinuria testing in normotensive women has been questioned, especially where dehydration is common.
Objective
We sought to determine prevalence and prognosis of baseline proteinuria in CLIP (Community Level Intervention in Pre-eclampsia, cluster randomised trials, NCT01911494).
Methods
In CLIP intervention clusters, women received enhanced antenatal care by trained community health care providers supported by the Piers-On-the-Move (POM) app. Each assessment included BP measurement (validated CRADLE device). The first and all hypertensive visits included proteinuria dipstick testing (visual). Progression to hypertension and adverse outcomes (not available in Nigeria) were compared by baseline proteinuria (chi-squared, $p<0.05$ significant).
Results
In 27 intervention clusters, 20,804 (64.3%) women received ≥1 POM visit and delivered by trial end (India, 6102; Pakistan, 10,932; Mozambique, 4310; Nigeria, 6999). Baseline proteinuria ≥1+ (assessed in >90%) was <5% (India, 3.8%; Pakistan, 2.9%; Mozambique, 2.3%; Nigeria, 4.1%); most women were normotensive (India, 96.2%; Pakistan, 83.5%; Mozambique, 99.0%; Nigeria, 84.3%). There was no consistent relationship between baseline proteinuria (negative/trace vs. 1+ vs. ≥2+) and complications: (i) progression to hypertension by POM: India (10.5% vs. 13.0% vs. 15.6%;p=0.21), Pakistan (8.0% vs. 9.4% vs. 9.4%;p=0.73), Mozambique (9.6% vs. 6.5% vs. 11.9%;p=0.68), Nigeria (9.7% vs. 10.7% vs. 9.7%;p=0.95); (ii) birth <37wks: India (22.3% vs. 17.2% vs. 24.2%;p=0.44), Pakistan (3.4% vs. 25.6% vs.29.7%;p=0.65), Mozambique (18.2% vs. 17.0% vs. 22.2%;p=0.76); (iii) maternal mortality/morbidity: India (5.5% vs. 5.2% vs. 7.3%;p=0.69), Pakistan (12.0% vs. 20.7% vs. 13.5%;p=0.004), Mozambique (10.0% vs. 17.0% vs. 8.9%;p=0.24); (iv) perinatal mortality: India (4.6% vs. 5.2% vs. 9.2%;p=0.08), Pakistan (8.6% vs. 6.2% vs. 10.8%;p=0.38), Mozambique (5.8% vs. 5.7% vs. 2.2%;p=0.59).
Discussion
With low prevalence of baseline proteinuria and lack of strong relationships with outcomes, these data question current WHO recommendations to routinely assess proteinuria in pregnancy.

Monday October 8, 2018:

Translational research in preeclampsia

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Effect of preventative treatment with placental growth factor-2 on experimental preeclampsia induced by TNF-a in pregnant mice

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Introduction: Placental growth factor (PlGF) is deficient in women with preeclampsia and treatment of experimental preeclampsia (EPE) with parenteral PlGF has been successful in animal models. Abnormal placentation is thought to be the initiating event in the pathogenesis of preeclampsia and this process may be mediated by PlGF.
Objective: To evaluate the effect of preventative treatment with PlGF-2 in pregnant mice with EPE induced by tumour necrosis factor-α (TNF-α) infusion.
Methods: C57/BL6 mice were treated with daily PlGF-2 (100 ng/kg) or control (phosphate buffered saline 100 uL) intraperitoneally from gestational day (gd) 10 onward. Mice were allocated to one of 3 experimental arms: 1) Animals (n = 5 per group) were euthanised on gd13 to assess the effect of PlGF-2 in early pregnancy; 2) Animals (n = 5 per group) had EPE induced by continuous TNF-α (500 ng/kg/day) infusion. These animals had continuous blood pressure (BP) measurement by radiotelemetry device inserted a minimum 10 days prior to timed mating; 3) Animals (n = 3 per group) had EPE induced as above and live placenta magnetic resonance imaging (MRI) in an 11.74 Tesla spectrometer on gd17. Animals in arm 2 and 3 were euthanized at gd17 and blood, urine and tissue samples were collected. Data was analysed with GraphPad Prism 7.
Results: PlGF-2 animals euthanised at gd13 demonstrated increased placenta PlGF ($p = 0.01$) and toll like receptor-3 (TLR-3) ($p = 0.03$) mRNA expression as compared with controls. In animals with EPE there was no difference in BP ($p=0.7$) or proteinuria ($p>0.9$) between control and PLGF-2 treated animals. There was no difference in T2 labyrinthine/junctional zone ratio in mouse placentas imaged ($p = 0.9$).
Discussion: Preventative treatment with PlGF-2 altered expression of PlGF and TLR-3 but did not ameliorate features of EPE or placental perfusion as assessed by live MRI.

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Changes in the reactive species interactome in oocyte donation pregnancies and pre-eclampsia.

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Introduction
Oocyte donation (OD) is an artificial reproductive technique after which the fetus is completely allogenic to the mother. OD pregnancies carry a higher-than-normal risk to develop pre-eclampsia, which is characterized by an angiogenic imbalance, endothelial dysfunction and oxidative stress.
Objective/Hypothesis
We sought to investigate oxidative stress status in OD and pre-eclampsia by the measurement of different elements of the reactive species interactome (RSI). We hypothesized that the RSI is affected by OD and pre-eclampsia.
Methods
Between 2012 and 2016, sera were collected from women with uncomplicated naturally conceived (NC) pregnancies (n=23), uncomplicated OD pregnancies (n=27), NC pregnancies complicated by pre-eclampsia (n=24) and OD pregnancies complicated by preeclampsia (n=5). Indicators for reactive species production such as free thiols, protein-bound nitric oxide (RxNO), nitrite, nitrate, 8-iso-prostaglandin F2a, sulfate, and thiosulfate were measured using a variety of analytical techniques in serum.
Results
Nitrite levels were higher in uncomplicated OD pregnancies compared to NC pregnancies ($p<0.001$) and free thiol levels seem lower in OD compared to NC pregnancies. OD pregnancies complicated by pre-eclampsia resulted in

decreased nitrite levels (p=0.001) and decreased free thiol levels (p<0.001) compared to uncomplicated OD pregnancies. Decreased nitrite (p=0.01) and free thiol levels (p<0.001) were also seen in NC pregnancies complicated by pre-eclampsia compared to uncomplicated NC pregnancies. RxNO levels(p=0.005) and sulfate levels (p=0.001) were increased in NC pregnancies complicated by pre-eclampsia compared to uncomplicated NC pregnancies.
Discussion
OD pregnancies differ from NC pregnancies with respect to the RSI. Changes in the RSI in uncomplicated OD pregnancies suggest a role for perturbations in redox status in the development of pre-eclampsia in OD. Redox differences between pre-eclampsia after OD and pre-eclampsia after NC pregnancy suggest variations in what triggers their initiation and progression. The RSI might represent a therapeutic opportunities to prevent pre-eclampsia in OD pregnancies.

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EGFR and the mitochondria; two parallel pathways regulating sFLT-1 secretion from placenta
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Introduction: Although discovered more than a decade ago, the molecular pathways regulating sFLT-1 release in preeclampsia are still poorly understood. We have discovered the EGFR superhighway and the mitochondria (either via inhibiting the electron transport chain (ETC) or increasing molecules associated with mitochondrial biogenesis) independently regulate sFLT-1 secretion from placenta. The aim of this study was to assess whether targeting both pathways simultaneously additively reduced sFLT-1.
Methods: Isolated primary trophoblast were used for all studies. Metformin is a mitochondrial ETC inhibitor and resveratrol stimulates expression of mitochondrial biogenesis molecules SIRT1, AMPK and PGC1a. We initially assessed their effects on EGFR expression and activation using western blot. Gefitinib is an EGFR inhibitor, PD98059 a MEK-1 inhibitor and AG490 a STAT3 inhibitor (pathways downstream of the EGFR). We assessed their effects on mitochondrial respiration using a seahorse flux analyser. Having identified molecules that were either "EGFR-specific" or "Mitochondrial specific" we subsequently treated primary trophoblast simultaneously with drugs targeting both pathways and measured the effect on sFLT-1 secretion.
Results: Treatment of primary trophoblast with metformin or resveratrol significantly reduced sFLT-1 secretion and increased down-stream mitochondrial biogenesis molecules but had no significant effect on EGFR, pEGFR or downstream adaptor molecules ERK, pERK, STAT-3 or pSTAT-3. Although inhibitors targeting the EGFR super-highway also significantly reduced sFLT-1 secretion, none significantly altered mitochondrial respiration, or ATP production. When we targeted the two pathways simultaneously (combining gefitinib and metformin, gefitinib and resveratrol, metformin and PD980 or metformin and AG490) we found the reduction in sFLT-1 was additive compared to targeting either pathway alone.
Conclusions: Our study identifies EGFR signalling and the mitochondria as two parallel pathways that both regulate sFLT-1 secretion and which, when targeted simultaneously, can additively reduce sFLT-1. These pathways provide new therapeutic targets to reduce excess sFLT-1 secretion in pathological conditions and improve vascular homeostasis.

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Investigating the therapeutic effects of L-Ergothionine as a treatment for pre-eclampsia
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Title: Investigating the therapeutic effects of L-Ergothionine as a treatment for pre-eclampsia
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Introduction: Pre-eclampsia is proposed to result from placental ischemia, exposing the placenta to elevated levels of oxidative stress. L-Ergothioneine is a natural water-soluble compound derived from histidine and is a physiological antioxidant due to its preferential concentration in high oxidative stress organs. L-Ergothioneine has been shown to possess antioxidant, cytoprotective and anti-inflammatory effects, establishing its potential as a treatment for pre-eclampsia.

Objectives: To investigate the therapeutic effects of L-ergothionine as a treatment for pre-eclampsia using the *in vivo* reduced uterine perfusion pressure (RUPP) rat model.
Methods: L-ergothionine (25mg/kg/day) was administered on gestational day 11 (GD11). RUPP was induced by placing silver clips on the abdominal aorta and the ovarian arteries on GD14. Mean arterial blood pressure (MABP) and vascular function were measured in all four groups. Pup and placental weights were also measured. Data is presented using the mean ± SD.
Results: L-ergothionine reduced MABP in the RUPP group compared to RUPP controls (134 mmHg v 143 mmHg). There was a significant reduction in pup weight in RUPP control group compared to sham controls (1.802 ± 0.07 v 2.245 ± 0.06, P>0.0001). L-ergothionine rescued fetal growth restriction in the RUPP group compared with the RUPP control group (2.048 ± 0.09 v 1.802 ± 0.07, P=0.05). Mesenteric arteries from the RUPP control group displayed impaired vasorelaxation, however pre-treatment with L-ergothionine ameliorated this endothelial dysfunction.
Conclusion: Pre-treatment with L-ergothionine in the RUPP model mediated some of the pathophysiological characteristics of pre-eclampsia therefore highlighting its potential as a treatment for pre-eclampsia.

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Seizure-Induced Cognitive Impairment in a Rat Model of Preeclampsia: Effects of Multiple Seizures and Anti-Seizure Treatments

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Introduction
Eclamptic seizures include tonic-clonic convulsions that can be recurrent and cause acute memory deficits and cognitive impairment. While a brief seizure may cause minimal injury, recurrent seizures can impair memory and cognition. In addition, whether preeclampsia (PE) increases the susceptibility to seizure-induced cognitive impairment, or if anti-seizure treatments are protective remains unclear.

