Maternal Origin, Deprivation and Pregnancy Complications

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1. **Arechvo A**, Voicu D, Gil MM, Syngelaki A, Akolekar R, Nicolaides KH. Maternal race and pre-eclampsia: Cohort study and systematic review with meta-analysis. *BJOG* 2022; 129: 2082-2093.

2. **Arechvo A,** Nikolaidi DA, Gil MM, Rolle V, Syngelaki A, Akolekar R, Nicolaides KH. Maternal Race and Stillbirth: Cohort Study and Systematic Review with Meta-Analysis. *J Clin Med* 2022; 11: 3452.

3. **Arechvo A**, Wright A, Syngelaki A, von Dadelszen P, Magee LA, Akolekar R, Wright D, Nicolaides KH. Incidence of pre-eclampsia: effect of deprivation. *Ultrasound Obstet Gynecol*. 2022 Sep 30. doi: 10.1002/uog.26084. Epub ahead of print.

4. **Arechvo A**, Nikolaidi DA, Gil MM, Rolle V, Syngelaki A, Akolekar R, Nicolaides KH. Incidence of stillbirth: effect of deprivation. *Ultrasound Obstet Gynecol.* 2022 Oct 23. doi: 10.1002/uog.26096. Epub ahead of print.

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
APS	Antiphospholipid syndrome
BMI	Body mass index
BP	Blood pressure
CH	Chronic hypertension
FGR	Fetal growth restriction
FMF	Fetal Medicine Foundation
FPR	False positive rate
HELLP	Hemolysis, elevated liver enzymes and low platelet
ISSHP	International Society for the Study of Hypertension in Pregnancy
IVF	In vitro fertilization
IMD	Index of multiple deprivation
IUFD	Intrauterine fetal death
MAP	Mean arterial pressure
MoM	Multiples of the median
NICE	National Institute for Health and Clinical Excellence
PAPP-A	Pregnancy-associated plasma protein A
PE	Pre-eclampsia
PlGF	Placental growth factor
PAPP-A	Pregnancy-associated plasma protein A
SES	Socioeconomic status
SGA	Small for gestational age
SLE	Systemic lupus erythematosus
sFLIT-1	Soluble fms-like tyrosine kinase-1
UK	United Kingdom
UtA-PI	Uterine artery pulsatility index
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

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ABSTRACT

In developed countries, women from more deprived socioeconomic backgrounds and minority racial/ethnic groups have a higher prevalence of adverse outcomes of pregnancy than do women from less deprived socioeconomic backgrounds and White women. However, there is a lack of evidence on the strength of the risk factors contributing to adverse pregnancy outcomes and on the size of their effect at the population level. This raises the question of whether observed disparities in pregnancy outcomes such as pre-eclampsia (PE) and stillbirth are due to maternal origin, socioeconomic status, a combination of both, or a factor that is not measured yet.

To answer this question, first, we performed systematic reviews and meta-analyses on available literature of studies on PE and stillbirth. Second, in a screening study from the Fetal Medicine Foundation (FMF) in England we examined in more than 150 000 pregnancies the association between maternal origin and PE and maternal origin and stillbirth after adjustment to maternal characteristics and medical history. Third, we examined the relationship between the English Index of Multiple Deprivation (IMD) and the incidence of PE and stillbirth and we evaluated the distribution of IMD in a multiethnic cohort of pregnant women in the South East of England. Last, we assessed whether IMD contributes to the prediction of PE and stillbirth.

This thesis demonstrates that first, in Black women the risk of PE and stillbirth, after adjustment for confounders, is higher than in White women, and second, the incidence of PE and stillbirth is higher in women living in the most deprived areas. However, in screening for PE and stillbirth, inclusion of IMD does not improve the prediction of these adverse outcomes provided by maternal origin and other maternal characteristics and elements of medical history.

1. INTRODUCTION

In developed countries, women from more deprived socioeconomic backgrounds and minority racial/ethnic groups have a higher prevalence of adverse outcomes of pregnancy than do women from less deprived socioeconomic backgrounds and White women. However, there is a lack of evidence on the strength of the risk factors contributing to adverse pregnancy outcomes and on the size of their effect at the population level. This raises the question of whether observed racial disparities in pregnancy outcomes such as pre-eclampsia (PE) and stillbirth are due to maternal origin, socioeconomic status, a combination of both, or a factor that is not measured yet.

In this chapter I will summarize the definition, incidence, pathophysiology, prenatal prediction and screening of PE and stillbirth. I will also summarize the definition of maternal origin, deprivation, which have been used for prediction of both PE and stillbirth and use of biomarkers of impaired placentation. This will set the background for the studies that will be undertaken in this thesis.

1.1 PRE-ECLAMPSIA

The term eclampsia was first introduced in 1739 by French physician François Boissier when he described the condition as an acute form of convulsion and differentiated by epilepsy known at that time as chronic convulsion.[1] In 1840 Pierre Rayer described protein in urine in pregnant women with seizures and in 1896 Riva-Rocci introduced the mercury manometer to measure blood pressure and allowed the recognition of high blood pressure as the cause that led to eclampsia[1]. The term PE was born in 1894 when Vinay described the relation between high blood pressure and proteinuria during the pregnancy independent of eclamptic seizures.[2]

1.1.1. Definition of PE

The PE definition has changed over the years. The traditional definition of PE includes hypertension, either chronic hypertension (CH) or new onset high blood pressure after 20 weeks of gestation together with proteinuria. But more recently International Society for the Study of Hypertension in Pregnancy (ISSHP) and the American College of Obstetrics and Gynecology (ACOG) have changed the definition of PE.[3,4] The definition of PE used in this thesis was that of ACOG[3]: diagnosis of CH or new onset hypertension (BP ≥140 /

≥90 mmHg) and at least one of the following: proteinuria (≥300 mg/24h or protein to creatinine ratio ≥30 mg/mmoL or ≥2 + on dipstick testing), renal insufficiency with serum creatinine >97 µmol/L in the absence of underlying renal disease, thrombocytopenia (platelet count <100,000/µL), hepatic dysfunction with blood concentration of transaminases more than twice the upper limit of normal (≥65 IU/L for our laboratory), neurological complications (e.g. cerebral or visual symptoms), or pulmonary edema.

1.1.2. Incidence of PE

Pre-eclampsia complicates about 2-4% of all pregnancies and it is associated with a global rate of about 46,000 maternal deaths a year, disproportionately by women in low-and-middle-income countries.[5,6] The incidence of PE is markedly influenced by age, maternal origin and genetic predisposition and it varies between populations from about 3-5% in White to up to 10% in Black women and the number may reach 20% in some countries in Africa.[7-9] Other factors may contribute to a higher incidence of PE such as nulliparity, obesity, conception by in vitro fertilization, concomitant conditions, such as chronic hypertension and diabetes mellitus, but also socioeconomic status.[10]

1.1.3. Pathogenesis of PE

The precise etiology and pathogenesis of PE is largely unknown but several factors are thought to play an important role in etiology and pathogenesis of PE: genetic factors, immunological maladaptation, placental factors, endothelial dysfunction and oxidative stress.

Genetic factors

PE is thought to have a genetic basis. The theory is based on the observation of the family history of PE. For instance, in women with a positive family history (patient's mother with history of PE), the risk of subsequent PE is increased about three times compared to those without such a family history.[11,12]

Many research efforts including studies of whole-exome sequencing identified multiple gene alleles and mutations associated with PE.[13,14] However, it is expected that no one gene will be identified as the sole risk factor for PE, as in the general population PE represents a complex multifactorial disorder.

