GENETIC AND EPIGENETIC PROFILING OF PLACENTAL INSUFFICIENCY:
IDENTIFYING BIOMARKERS OF PREECLAMPSIA AND INTRAUTERINE
GROWTH RESTRICTION

by

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Abstract

Preeclampsia (PE), characterized by maternal hypertension and proteinuria, is the leading cause of maternal and perinatal morbidity and mortality worldwide. PE can be subdivided into early-onset PE (EOPE), diagnosis <34 weeks, and late-onset PE (LOPE), diagnosis ≤34 weeks.

Intrauterine growth restriction (IUGR), pathologically poor fetal growth, often co-occurs with PE. Both conditions are thought to be due to the placenta, the organ responsible for oxygen and nutrient transport to the fetus, not functioning adequately; this is referred to as placental insufficiency (PI). Currently there is no consistent clinical test to predict pregnancies at risk of these conditions.

This dissertation investigated placental genetic and epigenetic profiles to assess their utility to identify novel protein biomarkers in maternal blood and to subclassify PE and IUGR placentas. DNA methylation (DNAm) in the placenta at delivery correlated to second trimester Inhibin alpha and third trimester fibronectin levels in maternal blood, indicating that DNAm alterations may be useful to identify novel biomarkers. Widespread DNAm alterations were identified in EOPE placentas, many of which validated in an independent cohort. These changes can be used to refine clinical diagnoses. Placental DNAm signatures can help to refine clinical diagnoses to create more homogenous pathological groups, aiding in more robust predictive algorithms for PI conditions.

Telomere length (TL) was also assessed as a potential biomarker, as it has been reported altered in placentas of PE and IUGR pregnancies. This is thought to be due to the hypoxic environment
associated with PI which results in DNA damage, and shortened TL. However, correcting for placental gestational age and fetal sex, TL was not shorter in LOPE or IUGR in our population. EOPE placentas trended towards shorter TL (p=0.1). Overall, these studies found that TL is not likely to be an informative marker of PI. These studies show the potential utility of DNAm in identifying novel protein biomarkers in maternal blood, refining clinical diagnoses to create more homogenous subtypes of PI, or as a potential biomarker itself for identifying pregnancies at risk of PI conditions.
Lay Summary

Health complications during pregnancy affect both the mother and baby. In ~10% of pregnancies babies fail to grow as expected. Slow growth can be seen with high blood pressure and high protein in the mother’s urine; called preeclampsia. These complications occur when the placenta, the organ that is responsible for regulating nutrients and oxygen transport to the baby, functions inadequately. Both of these complications can negatively affect the child’s health. Currently there is no conclusive method to predict which women will develop these complications. This dissertation investigates potential biomarkers to predict pregnancies at risk of these conditions. I found that DNA methylation, modifications to DNA that change how the gene operates, can be used to identify new biomarkers in the mother’s blood and help properly diagnose these conditions. Telomere length, repetitive regions at the end of chromosomes are likely not sufficient indicators of placenta not functioning properly.
Preface

Parts of this dissertation were previously published as follows:

1. A version of the Introduction and Discussion has been submitted as an invited review for publication by SL Wilson and WP Robinson (2017).

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As Chapter 3, 4, and 5 have remained relatively unchanged from their published versions (Chapters 3-5). I have preserved the use of plural first person nouns. In the remainder of the dissertation, I use first person pronouns.

Parts of this dissertation were performed by collaborators:

- **Chapter 3**
  - A subset of maternal plasma samples were ascertained by Dr. Peter von Dadelszen, others were recruited by members of the Robinson lab. Women were recruited either by the Robinson lab research coordinator (various) or referring physicians including Dr. Sylvie Langlois, Dr. Hayley Bos, Dr. Peter von Dadelszen. In addition some placental samples were obtained by Dr. Deborah McFadden and the Dept. of Pathology at BC Children’s and Women’s Health Centre. Placental sampling and DNA extraction were completed by Ruby Jiang and Dr. Maria Peñaherrera. All co-authors edited and contributed to the manuscript. Ethics approval was granted by the University of British Columbia and BC Women’s and Children’s Hospital Research Ethics Board (H04-70488). Experimental design and hypothesis were conceived by WP Robinson and myself. K Hogg helped design the pyrosequencing primers for PAPPA. I performed the experiments and data analysis.

- **Chapter 4**
Recruitment of women and placental processing in the discovery cohort were completed as per Chapter 3. Recruitment of samples from the validation cohort was completed by Katherine Leavey and Brian Cox. Early-onset preeclampsia and preterm controls samples on the Illumina Infinium HumanMethylation450 array were run by John Blair and Dr. Maria Peñaherrera. Late-onset preeclampsia, intrauterine growth restriction, and term control placentas on the Illumina Infinium HumanMethylation450 array were run with the help of Dr. Maria Peñaherrera. Experimental design and hypothesis were conceived by WP Robinson and myself. I performed the data analysis. All co-authors edited and contributed to the manuscript. Ethics approval was granted by the University of British Columbia and BC Women’s and Children’s Hospital Research Ethics Board (H04-70488).

Chapter 5

Recruitment of women and placental processing in the third trimester cohort were completed as per Chapter 3. In addition, samples from earlier in pregnancy were obtained with the help of Dr. Alex Beristain, Dr. Deborah McFadden and the Dept. of Pathology at BC Children’s and Women’s Health Centre. Placental sampling and DNA extraction were completed by Ruby Jiang and Dr. Maria Peñaherrera. Telomere length measurements by qPCR were complete with the help for Yao Liu. Early-onset preeclampsia and preterm controls samples on the Illumina Infinium HumanMethylation450 array were run by John Blair and Dr. Maria Peñaherrera. Late-onset preeclampsia, intrauterine growth restriction, and term control placentas on the Illumina Infinium HumanMethylation450 array
were run with the help of Dr. Maria Peñaherrera. Experimental design and hypothesis were conceived by WP Robinson and myself. I performed the data analysis. All co-authors edited and contributed to the manuscript. Ethics approval was granted by the University of British Columbia and BC Women’s and Children’s Hospital Research Ethics Board (H04-70488).
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β        DNA methylation measure
Δβ       Change in DNA methylation
<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>450K</td>
<td>Illumina Infinium HumanMethylation450 array</td>
</tr>
<tr>
<td>AC</td>
<td>Abdominal circumference</td>
</tr>
<tr>
<td>AFP</td>
<td>Alpha-fetoprotein</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CG</td>
<td>Cytidine-guanosine</td>
</tr>
<tr>
<td>CoV</td>
<td>Coefficient of the variance</td>
</tr>
<tr>
<td>CpG</td>
<td>Cytidine-phosphate-guanosine</td>
</tr>
<tr>
<td>CPM</td>
<td>Confined placental mosaicism</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribose nucleic acid</td>
</tr>
<tr>
<td>DNAm</td>
<td>DNA methylation</td>
</tr>
<tr>
<td>DNMT</td>
<td>DNA methyltransferases</td>
</tr>
<tr>
<td>ENCODE</td>
<td>Encyclopedia of gene elements</td>
</tr>
<tr>
<td>EOPE</td>
<td>Early-onset preeclampsia</td>
</tr>
<tr>
<td>EPIC</td>
<td>Illumina Infinium MethylationEPIC array</td>
</tr>
<tr>
<td>EVT</td>
<td>Extravillous trophoblast</td>
</tr>
<tr>
<td>EWAS</td>
<td>Epigenome-wide association studies</td>
</tr>
<tr>
<td>FDR</td>
<td>False discovery rate</td>
</tr>
<tr>
<td>FN1</td>
<td>Fibronectin 1</td>
</tr>
<tr>
<td>GWAS</td>
<td>Genome-wide association studies</td>
</tr>
<tr>
<td>hCG</td>
<td>Human chorionic gonadotropin</td>
</tr>
<tr>
<td>HELLP</td>
<td>Hemolysis, elevated liver enzymes, and low platelet count</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
</tr>
<tr>
<td>ICM</td>
<td>Inner cell mass</td>
</tr>
<tr>
<td>INHA</td>
<td>Inhibin A</td>
</tr>
<tr>
<td>INHBA</td>
<td>Inhibin beta alpha</td>
</tr>
<tr>
<td>IUGR</td>
<td>Intrauterine growth restriction</td>
</tr>
<tr>
<td>LOPE</td>
<td>Late-onset preeclampsia</td>
</tr>
<tr>
<td>miRNA</td>
<td>microRNA</td>
</tr>
<tr>
<td>MLPA</td>
<td>Multiplex ligation dependent probe amplification</td>
</tr>
<tr>
<td>MoM</td>
<td>Multiple of the median</td>
</tr>
<tr>
<td>nIUGR</td>
<td>Normotensive IUGR</td>
</tr>
<tr>
<td>PAPP A</td>
<td>Pregnancy associated plasma protein A</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PE</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>PIH</td>
<td>Pregnancy induced hypertension</td>
</tr>
<tr>
<td>PLGF</td>
<td>Placental growth factor</td>
</tr>
<tr>
<td>PMD</td>
<td>Partially methylated domain</td>
</tr>
<tr>
<td>qPCR</td>
<td>Quantitative polymerase chain reaction</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SGA</td>
<td>Small for gestational age</td>
</tr>
<tr>
<td>SNP</td>
<td>Single nucleotide polymorphism</td>
</tr>
<tr>
<td>SOGC</td>
<td>The Society of Obstetricians and Gynecologists of Canada</td>
</tr>
<tr>
<td>SPH</td>
<td>Symphysis fundal height</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>SWAN</td>
<td>Subset within-array normalization</td>
</tr>
<tr>
<td>TERC</td>
<td>Telomerase RNA component</td>
</tr>
<tr>
<td>TERT</td>
<td>Telomerase reverse transcriptase</td>
</tr>
<tr>
<td>TL</td>
<td>Telomere length</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>wks</td>
<td>Weeks</td>
</tr>
</tbody>
</table>
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Chapter 1: Introduction

1.1 Placental insufficiency

The term ‘placental insufficiency’ encompasses many conditions in which the placenta does not function adequately. Understanding pathogenesis and screening for placental insufficiency conditions is important as pregnancies with these conditions are at an increased risk of preterm birth which is associated with both short and long term adverse health effects on the baby. Most commonly reported are hypertensive disorders of pregnancy and fetal growth restriction, specifically intrauterine growth restriction (IUGR). Hypertensive disorders of pregnancy can be divided into chronic hypertension, pregnancy induced hypertension (PIH), HELP syndrome, and preeclampsia (PE).

1.1.1 Preeclampsia and other hypertensive disorders of pregnancy

Pregnancy induced hypertension (PIH), is defined by high blood pressure (BP) first observed in pregnancy, but not accompanied by any other clinical symptoms and returning to normal within 12 weeks of delivery (1). HELP syndrome commonly co-occurs with PE, but also occurs as non-hypertensive HELLP syndrome (2). It is characterized by Hemolysis, elevated liver enzymes, and low platelet count, giving rise to the name HELLP. HELLP syndrome can cause severe liver damage and may result in severe adverse health outcomes on both the mother and the fetus (2). Preeclampsia (PE) is a multi-system, maternal hypertensive disorder commonly characterized by high BP and proteinuria, after 20 weeks’ gestation (3). PE occurs in 2-8% of pregnancies worldwide, and is the leading cause of maternal and perinatal morbidity and mortality (4). While high BP is consistently
considered to be equal to or greater than 140/90 mm Hg, whether or not proteinuria is required, and the amount required for diagnosis remains controversial (Table 1.1) (3,5,6,7,8,9,10,11). This makes identifying PE cases and comparing research studies difficult. For the purpose of this study we have defined PE as per the Society of Obstetricians and Gynecologists of Canada (SOGC) guidelines (3) as: new or existing hypertension (BP 140/90 mm Hg) with one or more of the following i) new proteinuria (protein creatine ratio>30mg/mmol,>0.3g/day or >2+ dipstick) after 20 weeks gestation, or ii) one or more adverse maternal symptoms (headache, vision disruption, abdominal pain, severe nausea or vomiting, chest pain, dyspnea), maternal organ dysfunction (pulmonary edema, placental abruption), altered maternal lab results (elevated serum creatinine, AST, ALT, LDH, platelet count<100x109/L, or serum albumin <10g/L), or fetal morbidity (oligohydramnios, IUGR, and/or reversed end diastolic flow). We have opted not to include fetal mortalities in our cohort as stillbirth is a heterogeneous condition that can be caused by a number of etiologies (12).

PE is often subdivided into subtypes (13,14,15,16) in order to obtain groups that are more homogeneous. Early-onset PE (EOPE) and/or severe PE is more commonly associated with placental pathology and co-occurring IUGR (17,18,19). Molecular profiling of both the placenta and maternal serum reveal many different profiles of altered gene expression, DNA methylation (DNAm) or protein levels in PE pregnancies, suggesting that multiple subtypes of the disease may be present (20,21,22,23,24,25,26,27). LOPE, term PE, or mild PE, and EOPE, preterm PE, or severe PE are often used interchangeably, although these terms overlap, their definitions do differ. EOPE is defined as a diagnosis of PE prior to 34 weeks gestation, while LOPE is defined as a diagnosis after 34 weeks gestation (4,28). When defined by preterm PE, diagnosis of PE <37
weeks gestation, and term PE, diagnosis >37 weeks gestation, some LOPE cases become grouped with the EOPE cases. Mild and severe PE aim to define subtypes of PE based on severity, and as such are defined by maternal BP. Severe PE includes cases in which maternal BP > 160/110 mmHg, while mild PE is any case of PE where maternal BP sits between 140/90 mmHg and 160/110 mmHg, independent of gestational age (28). While both EOPE and LOPE are associated with maternal factors, there are some factors that are specifically associated with either EOPE or LOPE. Lisonkova and Joseph (2013) investigated 456,688 pregnancies and births, and found that nulliparity, young maternal age (<20 years), and diabetes mellitus was strongly associated with LOPE, while EOPE was more strongly associated with African-American race, chronic hypertension and congenital anomalies (29).

There are a number of factors that increase an individual’s risk of developing PE including: family history of or previous pregnancy with PE (4), advanced maternal age, ethnicity, and maternal obesity (Body Mass Index (BMI) >30) (30,31,32,33). Women with pre-existing chronic conditions, such as essential hypertension (34), diabetes, or vascular disease, develop PE more frequently than those that do not (35). Additionally, pregnancies that were conceived with donor sperm, donor oocytes or donor embryos have been associated with increased incidence of PE, likely due to immune intolerance (36). As one of the proposed pathogeneses of PE is inappropriate immune response, repeated or longer exposure to paternal antigens is thought to establish maternal immunity to paternal antigens, decreasing the risk of PE (37,38), although this has not been found conclusively (39). Fetal factors, such as multi-fetal pregnancies and fetal chromosomal abnormalities have also been known to co-occur with PE at a much higher rate (40,41,42). Risk factors and placental phenotypes associated with PE are outlined in Figure 1.1.
Currently treatment of PE is limited to antihypertensive medications to decrease maternal BP, and in some cases anticonvulsive medication (e.g. Magnesium sulphate) can be prescribed to treat eclamptic seizures (30), and if necessary, delivery of the baby. Whether or not these medications are good approaches to treating PE, as they could potentially harm the fetus long term, has been controversial. However, a recent study by Magee et al. (2015) found no difference in infant health a year after delivery in PE pregnancies treated with tighter regulation (target diastolic 85 mm Hg) compared to PE pregnancies under less tight regulation (target diastolic 100 mm Hg) (43). Managing both PE and IUGR requires balanced consideration of both maternal and fetal health by prolonging gestation to minimize poor neonatal outcome, but delivering early enough to avoid fetal demise and optimize maternal health outcomes. Daily aspirin has been suggested and is commonly used as a treatment to decrease the risk of developing PE in high-risk populations (44,45,46). However, decreased risk with aspirin prescription was observed when prescribing low dose aspirin to women at high risk of developing PE or IUGR; when expanding this finding to populations representing all risk levels, a large sample size was needed to observe a slight decrease in risk, for this reason low dose aspirin would only be beneficial in the high risk population (46,47,48). While low dose aspirin has been found to reduce PE risk in high risk populations, how different health systems identify high-risk pregnancies differs.
Table 1.1. Clinical diagnosis criteria of preeclampsia worldwide.

<table>
<thead>
<tr>
<th>Country</th>
<th>Citation</th>
<th>Definition</th>
<th>Blood Pressure</th>
<th>Proteinuria</th>
<th>Proteinuria req diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Hypertension in pregnancy. Washington, D.C.: American College of Obstetricians and Gynecologists. 2013.</td>
<td>Hypertension (BP 140/90 mm Hg) and Proteinuria (&gt;300 mg in 24 hour urine collection) after 20 weeks gestation or Hypertension in the absence of proteinuria with either i) thrombocytopenia (platelet count &lt;100,000/mL), ii) impaired liver function (twice the normal levels of liver transaminases), iii) new development of renal insufficiency (elevates serum creatinine &gt;1.1 mg/dL or double of serum creatinine), iv) pulmonary edema, or v) new onset of cerebral or visual disturbances.</td>
<td>BP 140/90 mm Hg &gt;300 mg in 24 hour urine collection</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>CANADA</td>
<td>Magee, Laura A., et al. &quot;Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy.&quot; Journal of Obstetrics and Gynecology Canada 30.3 (2008): S1-S2.</td>
<td>New or existing hypertension (BP 140/90 mm Hg) with one or more of the following: i) new proteinuria (protein creatinine ratio 50 mg/mmol ≥ 0.3 g/day or &gt;2+ dipstick) after 20 weeks gestation, ii) one or more adverse maternal symptoms (headache, vision disturbance, abdominal pain, severe nausea or vomiting, chest pain, dyspnea), maternal organ dysfunction (pulmonary edema, placental abruption), altered maternal lab results (elevated serum creatinine, AST, ALT, LDH, platelet count &lt;100,000/L, or serum albumin &lt;10 g/L), or fetal morbidity (oligohydramnios, IUGR, and/or reversed end diastolic flow, or stillbirth)</td>
<td>BP 140/90 mm Hg Protein creatinine ratio 50 mg/mmol ≥ 0.3 g/day or &gt;2+ dipstick</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>AUSTRALIA &amp; NEW ZEALAND</td>
<td>Lowe e et al. Guidelines for the management of hypertensive disorders of pregnancy. Society of Obstetric medicine of Australia and New Zealand 2008.</td>
<td>Hypertension (BP 140/90 mm Hg) as well as i) renal involvement: proteinuria: creatinine ratio (50 mg/mmol), serum of plasma creatinine (≥40 umol/l), or oliguria, ii) hematological involvement: thrombocytopenia, hemolysis or disseminated intravascular coagulation, iii) Liver involvement: elevated serum transaminases or severe epigastric or right upper quadrant pain, iv) Neurological involvement: convulsions, hyperflexia, severe headache, persistent visual disturbances, or stroke, v) Pulmonary edema, or vi) Fetal growth restriction, or vii) Placental abruption</td>
<td>BP 140/90 mm Hg 30 mg/mmol</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>UNITED KINGDOM</td>
<td>Royal College of Obstetricians and Gynaecologists (2006) The management of severe pre-eclampsia/eclampsia, National Institute for Health and Clinical Excellence (2008) Antenatal care. NICE clinical guideline 62. London: National Institute for Health and Clinical Excellence.</td>
<td>New onset of hypertension (140-90 mm Hg) after 20 weeks gestation with significant proteinuria (&gt;1+ dipstick with protein creatinine confirmation. protein creatinine ratio &gt;30 mg/mmol or urine collection protein &gt;300 mg). Other biochemical or haematological symptoms along with severe hypertension (BP 100/160 mmHg) constitutes as severe preeclampsia.</td>
<td>BP 140/90 mm Hg &gt;1+ dipstick with protein creatinine confirmation. protein creatinine ratio &gt;30 mg/mmol or urine collection protein &gt;300 mg</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>EUROPE</td>
<td>The Classification, Diagnosis and management of the Hypertensive Disorders of Pregnancy: A revised statement from the ISH/HP (2014)</td>
<td>Hypertension (140-90 mm Hg) after 20 weeks gestation in addition to one or more of the following: i) proteinuria (&gt;30 mg/mmol or 0.3 g/day or &gt;300 mg in 24 hours or 1 g/L or 2+ on dipstick), ii) Maternal organ dysfunction (renal insufficiency: creatinine &gt;90 umol/L or 1.02 mg/dl, liver involvement: elevated transaminases at least twice the upper limit of normal, right upper quadrant or epigastric abdominal pain, neurological complications: eclampsia, blindness, stroke, etc., haematological complications: thrombocytopenia, platelet count &lt;150,000/dl, DIC, haemolysis), iii) Uteroplacental dysfunction (IUGR)</td>
<td>BP 140-90 mm Hg &gt;30 mg/mmol or 0.3 g/day or &gt;300 mg in 24 hours or 1 g/L or 2+ on dipstick</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>AFRICA</td>
<td>Fokom-Domgue, Joel, and Jean Jacques N. Noalipia. &quot;Diagnosis of Hypertensive Disorders of Pregnancy in Sub-Saharan Africa: A Poorly Assessed But Increasingly Important Issue.&quot; The Journal of Clinical Hypertension 17.1 (2015): 70-73.</td>
<td>Diastolic BP &gt;90 mm Hg and proteinuria (&gt;300 mg in 24 hours) after 20 weeks gestation**</td>
<td>Diastolic BP &gt;90 mm Hg &gt;300 mg in 24 hour urine collection</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>SOUTH AMERICA</td>
<td>Guide of the Argentinian Society of Arterial Hypertension. Argentine Society of Hypertension</td>
<td>Hypertension (140-90 mmHg) in at least 2 measures in the same arm at 15 min intervals and proteinuria (&gt;300 mg in 24 hours or &gt;2+ on dipstick) after 20 weeks gestation</td>
<td>BP 140-90 mm Hg &gt;300 mg in 24 hour urine collection or &gt;2+ on dipstick</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

** May not be the most accurate criteria for Africa as black women have generally high BP, more likely to conceive with chronic hypertension and more likely to develop hypertensive diseases during pregnancy. Fokom-Domgue et al (2014) suggests re-evaluating how to define PE in an African population.
1.1.2 Intrauterine growth restriction

Intrauterine growth restriction (IUGR), is defined as poor fetal growth due to a pathological mechanism. This is distinct from low birth weight, which is defined as birth weight <2500g (not corrected for gestational age) by the World Health Organization (WHO) (49), and small for gestational age (SGA) infants, which is defined as birth weight <10th percentile for the gestational age and fetal sex (50,51,52). IUGR is also variously defined as birth weight <10th percentile (50,53,54), birth weight of <3rd percentile(3,15,55), <5th percentile(56,57), or <10th percentile with other indications of poor growth (abnormal doppler findings)(15,55). Fetal growth restriction is a term now being used instead of IUGR in attempt to clarify and distinguish between SGA infants that are constitutionally small, but otherwise healthy, and IUGR infants that are small due to a pathological mechanism. For the fetal growth restriction definition, Mamelle et al. (2001) proposed an individualized model of birth weight taking into account gestational age, fetal sex, birth rank, maternal age, maternal height and maternal weight; this method tries to estimate an individual’s genetic potential of birth weight rather than setting a percentile threshold (58). Gardosi et al. (2000) also proposed the idea of individualized growth trajectories for fetuses using a model that incorporates fetal weight, gestational age, sex, maternal weight and height, parity and ethnicity(59). Distinguishing between a baby that is small but healthy, from one that has had growth limited due to extrinsic factors is challenging, but necessary in order for clinicians to appropriately manage pregnancy.

Measurements in utero that may indicate a risk of IUGR may include: ultrasound findings of fetal abdominal circumference (AC) <10th percentile for gestational age and sex or estimated fetal weight <10th percentile for gestational age (60), symphysis-fundal height (SPH) measuring
the size of the uterus (61), placenta ultrasound measures (length, thickness, fetal:placental weight ratio), and uterine and umbilical artery measures (notching, blood flow, pulsatility) (62). While these measures are useful and help clinicians best assess which fetuses are growth restricted vs constitutionally small, using thresholds defined by a proportion of the population will unavoidably result in a heterogeneous population of both pathologic and normal fetuses and will not include growth restricted fetuses that are above those thresholds. While *in utero* measures are needed to measure fetal growth trajectories over time and to prospectively identify pregnancies at risk of IUGR, definitions based on birth weight may be more helpful in research circumstances to compare results across studies. Unifying and stricter definitions may aid in identifying a more homogenous group of IUGR and associated causal mechanisms.

