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A population-based study of risk factors for adverse pregnancy outcomes in northern rural Iran: a follow-up from pre-pregnancy to delivery

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ABSTRACT

There is a substantial lack of knowledge about adverse pregnancy outcomes and their risk factors in middle and low-income countries, including Iran. This thesis has endeavored to examine the association between maternal characteristics and risks of adverse pregnancy outcomes, using prospectively collected information from pre-pregnancy, antenatal visits and delivery records.

Our specific objectives were as follows: to investigate the association between parental consanguinity (first cousin marriage) and the risk of stillbirth, to examine whether risk of stillbirth is influenced by decreasing maternal blood hemoglobin concentrations before and during pregnancy, and to study the effects of maternal opium use during pregnancy on risks of spontaneous or medically induced preterm birth and fetal growth restriction. As a secondary aim, we examined the prevalence of previously reported risk factors in the study population.

This project was conducted in a rural part of the Golestan province in northern Iran which has a population of 1,700,000 (50% living in rural areas) where there are 17,000 registered pregnancies annually. The first study was restricted to singleton pregnancies who had received a pre-pregnancy visit. This case-control study consisted of 283 cases and 2,088 controls and was conducted to investigate the association between consanguinity and risk of stillbirth. The second study consisted of 495 singleton stillbirths (cases) and 2,888 singleton live births (controls). The third and fourth studies were population-based cohort studies, comprising a total of 920 opium users ("exposed") and 920 non-opium users ("unexposed") during pregnancy.

In the first study, our findings indicated that consanguinity was associated with an increased risk of preterm (<37 gestational weeks) stillbirth. The second study showed that compared with normal maternal hemoglobin concentration, high maternal hemoglobin concentrations (≥140 g/l) was associated with a more than twofold stillbirth risk. In addition, low maternal hemoglobin concentrations (<110 g/l) was associated with a reduction in stillbirth risk. The third study showed that compared with non-use of opium and tobacco, use of only opium during pregnancy was associated with an increased risk of preterm delivery and the risk was more than doubled among dual users of opium and tobacco. In the fourth study, a positive association was found between intrauterine opium exposure and risk of the birth of a Small for Gestational Age (SGA) infant. Among term births, opium use was also associated with short crown-heel length and small head circumference. These associations were slightly magnified for infants of dual user mothers.

In conclusion, this project reported that consanguineous marriage was associated with an increased risk of preterm stillbirth. High hemoglobin levels and an absence of hemoglobin dilution during pregnancy could be considered as an indicator of a high risk pregnancy. Opium use during pregnancy had an association with a higher risk of preterm delivery. Infants of

women who had used only opium had an increased risk of short crown-heel length and small head circumference at term birth. Opium use during pregnancy was also associated with a higher risk of Small for Gestational Age at birth.

LIST OF SCIENTIFIC PAPERS

I.   Siavash Maghsoudlou, Sven Cnattingius, Mohsen Aarabi, Scott Montgomery, Shahriar Semnani, Olof Stephansson, Anna-Karin Wikström, Shahram Bahmanyar
Consanguineous marriage, pre-pregnancy maternal characteristics and stillbirth risk: a population-based case-control study.
Acta obstetricia et gynecologica Scandinavica 2015; 94(10): 1095-101.

II. Siavash Maghsoudlou, Sven Cnattingius, Olof Stephansson, Mohsen Aarabi, Shahriar Semnani, Scott M. Montgomery, Shahram Bahmanyar
Maternal hemoglobin concentrations before and during pregnancy and stillbirth risk: a population-based case-control study.
BMC pregnancy and childbirth. 2016; 16(1):135.

III. Siavash Maghsoudlou, Sven Cnattingius, Scott Montgomery, Mohsen Aarabi, Shahriar Semnani, Anna-Karin Wikström, Shahram Bahmanyar
Opium use during pregnancy and risk of preterm delivery: a population-based cohort study. (Manuscript)

IV. Siavash Maghsoudlou, Sven Cnattingius, Scott Montgomery, Mohsen Aarabi, Shahriar Semnani, Anna-Karin Wikström, Shahram Bahmanyar
Opium use during pregnancy and infant size at birth: a population-based cohort study. (Manuscript)

CONTENTS

LIST OF ABBREVIATIONS

BMI	Body Mass Index
CI	Confidence Interval
cm	centimeter
g/l	gram per liter
Hb	hemoglobin
km²	square kilometer area
OR	Odds Ratio
SGA	Small for Gestational Age
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organization

1 INTRODUCTION

1.1 BACKGROUND

There is a substantial lack of knowledge about adverse pregnancy outcomes and related risk factors in middle and low-income countries, including Iran. In these countries, the importance of socio-demographic characteristics, anthropometric indexes, and lifestyle factors for adverse pregnancy outcomes has not been fully studied. Moreover, the prevalence of possible risk factors and adverse outcomes is also generally unknown. Globally, 2.6 (ranging between 2.4 and 3.0) million stillbirths were estimated in 2015 (1). Five stillbirths occur for every 1,000 deliveries in many high-income countries; this rate is up to tenfold higher in some low-income countries (2, 3). Preterm birth and fetal growth restriction are the leading causes of perinatal mortality and morbidity (4). Preterm birth has been documented as a major determinant of long-term morbidity, including learning disabilities, respiratory illnesses, hypertension, and cardiovascular events in adulthood (5-8). It was estimated that approximately 15 million babies were born preterm globally in 2010 (9). The preterm delivery rate in the United States is about 12% and in Europe about 7%, while in some low-income countries it can be as high as 28% (9-11). UNICEF has estimated that around 20 million infants are annually born with a birth weight of less than 2,500 grams (12). In some low-income countries, up to 50% of live births are Small for Gestational Age (SGA) at delivery, predicted largely on national rates for low birth weight, which were very high (13). It has been reported that infants born with a low birth weight for gestational age (SGA) are at increased risks of early life mortality and long-term morbidity, including learning disabilities, and glucose-impaired metabolism, diabetes mellitus, hypertension, and ischemic heart diseases in adulthood (14-19).

In recent decades, Iran has developed into a middle-income country, which has caused substantial changes in demographic patterns, lifestyle behaviors and anthropometry, which in turn influence health outcomes (20). With respect to reproduction, contraceptives are now commonly used in Iran and women deliver fewer babies than previously (21). According to the recommendation of the Alma Ata conference, women in rural parts of the Golestan province in northern Iran undergo physical examinations and laboratory tests and receive micro supplements during one pre-pregnancy and several antenatal visits (22). Approximately 95% of deliveries take place in hospitals and the rate of caesarean section (elective and emergency) is more than 45% (21).