Objective/Hypothesis
We tested the hypothesis that multiple seizures would cause greater memory impairment than a single seizure in PE versus normal pregnancy, and compared the protective effects of magnesium sulfate ($MgSO_4$) and diazepam (Dz) on seizure-induced cognitive dysfunction.
Methods
Pregnant (d19-20) Sprague Dawley rats were normal (Preg) or with PE (induced by a high cholesterol diet gestational d7-20). The chemoconvulsant pentylenetetrazol (PTZ; i.p.) was used to compare the effect of one versus multiple tonic-clonic seizures on cognition. Rats either received one PTZ injection (60mg/kg; n=6/group), multiple PTZ injections (5-40mg/kg; n=13/group), or vehicle (CTL; n=7/group). Rats having seizure(s) received $MgSO_4$ (270mg/kg i.p.) or Dz (10mg/kg i.p.) 20 min after PTZ. Short-term memory was tested 24 hours post-seizures using a novel object recognition task, and recognition index calculated: (novel object time)/(total object time). Data are mean±SEM and comparisons made using a Student's t-test.
Results
Preg and PE rats that had multiple seizures had decreased recognition indices compared to CTL (0.49±0.04 vs. 0.69±0.06, $p<0.05$ and 0.46±0.07 vs. 0.70±0.05, $p<0.05$) that was unaffected by $MgSO_4$ or Dz in PE rats (0.49±0.12 and 0.42±0.08, respectively) and Preg rats (0.46±0.08 and 0.51±0.04, respectively). A single seizure did not affect short-term memory in either group.

Discussion
Cognitive function was significantly impaired after multiple seizures in both Preg and PE rats; however, a single seizure did not affect memory function. Neither $MgSO_4$ nor Dz treatment improved cognition after multiple seizures, highlighting the importance of prevention of eclampsia and seizure cessation to maternal cognitive health.

Fetal Programming

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The association of umbilical cord blood vitamin D level with children's arterial stiffness at 7 years of age - HAPO follow up study

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Introduction
We recently reported the effect in utero exposure to maternal hyperglycaemia on children's risk of abnormal glucose tolerance, obesity and higher blood pressure (BP) at 7 years of age among 962 offspring from the Hyperglycemia and Adverse Pregnancy Outcome study (HAPO) study.
Objective
To investigate the association of maternal and umbilical cord vitamin D deficiency with children's cardiometabolic risk at 7 years of age.
Methods
Mothers who had joined the HAPO study, along with their children were assessed 7 years post-delivery for cardio-metabolic risk, which included carotid-femoral pulse wave velocity (cf-PWV). We performed interim analysis after 566 maternal serum at mid-gestation and 673 umbilical cord serum were analyzed for total vitamin D (25-OHD) levels using a liquid chromatography tandem mass spectrometry method which separates the biological inactive 3-epi-25(OH)D3 from 25(OH)D3, an isomer commonly present in infants.
Results
The mean maternal and umbilical cord 25-OHD levels were 58.52±20.68 nmol/L and 41.06±15.04 nmol/L respectively; 38.3% mothers had level below 50 nmol/l (vitamin D deficient). Maternal and umbilical cord 25-OHD significantly varied with the seasons. Umbilical cord, but not maternal, vitamin D level was negatively associated with children's cf-PWV (unstandardized coefficients=-0.005, p=0.003), independent of maternal glucose level at pregnancy, maternal hypertensive status at follow-up and other confounders, such as children's age, sex & height. The association remained significant even adjusting for children's BP (unstandardized coefficients = -0.004, p=0.006).
Discussion
The result suggests that in utero vitamin D deficiency may be an independent factor for children's future vascular risk. Further study is required to explore the association with the children's Vitamin D status and the underlying mechanism.

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Cardiovascular risk factors track from mother to child

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Background: Cardiovascular risk factors can track from mother to child via several pathways: intra-uterine programming, genetic inheritance and shared environmental risk factors after pregnancy. The degree of tracking and to which extend this is influenced by these pathways is unknown.
This study determined the degree of tracking between maternal and offspring micro- and macrovascular cardiovascular risk factors after pregnancy and the extent to which this is influenced by pregnancy complications and shared environmental risk factors.
Methods: We included 5624 mother-offspring pairs from The Generation R Study; an ongoing prospective population-based birth cohort. Information on pregnancy complications (pre-eclampsia, small for gestational age and preterm birth) was obtained through hospital charts. Mother-offspring associations were assessed six years after pregnancy (central retinal arteriolar and venular calibers, blood pressure, left atrial diameter, aortic root diameter, left ventricular mass, fractional shortening and pulse wave velocity) and nine years after pregnancy (blood pressure).
Results: We observed a positive association for all mother-offspring parameters six and nine years after pregnancy (*P*-values <.001). Results were similar when mother-offspring pairs with a previous pregnancy complication were excluded.
Conclusions: Six and nine years after pregnancy, an adverse cardiovascular profile in mothers is strongly associated with an adverse cardiovascular profile in their offspring. Results were not attenuated by environmental exposures or a previous pregnancy complication. This supports the hypothesis that cardiovascular risk factors (micro- and macrovascular) track from mother to child, regardless off the course of pregnancy and may aid in cardiovascular risk stratification.

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Effects of Prenatal Sildenafil Treatment On Long-term Cardiovascular Function In Offspring From Dahl salt-sensitive Rats

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Introduction: Fetal growth restriction (FGR) is associated with increased risk for cardiovascular disorders in later life. Cardiovascular disease is the most common cause of death worldwide. Previous studies report that prenatal sildenafil improves pregnancy outcomes, such as birthweight, in FGR animal models; however, whether sildenafil treatment is protective against long-term cardiovascular disease in these offspring is unknown.
Objective: We hypothesize that prenatal sildenafil reduces blood pressure and endothelial dysfunction in FGR offspring from Dahl salt-sensitive (SS) rats on normal salt intake.
Methods: Sildenafil citrate (60 mg/kg/day) or control gel diet was administered from gestational day 10 until birth. Birthweight and litter size were measured (treated n=10; untreated n=8 dams). Telemetry devices (DSI) were implanted via the femoral artery to measure mean arterial pressure (MAP) from weeks 5-8 in the offspring (treated n=12; untreated n=4). Aortic rings were isolated from 10 week old offspring to assess vascular sensitivity ($logEC_{50}$) to endothelial-dependent (acetylcholine) and -independent (sodium nitroprusside, SNP) vasorelaxation (treated n=10; untreated n=10). Data shown as mean ± S.E.M.
Results: No sex differences were observed in any variables; therefore, data were pooled between males and females. Sildenafil improved birthweight (treated 6.8±0.2; untreated 6.2±0.1 g; p=0.02) without significantly changing viable litter size (treated 9.6±0.9; untreated 7.9±1.0; p=0.23). While MAP at 5 weeks was similar between groups (treated 107±1; untreated 108±2 mmHg; p=0.55), there was a trend towards lower MAP in prenatally treated offspring at 8 weeks (treated 116±1; untreated 120±2 mmHg; p=0.09). Aortas from offspring of treated dams displayed enhanced sensitivity to acetylcholine ($logEC_{50}$: treated -7.4±0.3; untreated -6.6±0.3 mol/L; p=0.03), but not to SNP (treated -8.2±0.3; untreated -7.9±0.2 mol/L; p=0.43).
Discussion: Prenatal sildenafil treatment improves birthweight in a model of FGR. In young adult offspring, there was a trend towards a sex-independent lowering of blood pressure and increased endothelium-dependent relaxation.

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Short and long term maternal and child health outcomes following diagnoses of hypertension during pregnancy: A 16 year linked population data study in NSW Australia.

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Aim: To examine the association between hypertensive disorders: preeclampsia, gestational hypertension, chronic hypertension, superimposed preeclampsia and eclampsia (Hypertensive Disorders of Pregnancy - HDP) on the short and long term health of both mother and baby.
Method: Linked population datasets from birth and death records and subsequent hospital admissions utilising diagnoses and procedures (International Classification of Diseases ICD-10-AM) will be analysed comparing a HDP cohort against a normotensive cohort. These datasets comprise over 1 million births over a 16 year period in Australia. Australian populations are characterised by women from multicultural backgrounds with high rates of refugees and migrant populations, especially from South East Asia and Africa. Associations between HDP and future health will be adjusted for maternal health, pregnancy, birth and socio-economic factors which determine health outcomes to present adjusted odds ratios of events through logistic regression modelling.
Results: Currently under analysis, these results will provide the most comprehensive long term health outcomes to date utilising this robust and proven methodology and it is anticipated that this study will provide a benchmark against which other countries will be able to compare short and long term health for this vulnerable population.
Conclusion: Population incidence will be established, trends over time will be evident, short and long term health associations will be uncovered, benchmarks will be set and new vital information for use by women and clinicians will be manifested. The results of this undertaking will provide increased detailed and unprecedented long term health outcome knowledge in this field.

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Neonatal developmental and behavioral outcomes of immediate delivery versus expectant management in hypertensive disorders of pregnancy: 2-year outcomes of the HYPITAT II trial

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Background: In the management of hypertensive disorders(HD) in preterm pregnancy, maternal benefits of delivery need to be weighed against the neonatal consequences of preterm birth. We report 2-year child outcomes of the HYPITAT-II trial, which compared delivery versus expectant management(EM) in these women.
Objective: To compare effects of delivery versus EM in women with hypertension in late preterm pregnancy on neurodevelopmental and behavioral outcomes in their offspring at two years of age.
Study design: We studied children born in the HYPITAT-II trial, in which 704 women with a HD between 34 and 37 weeks of gestation were randomized to immediate delivery or EM. Participating women were asked to complete the Ages and Stages Questionnaire (ASQ) for developmental outcome and the Child Behavior Checklist (CBCL) for behavioral problems when their toddler was two years old. Outcomes were dichotomized and analyzed by logistic regression analysis.
Results: We approached 545 (77%) randomized women, of whom 344 (64%) participated. In the delivery group, 45/162 (28%) infants had an abnormal ASQ-score compared to 27/148 (18%) in the EM group (difference in percentage 9.6, CI 0.3 to 18.0); p = 0.045. An abnormal CBCL outcome was found in 31/175 (18%) in the delivery group versus 24/166 (15%) in the EM group (difference in percentage 3.2 (CI -4.6 to 11.0). After correction for maternal education, management strategy remained an independent predictor of abnormal ASQ-score (OR 0.48, CI 0.24 -0.96, p=0.03). In multivariable analyses, birth weight, maternal education and management policy were all significantly associated with an abnormal ASQ-score.
*Conclusions:*This study suggests that early delivery in women with late preterm HD results in poorer neurodevelopmental outcome at two years of age, indicating an increased risk of developmental delay compared to EM. This should be considered in the timing of delivery in women with a late preterm HD.

Genetics in preeclampsia

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Epigenetic changes of endothelial progenitor cells in preeclampsia

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Objective: The obstetrical history is an important component of the risk profile of women and their offspring for future cardiovascular diseases (CVD). The pregnancy-specific disease preeclampsia (PE) represents a separate, independent risk factor. Our research shows a diminished function of fetal endothelial progenitor cells (EPCs) in PE pregnancies. The aim of our study was to investigate whether the development of PE leads to changes in DNA methylation of fetal EPCs.