Risk factors of IUGR are similar to PE, and include i) pre-existing maternal conditions such as: chronic hypertension, diabetes and vascular disease (63); ii) previous pregnancy history such as a pregnancy diagnosed with IUGR or PE, iii) multi-fetal pregnancy, iv) some fetal and/or placental aneuploidies, and v) co-occurring PE itself (63). Figure 1.1 outlines both PE and IUGR risk factors. There are two different presentations of IUGR, i) asymmetrical IUGR, where the head is of normal measure (referred to as brain sparing), but the rest of the body is small and ii) symmetrical IUGR, where the fetus is overall small, but proportional. Pregnancies with asymmetric IUGR fetuses are at significantly higher risk of PE, and adverse neonatal and long term health outcomes (64,65). It has been hypothesized that asymmetric IUGR is the result of placental insufficiency, where reduced blood flow to the placenta and fetus result in favour of blood flow to the fetal brain. Whereas, symmetric IUGR is thought to be more commonly due to
teratogen or viral exposures during development, chromosome abnormalities, genetic syndromes or inborn errors in metabolism resulting in a proportional reduction in fetal size (66).

Both PE and IUGR are extremely heterogeneous conditions where many maternal, fetal and placental factors can contribute and influence the pathogenesis of disease (67,68,69,70). Asymmetric IUGR and EOPE are associated with abnormal placentation (66). In an attempt to adapt to the abnormal placentation, molecular characteristics in the placenta change and in many cases increased apoptosis and necrosis of placental cells which are then shed into maternal circulation, may result in an activated maternal immune response (71). It is unclear whether different subtypes of PE and IUGR are varying severities of the same condition (overall placental insufficiency), or whether they are distinct entities from one another. For example, it is unknown whether LOPE is a less severe phenotype of abnormal placentation and subsequent maternal immune response, or whether it is driven solely by maternal immune intolerance. Resolving this issue is essential to identifying sensitive and specific biomarkers to predict these conditions. Grouping together placental insufficiency conditions that are actually distinct entities will limit a study’s ability to identify true differences between the cases and controls, inhibiting our ability to identify the best candidate biomarkers. Subtypes with distinct entities will likely have different biomarkers that will predict each subtype, whereas subtypes that are different severities of the same condition could utilize the same panel of biomarkers.
Figure 1.1 Risk factors for preeclampsia (PE) and intrauterine growth restriction (IUGR).

Risk factors lead to abnormal placentation and/or maternal immune intolerance, resulting in altered placental pathology and molecular profiles, giving rise to maternal and fetal phenotypes.
1.2 The placenta and its development

1.2.1 Placental structure

The placenta is the organ involved in nutrient and gas exchange, blood flow to the fetus, hormone regulation and secretion, protection of the fetus from harmful xenobiotics, and blood cell production, once fully developed (72). The human placenta is made up of many tree-like structures, called chorionic villi. These chorionic villi are the sites at which nutrient and gas exchange take place. Distinct from some other placental mammals such as horses, cats and sheep, the human placenta is discoid in shape and is classified as hemochorial; meaning that the placental trophoblast cells come into direct contact with maternal blood, but the maternal and fetal vessels do not come into direct contact with each other (72,73). It is thought that the hemochorial placenta evolved as it possesses an advantage for more efficient nutrient transport resulting in a faster growth rate (74).

1.2.2 Placental development

1.2.2.1 Implantation

Placental development occurs rapidly after fertilization. Cell division occurs, taking the single-cell zygote to a multi-cell blastocyst. The blastocyst consists of an inner cell mass (ICM) and a single-cellular trophectoderm layer that surrounds the ICM, and forms the blastocyst cavity. The trophectoderm layer will differentiate into the trophoblast cell lineages of the placenta and the ICM will contribute both to the fetal and extraembryonic tissues (75) (Figure 1.2). Between 6-12 days post-fertilization, the blastocyst implants into the uterine wall (76). The trophoblast cells, surrounding the ICM secrete metalloproteinases, which degrade the uterine lining (77). Trophoblast cells differentiate into mono-nuclear cytotrophoblast cells (73) which form column
structures that will become the chorionic villi. Cytotrophoblasts differentiate into either terminally differentiated multi-nucleated syncytiotrophoblast cells (by fusion of cytотrophoblast cells to each other) or extravillous trophoblast (EVT) cells. The multi-nucleated syncytiotrophoblast cells make up the outer layer of the chorionic villi and are involved in the initiation of placental development, invading the uterine wall (endometrium) and eroding the maternal tissues. Once the syncytiotrophoblast layer has initially invaded the endometrium, a subset of the cytотrophoblast cells will differentiate into EVTs, which migrate beyond the chorionic villi and syncytiotrophoblast cells to invade and remodel the uterine spiral arteries for increased blood flow to the placenta. Cytotrophoblast columns will then advance past the syncytiotrophoblast and connect to one another, forming the cytотrophoblast shell. Empty spaces between the cytотrophoblast columns are termed lacunar spaces, lined by the syncytiotrophoblast (78). The outer syncytiotrophoblast layer is in direct contact with the maternal blood, involved in the transfer of oxygen and nutrients to the fetus (73,79). The cytотrophoblast shell regresses and eventually forms the placenta basal plate where the chorionic villi are anchored. At 10-12 weeks gestation blood flow between the mother and the placenta is established. At this time, the fetus will fully utilize the placenta for nutrients and blood flow and subsequently increase its growth rate (73).
Figure 1.2. Cell differentiation of cell types that comprise fetal tissues and the placenta.
1.2.2.2 Angiogenesis

Placental angiogenesis, the establishment of placental and fetal circulations, is essential to fetal health and development. While differentiation of cytotrophoblast cells into either syncytiotrophoblast or EVTs is regulated by changes in both DNA methylation (DNAm, mitotically stable modifications made to DNA that can influence gene expression) and gene expression, oxygen tension plays a critical role as well (80,81). During early embryonic development, spiral arteries are plugged by cytotrophoblast cells to create the hypoxic conditions needed to promote cytotrophoblast proliferation (82). Hence, there is no direct connection between the mother and embryo, therefore there is little oxygen transport to the fetus. These hypoxic conditions promote cytotrophoblast proliferation and are essential for placental angiogenesis (83). Key angiogenic factors involved in placental vascularization are regulated by hypoxia induced gene regulation (84). At approximately 10-12 weeks gestation, the uterine arteries become unplugged, allowing for oxygen perfusion of the placenta through the differentiation of the cytotrophoblast cells into EVTs which remodel the uterine spiral artery (82). Once blood flow is established, maternal blood can deliver oxygen and nutrients to the developing fetus.

1.2.2.3 Nutrient transport

During the first trimester, transport of nutrients from mother to fetus is histiotrophic through trophoblast phagocytosis (vesicle mediated) and/or endometrial glandular secretions. After 10-12 weeks, and the establishment of blood flow to the intervillous space, nutrient exchange is performed through the placenta (72). The primary mode of transport across the placenta is passive transport in which molecules move through the placental membrane based on the
concentration gradient (i.e. molecules move to the area with least concentration). This mode of
transportation does not require any energy input however, migration across the placenta is
dependent on the chemical properties of the molecule including polarity, hydrophilicity, size, and
protein concentration in both the maternal and fetal blood streams. This mode of transportation is
often used by hormones and oxygen exchange across the placenta (85). Active transport requires
energy input in order for protein transporters to assist the molecules across the barrier. Essential
nutrients are often transported through active transport as maternal concentrations of amino acids
are often lower, therefore an active transport mechanism is required to move these nutrients
across the placental barrier (86). Facilitated diffusion requires additional proteins to bind to the
molecule and aid in its transport across the placenta; this mechanism is utilized by glucose due to
its large size. Similar to passive transport, facilitated diffusion abides by a concentration gradient
and does not require energy input. Vesicular transport is used to transport large molecules,
able to pass through the placenta by any other means. The molecules cross by being engulfed
in microvilli that aid in their transportation (87). Modes of transport across the placenta and
molecules that utilize them are listed in Table 1.2.

Table 1.2. Methods of transport utilized by the placenta.

<table>
<thead>
<tr>
<th>Type of Transport</th>
<th>Molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple Diffusion/Passive transport</td>
<td>Fatty acids, lipids, water: cross readily across the placenta</td>
</tr>
<tr>
<td>Active Transport</td>
<td>Most amino acids, K, Mg, Ca, PO4; requires energy to transport across</td>
</tr>
<tr>
<td>Facilitated Diffusion</td>
<td>Glucose and essential nutrients; protein mediated</td>
</tr>
<tr>
<td>Rapid Diffusion</td>
<td>Oxygen, CO2, gases; rate limiting step is blood flow</td>
</tr>
</tbody>
</table>
1.2.2.4 Paracrine, endocrine, autocrine and immune functions in the placenta

During pregnancy, the embryo and later fetus, with half its DNA foreign to the mother, must evade the maternal immune system to ensure its survival. There are several processes that are thought to be involved in the maternal-fetal interface to aid in immunotolerance. Paracrine autocrine, and endocrine signaling between the mother and the fetus is essential for immunosuppression (88). A variety of proteins are secreted from the uterine lining and uterine wall to aid in the implantation process and also inhibit trophoblast cells from invading too far into the maternal myometrium (89). Trophoblast cells invading the maternal tissues will secrete metalloproteinases and urokinase plasminogen activator to erode the uterine wall during the implantation and trophoblast invasion processes (89). Additionally, trophoblast cells will also secrete an array of immunosuppressive factors, and also lack major histocompatibility complexes and some human leukocyte antigen (HLA) to prevent an attack by the maternal immune system (89). Shedding of placental trophoblast cells into the maternal circulation may be another process by which the maternal immune tolerance is achieved (89).

1.2.2.5 Placental development in preeclampsia and intrauterine growth restriction

The pathogenesis of PE and IUGR remains relatively unclear, however current hypotheses revolve around poor placental invasion and remodeling of the uterine spiral artery (4,30,67). This can result in decreased blood flow leading to hypoxia in the placenta and fetus. Hypoxia is a normal phase of development (67,90), however, prolonged hypoxic state results in rapid reoxygenation which inhibits trophoblast differentiation leading to a reduction of syncytiotrophoblast cells responsible for hormone production and nutrient regulation required for pregnancy maintenance as well as fetal and placental growth (91,92,93). Exposure to a prolonged
hypoxic state, and subsequent reoxygenation, can cause irreparable damage and result in increased shedding of microparticles into the maternal blood stream; this may produce an inflammatory response leading to the clinical phenotype of PE (94,95). Abnormal placentation may also be due to a negative response of the maternal immune system to the paternal antigens. An inflammatory response occurs when the female is exposed to paternal antigens. This response may be crucial to allow the maternal immune system to process paternal antigens and inhibit inflammatory responses against any future conceptus (30,33,96).

1.3 Current screening for placental insufficiency

1.3.1 Imaging tools

1.3.1.1 Ultrasound

Currently, ultrasound remains the standard approach to placental and fetal imaging during gestation. This is due to its minimal cost, safety (non-invasive and no radiation), and that information on the health of the placenta can be obtained as early as eight weeks of pregnancy (97). The Doppler ultrasound was developed to assess appearance and location of the placenta, but also measure blood velocity within the placenta. Therefore technicians can gauge fetal: placental perfusion as well as vascular impedance (97). However, ultrasound is limited by the angles in which the ultrasound wand can visualize the placenta. Placental magnetic resonance imaging (MRI) and positron emission topograph (PET) are able to overcome this particular obstacle.
1.3.1.2 Magnetic resonance imaging and positron emission topograph

Although not routinely used to assess the placenta, MRI and PET are exceptional tools to visualize both placental appearance and function. Overcoming the limitations of ultrasound, MRI and PET can produce images from all axes of the placenta (97). MRI has such fine resolution, that it can estimate blood flow within localized regions of the placenta (97). Commonly, MRI requires a contrast agent in order to visualize the placenta, and few studies have looked at the safety of using these agents in pregnant humans (98,99). For this reason, placental MRI is used mostly as a confirmatory tool in cases where the benefits of doing the imaging outweigh the risks; these are usually cases where it is hard to visualize the site of implantation, or hard to measure low velocity blood flow with great concern for the outcome and wellbeing of the fetus (100,101). However, recent studies have used a phase-contrast MRI, not requiring a contrast agent to measure blood velocity in the field (102). This methodology can potentially be used to measure blood velocity in the placenta. Similarly, PET imaging requires radioactive dye which can cross the placental barrier, thus it has not been recommended for use in humans (100). More recent studies have suggested that the amount of radioactivity would not be harmful (103), while others push for more animal trials to better understand radiation dose effects on the fetus (104).

Imaging the placenta during gestation can give us information as to the placental function, and a woman’s risk of developing complications due to placental insufficiency. Currently, a large meta-analysis using uterine artery Doppler ultrasound data on 55,974 first trimester pregnancies produced a sensitivity and specificity of detecting EOPE of 47.8% and 92.1%, respectively. Similarly, sensitivity and specificity of detecting symptoms indicative of early onset fetal growth restriction was 39.2% and 93.1%, respectively; and the sensitivity and specificity of detecting
symptoms of any onset of PE (26.4% and 93.4%, respectively) or IUGR (15.4% and 93.3%, respectively) (105). While current imaging techniques can be fairly certain in the high risk pregnancies they identify, they are missing a large proportion of high risk pregnancies. Additionally, other caveats remain to the efficiency of detecting high risk women. Although poor implantation or infarctions visible in the placenta would indicate a high risk pregnancy, in some cases the placenta is able to overcome these obstacles (106). Additionally, placental lesions and infarctions are commonly seen in healthy pregnancies especially at later gestational ages (107). Placental imaging as a whole is limited by cases in which abnormal blood flow to the placenta and/or placental appearance anomalies are detectable to call a high risk pregnancy. Many pregnancy complications will arise with no indication of placental abnormalities on ultrasound (106). To improve our ability to detect women at high risk of developing many types of pregnancy complications, due to many pathogeneses it has been suggested that combining ultrasound findings with maternal health history and maternal serum markers will increase sensitivity and specificity. Rolnik et al. (2017) (46) suggest the use of maternal factors, mean arterial pressure, uterine-artery pulsivity index, and maternal serum pregnancy-associated plasma protein A and placental growth factor, as used in Akolekar et al. (2013) with a detection rate of 76.6% of preterm PE and false discovery rate of 10% (108), however this is not significantly better than the results from using just Doppler ultrasound (105). Improving the identification of high risk pregnancies will allow for preventative treatment to pregnancies in need and aid in optimizing our identification of women who will subsequently develop complications such as PE and IUGR (109).
1.3.2 Maternal serum markers

Currently, women in Canada are offered maternal serum screening during their first and second trimesters of pregnancy to identify pregnancies at risk for fetal chromosome abnormalities (specifically trisomy 18 and 21), and neural tube defects. The maternal serum screening panel consists of five protein biomarkers: Pregnancy associated plasma protein A (PAPP-A), human chorionic gonadotropin (hCG), alphafetoprotein (AFP), estriol, and inhibin A (INHA), all of which are measured by blood tests (110,111,112). Abnormal levels of these markers that are not explained by chromosomal abnormalities or fetal anomalies may be indicative of obstetrical complications such as: placenta accreta, increta, or percreta, spontaneous abortion, preterm birth, IUGR, PE, intrauterine fetal demise, or placental abruption. Studies developed in the United Kingdom have shown much promise in using maternal screening markers to predict adverse pregnancy outcomes, particularly PE and IUGR (109). However, there are concerns as to whether these results are generalizable to other populations and whether PAPP-A and placental growth factor (PLGF) levels predict high risk women more than a basic personal and family history (113). New approaches are shifting the focus from ultrasound and protein biomarkers in maternal serum to the presence of cell free DNA, RNA and miRNA in maternal blood (114).

1.4 Molecular studies of the placenta in placental insufficiency

1.4.1 Chromosomal associations

One of the few genetic associations known to increase incidence of PE and IUGR is the presence of trisomic cells in the placenta (42). These could be cases of constitutional trisomy (trisomic cells also present in the fetus), or confined placental mosaicism (CPM) (trisomic cells confined to placenta). CPM occurs in up to 2% of pregnancies ascertained through chorionic villi
sampling (115) and is associated with increased incidence of IUGR (116). CPM involving trisomy 16 (CPM16) has been associated with increased incidence of PE (117). DNAm profiling showed that CPM16 placentas had an overlapping profile with EOPE placentas (118). Few genes located on chromosome 16 have been associated with PE, however chromosome 16 harbors several genes involved in placental development (ex: CDH1 and ERK1, involved in trophoblast differentiation and invasion, respectively) (119,120). It is hypothesized that the extra chromosome 16 results in shallow trophoblast invasion into the uterine wall, resulting in PE. However, the mechanisms of how this occurs remains unknown (118).

1.4.2 Genetic variants

Genetic studies investigating the heritability component of PE have estimated heritability to be between 0.22-0.54 (121,122,123). While there are gene mutations that appear to segregate within families along with PE development (124,125,126), there has only been one genome-wide study that identifies and validates a single gene variant associated with increased susceptibility to PE (127). PE and IUGR are multifactorial etiologies, where numerous low penetrant genetic variants contribute small risk of PE and/or IUGR development, combined with environmental and maternal health exposures, result in disease manifestation (128). Many of the studies take a candidate gene approach, investigating single nucleotide polymorphisms (SNP) in genes involved in pathways known to play a role in placental insufficiency. This approach reduces the number of multiple test corrections needed, and increases the power of the study. However, it makes an assumption of causative pathways based on the current understanding of the pathogenesis of PE and IUGR, which is still relatively unclear. Allelic variation in genes acting within the angiogenic pathway (129), solute carrier pathway (130), endoglin pathway (131), and
inflammatory and immune response pathways (132,133,134), have been identified. However, results from these candidate genes studies have low reproducibility rates in other cohorts (134,135). Major contributors to the low reproducibility rate may be different subtypes of PE and IUGR and how they are defined, different variants being present in different populations, and that we expect low effect sizes, and the small sample size used in many studies is severely underpowered to detect such minute differences (136).

In recent years, several groups have performed genome-wide association studies (GWAS) in an attempt to uncover some of the missing heritability of the disorder (137-144). While this approach allows for investigating all variants without an a priori hypothesis, the number of variants being assessed results in many multiple test corrections. For this reason, massive sample sizes are needed to have enough power to detect variants with small effect sizes. Early studies from Australia, Finland, Holland, and Iceland all identified PE associated risk loci in their cohorts. However, these results have not yet been validated in independent cohorts. A large-scale effort to identify PE-associated variants in the Netherlands (InterPregGen) consists of a discovery cohort of 57,600 maternal serum samples, of which 11,600 samples had diagnosed PE (142). The consortium also had an additional 14,000 samples, of which 9,200 had diagnosed PE in which to validate any potential findings. Recently, InterPregGen reported a genetic risk to PE development when individuals possessed a variant within FLT1 (127), a gene and subsequent protein that has been consistently associated with PE (129,145,146,147). However, this particular variant is very common and does not fully explain the heritable component of PE.
1.4.3 Telomere length variation

Telomeres are repetitive sequences of DNA, located at chromosome end to protect them from end-to-end fusion and DNA damage. As DNA polymerase cannot synthesize DNA in the 3’-5’ direction, telomeres are reduced in length with every cell division in the absence of telomerase activity. Oxidative stress is a known mechanism that increases DNA damage and results in shortened telomere length and cell death (148) and is thought to be involved in PE and IUGR (4). For this reason, altered telomere length in the placenta has been proposed as a marker of PE and IUGR and has been investigated by several studies. Some studies reported shortened telomere length in PE and IUGR placentas, while other were unable to reproduce their results (149,150,151,152,153). The lack of reproducibility may be explained by differing models; some studies include fetal sex and gestational age as confounding factors and others do not (149-153), while some studies combine all PE together and others subdivide cases into EOPE and LOPE (149-153).

1.4.4 Transcriptomic alterations

1.4.4.1 Altered gene expression in preeclampsia and intrauterine growth restriction

There are numerous studies investigating altered gene expression in placentas from pregnancies complicated by PE and/or IUGR (20,21,147,154,155-161). Genes involved in cell proliferation, cell structure, lipid metabolism, transport, and angiogenic factors regulated by hypoxia have been reported overexpressed in PE (147,157,162), while genes involved in cell proliferation immunity, cell adhesion, and cell motility have been reported under expressed in PE (147,154,163). Interestingly, Sitras et al. (2009) compared gene expression between EOPE and LOPE and found that altered expression of genes involved in oxidative stress, inflammation and
endoglin signalling were more associated with EOPE than LOPE (147). Transcriptomic profiling in PE, IUGR, and control placentas has revealed distinct clusters of transcriptomic profiles, indicating multiple subtypes of PE (20,21). Similar to placental DNAm, gene expression is highly variable across the placenta (164); as such, many studies will opt to sample numerous sites and pool the DNA and/or RNA together to give a more accurate representation of the placenta as a whole. Although gene expression alterations are more intuitive to understand in the context of gene regulation, gene expression is dynamic over gestational age and the alterations one is observing at the time of delivery may not necessarily reflect the alterations present at an earlier time point, which is when these alterations would be used to predict a future adverse outcome. Additionally, gene expression can differ between the mode of delivery (i.e. vaginal vs caesarean) (165,166), and mRNA rapidly degrades after birth, making sample processing time a confounding variable (164).

1.4.4.2 Altered miRNA profiles in preeclampsia and intrauterine growth restriction

As microRNA (miRNA) are important to gene regulation and are more stable than their mRNA counterparts, investigations into miRNA profiles in relation to PE and IUGR have been very popular. MiRNAs are involved in many processes during placental development, including: trophoblast invasion (miR-195, miR-21), migration (miR-376c, miR-378-5p), angiogenesis (miR-16, miR-29b), trophoblast cell differentiation (miR378a-5p,miR376c,miR-141), and apoptosis (miR-29b) (167). During pregnancy, miRNA, as well as other nucleic acids are released into maternal circulation, through cellular apoptosis and necrosis, or vesicle mediated transport (114). A number of circulating miRNA, both specific and non-specific to the placenta, have been proposed as potential biomarkers in PE prediction (167); specifically miR-210 has
been associated with PE and show promise in having clinical utility (168). No miRNAs have been proposed for potential prediction of IUGR yet (114). No miRNA or panel of miRNA have high enough sensitivity or specificity to be utilized in the clinic as of the publication of this dissertation.

1.5 DNA methylation

DNA methylation (DNAm) is a type of epigenetic mark. Epigenetics is defined as the study of mitotically stable chemical modifications made to DNA or the proteins around which DNA binds that do not change DNA sequence but influence gene regulation (169). Epigenetic marks include histone modifications, chromatin organization, and DNAm. DNAm is the most widely studied epigenetic mark, as it is relatively easy to measure, and the relationship between DNAm and gene expression has been extensively studied (170). DNAm is the addition of a methyl group by DNA methyltransferases (DNMT), most commonly to the 5-prime position of a cytosine base in cytidine-phosphate-guanosine (CpG) dinucleotides (171). During DNA replication DNMT1 recognizes hemimethylated CG sites in newly replicated DNA in which the template contains a methyl group and the product does not. DNMT1 is responsible for adding a methyl group to the complimentary strand in order to maintain the DNA methylation profile through cell division (172). In addition to DNMT1, DNMT3a and DNMT3b also have the ability to add methyl groups to CG sites. However, DNMT3a and DNMT3b do not recognize hemimethylated states; rather they can de novo methylate previously unmethylated CG sites and play a crucial role in establishing the methylation profile during embryonic development (173).
In some regions, CpGs are clustered together in “CpG islands”, regions of high CpG density which are generally found at promoters (174). How DNAm influences gene expression is dependent on genomic location. Many studies show correlation between DNAm and gene or protein expression, with DNAm in a promoter region generally correlating with reduced or no gene expression or protein expression (175,176). Methyl groups bound to DNA can repress gene expression by either actively preventing transcription factors from binding to the promoter or to enhancers, or recruiting methyl-binding proteins that compete with transcription factors in promoter binding. Although DNAm at promoter regions in the genome is most commonly studied, DNAm present outside of promoters can also influence or be associated with gene expression (177). For example, many DNAm changes occur in CpG island shores, the region directly adjacent to the CpG island. In these regions, decreased methylation is often associated with DNA polymerase activity and gene transcription (178).

1.5.1 Influencing variables of DNA methylation

1.5.1.1 Sex specific DNA methylation

DNAm differs between males and females (179,180). DNAm plays a role in X-inactivation, the silencing of the second X chromosome in XX female individuals, while X-inactivation does not occur in XY males (181). This process accounts for only some of the differences in DNAm patterns between male and females. Sex differences in DNAm has also been observed on autosomes, suggesting biological and epigenetic differences between males and females extend beyond the X and Y chromosomes (180). The reason for these differences remains largely unknown, however it has been postulated that DNAm differences between the sexes may be influencing gene expression within hormone secreting pathways (182). Additionally, studies
have shown altered DNA methylation (DNAm) patterns between males and females in response to environmental exposures and disease (182-185). For these reasons, when investigating differences in DNAm in association with a variable of interest, sex should either be adjusted for within a statistical model or the study groups should be matched for sex to reduce the chance of identifying changes in DNAm that are actually associated with sex rather than the variable of interest.