Thus, in the Golestan province, pre-pregnancy baseline information is commonly available, and there are also local risk factors which are hard to study in other populations, including opium use during pregnancy and consanguineous marriage. Both common and local risk factors of adverse pregnancy outcomes are well documented on pre-pregnancy, pregnancy and obstetrical paper forms archived at "health houses" in villages (see section 2.3 for more details on the Iranian healthcare system). We studied these prospectively collected medical records to

investigate risk factors of adverse pregnancy outcomes in different types of population-based studies.

1.2 STILLBIRTH

Stillbirth is defined as the delivery of a baby without any vital signs at 28 (or 22) weeks of gestational age or later. In recent decades, some countries have experienced substantial reductions in stillbirth rates while stillbirth rates have been stable or slightly declining in other countries (23). The global rate of stillbirth was 23.9 per 1,000 deliveries in 2000 and the risk varies greatly: in the United Kingdom, stillbirth rate is 5 per 1,000 pregnancies (24) and in Sub-Saharan Africa, the rate is 32.2 per 1,000 pregnancies (25). The stillbirth rate in Iran is reported to be between 10 and 14 per 1,000 births (Figure 1-1) (25-27).
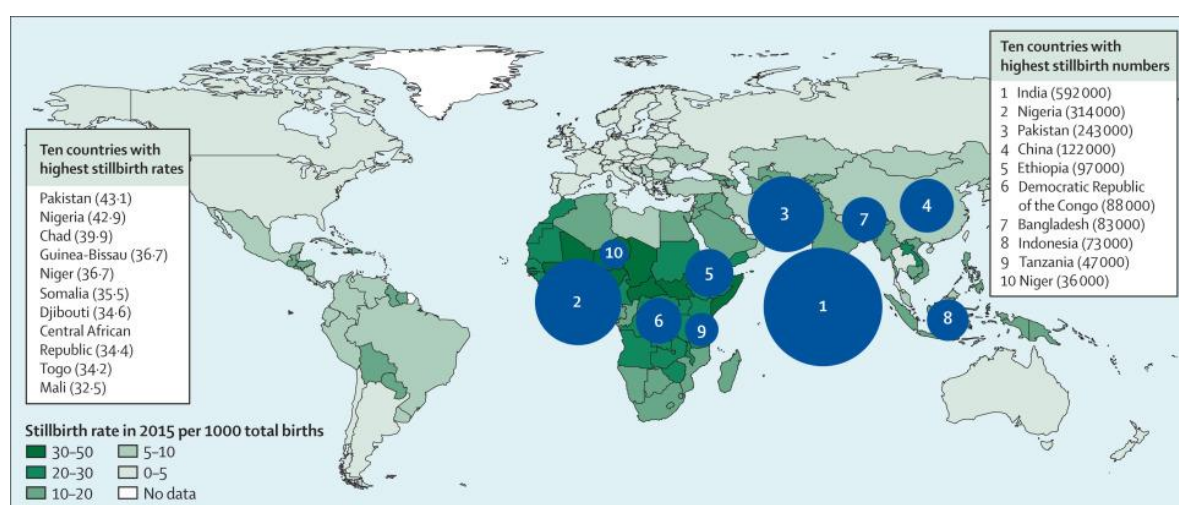
Figure 1-1: National, regional, and worldwide estimates of stillbirth rates in 2015 (28).

1.2.1 Risk factors

The most common risk factors of stillbirth are maternal age, Body Mass Index (BMI), and smoking. These factors vary in different regions (Figure 1-2) (29, 30). In high-income countries, maternal age older than 35 years is associated with a 65% increase in the odds of stillbirth (23). Williams et al. reported that association between stillbirth and advanced maternal age was due to increased rates of congenital anomalies and fetal growth restriction (31). Arnold et al. found that advanced maternal age (>40 years) was associated with a twofold increased risk of term stillbirth after excluding multiple pregnancies, stillbirths with a congenital anomaly and aneuploidy (32). The peak of the association was reported in term pregnancy (39 to 40 weeks of gestational age) (33). Another study showed there is a 3.5 times greater risk of intrapartum stillbirth among mothers over the age of 40 years compared with mothers aged 20 to 24 years (34).

Teenage pregnancy is a risk factor for adverse pregnancy outcomes, including stillbirth (35). The risk is 50% greater in teenage mothers with a singleton pregnancy while in twin pregnancies, the corresponding risk is almost doubled compared with women aged 20-24 years (36).
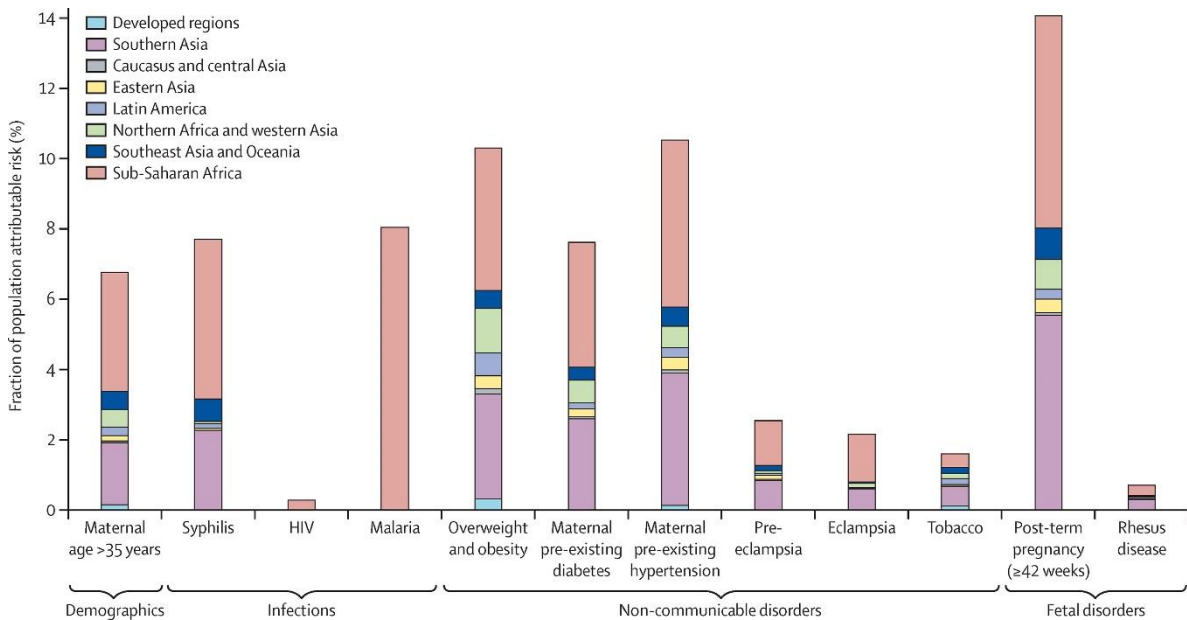
Figure 1-2: Regional variation in population attributable risk of stillbirth for common risk factors (1).