Methods: Endothelial colony-forming cells (ECFCs), a proliferative subgroup of EPCs, were isolated from umbilical cord blood of healthy and PE-affected pregnancies. Subsequently, the genomic methylation pattern of fetal EFCFs was examined and compared using the Illumina Infinium EPIC BeadChip Kit. Furthermore, the genomic methylation pattern of fetal EFCFs from low and advanced cell culture passages were compared to assess if culturing fetal ECFCs leads to changes in global methylation status and therefore cultured ECFCs are subject to “evolutionary” regulation across different passages.
Results: Overall, a differential methylation pattern of fetal ECFCs from PE was detected for a total of 1266 sites and has been assigned to different genes. The online platform Ingenuity Pathway Analysis classified the genes into 25 gene networks. These gene networks mainly affect endothelial health and the cell cycle.
Discussion: An epigenetically modified endothelial precursor may influence both normal morphogenesis and postnatal vascular repair capacity during embryo- and fetogenesis. Considering the potential of cell therapies based on EPCs, further studies on epigenetic modifications due to complicated pregnancies are urgently needed to develop epigenetically-based therapeutics for the prevention and treatment of cardiovascular alterations.

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The CYP1A1 and COMT genetic polymorphisms and the possible modulation on risk parameters in women who had hypertension during pregnancy

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Introduction:
The immunological alterations during pregnancy may contribute to the onset of preeclampsia (PE) and will affect the future cardiovascular risk (FC-risk) in women with previous PE.
Objectives/Hypothesis: Although not clear, beyond being involved in the metabolism of estrogens, *CYP1A1* and *COMT* polymorphisms may have a significant impact on immune response. We studied these polymorphisms in the development of PE and FC-risk.
Methods: We studied a case-control study of 142 pregnant women with normal blood pressure (BP) in pregnancy (NT) and 185 PE; a prospective sub-sample of 138 women of which 90 had PE during pregnancy, 2 to 16 years ago. The *CYP1A1* and *COMT* polymorphisms were evaluated by PCR-RFLP. The anthropometric, demographic, hemodynamic and biochemical parameters (hepatic function, lipid profile) were determined by conventional methods. Statistical analysis were binary logistic regression and comparison of means, consideringsignificant results for P<0,05.
Results: Women *COMT*-HL genotype had increased risk for ≤34 weeks of gestation (WG≤34), adjusted for age at pregnancy (OR=2.40, 95% IC [1.04-5.50], P=0.039]. In the sub-sample, women *CYP1A1*-TT genotype or *COMT*-HL genotype were at increased risk for PE, adjusted for age at pregnancy (*CYP1A1*-TT: OR=7.30, 95% IC [1.31-40.60, P=0.023; *COMT*-HL: OR=2.85 95% IC [1.08-7.54, P=0.034). Women who developed hypertension *CYP1A1*-TT genotype had higher values of apolipoprotein A (P=0.064) comparing with *CYP1A1*-TC+CC genotypes. Further, in this sub-sample, nitrites values were higher for *COMT*-HL genotype than *COMT*-HL+LL genotypes (P=0.007). Considering only risk genotypes, we found that women currently hypertensive and *CYP1A1*-TT, presented systolic(S)BP and diastolic(D)BP higher than NT; and *COMT*-HL had higher values of SBP, DBP, waist circumference, nitrates and lower HDL (P<0.05), comparing with NT.
Discussion: Our results suggested a genetic risk profile associated with *CYP1A1*-TT and *COMT*-HL genotypes for the development of PE and it may modulate the immune adaptation for FC-risk.

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Connections between circulating Argonaute-bound, exosomal and placental miR-210 expression patterns in preeclampsia

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Introduction
Placenta-specific miRNAs play important role in the regulation of pregnancy, and altered miRNA expression is associated with preeclampsia (PE). In PE, the placental dysfunction causes the abnormal release of extracellular miRNAs to the maternal circulation. These are highly stable, being encapsulated inside vesicles (e.g. exosomes) or bound to Argonaute (Ago) proteins. Previously we showed that the hypoxia-sensitive hsa-mir-210 is elevated in exosome fractions in case of PE.
Objective
Our aim was to analyze the expression of miR-210 in placenta, exosome and Ago-bound fractions comparing normal (N) and PE pregnancies. We investigated the Ago-bound/exosomal miRNA ratio and compared the expression profiles of the two fractions to the placental miRNA expression.
Methods
PE and N placenta samples were collected from C-sections and blood samples were drawn from each pregnant in the third trimester. Plasma was separated, and exosomes were isolated by membrane affinity spin column method. Short RNAs were extracted from exosomes and vesicle-free fractions, and total-RNA was isolated from the placenta samples. Expression analysis was carried out by qPCR with specific primers to target and reference miRNAs.
Results
The level of placental miR-210 was significantly higher in affected samples versus the control group. We found that miR-210 was overrepresented in the Ago-bound fractions compared to exosomal fractions in both groups. The ratio of Ago-bound/exosomal miR-210 was relatively higher in PE compared to N group. The placental miR-210 excess in

PE samples could be associated with higher levels of miR-210 in the Ago-fraction.
Discussion
We investigated placental, exosomal and Ago-bound miR-210 expression profile in PE vs N groups. The level of miR-210 was significantly higher in PE placentas, which could be related to the increase of circulating Ago-bound miR-210. In PE, apart from active exosomal secretion, there is also a large-scale passive release of Ago-bound miRNAs.

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MicroRNAs in Maternal Circulation as Predictors of Preeclampsia At Term
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Introduction:
MicroRNAs (miRs) are small RNA molecules involved in the negative regulation of genes, that are highly stable within the circulation. The FLAG study is a prospective collection of over 2000 maternal blood samples at 28 and 36 weeks gestation. 3.9% of FLAG patients developed preeclampsia(PE) after 36 weeks.

Objectives/Hypothesis:
We hypothesise that circulating miRs will be dysregulated in the blood of women preceding diagnosis of PE. Our objective was to screen women at 36 weeks gestation to identify potential biomarkers of PE.

Methods:
A panel of 41 miRs were selected for analysis: 32 were from the placental-specific C19MC cluster and 9 identified as previously associated with PE. A case-control group was selected from the FLAG cohort comprising n=196 controls and n=34 patients destined to develop PE. Whole blood RNA was extracted using PAXgene tubes and a custom qRT-PCR microarray containing 41 miRs and 3 housekeepers used to measure miRs at 36 weeks.

Results:
At 36 weeks gestation, miRs 18a, 1283, 16, 149, 363 and 424 were significantly decreased in mothers destined to develop PE ($p < 0.0001$-0.04). To assess the predictive capacity of miRs, we undertook multivariate logistic regression which identified that miRs 149 and 363 are associated with PE and give the optimum prediction model, with a sensitivity of 45.5% at a specificity of 90%. Assuming the prevalence of PE at 5%, we find a negative predictive value (NPV) of 97%.

Discussion:
Whilst the combined sensitivity of miR149 and 363 is low, the reasonable NPV highlights these miRs as potential contributors to a multi-analyte rule-out test at term which could save valuable time and resources. Moreover, these miRs hold potential for the prediction of PE at earlier gestations (if combined with other analytes), a consideration which will be the focus of future work.

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Association between Tumor Necrosis Factor Alpha (TNF-a) polymorphisms and haplotypes and preeclampsia risk
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Introduction: Preeclampsia is a multi-system disorder of pregnancy characterized by hypertension and proteinuria. Excessive release of pro-inflammatory cytokines, particularly tumour necrosis factor alpha (TNF-α) has been demonstrated to contribute to endothelial activation and default of trophoblasts invasion that result in the clinical symptoms of preeclampsia. Genetic polymorphisms of TNF-α could regulate its production and may play an important role in the pathogenesis of this disease.
Objective/hypothesis: The aim of this study was to evaluate the association of five different TNF-α gene promoter single nucleotide polymorphisms (SNPs), or their haplotype combinations, with the development of preeclampsia.
Methods: This a case-control study conducted on 300 women with PE and 300 age-matched women with normal

pregnancy from Tunisian hospitals. Genotyping of TNF-α -1031T/C, -376G/A, -308G/A, -238G/A, and +488C/T SNPs was performed on DNA extracted from blood samples. TNF-α genotyping was assessed using PCR-restriction fragment-length polymorphism (RFLP) analysis. Statistical analysis was performed using the chi-square test. P values less than 0.01 were considered statistically significant.
Results: Our results demonstrated a higher frequency of the minor allele -1031C ($p < 0.001$) in preeclampsia cases compared to the control group. Also, Haplotype analysis revealed that the haplotype -1031C and -376A (CA) was significantly more frequent in the preeclampsia cases compared to controls. Finally, we found that the major allele G of -308G\A is associated with lower systolic blood pressure while the minor allele is associated with increased diastolic blood pressure.
Discussion: These results demonstrate that TNF-α polymorphisms, in particular -1031C/A and -376 G/A, are significantly associated with preeclampsia. In addition, we found a protective effect of the major allele G of -308 G\A SNP on systolic blood pressure while increased diastolic blood pressure can be found in carriers of the minor allele A.

Immunology

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A Novel NF-kB Inhibitory Peptide-Based Therapeutic for the Management of Preeclampsia

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Introduction: Preeclampsia (PE) is a multifactorial disease in which little progress has been made to develop adequate therapy. One hallmark of this disease is a rise in systemic maternal inflammatory factors, many of which signal through the NF-kB pathway.
Hypothesis: We hypothesize that administration of a novel NF-κB antagonist, ELP-p50i, will attenuate the hypertension and inflammation in the preclinical RUPP model of placental insufficiency.
Methods: Animals were received on GD11 and received the sham or RUPP surgery on GD14 along with drug or vehicle administration. On GD18, carotid catheters were placed for blood pressure measurement on GD19. Aortic ET-1 was measured by qRT-PCR using Taq primers specific for rat ET-1 and normalized to rat β-actin (Thermofisher). Placental TNF-α was measured using a commercial ELISA specific for rat TNF-α (R&D).
Results: RUPP animals had significantly increased blood pressure (122.2$\pm$2.56 mmHg vs 99.3 $\pm$3.83 mmHg, $p<0.01$). ELP-p50i administration significantly reduced the blood pressure in RUPP animals (122.2$\pm$2.56 mmHg vs 110.9$\pm$1.61 mmHg, $p<0.05$). Additionally, there is a trend to increase aortic endothelin-1 expression in RUPP compared to controls (1.4 $\pm$ 0.2 vs 1.16$\pm$0.17 fold change, $p=0.47$, $n=4$), and ELP-p50i treated rats had significantly reduced endothelin-1 expression (1.4 $\pm$ 0.2 vs 0.66 $\pm$0.11 fold change, $p<0.05$). Additionally, placental TNF-α trended upward in RUPP animals compared to normal pregnant (25.3 $\pm$ 1.7 pg/mg vs 21.8 $\pm$ 1.5 pg/mg, $p=0.14$) and this increase in TNF-α was completely abolished by ELP-p50i treatment (25.3 $\pm$ 1.7 pg/mg vs 19.5$\pm$0.8 pg/mg, $p<0.5$).
Discussion: Our data suggest that ELP-p50i is able to attenuate placental ischemia-induced hypertension and correct symptoms such as endothelial dysfunction and increased inflammation, potentially creating a therapeutic option for preeclampsia.