Immunological factors

The placenta is fetal in origin but it has both maternal and paternal derived antigens and genetic determinants. During a normal pregnancy, the mother's modified immune system is tolerant of the foreign semi-allogenic fetus and antigens. From the observational studies we know, that in pregnancies complicated by PE, there is activation of a broad continuum of immune cells to induce immunity towards the fetus and placenta, rather than immune tolerance.[15,16] However, it is uncertain if the maternal immune system adaptation precedes the abnormal implantation of placenta and endothelial dysfunction or it follows it.[17]

What is suggested from epidemiological observations, supporting an immunological cause for PE, is that there is an abnormal and heightened maternal immune response due to paternally derived antigens on the trophoblast. The fact that PE is more common in a first pregnancy and that the risk of PE decreases after the first pregnancy due to the protection from repeated exposure to specific antigens from the same partner is supporting this hypothesis. Moreover, changing partners for a subsequent pregnancy has a role on the risk of developing PE.[18,19]

Placental factors

The placenta develops primarily from fetally derived cells known as trophoblasts. There are two types of trophoblastic cells: cytotrophoblasts and syncytiotrophoblasts. The cytotrophoblasts are the precursors to all subsequent trophoblast cells and the syncytiotrophoblasts are responsible for the invasion into the decidua and the maternal spiral arteries.

In normal pregnancy, after implantation, there are several important changes in the prognosis of pregnancy. There is a formation of the intervillous space and the spiral arteries, destined to become the uteroplacental arteries in the placental bed. The vessels undergo a complex series of morphological changes; the trophoblast invades the vessel wall and replaces the endothelium, muscular layer and neural tissue.[20-22] The result of these physiological changes in the uterine vasculature is the conversion of the diameter of the spiral arteries so that there is an increase in blood flow from 50 mL/min at 10 weeks' gestation to 600 mL/min at term.[20] This change optimizes the feto-maternal exchange in the intervillous space and the passage of nutrients to the fetus.[23-26]

In pregnancies complicated by PE the perivascular and endovascular trophoblastic invasion of spiral arteries is affected. The trophoblastic invasion into the spiral arteries does not extend into the myometrial segments, but to the decidual part of the vessels only.[21,22,27,28] In addition, there is evidence of atherosis is the case of PE.[29-31] This failure of the complete trophoblastic invasion of the maternal spiral arteries increase the resistance to blood flow and restricts feto-maternal exchange in the intervillous space.[21,23-25]

Endothelial dysfunction and oxidative stress

Following impaired placentation and placental hypoxia, intravascular inflammation, oxidative damage and endothelial dysfunction can be observed.[32] Potential mediators between placental hypoxia and endothelial dysfunction is the balance between the antiangiogenic sFLT-1 and angiogenic PlGF.[33] The elevated levels of sFLT-1 are affecting maternal endothelial cells by impairing their endogenous production of nitric oxide and causing vasoconstriction. As a consequence, reduced plasma volume and blood flow to maternal organs cause activation of the coagulation cascade, platelet activation and formation of thrombi in the microcirculation of different organs.[34-37]

1.1.4. Organ involvement in PE

Neurological complications: Severe hypertension increases the risk for blood accumulation in the brain causing hemorrhagic stroke, posterior reversible ischemic encephalopathy and the seizures of eclampsia.

Renal complications: Renal involvement in PE manifests as proteinuria due to endothelial dysfunction. Severe PE can lead to nephrotic-range proteinuria, acute tubular necrosis, and acute kidney injury.

Liver complications: Due to periportal inflammation and hepatocellular damage liver getting damaged, which can lead to subcapsular bleeding and liver failure.

Hematologic complications: PE affects hemoconcentration, leading to microvascular thrombosis and hemolysis and rarely to disseminated intravascular coagulation.

Placental complications: The main complications for the fetus and neonate include fetal growth restriction, oligohydramnios, intrauterine fetal death, preterm delivery and as a consequence increased risk of neonatal intensive care.

In conclusion, there is absence or inadequate maternal vascular response to placentation in pregnancies complicated by PE. This high-pressure system prevents the physiologic increase in blood supply required in pregnancy and leads to poor uteroplacental perfusion. However, not all pregnancies affected by PE present with the same picture and normal placentation may be found in pregnancies affected by PE as well. Inadequate trophoblast invasion can only be considered as a predisposing factor, with the maternal response contributing to the final consequences.

1.1.5. Classification of PE

PE is classified according to severity into mild and severe and according to gestational age at delivery into early (<34 weeks' gestation) and late (≥34 weeks) or preterm (<37 weeks), term (≥37 weeks) and postpartum. While individual actual risks are greater with preterm (vs term) PE, the term disease is 3-4 times more common that preterm PE and it is therefore associated with at least equivalent total numbers of maternal, and a significant proportion of perinatal, adverse events.

1.1.6. Prediction of PE

There is a need to effectively predict PE at the early stage of pregnancy to prevent or at least reduce the frequency of PE. It is important to identify women who are at high risk of developing PE and to undertake necessary measures to improve placentation and reduced the risk of other complications related to PE.

Risk scoring based on maternal factors and history

Currently in assessing the risk for delivery with PE the patients are classified as high-risk or low-risk based on the presence or absence of risk factors established from maternal characteristics and personal or familial medical history. For example in England, according to guidelines by the National Institute for Health and Clinical Excellence (NICE) if there is one high-risk factor or two moderate-risk factors women assessed at the first medical visit in pregnancy should be classified as being at high risk of developing PE and treated accordingly.[38]

The high-risk factors are concomitant chronic diseases such as chronic hypertension, diabetes mellitus, chronic kidney disease, autoimmune disease or history of hypertensive disease in a previous pregnancy and the moderate-risk factors are age ≥40 years first pregnancy, body mass index (BMI) at first visit of >35 kg/m2, inter-pregnancy interval >10 years, or family history of PE.

Similarly to the NICE guidelines, the risk scoring system is recommended by the ACOG and the Society for Maternal Fetal Medicine. The high-risk factors are identical to those of NICE guidelines and the moderate-risk factors are primigravida, inter-pregnancy interval more than 10 years, age over 35 years, BMI more than 30 kg/m2, family history of PE, women of Black ethnicity, low socioeconomic status, previous history of low birthweight and history of adverse pregnancy outcomes.[39]

The advantage of these strategies is that they are simple to perform, however, the performance of predicting PE is poor (detection rate for preterm PE (≈40%), term PE (≈35%), screen-positive rates of ≈10%[10,11,40] and the individual patient-specific risk is not quantified.

In Sweden similarly to NICE and ACOG recommendations women are classified into the high and low risk of developing PE based on maternal characteristics and maternal history. However, according to the national guidelines only 75mg of aspirin is recommended for women at high risk of developing PE. [41]

Competing risks model

The FMF “competing risks” model provides a personalized risk assessment for delivery with PE that could lead to personalised care, and personalised intensity of pregnancy monitoring, with recalculated risk on each visit based on biomarker measurements. The competing risk model is a multivariable model of clinical (i.e. BMI, maternal origin), ultrasonographic (UtA-PI) and laboratory assessment (PlGF, sFLIT-1) of uteroplacental perfusion and function. The competing risks model is based on a survival-time model that incorporates a prior distribution of gestational age at delivery with PE, derived from maternal characteristics, with likelihood functions from biomarkers, to estimate an individual woman’s risk of delivery with PE before a specified gestational age (e.g., <37 weeks’).[10]

This approach assumes that all pregnant women would develop at some point PE if the pregnancy were to continue beyond the expectant due date. There is competition between the development of PE and delivery for other reasons before the development of PE.

Bayes theorem is used to combine the prior distribution, based on maternal factors, and likelihoods from biomarkers measured at different times in pregnancy. Increased risk for the development of PE is provided by advancing maternal age, increasing weight, maternal origin (Black and South Asian), conception by in vitro fertilization (IVF), personal history of PE, medical history of chronic hypertension, diabetes mellitus, autoimmune diseases such as systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS) and family history of PE.[11] The risk for PE is reduced with increasing maternal height and in parous women with no previous PE.

In general, the level of biomarkers depends on maternal characteristics such as weight and maternal origin, method of conception, medical conditions and gestational age. The level of biomarkers depends on the technique and method used for measurement. The method of standardization of the level of biomarkers applied in screening in heterogenous populations is to express the measurements as multiples of the median (MoM) values specific to the maternal origin, weight etc. of each individual from which the measurements were taken.[42-45]

In pregnancies that are complicated by PE, there are some specific changes compared to normal pregnancies and these changes are expressed as higher MoM values of MAP, UtA-PI and sFLT-1 and lower PLGF levels. The effect sizes increase with increasing severity of the disease, quantified by the gestational age at delivery.

