PREGNANCY OUTCOME IN SOUTH AUSTRALIA

Population and Cohort Studies

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GENERAL INTRODUCTION AND OUTLINE
A quarter of first pregnancies are affected by adverse pregnancy outcomes, including spontaneous preterm birth (sPTB), fetal growth restriction (FGR)/small for gestational age (SGA), gestational diabetes mellitus (GDM) and hypertensive disorders of pregnancy (HDP)[1]. The aim of the studies presented in this thesis was to describe adverse pregnancy outcomes in South Australia in population and cohort studies with a particular focus on filling in gaps of knowledge of hitherto understudied predictive or associated factors.

**Preterm birth**

Preterm birth (PTB) is defined as birth before 37 weeks of gestation and can be further subdivided in early PTB (less than 34 weeks of gestation) and late PTB (34-36 6/7 weeks of gestation). PTB birth may be spontaneous or iatrogenic[2]. Common indications for an early iatrogenic birth may be because of conditions of the mother [e.g. preeclampsia (PE), eclampsia, placental abruption and placenta praevia] or of the fetus [e.g. FGR or fetal distress][2]. The incidence of PTB and the contribution of iatrogenic PTB varies between regions and countries[2], but globally the incidence of PTB is estimated at 11%[3,4] and still increasing[2]. Due to underreporting, specifically in undeveloped countries, it is likely that the exact number of PTB is much higher, reflecting a huge global burden on health care systems. sPTB is a heterogeneous syndrome, in which multiple pathways lead to the common endpoint we recognize as PTB. Not surprisingly many risk factors have been identified, such as ethnicity, adolescent pregnancies, advanced maternal age, stress, drug use, ascending infections, low maternal education, household smoking, cervical surgery and PTB in a previous pregnancy[2]. Currently, researchers are seeking simple and inexpensive methods to predict PTB, but thus far there is not a sensitive prediction model available[5]. PTB has huge implications for the neonate. Neonatal mortality and morbidity is increased in infants born preterm versus those born at term[2]. Short term implications of prematurity include increased risk of neonatal respiratory conditions, necrotizing enterocolitis, sepsis, neurological conditions, feeding difficulties and visual and hearing problems[2]. PTB has been linked to poorer neurodevelopmental outcomes, higher hospital admission rates, and behavioural, social-emotional and learning difficulties in childhood[2]. Later in life, former-preterm born neonates have higher risk of cardiovascular, metabolic and psychiatric disorders[6,7].

**Fetal growth restriction and small for gestational age infants**

Fetal growth restriction (FGR), also referred to as intra-uterine growth restriction, refers to an insufficient rate of fetal growth in relation to an infants’ ethnic and sex-specific growth potential and is present in 3-7% of pregnancies[8]. Those neonates whose birthweight is less than the 10th population-based, sex-specific birthweight percentile, for gestational age are considered small for gestational age (SGA)[8]. In the literature the definitions of FGR and SGA are often used interchangeably, despite dissimilarities between their definitions. Underlying mechanisms that result in FGR are not fully understood, but as a consequence of maternal, placental or fetal pathology the fetus cannot fully achieve its growth potential[8]. FGR/SGA are therefore very heterogeneous conditions. Growth restricted neonates have an increased risk for acute problems including perinatal asphyxia, hypothermia, hypoglycaemia and polycythemia[8]. Later in life, individuals born SGA have higher risk of renal, cardiovascular and metabolic disease[6,9,10].