1.5.1.2 Environmental exposures

The term environmental exposures encompasses many factors, such as: smoking, air pollution, diet, teratogen, radiation, and general stress, to name a few. In evidence of environmental influences on DNAm, monozygotic twins, who share their DNA sequence, exhibit different DNAm patterns suggesting external influences on DNAm (186-188). This could just be CpG sites that are influenced by stochastic factors or not maintained; however, there is a wide array of literature on alterations in DNAm in association with many environmental exposures, such as maternal smoking. An area that has gained much interest in research of DNAm and the placenta, and factors that influence DNAm in the placenta is the developmental origins of health and disease (DoHAD) hypothesis, whereby in utero exposures influence long term health outcomes in adult life (e.g. obesity, diabetes and cancer) (189-191).

1.5.1.3 Disease state

Alterations in DNAm have been widely reported in many diseases using both specific candidate gene driven approaches and genomic-wide approaches (22,192,193,194,195,196). While disease outcomes have often been studied in the context of gene mutations, in most cases, those mutations do not account for all subtypes or incidences of the disease. Alterations in DNAm (and
other epigenetic marks) may explain the missing mechanisms of disease not associated with genetic sequence (197,198). As such, DNAm profiling has been used to obtain insight into disease pathogenesis and to identify candidate biomarkers (199,200,201). DNAm biomarkers are already being utilized in the clinic, with the use of Septin 9 (SEPT9) promoter DNAm being used to diagnose colorectal cancer (202). Further studies are underway to characterize the DNAm profiles of many different cancers, and to utilize the circulating cell-free DNA in blood to non-invasively detect cancer, its location, and prognosis of the patient (203,204,205,206). These methods are also being used in complex diseases where genetic profiling has yielded few associations (e.g. Alzheimers, Parkinson’s and Heart disease) (207,208,209).

1.5.1.4 Tissue-specific DNA methylation

DNAm varies widely across cell types (210,211). This is thought to be related to the epigenetic commitment of cell fate, where epigenetic marks, such as DNAm, fine-tune gene expression, specifically at transcription factors, to fixate cell lineage and fate (212). As such, different cell types or tissues retain unique epigenetic signatures (210). In samples where there are mixed cell type populations (e.g. blood), a change in DNAm could either mean an average change in DNAm across all cell types in the sample or an alteration in the ratio of different cell types. While making this distinction may not be important for the aim of developing biomarkers of disease, it could be relevant to distinguishing an epigenetic change from a cell type-ratio change. Algorithms have been developed to correct for cell type composition in studies where DNAm changes may be influenced by altered cell populations between the cases and controls. In well-studied samples, where cell sorting is relatively easy (e.g. blood and brain), reference based methods for cell-type correction have been developed (213,214). For tissues, where reference
based methods have not been developed, a reference-free method has been developed to try to mediate the effects of cell composition in complex tissues (215). However, as changes in DNAm differ widely across tissues, and constitute the most variation in data, the reference-free method to correcting for cell composition assumes that the first few principal components in the data are due to cell composition, and removes them. This may remove some variance associated with the variable of interest, and does not take into account that some cell types will be more related to each other than others, meaning there still could be variation in the data due to cell composition. Additionally, in some situations, alteration in cell composition may be associated with the disease pathogenesis itself. If one were to correct for cell composition, then the variance due to pathology may be significantly reduced or eliminated.

In the placenta, no reference method has been developed to assess alterations in cell composition. While knowing whether DNAm alterations are an average change across all cells sampled, or whether DNAm alterations represents a change in cell composition does need to be addressed and will give insight to the pathogenesis of PE and IUGR, it will not affect the utility of DNAm as a biomarkers for pregnancies at risk of developing PE and/or IUGR. DNAm marks and biomarkers in general do not need to be directly involved in the pathogenesis to be a good indicator of placental insufficiency or the variable of interest.

1.5.1.5 Age associated DNA methylation

Individual/patient age is a factor widely known to influence DNAm (216,217). Numerous pan-tissue or tissue specific epigenetic clocks have been developed (218-221), try to predict chronological age. The biological meaning of CpG sites that correlate with chronological age
remains unclear. However the ‘epigenetic age’ of an individual has been associated with time to death (222,223), cancer (223-225), chronic stress (226), degenerative disease (227), and obesity (228). Similar to changes in DNAm observed in association with chronological age, DNAm in the placenta changes over gestational age (229,230). For this reason, gestational age should be accounted for in statistical models or have the study groups matched for gestational age.

1.5.2 The placental methylome

Human development starts with a single cell zygote. This cell begins in a totipotent state dividing and differentiating into many different cell types, contributing to the fetal tissues, placenta and extraembryonic membranes (231). As cells each contain the same DNA sequence, a mechanism must exist in order for cells to differentiate into different cell types. Alterations in epigenetic marks, specifically DNAm, distinguish different cell or tissue types. Very early in development cells undergo ‘epigenetic reprogramming’, a process by which the epigenetic marks are erased from the genome and re-established as specific cell or tissue profiles (232).

The DNAm profile of the placenta is quite different to other somatic tissues. There are many partially methylated domains (PMDs)(233) and imprinted genes within the placenta(234). This results in a trimodal distribution of DNAm measures, where many CpG sites have an average 50% methylation resulting in a third peak, as opposed to the bimodal distribution of somatic tissues, where most sites are either on average 0% methylated or 100% methylated(235). The placenta is globally hypomethylated, with DNAm in the chorionic villi showing up 25% less DNAm than fetal tissues(236). Additionally, the placenta also contains partially methylated domains (PMD); these are large genomic regions (>100kb) with reduced DNAm interrupted with
regions of higher DNAm(233). Retrotransposable elements have been reported to be hypomethylated in the placenta(237). The placenta is highly heterogeneous and DNAm is incredibly variable across a single placenta and between individuals (238). This variability can be attributed to a number of factors known to influence DNAm.

1.5.3 DNA methylation in preeclampsia and intrauterine growth restriction

Alterations in DNAm in both PE and IUGR have been reported with both candidate gene targeted approaches and genome-wide approaches (15,22,23,50,51,52,53,54,56,118,196,221,239-270) (Supplementary Table A.1). Many genome-wide DNAm studies show alterations in genes associated with oxidative stress, cell proliferation, inflammation and immune response (53,241,243,249). However, not all potential confounding factors, such as fetal sex and gestational age, are assessed in many of these studies. Therefore many of the PE/IUGR ‘hits’ may actually be artifacts of gestational age or fetal sex.

Within the literature, there is an inconsistent definition of what is useful to use as a control, when comparing to PE and IUGR. Some studies will compare preterm PE and IUGR to preterm control placentas (22); however, preterm birth are still abnormal, meaning that changes in DNAm may actually be changes related to the cause of the preterm birth group rather than the PE or IUGR group. To minimize this effect, using a variety of preterm birth aetiologies (ex: spontaneous premature rupture of the membranes, incompetent cervix or chorioamnionitis) will mitigate the likelihood that a change in DNAm is due to a singular cause of preterm birth. Other studies opt to compare PE and/or IUGR to healthy term placentas (243,244,254), however, this often results in the pathology and control groups being confounded by gestational age. Although
DNAm alterations are reported in both PE and IUGR, few studies validate their findings in an independent cohort, and reproducibility rate and prediction rate remains relatively low (240). Validation and reproducibility will be discussed in detail in the discussion.

1.5.4 Measuring DNA methylation

There are numerous methods that have been developed to measure DNAm both across the genome and in smaller more targeted approaches. Which method to use, will depend on the experimental question and the genomic region of interest. Some considerations to take into account when choosing a platform are: cost, amount of input DNA required, if any pre-treatment is necessary and if that will result in any DNA loss, technical variability, how many CpGs are covered by the platform, whether there is any bias in the genomic regions covered and the experimental question.

1.5.4.1 Genome-wide DNA methylation measures

DNAm microarrays are a commonly used method to measure DNAm across the genome. They cover a small percentage of total CpG sites within the genome, and are enriched at high CpG density regions of the genome (271). The Illumina microarrays will be discussed in more detail in Chapter 2. Reduced representation bisulfite sequencing (RRBS) involves methylation sensitive enzymatic digestion and size selecting for small fragments (CpG dense regions). This method covers a higher proportion of CpG sites compared to microarray (272). Methylation DNA immune precipitation (MeDIP) sequencing interrogates DNAm at methylated regions, as antibodies specific to 5-methylCytosine are used to isolate methylated fragments of DNA (272). While this reduces the number of sites being assessed, it is difficult to determine if no reads are
reported, if the result is truly no methylation or whether it is a technical artifact (no reads) (273). Whole genome bisulfite sequencing covers all sites in the genome, but this generates a lot of data where identifying significant differences is hindered by multiple test correction and the relationship between DNA methylation (DNAm) and gene expression can be less intuitive in some genomic regions (274). Measuring DNAm at repetitive regions (e.g. LINE1 and ALU) have been used as surrogates for global DNAm levels. However, assays measuring global DNAm appear to be assessing different combinations of these repetitive elements and global DNAm levels do not correlate between the different assays or elements (237). The coverage of DNAm measures and the affordability of the techniques vary widely. Which technique to utilize for a given study will depend on the research question, and goals of interest.

1.5.4.2 Candidate gene DNA methylation measures

Experimental questions investigating targeted sites or a small subset of sites will often use bisulfite pyrosequencing which can cover up to 350bp with one sequencing primer, and DNAm at numerous CpGs within those base pairs(275,276). The accuracy, efficiency, high correlation to other techniques, small amount of input DNA required and low cost per sample make this an ideal approach for those interested in studying candidate regions within the genome(275,276). Other methods utilizing methylation specific enzymatic digestion and amplification (PCR), custom microarray chips, targeted bisulfite sequencing are also used.

1.6 Research hypothesis and objectives

Previous students in the Robinson lab have investigated placental DNAm for both its underlying biological properties and its association with disease. Novakovic et al. (2011) utilized the
Illumina 27K array platform to profile DNA methylation patterns in placental and fetal tissues over gestational age (277). Yuen et al. (2010) also identified promoter hypomethylation in EOPE placentas (23). Following up this work and expanding the number of CpG sites assessed to >480,000 sites across the genome, using the 450K array, Blair et al. (2013), identified enhancer hypomethylation in EOPE placentas (22). Blair also identified overlapping DNA methylation alteration in trisomy 16 placentas, which confer a higher risk of developing PE (118). In this dissertation genetic and epigenetic profiles in EOPE, LOPE, and IUGR were assessed. I hypothesized that EOPE, LOPE and IUGR were distinct entities from one another and would therefore have unique genetic and epigenetic profiles that could potentially be utilized for biomarker development. The research objectives of this dissertation were to i) assess the utility of DNA methylation variation in biomarker development, ii) reassess and characterize the DNA methylation profiles of EOPE, adding a few new samples and new bioinformatic analysis and expand the analysis to encompass LOPE and IUGR, and iii) to assess the utility of placental telomere length as an indicator of placental stress during gestation. To complete these objectives, I undertook the following studies:

(i) A comparison and correlation between DNA methylation in the term placenta to protein levels in maternal serum during the first, second and third trimesters of pregnancies.

(ii) A characterization of the DNA methylation profiles associated with EOPE, LOPE, and IUGR compared to control placentas. DNA methylation profiles were further refined with the use of an independent validation cohort obtained from Dr. Brian Cox’s lab at the University of Toronto.

(iii) An assessment of telomere length dynamics in the placenta over gestational age and whether telomere length is altered in EOPE, LOPE, and IUGR compared to control placentas, taking into account gestational age and fetal sex.
These studies resulted in further insight into the relationship between EOPE and LOPE and ideas as to how DNAm can be utilized to improve PE prediction.
Chapter 2: Methods

In this dissertation, placental sampling and genome-wide DNA methylation measurement using the Illumina Infinium HumanMethylation450 array (450K) platform were performed the same way through multiple data chapters. The methods of these protocols are outlined in this chapter.

2.1 Case ascertainment

Ethics approval was granted by the University of British Columbia and BC Women’s and Children’s Hospital Research Ethics Board (H04-70488) for our EPIC study (Epigenetics of the Placenta in Complications of Pregnancy). This study includes two groups: PM (database name) cases with informed consent and full clinical details and PL (database name) cases obtained predominantly from the embryo-pathology lab and have been de-identified with minimal clinical details. Maternal clinical details include: self-reported ethnicity, pre-pregnancy body mass index (BMI), obstetric history, substance use in pregnancy, maternal health status (diabetes, chronic hypertension, other complications), medications and other supplements. Fetal and pregnancy details include: mode of delivery, infant sex, birth weight, and gestational age at delivery. We calculated birth weight defined by its’ standard deviation (SD) relative to normative values by gestational age and fetal sex (278). In cases of preterm birth, known etiologies such as: spontaneous premature rupture of the membranes, spontaneous preterm birth, incompetent cervix, preeclampsia, and IUGR are recorded. All data is in a REDCap database hosted at the BC Children’s Hospital Research Institute affiliated with the University of British Columbia.
2.1 Placental sampling

Chorionic villi samples, approximately 2 cm³, were taken from the fetal side of the placenta from four distinct placental cotelydons (164). One site was located near the umbilical cord and one near the periphery of the placental disk. Other sites sampled were located approximately halfway between the cord and placental edge and well-spaced across the placenta. The amnion and chorion (fetal membranes) were removed from the placental surface of each sample site and whole chorionic villi were dissected with tweezers, followed by thorough sample washing to remove potential contamination of maternal blood. DNA was extracted from each sample by a standard salting out method, and then pooled together in equal amounts. The salting out method involves the use of high concentration of salts to precipitate proteins to the bottom of the solution. The DNA, within the supernatant is then precipitated and extracted using isopropanol. DNA integrity was assessed in all samples upon extraction. DNA purity and concentration were assessed using the Nanodrop 1000 spectrophotometer (ThermoScientific, Wilmington, DE, USA). Multiplex ligation-dependent probe amplification (MLPA) was used to screen all placentas for chromosome abnormalities.

2.2 Clinical definitions of preeclampsia and IUGR

Preeclampsia (PE) was defined according to the Society of Obstetricians and Gynecologists of Canada (SOGC) criteria as gestational hypertension (existing or new) with one or more of the following i) new proteinuria (protein creatine ratio>30mg/mmol,>0.3g/day or >2+ dipstick) after 20 weeks gestation, or ii) one or more adverse maternal symptoms (headache, vision disruption, abdominal pain, severe nausea or vomiting, chest pain, dyspnea), maternal organ dysfunction (pulmonary edema, placental abruption), altered maternal lab results (elevated serum creatinine,
AST, ALT, LDH, platelet count<100x10^9/L, or serum albumin <10g/L), or fetal morbidity (oligohydramnios, IUGR, and/or reversed end diastolic flow), or HELLP syndrome with or without hypertension(279). However, we did not consider hypertension with stillbirth a PE diagnosis, as we felt stillbirth could be due to a number of etiologies (12). PE was subdivided into early-onset PE (EOPE), defined as a diagnosis of PE before 34 weeks gestation, and late-onset PE (LOPE), defined as a diagnosis of PE at or later than 34 weeks gestation (280).

IUGR was also defined following SOGC criteria (278) as birth-weight <3rd percentile accounting for both fetal sex and gestational age, or birth-weight <10th percentile with additional clinical findings indicative of poor placental function such as: absent or reversed end diastolic velocity on Doppler ultrasound, or oligohydramnios. Criteria for exclusion were multi-fetal pregnancies, and fetal chromosomal abnormalities. Controls were selected based on absence of any criteria listed above and a placenta with no observable pathology. In some cases we define a normotensive IUGR (nIUGR) group, which are cases diagnosed as IUGR but after excluding maternal hypertension and/or preeclampsia.

2.3 DNA methylation microarray- Illumina Infinium HumanMethylation450 array

Microarrays are widely used to evaluate DNA methylation (DNAm) at CpG sites across the genome, typically enriching for CpG dense regions, promoters and enhancers (271,281). For this dissertation, genome-wide DNAm was measured using the 450K platform, measuring 485,512 CpG sites across the genome. Relative to whole genome analysis such as whole genome bisulfite sequencing (WGBS), microarrays have a lower cost per sample and can limit the number of multiple test corrections needed, and give information on a site by site basis. Limitations of the
microarray approach are i) there is less complete coverage of the genome and ii) a higher quantity of input DNA is required compared to bisulfite sequencing techniques, which measure DNAm across the entire genome, not just at a subset of sites (272).

750ng of DNA purified using Qiagen blood and tissue kit was bisulfite converted using the EZ DNA Methylation Kit (Zymo Research, Irvine, USA). Samples were PCR amplified before being hybridized to the microarray chip as per the manufacturer’s protocol, and microarray chips were scanned by a HiScan 2000 (Illumina). On the Illumina Infinium HumanMethylation450 (450K) array, each microarray chip can analyze 12 samples concurrently. The surface of the microarray contains thousands of beads, with many probes (single stranded DNA sequence, complementary to a genomic region) attached. These probes will complementarily bind to the target genomic location of interest and measure DNAm at its target site. DNAm is measured based on genotyping of C/T SNPs following bisulfite conversion; whereby unmethylated cytosines are converted to uracil, and ultimately replaced with thymine upon PCR amplification (271). Each fragment of DNA bound to a bead will be either methylated or unmethylated, a C or a T genotype. The DNAm measure reported is an average of a particular CpG within an entire sample. On the 450K array there are two types of probes, differing by the chemistry of their design and the genomic regions which they target. Type I probes utilize a 2-bead system, a methylated and unmethylated bead, where the probe sequence differs by the C/T genotype of the target CpG. The type II probes utilize different colour fluorescence (red and green) to label the methylated and unmethylated fragments. Fluorescent intensity is translated into DNAm values for each CpG site. Type I probes are utilized to cover high CpG density regions, while type II probes are used to cover lower CpG density regions (271). While this is needed in order to obtain
DNAm measures for different regions of the genome, it results in DNAm values being confounded by the probe type used to assess specific CpGs. Normalization is used to correct for probe type and other technical artifacts in the data. While there are a variety of normalization methods developed for the 450K array (e.g. Functional normalization (282), subset-within array normalization (SWAN)(283), Peak based correction (284), β-mixture quantile normalization(285)), some of these methods do perform better than others depending on the sample tissue type and the magnitude of change that is expected between the variable of interest and control (286,287,288).

In chapter 3, DNAm microarray data from Blair et al. (2013) was used to identify the candidate CpG sites. This data differs from the DNAm analyses in chapters 4 and 5, as it uses subset within-array normalization (SWAN) (22). In chapter 4 and 5, raw data (IDAT Files) were read into R statistical software, version 3.2.4, where functional normalization (282), background subtraction and colour correction were performed. Functional normalization utilizes the 848 control probes on the array to estimate changes in DNAm that are due to technical effects (e.g. sample placement on microarray, whether between microarrays in study or on the array itself) (282). In chapter 5, batch effects were corrected using ComBat (289). However, after publication of chapter 5, I realized that because our samples’ gestational ages were not evenly distributed across batches, I increased the risk of introducing spurious finding in the data (290). For this reason, chapter 4 does not correct for batch effects and instead utilizes an independent validation cohort to identify true differentially methylated sites, as batch effects are unlikely to affect two cohorts the same way.
The discovery cohort is used in both chapters 4 and 5, while the validation cohort is used only in chapter 4. In both chapters, bad quality probes, those that had a missing beta value (value on <3 beads on the array) in > 5% of samples or a detection p-value (background intensity; used to determine if intensity values are likely true) <0.01 were removed from the analysis (Discovery N=1,402, Validation N=1,115). To minimize fetal sex effects, probes on the X and Y chromosomes (Discovery N= 11,648, Validation N=11,302), probes that cross hybridize to the X and Y chromosomes (Discovery N= 11,412, Validation N=10,734), and probes containing a SNP at the CpG of interest were also removed (Discovery N= 19,957, Validation N= 20,398) (291). This left 440,093 CpG sites for the analysis in the discovery cohort and 441,963 CpG sites in the validation cohort (Supplementary Table B.1).
Chapter 3: Placental DNA methylation at term reflects maternal serum levels of INHA and FN1, but not PAPPA, early in pregnancy.

3.1 Introduction

Early diagnosis of preeclampsia (PE) and intrauterine growth restriction (IUGR) before clinical signs of disease can improve management and outcomes of affected pregnancies. Placental-derived proteins may be released into the maternal circulation where they can be quantified and used to assess placental function during pregnancy (292,293,294,295). Such protein markers have been investigated for the prediction of PE and/or IUGR with varying success (109,113,296). Nicolaides et al. (2013) reported a detection rate of 95% for early-onset PE (EOPE, diagnosis <34 wks) using decreased levels of maternal serum markers, pregnancy associated plasma protein A (PAPPA) and placental growth factor (PLGF), in combination with maternal factors (109). However, these measures might not be generalizable, as the etiology and confounding environmental factors vary between populations (113). Moreover, the ability to predict women at risk of late-onset PE (LOPE, diagnosis ≥34 wks) and IUGR is limited using these markers.

Differential gene expression between placentas from PE and/or IUGR pregnancies (27,147,296,297) may be utilized to identify additional biomarkers to distinguish women at high risk of these complications early in gestation. DNA methylation (DNAm) is associated with gene expression, but is more robust to variation in technical conditions and less subject to short-term biological change (164). Alterations of placental DNAm were noted in genes for which the expression of the encoded protein is altered in maternal blood in PE and/or IUGR pregnancies.
(e.g.: \textit{PAPP\text{A}, sENG, PAPP\text{A2}}) (22). Furthermore, we found that sites of altered DNA\text{m} in PE frequently reflected changes in gene expression (22). While proteins produced in the placenta can be released into maternal circulation, their levels in maternal serum may be affected by many additional factors including size of the placenta, the cell type expressing the protein, and how such proteins are transported and metabolized. The purpose of this study was to delineate the relationship between changes we observed in DNA\text{m} at term and maternal protein levels in early pregnancy. We selected three genes for which there was evidence for both altered maternal protein levels and altered DNA\text{m} in PE (22); we then evaluated 1) the relationship between placental DNA\text{m} and gene expression; 2) the role of variables that might confound measurement of DNA\text{m}, mRNA or protein levels including gestational age, fetal sex, placental efficiency (fetal: placental weight ratio), birth weight, placental breadth: width ratio and maternal body mass index (BMI); and 3) whether placental DNA\text{m} at term reflected protein levels in maternal blood during gestation after correcting for these variables.

3.2 Methods

3.2.1 Sample information

We used a total of 171 placentas for our studies, not all placentas were used in all studies as we were limited by samples run on the Illumina HumanMethylation450 array (450K) (N=66); samples run on the Illumina expression array (N=16), maternal serum screening results (first trimester N=34, second trimester N=36), or maternal serum samples for Fibronectin (FN1) testing (N=114). Supplementary Table C.1 outlines a list of all samples and which analyses they were used in.
3.2.2 Gene expression analysis

Gene expression was measured with the HT-12v4 Expression BeadChip (Illumina, Inc.) as per Blair et al. (2013) protocol, comparing eight EOPE and eight controls (22) (Supplementary Table C.2).

3.2.3 DNA methylation analysis

3.2.3.1 Illumina Infinium HumanMethylation450 beadchip array

To compare the DNAm differences between pathological groups for each of our candidate genes 20 EOPE, 11 LOPE, 8 LOPE+IUGR, 10 IUGR, and 37 control cases were run on the 450K array, which interrogates >480,000 CpG sites in >20,000 genes (271). Some of these samples were previously analyzed in the study reported by Blair et al. (2013).

3.2.3.2 Bisulfite pyrosequencing

Candidate CpGs determined from the 450K array data in Blair et al. (2013) were followed up with bisulfite pyrosequencing in control cohorts for each candidate gene (Table 3.1). To compare the association between DNAm and protein levels in maternal blood, 122 placental DNA samples (750ng) were bisulfite converted using the EZ DNA methylation-Gold kit (Zymo Research Corp, Irvine, CA, USA) as per manufacturer’s protocol. Bisulfite converted DNA was PCR amplified prior to pyrosequencing. PCR reactions consisted of 20ng of bisulfite converted DNA, 1x PCR buffer (with MgCl₂) (Qiagen Ltd.), 0.18U DNA polymerase (HotStarTaq, Qiagen Ltd.), 0.2mM dNTP (Invitrogen, Carlsbed, CA), 0.4uM forward and reverse primers (Integrated DNA Technologies, Coralville, IA) for Inhibin beta alpha (INHBA), Pregnancy associated plasma protein A (PAPPA), and Fibronectin (FN1). PCR conditions were 95°C (15min), [95°C (30s),
55°C (30s), 72°C (30s)] x 40 cycles, 72°C (10min). Pyrosequencing assays for the candidate genes were designed in PSQ Assay Design software (Biotage, Upsalsa, Sweden) and run on a Qiagen Pyromark Q96 MD (Qiagen) (Supplementary Table C.3).