In the first trimester, the competing risks approach can be used to identify high-risk women of developing preterm PE by using maternal factors, MAP, UtA-PI and PLGF at the rate of 10% screen positive. This was shown in studies predicting 90% of cases of early-PE and 75% of cases with preterm-PE both training and two validation datasets.[42,46-49]

In the second and third trimesters, the competing risks approach can be used for stratification into high-, intermediate and low-risk patients of developing PE.[49-53] For example, women assessed at 20 weeks' gestation, would be classified as high-risk if their calculated probability for developing PE at <32 weeks is above a high-risk cut-off or as being low-risk if their chances for developing PE at <36 weeks is below a low-risk cut-off.

The high-risk group, which is about 1% of the total population of pregnant women, and comprises almost all cases of PE at <32 weeks, would require regular BP and proteinuria monitoring starting from 24 weeks. The intermediate-risk group together with the pregnancies from the high-risk group that had not delivered yet (about 10% of the total population), which would contain about 90% of PE at 32-35 weeks would be reassessed at 32 weeks' gestation to identify those at high-risk that would require blood pressure and proteinuria monitoring at 32-35 weeks. The low-risk group, which contains almost 90% of the total population does not need to follow up antenatal visits because they are unlikely to develop PE before the routine visit at 36 weeks. Recalculation of risk at 36 weeks is necessary and recommended for all women that remain pregnant because the performance of screening at 20 weeks' gestation for PE at term is proven to be poor.

As conclusion, the "competing risks" model provides a personalized risk for delivery with PE by providing stratification of the intensity of pregnancy monitoring, with recalculated risks on each visit based on biomarker measurements. In countries, where access to health care is limited, stratification of women into high-risk of developing preterm PE group can be done based on maternal factors and MAP. Thereafter, a risk assessment by PLGF and UtA-PI can be done for a selected population based on the risk derived from screening by maternal factors and MAP.

1.1.7. Prevention of PE

Prevention of pre-eclampsia is a healthcare priority, given that only delivery of the placenta is proven to initiate the resolution of PE once it has developed. The term 'primary prevention' describes preventing the occurrence of a disease. The identification and manipulation of recognised risk factors might allow primary prevention. PE is a multi-system disorder of complex etiology. Preventative therapies have been based on the pathogenesis of PE and focused on angiogenic imbalance, endothelial activation, oxidative stress, inflammation, and/or vasoconstriction.

Aspirin

Aspirin (acetylsalicylic acid) has been used in medicine to prevent PE since 1986. In pregnancies complicated by PE observed vasospasm and coagulation abnormalities are partly related to the imbalance in the thromboxane A2 to prostacyclin ratio. Aspirin is used

as a prophylaxis of PE by affecting the biosynthesis of platelet thromboxane A2 and the balance of the vascular prostacyclin.[55]

Studies in the 1980s did suggest that low-dose aspirin in high-risk women reduces the prevalence of fetal growth restriction and PE.[56,57] In the randomized control ASPRE trial, results showed that in the aspirin group versus the placebo group, there was a greater than 60% reduction of preterm PE (OR 0.38, 95% CI 0.20-0.74), but there was no reduction in term PE.[58] A meta-analysis of 16 studies reported that the beneficial effect of aspirin is restricted to preterm PE (RR 0.62, 95% CI 0.45-0.87), not term PE (RR 0.92, 95% CI 0.70-1.21), provided that the treatment is initiated by 16 weeks and in a dosage of at least 100 mg/day.[59] The difference of aspirin on preterm and term PE may be related to differences in predominant pathogenesis and/or a shift in diagnosis to later gestational age, so term cases prevented are replaced by cases that would have been delivered earlier.

In conclusion, following first-trimester screening for preterm PE, women identified at high risk should receive aspirin prophylaxis before 16 weeks of gestation at a dose of ~150 mg to be taken every day until 36 weeks of gestation (in order to reduce the potential risk of antepartum bleeding).

Calcium

The rationale linking the use of calcium for the prevention of PE comes from observational studies showing that women with calcium enriched diet had a lower incidence of PE.[59,60] Low calcium diet by stimulating either parathyroid hormone or renin release is causing increasing intracellular calcium in vascular smooth muscle and leading to vasoconstriction, hence increased blood pressure.[60] Calcium supplementation during pregnancy can normalise parathyroid hormone release and intracellular calcium thus reducing vasocontractility.

A recent meta-analysis of studies on calcium supplementation during pregnancy has shown that such therapy reduces the risk of pre-eclampsia (RR 0.49, 95% CI 0.39-0.61; 31 trials, 20,445 women), at term or preterm gestational age, and regardless of whether calcium is initiated before or after 20 weeks; given with or without vitamin D; or the dose is high (≥1g/day) or low (usually 500 mg/day).[61]

Other factors

A randomized controlled trial recruiting patients between 8 and 16 weeks of gestation showed that folic acid (4mg/day) does not prevent pre-eclampsia among women at high risk.[62]

The use of low molecular weight heparin alone or in combination with an anti-platelet drug has been suggested for women with known thrombophilic tendencies,[63] however the effectiveness of low molecular weight heparin in prevention of PE remains uncertain.

1.2. STILLBIRTH

1.2.1. Definition of stillbirth

Pregnancies resulting in a pregnancy loss occurring ≥ 24 weeks of gestation are classified as stillbirths. The legal definition of stillbirth in England is “a child that has issued forth from its mother after the 24th week of pregnancy and which did not at any time after being completely expelled from its mother breathe or show any other signs of life”.[64]

The definition according to World Health Organization (WHO) is different and is defined as the birth of a baby after 22 completed weeks of gestation, or if the gestational week is uncertain with a birth weight of 500 gram or more, or a body length of 25 centimetres or more, who died before or during birth.[65] The Swedish definition of stillbirth is corresponding with the WHO definition of stillbirth.[66]

1.2.2. Incidence of stillbirth

Every year stillbirth is affecting more than two million families worldwide. The burden of this adverse event is affecting women and their families, health institutions and wide society. The rate of stillbirth is considered to be a marker of the quality of maternal care. The reported rates vary from 22.8 stillbirths per 1000 total births in Africa and around 3 per 1000 births in western Europe.[67] Rates of stillbirth are less common in developing countries but are still common. Studies reporting on the rate of stillbirth from developed countries have shown an increased incidence of stillbirth among women of African origin in comparison to women of European origin.[68-71]

The stillbirth rates have declined but more slowly than expected and certainly more slowly than the rate required to meet the target set to end preventable stillbirths. The World Health Assembly endorsed a target of 12 or less stillbirths per 1000 births in every country by 2030.[72]

1.2.3. Causes and risk factors of stillbirth

Although several conditions have been linked to stillbirth, it is difficult to define the definite cause of stillbirth in many cases. Common causes are congenital abnormalities, antepartum hemorrhage, maternal medical conditions and infections.[73]

Hypertension, diabetes mellitus, and obesity are some of the more common stillbirth risk factors. In the case of hypertensive disorders, there have been major improvements in management in high-income regions, but in low-income regions, the necessary treatments are often unavailable. Still, greater use of low-cost treatments such as aspirin for PE could significantly lower stillbirth rates in low-income regions.

The difficulties with managing diabetes mellitus are similar to those of pregnancy complications due to hypertensive disorders. When left uncontrolled, diabetes mellitus can lead to hyperglycaemia, which can cause stillbirth through affected fetal anaerobic metabolism with hypoxia and acidosis.[74]

Obese women have 3 fold higher risk for stillbirth compared to women with body mass indexes < 30 kg/m^2, with no relation between maternal weight gain during pregnancy and stillbirth.[75] Authors of a Swedish study reported, using data from a homogenous population, an increased risk of antepartum stillbirth with higher maternal pre-pregnancy BMI as compared with women of normal BMI.[76] This excess risk of stillbirth in overweight and obese women is in part explained by their greater risk for other pregnancy complications such as hypertensive disorders, diabetes mellitus, and gestational diabetes, compared to non-obese women, although these factors do not completely attenuate the relation between maternal obesity and stillbirth.[77] The pathway between maternal obesity and stillbirth remains incompletely understood.