Maternal underweight (BMI < 18.5) in early pregnancy was reported as a risk factor for adverse pregnancy outcomes such as spontaneous abortion (37), congenital anomalies (38, 39), particularly cardiovascular anomalies (40), preterm delivery, and low birth weight (41). However, studies did not report any significant association between maternal underweight and stillbirth risk (41-44). In fact, an inverse association between maternal underweight and late stillbirth has been reported (45).

A meta-analysis of 9 studies showed that overweight (BMI 25 to <30) and obesity (BMI ≥30) were associated with approximately 50% and twofold higher risk of stillbirth, respectively (46). Stephansson et al. reported that maternal obesity and overweight are associated with a higher risk of antepartum stillbirth, particularly term antepartum stillbirth (Odds Ratio=2.9), regardless of maternal weight gain during pregnancy (47). A nationwide Swedish study reported that risk of stillbirth increased linearly with weight gain (63% greater risk when BMI increases by 3 or more units) between pregnancies (48).

Compared with multiparous mothers, nulliparous women had a higher risk of stillbirth (49, 50). It has been shown that grand multiparity (more than 4 previous live births) is associated with a higher risk of stillbirth and the risk was substantially higher for women with extremely high parity (51).

A meta-analysis of 34 studies showed that smoking during pregnancy was associated with 47% higher risk of stillbirth and a subgroup analysis revealed that 1 - 9 cigarettes per day and more than 9 cigarettes per day were associated with 9% and 52% increased risk of stillbirth, respectively (52). Using a moist powder tobacco product (*snus*) was associated with a 60% increase in the risk of stillbirth (53). Maternal moderate alcohol consumption was associated with more than a twofold higher risk of stillbirth (54).

Medical complications (55, 56), including hypertension before (57) or during pregnancy (58), pre-existing diabetes (50), and gestational diabetes (59), are associated with increased stillbirth risk.

Infertility is associated with stillbirth and death during the first week after birth (60). Pregnancies achieved after using assisted reproduction technology often had an increased stillbirth risk (61).

Obstetric histories associate with an increased risk of stillbirth. Mothers with a positive history of preeclampsia had approximately 43% higher risk of stillbirth (62). Women with a history of preeclampsia or placenta abruption had a 60% and 300% increased risk of stillbirth, respectively (57, 63). A history of birth of a SGA or low birth weight infant is associated with a higher risk of stillbirth (OR: 3.65) for index pregnancy (32). A comprehensive study among parous mothers reported that the risk of stillbirth among parous mothers subsequent to a previous term SGA delivery was more than doubled. This study also found 3.4 and 5 times higher risks of stillbirth subsequent to an SGA and moderate preterm (32 to 36 weeks of gestation) or SGA severe preterm (before 32 weeks of gestation) birth, respectively (64). The risk of recurrent stillbirth was reported as six times greater compared with parous mothers without a history of stillbirth. The risk of recurrence for different subtypes of stillbirth was estimated as (OR: 10.3, 95% CI [6.1, 17.2]) for early stillbirths (20-28 weeks) and (OR: 2.5, 95% CI [1.0-6.0]) for late stillbirths (≥29 weeks) and also for intrapartum (OR: 12.2, 95% CI [4.5-33.3]) and (OR: 4.2, 95% CI [2.3-7.7]) for antepartum stillbirths (65). Ofier et al. showed that not only the risk of consequent stillbirths increased; in addition, other adverse pregnancy outcomes and complications increased among mothers with a history of prior stillbirth (66).

Consanguinity (cousin marriage) has been reported as being associated with approximately 30% increased stillbirth risk (67, 68). First cousin couples had a higher risk of recurrent stillbirth (69). Consanguinity was associated with pregnancy wastage (a combination of abortion and stillbirth) (70, 71), and increased risk of infant (72) and child (73) mortality in some other studies. Consanguinity was also associated with 80% increased risk of low birth weight (74) and 2.5 times higher risk of congenital anomalies (75, 76), which in turn are risk factors for stillbirth, infant and childhood mortality and morbidity (73, 77-79). Culprit genes have been identified in associations between consanguinity and hearing loss (80), familial Mediterranean fever (81), and intellectual disability (82, 83).

Results of studies of maternal hemoglobin concentrations and stillbirth risk are inconclusive (84). Some studies documented that both low and high hemoglobin concentrations

during pregnancy may increase stillbirth risk (85, 86). However, other studies have found that increased stillbirth risk is restricted to women with either low (87) or high (88) hemoglobin levels. Moreover, some studies found that increased maternal hemoglobin levels in early (85, 89) or late pregnancy (90) were associated with increased stillbirth risks (91-93). Socioeconomic circumstances such as level of health services (94), insurance status (32), quality of obstetric care (95), marital status (96), and socioeconomic factors (97) including income (98, 99) deprivation index, paid employment (100), professional classifications (101), and particularly maternal education are also associated with a risk of stillbirth (57, 102). Finally, mothers of twins have increased risks of pregnancy complications and stillbirth (103, 104).

1.2.2 Classification

The purpose of classifying stillbirth is to evaluate the effects of different risk factors and to define possible causal pathways.

- *Intrapartum versus antepartum stillbirth*

Some studies separate stillbirths into antepartum deaths (fetal deaths that occur before labor) and intrapartum deaths (those that occur during labor and delivery) (34, 43, 47, 105-107). Intrapartum stillbirths have virtually disappeared in many high-income countries (35). Studies have suggested that more than 20% of intrapartum stillbirths would be preventable with sufficient prenatal and obstetrical care (108, 109). Advanced maternal age ($\geq$35) is a risk factor for both intrapartum and antepartum stillbirth, but the risk is reported to be higher for antepartum stillbirth (OR: 1.68) (43, 105).