### Table 3.1. Candidate CpG sites chosen from Blair et al. (2013) for follow-up

<table>
<thead>
<tr>
<th>Gene</th>
<th>Site</th>
<th>Genomic Region</th>
<th>Distance to TSS (base pairs)</th>
<th>EOPE β value (Δβ from control group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INHBA</td>
<td>cg11079619</td>
<td>Active Promoter</td>
<td>76</td>
<td>0.434 (-0.162)</td>
</tr>
<tr>
<td>PAPPA</td>
<td>cg08189448</td>
<td>Active Promoter</td>
<td>-163</td>
<td>0.326 (-0.074)</td>
</tr>
<tr>
<td>FN1</td>
<td>cg12436772</td>
<td>Intergenic/Upstream enhancer</td>
<td>-101593</td>
<td>0.465 (-0.240)</td>
</tr>
</tbody>
</table>

#### 3.2.4 Candidate DNA methylation selection

CpG sites chosen to investigate in the present study were selected on i) a significant change in placental DNAm, defined as a false discovery rate (FDR)<0.05, and a biological threshold of Δβ>0.05 (i.e. at least 5 percentage points difference in DNAm), a cut-off that enriches for changes in DNAm that would likely have biological impact (298), in placentas associated with PE and ii) genes encoding for proteins reported to show altered levels in maternal blood in pregnancies complicated by PE and/or IUGR. We chose FN1 since the difference in DNAm between EOPE and controls was high (Δβ= 0.24). INHBA (Δβ=-0.16, FDR<0.05) and PAPPA (Δβ=-0.074, FDR<0.05) were selected because they additionally encode for proteins for which
first (PAPPA) or second trimester (INHA) maternal serum measures were available from clinical prenatal serum screening testing. Previous studies have shown upregulation of both PAPPA and INBHA in the placentas of pregnancies complicated by PE and IUGR (22,297,299,300). In addition, several studies have reported DNAm alterations in placentas from pregnancies complicated by PE and/or IUGR (15,22,301). We also took into account where the DNAm alterations were in the genome, taking interest in alterations in gene regulatory elements (Table 3.1). The CpGs of interest for INHBA and PAPPA were 76 base pairs (bp) and 163bp upstream of the transcriptional start sites, respectively. In relation to FNI, the CpG site was ~100 kb upstream of the transcriptional start site, within an enhancer region.

3.2.5 Maternal blood protein measurements

Measurements of PAPPA and INHA were obtained from clinical maternal serum screening data for 36 and 33 women, respectively, and are measured in multiples of the median (MoM). Blood was drawn in EDTA tubes during the second trimester for a subset of 158 women (Table 3.2). Plasma was obtained via centrifugation at 3000rpm for 10 minutes 4⁰C. Plasma FN1 was measured using a FN1 ELISA kit (eBioscience, San Diego, CA, USA). FN1 measurements were run in duplicate and absorbance was measured at 450nm. A 5 parameter asymmetrical logistic curve was generated from the standard data points which ranged from 0.31-20.0ng/mL. Samples were diluted as per manufacturer’s protocol; samples which FN1 concentration was over the standard curve were diluted to 1 in 80,000, and 4 samples which remained were further diluted to 1 in 100,000.
Table 3.2. Samples used for pyrosequencing and measuring maternal FN1 protein levels.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>EOPE</th>
<th>LOPE+IUGR</th>
<th>LOPE</th>
<th>IUGR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INHA N=</strong></td>
<td>36</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean GA at blood draw (weeks ±SD)</td>
<td>14-20wks</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean GA at delivery (weeks ±SD)</td>
<td>39.3 (±1.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean BW (grams ±SD)</td>
<td>3480.3 (±483.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean MA (years ±SD)</td>
<td>33.5 (±4.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sex (Female/N, %)</td>
<td>18/36, 50%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>PAPPA N=</strong></td>
<td>33</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean GA at blood draw (weeks ±SD)</td>
<td>11-13wks</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean GA at delivery (weeks ±SD)</td>
<td>39.6 (±1.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean BW (grams ±SD)</td>
<td>3428.9 (±355.9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean MA (years ±SD)</td>
<td>34.2 (±4.6)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sex (Female/N, %)</td>
<td>18/34, 53%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>FN1 N=</strong></td>
<td>76</td>
<td>13</td>
<td>6</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>EOPE</td>
<td>LOPE+IUGR</td>
<td>LOPE</td>
<td>IUGR</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Mean GA at blood draw (weeks ±SD)</td>
<td>31.6 (±6.1)</td>
<td>32.3 (±3.2)</td>
<td>35.9 (±1.3)</td>
<td>37.4 (±2.4)</td>
<td>33.5 (±4.5)</td>
</tr>
<tr>
<td>Mean GA at delivery (weeks ±SD)</td>
<td>39.1 (±2.9)</td>
<td>33.1 (±3.2)</td>
<td>36.1 (±1.1)</td>
<td>38.4 (±1.9)</td>
<td>35.2 (±4.5)</td>
</tr>
<tr>
<td>Mean BW (grams ±SD)</td>
<td>3465.3 (±398.94)</td>
<td>1663.3 (±710.5)</td>
<td>1921.7 (±402.5)</td>
<td>3187.0 (±683.3)</td>
<td>1932.2 (±746.0)</td>
</tr>
<tr>
<td>Mean MA (years ±SD)</td>
<td>33.5 (±3.6)</td>
<td>33.4 (±6.4)</td>
<td>32.4 (±5.3)</td>
<td>35.5 (5.5)</td>
<td>33.5 (±3.5)</td>
</tr>
<tr>
<td>Sex (Female/N, %)</td>
<td>*36/74, 49%</td>
<td>6/13, 46%</td>
<td>3/6, 50%</td>
<td>6/10, 60%</td>
<td>6/9, 66%</td>
</tr>
</tbody>
</table>

*Sex not available on 2 samples
3.2.6 Statistical analysis

DNAm at the two CpGs in the PAPPA pyrosequencing assay were correlated (r=0.85, p<0.001, Spearman’s correlation) and the measurements for these two sites were thus averaged (Supplementary Figure C.1). Potential covariates which may be associated with either DNAm or protein concentration in maternal blood were assessed for each candidate site. Univariate linear regression analyses were performed, investigating gestational age at delivery, fetal sex, birth weight (SD), fetal: placental weight ratio, placental length: breadth ratio, maternal body mass index (BMI), and when appropriate, gestational age at blood draw. As absolute birth weight is confounded by gestational age at delivery, birth weight was measured as a standard deviation relative to the mean for that gestational age and infant sex. PAPPA and INHA protein levels were expressed in MoM to correct for gestational age at blood draw.

Correlations were performed when testing any association between placental gene expression at term and placental DNAm at term. Spearman’s correlations were performed between protein concentration and DNAm in sites where there were no covariate factors. For sites with covariate factors, partial correlations were performed. Non-parametric t-tests were performed to determine if DNAm in the EOPE, LOPE+IUGR, LOPE, and IUGR placentas were significantly different from controls. Statistics were calculated using SPSS v19.0 statistical package.

3.3 Results

3.3.1 Candidate site selection and characteristics

Although candidate sites were selected based on a significant association with EOPE (See methods) (22), we also wanted to know if these changes were conserved in other pathological
groups (Figure 3.1). In addition to hypomethylation of these sites in EOPE, the LOPE+IUGR
group was hypomethylated for the INHBA (promoter) ($\Delta\beta=-0.18$, $p<0.001$) (Figure 3.1a) and the
FN1 upstream enhancer ($\Delta\beta=-0.25$, $p<0.01$) (Figure 3.1c). While reduced DNAm at the PAPPA
promoter was only found in EOPE (Figure 3.1b).
Figure 3.1. DNA methylation measures at candidate sites.

β values ±SD obtained from microarray data (450K) at each site across pathological groups for A) INHBA, B) PAPPA, and C) FN1. EOPE= early-onset PE (N=20), LOPE=late-onset PE (N=11), IUGR=Intrauterine growth restriction (N=12), Control (N=37). *p<0.05
3.3.2 Is DNA methylation at candidate sites inversely correlated with gene expression?

To confirm that the DNAm change resulted in a change in gene expression, we assessed the relationship between placental DNAm (by 450K) and gene expression at these three candidate sites. *FN1* showed an inverse correlation between DNAm of an upstream enhancer and gene expression at term ($r=-0.88$, $p<0.0001$). *INHBA* and *PAPPA*, showed a non-significant trend with increasing DNAm being associated with decreased gene expression in the placenta (Figure 3.2). For all candidate genes, there was an observable divide between the controls and EOPE cases, where cases had decreased DNAm corresponding to increased gene expression in the placenta.
Figure 3.2. Correlation between DNA methylation and left) gene expression, right) protein levels.

Correlation between DNA methylation and gene expression in eight early-onset PE and eight control placentae in A) INHBA B) PAPPA and C) FN1† FN1 graph produced from data published in Blair et al. (2013).

Relationship between D) INHBA (N=36) promoter DNAm in the term placenta and second trimester INHA levels in maternal blood, plotted as residuals corrected for fetal birth weight (SD) and fetal: placental ratio, E) PAPPA (N=34) promoter DNAm in the term placenta and first trimester PAPPA levels in maternal blood, and F) FN1(N=76) enhancer DNAm in the term placenta and second/third trimester FN1 levels in maternal blood, plotted as residuals corrected for fetal birth weight (SD), gestational age, and maternal body mass index (BMI). MoM=multiple of the median.
3.3.3 What clinical factors are associated with DNA methylation at candidate sites?

To better understand what factors might affect the measurement of DNAm and therefore the relationship with protein expression levels in maternal blood, we also evaluated several potential confounding factors including gestational age at delivery (277), fetal sex (302,303), fetal birth weight (304), placental dimensions and maternal BMI. Bisulfite pyrosequencing was used to extend our assessment of DNAm at the candidate sites into a larger cohort of controls for which clinical serum measurements (INHBA N=36, PAPPA N=33) or serum samples for assaying FNI (N=76) were available.

Birth weight standard deviation (SD) was associated with DNAm at the INHBA promoter (p=0.05) and the upstream enhancer of FNI (p=0.02). Gestational age was only associated with FNI DNAm (p=0.03). None of the clinical factors assessed was associated with DNAm at the PAPPA site (Table 3.3).

Table 3.3. Univariate linear analysis results for DNA methylation vs. clinical parameters.

Samples are all controls. Reported in correlation coefficient (r) values. *p<0.05

<table>
<thead>
<tr>
<th>Gene</th>
<th>N=</th>
<th>Fetal Sex</th>
<th>Gestational Age at Delivery</th>
<th>Birth Weight (SD)</th>
<th>Fetal: Placental Weight</th>
<th>Placental Length: Breadth</th>
<th>Maternal BMI (Number of samples BMI was available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INHBA</td>
<td>36</td>
<td>0.53</td>
<td>0.055</td>
<td>0.29*</td>
<td>0.08</td>
<td>0.01</td>
<td>0.35 (N=18)</td>
</tr>
<tr>
<td>PAPPA</td>
<td>34</td>
<td>0.18</td>
<td>0.17</td>
<td>0.24</td>
<td>0.00</td>
<td>0.26</td>
<td>0.25 (N=21)</td>
</tr>
<tr>
<td>FNI</td>
<td>76</td>
<td>0.12</td>
<td>0.22*</td>
<td>0.23*</td>
<td>0.10</td>
<td>0.23</td>
<td>0.30 (N=75, all samples)</td>
</tr>
</tbody>
</table>

0.12 (N=37, control only)
3.3.4 What clinical factors are associated with protein concentration in maternal blood?

We also assessed the same clinical parameters for association with protein concentration in maternal blood (Table 3.2). Gestational age at blood draw was only assessed as a covariate for FN1 as clinical values for INHA and PAPPA were given in multiples of the median (MoM), which was already corrected for GA at blood draw. Placental efficiency (fetal: placental weight-ratio, at birth) was associated with increased second trimester INHA levels in maternal blood. FN1 level was not associated with maternal BMI in the controls for which we had this information (N=37), though it was significant when evaluating all clinical groups together (EOPE, LOPE, IUGR, Controls) (N=75). It was therefore included in subsequent analyses. None of the assessed factors were associated with PAPPA maternal blood levels during pregnancy (Table 3.4).

Table 3.4. Univariate linear analysis results for protein Levels vs. clinical parameters.

Samples are all controls. Reported in correlation coefficient.

<table>
<thead>
<tr>
<th>Protein</th>
<th>N</th>
<th>Fetal Sex</th>
<th>Gestational Age at Delivery</th>
<th>Gestational Age at Blood Draw†</th>
<th>Birth Weight (SD)</th>
<th>Fetal Weight:Placental Weight</th>
<th>Placental Length:Breadth</th>
<th>Maternal BMI (Number of samples BMI was available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INHA</td>
<td>36</td>
<td>0.20</td>
<td>0.00</td>
<td>NA</td>
<td>0.12</td>
<td>0.44*</td>
<td>0.30</td>
<td>0.34 (N=18)</td>
</tr>
<tr>
<td>PAPPA</td>
<td>34</td>
<td>0.11</td>
<td>0.20</td>
<td>NA</td>
<td>0.26</td>
<td>0.08</td>
<td>0.00</td>
<td>0.05 (N=21)</td>
</tr>
<tr>
<td>FN1</td>
<td>76</td>
<td>0.05</td>
<td>0.10</td>
<td>0.16</td>
<td>0.11</td>
<td>0.13</td>
<td>0.063</td>
<td>0.25* (N=75, all samples)</td>
</tr>
</tbody>
</table>

*p<0.05
† Only measured for FN1 as INHA and PAPPA levels were obtained from maternal serum screening program and already corrected for gestational age at blood draw.
3.3.5 What is the relationship between DNA methylation (DNAm) and maternal serum levels?

DNAm in the promoter of INHBA correlated with second trimester protein levels in maternal blood ($r=-0.50$, $p=0.01$) while modeling for both birth weight (SD) and fetal: placental weight ratio (Figure 3.2d). Additionally, DNAm in an upstream enhancer of FN1 correlated with third trimester protein levels in maternal blood ($r=-0.38$, $p=0.009$) while adjusting for birth weight (SD), gestational age, and maternal BMI (Figure 3.2f). In contrast, a similar result was not observed for PAPPApPAPPA (Figure 3.2e).

3.3.6 Are there any differences in protein levels between case and control placentas?

To confirm a previous report of altered maternal FN1 in association with PE and/or IUGR(305), FN1 levels were measured in maternal blood samples from pregnancies which subsequently developed EOPE, LOPE+IUGR, LOPE without IUGR, or normotensive IUGR, in addition to our control cohort (Table 3.2). Similar to the alterations in DNA methylation (DNAm), changes in FN1 levels were found to be significantly different from controls only in the EOPE group (Mann U Whitney test), although there was a trend of increased FN1 levels between LOPE+IUGR and controls ($p=0.08$) (Figure 3.3).
Figure 3.3. Fibronectin 1 (FN1) levels in each pathological group.

FN1 levels (Median with interquartile range) in maternal blood during third trimester. EOPE= early-onset PE (N=20), LOPE=late-onset PE (N=11), IUGR=Intrauterine growth restriction (N=12), Control (N=37).

**p<0.05, *p<0.1

3.4 Discussion

The differences in DNAm in our candidate genes were only found in the EOPE and LOPE+IUGR groups. Therefore the utility of these potential candidate genes/biomarkers would be limited to identifying this subset of pregnancies (306). Markers useful to detect LOPE or normotensive IUGR may be more challenging to identify due to their weak association with placental pathology.

The observed relationship between DNAm in the term placenta to second trimester (INHBA/INHA) and third trimester (FN1/FN1) maternal serum levels supported our prediction that DNAm changes observed in the placenta could explain some of the previous reports of altered INHA and FN1 levels in maternal blood in PE. It is remarkable that these serum
measurements from the second and third trimesters of pregnancy reflected DNAm at term. This implies that this DNAm change may be an early alteration in PE.

We had predicted that protein levels in maternal blood would reflect placental DNAm and gene expression. While this may be true in some instances (e.g. INHA, FN1), in other cases establishing a relationship may be challenging (e.g. PAPPA/PAPPA). Establishing such a relationship may be complicated by several factors. Protein level depends not only on the level of gene expression, but also on the total number of cells expressing that protein, the number of mRNA transcripts being translated into protein in those cells, and the rate and mode of release of the protein into maternal blood. These factors may be influenced by the underlying pathology (i.e. more protein may be released with increased apoptosis) and placental size; which, in turn may be associated with fetal weight and/or fetal: placental weight ratio. Other factors such as expression of the same protein from maternal tissues, and the metabolism of proteins by the placenta, reducing the amount of protein being secreted into the maternal circulation, may have a substantial influence of the total protein concentration in maternal blood (Figure 3.4). PAPPA has been found to be expressed from other maternal sources (e.g. ovary, some epithelial and endometrial cells, and breast) besides the placenta, and it is possible that these sources mask any relationship between placental derived protein and DNAm in the placenta (307,308,309,310). It is also important to note that PAPPA maternal protein levels were measured in the first trimester and additional variation may arise over gestation affecting correlation with placental DNAm at term.
Figure 3.4. Processes that may influence the relationship between DNA methylation, gene expression and protein expression.

Outlines reasons why we may not see a correlation between placental DNA methylation and gene expression or between placental gene expression and circulating levels of placental-specific proteins in maternal blood.
Our results were in concordance to Auer et al. (2010) who also reported increased levels of maternal FN1 in pregnancies complicated by EOPE and LOPE+IUGR (305). We did not confirm their observation of a decrease of FN1 in pregnancies complicated by IUGR; however, we may have been under-powered to observe this small difference. Furthermore, although we observe a difference in EOPE and LOPE+IUGR compared to controls, the range of FN1 levels completely overlap between the groups, hindering FN1 to be an adequate biomarker when used alone.

This study provides a link between changes in placental DNAm at term and protein biomarkers present in the mother’s circulation earlier in pregnancy. It emphasizes the many confounding factors that may influence this relationship, explaining why this linkage may not be observed for all loci. We chose three genomic sites with significantly altered DNAm in term placenta associated with PE and that were associated with genes for which the protein product is altered in PE/IUGR. We found a correlation between placental DNAm of INHBA and FN1 at delivery and second and third trimester maternal serum protein expression, respectively. This may suggest that other DNAm marks may be associated with early differences in gene expression. Furthermore, with the advent of techniques to quantify placental nucleic acids in maternal serum (114), DNAm changes may be more directly linked to measurable miRNA and RNA in maternal blood. Factors such as placental surface area and mechanisms for release into maternal blood, will also affect serum levels of placental nucleic acids (311). Future studies measuring protein levels directly in placental tissue, correlating with maternal levels and investigating the factors affecting rate of release are needed to help translate findings measured in the term placenta into maternal biomarkers of pregnancy outcomes in early gestation. Following up DNAm alterations
in future studies, it is imperative to assess DNAm alterations that are reproducible. For this reason, future studies should validate their finding in an independent cohort.
Chapter 4: Utility and validation in placental DNA methylation profiling of preeclampsia and intrauterine growth restriction

4.1 Introduction

Both preeclampsia (PE) and intrauterine growth restriction (IUGR) are heterogeneous in etiology, with many different factors contributing to these phenotypes (67,280,312). Due this heterogeneity, the ability to sub-classify placentas into more homogeneous groups can aid in our understanding of disease pathogenesis and prediction. For example, by defining ‘placental IUGR’ on the basis of a detailed scoring system for placental pathology, Benton et al. showed this subset was associated with very low maternal serum placental growth factor (PLGF) and also had the most severe perinatal and postnatal risks (313). In some cases, PE and normotensive IUGR (nIUGR) may represent two facets of a common underlying etiology, while in others the associated placental pathology and molecular changes may be distinct. Enforcing stringent criteria for defining and grouping samples may increase the reproducibility for reported molecular changes. For this study, we subdivide our samples into early-onset PE (EOPE), late-onset PE (LOPE), and nIUGR based on clinical obstetric criteria.

Molecular profiling has the potential to refine these clinically-defined group definitions further and improve our current understanding of the etiology of EOPE, LOPE, and nIUGR and their relationship to one another. Placental transcriptome profiling from pregnancies associated with PE and healthy controls provide evidence for multiple subtypes of PE (20). DNA methylation (DNAm) profiling is an alternative or complementary approach to gene expression profiling to identify subgroups of placental phenotypes. DNAm is more stable than mRNA and hence is less
subject to changes with sample processing time (164); it may also retain a “memory” of earlier in utero exposures and hence be linked to early effects in the disease process.

The aims of the present study were to build on our understanding of DNAm changes in placental insufficiency and to i) reanalyze our previous EOPE data with more sophisticated approaches; ii) extend our analysis to LOPE and nIUGR to investigate potential relationships between the three conditions and, iii) validate differentially methylated sites in an independent cohort. We will also discuss challenges to validation and future directions for epigenetics in the placental biology field.

4.2 Methods

4.2.1 Sample information

4.2.1.1 Discovery cohort

The discovery (Vancouver) cohort consisted of 22 EOPE, 18 LOPE, 11 nIUGR and 43 control placentas (Table 4.1). A subset of 18 EOPE samples and 19 preterm control samples in this study was previously used in Blair et al. (2013) (22).
Table 4.1. Sample information on the discovery and validation cohorts.

<table>
<thead>
<tr>
<th></th>
<th>Discovery Cohort</th>
<th>Validation Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EOPE (mean)</td>
<td>EOPE (mean)</td>
</tr>
<tr>
<td></td>
<td>LOPE (mean)</td>
<td>LOPE (mean)</td>
</tr>
<tr>
<td></td>
<td>IUGR (mean)</td>
<td>IUGR (mean)</td>
</tr>
<tr>
<td></td>
<td>Preterm “Control” (mean)</td>
<td>Preterm “Control” (mean)</td>
</tr>
<tr>
<td></td>
<td>Term Control (mean)</td>
<td>Term Control (mean)</td>
</tr>
<tr>
<td>N=</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Fetal birth weight</td>
<td>-8.18 – 3.77 (1.65)</td>
<td>-2.46-0.01 (1.40)</td>
</tr>
<tr>
<td>Standard deviation range</td>
<td>-2.9 – 2.57 (-0.96)</td>
<td>-2.92 -0.01 (-0.84)</td>
</tr>
<tr>
<td></td>
<td>-2.57 - -1.22 (-1.99)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>-1.61 – 3.23 (0.51)</td>
<td>-1.02- 0.05 (-0.16)</td>
</tr>
<tr>
<td></td>
<td>-0.94- 0.98 (-0.09)</td>
<td>-1.11- 3.60 (0.61)</td>
</tr>
<tr>
<td>Fetal Sex (M:F)</td>
<td>14:8</td>
<td>9:13</td>
</tr>
<tr>
<td></td>
<td>10:8</td>
<td>7:4</td>
</tr>
<tr>
<td></td>
<td>4:7</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>16:8</td>
<td>4:2</td>
</tr>
<tr>
<td></td>
<td>9:10</td>
<td>6:3</td>
</tr>
<tr>
<td>Maternal Age (years)</td>
<td>19.7-42.9 (33.3)</td>
<td>26.0-34.0 (30.5)</td>
</tr>
<tr>
<td></td>
<td>23.1-41.3 (34.0)</td>
<td>35.0-37.0 (36.4)</td>
</tr>
<tr>
<td></td>
<td>33.3-38.0 (34.3)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>22.2-41.1 (32.5)</td>
<td>27.0-33.0 (30.8)</td>
</tr>
<tr>
<td></td>
<td>30.0-40.2 (34.9)</td>
<td>38.0-40.0 (38.8)</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>24.9-38.4 (32.0)</td>
<td>26.0-34.0 (30.5)</td>
</tr>
<tr>
<td></td>
<td>34.6-41.3 (37.4)</td>
<td>35.0-37.0 (36.4)</td>
</tr>
<tr>
<td></td>
<td>34.6-38.0 (36.6)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>25.0-36.7 (32.6)</td>
<td>27.0-33.0 (30.8)</td>
</tr>
<tr>
<td></td>
<td>37.3-39.9 (38.4)</td>
<td>38.0-40.0 (38.8)</td>
</tr>
</tbody>
</table>

Discovery Cohort: $^1\ p= 6.9e-6$ vs PTB “Control”, $^2\ p=0.014$ vs Term Control, $^3\ p=1.7e-5$ vs Term Control, $^4\ p=3.3e-4$ vs Term Control

Secondary Cohort: $^5\ p=0.004$ vs PTB “Control”, $^6\ p=0.0005$ vs Term Control, $^7\ p=0.0001$ vs Term Control

Between Cohorts: $^7\ p=0.04$ PTB (discovery) vs PTB (secondary)
Technical batch effects, related to the plate, microarray chip, and sample position on the Illumina Infinium HumanMethylation450 (450K) are potential confounding factors within our data. Our samples were run in five batches over a 4 year period, and pathology and gestational age were confounded with batch as EOPE and preterm controls were largely run earlier. In this situation, correction for batch effects can introduce spurious findings (290) (Supplementary Figure D.1 and Supplementary Figure D.2). We, therefore, instead compared EOPE to preterm birth controls and LOPE/nIUGR to term controls only, which were relatively matched for batch, and thus the confounding by gestational age and its interaction with batch was minimized. We acknowledge that some of the differentially methylated sites that we found may be due to technical artifacts, but focusing on those hits that are reproduced in the validation cohort largely eliminated these effects.