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Immune-driven polyunsaturated fatty acid (PUFA) metabolism in preeclampsia

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Introduction: Placental macrophages regulate villous trophoblast differentiation and activity. Disturbance of this well-balanced immune-regulation and a pro-inflammatory cytokine milieu can lead to dysfunctional placentas and preeclampsia. Cluster of differentiation 74 (CD74) downregulation in placental macrophages leads to altered macrophage-trophoblast interaction, a pro-inflammatory status and is involved in preeclampsia. Oxylipins, metabolites derived from polyunsaturated fatty acids (PUFAs), are implicated in the development of preeclampsia.
Hypothesis: Disturbed pro-inflammatory cytokine milieu activates a dysregulated PUFA metabolism enzyme expression pattern leading to disturbed oxylipin levels that can be detected in circulation of preeclamptic mothers.
Methods: A trophoblast-derived cell line (SGHPL-4) and first trimester villous explants were stimulated by the pro-inflammatory cytokines TNFa, CCL5 and MCP-1. Furthermore, we analyzed placental expression pattern of cytochrome P450 epoxygenases, cyclooxygenases and lipoxygenases by microarray and qRT-PCR from human

cohorts and analyzed serum from preeclamptic and uneventful pregnancies by mass spectrometry.
Results: Microarray studies of preeclamptic placentas revealed a distinguished expression pattern of PUFA metabolism enzymes. Results could be confirmed on two different cohorts (qRT-PCR). Stimulation of SGHPL-4 and villous explants by the pro-inflammatory cytokines TNFa, CCL5 and MCP-1 resulted in similar expression pattern. Oxylipins were dysregulated in the circulation of preeclamptic women compared to uneventful pregnancies atgestational week 28 and week 9-12. Composition of oxylipins at week 9-12 in women that later develop preeclampsia showed a good ROC predictive performance with an AUC=0.8.
Conclusion: The pro-inflammatory cytokine milieu induced by the disturbed macrophage-trophoblast interaction induces a distinguished PUFA metabolism leading to dysregulated oxylipins that can predict preeclampsia before onset of clinical symptoms.

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DECIDUAL INFLAMMATION IN NORMAL AND PREECLAMPTIC PREGNANCIES

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Introduction
Preeclampsia is characterized by reduced trophoblast invasion in the uterine wall decidua, harmful placental inflammation, and elevated systemic inflammation and sFlt-1 levels. Danger sensors like toll-like receptor (TLR)2, TLR4 and the nod-like receptor protein (NLRP)3 inflammasome initiate inflammation. These sensors have been associated with placental inflammation in preeclampsia, and maternal cholesterol and uric acid levels represent relevant activators. We have previously shown that trophoblasts have potent inflammatory properties, but it has not been determined how these sensors affects their communication with maternal immune cells in the decidua.
Objectives
We aimed to investigate cell specific inflammation through TLR2, TLR4 and NLRP3 in decidual trophoblasts and maternal immune cells, and assess the contribution to the harmful placental inflammation in preeclampsia.
Methods
Decidual biopsies obtained from 44 normal and 48 preeclamptic pregnancies during cesarean sections were analyzed by immunohistochemistry for cell markers and TLR2, TLR4, NLRP3 and IL1-β expression. Automated protein quantification was done in MATLAB. Decidual explants and trophoblasts were primed and stimulated with cholesterol crystals in vitro. IL-1β response was quantified by ELISA. Serum total cholesterol, uric acid, sFlt-1 and C-reactive protein (CRP) were measured by enzymatic assays or ELISA.
Results
TLR4, NLRP3 and IL1-β were markedly expressed by both trophoblasts and maternal immune cells in the decidua, while TLR2 was mainly expressed by maternal immune cells. Cholesterol crystals induced IL-1β in trophoblasts. Serum cholesterol levels were elevated in preeclamptic compared to healthy pregnancies, correlating to concentrations of hsCRP and sFlt-1. Quantification of danger sensor protein expression comparing normal and preeclamptic pregnancies will be presented.
Discussion
The expression and function of TLR4 and NLRP3 in trophoblasts and maternal immune cells suggests an inflammatory role in intercellular decidual maternal-fetal communication with potential involvement in preeclampsia.

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Human myometrial T cells at the maternal-fetal interface are tissue-resident memory T cells, which show site-specific adaptation within one tissue.

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Introduction
The uterine myometrium is a unique immune environment, capable of harboring a 'foreign' fetus without eliciting an immune response.

Objective
In this pilot study we aimed to investigate the local presence, adaptation and function of human myometrial CD4+ T cells at the maternal-fetal interface in uncomplicated pregnancy.
Methods
Myometrial biopsies were obtained at caesarean section from placental and incision site. Lymphocytes were isolated through dissection and digestion with collagenase IV. CD4+ T cells were analyzed by flow cytometry or FACS sorted for RNA sequencing with CEL-seq protocol. Suppression assays were performed with FACS sorted uterine Tregs added to 15,000 healthy donor PBMC in different ratios, in 0.1 µg/mL anti-CD3 coated plates.
Results
Flow cytometry revealed that 70-80% of myometrial CD4+ T cells were CD69+ memory cells, suggesting a tissue-resident memory (TRM) phenotype. RNA sequencing confirmed a TRM-like profile in CD69+ cells, with high expression of CD49a, CXCR6, DUSP6, PD-1 and low expression of CD62L, KLF2/3 and S1PR1 compared to blood memory CD4+ T cells. Especially at the placental site, we observed a high expression of negative costimulatory molecules PD-1, TIGIT, Lag3, TIM-3 and CTLA4 and a high percentage of Tregs. Expression was intermediate at the incision site and low in blood. Suppression assays confirmed the suppressive capacity of myometrial Tregs.
Conclusion
Myometrial CD4+ T cells at the maternal-fetal interface are TRM cells with a high expression of negative costimulatory molecules and a high abundance of functional Tregs. The distribution pattern of these immunoregulatory features indicates that T cells may not only adapt to a tissue, but also to specific sites within one tissue, possibly depending on the local micro-environment.

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Lower memory T cell proportions in decidual tissue from pre-eclamptic pregnancies compared to healthy controls
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Previous studies indicate that pregnancy persistently affects memory T lymphocyte populations. However, their function and relevance in fetal-maternal immune tolerance and therewith immune related complications of pregnancy are not known. This study aims to show differences in memory T lymphocyte populations in decidual tissue of pre-eclamptic versus healthy controls.
Decidua basalis and decidua parietalis from placentas from pre-eclamptic (n=6) and healthy uncomplicated (n=13) pregnancies were collected. In the decidual tissue, CD4 effector- (CCR7-), central- (CCR7+), tissue resident- (CD103+), and regulatory (FOXP3+) memory cell (CD45RO+) populations were analyzed using flow cytometry. Comparison was performed between placentas from pre-eclamptic patients and healthy controls using Mann-Whitney U test, $p<0.05$.
The total memory T cell proportion (CD45RO+) of CD4+ T lymphocytes was significantly lower in the decidua parietalis from pre-eclamptic pregnancies compared to decidua parietalis of healthy controls. A trend ($p<0.1$) towards lower T effector memory and lower T central memory cells was observed in decidua basalis and parietalis from pre-eclamptic pregnancies compared to healthy controls. In the decidua basalis from pre-eclamptic patients, significantly lower expression of the activation marker CD69 was observed on all different memory cell subset that were analyzed.
We show that CD4+ memory T lymphocytes at the fetal maternal interface are present at lower levels and have a lower activation status in decidual tissue of pre-eclamptic pregnancies compared to healthy uncomplicated pregnancies. These findings suppose reduced imprinted memory with possible consequences for the current and subsequent pregnancy.

Biomarkers

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Sex and growth specific characteristics of small for gestational age neonates: a prospective cohort study
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INTRODUCTION: Male bearing pregnancies and asymmetric fetal growth are associated with preeclampsia (PE). However, this has not been studied in small for gestational age (SGA) neonates, a group that is also associated with PE.
OBJECTIVE: To provide insight regarding risk factors and differences in neonatal outcome for SGA neonates based on sex and growth symmetry.

METHODS: Data from the Screening for Pregnancy Endpoints (SCOPE) study were used with 5,628 nulliparous participants, of which 633 pregnancies were complicated with SGA and 3,376 women had uncomplicated pregnancies. SGA pregnancies were grouped based on fetal sex (male/female) and growth symmetry [ponderal index below (asymmetric) and above (symmetric) the 10th percentile for gestation]. Association between risk factors for SGA, SGA subgroups and uncomplicated pregnancies were assessed with multinominal analyses.

RESULTS: Of all asymmetric neonates, 24.2% were SGA, while 7.4% of all symmetric neonates were SGA. Of all SGA neonates, 45.8% showed asymmetric growth, while 5.5% of neonates with a customised birthweight >90th percentile (p<0.000) showed asymmetric growth. Asymmetric growth restriction was predominant in males [22.5% vs 18.4%, p<0.000]. Abnormal (>90th percentile) umbilical Doppler resistance index (RI) at 20 weeks' gestation was more common in SGA females (9.6% vs 17.8% p =0.003) but did not differ between symmetric and asymmetric SGA neonates. The presence of abnormal uterine artery Doppler RI at 20 weeks' gestation did not differ between SGA subgroups. In each SGA subgroup PE incidence was increased (28.2% in symmetric SGA, 26.1% in asymmetric SGA, 27.2% in SGA male and 25.3% in SGA female bearing pregnancies) compared to non-SGA pregnancies (4.2%). The incidence of PE did not differ between SGA subgroups.
DISCUSSION: A quarter of asymmetric neonates are SGA. Asymmetric SGA associates with male neonates. In contrast with literature, PE was associated with both symmetric and asymmetric growth in SGA neonates.

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EVALUATION OF THE FULLPIERS MODEL AND PLGF AS PREDICTORS OF ADVERSE OUTCOMES IN WOMEN WITH HYPERTENSIVE DISORDERS OF PREGNANCY

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Introduction - Singling out high-risk patients from the diverse hypertensive disorders of pregnancy (HDP), and not only preeclampsia, is a challenge for clinicians.
Objectives - The aim of the study is to evaluate the performance of the fullPIERS model and the placental growth factor (PlGF) to predict adverse outcomes in women with HDP.
Methods - A prospective cohort study carried out at a teaching hospital in Brazil enrolling pregnant women admitted with a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg from the 20th week of gestation. First 48 hours of admission worst clinical and laboratory data were recorded and adverse maternal outcomes were evaluated up to 14 days. Admission maternal plasma PlGF concentrations were measured.
Results – 351 women were included in the fullPIERS model analysis, 20 (5%) developed one of the combined maternal adverse outcomes. The fullPIERS model had poor outcome discrimination within 48h [AUC 0.639 (95% CI 0.458-0.819)] and 14 days [AUC 0.637 (95% CI 0.491-0.783)]. PlGF analysis included 392 women. PlGF < 5th percentile predicted maternal adverse outcomes within 48h in women with gestation < 35 weeks with negative predictive value (NPV) of 0.98 (0.9-0.99) and AUC ROC of 0.672 (CI 95%0.5-0.9). PlGF had good performance to predict delivery within 14 days in women presenting before 35 weeks, AUC ROC 0.720 (0.64-0.80). PlGF <5th percentile predicted small for gestational age (SGA) newborn with NPV 0.87 (0.75-0.94) and AUC ROC 0.698 (0.60-0.79), in women with gestation < 35 weeks.
Conclusion - The fullPIERS model and PlGF were limited predictors of maternal adverse outcomes in pregnant women with HDP, including preeclampsia, in our sample. PlGF appears to be an additional tool to predict delivery within 14 days and SGA newborn in women before 35 weeks gestation.

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Peripheral maternal haemodynamic adaptation across gestation in hypertensive disorders of pregnancy.