Obesity and overweight are risk factors for both intrapartum and antepartum stillbirth, but the risk was reported to be higher (OR: 2.07 versus 1.5) for intrapartum stillbirth in a study by Ruth et al. (105). A Swedish study also reported that compared with underweight women (Body Mass Index$\leq$ 19.9), overweight and obese women have a higher risk of late antepartum stillbirth (OR: 2.1 and 2.4, respectively) (47). On the other hand, Getahun et al. reported that the association between BMI and antepartum stillbirth was related to ethnicity and that the association between obesity and antepartum stillbirth was stronger among white women (43). Furthermore, they showed that underweight mothers had a higher risk of antepartum stillbirth, but this risk increase was only found among Afro-American women (OR: whites 0.7 versus Afro-Americans 1.4). Delivery complications, including premature rupture of membrane with/without fever, placenta abruption, placenta previa, excessive bleeding, fetal distress, and cord complications have stronger associations with intrapartum stillbirth (43).

- *Early versus late (preterm versus term) stillbirth*

The International Classification of Diseases, the 10th revision (ICD-10), classifies late fetal deaths as death of a fetus greater than 1,000 grams or after 28 weeks, and early fetal deaths as death of a fetus 500 to 1,000 germs or 22-28 weeks (110). Some studies also divided stillbirth according to the gestational age at birth: early stillbirths (20–28 weeks gestation) and late

stillbirths (after 28 weeks) (65, 111, 112). The most important risk factors for late stillbirth are maternal obesity, smoking, drug use, low socioeconomic status (100), short maternal stature, maternal age, grand multiparity, previous adverse obstetrical history, late antenatal or intrapartum vaginal bleeding, intrapartum hypertension, dystocia, and infection (113). Thilaganathan et al. showed that compared with di-chorionic twins, the risk of late stillbirth is higher in mono-chorionic twin pregnancies (114).

Alcohol consumption during pregnancy (111) and high hemoglobin concentrations (85) are associated with an increased risk of early stillbirth.

Among primary causes of stillbirth, preeclampsia, gestational hypertension, and placental abruption are more frequent among preterm stillbirths (77) and umbilical cord complications and infections are more frequent in term stillbirths compared with preterm stillbirths (77).

- *Classification based on causal factors*

Some studies classified stillbirth on the basis of etiology, including maternal conditions, neonatal factors and placenta anomalies (115-122). For example, the "Stockholm method" categorized stillbirth with relation to conditions such as intrauterine growth restriction/placental insufficiency, infection, and malformations/chromosomal abnormalities (118).

1.3   PRETERM BIRTH

Preterm birth is one of the main causes of infant mortality (123). This is defined as delivery before the thirty-seventh week of gestational age. In total, 11% of all live births are preterm (approximately 14.9 million) (9). This rate ranges between 5% of live births in northern Europe to 25% in some low and middle-income countries, including Iran (Figure 1-3) (124-126).
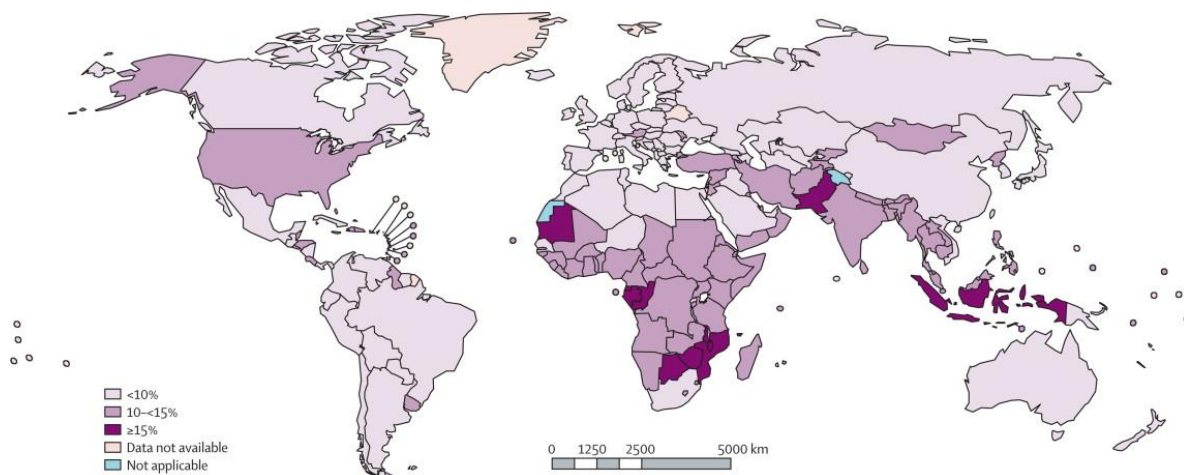

Figure 1-3: National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications (9).

Globally, 14% of deaths under 5 years old and 35% of neonatal deaths are associated with preterm birth (127). It is a major determinant of neonatal mortality, short and long-term morbidity including increased risks of cerebral palsy, sensory deficits, learning disabilities, respiratory illnesses, hypertension and cardiovascular event in adulthood (5, 7, 8, 128-131).

1.3.1 Risk factors

The most common risk factors of preterm birth include genetic factors, maternal anthropometric characteristics (maternal short stature, overweight or underweight) and advanced maternal age (38, 39, 132). Maternal obesity and overweight are associated with a higher risk of both spontaneous and elective preterm delivery (133, 134). The relation between maternal obesity and spontaneous preterm birth may be caused by premature rupture of membranes (135) or by higher levels of pro-inflammatory cytokine and inflammatory regulation in obese mothers during pregnancy (136). It seems that the association between maternal BMI and preterm delivery varies in different ethnicities (137, 138). Studies showed that the association between BMI and preterm delivery may be greater with lower maternal weight gain during pregnancy (139, 140) Very high weight gain during pregnancy has also been associated with a higher (twofold) risk of preterm delivery (141). It has been reported that maternal weight gain during pregnancy was associated with preterm delivery and this association varied by maternal BMI before pregnancy. The association was stronger for underweight mothers (142).

Teenage motherhood is a risk factor for preterm birth (36, 143). Restrepo-Mendez et al. found a higher risk of low birth weight and preterm birth among extremely young mothers (≤ 16 years old), but it is suggested that an elevated risk among teenage mothers could be explained by their lower socioeconomic status (144).