As placental DNAm changes with gestational age, the comparison groups included placentas from healthy term births (≥37 weeks) and preterm births (<37wks) with normally grown babies and no evidence of maternal hypertension. EOPE placentas were compared to 24 preterm controls (as in Blair et al. 2013). LOPE and nIUGR placentas were compared to a separate set of 19 term control placentas. This was to test for overlap between DNAm changes identified for LOPE and nIUGR with those for EOPE. We did not want the use of a common control group driving any potential overlap. To reduce the chance of differences being driven by the preterm birth group, we used placentas from preterm births from a variety of etiologies (e.g. premature rupture of the membranes, incompetent cervix, chorioamnionitis), while any term control samples with evidence of pathology involving the chorionic villi were excluded.
4.2.1.2 Validation cohort

The validation (Toronto) cohort consisted of 22 EOPE, 11 LOPE, and 15 control placentas (Table 4.1). For the validation cohort, placental samples were purchased through the Research Centre for Women’s and Infants’ Health BioBank (Mount Sinai Hospital), details in the sample processing can be found in Leavey et al. (2016) (21). DNA was extracted from the pooled placental tissue by ethanol precipitation using the Wizzard® Genomic DNA Purification Kit (Promega). Gestational age at delivery and fetal birth weight were collected for each case. For this cohort, ethics approval was obtained from both Mount Sinai Hospital (#13-0211-E) and the University of Toronto (#29435).

The validation cohort represents a subset of samples from the Leavey et al. (2016) study (21). PE was defined as BP > 140/90mm Hg after 20 weeks gestation and proteinuria >300mg/day or >2+ by dipstick (314). As the time of diagnosis was unknown, we subdivided the PE samples from this cohort into EOPE and LOPE based on the gestational age at delivery. Exclusion criteria included diabetes, sickle cell anemia, morbid obesity, and multi-fetal pregnancies. The division of the term and preterm controls was also done in the validation cohort, which consisted of 6 preterm control and 9 term control placentas.

4.2.1.3 DNA methylation analysis

Samples were run on the 450K array. To minimize any effects of sample processing between the validation and discovery cohorts, arrays were run in the same batch and with the same operators as a subset of the samples from the discovery cohort (Chips 5013, 5015, 3024,3037,3038,3110, See Supplementary Figure D.1 and Supplementary Figure D.2). This DNAm data for the
discovery and validation cohorts is available from the Gene Expression Omnibus (GEO) database under the accession numbers GSE100197 and GSE98224, respectively.

### 4.2.1.4 Differential DNA methylation analysis

All statistical analyses were performed using R version 3.2.4. Differentially methylated sites were identified using statistical, i.e. false discovery rate (FDR) <0.05, and biological, i.e. a change in DNAm (Δβ)>0.1, criteria. We corrected for fetal sex in our linear regression model, but we did not adjust for birth weight, as it is closely related to pathology. As our groups were matched to controls of a similar gestational age, our final model where DNAm alterations were identified took into account fetal sex only. Only those sites that met both these criteria were then evaluated in the validation cohort. In this case, linear regression was used, and sites were considered to be persistent hits if the nominal p-value <0.05 and the change in DNAm was in the same direction as the discovery cohort. Bonferroni correction p <0.05 was also used on the 1703 EOPE differentially methylated sites to investigate how many hits would be validated with a more stringent threshold. To compare the heterogeneity of the samples in each cohort, sample by sample Pearson’s correlations (correlating all DNAm measures in each sample to every other sample in the study) were performed, and the average correlation of each sample was compared between the two cohorts by Student’s t-test separately for the control (Term + Preterm) and EOPE samples.

To investigate whether the Bonferroni corrected hits and the nominal p-value validated hits were more than would be expected by chance, 1703 sites (number of EOPE hits in the discovery cohort) were randomly sampled from the validation cohort data and run through a linear model,
correcting for fetal sex. One thousand permutations were run and the number of sites that met a nominal p-value < 0.05 in each iteration was recorded. The number of randomly sampled sites to meet a nominal p-value < 0.05 were compared to the actual number of sites that validated in our data (N=42 (Bonferroni corrected) and N=599 (nominal p-value)).

4.2.1.5 Clustering analysis

Hierarchical clustering was performed on the persistent hits to investigate whether samples clustered according to their clinically diagnosed pathology, or whether DNAm profiling could suggest an improved definition of pathological groups. The pvClust package in R (315) assessed how stable any resulting clusters were, using 1000 iterations. The sigClust2 package (316) determined if any clusters were significantly different from one another, also using 1000 iterations. To investigate whether differences in DNAm between the clusters were enriched for any specific pathway(s), linear regression was used to identify differentially methylated sites between clusters. Differentially methylated sites were annotated to genes using the Price et al. annotation, closest transcriptional start site (291), and then input into ermineJ, a gene ontology tool (317). ErmineJ allows us to input a background gene list specific to the Illumina 450K array, accounts for multifunctionality (gene ontology terms that appear frequently due to the number of genes involved in the pathway), and allows for multiple iterations to be run to strengthen the power of the analysis.
4.3 Results

4.3.1 Widespread DNAm changes are associated with EOPE but not LOPE and nIUGR in our Discovery cohort

Our first goal was to confirm our previous report of widespread changes in EOPE (22) and then to test for similar changes in LOPE and nIUGR using the same approach. We chose less stringent cutoffs for significance in this analysis (FDR<0.05 & Δβ>0.1) as compared to Blair et al. (2013) (FDR<0.01 & Δβ>0.125) (22) as our aim was to identify a larger number of differentially methylated sites that could be used for further validation. Based on these criteria, a total of 1703 sites were differentially methylated between EOPE and preterm controls (Figure 4.1). As expected, the majority (261/286) of EOPE hits reported in Blair et al. were also identified as hits in this analysis. Differences between the two analyses are likely explained by the use of different normalization methods, correction for fetal sex in the present study, and the inclusion of a few additional samples in this study compared to the previous one.

We used the same approach to identify differential methylation associated with LOPE or nIUGR as compared to the healthy term control group. In contrast to the EOPE comparison, only 5 sites were differentially methylated between LOPE and term controls, and no sites were differentially methylated between nIUGR and term controls (Figure 4.1). The 5 differentially methylated sites between LOPE and term controls were not unique to LOPE, as they were also included amongst the 1703 sites identified as differentially methylated in EOPE. The weaker signal may be explained if only a few of the LOPE cases have an underlying pathology similar to that in the EOPE cases, driving these changes.
Figure 4.1. Volcano plots depicting differentially methylated sites.

Differentially methylated sites between A) EOPE and preterm controls (preterm-EOPE), B) LOPE and term controls (term-LOPE), and C) IUGR and term controls (term-IUGR). $-\log_{10}$ of the adjusted p-value is plotted on the y axis and the change in DNAm ($\Delta \beta$) is plotted on the x axis. Sites highlighted in red are hypermethylated in the pathology compared to controls. Sites highlighted in green are those that are hypomethylated in the pathology compared to controls.
4.3.2 Validation of the EOPE hits in an independent cohort

We next investigated if the EOPE hits from our discovery cohort could be validated in an independent cohort. We first tested whether the $\Delta \beta$ values in the discovery and validation cohorts were correlated using all sites that met an FDR<0.05 in the discovery cohort, without imposing an additional $\Delta \beta$ threshold. At these sites, the correlation was significant ($R=0.62, p<2.2e-16$, Figure 4.2a). This indicates that largely similar changes in DNA methylation (DNAm) are being observed in the EOPE placentas in both cohorts. Amongst the most highly significant hypomethylated sites ($\Delta \beta >0.15$) in both cohorts were CpGs associated with *KRT15, FNI, TEAD3, JUNB, ST3GAL1, PKM2, NDRG1, PAPPA2, CHI3L2*, and *INHBA*. Many of these genes have previously been shown to have altered gene expression in preeclampsia and *JUNB* has been specifically implicated as a key player in the response to hypoxia in trophoblast cells (318). Amongst the most highly hypermethylated sites ($\Delta \beta <-0.10$) in both cohorts were several sites associated with *FAM3B, SYNE1*, and *AGAPI*. However, it should be noted that there were also many sites with a high $\Delta \beta$ in the discovery cohort that had a much smaller or sometimes opposite direction $\Delta \beta$ in the validation cohort.

To narrow down the original 1703 EOPE hits from the discovery cohort to a high-confidence hit list, we first asked, how many of these hits met similarly stringent criteria (FDR<0.05 and $\Delta \beta>0.1$) in the validation cohort? We found that only 38 probes (2.2%) met these strict criteria. Using such arbitrary cut-offs in both populations and a strict definition for a “hit” may not be a powerful approach to assess the degree of overlap in the data. Furthermore, requiring assay-wide correction for multiple testing in the validation cohort is overly conservative and reduces power. Running the linear regression on only the 1703 sites differentially methylated in the discovery
cohort reduces the number of multiple test corrections needed in the validation cohort. Based on the distribution of nominal p-values among the 1703 EOPE associated sites in the validation cohort, shown in Figure 4.2b, there are many more sites that meet a nominal p-value<0.05 than expected, even if these do not meet a multiple test correction. Hence, we opted to use a nominal p-value<0.05 and a change in DNAm in the same direction as the discovery cohort to define validated (i.e. high confidence) hits. Based on these criteria, 599 of the 1703 (35.1%) EOPE hits were considered to be validated (Figure 4.2b). This is higher than what we would expect by chance (p=0.0001). This reproducibility rate was similar to the rate reported by Yeung et al. (2016), who validated their own differentially methylated regions with our published cohort (Blair et al. (2013))(240). As PE and IUGR are heterogeneous conditions, it is possible that the reproducibility rate may be affected by the samples chosen for each cohort. We were interested in whether the samples in the cohorts were similarly correlated (i.e. is one cohort more heterogeneous than the other). We investigated these correlations in the control samples (term and preterm) (Supplementary Figure D.3) and the EOPE samples (Supplementary Figure D.4). In both pathologies, samples in the discovery cohort were more heterogeneous (more variability in DNAm measures) than the samples in the validation cohort.
Figure 4.2. Validation of DNA methylation alterations.

A) The correlation between the change in DNA methylation ($\Delta \beta$ values) between EOPE and preterm controls (preterm-EOPE), between the discovery and validation cohorts ($R=0.62, p<2.2e^{-16}$). The sites highlighted in red are the top sites labeled by the gene the CpG site is located in. B) P-value distribution of the 1703 EOPE hits from the discovery cohort, in the validation cohort. There were 599 sites of the 1703 EOPE sites (35.1%) that validated.
These validated sites were not enriched for any gene ontology terms using ermineJ, with a 450K array specific background (317). A list of these sites and relevant gene information can be found in Supplementary Table D.1. These sites include ones associated with genes known to be relevant to EOPE from gene expression studies including CGA, INHBA, PAPPA2, and ADAM12.

4.3.3 Effects of varying validation criteria
To evaluate the effect of varying FDR and Δβ cutoffs to establish the most ‘reproducible’ results, we plotted the percentage of probes that showed Δβ concordance in directionality between the validation cohort and the discovery cohort using different FDRs and Δβ thresholds in the discovery set (Supplementary Figure D.5a). Different FDR thresholds did not influence DNAm concordance rate when the Δβ thresholds were above 0.2. FDR thresholds appear to be more important when trying to identify small changes in DNAm. We also investigated the number of hits that each threshold would obtain. Supplementary Figure D.5b plots the number of hits at each FDR and Δβ cutoff. Allowing smaller changes in DNAm produces many more hits, but with a lower reproducibility rate. This is likely because this is in the range of normal variability for a site. This highlights the importance of considering both the biological and statistical thresholds depending on the magnitude of the anticipated DNAm change and the overall research objective.

4.3.4 Hierarchical Clustering
Next, we evaluated the degree to which the 599 validated sites can discriminate EOPE from all other placentas in both cohorts, using hierarchical clustering (Figure 4.3). Although we expected an EOPE methylation cluster to be defined, since we are clustering based on our EOPE hits, this
approach can inform us about the relationships between individual samples and, furthermore, allow comparisons to term controls, and LOPE and nIUGR cases which were not involved in the selection of these EOPE hits. Interestingly, both cohorts clustered into 3 stable methylation clusters, rather than just two as we had expected. When the cohorts were clustered on the 599 validated hits separately, methylation cluster 1 included almost all EOPE suggesting a consistent phenotype in this group. In the discovery cohort cluster, 6 LOPE samples clustered with the EOPE samples. In the validation cohort, 7 LOPE samples and 1 preterm control clustered with the EOPE samples. Additionally, in both cohorts, methylation sub-clusters were identified within the larger EOPE group (methylation cluster 1), which were also stable and significantly different from one another, suggesting a possible further subdivision or distinct groups within methylation cluster 1. There was no obvious difference between these subclusters clinically (including sex, ethnicity, disease severity etc.); however, gestational age was decreased in the EOPE methylation subcluster 1 compared to subcluster 2 (p<0.01) in the validation cohort (Table 4.2)
Figure 4.3. Hierarchical clustering (Euclidean) on the 599 validated hits in both the discovery (left) and validation (right) cohorts. Numbers represent the percentage of times these clusters formed when using 1000 iterations with pvclust. Those highlighted in green are considered stable, where clusters formed >75% of the time. P values signify clusters are significantly different from one another.
**Table 4.2.** Clinical information on samples assigned to methylation clusters.

Methylation cluster 2 was compared to methylation cluster 3 and EOPE methylation subcluster 1 was compared to EOPE methylation subcluster 2.

<table>
<thead>
<tr>
<th></th>
<th>DISCOVERY COHORT</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methylation 2</td>
<td>Methylation 3</td>
<td>EOPE Subcluster 1</td>
<td>EOPE Subcluster 2</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>43</td>
<td>27</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>IUGR Status (IUGR/Total)</td>
<td>10/43 (23%)*</td>
<td>2/27 (7%)</td>
<td>7/8 (88%)</td>
<td>14/16 (88%)</td>
<td></td>
</tr>
<tr>
<td>Fetal Sex (F/Total)</td>
<td>22/43 (51%)</td>
<td>11/27 (41%)</td>
<td>5/8 (63%)</td>
<td>3/16 (19%)*</td>
<td></td>
</tr>
<tr>
<td>Gestational Age (weeks) (range (mean))</td>
<td>25.0-40.0 (36.0)</td>
<td>28.0-41.3 (35.7)</td>
<td>24.9-36.0 (31.7)</td>
<td>26.0-37.3 (32.6)</td>
<td></td>
</tr>
<tr>
<td>Fetal Birth Weight (SD) (range (mean))</td>
<td>-2.78 – -3.77 (-0.44)**</td>
<td>-2.16 – -1.70 (0.18)</td>
<td>-2.90 – -1.17 (-1.87)</td>
<td>-8.19 – -0.58 (-2.26)</td>
<td></td>
</tr>
<tr>
<td>Chronic Hypertension (CH/Total)</td>
<td>7/43 (16%)</td>
<td>2/27 (7%)</td>
<td>2/8 (25%)</td>
<td>5/16 (31%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes (Pre-existing or Gestational) (Diabetes/Total)</td>
<td>2/43 (5%)</td>
<td>0/27 (0%)</td>
<td>1/8 (13%)</td>
<td>1/16 (6%)</td>
<td></td>
</tr>
<tr>
<td>Chorioamnionitis (CA/Total)</td>
<td>7/43 (16%)</td>
<td>5/27 (19%)</td>
<td>0/8 (0%)</td>
<td>0/16 (0%)</td>
<td></td>
</tr>
<tr>
<td>Premature Rupture of Membranes (PPROM/Total)</td>
<td>3/43 (7%)</td>
<td>4/27 (15%)</td>
<td>0/8 (0%)</td>
<td>0/16 (0%)</td>
<td></td>
</tr>
<tr>
<td>Ultrasound Findings (Findings/Total)</td>
<td>7/43 (16%)</td>
<td>2/27 (7%)</td>
<td>3/8 (38%)</td>
<td>4/16 (25%)</td>
<td></td>
</tr>
<tr>
<td>Placental Pathology Noted (Notes/Total)</td>
<td>17/43 (40%)</td>
<td>7/27 (26%)</td>
<td>4/8 (50%)</td>
<td>10/16 (63%)</td>
<td></td>
</tr>
</tbody>
</table>

|                  | VALIDATION COHORT |                  |                  |                  |                  |
|                  | Methylation 2    | Methylation 3    | EOPE Subcluster 1| EOPE Subcluster 2|
| N                | 7                | 11               | 19               | 11               |
| IUGR Status (IUGR/Total) | 0/7 (0%)        | 0/11 (0%)       | 11/19 (58%)     | 7/11 (64%)       |
| Fetal Sex (F/Total)      | 1/7 (14%)        | 5/11 (45%)      | 9/19 (47%)      | 7/11 (64%)       |
| Gestational Age (weeks) (range (mean))    | 30.0-37.0 (33.0)*** | 37.0-40.0 (38.4) | 27.0-37.0 (32.8)*** | 26.0-34.0 (29.8) |
| Fetal Birth Weight (SD) (range (mean))    | -0.48 – -0.50 (-0.06) | -1.11 – -3.60 (0.34) | -2.27 – -2.92 (-1.12) | -2.46 – -0.86 (-1.59) |
| Chronic Hypertension (CH/Total)            | 1/7 (14%)        | 1/11 (9%)       | 7/19 (37%)      | 3/11 (27%)       |

* p<0.1, ** p<0.05, ***p<0.01
The remaining non-EOPE samples also clustered into two methylation clusters in both cohorts. We refer to these clusters as methylation clusters 2 and 3. Methylation cluster 3 in both cohorts was predominantly composed of controls. Within the discovery cohort, methylation cluster 2 consisted of the majority of the nIUGR and LOPE cases, a few EOPE cases, and some preterm and term controls; Decreased birthweight (p<0.01) and a trend towards increased IUGR diagnosis (p<0.1) was observed in methylation cluster 2 vs. 3. In the validation cohort, methylation cluster 2 consisted of preterm controls and LOPE samples and was associated with decreased gestational age (p<0.01) (Table 4.2).

4.3.5 Cluster gene ontology

As it was unexpected that the control samples divided into two distinct methylation clusters, and the EOPE samples divided into two distinct subclusters, we were interested in investigating the differences between the two control methylation clusters (methylation clusters 2 and 3) and between the EOPE methylation subclusters (EOPE methylation subclusters 1 and 2). Linear regression was used on the 599 persistent hits, accounting for fetal sex, to identify DNAm differences between methylation cluster 3 and methylation cluster 2 and between EOPE methylation subcluster 1 and EOPE methylation subcluster 2. There was no enrichment in gene ontology terms in either ermineJ (with a 450K array specific background), or DAVID. Between methylation cluster 2 and methylation cluster 3, 244 sites were differentially methylated in both cohorts. Information on these sites can be found in Supplementary Table D.2. There was no gene ontology enrichment by ermine or DAVID. Between EOPE methylation subcluster 1 and EOPE methylation subcluster 2, 207 sites were differentially methylated in both cohorts. Information on these sites can be found in Supplementary Table D.3. There was no gene ontology enrichment by
and symporter activity was the only gene ontology term in DAVID to meet multiple test corrections.

4.4 Discussion

We previously reported widespread changes in DNAm associated with EOPE (22). In the present study, we extend this analysis to LOPE and nIUGR; however, using the same approach, we were unable to identify DNAm changes that were unique to these groups. While these latter comparisons were limited by small sample size, we were able to obtain significant associations with EOPE with similarly small sample sizes. The reduced number of changes in the LOPE and nIUGR groups can occur for two main reasons: 1) there may be much more limited placental pathology with these diagnoses and the phenotype is largely driven by maternal factors, or 2) they may be more heterogeneous etiology thereby limiting power to detect changes in the group as a whole. If we want to improve biomarker discovery in these groups, we may need to identify more homogeneous subgroups using a combination of clinical parameters, pathology reports and/or already proposed biomarkers, along with larger sample sizes.

The LOPE samples in the discovery cohort that clustered with the EOPE samples all presented with PE between 34.0 weeks and 35.9 weeks gestation and had co-occurring IUGR. While it’s possible that PE symptoms were present but not diagnosed until after 34.0 weeks, there may also be inaccuracies in dating the pregnancy and/or there is simply a grey zone in the distinction between EOPE (placenta-driven) and LOPE (maternal-health driven). It is important to note that the 34 week cut-off between EOPE and LOPE was chosen somewhat arbitrarily to note that prematurity has a much more severe effect on the baby. Therefore, not all cases likely influenced
by ‘placental-mediated’ PE will be correctly classified by the 34 week definition of EOPE and LOPE. There were also four cases of EOPE within the discovery cohort that did not cluster with other EOPE cases. One was diagnosed with hemolysis elevated liver enzymes and low platelet (HELLP) syndrome and delivered at 33.3 weeks gestation, one also had chorioamnionitis (which may have contributed to early delivery); one had preexisting hypertension and was diagnosed early but did not deliver until 37 weeks and hence may have been milder in presentation; the fourth was delivered at 33.3 weeks with no other placenta or maternal health notes. Of note, none of the EOPE cases that clustered outside of the EOPE cluster had co-occurring IUGR and were generally diagnosed at close to 34 weeks gestation. Thus, the presence of IUGR in cases diagnosed between 32 and 36 weeks may be the more defining feature as to whether an altered placental DNAm profile, and therefore placental-mediated disease is observed or not. Powers et al. (2012) showed that there are two types of PE pregnancies: those with and without altered angiogenic factors (26). As alterations in the angiogenic factors have also been observed in IUGR cases (319,320), Myatt and Roberts suggested that an imbalance in these factors may represent a measure of placenta growth, development, and function (321). As such, the EOPE cases clustering outside the EOPE methylation cluster may be more likely related to other contributing factors than placental dysfunction.

While we expected to see an EOPE methylation cluster, as the validated hits were chosen based on differentially methylated sites between EOPE and preterm controls, we were surprised that both the EOPE and control groups each formed two subclusters. The driving differences between these subclusters were not clear, though the tendency to lower gestational ages and fetal birth weights (SD) in cluster 2 could suggest features linked to preterm birth (Table 4.2). The presence
of two distinct subclusters within the EOPE methylation cluster could reflect PE severity, or perhaps unmeasured factors such as medical treatments given or duration of hypertension. Unfortunately, we had insufficient information on the treatment of each case to evaluate the influence of medical care on the placental methylation profile.

While altered placental DNAm has been reported for pregnancies complicated by PE (13,16,246,322) and IUGR (50,53,323), only one study validated their findings, using the same technology, in an independent cohort with 34.7% of their differentially methylated regions validating (240). In this study, 35.1% (N=599) sites were found to be differentially methylated between EOPE and preterm controls in both the discovery and validation cohorts using validation criteria of a nominal p<0.05 and change in DNAm in the same direction as the discovery cohort. The extent of validation, however, is dependent on the initial criteria chosen to define ‘hits’, the criteria for validation, the similarity of the populations of samples, the size of the study populations (power to detect changes), and the similarity in processing the samples. In our study, the validation cohort was from a roughly similar urban population (Vancouver vs. Toronto) from the same country (Canada). We also tried to minimize technical factors that may influence results by using similar placental sampling protocols, processing the arrays with a subset of the discovery and validation cohorts on the same microarray chips at the same time, with the same technicians, and using the same pre-processing methods on the raw data. Even with these considerations, a significant number of our original hits were not validated. This may be because of chance variation in causes of PE and IUGR in the two cohorts due to limited sample size. Additionally, there are genetic, environmental, and maternal factors that pre-dispose a pregnancy to developing placental insufficiency, which may have varied between populations.
Changes in DNAm could mean i) an average change in DNAm across our sample, or ii) a change in the cell type proportions within a sample, as DNAm varies widely across different cell types (210). In the context of EOPE, DNAm alteration may reflect a combination of altered gene expression pathways associated with PE (e.g. related to known effects such as oxidative stress and altered angiogenesis (26,67)) or altered cell type proportions related to PE pathology (e.g. decreased proliferation of extravillous trophoblast cells or alterations to the rate of trophoblast proliferation (324)). As cell-type specific profiles have not been developed for all placental cell types, it is not possible to use the DNAm profile to estimate cell proportions, as it has been applied to blood (213). While reference-free methods for deconvolution of cell proportions have been developed (325), these methods remove variance within the data attributed to cell composition but cannot inform us of what cell types specifically are altered in EOPE.