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Introduction: Preeclampsia is characterized by haemodynamic maladaptation but the timing of its onset is controversial.
Objective: To evaluate maternal haemodynamics across pregnancy in hypertensive disorders of pregnancy (HDP) compared to uncomplicated pregnancies.
Study design: Prospective cohort study from 2015-2018 of healthy, nulliparous, singleton-bearing women. Maternal haemodynamic adaptation between 11 and 32 weeks' gestation in pregnancies complicated by HDP: preeclampsia with severe (sPE) and without severe features (nsPE), gestational hypertension (GH) and occasionally hypertensive (OH) were compared uncomplicated pregnancies using mixed-effects linear modelling.
Main outcome measures: Maternal haemodynamics assessed by Uscom BP+ [peripheral and central blood pressure (BP), augmentation index (AIx)] in uncomplicated pregnancies and those complicated by HDP.
Results: Maternal haemodynamics at 11 weeks' were different in all hypertensive groups compared to uncomplicated pregnancies (n=286). When corrected for initial measurement, women who developed sPE (n=12) and nsPE (n=49) had a relative haemodynamic maladaptation by 34 weeks'. Compared to those with uncomplicated pregnancies, preeclamptics showed an additional increase in peripheral systolic BP [SBP; 14.33mmHg, 8.61-20.05 (sPE)], peripheral diastolic BP [DBP; 7.70mmHg, 3.31-12.09 (sPE); 2.58mmHg, 3.31-12.09 (nsPE)], peripheral mean arterial pressure [MAP; 10.60mmHg, 5.75-15.45 (sPE); 3.39mmHg, 0.83-5.96 (nsPE)], peripheral pulse pressure [PP; 6.63mmHg, 2.13-11.13 (sPE)], central SBP [15.83mmHg, 10.43-21.22 (sPE); 2.94mmHg, 0.08-5.80 (nsPE)], central DBP [8.26mmHg, 3.89-12.64 (sPE); 2.46mmHg, 0.15-4.78 (nsPE), central MAP [10.79mmHg, 6.39-15.19 (sPE); 2.62mmHg, 0.29-4.95 (nsPE)], central PP [7.57mmHg, 3.85-11.28 (sPE)] and AIx decreased less (15.48% 6.32-24.65 (sPE); 9.00% (4.15-13.56 (nsPE)]. Haemodynamic adaptation in women who developed GH (n=25) and OH (n=33) was similar to those with uncomplicated pregnancies.
Conclusion: Haemodynamic adaptation in women who develop preeclampsia was altered, while those who develop GH or OH had comparable haemodynamic changes, to those with uncomplicated pregnancies. These data indicate that women with preeclampsia fail to undergo proper cardiovascular adaptation to pregnancy. This occurs as early as the first trimester.

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CREATINE KINASE: AN INDEPENDENT RISK FACTOR FOR HIGH BLOOD PRESSURE DURING PREGNANCY

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Hypertensive disorders in pregnancy not only pose a major burden during pregnancy, but are also associated with an increased risk for hypertension later in life. Plasma creatine kinase (CK) activity is identified in the general population as an independent risk factor for hypertension. We hypothesize that plasma CK activity is similarly associated with blood pressure during pregnancy.
Women who participated in the Amsterdam Born Children and their Development-study were eligible for the current study. The associations between plasma CK activity and blood pressure measurements during pregnancy, and between plasma CK activity and hypertensive disorders in pregnancy (gestational hypertension, HELLP, preeclampsia and eclampsia) were evaluated using multiple linear- and logistic regression models, respectively.
In 3.619 pregnant women, plasma CK activity was significantly associated with all blood pressure outcomes. This was most pronounced for the mean systolic blood pressure with a regression coefficient of 3.48 mmHg (CI 1.67 to 5.28, $p<0.001$) per 1-unit logCK. Concerning the hypertensive disorders in pregnancy we found a significant association between severe gestational hypertension diagnosed before 34 weeks of gestation (OR 9.16, CI 1.32 ; 63.86, $p=0.025$) per 1-unit logCK activity. HELLP and preeclampsia were not significantly associated.
Our data show that high plasma CK activity measured in early pregnancy is an independent risk factor for high blood pressure during pregnancy and is associated with severe gestational hypertension diagnosed before 34 weeks of gestation, while no significant association was found between CK and other hypertensive disorders in pregnancy.

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Detection of predictive makers for preeclampsia using NMR and GC-MS/MS metabolomics

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Introduction
The Birth and Three Generation Cohort Study was initiated by Tohoku Medical Megabank Organization (ToMMo), Tohoku University, Japan. A total of 73 085 participants, spanning 3 generations and including 22 493 pregnant women, have been recruited as of January 18, 2018. This cohort study was designed to establish methods for personalized early prediction of multifactorial diseases using cutting-edge technology and an integrated biobank, with a focus on genetic and environmental interactions.
Objectives
Our aim is to discover early predictors of preeclampsia using nuclear magnetic resonance (NMR) spectroscopy and gas chromatography-tandem mass spectrometry (GC-MS/MS) metabolomics to evaluate maternal plasma samples from the first trimester of pregnancy.
Methods
Plasma samples collected during the first trimester from pregnant women who later developed preeclampsia were obtained from the ToMMo biobank. There were 298 patients who developed preeclampsia, including 45 with early onset and 253 with late onset; these patients were compared with 338 patients with normal pregnancies, randomly selected from the database. We performed NMR and GC-MS/MS to detect circulating metabolites which could be candidates for early predictors of preeclampsia. The present study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of ToMMo.
Results
Using NMR metabolomics, 36 metabolites were identified and quantified from each plasma sample. A total of 5 early-onset and 8 late-onset metabolites had significantly different values between the case- and control groups. On GC-MS/MS analysis, 155 metabolites were quantified satisfactorily; 15 early-onset and 31 late-onset metabolites had statistically significant differences between groups.
Conclusions
We identified several candidate predictors using NMR and GC-MS/MS metabolomics in pregnant women who later developed preeclampsia. These results might bring new insights into the establishment of early-prediction formulae, in combination with additional genetic and epidemiologic information.

Placenta

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Syncytiotrophoblast Derived Human Placental Microvesicles and Exosomes Carry Placental Protein-13 (PP13) and Their Level Is Decreased In Preeclampsia

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BACKGROUND
Extracellular vesicles (EVs) are communicating physio/pathological signals between organs. In preeclampsia (PE) – a life threatening pregnancy complication - there is an elevated shedding of EVs by the placental syncytiotrophoblast (STB-EVs) into the maternal circulation. Different STB-EVs subtypes carries each a large repertoire of proteins and RNAs to signal the maternal organs. Here we set to determine placental protein 13 (PP13) to identify if it is included in the STB-EVs' cargo, whether it is located inside or outside, and if and how it change in PE given that maternal serum PP13 is reduced during the first trimester in patients who subsequently developed PE. Furthermore, PP13 causes expansion of the maternal uterine arteries to accommodate the increase blood flow in pregnancy, induces apoptosis of lymphocytes and enhances cytokines secretion related to immune functions.
METHODS
Placentae were obtained at caesarean section deliveries of 20 PE and 19 controls. The STB-EVs were collected from the maternal side perfusate by the dual placental lobe perfusion, sequential centrifugation and filtration. Three population subtypes were isolated: STB microvesicles (STB-MVs), STB-Exosomes (STB-EXs) and total STB-EVs. Placental origin was assessed by Western blot and size distribution by Nanoparticle Tracking Analysis. PP13 was

quantified by ELISA.
RESULTS
All STB-EVs preparation had placental alkaline phosphatase (PLAP) biomarker. ALIX and CD9 were exclusively expressed in STB-EXs. PP13 was determined for the first time in all three STB-EVs preparations, and was expressed in both their inside and their surface. PP13 was significantly lower in PE compared to control in the total STB-EVs and STB-MVs, but not in STB-EXs.
CONCLUSION
At delivery there is a decreased in PP13 levels in STB-EVs derived from PE. Circulating PP13 is therefore either soluble or associated with STB-EVs, and each may deliver distinct PE associated signals.
FUNDING
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LOSS OF PLACENTAL NR4A2 MAY CONTRIBUTE TO THE PATHOGENEISIS OF PRE-ECLAMPSIA

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INTRODUCTION: Placental dysfunction is a key contributor in the development of pre-eclampsia. Recently, we identified *NR4A2* mRNA to be altered in the maternal circulation in pregnancies complicated by severe, early onset fetal growth restriction and pre-eclampsia (PE).
OBJECTIVE: The current study aimed to determine whether *NR4A2* expression was altered in the human placenta with hypoxic insult and pre-eclampsia.
METHODS: Isolated primary cytotrophoblasts (n=5) and placental explant tissue (n=4) from normal term placentas were cultured under normoxia (8% oxygen) and hypoxia (1% oxygen) for 24 hours. Expression of *NR4A2* was assessed by qPCR. Placental tissue was collected from severe early onset PE (n=49) and gestation matched controls (n=47) to test *NR4A2* mRNA expression. NR4A2 protein was assessed in PE (n=31) and preterm (n=22) placenta by Western blotting. Primary cytotrophoblasts were transfected with *NR4A2* siRNA (n=3) to silence gene expression (under normoxia and hypoxia for 48 hours). sFLT-1 secretion was assessed by ELISA and expression of the sFLT-1 variants (*e15a* and *i13)* and cell survival associated genes by qPCR. Normality (Gaussian distribution) was assessed in each case and appropriate post-hoc analysis was performed.
RESULTS: *NR4A2* mRNA expression was significantly reduced with hypoxia in trophoblast, but not placental explants*.* Additionally, *NR4A2* mRNA expression was significantly reduced in PE placenta. However, there was no difference in NR4A2 protein expression between PE and controls. Silencing *NR4A2* significantly increased anti-angiogenic factor sFLT-1 secretion, but not sFLT-1 mRNA expression. Furthermore, loss of NR4A2 in the trophoblast reduced pro-survival IGF2 gene expression and increased NOX4 (oxidative stress marker) expression.
CONCLUSION: NR4A2 is reduced in the trophoblast with hypoxia and mRNA expression is low in the PE placenta. Signs of placental dysfunction were observed with the silencing of *NR4A2* in the trophoblast and an increase in sFLT-1 secretion suggests potential roles for NR4A2 in the pathogenesis of PE.

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Shedding of the Placental Glycocalyx in Response to Ischemia and Hypoxia

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Introduction: Placental ischemia appears to be a central causative factor in the maternal symptoms of preeclampsia. The maternal/fetal interface in the placenta is covered in a meshwork resembling the endothelial glycocalyx; consisting of proteoglycans like Syndecan-1 (SDC-1). This glycocalyx is essential for preventing immune cell adherence, and shed glycocalyx fragments are pro-inflammatory.
Objective/Hypothesis: We hypothesize that hypoxia/ischemia will cause degradation and shedding of the placental glycocalyx.
Methods: Placental ischemia was studied using the rodent RUPP model, which induces placental ischemia from GD14-19. Acute hypoxia utilized culture BeWo trophoblasts exposed at 8% or 1% oxygen for 24 hours to simulate the normal or ischemic placenta respectively. SDC-1 was measured via western blot in placenta and by commercial ELISA in cell culture.
Results: RUPP rats showed a significant decrease in placental syndecan-1 compared to sham controls (100±33% vs 67±17%, $p<0.05$) In response to acute hypoxia, shedding of SDC-1 by BeWo cells increased significantly

(199±25 pg/ml vs 276±56 pg/ml, p<0.05). This effect was completely blocked by administration of a heparanase inhibitor (199±10pg/ml, p<0.05), as heparanase is a known regulator of extracellular matrix degradation. It has been previously been shown that syndecan shedding can be regulated by MMP expression and oxidative stress. Indeed, in separate experiments, we found a decrease in hypoxia-induced soluble SDC-1 in response to a general MMP inhibitor, actinonin (575±70 pg/ml vs 492±39 pg/ml, p<0.05) or a combination of superoxide scavenger/NADPH oxidase inhibitor (tempol/apocynin) (1021±430 pg/ml vs 666±123 pg/ml, p<0.05). These data suggest that MMPs, heparanase, and ROS regulate hypoxia-induced SDC-1 shedding from trophoblasts.
Discussion: Placental ischemia and acute hypoxia both contribute to trophoblast shedding of the placental glycocalyx in a manner dependent on heparanase, MMP activity, and oxidative stress.