**Gestational diabetes mellitus**

Gestational diabetes mellitus (GDM) is carbohydrate intolerance, with onset or first recognition during pregnancy. It is an important contributor to fetal and neonatal morbidity and mortality. Women who develop GDM are also at increased risk for HDP and giving birth by caesarean section[11,12]. In a hyperglycemic woman, excess transport of glucose through the placenta forces the fetus to increase its own insulin production[13]. This puts the fetus at an increased risk of perinatal metabolic disturbances, potentially resulting in stillbirth, macrosomia, or birth-related problems[14]. Following a GDM complicated pregnancy, both mother and
neonate have increased long-term risk of cardiovascular disease (CVD), type 2 diabetes mellitus and metabolic syndrome\[13,15,16\]. The pathophysiology of GDM is not completely understood, but most data indicate that the additional insulin resistance caused by some of the major placental hormones, including human placental lactogen (hPL) and oestrogen, are superimposed in pre-existing insulin resistance\[17\]. When the combined degree of pre-existing plus pregnancy-induced insulin resistance due to these hormones exceeds the pancreatic capacity, hyperglycaemia ensues. Therefore, the risk factors for GDM include the typical risk factors for type 2 diabetes mellitus, including maternal overweight and obesity, low maternal birth weight, specific ethnicity (Indian or Australian indigenous descent), advanced maternal age, family history of type 2 diabetes mellitus, history of previous fetal death and previous birth of a macrosomic infant\[18,19\]. For many years, there has been a continuing controversy regarding associated risk, diagnostic criteria, screening, and treatment of GDM and to date, there is still no global clinical consensus\[14,19\]. Regardless of the used criteria of GDM, its incidence is increasing worldwide\[14\]. Globally, GDM is present in around 7% of all pregnancies, but the incidence of GDM is population-specific, varying from 1-10%\[20\]. GDM and its long-term risks stresses health care systems significantly\[14\].

**Hypertensive disorders of pregnancy**

Preeclampsia (PE) is a systemic syndrome that occurs during pregnancy or shortly postpartum. It is traditionally diagnosed by the combined presentation of hypertension (≥140mmHg systolic and ≥90mmHg diastolic blood pressure) and proteinuria (spot urine protein/creatinine ≥30mg/mmol [0.3mg/mg] or ≥300 mg/day or at ≥1g/L [‘2+’] on dipstick testing) in the second half of pregnancy, in previously normotensive women\[21,22\]. The International Society for the Study in Hypertension in Pregnancy (ISSHP)’s definition for PE also includes maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological or haematological complications or uteroplacental dysfunction, including FGR/SGA\[23\]. PE affects 3-5% of pregnancies and is one of the main causes of maternal, fetal and neonatal morbidity and mortality\[22,24\]. Maternal complications include placental abruption, pulmonary oedema, eclampsia, liver failure or liver haemorrhage, stroke or death (both rare) and long-term cardiovascular morbidity\[21,22\]. Possible neonatal complications are iatrogenic PTB, FGR/SGA, and long-term cardiovascular morbidity associated with low birthweight\[21,22\]. Numerous risk factors for PE have been identified, including genetic predisposition, primiparity, primipaternity, limited sperm exposure, advanced maternal age, ethnicity, metabolic risk factors and infections\[21,22\], but the exact pathophysiology of PE remains unclear. Since PE is present in pregnancies only, it has been hypothesised that PE is caused by the presence of the placenta or by the maternal response to placentation\[21,22\]. Currently, the only cure for PE is delivery of the placenta\[22,24\].

Apart from PE, another common HDP is gestational hypertension (GH). GH is defined as _de novo_ hypertension in second half of pregnancy, in the absence of proteinuria or other maternal organ dysfunction as described above\[23\]. GH affects 5-8% of pregnancies and has important similarities and differences in risk factors and pathophysiology to PE\[25\]. It is likely that many GH cases reflect chronic hypertension first diagnosed in pregnancy\[23\]. In a quarter of GH cases, the condition progresses to PE. Both GH and PE are associated with increased risk of subsequent CVD\[25,26\], and the highest risk is for those with hypertension combined with FGR and/or PTB\[25\].