Maternal medical complications are also associated with a higher risk of preterm birth. Chronic hypertension and diabetes mellitus increase the risk of indicated preterm delivery (145). Maternal hyperglycemia, pre-gestational and gestational diabetes increase the risk of spontaneous and medically indicated preterm delivery (146). Iron deficiency (147) and anemia (148, 149) during pregnancy are risk factors for preterm delivery. Depression and anti-depression therapy are associated with a higher risk of preterm delivery (150, 151). It has been clearly shown that inflammatory and infectious diseases are associated with a higher risk of, especially, very preterm birth. Vaginal infections, including abnormal vaginal flora, bacterial vaginitis and aerobic vaginitis, are associated with a higher risk of preterm delivery (152). Periodontal infection is also associated with a higher risk of preterm delivery (153, 154).

Mothers with a positive history of abortion have a higher risk of preterm delivery (155). Previous singleton preterm delivery is associated with a higher risk of preterm delivery for the index pregnancy (156). A meta-analysis of 17 studies showed that a history of infertility and infertility treatments was associated with more than a 30% increased risk of preterm birth (157). Socioeconomic factors, including maternal education level (158), deprivation (159-161), occupational classification (162), physically demanding professions (163) and emotional stress

(164), are associated with an increased risk of preterm delivery. This association may be generated by neuroendocrine secretion or immune/inflammatory and vascular processes (165).

Maternal smoking during pregnancy is associated with placental complications, premature rupture of the membranes, and preterm birth (166-170). Robert et al. reported that smoking could be responsible for approximately 15% of all preterm births (171). Drug and alcohol abuse during pregnancy is a significant concern worldwide (172). According to a national survey conducted in the United States in 2012-2013, approximately 5% of pregnant women aged 15 to 44 years used illicit substances. This rate was 2.9% in 2004-2005, 5.1% in 2007-2008, and 5% in 2010-2011 and pregnant women aged 15 to 17 represented the highest risk group, with 20.9% indicating usage (173, 174). Alcohol consumption, particularly heavy drinking patterns, is associated with a higher risk of preterm delivery (175, 176). The association between maternal opium use during pregnancy and neonatal abstinence syndrome is well established. There is, however, limited knowledge about opium use and risk of adverse pregnancy outcomes (177-180). Reported associations might be confounded by other factors, such as poor dietary habits, vitamin deficiencies, domestic violence and other high-risk behaviors.

Multiple pregnancies are associated with a number of complications including preterm birth (181, 182). Ethnicity (160, 183) and short birth interval between pregnancies (161) are associated with preterm birth. Maternal medical conditions which cause elective preterm delivery include preeclampsia, SGA, placental abruption and fetal distress. Elective preterm delivery (induction of labor or pre-labor caesarean section) constitutes about 23% of all preterm deliveries (184). Finally, the rare occurrence of iatrogenic preterm delivery still happens when a woman with incorrect dating is medically induced before 37 weeks of gestational age (185).

1.3.2 Classification

Preterm born babies are included in several subgroups, which may differ with respect to risk factors and physio-pathological explanations. In addition, these subgroups may differ with respect to future health complications. Consequently, it is important to diagnose different categories and risk factors for each subgroup. The two most common classifications of preterm birth are based on reason for delivery (spontaneous versus medically induced preterm birth) and gestational age at time of birth.

- *Spontaneous and medically induced (elective) preterm birth*

The common classification of preterm birth is by clinical presentation including spontaneous preterm birth and medically induced preterm birth. Approximately two thirds of all preterm births occur spontaneously; the rest are electively delivered due to concerns about fetal or maternal well-being (168). Medically indicated preterm birth occurs in about 23% of all preterm births (184), indicating a wide spectrum of complicated pregnancies such as antepartum hemorrhage, placental abruption, hypertension, severe preeclampsia, eclampsia (186, 187).

- *Gestational age at preterm birth*

Preterm births are also classified on the basis of gestational age into three categories: extremely preterm (births from 20 to 27 weeks of gestational age), very preterm (births from 28 to 31 weeks), and moderately preterm (births from 32 to 36 weeks gestational age) (188). This categorization predominantly considers the differences in survival, and long and short-term mortality and morbidity (189).

1.4   SMALL FOR GESTATIONAL AGE

Fetal growth restriction is a major determinant of stillbirth (190). Low birth weight has been classified by WHO as a birth weight below 2,500 g. It is estimated that between 4% and 28% of worldwide newborn infants have a low birth weight (191, 192). However, low birth weight infants includes both preterm and SGA infants. In addition, normal fetal growth is limited by the genetically preset growth potential and further modified by maternal, fetal, placental and environmental factors. The label "Small for Gestational Age", SGA, is generally used to describe fetuses or new-born infants whose weight and/or crown-heel length is 2 standard deviations less than the mean for their gestational age and sex and is a sign of a pathologic restriction of growth due to adverse intrauterine environment or genetic influences (193, 194).

National prevalence of SGA (%)
☐ 0–10 ☐ 10–20 ☐ 20–30 ■ 30–40 ■ 40–50 ☐ Not estimated
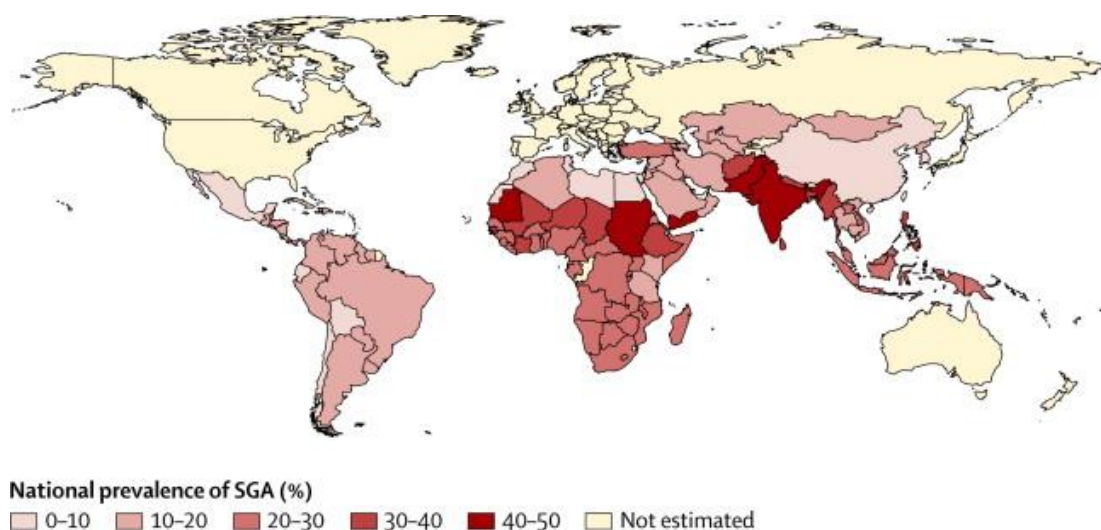
Figure 1-4: National and regional estimates of term and preterm babies born Small for Gestational Age in 138 low-income and middle-income countries in 2010 (13).