Other maternal conditions significantly increase the risk of stillbirth. The autoimmune disorder systemic lupus erythematosus (SLE), leads to stillbirth rates of 40-150 deaths per 1,000 total births in high-income countries. The wide range is attributable to increased stillbirth risk when the onset of SLE is during pregnancy, compared to when the onset is prior to conception.[78] Uncontrolled chronic renal disease[79] and intrahepatic cholestasis of pregnancy increase the risk for stillbirth.[78]

Previous pregnancy history also affects risk for stillbirth, as previous history of stillbirth, primiparity, and previous spontaneous miscarriages all increase the risk of subsequent stillbirth, and these women require additional monitoring during pregnancy. Other social risk factors for stillbirth include alcohol consumption or use of drugs, smoking during the pregnancy, maternal age. Maternal age is known risk factor for stillbirth. Due to increased health risks such as hypertension, gestational diabetes, congenital anomalies, and the effects of IVF, including multiple gestation, women aged 35 years or more face

significantly higher risk for stillbirth than younger women, with the effect most profound in women about 40 years of age.[80]

Young mothers face an increased risk of stillbirth as well. Women below 15 years of age have a significantly higher risk for stillbirth than those aged 15 years or greater.[81]

Worldwide, there are intranational, racial/ethnic variations for stillbirth rates.[68-71] These racial/ethnic variations in stillbirth might be due to ethnic associations with stillbirth, maternal characteristics or genetic factors. Socioeconomic status might contribute to these racial/ethnic disparities in stillbirth rates through its possible association with access to adequate antenatal care, cultural behaviours, and the ability to obtain quality medical pregnancy care.

The availability of adequate health care and preconception care varies from country to country. High-quality prenatal care allows healthcare workers and physicians to screen for congenital anomalies, monitor and manage maternal illnesses, and manage fetal and pregnancy complications.[82]

To reduce the rate of stillbirth all these risk factors have to be taken into consideration. Close monitoring of pregnancies at high risk of stillbirth and of women developing pregnancy complications is important, especially trying to identify growth-restricted fetuses, since stillbirth is associated with restricted fetal growth, without any other direct causes is one of the major types of stillbirth.

1.2.4. Classification of stillbirth

Antepartum stillbirths can be classified into those that are due to placental dysfunction-related stillbirth and those that are unexplained or due to other causes; the rationale for classification of stillbirths according to the likely underlying cause is that may improve antenatal and preventive strategies, that could potentially be undertaken more effectively.[83]

In a large study population from several hospitals in the UK, 58% of antepartum stillbirths were related to placental dysfunction and 42% were of unexplained reasons or due to other causes.[84]

Intrapartum stillbirths occur due to the labor trauma (cranial, extracranial), hypoxia, infections and uncontrolled pregnancy complications such as PE.

1.2.5. Prediction of stillbirth

The prediction of stillbirth at first-trimester by a combination of maternal characteristics, including weight, maternal origin, method of conception, cigarette smoking and history of diabetes mellitus, CH, SLE and APS is possible and can predict about 30% of stillbirths (false-positive rate of 10%).[85] A first-trimester study combining maternal characteristics with measurements of UtA-PI, fetal ductus venosus pulsatility index and maternal serum PAPP-A, which provide indirect information on placentation, reported that, at a false positive rate of 10%, the detection rate (DR) of stillbirth due to placental dysfunction improved to 55%, whereas the DR of stillbirths due to other causes was 24%.[86]

Screening method based on UtA-PI alone or combined with maternal characteristics, fetal biometry, and PlGF had higher detection rates of stillbirth in fetuses aged < 32 weeks of gestation compared with stillbirth in fetuses aged ≥37 weeks.[83,87] Such results demonstrate that a high proportion of stillbirths due to placental dysfunction can be identified effectively at an early stage of pregnancy.[84]

As uncontrolled hypertensive disorders are leading to abnormal placental function causing growth restriction, a screening for PE at 11-13 weeks' gestation and treatment of the high-risk group by aspirin is an effective method in the prevention of preterm PE and in the prevention of early small for gestational age (SGA) in the absence of PE.[41,48,49,58,59,88]

Screening during the routine second trimester scan (20-24 weeks) by a combination of maternal risk factors, estimated fetal weight and UtA-PI, can identify patients being at risk of placental dysfunction related stillbirths that can occur at 24-37 weeks' gestation. For this high risk group close monitoring with regular ultrasound examinations for early diagnosis of SGA fetuses can prevent at least some of such stillbirths by identifying best timing of delivery.[89-91]

Routine ultrasound examination at 36 weeks' gestation is a more effective method of screening for late SGA; the detection rate for term SGA by assessment at 36 weeks' gestation is twice as high as with screening at mid-gestation.[92,93]

1.3. BIOMARKERS OF IMPAIRED PLACENTATION

1.3.1. Mean arterial pressure

The MAP is calculated based on patient's systolic blood pressure (BP) and diastolic BP. Hypertension is an early indication of maternal cardiovascular dysfunction and predisposition to PE. High blood pressure developed for the first time during pregnancy is a consequence of vasoconstriction and reduced peripheral vascular compliance due to impaired placentation and antiangiogenic circulating factors with systemic effects. Regular monitoring of BP during antenatal care is useful not only in detecting PE, but also an important component in screening methods for pregnancies that will end in developing hypertension disorders or in detecting women with pre-existing hypertension as pregnancy may often be the first opportunity for young women to have a thorough medical examination.

Accurate measurement of MAP requires the adherence to a strict protocol.[94] For correct measurement several steps should be followed. First, the women should be in the sitting position, holding both their arms at the level of the heart, after rest for 5-10 minutes, second, an appropriate cuff size should be used depending on the arm circumference, small (22 cm), normal (22 to 32 cm) or large (33 to 42 cm), third, automated devices used should be validated, fourth, blood pressure measurement should be performed simultaneously in both arms and a series of four recordings are made at 1 min intervals. The final MAP should be calculated as the average of all four measurements

1.3.2. Uterine artery Doppler

The uterine artery arises from the anterior divisions of the internal iliac arteries and is the major blood supply to the uterus; it also supplies blood to the upper vagina, cervix and fallopian tubes. A smaller proportion of blood to the uterus is derived from the ovarian arteries. Uterine artery crosses the ureter anteriorly to reach the uterus by traveling in the cardinal ligament and going through the parametrium of the inferior broad ligament. This artery anastomoses with the ovarian artery at the cornu and gives rise to arcuate arteries that penetrate and assume a circumferential course in the myometrium. These vessels divide into the basal arteries, which supply the myometrium, and the spiral arteries, which supply the intervillous space of the placenta.

Uterine artery Doppler is a non-invasive measure of the resistance of uteroplacental circulation. In normal pregnancy, in the early stages, a normal trophoblastic invasion transforms spiral arteries into low-resistance vessels and as a consequence of this physiological process, the impedance to flow in the uterine arteries decreases with gestation.[95] In pathological processes, such as PE and pregnancies with SGA, there is increased resistance in the uterine arteries identified as early as the first trimester as a diastolic notch and reduced end-diastolic flow velocity and these pathological changes would persist throughout pregnancy until the third trimester.

Measurement of UtA-PI should follow a strict protocol depending on the gestational age and route of assessment (transabdominally or transvaginally). Early in pregnancy, for the measurement of UtA-PI transabdominally, a sagittal section of the uterus the cervical canal and internal cervical os are identified. Subsequently, the transducer is gently tilted from the midline to the side and using color flow mapping each uterine artery is identified at the level of the internal os. Pulsed-wave Doppler is used with the sampling gate set at 2 mm and the angle of insonation less than 30 degrees. After obtaining three similar consecutive waveforms the UtA-PI is measured on the left and right side and the mean UtA-PI is calculated as an average between the two.