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Effect of placental growth factor on trophoblast integration into endothelial cell networks in the presence of inflammation

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Introduction: Invasion of maternal spiral arterioles by trophoblast cells is fundamental to normal placental development. Abnormal spiral arteriole remodelling is often present in pregnancies affected by preeclampsia. Placental growth factor (PlGF) is produced by the placenta and this molecule is decreased during early pregnancy of women with preeclamptic pregnancy as compared to unaffected women. The influence of PlGF on the processes of early placentation is not known.
Objectives: To observe the effect of supplemental PlGF upon capillary-like uterine endothelial cell networks and a first trimester human trophoblast cell line in the presence or absence of inflammation induced by exogenous tumour necrosis factor-alpha (TNF-α).
Methods: 24-well tissue culture plates were coated with 300 uL of undiluted Matrigel and allowed to gelatinise at 37^{o}C for 30 minutes. Fluorescent labelled uterine microvascular endothelial cells and HTR8/SVNeo cells were co-cultured (1 X 10^{5} per well) for 20 hours treated with PlGF (10 ng/mL) and /or TNF-α (0.5 ng/mL). Images were captured by fluorescence microscopy and analysed using ImageJ. Experiments were repeated 8 times, data was analysed using SPSS v24.
Results: TNF alpha reduced trophoblast cell integration into endothelial networks (Control vs TNF-α $p = 0.006$) but this was not ameliorated by addition of PlGF (TNF-α vs TNF-α + PlGF $p > 0.9$). Furthermore, PlGF supplementation itself did not improve cell integration (Control vs PlGF $p = 0.2$).
Discussion: PlGF not improve trophoblast cell integration into endothelial cell networks nor reverse the inhibitory effect of TNF-α.

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sFlt-1 leads to severe changes in placental differentiation and maternal and fetal vessel formation in transgenic sFlt-1 preeclampsia / IUGR mouse models

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Introduction: The anti-angiogenic factor sFlt-1 is the main candidate in the progression of preeclampsia, a disease which causes placental dysfunctions often leading to IUGR. Mostly is known about the impairment of the endothelial cell function by sFlt-1, but how sFlt-1 leads to IUGR and affects the placenta and fetus is currently unknown as well as therapeutic agents against such diseases are missing. **Objectives:** Therefore we have established two transgenic, inducible sFlt-1 mouse models: (1) maternal ubiquitous (sFlt-1/rtTA mice) and (2) placental (sFlt-1/tTA/TpbpaCre mice) overexpression of human sFlt-1. We hypothesize that sFlt-1 is involved in the development of IUGR by influencing placental development and function and is therefore a potential candidate for intervention strategies.
Material and Methods: We examined the effects of sFlt-1 on placental morphology and function at 18.5 dpc with morphometric and immunohistochemical analyses and transcript expression of placental marker genes, nutrient

transporters and proteomic analyses.
Results: Ubiquitous overexpression of sFlt-1 led to IUGR of the fetuses as shown by reduced fetal weights and signs of retardation. In addition, we observed a severely impaired placental phenotype shown by enlarged maternal blood sinusoids, a reduced number of fetal vessels and an inadequate placental differentiation of the labyrinth. Glucose, fatty acid and amino acid transport seem to be negatively affected. Preliminary results of the placental overexpression of sFlt-1 revealed while expressing lower levels of sFlt-1 also IUGR.
Conclusion: We assume that sFlt-1 has an inhibitory effect on placental differentiation, especially on fetal vessel development. A possible reactive response could be an increase in maternal blood flow promoting dilatation of the maternal sinusoids to fulfil the nutrient requirements of the fetus. This ultimately resulted in an uteroplacental insufficiency leading to IUGR. Thus, we speculate that the alterations triggered by increased anti-angiogenesis upon sFlt-1 strongly may affect fetal outcome and programming.

Young Investigators Awards

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Dysregulated circulating microRNAs in preeclampsia: The role of miR-574-5p and miR-1972 in endothelial dysfunction

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Introduction: MicroRNAs are small non-coding RNAs responsible for post-transcriptional regulation of gene expression. MicroRNAs might be involved in the pathogenesis of endothelial cell dysfunction of preeclampsia.
Objective: Compare circulating microRNA concentrations in early-onset preeclampsia with healthy pregnancy. Subsequently determine if the differentially expressed microRNAs contribute to endothelial cell dysfunction *in vitro.*
Methods: Total RNA was isolated from plasma EDTA samples of early-onset preeclamptic patients (n=10) and gestational age-matched healthy pregnant women (n=10). MicroRNA expression was measured by miRNA 3.1 arrays (Affymetrix) and validated by RT-RT-PCR. Subsequently, human umbilical vein endothelial cells (HUVEC) were transfected (lipofectamine RNAiMAX), with microRNA mimics (Invitrogen) of the 3 most significantly upregulated microRNAs in preeclampsia. Tube formation, wound healing, and proliferation assays were performed to study endothelial cell function. Microarray (Affymetrix) on pooled RNA samples of transfected HUVEC was done and validated by RT-RT-PCR.
Results: 41 microRNAs were differentially expressed ($p < 0.01$, fold change >1.2 or <-1.2) in preeclamptic women compared to healthy pregnant women. The top 3 upregulated microRNAs were miR-1972, miR-574-5p and miR-4792-3p; the top 3 downregulated microRNAs were miR-548a-3p, miR-874 and miR-451. Transfection of HUVEC with the miR-574-5p mimic decreased the wound healing capacity after 12 h (66%), and reduced proliferation of HUVEC (32%); transfection with the miR-1972 mimic reduced the tube formation capacity (number of loops formed decreased 19%). Using these assays no effects of the miR-4793-3p mimic on endothelial cell function were found. Array and RT-RT-PCR data revealed that the miR-574-5p mimic significantly decreased the expression of the proliferation marker MKI67.
Discussion: Differentially expressed microRNAs during preeclampsia might affect endothelial cell function. The negative effects of the microRNA mimics on proliferation and tube formation might indicate decreased proliferation and angiogenesis capacity of endothelial cells during preeclampsia. These microRNAs thus might be key modulators of endothelial dysfunction during preeclampsia.

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Molecular and functional memory in decidual NK cells of parous women

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Introduction: Natural killer (NK) cells are abundant in the human decidua. These decidual NKs (dNK) produce cytokines, growth and angiogenic factors beneficial for the development of the placental bed. Preeclampsia and several of the “Great Obstetrical Syndromes” with a basis of poor placental development, are associated with first pregnancies. Thus, we investigated differences in dNKs in pregnancies of primigravid vs parous women.
Hypothesis: Human dNK cells remember pregnancy, thus better supporting subsequent pregnancies.
Methods: dNKs isolated from elective pregnancy terminations of primigravid and parous women (450 samples)

were characterized by assays including FACs, RNA-seq and epigenetic analysis (ATAC-seq, CHIP-seq) followed by angiogenic and growth factor functional experiments. Endometrial NK cells from menstrual blood were also tested before and following pregnancies.
Results: We discovered a dNK population unique to pregnancies of parous women, possessing a novel transcriptome and epigenetic signature, characterized with high expression levels of the receptors NKG2C and LILRB1. Activation of these receptors leads to increased production per cell and secretion of IFNγ and VEGFa, the latter found to support vascular sprouting and trophoblast-tumor growth. Higher expression of these receptors was found on endometrial NK cells following first pregnancy.
Discussion: We propose that this population termed as Pregnancy Trained decidual NK cells (PTdNKs) represents NK "memory" of pregnancy. We further suggest that the precursors of PTdNKs are found in the endometrium. These findings lend molecular and functional support for the observation that pregnancy is more robust in parous women. Our study offers an explanation of first pregnancy as a risk factor for development of preeclampsia. PTdNKs may prove useful in understanding and treating disorders of poor placentation.

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Retinoic Acid down regulates sFlt1 in decidual stromal cells independent of decidualization. Implications to Preeclampsia

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Introduction: Retinoic acid (RA) plays a vital role during pre- and early pregnancy stages at the maternal-fetal interface (decidua). We recently showed that RA levels are reduced in the decidua of women with preeclampsia (PE). This finding, combined with the knowledge that PE decidual stromal cells (DSC) secrete elevated levels of the anti-angiogenic factor sFlt1 and that the promoter of this protein has a putative RA binding site, suggests the possibility that RA plays a direct role in regulating sFlt1 expression in DSC. This study was to determine the effects of RA on sFlt1 production in DSC. The relationship of these effects to DSC decidualization, known to be defective in PE, was also investigated.

Methods: Primary DSCs (n=6 in each group, normotensive (NT) and PE) were treated with 0.1μM of RA, 1μM BMS493 (pan RA antagonist) or 0.5mM cAMP (to induce decidualization) for 12 days. sFLT1 and PRL levels were determined by using both qPCR and ELISA. Group means were analyzed by Mann-Whitney U test. $p \leq 0.05$ is considered significant.
Results: RA treatment of NT-DSCs and PE-DSCs inhibited sFlt1 production to 44±24% and 24±13% of controls but did not affect DSC decidualization as quantified by prolactin (PRL) secretion. Independent of RA, cAMP-mediated decidualization reduced sFlt1 and increased PRL levels in NT-DSC but only moderately in PE-DSC. BMS493 blocked the effects of RA and, by itself, induced upregulation of sFlt1. Studies using decidualization defective stromal cells confirmed that reduction of sFlt1 by RA is independent of decidualization.
Conclusion: RA downregulates sFlt1 production in DSCs independent of decidualization. PE-DSCs are significantly more responsive to sFlt1 inhibition by RA than are NT-DSC. Our finding of reduced RA levels in PE decidua, combined with studies by us and others that PE women show defective decidualization, may help explain elevated sFlt1 expression in maternal PE decidua.

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Risk of cardiovascular mortality in women with a history of Hypertensive Pregnancy Disorders: a nationwide cohort study

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Introduction: Hypertensive pregnancy disorders (HPD) are associated with cardiovascular disease (CVD) later in life. Since hypertension in pregnancy occurs at a relatively young age this may signal an opportunity for preventive measure for CVD at a relative early age. This study investigated the relationship between HPD and cardiovascular mortality in a large national cohort.
Methods: Women who gave birth during 1995 - 2015 (registered in the Dutch National Birth Registry) were linked with the National Death Registry. The risk of cardiovascular mortality (CVM) after HPD was analyzed prospectively in two different cohorts: Women with a history of HDP in one or more pregnancies and HDP in the first pregnancy of the women. Cox-regression models with survival curves were executed.