**Part 1 – Trends, sexual dimorphism and seasonality of pregnancy outcome.**

The first part of this thesis describes a series of four population studies in South Australia. Each of the studies used data from the South Australian Perinatal Statistics Collection (SAPSC), a state-wide registry of all characteristics and clinical outcomes of all South Australian births notified by hospital and home birth midwives and neonatal nurses.
Long-term trends in adverse pregnancy outcome
As described previously, in summary, adverse pregnancy outcome, like sPTB, FGR/SGA, GDM and HDP, are common heterogeneous conditions of which the pathophysiology is not fully understood. These four pregnancy complications combined affect 25-40% of pregnancies[27–30]. They have serious potential short- and long-term consequences for both mother, fetus and neonate and therefore form a significant burden on healthcare systems[27–30]. In order to study the long-term trends in the prevalence of PTB and rates of PTB in singleton pregnancies complicated by HDP, SGA and preterm prelabor rupture of the membranes (PPROM) in South Australia, we conducted a population wide study (Chapter 1).

Sexual dimorphisms in adverse pregnancy outcome
The ‘developmental origins of health and disease’ (DOHaD) hypothesis suggests that the foundation of lifelong health in both women and men is established in utero. Therefore, an adverse intrauterine environment has long-term health consequences for the offspring[6]. The National Institutes of Health has highlighted the importance of evaluating sex differences in health and disease. Fetal sex has been suggested as an independent risk factor for adverse pregnancy outcomes[31–33]. Chapter 2 describes the presence of sexual dimorphisms for PTB, birthweight, HDP and GDM in a retrospective population-based cohort study. It presents a coherent framework based on two analytical approaches to assess and interpret the sexual dimorphisms for these major adverse pregnancy outcomes at a population level.

Seasonal variation of adverse pregnancy outcome
Some of the identified risk factors for adverse pregnancy outcomes are not condition-specific. The presence of advanced maternal age, maternal obesity, complicated medical (obstetric) history, ethnicity and male fetal sex increase the risk of all previously described adverse pregnancy outcomes[2,8,14,21,24]. In addition to these traditional risk factors, multiple environmental and lifestyle factors have also been associated with adverse pregnancy outcome[18,34–45].

Increased ambient temperature[34], lack of physical activity in the period before pregnancy and in early pregnancy[38], high dietary intake of fat at the time of diagnosis[18,39] and vitamin D deficiency[40] are associated with an increased risk for GDM. Similarly, vitamin D deficiency[41–43], reduced intake of calcium[44], folic acid[45] and zinc[35] and lack of physical activity[36,37] are associated with an increased risk of HDP. These risk factors for GDM and HDP have periodicity in common[46–48]. In an effort to increase the knowledge of mechanisms regarding early pregnancy exposures that may influence the development of GDM and HPD, we aimed to assess the seasonal variation of these two conditions. The seasonality of GDM and HDP in South Australia are described in Chapters 3 and 4, respectively.

Part 2 - Maternal haemodynamics in pregnancy
The second part of this thesis describes the first results of the Screening Tests to predict poor Outcomes of Pregnancy (STOP) study, a prospective observational cohort study aiming to establish and validate sensitive prediction models for sPTB, SGA, GDM and HDP. Dr Verburg coordinated the STOP study and was responsible for patient recruitment, blood sampling throughout, conducted all of the haemodynamics studies at 11 and 34 weeks’ gestation and database management.

Maternal haemodynamics in hypertensive disorders of pregnancy
The full etiology of HDP is still elusive but some of its pathological mechanisms may have their origin in early pregnancy and it is likely that the etiology involves exposures that occur before HDP is clinically recognized. HDP
is thought to be caused by both vascular and immune maladaptation, two processes intimately associated with inflammation[21]. Pregnancy is a physiological stress-test. To meet the demands of pregnancy, most maternal organ systems undergo complex adaptations and dramatically increase their functionality. Haemodynamic changes occur to ensure adequate placental perfusion, as well as nutrient and gaseous transport, to sustain fetal growth and development[49]. Altered maternal haemodynamic adaptation has been identified in women who develop pregnancy complications, specifically in those who develop PE[50–54]. In Chapter 5 we describe the maternal haemodynamic adaptation throughout gestation in uncomplicated pregnancies versus those complicated by HDP.
References


PART 1

TRENDS, SEXUAL DIMORPHISM AND SEASONALITY OF PREGNANCY OUTCOME