In the second and third trimesters of pregnancy, the uterine artery can be identified by holding the transabdominal transducer in the longitudinal axis and lateral to the uterus at the level of the maternal iliac fossa. In that position, one can identify the bifurcation of the common iliac artery into external and internal iliac arteries and the cross-over of the uterine artery and the external iliac artery (Figure 3).

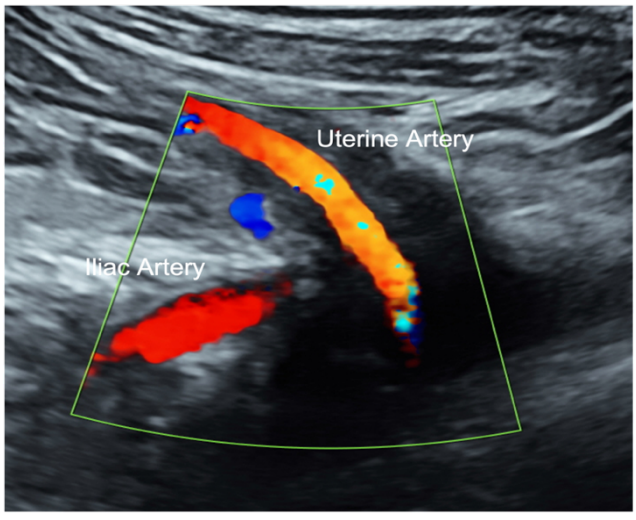

Figure 3. Transabdominal technique in obtaining uterine artery waveform.

Transvaginally, the ultrasound probe is placed into the lateral fornices and the uterine arteries are identified at the level of the internal cervical os. In pregnancies that subsequently develop PE the flow velocity waveform demonstrates increased resistance to flow which is reflected in an early diastolic notch and poor end diastolic flow (Figure 4).

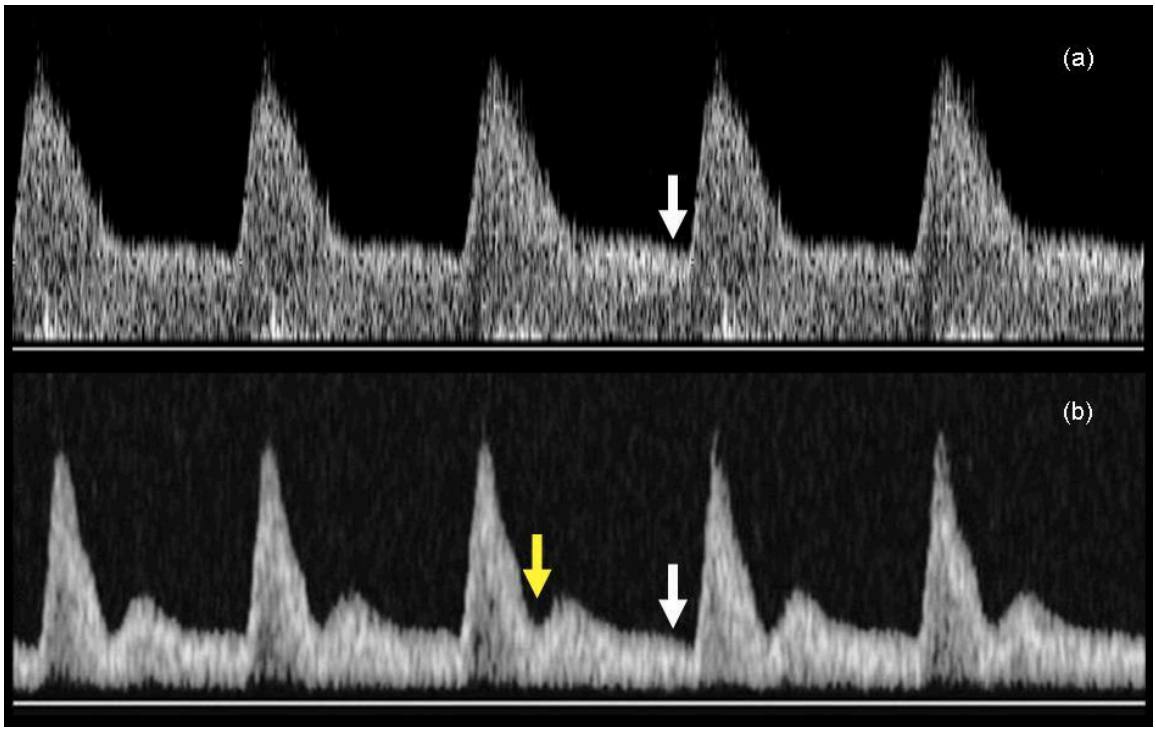

Figure 4. Pulsed wave signals of uterine artery blood flow (a) normal waveform: the arrow points the abundance of end-diastolic flow velocity; (b) abnormal waveform suggesting impaired placentation: yellow arrow early diastolic notch and white arrow the reduced end-diastolic flow velocity.

The UtA-PI has been proved to be an important marker in prediction of preterm PE and it is incorporated into the first, second and early third trimester screening tests.[11] Unlike preterm PE, its utility was not demonstrated in the third trimester for prediction of late PE. In a study involving 13,350 pregnancies, the performance of screening at 35-37 weeks of gestation by using maternal factors, MAP, PLGF and sFlt-1 was not significantly improved by the addition of UtA-PI.[55]

1.3.3. Biochemical markers

PLGF, a glycosylated dimeric protein, is a member of the vascular endothelial growth factor sub-family and plays a key role in angiogenesis and vasculogenesis by binding to VEGF receptor-1 to facilitate its actions on angiogenesis. PlGF is produced mainly in

villous and extravillous cytotrophoblast and has a role in trophoblast growth and differentiation from a branching to a non-branching phenotype stimulating the formation of the capillary network. Normal levels are essential for a normal pregnancy due to its angiogenetic properties and decreased levels of PlGF or increased levels of its inhibitory receptor have a key role in hypertensive disorders during pregnancy.[96-98]

sFLT-1 is the soluble form of VEGFR-1 and it is primarily produced by the syncytiotrophoblast through alternative splicing of the FLT-1 gene. sFLT-1 is a shortened form of the VEGF receptor Flt-1. During pregnancy the placenta is the major source of sFLT-1and its production is stimulated by hypoxic condition. In pregnancies with impaired throphoblastic invasion and consequently with placental dysfunction, the hypoxia is more pronounced than in normal pregnancies and therefore the production of sFLT-1 is estimated to be almost 40 times higher.[99-101]

In normal pregnancies, serum PLGF increases with advancing gestational age to reach a peak at around 30 weeks and decreases thereafter until delivery, whereas sFLT1 is low until 30 weeks and increases exponentially thereafter.[97] In women that develop PE PLGF is reduced from as early as the first trimester, whereas sFLT-1 increases substantially within five weeks of the development of the clinical features of PE, potentially facilitating its prediction and prevention.[97]

1.4. MATERNAL ORIGIN

Maternal origin, race and ethnicity are variables used in epidemiology and public health. There is no consensus on the appropriate use of these terms in the scientific study of health despite the growing interest in the analysis of differences in the pattern of population-related health and disease and different origins/races and/or ethnicities.

Race is defined as “a category of people that shares certain distinctive physical traits.” [102] The idea of "race" as a social label first was described by anthropologists and philosophers in the 18th century. For instance, skin color as a physical trait is used to place people into different racial groups.[103] Since individuals with a common broad genetical background may share susceptibility for certain diseases, many epidemiological studies have included race, largely referring to geographical continental ancestry, among studied variables known as risk factors for diseases. Race as a variable in research is however weakly described, measured and reported. Race as a variable is imperfect because as a variable is often associated with racism, and historical relics. However, removing race from the research and entirely abandoning the fact that there are health differences in groups with different ancestry origin might hide health disparities.