Results: Of 1,625,246 parous women 21.9% had a history of HDP. Both gestational hypertension (GH; 18.1%) and preeclampsia (PE; 3.8%) were associated with a 2 - 3 times higher CVM risk compared to women without a history of HPD.
Similar results were found in the cohort of 1,243,890 women whose first nulliparous pregnancy was analyzed. Women with HDP, delivery <37weeks and IUGR had a 5-6-fold higher CVM-risk and women with HDP with a diastolic blood pressure> 110mmHg had a 4.5-fold higher CVM-risk. Women were followed for a mean time of 10.4 years and died at a mean age of 40 years old.
Conclusion: Women with a history of HDP have a 2-3-fold times higher CVM risk. Cardiovascular mortality risk is present at a relatively young age (<50 years). This accentuates the need of development of a cardiovascular management program which is designed to follow-up women directly after the index pregnancy and trace and treat women with cardiovascular disease.

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Placental growth factor to Assess and diagnose hypeRtensive pRegnant wOmen: a stepped wedge randomised controlled trial (PARROT)
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Introduction
Angiogenic factor measurements have shown potential for assisting in the diagnosis of pre-eclampsia in prospective cohort studies, but their diagnostic ability and clinical impact when revealed to clinicians remains uncertain.
Hypothesis
In women presenting with suspected pre-eclampsia, use of placental growth factor (PlGF) testing decreases time to clinician-recognised diagnosis of pre-eclampsia (primary outcome) and decreases maternal and perinatal morbidity, and has an impact on health resource use (secondary outcomes).

Methods
Design: Multi-centre, pragmatic, stepped-wedge cluster randomised controlled trial. Setting: Eleven UK maternity units (size range 3000-9000 deliveries per annum). Intervention: PlGF measurement with result revealed to clinical team and management guidance. Randomisation: Hospitals were randomly allocated to the order in which the intervention was implemented. Population: Women who presented to maternity services with suspected pre-eclampsia between 20+0 and 36+6 weeks' gestation, providing individual-level consent.

Results
Between June 2016 and October 2017, 1023 women with suspected pre-eclampsia were recruited. The median time to diagnosis of pre-eclampsia was from 4.1 days (usual care) to 1.9 days with PlGF testing (time ratios 0.39 (95% CI 0.17-0.91) by parametric survival analysis). There was a reduction in maternal severe adverse outcomes (as defined in the fullPIERS consensus) from 5.4% (concealed PlGF group) to 3.8% (revealed PlGF group) adjusted OR 0.32 (95% CI 0.11-0.96) with no evidence of a significant difference in perinatal adverse outcomes.

Discussion
PlGF testing has been shown to be acceptable and clinically useful in substantially reducing the time to clinical recognition of pre-eclampsia. Where PlGF is implemented there is a reduction in maternal adverse outcomes, consistent with targeted enhanced surveillance as recommended in the trial management guidance for clinicians. Adoption of PlGF testing in women with suspected pre-eclampsia is supported by the results of this study.

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Maternal lipid profile in early pregnancy and the link with blood pressure and pregnancy complications
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Introduction: An atherogenic lipid profile is a risk factor for atherosclerosis and consequently for stroke and cardiovascular disease (CVD). An atherogenic lipid profile can cause endothelial dysfunction and consequently higher blood pressure (BP). Placentas of women with a gestational hypertensive disorder (GHD) are histologically

comparable to an early stage of atherosclerosis.
Objective: To determine the association between maternal lipid profile in early pregnancy, GHD and BP throughout pregnancy and six and nine years after pregnancy.
Methods: We included 5692 women from The Generation R Study; an ongoing population-based prospective birth cohort. 218 (4.1%) women developed gestational hypertension (GH) and 139 (2.6%) women developed pre-eclampsia (PE). Maternal lipid levels included total-cholesterol, triglycerides and HDL-c, and were measured in early pregnancy (median 13.4 weeks of gestation). LDL-c, remnant cholesterol and non-HDL-c were calculated. Systolic and diastolic BP were measured in early, mid- and late pregnancy, and six and nine years after pregnancy.
Results: In the total population, total-cholesterol, triglycerides, LDL-c, remnant cholesterol and non-HDL-c were positively associated with BP in early, mid- and late pregnancy, six and nine years after pregnancy. Women with PE had higher levels of triglycerides and remnant cholesterol in early pregnancy compared to those with a normotensive pregnancy. Maternal lipid levels in early pregnancy were not associated with GH.
Discussion: An atherogenic lipid profile in pregnancy is positively associated with BP throughout pregnancy, and six and nine years after pregnancy. In particular triglycerides are important for the risk for PE. Lipid levels in early pregnancy might help to identify women at risk for not only PE, but also future hypertension and consequently initiate early prevention of future CVD.

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Life style interventions

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Association between maternal age and adverse outcomes in pre-eclampsia
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Introduction: Studies have reported that women at more advanced maternal age are associated with a higher risk of developing pre-eclampsia and other pregnancy-related complications. However, fewer studies have explored the association of maternal age of women diagnosed with pre-eclampsia, with demographic characteristics, management and outcomes.
Objective: To examine pregnancy characteristics associated with maternal age for women admitted with pre-eclampsia and to compare the odds of increasing adverse maternal and perinatal outcomes with increasing age.
Methods: In total, 2427 women admitted with pre-eclampsia from 2003 to 2016 from tertiary hospitals in Canada, United Kingdom, Finland and USA were used for this study. Pregnancy characteristics were compared between women of 6 age groups: (i) < 21 years old, (ii) 21-24 (iii) 25-29 (iv) 30-34 (v)35-39 and (vi)40 years old and above. Odds ratios for developing adverse maternal and perinatal outcomes were calculated for increasing maternal age.**Results:** Most women admitted with pre-eclampsia were between 30 to 34 years old. The gestational age at disease onset and blood pressure appeared to increase, while the prevalence of smoking decreased, as maternal age increased. Women at the extreme age groups (< 21 years or ≥ 40 years) were more likely to be multiparous. Similarly, the rate of antihypertensive medications use appeared to be higher for the extreme age groups than for women between 29 to 39 years old. Women aged ≥ 40 years were more likely to have multiple pregnancy than all other groups. There were no significant differences in the odds of experiencing an adverse maternal or perinatal outcome between different maternal age groups.
Discussion: Increasing maternal age was not associated with increased risk of adverse maternal or perinatal health outcomes for women admitted with pre-eclampsia. However, this study supports findings that maternal age is more strongly associated with late onset than early onset pre-eclampsia.

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The P4 study: Micronutrient intake in women 6 months after hypertensive versus normotensive pregnancy
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Introduction: Hypertensive disorders and poor dietary quality are associated with increased long-term risk of cardiovascular and metabolic disease. Energy intake patterns after hypertensive (HP) versus normotensive pregnancy (NP) may provide insight into these risk associations and their mechanisms.
Objective/hypothesis: Assess diet quality as measured by micronutrient and macronutrient intake six months after NP versus HP (either preeclampsia or gestational hypertension).
Methods: Prospective sub-study of the P4 (Postpartum, Physiology, Psychology and Paediatrics) study. Women were studied 6 months after NP versus HP. Energy intake (EI) was measured using a self-reported, three-day food diary and FoodWorks™ to calculate macronutrient and micronutrient intake.
Results: 74 women (60 NP, 14 HP) had complete, analysable 3-day food diaries 6 months postpartum. Maternal age (32 NP, 31 HP) was similar, however less (4/14; 29%) of the HP group were still breastfeeding (50/60; 83% of NP, p<0.001). Mean BMI was higher postpartum in HP (29 ± 8 versus 24 ± 4, p =0.02). Total average EI was 17% lower in HP (7909kJ versus 9534kJ NP, p = 0.02). Macronutrient intake (carbohydrate, fat and protein) was similar between groups. However, intake of several important micronutrients was significantly lower after HP, even allowing for the lower total EI, including Vitamin A (43% lower), riboflavin (36% lower), magnesium (34%), calcium (29%), iodine (29%) and phosphorus (24%). Women breastfeeding at 6 months (both after NP and HP, n=54) had higher carbohydrate and fat (but not protein) intake compared to women not breastfeeding (n=20), and also increased intake of Vitamin A, riboflavin, magnesium and iron. However, breastfeeding women also had higher EI, with their increased macronutrient and micronutrient intake approximately in proportion to their overall EI versus women not breastfeeding.
Discussion: Six months postpartum, women with previous HP have significantly lower reported micronutrient intake compared to NP, possibly reflecting poorer diet quality.

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Beneficial Effects of Exercise Training on the uterine artery and cardiometabolic profile in a Mouse Model of preeclampsia

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Background: The renin-angiotensin system (RAS) is involved in systemic regulation of cardiovascular homeostasis and contributes to maternal adaptations during pregnancy. The RAS components are expressed in several tissues which contribute to systemic and local RAS effects. Interestingly, we have reported a shift in the balance of local components of the angiotensin-(1-7) axis compared to those of angiotensin-II favoring the latter in the placenta and aorta in a preeclampsia mouse model, mice overexpressing human renin and angiotensinogen (R**+**A**+**). This could contribute in these tissues to exaggerated angiotensin-II effects, such as vasoconstriction, which has been associated with preeclampsia. Also, exercise training (ExT) prevented preeclampsia features, such as hypertension and proteinuria, in this model, which was associated with a normalization of placental RAS components.
Objective/hypothesis: Changes in blood vessels reported in the aorta may also lead to improved uterine artery function which may contribute to the improved fetal growth observed with ExT. As ExT can reduce adiposity, our hypothesis is that ExT modulates adipose tissue function and contributes to the prevention of preeclampsia in R**+**A**+** mice.

Method: Female R**+**A**+** mice and controls had access to a running wheel or remained sedentary during 4 weeks prior to and throughout gestation. Uterine artery velocity was assessed by Doppler (Vevo 2100) and adipokines using the Adipokine Array™.

Results: Total fat mass was reduced 33% ($p<0,05$) independently of genotype before and at the end of gestation. R+A+ mice had reduced uterine artery blood flow ($p<0,05$) while ExT increased blood flow ($p<0,001$) without any changes in resistance or pulsatility index. ExT also reduced circulating leptin ($p<0,05$) and increased VEGF ($p<0,05$) independently of genotype.
Discussion: ExT before and during pregnancy may promote healthier adipose tissue function through modulation of the adipokine profile and improve uterine artery blood flow. This may contribute to the beneficial effects of ExT on preeclampsia.

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Altered composition of the gut microbiota in women who develop hypertensive disorders of pregnancy

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Introduction: Metabolites released by the gut microbiota affect host physiology. Hypertension is associated with altered composition of the gut microbiota. In early pregnancy, the abundance of bacteria producing the short-chain fatty acid butyrate, is negatively correlated with blood pressure in the mother. Butyrate may affect blood pressure through affecting GPR41 and 43 signalling. It is unclear if gut microbiota composition is altered in women who develop hypertensive disorders of pregnancy (HDP).
Objective: To compare the composition of the gut microbiota at 28 weeks gestation between women who do and do not develop HDP later in pregnancy.
Methods: Gut microbiota composition was assessed by 16S rRNA sequencing in faecal samples obtained from participants in the Study of Probiotics IN gestational diabetes (SPRING) RCT at 28 weeks gestation. In SPRING, women were randomised to a probiotics or placebo intervention from 16 weeks gestation. Gut microbiota composition was assessed using the QIIME and Calypso software suites. The composition was compared between women with future HDP (N=32) and those who remained normotensive (N=182).
Results: Rates of HDP and overall gut microbiota composition were similar between women randomised to probiotics (7.1%, N=15) and placebo (8.0%, N=17; P=0.85) and the treatment groups were therefore pooled. At 28 weeks gestation, the women with future HDP already had significantly higher systolic and diastolic blood pressures than those who remained normotensive. Women with future HDP had higher abundance of *Collinsella aerofasciens*, *Ruminococcus gnavus*, *Blautia producta* and *Bifidobacterium longum*. They had lower abundance of *Faecalibacterium prausnitzii*, *Coprococcus eutactus* and *Roseburia faecis*, which are all known butyrate producers.
Discussion: The gut microbiota of women with future HDP has lower abundance of butyrate-producing bacteria at 28 weeks gestation prior to the development of overt hypertension. This may suggest that lower abundance of short-chain fatty acid producers predisposes to the development of HDP.