Our data demonstrate some of the challenges in identifying changes specific to clinically defined etiologies. Heterogeneity and milder phenotypes in LOPE and nIUGR likely limit the power to detect differences using a differential methylation type approach and mask the subset of cases that do exhibit altered pathology (based on sample clustering using our EOPE defined hits). An alternative approach may be to reduce the dimensions in the data by 1) removing non-variable probes across all cell types (326), 2) focusing on alterations in pathway modules, as in weighted gene co-expression network analysis (327), or 3) evaluating differentially methylated regions (DMRs) rather than individual CpG sites to combat multiple test correction (328,329). In contrast, the more severe pathology underlying EOPE results in many readily detected DNAm changes. However, even in the case of EOPE, where many large changes in DNAm are
identified and can be validated based on a nominal p-value<0.05 in an independent cohort, those sites selected for having the highest magnitude of change rarely showed the same degree of difference in the second cohort.

In conclusion, whether in the context of PE, or other heterogeneous diseases, DNAm may be a useful tool to independently and qualitatively classify pathological groups prior to analysis. This method may aid in creating more robust prediction algorithms for predicting pathology versus controls. Further studies with larger sample sizes and additional clinical variables are needed to confirm the presence of multiple subtypes of placental-mediated PE and identify what is driving these different subtypes.
Chapter 5: Placental telomere length decline with gestational age differs by sex and TERT, DNMT1, and DNMT3A DNA methylation

5.1 Introduction

Telomeres, repetitive sequences located at the end of each chromosome, protect chromosome ends from degradation and end-to-end fusion. As DNA polymerase cannot synthesize DNA in the 3’- 5’ direction, telomere length (TL) decreases with every cell division in the absence of telomerase activity. For this reason, TL has been viewed as a mitotic clock, whereby shorter telomeres are associated with advanced biological age (330). However, other factors in addition to age/cell-division can influence TL.

Initial TL depends on the average length inherited in the gametes, which is positively affected by paternal age (331). It also depends on telomerase activity, the enzyme responsible for telomere maintenance and lengthening. Telomerase is composed of a subunit with telomerase reverse transcriptase (TERT) activity and a non-coding RNA encoded by telomerase RNA component (TERC) and having sequence complementary to the hexameric telomeric repeat (TTAGGG) (332). Telomerase is active in the gametes, early embryo, and placenta but is mostly silent in somatic tissues after birth (333). Telomerase activity is also positively influenced by estrogen level, such that high estrogen is associated with longer telomeres (334). This relationship may be explained by presence of an estrogen response element (ERE) in the promoter of the telomerase reverse transcriptase gene TERT (334). Guanine repeats within the telomeric region are
susceptible to oxidation, causing them to be a genomic location susceptible to DNA damage (148). The resulting DNA repair process can also result in telomere shortening (335).

While few genetic variants have been associated with TL, (336), mutations in \textit{TERC} can lead to Dykeratosis Congenita, a premature aging disease (337,338,339) and polymorphisms in \textit{TERC} have been linked to changes in TL (340). As little of the estimated 30-80% TL heritability can be explained by these or other variants, it was proposed that epigenetic variation may additionally influence TL (341). Mutations in DNA methyltransferase (DNMT) genes, responsible for establishing and maintaining DNAm across the genome, have also been associated with aberrant TL (303), providing evidence for a role of DNAm in telomere maintenance. Mutations in \textit{DNMT3B} lead to immunodeficiency-centromeric instability-facial anomalies syndrome (342), characterized by hypomethylation at subtelomeric regions, which results in short TL (343). Additionally, knock out studies of DNMTs in mice result in abnormal telomere elongation (344).

A few studies have reported reduced TL in placentas associated with adverse outcomes compared to controls (149,150,152). Oxidative stress is thought to be increased in placentas and fetuses associated with preeclampsia (PE) and/or intrauterine growth restriction (IUGR), due to inefficient remodeling of the uterine spiral artery and resulting in reduced blood and oxygen flow to the placenta and fetus (4). This increased oxidative stress may result in reduced TL in placentas from pregnancies complicated by PE and/or IUGR (150). However, very little is known about TL dynamics in the human placenta during gestation.
In this study, TL was evaluated in a set of 140 placentas from healthy and complicated pregnancies, using quantitative PCR (qPCR). The effects of factors that may influence placental TL in healthy pregnancies including gestational age, fetal sex, maternal age, and birth weight was first assessed. The relationship of TL with pregnancy complications was evaluated after considering these covariates. DNAm was measured in a subset of 58 placentas using the Illumina Infinium HumanMethylation450 BeadChip array (450K). TL was first compared to DNAm at biologically relevant genes (TERT, TERC and DNMTs) and then to all sites targeted by the array.

5.2 Methods

5.2.1 Sample Information

To study TL across gestation, 92 placental samples were used that spanned from 6 weeks gestation to term (Table 5.1). Sources included elective termination (N= 17), preterm birth due to various etiology with minimal placental involvement (e.g. incompetent cervix, spontaneous premature rupture of the membranes, and preterm labor) (N= 55) and healthy term deliveries (N= 20). To compare TL between pathological groups to control placentas, only the subgroup of 59 preterm control placentas from viable pregnancies (25.7-40.3wks GA) was used.

<table>
<thead>
<tr>
<th>Group</th>
<th>N=</th>
<th>Gestational Age Range (weeks)</th>
<th>Sex (F:M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm (&lt;24wks)</td>
<td>33</td>
<td>6.4-23.9</td>
<td>19:14</td>
</tr>
<tr>
<td>Controls (&gt;24wks)</td>
<td>59</td>
<td>25.7-40.3</td>
<td>27:32</td>
</tr>
<tr>
<td>EOPE</td>
<td>21</td>
<td>24.9-37.6</td>
<td>8:13</td>
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<tr>
<td>LOPE</td>
<td>18</td>
<td>34.6-41.3</td>
<td>9:9</td>
</tr>
<tr>
<td>IUGR</td>
<td>9</td>
<td>35.4-38.0</td>
<td>5:4</td>
</tr>
</tbody>
</table>

Table 5.1. Placental samples and clinical data for which telomere length was measured.
5.2.2 Telomere length measures

Average relative TL was measured in 92 control, 21 EOPE, 18 LOPE, and 9 IUGR placentas by qPCR as described by Cawthon et al. (2002) (345), with several modifications described in Hanna et al. (2009) (346). Average TL is reported as a Telomere/Single gene (T/S) ratio which is the amplification of the telomere repeat region (T) relative to the amplification of a single copy housekeeping gene (S), 36B4. Samples were run in triplicate on 96-well plates. Each plate contained 23 samples, a standard curve made up of reference DNA, serially diluted from 20ng to 0.625ng, a no-template control, and both a long and short telomere reference control. 7.0ng of DNA was loaded into each well. To make certain that only our targeted amplicons were being amplified, dissociation melting curves were run after each sample. In cases where the standard deviation (SD) between the triplicate sample were >0.2, the sample was removed and re-run on the next plate. Additionally, samples which had a coefficient of the variance (CoV) >0.15 were also removed and re-run. Each sample was replicated (in triplicate) on a separate plate to ensure that T/S values were reliable. The average of these two independent T/S values is reported for each sample. In cases where the CoV between the two T/S values was >0.15, the sample was re-run and the average between the two most similar runs is reported.

5.2.3 DNA methylation analysis

DNAm was measured on the Illumina Infinium HumanMethylation450 (450K) array for 20 EOPE, 17 LOPE, 8 IUGR and 13 control placentas for which TL was available. We first examined DNAm alterations at six candidate genes (TERT, TERC, DNMT1, DNMT3a, and
DNMT3b) relevant to telomerase and DNAm establishment and maintenance, then performed a genome-wide approach utilizing the entire array.

5.2.4 Statistical analysis

Linear modeling was used to assess the change in TL with gestational age, maternal age, birth weight and pathological groups. These analyses used only the preterm placentas >24 weeks gestation (N=59). Two-tailed t-tests were used to determine whether placental TL differed between fetal sexes. Linear modeling, accounting for fetal sex and gestational age, was used to compare mean TL in pathological groups to the control group. A further subset of controls for which 450K array data was available (28-38wks gestation) was used to evaluate the association between DNAm and TL. To estimate global DNAm, we averaged the DNAm measure of all 441,093 probes in our analysis for each of our samples to yield a global average DNAm value. For the array-wide analysis, we set a false discovery rate (FDR) <0.05 and a change in DNAm (Δβ) >0.05 with every 1.0 change in T/S value. All statistical analysis was performed in R, version 3.2.5(347).

5.3 Results

5.3.1 Telomere length is associated with gestational age and fetal sex

TL dynamics spanning all three trimesters of pregnancy showed shorter TL in male fetuses compared to female fetuses, independent of gestational age (Figure 5.1, R=-0.43 p=0.001). Maternal age was not associated with TL (Figure 5.2a; R=-0.001, p=0.92), nor was birth weight (Figure 5.2b; R=-0.008, p=0.36). Gestational age at delivery was negatively associated with TL (Figure 5.2c; R=-0.04, p=0.02). On average, female placentas had longer telomeres than male
placentas, even when gestational age was considered (Figure 5.2d, p=0.004). Based on this analysis, both gestational age and fetal sex were adjusted for in subsequent analyses.

**Figure 5.1.** Fetal sex is associated with telomere length.

Taking into account gestational age, fetal sex is significantly associated with telomere length (R=-0.43; p=0.001).

Average telomere length as a T/S ratio is on the y-axis and gestational age (weeks) is on the x-axis.
Figure 5.2. Variables assessed as potential confounders with telomere length.

In each graph, average telomere length, measured as a T/S ratio, is depicted on the y-axis in comparison to A) maternal age, B) birth weight, measured as standard deviation (SD), C) gestational age, and D) fetal sex.
5.3.2 Telomere length does not differ between EOPE, LOPE, IUGR and controls

Adjusting for gestational age and fetal sex, there were no significant differences in placental TL between EOPE, LOPE, or IUGR compared to controls (Figure 5.3), though TL tended to be shorter in EOPE placentas compared to controls (R=-0.25, p=0.10). TL was significantly longer in LOPE placentas as compared to EOPE placentas (R=0.48, p=0.02).
Figure 5.3. Boxplots depicting telomere length (T/S ratio) between pathological groups.

EOPE, early-onset preeclampsia; LOPE, late-onset preeclampsia; IUGR, intrauterine growth restriction. † p=<0.1, * p<0.05.
5.3.3 Telomere length is associated with DNA methylation at TERT, DNMT1, and DNMT3A

We assessed whether DNAm at TERT or TERC was associated with TL. There were 99 and 15 probes on the 450K array that are within TERT and TERC, respectively. Assessing each CpG site independently, adjusting for gestational age and fetal sex, no association was found between TERC DNAm and average TL. An association between DNAm at a CpG site upstream of the TERT promoter CpG island and a CpG site in the gene body of TERT was significant (cg01934390 $\Delta\beta=0.053$ for every 1.0 T/S unit, $p=0.003$, cg11832804 $\Delta\beta=0.052$ for every 1.0 T/S unit, $p=0.01$), whereby longer TL was associated with increased DNAm at these sites (Figure 5.4a). Overall, 19 of the 99 TERT probes were nominally significant without an additional $\Delta\beta$ cutoff, of which 18 showed increased DNA methylation associated with longer telomeres.

DNAm of two CpG sites within DNMT1 were associated with TL, although the change in DNAm per 1.0 unit change in T/S ratio was slightly below our arbitrary cutoff (cg07267628 $\Delta\beta=0.043$, $p=0.007$, cg26538782 $\Delta\beta=0.044$, $p=0.03$, Figure 5.4b). Cg07267628, is located in DNMT1, downstream of the transcriptional start site and in the first exon of an alternate transcript of DNMT1, while, cg26538782, is located within an enhancer, upstream of DNMT1. DNAm at a CpG within the gene body of DNMT3A and upstream of the promoter region of an alternate transcript was also associated with TL (cg11779362, $\Delta\beta=0.051$, $p=0.004$, Figure 5.4c). There was no association between DNAm within DNMT3B and TL.
Figure 5.4. Sites in TERT, DNMT1 and DNMT3A with association between DNA methylation and telomere length. Change in DNAm (Δβ) with every 1.0 change in T/S ratio is on the y-axis. CpG site (IlluminaID name) in genomic order is on the x-axis. Sites marked with an X meet false discovery rate (FDR) <0.05. Gene map is depicted below the line graph, where green is the CpG islands, red in the promoter region, yellow in enhancer and blue is CTCF binding sites. Alternative transcripts are in grey.
We further investigated if DNAm at the sites that associate with TL (*TERT, DNMT1*, and *DNMT3A*), differed between EOPE, LOPE, IUGR and controls. Adjusting for fetal sex and gestational age, DNAm at cg01934390 within *TERT* differed between EOPE and controls (p=0.02), and EOPE and LOPE (p=0.04, Figure 5.5Ai). No differences in DNAm were observed at cg11832804 within *TERT* (Figure 5.5Aii). Within *DNMT1*, DNAm at cg07267628 differed between EOPE and controls (p=0.001), LOPE and controls (p=0.009), and IUGR and control (p=0.001) (Figure 5.5Biii) groups. DNAm at cg26538782, within *DNMT1* only differed between EOPE and controls (p=0.03, Figure 5.5Biv). Similarly, *DNMT3A* only showed significant changes between EOPE and controls (p=0.03, Figure 5.5Cv).
Figure 5.5. DNA differences within TERT, DNMT1, and DNMT3A.

A) DNA methylation between placental pathology groups within TERT at i) cg01934390 and ii) cg11832804. B) DNA methylation between placental pathology groups within DNMT1 at iii) cg07627628 and iv) cg26538782. C) DNA methylation between placental pathology groups within DNMT3A at site cg11779362.
5.3.4 Genome-wide DNA methylation analysis

Taking an array-wide approach using all the probes on the array that passed quality control (n=441,093), no CpG sites were associated with TL using a threshold of a FDR <0.05 and Δβ >0.05 for every 1.0 T/S unit. The Δβ cutoff was used to enrich for sites with larger changes in DNAm which may have more biological relevance but does not mean sites not meeting the cutoff are any less meaningful. Despite changes in DNAm within DNMTs, we observed no difference in average global DNAm (average DNAm across all probes on the 450K array) with varying TL (R=-0.003, p=0.79).

5.4 Discussion

TL has been reported to differ between the sexes in a number of tissues (348,349); however, few studies assessed the relationship between fetal sex and TL in the placenta or assessed variation in placental TL between fetal sexes over gestation (152,153). We observed longer telomeres in female placentas compared to male placentas, which may be related to differences in the levels of estrogen, a hormone known to activate telomerase (334). Gielen et al. (2014) (153) previously found no difference in placental TL between male and female fetuses within dizygotic twin pairs. However, Benetos et al. (2014) observed that leukocyte TL in female fetuses that were part of a male-female twin pair had shorter TL compared to those from a female-female twin pair, and similar TL to their male twin. They proposed that the hormone environment in utero influences TL independent of biological sex (349).

After accounting for fetal sex and gestational age, we did not confirm previous reports (152) (350) of shorter TL in placentas from pregnancies complicated by EOPE, LOPE or IUGR. These
later studies did not correct for sex differences, which may have affected the results as preeclampsia and IUGR are generally more common in male than female pregnancies. Gielen et al. (2014) (153) also failed to observe a difference in PE and IUGR associated placentas compared to controls. We did however, observe a trend to shorter telomeres in EOPE, which was significant in comparison to LOPE (p=0.01). Our power to detect a difference may have been limited by small sample size.

Telomere attrition may be rescued by telomerase activity. As TERT expression is the rate-limiting factor to telomerase activity (351), it is interesting that we found an association between shorter TL and less DNAm within the TERT gene body and upstream of the transcriptional start site. Moreover, without using a biological cutoff, 19 of the 99 probes within TERT showed nominally significant alterations in DNAm associated with TL. In contrast to many genes, hypermethylation within at least part of the TERT promoter is associated with TERT expression, thereby leading to increased telomerase activity (352). However, epigenetic regulation of the TERT promoter is complex; DNAm at a CTCF binding site near the promoter region is necessary for TERT transcription (to prevent transcription factors from binding to this site), while selective hypomethylation of part of the promoter is required to allow the transcription factors that aid in TERT transcription to bind(352). Changes in DNAm observed throughout the entire TERT gene region will need further investigation to elucidate the biological relevance of these changes.

DNAm alterations in DNMTs (DNMT1 and DNMT3a) further support the previous suggestions that epigenetic variation may contribute to TL (344,353). DNAm changes were observed at cg11779362 upstream of the promoter region to an alternative transcript of DNMT3a. This
alterative transcript, referred to as $DNMT3a2$ is highly expressed in embryonic stem cells and is thought to preferentially methylate euchromatin domains compared to $DNMT3a$ which preferentially methylates heterochromatin domains (354). However, it is unclear whether these alterations in DNAm have biological consequences and would subsequently affect telomere biology. Despite the DNAm changes in $DNMT1$ and $DNMT3A$, we failed to see alterations in average array-wide DNAm; though this may be related to specific gene expression patterns of these genes in the trophoblast, not genome-wide effects (355).

Understanding placental telomere biology and how it relates to normal and abnormal placental development remains of continued interest. Although this study indicates no major difference in TL with EOPE, LOPE, and IUGR, TL has been suggested to act as a biological clock, potentially signaling the onset parturition (356) and may have implications for pregnancy complications.
Chapter 6: Discussion

6.1 Summary of Dissertation

In this thesis I investigated genetic and epigenetic profiles in placentas from pregnancies affected by placental insufficiency conditions to assess biomarker utility of these molecular marks. These analyses included i) characterizing DNA methylation (DNAm) profiles, ii) assessing whether DNAm in the term placenta can reflect protein levels in maternal blood earlier in gestation thus, whether DNAm could be used to identify novel protein biomarkers, and iii) measuring placental telomere length in preeclampsia (PE) and/or intrauterine growth restriction (IUGR) placentas. In this discussion, I will review the main findings of this dissertation and their significance, outline the strengths and limitations of these studies, discuss reproducibility and responsible reporting of differential methylation, and future directions for the field of placental insufficiency.

6.2 Significance and contribution

In chapter 3, I assessed whether DNAm in the term placenta reflects protein levels in maternal blood during the first, second and third trimester. While DNAm in the term placenta was correlated to Inhibin A (INHA) protein levels in maternal blood in second trimester and Fibronectin (FN1) protein levels in the third trimester, it did not correlate in the first trimester pregnancy associated plasma protein A (PAPP A) levels. This study suggests a link between placental DNAm at delivery to earlier changes in gene expression and protein levels for some markers in maternal blood; supporting the hypothesis that DNAm may represent a ‘cellular memory’ of altered molecular changes occurring at earlier developmental time points (357). While it is possible to utilize DNAm to identify novel protein biomarkers in maternal blood earlier in gestation, this may not be possible for first trimester biomarkers as DNAm in the term
placenta may not reflect gene expression or protein expression alterations in the first trimester. A number of confounding factors can also inhibit the utility of DNAm to reflect protein levels in maternal blood (Figure 3.4). This study provides evidence that DNAm at delivery may correlate with altered protein levels earlier in gestation, providing an alternate route of investigation in identifying biomarkers with the potential of predicting pregnancies at risk of developing placental insufficiency conditions.

Chapter 4 characterizes the placental DNAm profiles of early-onset PE (EOPE), late-onset PE (LOPE), and IUGR in comparison to preterm birth and term birth controls. I observed widespread DNAm alterations in EOPE compared to preterm controls, but not in LOPE or IUGR compared to term controls. There were 599 CpG sites identified that validated in an independent cohort. Clustering on these validated sites revealed 3 distinct clusters in both cohorts. Interestingly, the LOPE cases with other indications of placental insufficiency (e.g. fetal growth restriction) clustered with the EOPE cases, which are more commonly associated with placental insufficiency. Our data suggested that DNAm profiling may be valuable as an independent tool to help classify the hard to diagnose cases being diagnosed with PE in the grey zone between calling a case EOPE or LOPE. This was the first study to assess genome-wide DNAm and validate differentially methylated sites in an independent cohort, in EOPE, LOPE and IUGR placentas.

Chapter 5 assessed telomere length dynamics in the human placenta across gestation and between placental insufficiency conditions and controls. It was found that telomere length decreased over gestational age, and that telomere length was shorter in male placentas compared
to female placentas. While telomere length has been reported to be shorter in PE and IUGR placentas (150,152,358), I was unable to confirm this result when correcting for both gestational age and fetal sex; although telomere length did trend toward shorter length in EOPE placentas. This was the first study to assess telomere length dynamics in the placenta across all three trimesters of pregnancy.

In this dissertation I demonstrate the utility of DNAm studies for identifying novel biomarkers or epigenetic signatures capable of predicting pregnancies at risk of placental insufficiency conditions. While there are many obstacles that will need to be overcome, such as how to identify placental specific DNAm in maternal blood, DNAm studies hold much promise for assessing placental health. Placental DNAm studies can provide insight into normal placental development and pathogenic mechanisms associated with placental insufficiency conditions. Additionally, placental DNAm studies can also shed light onto the ramifications of environmental exposures to placental and fetal health (359). These DNAm alterations can be taken to identify and refine prediction algorithms for studying disease and exposure phenotypes.

6.3 Strengths and limitations

Evaluating genetic and epigenetic placental profiles in these studies is underpowered to detect small differences. I have tried to mediate this limitation by setting a $\Delta\beta$ threshold >0.10 (10% points difference between cases and controls) to enrich for sites more likely to be biologically relevant, and not within the normal variability of a site. Additionally, while clinical information on gestational age, fetal sex, birth weight, maternal age, etc. were collected to try to mediate any confounding relationships between telomere length or DNAm and placental insufficiency, it is
possible that there are other variables influencing both telomere length and DNAm that have not been reported or assessed. Many of the limitations of this dissertation are limitations of DNAm studies in general and will be further discussion in section 6.6. These studies are limited to investigating DNAm at sites that are present on the Illumina Infinium HumanMethylation450 (450K) array. The 450K probes are enriched for promoters and high-density CpG regions of the genome, which have been more often associated with altered gene expression. However, this limits any assessment of altered DNAm at many intergenic and low CpG density regions in association with PE and IUGR. Additionally, the annotation of enhancer and other regulatory regions were determined by ENCODE and Illumina on non-placental cell types (360); without further studying of basic placental biology, it will be difficult to fully elucidate the consequences of DNAm alterations at these regions in the placenta. The 450K methylation array is enriched for specific genomic regions, which in some sense may limit these studies. By restricting CpG sites to be investigated to sites more likely to have a biological effect makes data interpretation somewhat easier and reduces the number of multiple test corrections needed, increasing power of the study. The microarray is a highly validated technique that correlates well to other methods of measuring DNAm (273), and correlates well between batches of microarrays (271). As it is such a widely used method and open source data is available publically, using 450K or similar platforms make it easier to compare to results from other studies. A limitation with this data is that probes present on the 450K array are enriched for developmental pathways, transcription factor binding and, cell differentiation gene ontology terms (361). This adds another layer of complexity when interpreting gene ontology analysis results from 450K array results. To mediate this effect, gene ontology analysis using ermineJ software was completed with a 450K background annotation.
The placenta is an extremely heterogeneous tissue, comprised of many different cell types. Variation in DNAm across the placenta has been reported (238). To account for this variation in our studies, multiple sites in the placenta were sampled and DNA was pooled together in equal amounts to give a more accurate representation of the placenta as a whole. Details on this can be found in chapter 2.

6.4 Approaches and considerations in reproducibility of DNA methylation studies

Many studies have reported altered DNAm at CpG sites within the placenta from pregnancies complicated by PE (13,16,246,322) and IUGR (50,53,323). Although findings have been reported in numerous studies, only one study validated their findings, using the same technology, in an independent cohort (240). As DNAm is susceptible to technical and batch effects, validating hits is imperative to understanding what is truly associated with pathology. In chapter 4, 35.1% (N=599) sites were found to be differentially methylated between EOPE and preterm controls in both the discovery and validation cohorts using validation criteria of a nominal p-value<0.05 and change in DNAm in the same direction as the discovery cohort. The extent of validation, however, is dependent on the initial criteria chosen to define ‘hits’, the criteria for validation, the similarity of the populations of samples, the size of study populations (power to detect changes) and the similarity of processing of samples.