The classification of SGA was defined by WHO as infants below the 10th centile of a birthweight for a gestational age, gender-specific reference population (195). The prevalence of SGA in middle and low-income countries ranges from 5.3% in East Asia to as high as 41.5% in southern Asia. The rate of SGA in Iran is estimated as 12.0% (7.9-18.6) of live births (Figure 1-4) (13) but this could be a large underestimation (196). The classification of SGA was defined by WHO as infants below the 10th centile of a birthweight for a gestational age, gender-specific

reference population (195). In addition, many studies set the cut-off point for SGA as below the 5th or 10th percentile for gestational age (197).

1.4.1 Classification

The most common cause of low birth weight is preterm birth. SGA may be categorized on the basis of gestational age (term and preterm) (198, 199). Some studies also classify SGA on the basis of dominant risk factors, including maternal, placental and fetal related risk factors (200). Small for Gestational Age was categorized on the basis of maternal hypertension during pregnancy into normotensive and hypertensive SGA by McCowan et al. (201). The purpose of this categorization is to define different pathologies and causes.

1.4.2 Risk factors

Risk factors for Small for Gestational Age are usually but not always also associated with a higher risk of preterm birth (198). Maternal pre-pregnancy characteristics, including maternal age, anthropometric index, lifestyle (notably smoking), and socioeconomic circumstances, are the most common risk factors for SGA.

A maternal age of more than 35 years is documented as a risk factor for SGA in many studies (198, 202). However, other studies have found that the effect of maternal age was not significant after adjustment for confounding factors (203). Maternal underweight is also associated with a higher risk of low birth weight (139) and intrauterine growth restriction (138). Maternal short stature, smoking and poor socioeconomic circumstances are also associated with a higher risk of SGA at birth (198, 204).

Nulliparity and maternal hypertension during pregnancy are well-known risk factors for low birth weight and SGA (201 , 204). Several studies have revealed that Afro-American, Indian and Asian mothers have an increased risk of having SGA babies compared with white women in high-income countries (203, 205, 206). The risk of an SGA born father and an SGA born mother having a SGA baby is reported as being more than 3.5 and 4.7 times higher, respectively, while the risk was 16 times greater if both parents had a low birth weight (207).

Maternal medical complications, including cardiac (208, 209) and renal (210) malfunction, increase the risk of having an SGA baby. Other maternal chronic diseases, such as asthma (211), anti-phospholipid antibody (212) and systemic lupus erythematosus, were also associated with delivering an SGA baby (213). Hyperthyroidism is associated with a higher risk of low birth weight and preterm delivery (214, 215). In addition, hypothyroidism was associated with a higher risk of preterm birth and large for gestational age infant in a meta-analysis of 13 studies (216). Preexisting diabetes and gestational diabetes mellitus are associated with macrosomia but diabetes accompanied with vasculopathy is associated with a higher risk of impaired fetal growth (217).

Using opiates during pregnancy is associated with an increased risk of low birth weight (218) and SGA (219, 220). Meta-analysis studies showed that using any kind of opiates during

pregnancy is associated with a threefold higher risk of perinatal mortality (221) and more than a fourfold higher risk of low birth weight (222). However, the association might be confounded by social factors, lifestyle and other factors related to high-risk behaviors including the use of other harmful substances (223). Therefore, it is difficult to differentiate the effects of opioid use from effects of other risk factors (224). A history of infertility is also associated with a higher risk of low birth weight and SGA (157).

1.5 ADVERSE PREGNANCY OUTCOMES AND RISK FACTORS IN IRAN

There is limited knowledge about adverse pregnancy outcomes and their risk factors in Iran. Stillbirth and preterm delivery are far more frequent in low and middle-income countries (225). In recent decades, the incidence rate of stillbirth has had a downward trend in Iran (226) and estimated stillbirth rates were 18 and 13 per 1,000 births in 1995 and 2009, respectively (227) Frequency of preterm delivery was reported between 9 and 17 % in different published studies in Iran (228-230). A hospital-based study reported that about 12% of infants had a birth weight of less than 2,500 grams in the south east of Iran (231). In a nationwide, comprehensive study, Rashidian et al. reported that 7.74% and 0.85% of live newborns in Iran had a birth weight of less than 2,500 and 1,500 grams, respectively (21).

1.5.1 Risk factors in Iran

In a cohort study in northern Iran, the overall age-adjusted prevalence rate of overweight and obesity (BMI >25.0) was 62% (232). The frequency of pregnant women with BMI >25.0 was 37.1% in one hospital-based study in north-west Iran (233). In a hospital-based study, the frequency of obesity (BMI >30.0) was 14%, maternal age older than 30 years was 19.1% and gestational diabetes was 4.8% (234). A hospital-based study in Shiraz in the center of Iran reported that more than 2% of women were older than 40 years at delivery time (126). The frequency of teenage pregnancy in Iran was reported between 5 and 16% in different studies (235-238). Despite good prenatal care, the prevalence of preterm delivery, intrauterine growth restriction and placenta previa in the south-east of Iran was higher in teenage pregnancies (236). The frequency of preeclampsia was reported as between 2 to 8% in different regions of Iran (239, 240). One study showed that preeclampsia was the cause of 14% of maternal mortality during and after pregnancy in 2005 in Iran (241). The prevalence of gestational diabetes in different countries ranges from 1 to 14% of all pregnancies, and it seems to vary between different regions of Iran, ranging from 1.3 to 10% (234, 242, 243).

The overall rate of consanguineous marriage in Iran was reported as being more than 38% (27% first cousin), ranging from 16% in the northern provinces to 47% in the eastern provinces, in a comprehensive study (244).