The word ethnicity originates from the Greek word *ethnos*, or a nation. Ethnicity can be defined as the social group that a person self-identifies with and belongs to. Ethnical social grouping can be based on language, religion, cultural factors, ancestry, physical factors and other factors. The ethnical grouping is an attempt to further differentiate racial groups. Like race, ethnicity has its own historical, political, and social baggage. Race and ethnicity are two terms related to human ancestry and are increasingly used as synonyms.[102]

The currently favoured groupings of people used in the United Kingdom based on their ethnicity include White, Black, Asian and Mixed. Based on the Office for National Statistics, the distribution of ethnic groups in England and Wales in 2019 was White 84.8%, Asian 8%, Black 3.5% and Mixed 1.8%.[104] In the meantime in Sweden, due to historical events, the term “Country of origin” is used in most of the research. The biggest proportion of foreign-born in Sweden are mainly from Syria, Irak, Finland, Polen, Iran and Somalia.[105]

Categorization of people by ethnicity might hide massive within group heterogeneity, and it is likely that there might be variations in adverse pregnancy outcomes in subgroups

within each ethnical category. There may be differences in pregnancy outcomes among Black women who have a different origin (African and Caribbean), as well as differences between those who are first, second or third generation immigrants. For example, Black people that live in London for several decades may have very different cultural values from those that live in Africa or the Caribbean Islands. Values, beliefs and perceptions about healthcare discrimination may be poles apart. In addition, many individuals self-identify with more than one ethnic group, which can be difficult to ascertain in research. Wide disparities in pregnancy outcomes can be partly explained by health behaviors, genetics, the physical and social environments, and access to health care.[106]

In our studies included in this thesis, participants self-identified their origin. Moreover, the maternal origin was specified by recording data on the country of birth of each patient's parent. In our studies we used self-identified ethnicity based on the following groups:

White: A person with European ancestral origins who identifies as White or European or Caucasian.

Black: A person with African origins, who identifies as Black, African or Afro-Caribbean.

South Asian: A person with Indian or Indian subcontinent origin, including India, Pakistan, Bangladesh, and Sri Lanka ancestry.

East Asian: A person whose ancestry is in the countries of China, Japan, Mongolia, North and South Korea, Taiwan.

Mixed: A person whose ancestry is of mixed origin.

1.5. DEPRIVATION

There is a well reported association between socioeconomic deprivation and health outcomes.[107] Socioeconomic disparities are associated with a reduced life expectancy of up to ten years in developed countries.[108] Studies from high-income countries show worse pregnancy outcomes among women living in more deprived communities.[109]

Lower socioeconomic status is usually related to higher incidence of risk factors related to adverse pregnancy outcomes. One of the key indicator for population socioeconomic inequalities is perinatal mortality.[110] Socioeconomic deprivation is associated with poor access to education and healthcare, lower income levels, decreased wealth and living conditions leading to increased physiological stress, worse nutrition and healthcare access and as a consequence worse health outcomes and pregnancy outcomes.[110,111]

Deprivation is often characterized by indexes with cut-off points to categorize deprivation levels (a measure of poverty). The Index of Multiple Deprivation (IMD) is an official measure of socioeconomic relative deprivation for small areas (or neighbourhoods) in England. The IMD is designed to identify aspects of deprivation across seven domains:

(i) income, which measures the proportion of the population with low income;
(ii) employment, which measures the proportion of the working-age population in an area involuntarily excluded from the labor market;
(iii) education, skills, and training, which measures the lack of attainment and skills in the local population;
(iv) health and disability, which measures the risk of premature death and the impairment of quality of life through poor physical or mental health;
(v) crime, which measures the risk of personal and material victimisation at the local level;
(vi) barriers to housing and services, which measures the physical and financial accessibility of housing and local services;
(vii) living environment, which measures the quality of the local environment. These domains are combined, using appropriate weights, to calculate the IMD for each neighborhood in England.

The overall IMD is based on the several domains that are combined together using the following weights: first, income deprivation (22.5%); second employment deprivation (22.5%); third education, skills, and training deprivation (13.5%); fourth health deprivation

and disability (13.5%); fifth crime (9.3%); sixth barriers to housing and services (9.3%) and seventh living environment deprivation (9.3%). Each neighbourhood is then categorised according to its level of deprivation in relation to that of other areas, with categorization into one of five equal groups, with quintile 1 containing those areas that are in the 20% most deprived, and quintile 5 containing areas that are in the 20% least deprived. We used the postcode of each patient to determine their IMD.[112]

Studies have reported a relation between socioeconomic deprivation and pregnancy complications, such as PE and stillbirth,[113,114] but it is uncertain whether there is an independent contribution to these outcomes from maternal origin and deprivation, because women of other origins than White women more often live in more deprived areas.

Women from deprived neighbourhoods and Black women may be at a disadvantage because of their environment, while White women may more readily obtain the benefits associated with advanced education than Black women: income, medical care, and housing opportunities. Interestingly, the study of 14,950 low-income women has shown that adequate prenatal care alone does not reduce the marked racial disparities in adverse pregnancy complications.[115]

2. OBJECTIVES OF THE THESIS

The main objective of the Thesis was to examine ethnical and socioeconomic inequalities in pre-eclampsia and stillbirth taking into account maternal characteristics and risk factors of pregnancy complications in a large multiethnic and socioeconomically diverse population with the same access to prenatal care from the beginning of the pregnancy.

A total of four studies were carried out and in each, I addressed different components of the primary aims outlined below.

Study 1: Maternal race and pre-eclampsia: Cohort study and systematic review with meta-analysis.

The objectives of this extended study of 168,966 singleton pregnancies with a live fetus recruited at 11^{+0} to 13^{+6} weeks are first, to investigate the association between maternal race and PE after adjustment for confounding factors in maternal demographic characteristics and medical history in the data from the FMF, and second, to carry out a systematic review of the literature and meta-analysis of all studies on this topic.

Study 2: Maternal Race and Stillbirth: Cohort Study and Systematic Review with Meta-Analysis.

The aims of our screening study of 168,966 singleton pregnancies are first, to investigate the association between maternal race and stillbirth after adjustment for confounding factors in maternal characteristics and medical history, and second, to carry out a systematic review of the literature and meta-analysis of the data from independent primary studies focused on race and stillbirth.

Study 3: The incidence of pre-eclampsia: Effect of deprivation.

The objectives of the study were to: report the distribution of IMD in a cohort of racially diverse pregnant women living in England; examine the relationship between IMD and the incidence of PE; and assess whether IMD contributes to the prediction of PE, over and above what is provided by the competing risks model based on maternal characteristics and medical history.

Study 4: Incidence of stillbirth: Effect of deprivation.

The aims of our screening study of 159125 singleton pregnancies are first, to examine the relationship between IMD and the incidence of stillbirth in a cohort of racially diverse pregnant women living in England, and second, to assess whether IMD contributes to the prediction of stillbirth, over and above what is provided by a combination of maternal race and other maternal risk factors.

3. METHODS

The Thesis is based on four studies. The first two examine the relationship between maternal origin and incidence of pre-eclampsia (PE) and stillbirth, respectively. The second two studies examine the relationship between maternal deprivation and the incidence of PE and stillbirth, respectively.

In all four studies, a cohort of more than 150,000 women with singleton pregnancies attending their first routine hospital visit at 11 + 0 to 13 + 6 weeks of gestation at two maternity hospitals in the UK was examined. The visit included recording of maternal demographic characteristics and medical history. In relation to maternal origin, the participants were asked to choose one of White, Black, South Asian, East Asian, or mixed and they were also asked to record the country of origin of each parent. The inclusion criteria were singleton pregnancies delivering a live birth or stillbirth at ≥24 weeks' gestation. We excluded pregnancies with aneuploidies or major fetal abnormalities diagnosed either prenatally or in the neonatal period.

Studies 1 and 2

There were two components to studies 1 and 2. Firstly, multiple logistic regression analysis was performed for PE and stillbirth, respectively, using maternal characteristics and elements of medical history. Secondly, systematic review and meta-analysis of studies reporting on the relationship between maternal origin and PE and stillbirth, respectively, was carried out.