The reproducibility rate depends on how validation is defined. Often top hits in the discovery cohort are compared to the top hits in the validation cohorts using both a statistical and biological (Δβ) threshold. This can be a very stringent approach and may eliminate sites that are concordant
between cohorts, but just do not reach the same level of significance in both. For this study I opted to be less stringent and used a nominal p-value to call a hit validated. However, when I used a Bonferroni-corrected p-value <0.05, validated hits decreased from 599 (35.1%) to 42 (2.5%). Although reducing the data to 42 hits may have some benefits, it can become problematic when it reduces the data so much that it is biologically meaningless. False discovery rate (FDR) is a statistical measure of significance often used to correct for multiple testing. I used FDR in the discovery cohort as it corrects for multiple test corrections but is less stringent than the Bonferroni test correction. However, it should be pointed out that an FDR<0.05 is not the same as a p-value<0.05. Where a p-value<0.05 is interpreted as 5% of the total tests would be a false positive, an FDR is calculated based on the p-value distribution of a specific dataset and an FDR<0.05 is interpreted as 5% of the identified positive hits are actually false positive.

Determining what statistical and biological thresholds to use will depend on the question of the study. Less stringent criteria might be used if the goal is simply to characterize a pathology, while more stringent criteria may be important if the purpose is to develop a panel of biomarkers for screening. An alternative approach may be to reduce the dimensions in the data by 1) removing probes that are non-variable removing across all cell type (326), 2) or focusing on alterations in pathway modules, as in weighted gene co-expression network analysis(327) or 3) evaluate differentially methylated regions (DMRs), rather than individual CpG sites as is often used to combat multiple test correction (328,329).

When studying complex multifactorial diseases, reproducibility is likely to be increased by rigorously defining and classifying the disease of interest to create more homogenous groups. In
many cases, as with PE and IUGR, disease phenotypes consist of a variety of subtypes. Studies tend to focus on identifying homogenous subtypes of pathologies to increase the likelihood that molecular changes will be identified. However, the selection of control samples should also be considered. In this dissertation, to match gestational age of controls with EOPE, I needed to use cases of preterm birth, which can include a variety of abnormal etiologies. In the discovery cohort preterm births were selected to represent a range of causes in order to reduce the chance that changes observed were due to pathology associated with preterm birth rather than EOPE. Some studies will opt to not use preterm births as controls, comparing only to healthy term placetas (13,53,244). However, this introduces the limitation that the pathology and control groups are completely confounded by gestational age. A potential solution would be to identify sites that are differentially methylated between EOPE and preterm controls and also differentially methylated between EOPE and term controls. While this is likely going to eliminate some true differentially methylated sites, we can be more confident in the smaller subset of sites that is identified with this method. Unfortunately in our dataset this was not an option as preterm and term controls were run in separate batches and therefore batch effects might still have been an issue.

6.5 Understanding limitations and responsible reporting of results in EWAS studies

While epigenetic-wide association studies (EWAS) have become very common for assessing changes in response to perturbations, there are still many limitations that need to be considered when interpreting the results. I will be discussing limitations specifically in the context of DNAm, although many of these limitations are also relevant to other epigenetic marks. The relationship between DNAm and gene expression has been widely studied and is thus more
intuitive than other epigenetic marks, however, the interpretability and biological meaning of a change in DNAm is relatively unclear. DNAm changes are often interpreted as causation for a perturbation or pathogenesis (DNAm alterations causing phenotype); however, DNAm can change in response to or as an adaptation and therefore secondary to the perturbation (Phenotype causes DNAm change). Moreover, as DNAm patterns differ widely between cell types (210), DNAm alterations may reflect altered cell composition in the tissue of interest. Variance due to altered cell type proportions is often removed from DNAm studies (362,363,364,365), as it is thought to be a confounding variable of phenotype. However, more thought should be taken before removing cell type proportion variance out of the data, as cell type proportion may actually be causal to the phenotype of interest. In a recent review by Lappalainen and Greally (2017), the term polycreodism is used to define cell type proportion variation that arises in response to an exposure or perturbation during development (357). Therefore, DNAm changes that reflect altered cell type proportions may actually be biologically relevant and related to the phenotype of interest. In the context of EOPE, most studies focus on DNAm altering gene expression pathways associated with PE (e.g. related to known effects such as oxidative stress and altered angiogenesis (26,67)). However, DNAm changes may reflect altered cell type proportions related to PE pathology, such as decreased proliferation of extravillous trophoblast cells or alterations to the rate of trophoblast proliferation (324). As cell-type specific profiles have not been developed for all placental cell types, it is not possible to use the DNAm profile to estimate cell proportions, as has been applied to blood (213). While reference-free methods for deconvolution of cell proportions have been developed (325), these methods remove variance within the data attributed to cell composition but cannot inform us of what cell types specifically are altered in EOPE. Even when removing variability due to cell type with current methods, cell
type variability will likely persist, as it is not clear exactly how many cell types are present
within a specific tissue and whether cell type is a discrete categorical variable or a continuous
variable defined by alterations in molecular profiles (357). Another limitation of EWAS studies
is often there is no hypothesis driving the study, we are searching for differences in DNAm with
no clear hypothesis as to whether these changes are causal or secondary to the phenotype of
interest. In the case of studies attempting to identify biomarkers for a phenotype, a clear
hypothesis is less important as biological meaning and interpretation is not a priority over the
DNAm mark’s predictive capabilities. This is discussed in further detail in Lappalainen and
Greally (2017) (357).

Many variables, independent of the phenotype of interest, influence DNAm, and need to be
accounted for in the experimental design. While variables such as age and sex are almost always
adjusted for in DNAm studies, it is often forgotten how intertwined epigenetics is with DNA
sequence. Methylation quantitative trait loci (mQTL) are CpG sites where the DNAm status is
influenced by nearby single nucleotide polymorphisms (SNPs)(366). As such, an individual’s
genetic ancestry can impact DNAm status across the genome (179,367). A challenge in
epigenetic studies is that reported ethnicity does not always accurately represent an individual’s
genetic ethnicity (368). To account for this, numerous studies have utilized ancestry informative
markers (AIMs) to more accurately correct for ethnicity within their studies (369). DNAm
markers have also been developed to predict ethnicity in studies where ethnicity may not have
been available (370). However, genetic variation associated with ancestry is unlikely to explain
all genetic variability present in epigenetic studies. This likely results in many DNAm alterations
reported that are actually genetic effects on phenotype rather than alterations due to
environmental exposure or disease phenotype. For example, genetic variants associated with other factors such as hypertension, body mass index (BMI), or diabetes, may affect DNA methylation (DNAm). Since these are all also risk factors for PE, we could identify changes in DNAm that actually reflect genetic variation associated with the risk factor rather than PE itself.

6.6 Future directions of preeclampsia and intrauterine growth restriction prediction

Molecular profiling (transcriptomics, DNA methylation, miRNA profiling, proteomics) are all paving the way for understanding the pathogenesis of PE and IUGR, and the multiple subtypes that make up the broader disease. Further research in these areas will be needed to fully understand placental insufficiency conditions. Integrating these different data types into multiple ‘omics’ studies will create a clearer representation of the relationships between pathway systems and the development or PE and IUGR. In particular, determining if altered DNAm in placentas associated with PE is a cause or a consequence to the pathology of PE, and whether the DNAm changes are actually reflecting polycreodism, altered cell type proportions in the placenta, will be a major area of research in the coming years.

While DNAm alterations are reported in PE placentas (Supplementary Table A.1), these DNAm alterations can only be used as biomarkers i) through placental sampling, which would be an invasive test not applicable to the general population, or ii) if these DNAm are detectable in the maternal serum. As outlined in chapter 3, there are many obstacles that may prevent these DNAm alterations from being detectable in maternal blood during gestation. However, studies utilizing the global hypomethylation and promoter hypermethylation profile of cancer have used methylated DNA immunoprecipitation (MeDIP) analysis to capture cell free tumour DNA in the
patient’s serum (371,372). The same technique has been utilized to capture cell free placental DNA in maternal serum for identification of chromosomal abnormalities (373,374). Future PE and IUGR DNAm profiling for the intent of biomarker identification should consider utilizing this technique, or similar method to characterize the DNAm profile in maternal blood. This will eliminate the limitations of placental DNAm profiling, as DNAm changes will be detectable in maternal blood, and the test is non-invasive, making it available to all pregnancies, and easily incorporated into the maternal serum screen.
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Appendices

Appendix A Supplementary tables and figures for Chapter 1

Supplementary Table A.1. Summary of preeclampsia and intrauterine growth restriction DNA methylation studies with both genome-wide and targeted approaches.

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<td>Kim, Jeong-Hyun, et al. &quot;Genome-wide DNA methylation profiles of maternal peripheral blood and placentas: potential risk factors for preeclampsia and validation of GRK5.&quot; Genes &amp; Genomics: 1-10.</td>
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<td>PE- BP&gt;140/90 mmHg and proteinuria &gt;300mg/day or &gt;2+ dipstick) after 20 weeks gestation.</td>
<td>PE (N=6) Control (N=6)</td>
<td>p&lt;0.01, Δβ&gt;0.17</td>
<td>Not clear</td>
<td>Matched gestational age</td>
<td>365 differentially methylated sites were identified between PE and controls</td>
<td>Illumina 450K Array</td>
<td>No</td>
<td>NA</td>
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<tr>
<td>2016</td>
<td>Roifman, Maian, et al. &quot;Genome-wide placental DNA methylation analysis of severely growth-discordant monochorionic twins reveals novel epigenetic targets for intrauterine</td>
<td>Discordant monzygotic twins for IUGR</td>
<td>IUGR- Fetal birthweight &lt; 10th percentile</td>
<td>Monozygotic monchorionic twin pairs discordant for</td>
<td>p&lt;0.05, Δβ&gt;0.1, and more than 3 CpG sites in the region</td>
<td>Not clear</td>
<td>Fetal sex Maternal age Gestational age</td>
<td>Bump Hunting: Increased DNAm in DECR1, ZNF300, LEPR, HSPA1A/L, GST01, GNE. Decreased DNAm in DNAJ4 and CCL28. Array-wide: 296 differentially</td>
<td>Illumina 450K Array</td>
<td>No</td>
<td>NA</td>
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<td>2016</td>
<td>Yeung, Kristen Rose, et al. &quot;DNA methylation profiles in preeclampsia and healthy control placentas.&quot; <em>American Journal of Physiology-Heart and Circulatory Physiology</em> (2016): ajpheart-00958.</td>
<td>PE Control</td>
<td>PE- BP&gt;140/90 mmHg after 20 weeks gestation, proteinuria (&gt;2+ dipstick or 300mg/24h), or renal insufficiency, liver disease, neurologic problems, haematological disturbances. All were late-onset PE. Control- Uncomplicated term pregnancies</td>
<td>PE (N=8) Control (N=16)</td>
<td>Adjusted p&lt;0.05</td>
<td>Yes</td>
<td>Gestational age</td>
<td>At an adjusted p value &lt;0.05, no site on the array was found to be significant between PE and Control. 303 differentially methylated regions were identified using DMRcate between PE and controls after adjusting for gestational age. 92 of these site (34.7%) remained significant in the secondary cohort.</td>
<td>Illumina 450K Array</td>
<td>Yes</td>
<td>Sites were validated an independent cohort from GEO (Blair et al 2013).</td>
</tr>
<tr>
<td>2016</td>
<td>He, Zhiming, et al. &quot;The promoter methylomes of monochorionic twin placentas reveal intrauterine Monchorionic twins discordant for IUGR</td>
<td>Monchorionic twins discordant for IUGR</td>
<td>IUGR- fetal birth weight &lt;10th percentile for gestational age</td>
<td>Discovery (N=7 pairs) Validation</td>
<td>p&lt;0.05, Δβ&gt;0.2</td>
<td>Not to identify initial differentially methylated sites.</td>
<td>None</td>
<td>Genome wide promoter methylation was significantly lower in the IUGR placenta</td>
<td>Bisulfite genomic sequencing enriched for</td>
<td>No</td>
<td>NA</td>
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<td>2015</td>
<td>Hillman, Sara L., et al. &quot;Novel DNA methylation profiles associated with key gene regulation and transcription pathways in blood and placenta of growth-restricted neonates.&quot; <em>Epigenetics</em> 10.1 (2015): 50-61.</td>
<td>IUGR</td>
<td>IUGR- fetal birth weight &lt;10th percentile for gestational age, adjusted for maternal weight, height, parity and ethnicity. AGA- appropriately growth fetuses between &gt;10th-&lt;95th percentile, born &gt;255 day gestation.</td>
<td>(N=10 pairs)</td>
<td>Differentially methylated sites were merged into candidate DMRs based on defined criteria. Candidate DMRs were considered differentially methylated if they met FDR&lt;0.05</td>
<td></td>
<td>Yes</td>
<td>compared to the non-IUGR twin. 4,605 sites were differentially methylated between IUGR and AGA twin.</td>
<td>Illumina 450K Array</td>
<td>No</td>
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<td>2015</td>
<td>Zhu, Lisha, et al. &quot;Genome-wide mapping of 5mC and 5hmC identified LOPE Control PE- BP&gt; 140/90 mmHg, proteinuria &gt;+2 or 300mg/24h, all samples were &gt;37 weeks</td>
<td>LOPE Control (N=4)</td>
<td>LOPE Control (N=4)</td>
<td>&gt;2 fold, p&lt;0.05</td>
<td>No</td>
<td>None</td>
<td>714 sites were found to be differentially methylated in MeDiP</td>
<td>No</td>
<td>NA</td>
<td></td>
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<td>2014</td>
<td>Blair, J. D., et al. &quot;Overlapping DNA methylation profile between placentas with trisomy 16 and early-onset preeclampsia.&quot; Placenta 35.3 (2014): 216-222.</td>
<td>1st trimester control 1st trimester trisomy 16 3rd trimester control 3rd trimester CPM16</td>
<td>1st trimester control- chromosomally normal, termination or spontaneous abortion &lt;12 weeks gestation 1st trimester trisomy 16 terminations or spontaneous abortion with confirmed trisomy 16 &lt;12 weeks gestation 3rd trimester control- included both term (&gt;37 weeks) and preterm (&lt;37 weeks) placentas. Preterm births were due to a variety of etiologies 3rd trimester</td>
<td>1st trimester control (N=5) 1st trimester trisomy 16 (N=5) 3rd trimester control (N=10) 3rd trimester CPM16 (N=10)</td>
<td>Different FDR thresholds (0.01, 0.05, 0.1, 1) and different ∆β thresholds (0%, 5%, 10%, 15%) were investigated.</td>
<td>Yes</td>
<td>Gestational age</td>
<td>Widespread DNAm alterations were reported between CPM16 and 3rd trimester controls. A significant overlap of altered DNAm in previously reported in EOPE was found in the sites differentially methylated in CPM16 placentas.</td>
<td>Illumina 450K Array</td>
<td>Yes</td>
<td>DNAm alteration were follow up with pyrosequencing on an independent set of 8 CPM16 and 3rd trimester control.</td>
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<td>2014</td>
<td>Anton, Lauren, et al. &quot;Differential methylation of genes associated with cell adhesion in preeclamptic placentas.&quot; <em>PLoS One</em> 9.6 (2014): e100148.</td>
<td>Term PE</td>
<td>Preterm PE</td>
<td>Term Control</td>
<td>CPM16- placentas with confirmed CPM16 &gt;24 weeks gestation.</td>
<td>Preterm PE (N=19) Preterm PE (N=12) Term Control (N=14)</td>
<td>Preterm PE vs Term Control- FDR&lt;0.01, Δβ&gt;0.05 Other thresholds were also looked at</td>
<td>Yes</td>
<td>None</td>
<td>At FDR&lt;0.01, Δβ&gt;0.05, 421 CpG sites were differentially methylated between Preterm PE and term controls. None were differentially methylated between term PE and term controls</td>
<td>Illumina 450K Array</td>
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<td>2014</td>
<td>Ching, Travers, et al. &quot;Genome-wide hypermethylation coupled with promoter hypomethylation in the chorioamniotic membranes of early onset pre-eclampsia.&quot; Molecular human reproduction 20.9 (2014): 885-904.</td>
<td>Early-onset PE (EOPE) Term Controls</td>
<td>EOPE- PE diagnosis ≤34 weeks gestation Term controls- Healthy placenta ≥37 weeks gestation</td>
<td>EOPE (N=30) Term controls (N=17)</td>
<td>Bonferroni adjusted p-value&lt;0.05 Top hits used Δβ&gt;0.2</td>
<td>Yes</td>
<td>None</td>
<td>Found that of sites that met Bonferroni correction, there was an enrichment for global hypermethylation and enrichment of hypomethylation at promoter regions of genes</td>
<td>Illumina 450K Array</td>
<td>No</td>
<td>NA</td>
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<tr>
<td>2014</td>
<td>Anderson, Cindy M., et al. &quot;DNA methylation as a biomarker for preeclampsia.&quot; Biological research for nursing 16.4 (2014): 409-420.</td>
<td>PE Control</td>
<td>PE- BP&gt; 140/90 mmHg, proteinuria &gt;+1 or 300mg/24h Control- Healthy uncomplicated control</td>
<td>PE (N=6) Control (N=6)</td>
<td>p-value &lt;0.05, Δβ&gt;0.2</td>
<td>No</td>
<td>None</td>
<td>Found 206 sites that were differentially methylated in maternal blood. Of which 64% of those that were hypermethylated, and 24% that were hypomethylated were also altered in placental tissue.</td>
<td>Illumina 450K Array</td>
<td>No</td>
<td>NA</td>
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<td>2014</td>
<td>Chu, Tianjiao, et al. &quot;Comprehensive analysis of preeclampsia-associated DNA methylation in the placenta.&quot; PloS one 9.9 (2014): e107318.</td>
<td>PE Control</td>
<td>PE- BP &gt; 140/90 mmHg, proteinuria &gt;+1 (catherized sample), 2+ (dipstick) or 300mg/24h</td>
<td>PE (N=24) Control (N=24)</td>
<td>FDR&lt;0.1, Δβ&gt;0.1</td>
<td>Yes</td>
<td>None</td>
<td>28 differentially methylated CpG sites were identified between PE and control when X chromosome probes were removed from the analysis. 11 differentially methylated sites were identified when analysis was only completed on female placetas.</td>
<td>Illumina 27K array</td>
<td>Partially</td>
<td>Results were confirmed by Sequenom Epityper Epityper Epityper and bisulfite sequencing. Results were compared to previously reported alterations in the literature (Yuen et al. 2010 and Blair et al. 2013). With little overlap</td>
</tr>
<tr>
<td>2014</td>
<td>Nomura, Yoko, et al. &quot;Global methylation in the placenta and umbilical cord blood from pregnancies with maternal gestational diabetes, preeclampsia, and obesity.&quot; Reproductive sciences 21.1 (2014): 131-137.</td>
<td>Gestational Diabetes PE</td>
<td>Gestational diabetes- GCT &gt;100mg/dL or GTT &gt;95mg/dL fasting or &gt;180,155, and 140mg/dL at 1,2,3 hours, respectively. PE- BP&gt;140/90 mmHg, proteinuria &gt;300mg/24h or +2 dipstick after 20 weeks gestation Obesity- pre-pregnancy maternal BMI &gt;30</td>
<td>Ns not specified</td>
<td>p value&lt;0.05</td>
<td>Not clear</td>
<td>Not specified</td>
<td>Global DNAm was significantly lower in gestational diabetes and PE placentas than controls. Global DNAm was lower in obesity placentas than Controls</td>
<td>LUMA Assay</td>
<td>No</td>
<td>No</td>
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<td>2013</td>
<td>Blair, John D., et al. &quot;Widespread DNA hypomethylation at gene enhancer regions in placenta associated with early-onset preeclampsia.&quot; <em>Molecular human reproduction</em> (2013) : gat044.</td>
<td>Early-onset PE (EOPE) Control</td>
<td>EOPE- PE diagnosis prior to 34 weeks gestation Control- gestationally age matched control. Preterm births due to a variety of aetiologies.</td>
<td>EOPE (N=20) Control (N=20)</td>
<td>FDR&lt;0.01, Δβ&gt;0.125</td>
<td>Yes</td>
<td>Birth weight Gestational age Head circumference Body length at birth</td>
<td>Illumina 450K Array</td>
<td>No</td>
<td>NA</td>
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<tr>
<td>2013</td>
<td>Yan, Y. H., et al. &quot;Screening for preeclampsia pathogenesis related genes.&quot; <em>Eur Rev Med Pharmacol</em></td>
<td>PE Control</td>
<td>PE- definition not specified, all samples 3rd trimester Control- uncomplicated</td>
<td>PE (N=30) Control (N=30)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>Candidate genes were chosen from sites that were differentially methylated (specifics of DNA methylation array not specified)</td>
<td>No</td>
<td>NA</td>
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<td>2011</td>
<td>Banister, Carolyn E., et al. &quot;Infant growth restriction is associated with distinct patterns of DNA methylation in human placentas.&quot; Epigenetics 6.7 (2011): 920-927.</td>
<td>SGA and IUGR Term Controls</td>
<td>SGA/IUGR- Fetal birthweight &lt; 10th percentile for its gestational age Term Control- Healthy placenta ≥36 weeks gestation</td>
<td>SGA &amp; IUGR (N=89) Term Controls (N=117)</td>
<td>Not specified</td>
<td>No</td>
<td>Fetal sex Maternal age Mode of delivery</td>
<td>22 loci identified in the training data set predicted 76% of SGA and IUGR placentas in the testing dataset</td>
<td>Illumina 27K Array</td>
<td>Yes</td>
<td>Cohort was divided into testing and training dataset</td>
</tr>
<tr>
<td>2010</td>
<td>Liu, Lan, et al. &quot;Distinct DNA methylomes of human placentas between pre-eclampsia and gestational diabetes mellitus.&quot; Cellular Physiology and Biochemistry 34.6 (2014): 1877-1889.</td>
<td>Control Gestation Diabetes PE</td>
<td>Control-uncomplicated term pregnancies Gestational Diabetes- 75g oral glucose tolerance test resulted in glucose level of ≥5.1mmol/L glucose and/or at 2 hours plasma glucose level ≥8.1mmol/L glucose. PE- BP ≥140/90 mmHg and proteinuria ≥2+ dipstick or ≥300mg/24h</td>
<td>Control (N=30) Gestational Diabet es (N=28) PE (N=27)</td>
<td>p value&lt;0.05</td>
<td>Yes</td>
<td>None</td>
<td>DNAm profiles in both PE and gestational diabetes were altered. 64.4% of the DNAm alterations were shared in both PE and gestational diabetes. These sites were enriched for pathways such as cell adhesion and cell differentiation and metabolism.</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
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<td>2010</td>
<td>Yuen, Ryan KC, et al. &quot;DNA methylation profiling of human placentas reveals promoter hypomethylation of multiple genes in early-onset preeclampsia.&quot; <em>European Journal of Human Genetics</em> 18.9 (2010): 1006-1012.</td>
<td>Control Early-onset PE (EOPE) Late-onset PE (LOPE) IUGR</td>
<td>Controls- uncomplicated pregnancy. Divided into early controls (preterm births due to varying aetiologies), late controls and controls (mean gestational age 37). EOPE - diagnosis of PE &lt; 34 weeks gestation. LOPE - diagnosis of PE &gt;34 weeks gestation. IUGR - fetal birth weight &lt; 3rd percentile, or &lt; 10th percentile with other indications of poor growth.</td>
<td></td>
<td>Early control (N=4) Late control (N=5) Control (N=5) EOPE (N=4) LOPE (N=4) IUGR (N=4)</td>
<td>FDR&lt;0.1, Δβ&gt;0.1</td>
<td>Yes</td>
<td>Matched gestational age</td>
<td>Gene specific hypomethylation was observed in EOPE, but not LOPE or IUGR.</td>
<td>Golden gate array</td>
<td>Yes</td>
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<td>2017</td>
<td>Rahat, Beenish, et al. &quot;The role of aberrant methylation of trophoblastic stem cell origin in the pathogenesis and diagnosis of placental disorders.&quot; <em>Prenatal Diagnosis</em> 37.2 (2017): 133-143.</td>
<td>PE 1st trimester control</td>
<td>PE- BP&gt;140/90 mmHg and proteinuria &gt;300mg/24h All Controls singleton, uncomplicated, pregnancy Molar- Diagnosed by ultrasound and confirmed with histopathology</td>
<td>PE (N=30) 1st trimester control (N=30) 2nd trimester control (N=30) 3rd trimester control (N=30) Molar (N=15)</td>
<td>p-value&lt;0.05</td>
<td>No</td>
<td>Matched gestational age</td>
<td>MS-HRM</td>
<td>No</td>
<td>NA</td>
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**TARGETED ANALYSES**