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Blood pressure of 12-years-in children born after foetal growth restriction due to hypertensive disorders of pregnancy; relation to neonatal, child, and maternal characteristics.

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Background: Children born from pregnancies that were complicated by hypertensive disorders of pregnancy (HDP, i.e. pre-eclampsia or HELLP syndrome) are at risk for elevated systolic and diastolic blood pressure (SBP/DBP) in childhood.
Aims: To examine which neonatal, child and maternal characteristics are associated with SBP/DBP.
Study design: Prospective cohort.
Subjects: 12-years-old preterm and growth restricted children born to women with severe early-onset HDP.
Outcome measures: SBP/DBP standard deviation scores (SDS), corrected for age, gender and height.
Results: 92 of the 174 mother-child pairs participated at age 12 years (mean gestational age 32 weeks, range 27 to 38 weeks, mean birth weight ratio (BWR)0.68, range 0.33 to 0.99). Maternal BMI at child age 12 was 26.4 ± 4.8 kg/m^2. Maternal hypertension at child age 12 was reported by 32% of the women.
Mean child SBP SDS was 0.70 ± 0.81 and mean child DBP SDS was 0.14 ± 0.78. SBP SDS was associated with very preterm birth (B = .41, 95% CI .08 to .75, beta 0.28, p =.015), with child BMI SDS (B = .15, 95% CI .01 to .30, beta .25, p = .042), and current but not pre-pregnancy maternal BMI ≥ 25 kg/m^2 (B = .38, 95% CI .05 to .72, beta .25, p =.026). DBP SDS was associated with current maternal BMI ≥ 25 kg/m^2 (B = .54, 95% CI .21 to .88, beta .35, p .002). BWR nor maternal hypertension was associated with blood pressure.
Conclusions: In 12-years old children born to women with HDP, higher blood pressure values were associated with very preterm birth, child BMI, and current maternal BMI ≥ 25 kg/m^2. BWR was not associated with boodpressure. Life style adaptations may benefit long term cardio vascular health in mother and child.

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Expectant management of severe preeclampsia in a developing country: maternal outcomes and perinatal survival

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BACKGROUND: Management of severe preeclampsia which develops prior to 34 still debatable. Immediate delivery leads to high neonatal mortality and morbidity due to prematurity, conversely expectant management may potentially increase maternal morbidity and mortality. **O**bjective of this study was to determine maternal outcomes and perinatal survival achieved with expectant management in patients presenting with preeclampsia <34 weeks.

STUDY DESIGN: A retrospective cohort analysis of outcome in patients with severe preeclampsia in a tertiary hospital in Indonesia during 3 years: 165 patients (178 fetuses) managed expectantly were studied. Neonatal outcomes (birth weight, APGAR score, fetal growth restriction (FGR), intrauterine fetal death (IUFD), early neonatal death, and maternal complications (HELLP syndrome, pulmonary edema, eclampsia, renal insufficiency, and placental abruption) were registered.

RESULTS: 25 patients had a preeclampsia disease onset <28 weeks, 72 patients onset 28 0/7 - 30 6/7 weeks and 68 patients onset 31 0/7 -33 6/7 weeks; 13 patients had twins. Mean days of prolongation was 9.3 days (range 2-64). Overall neonatal survival was 64,6%. Mean birth weight was 1323.08 ± 383.55 gram, 23,59% of the neonates had a birth weight <10th centile. IUFD ocured in 7.9% of pregnancies, and 25.3% of the remaining babies died during early neonatal period. There were no neonatal survivors in those with a GA <26 weeks. At 26 to 27 6/7 weeks GA, 38.5% offspring survived. Regarding maternal outcome, 7.3% of the patients developed pulmonary edema, 5.5% HELLP syndrome, 0.6% renal insufficiency and 0.6% placental abruption. In this patient cohort, none of the patients developed eclampsia, whereas one patient died post-partum due to stroke emboli.
CONCLUSION: Neonatal outcome in preterm severe preeclampsia depends mainly on GA at onset of preeclampsia and GA at delivery. Expectant management of preeclampsia presenting at less <28 weeks is not recommended in a developing country with limited neonatal resources.

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Use Magnesium sulfate (MgSO4) in low resource setting: A case narrative of two counties in Kenya

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Introduction

Hypertension in pregnancy, particularly pre-eclampsia/eclampsia (PE/E) is a major cause of maternal morbidity and mortality in low income settings. $MgSO_4$ is used extensively for prevention of eclamptic seizures. Appropriate administration of $MgSO_4$ to manage pre-eclampsia or eclampsia is critically important in reducing maternal and neonatal complications.

Objective

To explore health systems challenges to the use $MgSO_4$ in two counties in Kenya.

Methods

We conducted 60 in-depth interviews with providers at various levels of health care on their perceptions, knowledge and practice on $MgSO_4$ in prevention and management of eclampsia. Respondents were purposefully selected in consultation with respective county health managers. The interviews were conducted in Kiswahili or English, transcribed, translated and analyzed with NVIVO 10.

Results

Although respondents describe $MgS0_4$ as being widely available at the national stores, one county reported un-interrupted supply while the other faced periodic stock outs. Both counties cite challenges in accountability and governance in health care management affecting procurement and supply process as factor that influence $MgS0_4$ use. Most providers in hospitals are aware of the recommended $MgS0_4$ dosages and have the necessary skills and knowledge, but those at health centers often lack the knowledge, skills and confidence to administer the drug. Provider training, accessibility and visibility of policy guidelines, operational level protocols and job aids at primary health care facilities affect providers' knowledge, and practice on use of $MgS0_4$. Severe pre-eclampsia or eclampsia patient caseloads at different levels of health facilities also seem to influence providers' skills and practice its use, hence the quality of care.

Discussion

There is a need to strengthen capacity for improved coordination between national and county governments to ensure adequate supply of essential PE/E management commodities. Building confidence through training and mentorship of primary level providers to effectively use $MgSO_4$ in PE/E prevention and management.

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Vitamin D modulates the inflammatory response in T cell subsets from pregnant women with preeclampsia

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Introduction: Preeclampsia (PE) is a specific pregnancy syndrome characterized by an imbalance between the inflammatory T cell (Th1 and Th17) and the anti-inflammatory (Th2 and Treg) profiles. It seems to be dependent on the deficiency of regulatory factors such as vitamin D (VD), which exerts modulatory effects on cells of the adaptive immune system, especially T cells.

Objective: The study aimed to evaluate the modulatory effect of VD on T cell subsets and the production of cytokines in preeclamptic women.

Methods: Peripheral blood mononuclear cells obtained from 12 pregnant women with PE and 12 NT were cultured with or without VD. The cytokines IL-6, IL-10, IL-17 and TNF-α were evaluated by cytometric bead array (CBA) or ELISA. The gene expression of the transcription factors T-bet (Th1), GATA-3 (Th2), RORγt and RUNX1 (Th17), FoxP3 (Treg) and vitamin D receptor (VDR) were determined by the qPCR.

Results: Endogenous mRNA levels of T-bet, RORγt and RUNX1 were significantly higher, whereas GATA-3 and FoxP3 mRNA levels were lower in PE group when compared to NT women. Cell treatment with VD decreased the gene expression of T-bet, RORγt and RUNX1 and increased that of GATA-3, FoxP3 and VDR in preeclamptic women. Regarding the endogenous cytokines production IL-17 and TNF-α were significantly higher, while IL-10 was decreased in PE when compared to NT group. VD treatment decreased the production of IL-17 and led to a tendency of decreased levels of IL-6 and TNF-α in PE group. On the other hand, IL-10 levels increased significantly after treatment with VD in both groups.

Discussion: VD treatment increased GATA-3, FoxP3 and IL-10, demonstrating that this molecule is able to polarize the inflammatory response present in PE to the anti-inflammatory profile. It confirms the important immunomodulatory effect of VD in this disease.

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Geographic mediation of dose for PIERs On the Move (POM) in the Community Level Intervention for PreeclmpsIa (CLIP) in Mozambique

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Introduction
Travel time and distance to health facilities are known barriers for accessing maternal health care, particularly in Mozambique. Community health workers (CHWs) are responsible for extending the reach of antenatal care to isolated communities. Less is known about the geographical barriers faced by CHWs that may hamper their access to these isolated communities.
Objective
This study aimed to evaluate the extent to which related to dose of CHW-led PIERS On the Move (POM) study visit, delivered as an intervention in the Community Level Intervention for Pre-eclampsia trial (NCT01911494) in six clusters in Maputo and Gaza provinces.
Methods
Access to care was measured by calculating the walking time from each community to the nearest PHC using ArcGIS software. Dose of the intervention was measured by the average number of POM visits during pregnancy. A spatial autocorrelation analysis using the Moran I statistic was used to identify regional clusters of communities with both high and low doses of POM visits and how this compared with access to PHCs.
Results
Regional clusters (Moran I $p < 0.001$) of communities with poor access to PHCs had significantly lower doses of POM. The high dose areas had POM visits that were almost seven-fold higher than the POM visits in the low POM dose areas. The low dose areas required more that an additional hour of walking time to PHCs.
Discussion
Inequities in access to pregnancy related care persist, even when the reach of care through community health workers are implemented. Further strategies in addition to assigning community health workers are needed to counter the role of geography in mediating community interventions.

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Defective angiogenic markers and poor pregnancy outcomes in patients with Hypertensive disorders of pregnancy: A pilot study in an Indian Population.

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Objectives: To assess angiogenic factors, matrixmetalloproteinases, and their inhibitors and cell adhesion molecules in maternal blood and placenta of various types of hypertensive disorders of pregnancy and to correlate with the pregnancy outcomes.
Methods: Plasma levels of soluble Vascular Endothelial Growth Factor Receptor 1 (sVEGFR1), soluble Endoglin (sENG), Transforming Growth factor beta (TGF-b), VEGF, Placental Growth Factor (PLGF), Matrixmetalloproteinases (MMPs), Tissue inhibitors of Matrixmetalloproteinases (TIMPs) and Cell adhesion molecules were analysed by ELISA kits in Gestational hypertension (GH), Late onset preeclampsia (LOPE), Early onset preeclampsia (EOPE), Eclampsia (E) and Control pregnant women (CPW) during third trimester. The mRNA/ protein expressions were assessed by RT-PCR/westernblot/IHCp respectively. The Pregnancy outcomes like the gestational age at the time of delivery (GA) and birthweight (BW) and APGAR score of the baby also were measured.
Results: The GA, BW, APGAR score of the baby were found to be significantly lower in EOPE and Eclampsia compared to CPW. The angiogenic factors, PLGF, TGF-b were significantly decreased in EOPE and Eclampsia compared to CPW, GH. Besides, the antiangiogenic factors sVEGFR1 and sEng were found to be elevated in HDP when compared to CPW. A significant correlation was observed between the angiogenic factors and the pregnancy outcome in HDP.
Conclusions: A defective angiogenic profile and poor birth outcomes were observed in Hypertensive disorders of pregnancy.