A nationwide study reported that 24.9% of Iranian couples have a history of primary infertility and 3.4% of them have suffered from this problem throughout their lives (245). The prevalence of iron deficiency and anemia among reproductive women in the Golestan province in the north of Iran was reported as 35% and 25% respectively (246).

A UNICEF report states that 97% and 80 % of Iranian females in the officially corresponding age group graduated from primary and secondary school, respectively (247).

The use of opioids or other recreational drugs has been associated with adverse pregnancy outcomes such as preterm birth. Opium (Poppy tears, Lachryma Papaveris, Theriac) has traditionally been used in southern Asia and middle-eastern countries such as Iran as a sedative and for pleasure (248, 249). Opium (opium poppy and derivatives of opium i.e. tincture, syrup, extract and opium powder) abuse is the most common illicit drug use in the rural part of the Golestan province, and is usually smoked (128). In the Golestan province in northern Iran, some women use opium even during pregnancy. However, there are no published data on the prevalence of opium use among pregnant women in Iran but opium use among women is not uncommon (232). In the Golestan province, the frequency of opium use (mainly smoking), based on self-reporting among women aged 40 to 75 years, was 8.1% (128).

1.6 AIMS AND OBJECTIVES

This project included four studies with different designs using prospectively collected information from pre-pregnancy between 2007 and 2010.

The principal aim of this population-based research project was to investigate possible associations between maternal characteristics and risk factors which were identified during pre-pregnancy or pregnancy visits with adverse pregnancy outcomes, using medical records in the rural part of the Golestan province, northern Iran. The purpose of these studies was to examine the relationship between different risk factors including local and rarely studied risk factors such as consanguineous marriage and opium use and adverse pregnancy outcomes such as stillbirth, preterm birth, and SGA in the rural part of the Golestan province.

Our secondary aims were to estimate the prevalence of adverse pregnancy outcomes in the study population. Moreover, we aimed to evaluate the prevalence of the risk factors perceived during pre-pregnancy or antenatal visits including teenage pregnancy, short stature, maternal underweight and overweight, positive history of infertility and previous pregnancy complications, maternal blood hemoglobin concentration during pregnancy, maternal smoking and low social status.

2   METHODS

2.1   STUDY POPULATIONS

This project was conducted in a rural part of the Golestan province between 2007 and 2010. The size of this area is approximately 20,000 km², with a population of 1.7 million, half of whom live in rural areas. The Golestan province is one of the 31 provinces of Iran located in the northeastern part of the country, south of the Caspian Sea. It is limited northwards by Turkmenistan, southwards by the Semnan province, eastwards by the Northern Khorasan province, and westwards by the province of Mazandaran. The province (2009) includes 13 districts (consisting of one city with several surrounding villages), 29 cities, 60 sub-districts and 871 villages. Gorgan city is the capital and the biggest city in the province.

Figure 2-1: The Golestan province and its geographic subdivisions.
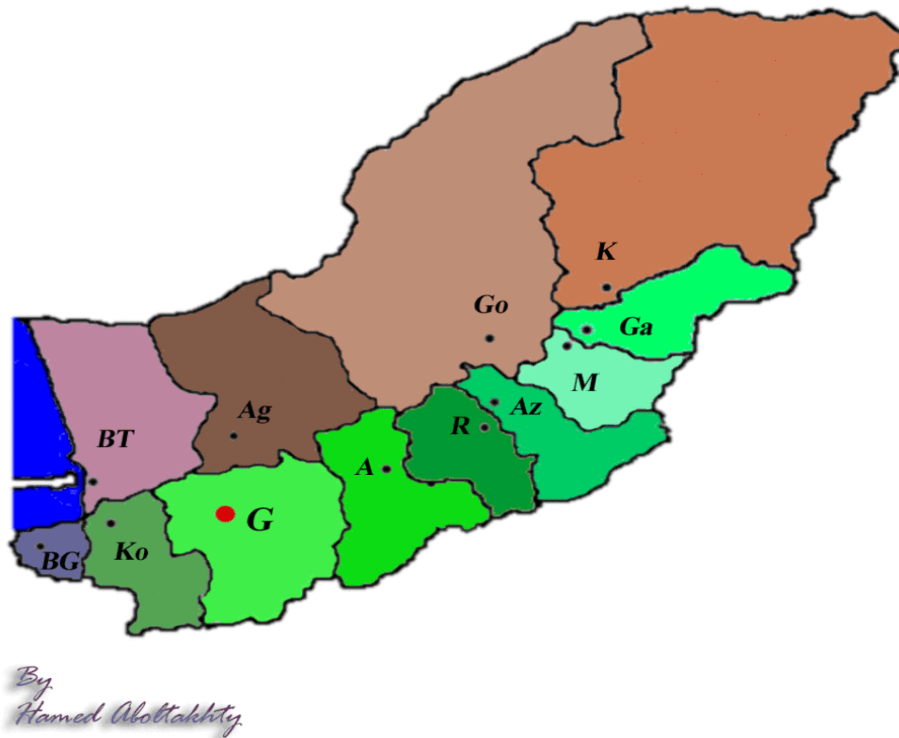
The Golestan province has been divided into three areas – mountains, foothills and plains – and it has both a mountainous (Mediterranean) climate and a semi-arid climate with different rainfall profiles (Figure 2-1) (250) which in turn has a substantial impact on agriculture and agricultural industries which are the major source of revenue in the province (251).

2.2 EXPOSURES AND OUTCOMES

2.2.1 Exposures

In the first study, the main exposure was parental consanguinity which is culturally accepted in the rural parts of the province. Marriage between first cousins is registered as a first cousin marriage in the health files and considered to be consanguineous marriage. People living in the small villages of the Golestan province are mostly related to each other; thus second and third cousin marriages are much more common than first cousin marriage.

In the second study, we investigated the associations between maternal blood hemoglobin concentration and dilution during pregnancy and the risk of stillbirth. Blood tests were taken during the year before pregnancy and twice during pregnancy (at 6 to 10 gestational weeks and at 26 to 30 weeks), based on "Antenatal Care" protocols from the Iranian primary healthcare system. The blood laboratory analyses included complete blood count, measuring hemoglobin and other blood chemical biomarkers. We calculated hemoglobin dilution during pregnancy as the difference in maternal blood hemoglobin concentration between pre-pregnancy and last blood sampling during pregnancy divided by weeks of gestational age at the last blood sampling. We also estimated hemoglobin dilution during the second trimester of pregnancy as the difference between blood hemoglobin concentration at the first and last measurement during pregnancy divided by the time period (completed weeks) between the two measurements (mean change in hemoglobin concentration per gestational week).