- EFGR promoter region was <2.5% methylated in each of the study groups, with no significant differences between them. *VEGF* and *c-jun* promoter regions were differentially methylated. PE was increased at *VEGF* and *c-jun* promoters. Molar pregnancies were hypomethylated at *VEGF* and *c-jun* promoters.
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<th>Pathology</th>
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<th>Thresholds ( \text{p value} &lt; 0.05 )</th>
<th>Multiple test corrections</th>
<th>Confounders</th>
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<tbody>
<tr>
<td>2017</td>
<td>Majchrzak-Celińska, Aleksandra, et al. &quot;HSD11B2, RUNX3, and LINE-1 Methylation in Placental DNA of Hypertensive Disorders of Pregnancy Patients.&quot; <em>Reproductive Sciences</em> (2017): 1933719117692043</td>
<td>Gestational Hypertension</td>
<td>Gestational hypertension-hypertension after 20 weeks gestation, and normalization of BP postpartum. PE- BP &gt; 140/90 mmHg and proteinuria (&gt;0.3g/24h) after 20 weeks gestation. Chronic hypertension-prepregnancy hypertension or hypertension &lt;20 weeks gestation. Control-normotensive women, no proteinuria and no IUGR.</td>
<td>PE (N=11)</td>
<td>Chronic hypertension (N=10) Normotensive control (N=25)</td>
<td>No</td>
<td>Gestational age Maternal age Fetal sex</td>
<td>All models were corrected for gestational age and fetal sex. By linear regression, no differences in DNA methylation in HSD11B2, RUNX3, LINE-1 were observed between PE, gestational hypertension, chronic hypertension and control. 1 CpG in HSD11B2 was significantly increased in PE compared to control with a student's t-test, however the effect went away once gestational age and fetal sex were corrected for.</td>
<td>Methylaton specific PCR and pyrosequencing</td>
<td>No</td>
<td>NA</td>
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<td>2017</td>
<td>Xiao, Xirong, et al. &quot;Hypomethylation of tissue factor pathway inhibitor 2 in human placenta of preeclampsia.&quot; <em>Thrombosis Research</em> 152 (2017): 7-13.</td>
<td>PE Control</td>
<td>PE- onset of hypertension in previously normotensive women and proteinuria (&gt;0.3g/24h) Control- uncomplicated healthy pregnancies, undergoing elective caesarean.</td>
<td>PE (N=19) Control (N=10)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>None</td>
<td>DNA methylation levels were altered along the <em>TFPI-2</em> gene in PE placentas compared to controls.</td>
<td>MassArray EPITYPER</td>
<td>No</td>
<td>NA</td>
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<td>2016</td>
<td>Ye, Weiping, et al. &quot;Preeclampsia is Associated with Decreased Methylation of the GNA12 Promoter.&quot; <em>Annals of human genetics</em> 80.1 (2016): 7-10.</td>
<td>PE Control</td>
<td>PE- BP&gt;140/90 mmHg and proteinuria (&gt;300mg/24h) after 20 weeks gestation. Control- Uncomplicated healthy pregnancy</td>
<td>PE (N=50) Control (N=50)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>None</td>
<td>DNA methylation was significantly lower in 3 of the 8 CpG sites analyzed within the <em>GNA12</em> promoter in PE compared to controls. When dividing PE group into mild vs severe or early-onset and late-onset, no significant differences in DNA methylation were observed.</td>
<td>MassArray EPITYPER</td>
<td>No</td>
<td>NA</td>
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<td>2016</td>
<td>Lin, Liang, et al. &quot;Significant hypomethylation of TNFAIP8 and increased expression in the placenta and peripheral blood cells from early-onset preeclamptic patients.&quot; INTERNA TIONAL JOURNAL OF CLINICAL AND EXPERIMENTAL MEDICINE 9.6 (2016): 10384-+.</td>
<td>Early-onset PE (EOPE) Late-onset PE (LOPE) Term Control</td>
<td>EOPE - PE diagnosis &lt; 34 weeks gestation LOPE - PE diagnosis &gt;34 weeks gestation Term control - healthy pregnancy delivered at term.</td>
<td></td>
<td></td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>None</td>
<td>Two sites in the promoter region of TNFAIP8 were assessed. DNA methylation at site 1 was significantly different between LOPE and control and LOPE and EOPE. No other significant differences were found.</td>
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<td>2015</td>
<td>Anderson, Cindy M., et al. &quot;First trimester vitamin D status and placental epigenomics in preeclampsia among Northern Plains primiparas.&quot; Life sciences 129 (2015): 10-15.</td>
<td>PE Control</td>
<td>This was a prospective study, PE was defined at BP&gt; 140/90 mmHg and proteinuria (&gt;300mg in 24h)</td>
<td>PE (N=3)* Control (N=3)*</td>
<td>None specified</td>
<td>No</td>
<td>None</td>
<td>DNAm was increased at CYP27B1, VDR, and RXR (Involved in vitamin D metabolism) promoter regions.</td>
<td>Human DNA Methylat ion 2.1 M Microarr ay (NimbleG en)</td>
<td>No</td>
<td>NA</td>
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<td>2015</td>
<td>Tang, Yao, et al. &quot;Hypermethylation of the HLA-G promoter is associated with preeclampsia.&quot; Mol</td>
<td>PE Control</td>
<td>PE - BP&lt; 140/90 mmHg after 20 weeks gestation and proteinuria (&gt;300mg/24h or &gt;1+ dipstick).</td>
<td>PE (N=19) Control (N=20)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>None</td>
<td>HLA-G promoter shows differential methylation at some CpG sites in PE placentas</td>
<td>Pyrosequencing</td>
<td>No</td>
<td>NA</td>
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<td>2015</td>
<td>Iglesias-Platas, I., et al. &quot;Distinct promoter methylation and isoform-specific expression of RASSF1A in placental biopsies from complicated pregnancies.&quot; <em>Placenta</em> 36.4 (2015): 397-402.</td>
<td>IUGR</td>
<td>IUGR was classified by most severe ultrasound abnormality. PE was included in this cohort</td>
<td>IUGR (N=47) AGA (N=67)</td>
<td>p value&lt;0.05</td>
<td>Yes</td>
<td>Gestational age</td>
<td>A CpG site in the RASSF1A promoter was hypermethylated in IUGR placentas compared to controls. The DNA methylation change was confirmed in a subset of IUGR and AGA that were run on the array using pyrosequencing.</td>
<td>Illumina Goldengate array</td>
<td>No</td>
<td>NA</td>
</tr>
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<td>2015</td>
<td>Xiao, Xirong, et al. &quot;Fetal growth restriction and methylation of growth-related genes in the placenta.&quot; (2015).</td>
<td>IUGR</td>
<td>IUGR- fetal growth &lt;10th percentile for gestational age, based on ultrasound measures. Control- Appropriately grown fetuses</td>
<td>IUGR (N=80) Control (N=101)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>Gestational age</td>
<td>DNA methylation within HSD11B2 was significantly decreased in IUGR placentas compared to controls, after correction for gestational age, prenatal vitamin use, and maternal smoking status.</td>
<td>Pyrosequencing</td>
<td>No</td>
<td>NA</td>
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<td>2014</td>
<td>Lu, Linshan, et al. &quot;Methylation pattern of H19 exon 1 is closely related to preeclampsia and trophoblast abnormalities.&quot; International journal of molecular medicine 34.3 (2014): 765-771.</td>
<td>First trimester controls</td>
<td>First trimester controls collected between 6-9 weeks Term Control- Health placenta in the third trimester Severe PE- Hypertension (160/110 mmHg) and proteinuria after 20 weeks gestation. Sample collected in third trimester</td>
<td>First trimester (N=6) Term Placenta (N=16) Severe PE (N=15)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>None</td>
<td>DNAm at 7 CpG sites (averaged) within the first exon of H19 were hypomethylated in first trimester placenta compared to term. The average methylation across the region was not different between term and severe PE placentas. Looking at the 7 CpG sites individually, only DNAm at CpG site 1 was significantly different between term placenta and severe PE. No other comparisons were significant.</td>
<td>Pyrosequencing</td>
<td>No</td>
<td>NA</td>
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<td>2014</td>
<td>Liu, Q., et al. &quot;Promoter hypomethylation and increased maspin expression in preeclamptic placentas in a Chinese population.&quot; Placenta 35.11 (2014): 876-882.</td>
<td>PE</td>
<td>PE-definition not specified Control-uncomplicated pregnancies</td>
<td>PE (N=12) Control (N=12)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>None</td>
<td>DNA methylation in the MSP promoter was significantly decreased in PE placentas compared to controls. No differences were observed between male and female placentas.</td>
<td>Methylaton specific PCR and pyrosequencing</td>
<td>Maybe</td>
<td>24 placental samples were assessed DNA methylation in the MSP promoter region. It was again hypomethylated in the PE group compared to control. It is unclear if this is an independent cohort or a subset of the original cohort.</td>
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<tr>
<td>2014</td>
<td>Zhao, Yan, et al. &quot;Site-specific methylation of placental HSD11B2 gene promoter is related to intrauterine growth restriction.&quot; European Journal of Human Genetics 22.6 (2014): 734-740.</td>
<td>IUGR</td>
<td>IUGR- diagnosed if they had 3 of the following ultrasound findings: 1. abdominal circumference&lt;3rd percentile for gestational age, 2. abnormal umbilical artery Doppler, 3. oligohydramnios, or 4. abnormal fetal growth velocity&lt;1.5</td>
<td>IUGR (N=22) (Some also had PE) Control (N=22)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>Gestational age Fetal sex Maternal age Maternal BMI Smoking Pregnancy weigh gain</td>
<td>Promoter DNA methylation of HSD11B2 were increased in IUGR placentas compared to controls. After correction for clinical variables, only 2 CpG sites in the promoter were associated with birth weight.</td>
<td>Pyrosequencing</td>
<td>No</td>
<td>NA</td>
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<td>2013</td>
<td>Sundrani, Deepali P., et al. &quot;Differential placental methylation and expression of VEGF, FLT-1 and KDR genes in human term and preterm preeclampsia.&quot; Clinical epigenetics 5.1 (2013): 6.</td>
<td>Term PE Preterm PE Term Control</td>
<td>Term PE- diagnosis ≥37 weeks gestation Preterm PE- diagnosis ≤37 weeks gestation Term Control- Healthy placenta ≥37 weeks gestation</td>
<td>Term PE (N=48) Preterm PE (N=45) Term Control (N=46)</td>
<td>p value&lt;0.05</td>
<td>None</td>
<td>Mean promoter DNAm at VEGF promoter hypomethylated in preterm PE compared to term controls. No significant difference in either FLT1 or KDR promoter regions. Hypomethylation at single sites within FLT1 in both term and preterm PE. Hypermethylation in single site in KDR promoter in both term and preterm PE.</td>
<td>Sequenom Epityper</td>
<td>No</td>
<td>NA</td>
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<td>2013</td>
<td>Xiang, Yuqian, et al. &quot;Up-regulated expression and aberrant DNA methylation of LEP and SH3PXD2A in pre-eclampsia.&quot; <em>PloS one</em> 8.3 (2013): e59753.</td>
<td>PE Uncomplicated Pregnancy</td>
<td>PE- BP 140/90 mmHG &amp; proteinuria &gt;0.3mg/24h Uncomplicated pregnancy- normal pregnancy</td>
<td>PE (N=16) Uncomplicated pregnancy (N=16)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>Gestational age</td>
<td>DNAm at transcriptional binding sites Sp1,LP1, and CEBPα, as well as DNAm at transcriptional start site of LEP, and several gene body CpG sites in <em>SH3PXD2A</em> were differentially methylated.</td>
<td>Sequenom Epityper</td>
<td>No</td>
<td>NA</td>
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<td>2013</td>
<td>Xiang, Yuqian, et al. &quot;Promoter hypomethylation of TIMP3 is associated with pre-eclampsia in a Chinese population.&quot; <em>Molecular human reproduction</em> 19.3 (2013): 153-159.</td>
<td>PE Control</td>
<td>PE- BP&gt;140/90 mmHg and proteinuria (&gt;0.3g/24h) after 20 weeks gestation Control- healthy pregnancies undergoing caesarean</td>
<td>PE (N=41) Control (N=22)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>None</td>
<td>The <em>TIMP3</em> promoter was hypomethylated in PE compared to controls in the Han Chinese population. As it was in the Canadian population.</td>
<td>MassArray EPITYPER</td>
<td>Yes</td>
<td>This study itself a validation of the <em>TIMP3</em> promoter methylation reported Yuen et al (2010), an independent cohort.</td>
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<td>2013</td>
<td>Hogg, Kirsten, et al. &quot;Early onset pre-eclampsia is associated with altered DNA methylation of cortisol-signalling and steroidogenic genes in the placenta.&quot; PloS one 8.5 (2013): e62969.</td>
<td>Early-onset PE (EOPE) Late-onset PE (LOPE) normotensive IUGR (nIUGR) Control</td>
<td>EOPE- PE diagnosis ≤34 weeks gestation LOPE- PE diagnosis&gt;34 weeks gestation nIUGR- Fetal birth weight&lt; 3rd percentile or &lt;10th percentile with other indications of poor growth Control- Uncomplicated pregnancies with no known placental pathology. Some of these samples include preterm birth due to a number of aetiologies not such as: premature rupture of membranes, incompetent cervix, and chorioamnionitis.</td>
<td>EOPE (N=19) LOPE (N=18) nIUGR (N=13) Control (N=111)</td>
<td>p value&lt;0.01, Δβ&gt;0.05</td>
<td>Yes</td>
<td>Birth weight, gestational age, maternal age, fetal sex, presence/absence of labour all assessed, confounder included if statistically significant</td>
<td>DNAm was increased within NR3C1, CRHBP, and CRH in EOPE compared to control. No differential DNAm was observed in HSD11B2 gene promoter. DNAm was decreased CYP11A1, HSD3B1, TEAD3, and CYP19 in EOPE and LOPE, but not nIUGR.</td>
<td>Pyrosequencing</td>
<td>Partially (in EOPE)</td>
<td>Initial differences in DNAm were observed between EOPE and Cont using the Illumina Array. This subset of samples was expanded and LOPE and nIUGR samples added in and DNAm assessed pyrosequencing.</td>
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<tr>
<td>2013</td>
<td>Janzen, Carla, et al. &quot;Placental glucose transporter 3 (GLUT3) is up-regulated in human pregnancies&quot;</td>
<td>IUGR PE Control</td>
<td>IUGR- fetal birth weight &lt;10th percentile and other indication of poor growth PE- definition not met</td>
<td>IUGR (N=10) PE (N=5) Control (N=10)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>None</td>
<td>No differences in DNA methylation were found in GLUT3 in IUGR or PE placentas</td>
<td>Pyrosequencing</td>
<td>No</td>
<td>NA</td>
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<td>2011</td>
<td>Ferreira, Jose Carlos, et al. &quot;WNT2 promoter methylation in human placenta is associated with low birthweight percentile in the neonate.&quot; <em>Epigenetics</em> 6.4 (2011): 440-449.</td>
<td>SGA Control</td>
<td>SGA- fetal birth weight &lt;10th percentile Control- fetal weight appropriate for gestational age</td>
<td>SGA (N=8) Control (N=8)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>Matched gestational age</td>
<td>WNT2 promoter DNA methylation was showed 1.9x fold change across the promoter in SGA vs controls (p value not given), using the Agilent array. Change in DNA methylation at the WNT2 promoter was confirmed in the same samples using pyrosequencing.</td>
<td>MeDIP and 244K Agilent Microarray</td>
<td>No</td>
<td>NA</td>
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<td>2011</td>
<td>Koukoura, O., et al. &quot;Hypomethylation along with increased H19 expression in placentas from pregnancies complicated with fetal growth restriction.&quot;</td>
<td>Control Fetal growth restriction (FGR)</td>
<td>Control- uncomplicated term placenta FGR- Fetal birth weight &lt; 5th percentile in addition to other indications of poor growth.</td>
<td>Control (N=17) FGF (N=31)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>Birth weight Gestational age</td>
<td>DNAm at two regions within H19 were measured. DNAm between 6156bp-6245bp upstream of the TSS were not significantly different, although trended</td>
<td>MethylLight Assay</td>
<td>No</td>
<td>NA</td>
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<td>2011</td>
<td>Koukoura, Ourania, et al. &quot;Loss of imprinting and aberrant methylation of IGF2 in placentas from pregnancies complicated with fetal growth restriction.&quot; <em>International journal of molecular medicine</em> 28.4 (2011): 481.</td>
<td>IUGR Control</td>
<td>IUGR- fetal birth weight &lt;5th percentile and other indications of poor fetal growth Control- Term, uncomplicated, appropriate for gestational age growth between &gt;10th-&lt;90th percentiles.</td>
<td>IUGR (N=31) Control (N=17)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td></td>
<td>Birth weight Gestational age</td>
<td>No difference in DNA methylation observed at <em>IGF2</em> between IUGR and control placentas</td>
<td>MethylLight Assay</td>
<td>No</td>
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<td>2011</td>
<td>Gao, Wen-long, et al. &quot;Detection of global DNA methylation and paternally imprinted H19 gene methylation in preeclamptic placentas.&quot; <em>Hypertension Research</em> 34.5 (2011): 655-661.</td>
<td>Early-onset PE (EOPE) Late-onset PE (LOPE) Controls</td>
<td>EOPE- diagnosis of PE &lt;34 weeks LOPE- diagnosis of PE &gt;34 weeks Controls- not specified but appear to be term</td>
<td>EOPE (N=10) LOPE (N=14) Control (N=24)</td>
<td>p&lt;0.01, Δβ&gt;0.17</td>
<td>No</td>
<td>None</td>
<td>Global DNAm, measured by both immunohistochemistry and LINE1 and ALU pyrosequencing revealed higher DNAm levels in EOPE than controls. LINE1 and Alu were also significantly higher in LOPE. H19 DNAm, measured by MS-HRM, was also reported higher in EOPE than controls</td>
<td>immuno histochemistry LINE1 and ALU pyrosequencing MS-HRM</td>
<td>No</td>
<td>NA</td>
</tr>
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<td>2011</td>
<td>Lambertini, Luca, et al. &quot;Differential methylation of imprinted genes in growth-restricted placentas.&quot; <em>Reproductive sciences</em> 18.11 (2011): 1111-1117.</td>
<td>IUGR Adequate for gestational age (AGA)</td>
<td>IUGR- fetal birth weight &lt;5th percentile and associated with either absent end-diastolic slow or reverse end diastolic slow of the umbilical artery AGA- pregnancies delivering&gt;37 weeks gestation, &gt;10th percentile in fetal birth weight and no signs of</td>
<td>IUGR (N=7) AGA (N=10)</td>
<td>p&lt;0.01</td>
<td>No</td>
<td>None</td>
<td>Imprinted genes in the placenta had a trend toward hypermethylation in IUGR placentas.</td>
<td>MeDIP</td>
<td>No</td>
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<td>Bourque, D. K., et al. &quot;Decreased placental methylation at the H19/IGF2 imprinting control region is associated with normotensive intrauterine growth restriction but not preeclampsia.&quot; <em>Placenta</em> 31.3 (2010): 197-202.</td>
<td>Control</td>
<td>Control- Uncomplicated term placenta</td>
<td>Control (N=22) IUGR (N=13) PE (N=17) PE + IUGR (N=21)</td>
<td>p value&lt;0.05</td>
<td>Yes</td>
<td>None</td>
<td>DNAm at ICR1, associated with <em>H19</em> and <em>IGF2</em> gene expression was reduced in nIUGR placentas, but not PE. DNAm at ICR2, associated with <em>KvDMR1</em> and <em>CDKN1C</em> gene expression, was not significantly altered in either PE or nIUGR placentas.</td>
<td>Illumina Goldengate, pyrosequencing, MS-SNuPE assay</td>
<td>Yes</td>
<td>Initial DNA was measured on a small set of samples using the golden gate array. DNA was validated with a larger cohort using the MS-SNuPE assay</td>
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<td>Wang, Zhuoqun, et al. &quot;Expressional and epigenetic alterations of placental matrix metalloproteinase 9 in preeclampsia.&quot; <em>Gynecological Endocrinology</em> 26.2 (2010): 96-102.</td>
<td>PE Control</td>
<td>PE- BP 140/90 mm HG &amp; proteinuria &gt;0.3mg/24h Uncomplicated pregnancy- normal pregnancy Control-Health uncomplicated third trimester placenta</td>
<td>PE (N=20) Control (N=18)</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>None</td>
<td>A CpG site at -712bp from the transcriptional start site showed altered DNAm in the PE group compared to the control. Magnitude of change was not reported.</td>
<td>Methylationsensitive restriction enzyme digest, followed by PCR</td>
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<td>Guo, Lin, et al. &quot;Altered gene expression and methylation of the human chromosome 11 imprinted region in small for gestational age (SGA)&quot;</td>
<td>SGA Controls IUGR</td>
<td>SGA- &gt;26 weeks of gestation with fetal growth &lt;10th percentile Control- fetal birth weight&gt;10th percentile, without any complications IUGR- SGA placentas with SGA (N=24, 2 were twins) Control (N=20, 8 were twins) IUGR (N=15,</td>
<td>p value&lt;0.05</td>
<td>No</td>
<td>None</td>
<td><em>KvDMR and H19</em> were not differentially methylated in IUGR compared to AGA controls. One SGA sample showed loss of imprinting.</td>
<td>Methylation sensitive enzyme digestion with southern blotting</td>
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<td>Chelbi, Sonia T., et al. &quot;Expressional and epigenetic alterations of placental serine protease inhibitors.&quot; Hypertension 49.1 (2007): 76-83.</td>
<td>PE</td>
<td>BP&gt;140/90 mmHg and proteinuria &gt;0.3g per 24h. IUGR- fetal birth weight &lt;10th percentile</td>
<td>PE (N=9)</td>
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<td>Promoter region of SERPINA3 is hypomethylated in PE compared to control.</td>
<td>Sequencing and pyrosequencing</td>
<td>Yes</td>
<td>DNA methylation of the promoter region of SERPINA3 was validated in a large secondary cohort consisting of 47 PE, 16 IUGR, and 18 control placentas.</td>
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Appendix B  Supplementary tables and figures for Chapter 2

Supplementary Table B.1. List of probes filtered from the discovery and validation cohorts.

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Appendix C  Supplementary tables and figures for Chapter 3

Supplementary Table C.1 All samples used in Chapter 3 and what measures were completed on each sample.

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**Supplementary Table C.2.** Samples used to assess the relationship between DNA methylation and gene expression in the term placenta in Chapter 3.

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<td>Mean BW (grams ±SD)</td>
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<td>Mean MA (years ±SD)</td>
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<td>Sex (Female/N, %)</td>
<td>2/8, 25%</td>
<td>2/8, 25%</td>
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† Previously published in Blair *et al.* 2013.
**Supplementary Table C.3.** Primer sequences for bisulfite pyrosequencing in Chapter 3. Specific locations are based on UCSC hg/18 assembly.

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**FNI**

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Supplementary Figure C.1. A Spearman’s correlation was performed between CpG 1 and CpG 2 within the PAPPA assay. DNA methylation was averaged over the two CpGs.
Appendix D  Supplementary figures and tables for Chapter 4

Supplementary Figure D.1. Sample placement on the 96 well plates (Plate) and the microarray chips for the discovery cohort.
Supplementary Figure D.2. Sample placement on the 96 well plates (Plate) and the microarray chips for the validation cohort.
Supplementary Figure D.3. Sample-sample correlations for both the discovery and validation cohort in the control samples (both term and preterm). P-value from Student’s t-test indicates that the discovery cohort is more heterogeneous (less correlated) than the validation cohort.
Supplementary Figure D.4. Sample-sample correlations for both the discovery and validation cohort in the EOPE samples. P-value from Student’s t-test indicates that the discovery cohort is more heterogeneous (less correlated) than the validation cohort.
Supplementary Table D.1. CpG site and gene information on the 599 validated hits.

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<th>EOPE vs Preterm p-value Discovery Cohort</th>
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Supplementary Figure D.5. A) The concordance rate (sites where DNAm change is in the same direction in both cohorts) for different FDR and Δβ thresholds. Concordance rates (%) are plotted on the y-axis and FDR thresholds are on the x-axis. B) The number of identified hits for different FDR and Δβ thresholds. The number of hits is plotted on the y-axis and the FDR thresholds are on the x-axis.
**Supplementary Table D.2.** Site and gene information on the 244 CpG sites that were differentially methylated between methylation cluster 2 and methylation cluster 3 in both the discovery and validation cohorts.

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