Studies 3 and 4

In studies 3 and 4 the UK Index of Multiple Deprivation (IMD) was calculated for each patient as a measure of socioeconomic status. For Study 3 we used the competing risks model for prediction of delivery with PE to determine the potential contribution of IMD, over and above that of maternal origin and other maternal characteristics. For Study 4 multiple logistic regression analysis was performed for stillbirth using IMD, maternal origin and other maternal characteristics.

4. RESULTS

4.1. Study 1: Maternal race and pre-eclampsia: Cohort study and systematic review with meta-analysis.

There are three main findings from the cohort study. First, increased risk for PE is provided by Black race and several other elements of maternal characteristics, such as maternal age and weight, and factors from the medical history, such as previous pregnancy affected by PE. Second, in Black women, compared to White women, after adjustment for elements of maternal characteristics and medical history there is a 2-fold, 2.5-fold and 3-fold higher risk of total PE, preterm PE and early PE, respectively. Third, in women of South Asian race, compared to White women, there is a 1.5-fold higher risk of preterm and early PE but no statistically significant difference in total PE.

The literature search identified only 19 studies that provided data on the incidence of PE in some of the racial groups as defined by the FMF study. However, most studies were considered to be at high risk of bias. Additionally, only three of the previous studies provided adjusted ORs, with adjustment for very few relevant maternal characteristics. In the combined data from these three studies with those of our study the risk of PE in women of Black and South Asian race, compared to White women, was increased.

4.2. Study 2. Maternal race and stillbirth: cohort study and systematic review with meta-analysis.

There are two main findings from the cohort study. First, increased risk for stillbirth is provided by Black race and several other elements of maternal characteristics, such as maternal body mass index and cigarette smoking, and factors from the medical history, such as previous pregnancy affected by stillbirth. Second, in Black women, compared with White women, after adjustment for elements of maternal characteristics and medical history there was a 2.4-fold higher risk of stillbirths; in South and East Asian women the rate of stillbirth was not significantly different from that in White women.

The literature search identified only 20 studies that provided data on the incidence of stillbirth in some of the racial groups as defined by the FMF study. However, most studies were considered to be at high risk of bias. Additionally, only 11 of the previous studies provided adjusted ORs, with adjustment for very few relevant maternal characteristics. In

the combined data from these studies with those of our study the risk of stillbirth in Black women was 1.8-fold higher and in South Asian women the risk was 1.6-fold higher than in White women; there were no studies providing adjusted ORs in women of East Asian race.

4.3. Study 3. The incidence of pre-eclampsia: effect of deprivation.

There are three main findings of this study. First, the incidence of PE was higher in women living in the most (vs. least) deprived areas. However, such a relationship between IMD and the incidence of PE is likely to be mediated by several maternal characteristics and elements from the maternal history that are known to be associated with an increased risk of PE. Second, the incidence of PE in Black women was more than twice as high as the incidence in White women. Such increased incidence of PE could be attributed to the lower socioeconomic status of Black, compared with White, women. However, after accounting for IMD, the incidence of PE in Black women was still higher than in White women. Third, in screening for PE by the competing risks model, inclusion of IMD does not improve the prediction of PE provided by maternal origin, other maternal characteristics and elements of medical history.

4.4. Study 4. Incidence of stillbirth: effect of deprivation.

There are two main findings of this study. First, although univariate analysis demonstrated that the risk of stillbirth (all, antenatal and placental dysfunction-related) was higher in women living in the most (vs. least) deprived areas, in multivariate analysis there was no significant contribution from IMD in the prediction of stillbirth provided by maternal origin, other maternal characteristics and elements of medical history. Significant prediction of stillbirth was provided by low and high maternal age, increasing body mass index, and history of chronic hypertension, diabetes mellitus type 1, previous stillbirth, smoking and Black women. Second, in Black (vs. White) women, the risk of all and antenatal stillbirth, after adjustment for other maternal risk factors, was 2.4-fold higher and the risk of placental dysfunction-related stillbirth was 2.9-fold higher.

5. DISCUSSION

5.1. Interpretation of results and implications for clinical practice

Prediction of pregnancy adverse outcomes necessitates first, data obtained from large prospective observational studies with accurate recording of detailed maternal demographic characteristics and medical history and the appropriate infrastructure for obtaining the necessary outcome measures, and second, multiple logistic regression analysis which defines the independent contribution of each risk factor. The data from the studies included in this thesis fulfil these criteria.

In this thesis, I described several elements from the maternal history that contribute to PE and stillbirth. In defining the specific contribution of one risk factor, such as African origin, it is essential that all other factors are taken into account. The relationship between maternal origin and PE and maternal origin and stillbirth has implications for the prediction of these adverse pregnancy outcomes. In particular, as shown in this thesis, the incidence of PE and stillbirth in women of African origin or Black women is at least double that in White women. The majority of stillbirths are related to placental dysfunction, reflected in the coexistence of SGA fetuses and/or PE and important components of screening for SGA fetuses and PE. A high proportion of placental dysfunction-related stillbirths can potentially be prevented by implementing screening for PE and treatment of the high-risk group with aspirin. This can help to prevent preterm PE but also can help to identify early SGA fetuses.

As is shown in this thesis, given the association between deprivation and a higher incidence of PE and stillbirth, I believe that improving the socioeconomic status of the poorer segments of society has the potential to reduce the incidence of adverse pregnancy complications. This would likely be through deprivation as a social determinant of health, to improve maternal characteristics and medical conditions that are risk factors for PE and stillbirth. Maternal origin as a risk factor for PE and stillbirth must be reflected in clinical practice guidelines.

5.2. Strengths and limitations

There are several strengths of the studies included in this thesis. First, prospective examination of a large multiethnic population of women with singleton pregnancies attending for their routine pregnancy care at the first trimester between 11-13 weeks' gestation, second, recording of detailed maternal and pregnancy characteristics that have previously been reported to be associated with the development of hypertensive disorders of pregnancy and stillbirth, third, the use of multiple logistic regression analysis that showed which factors are statistically significant in independent contribution to PE and stillbirth, fourth, examination of independent effects of maternal origin and deprivation, to address whether the higher incidence of PE and stillbirth in Black vs. White women living in England is associated with ethnical or socioeconomic differences between the two groups and whether IMD adds value to prediction of PE and stillbirth, over and above other known clinical risk factors, including maternal origin.

There are several limitations of the studies included in this thesis. The main limitation is that maternal origin was classified into five broad categories (White, Black, South Asian, East Asian and Mixed) according to the Office for National Statistics. I believe, that most likely there would be variations in outcome in subgroups within each category, such as between different regions of Africa and between African and Caribbean women classified as Black. People from different parts of the world have different risk factors for some diseases. However, the main objective of included studies was to examine the relative incidence of PE and stillbirth in the different groups of maternal origin rather than examine whether the origin of such differences was genetic or environmental.

Another limitation is the use of IMD, as it is not a suitable tool for targeting individuals, but a measure of relative deprivation based on the postcode of residence; not every person in a highly deprived area is necessarily deprived and some deprived people live in the least deprived areas.

Last, the limitation of the studies related to the findings of the systematic review of the literature and meta-analysis. The systematic review and meta-analysis as the way of analysing the data have highlighted the weakness of such approach in defining the contribution of one specific risk factor such as maternal origin. Although the combined number of patients arising from such studies can be very large the heterogeneity between individual studies and the lack or minimal adjustment for confounders produces results that cannot be used for accurate prediction of the outcome under investigation.

5.3. Relevance of results to Swedish population

The overall objective of public health policy and maternity health care in Sweden is to create conditions in society so that the entire population can enjoy good health on equal terms. Individuals of other origins than Swedish living in Sweden are heterogeneous populations. These populations have different experiences, backgrounds, health needs, and health-related behaviours.

Swedish population can be described as multiethnic. The proportion of foreign-born individuals registered in Sweden is about 19%.[116] The biggest proportion of foreign-born in Sweden are mainly from Syria, Irak, Finland, Polen, Iran and Somalia[105] while the biggest proportion of immigrants is 25-34 years old women, women of fertile age are mainly from India, Afghanistan, Syria, Eritrea, and Pakistan.[117]

In 2018, Statistics Sweden launched a new geographic division referred to as DeSO (Demografiska statistikområden) in Swedish, with the aim to facilitate the monitoring of socioeconomic status in small areas.[118] The creation of this new geography offers opportunities to develop new small-area level indices of socioeconomic status and to reflect on other important variables to account for. However, no available studies are present in the literature that tried to determine the association between DeSO and pregnancy adverse outcomes such as pre-eclampsia and stillbirth.

A Swedish study of 46,618 ethnically diverse pregnancies showed that low-income levels were associated with a higher risk for PE, adjusted risk ratio (aRR) = 1.25, 95% CI: 0.99, 1.59), however, the authors did not find an increased risk for women born in African countries.[119] The most likely explanation for such a finding is that only 2.1% of their cohort was of African origin (compared with 16% of ours), limiting their statistical power to detect associations between African origin and PE after adjustment for low-income level, as the findings of our studies suggest. However, this fact must not prevent Swedish healthcare from acting accordingly to the international studies that are in force, e.g. individuals of African origin.

A Swedish study of 1,313,978 single births, including 4,359 stillbirths, showed twice as high OR of stillbirth (OR 2.27 (95% CI 1.84-2.80)) for births to women of African

origin compared with births to Swedish women and the maternal socioeconomic factors, such as disposable income, the latter did not explain much of the disparities in risk.[120]

A population-based study of over two million individuals demonstrated that even in Sweden, a country where health care is universally provided, higher socioeconomic status is associated with decreased overall and cause-specific mortalities.[121]

In this thesis I emphasize the importance of PE screening to reduce the rate, or adverse effects of PE and stillbirth: first, screening for PE in the first trimester of pregnancy and offering aspirin in the high-risk population, second, a second-trimester scan to stratify the risk and define the intensity of subsequent monitoring, and third, a routine third trimester scan for effective identification of SGA fetuses with subsequent monitoring and timely delivery. In this thesis, I emphasize the importance of learning from studies based on heterogenous populations taking into account all known risk factors.

It is important to create opportunities and good care for all pregnant women, regardless of the country of birth or maternal origin. I believe that the results of my studies included in this thesis can be applied to the Swedish population as well to improve prenatal care, and to offer individual screening for pregnancy complications. This is extremely important, particularly taking into account that compliance with participation in Swedish antenatal care is extremely high. It is important to carry out studies within the Swedish population taking into account maternal characteristics, including country of origin and more extended socioeconomic status to investigate which are the factors that contribute to adverse pregnancy outcomes.

I believe that pregnancy is a window of opportunity to apply health care to women, their children and their families and it can have a huge effect on the whole population in a longer perspective. As we know, that there is a relationship between maternal origin or country of birth and adverse pregnancy outcomes, the research should now focus on illuminating what is represented by maternal origin. Once such factors are identified the appropriate political and medical strategies could be developed to reduce adverse outcomes. I believe that my studies included in this thesis are just the beginning of future discoveries.

6. CONCLUSIONS

This Thesis is based on four studies. Below I outline the conclusions of each study.

Study 1. Maternal race and pre-eclampsia: Cohort study and systematic review with meta-analysis.

It was concluded that in women of Black and South Asian origin the risk of PE, after adjustment for confounders, is higher than in White women.

Study 2. Maternal race and stillbirth: Cohort study and systematic review with meta-analysis.

It was concluded that in women of Black origin the risk of stillbirth, after adjustment for confounders, is about 2-fold higher than in White women. Consequently, closer surveillance should be granted for these women.

Study 3. The incidence of pre-eclampsia: effect of deprivation

It was concluded that the incidence of PE is higher in women living in the most deprived areas in England, and in Black women (vs. those in other racial groups), who also live in areas of higher deprivation. However, in screening for PE, inclusion of IMD does not improve the prediction of PE provided by race and other maternal characteristics and elements of medical history.

Study 4. Incidence of stillbirth: effect of deprivation

It was concluded that the incidence of stillbirth, particularly placental dysfunction-related stillbirth, is higher in women living in the most deprived areas in England. However, in screening for stillbirth, the inclusion of IMD does not improve the prediction provided by race and other maternal characteristics and elements of medical history.

7. PERSONAL CONTRIBUTION AND FUNDING

The work involved for the Thesis was carried out during a period of 27 months when I was a research Fellow at Kings' College Hospital in London after receiving a scholarship from the Fetal Medicine Foundation.

The data used for the Thesis were collected from Kings' College Hospital, London and Medway Maritime Hospital, Kent, both in England and for such collection many doctors were involved over many years.

I participated in the collection of data and carried out a search of the databases of the fetal medicine units of the two hospitals and created a research file. I examined all demographic characteristics and medical history, results of tests and pregnancy outcomes to identify any missing data of obviously wrong entries. I then searched the primary source of the data, such as hospital notes, and databases of laboratories and labour wards to ensure accurate recording of results.

I carried out an extensive search of the literature on the prediction of PE and stillbirth and developed the objectives of the studies for the Thesis. I participated in the analysis of results and played an active role in the writing of the papers which were published in high-impact scientific journals. I wrote the Thesis on my own.

The studies in this thesis were supported by grants from the Fetal Medicine Foundation (UK Charity No: 1037116). This body had no involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

8. POPULÄRVETENSKAPLIG SAMMANFATTNING

I utvecklade länder har kvinnor från lägre socioekonomisk bakgrund än kvinnor från högre socioekonomisk bakgrund och av annat etnisk bakgrund än vita kvinnor en högre förekomst av fler komplikationer under graviditeten. Det finns dock få studier som visar hur socioekonomisk bakgrund och etnisk bakgrund påverkar risken för graviditetskomplikationer. Detta väcker frågan om observerade skillnader i graviditetsutfall, såsom havandeskapsförgiftning och dödfödsel, mellan kvinnor med olika etnisk bakgrund beror på socioekonomiska faktorer eller andra bakomliggande faktorer.

För att försöka besvara dessa frågor utförde vi först systematiska översikter med sammanställningar av tillgängliga studier över preeclampsi (PE) eller havandeskapsförgiftning och dödfödsel hos kvinnor med olika etnisk bakgrund.

Systematiska litteratur-översikter identifierade studier med kombinerade resultat på flera miljoner graviditeter. De flesta studier bedömdes dock vara förknippade med hög risk för partiskhet och i de flesta justerades inte resultat för maternella bakgrundsfaktorer.

Vidare undersökte vi samband mellan PE och självdefinierad ras (vit, svart, sydasiatisk, östasiatisk och blandad) hos drygt 150,000 gravida kvinnor som inkluderats i en screeningstudie vid Fetal Medicine Foundation i England. Härvid justerade vi för bakgrundsfaktorer såsom moderns ålder, vikt, längd, befruktningsmetod (naturlig eller med hjälp av IVF eller användning av ägglossningsläkemedel), cigarrettrökning under graviditet, medicinsk historia av kronisk hypertoni, diabetes mellitus, systemisk lupus erythematosus eller antifosfolipidsyndrom, familjehistoria med havandeskapsförgiftning hos patientens mor och obstetrisk historia som inkluderade paritet (förstföderska eller omföderska), tidigare graviditet med PE och tidigare födsel av litet barn för tiden).

För det tredje undersökte vi sambandet mellan det engelska indexet för socioekonomiskt nivå (Index of Multiple Deprivation (IMD)), och förekomsten av PE och dödfödsel i en stor multietnisk grupp av gravida kvinnor i sydöstra England och bedömde om IMD bidrar till förutsägelsen av PE och dödfödsel.

Denna avhandling visar för det första att risken för PE och dödfödsel hos kvinnor i England som definierar sig som svarta, efter justering för bakgrundsfaktorer, är högre än hos kvinnor som definierar sig som vita, och för det andra att förekomsten av PE och dödfödsel är högre hos kvinnor som bor i de mest socioekonomiskt eftersatta områdena. Inkludering av IMD i en screening för PE och dödfödsel förbättrade dock inte förutsägelsen av dessa sämre graviditetsutfall jämfört med att enbart inkludera självdefinierad ras.

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