In the third and fourth studies, we focused on the association between maternal opium use during pregnancy and reproductive outcomes. The exposed mothers were defined as randomly selected pregnant women with a self-reported history of using any variety of opiates during the index pregnancy. The unexposed group included women who did not have a positive history of opium use before or during pregnancy. Opium is obtained from the unripe seed capsules of the poppy plant, Papaver somniferum, which contains a number of alkaloids, including Morphine (10% of opium), Codeine (0.5%), Thebaine (0.2%), Papaverine (1%), and Noscapine (6%) (252). There is a tradition of opium use in some Middle East and south Asian countries, such as Iran, Afghanistan, Pakistan, India, and China (249, 253). It is used for pleasure, as a sedative, provides symptomatic relief for acute or chronic pain, and for treatment of premature ejaculation (254).

2.2.2 Outcomes

Stillbirth was the outcome of the first and second studies. We defined stillbirth as delivery of a baby without any vital signs at 28 gestational weeks or later. We investigated the risk of preterm birth in the third study. Preterm birth was defined as a live birth before 37 completed gestational weeks. Finally, in the fourth study, we examined the risk of fetal growth restriction, including a low birth weight for gestational age (SGA), small head circumference, and short crown-heel length. In this study, SGA was defined as a birth weight below the 10th percentile for gestational age, based on a gestational age-specific global reference for birth weight in each week of gestational age (197). A short crown-heel length and a small head circumference was

below the 5th percentile curve of unexposed and term pregnancies; short crown-heel length was < 47 cm and small head circumference was <33 cm (194).

2.3 STUDY SETTING

We used prospectively collected information from medical records produced at pre-pregnancy and antenatal visits by Iran's public health organization. Iran's public (primary) healthcare system is organized through a hierarchical system of 'health houses' (in rural areas, managed by fulltime health workers "Behvarz"), rural and district health centers (giving health services by at least one medical doctor, nurse and midwife, and public health technician), local hospitals and university hospitals. A Behvarz is a highly respected person who lives in the village and has adequate personal knowledge about the inhabitants and at least two years education from a medical school.
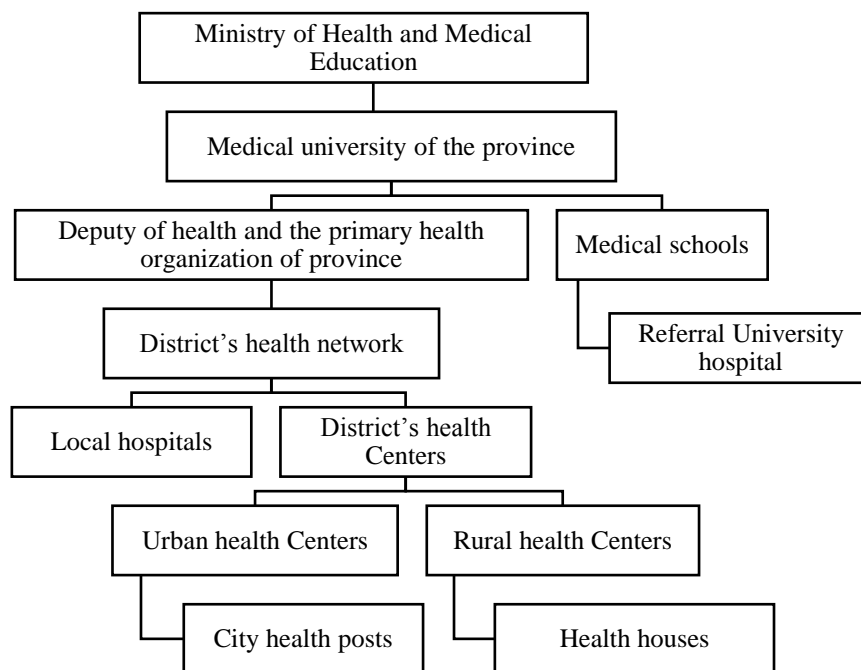
Figure 2-2: Structural hierarchy of Iran's public health organization.

In rural parts of Iran, each family is registered at a local health house which acts as an initial point of primary healthcare service. Each village has at least one health house that serves several hundred families (1,500 people on average). Around five local health houses fall under the authority of a more specialized local health clinic, which in some cases is accompanied by a maternity center. This is likely to improve the completeness and quality of reported information, even where it may be sensitive, such as for opium use. Since the early 1980s, complete information on almost all pregnancies has been collected in the rural areas of Iran.

Based on the "Iranian National Antenatal Care" protocols in the primary healthcare system, virtually all pregnant women receive modern antenatal and obstetric care. The majority, 77%, of young married women use contraception and visit the "Behvarz" when they want to stop using contraception and plan a pregnancy and inform the local health worker (21). Consequently, they have a pre-pregnancy visit followed by a series of antenatal check-ups by a university-trained midwife or general practitioner. Laboratory testing (included complete blood count test, blood biochemistry profile and urine analysis) was performed during the year before pregnancy and twice during pregnancy: at the first trimester and at the end of the second trimester of pregnancy (at 6 to 10 and at 26 to 30 gestational weeks, respectively). Mean gestational ages, pregnancy-related information, results of ultrasound and laboratory examinations are recorded in health forms. All pregnant women also receive folate and iron supplements from before pregnancy. Almost all deliveries take place in hospitals. The recorded information on pregnancy outcomes and delivery are sent to the health houses by hospitals.

Pilot study: We also performed a pilot study on extracted data from 86 randomly selected pre-pregnancy, pregnancy and delivery files from villages in the Golestan province. The information in the forms from the archives was of high quality and the variables of interest appeared to be accurate with very little missing information. Based on the experience from the pilot study, we constructed a computer-based data extraction form, fulfilling both local needs for data collection and our analytical needs. This work was a joint effort of researchers in Iran and Sweden, who were guided by a database manager.

2.3.1 Data collection

Information on maternal and pregnancy characteristics were collected from medical records by midwifes who work as healthcare providers for pregnant women at the health centers. Data were abstracted from pre-pregnancy, pregnancy and delivery records, and the information was computerized by ten specially trained medical students. Each file, including information on the mother, infant, and spouse, received a unique code at the time of data collection, which made it possible to analyze the data anonymously.

As a quality control, we collected and computerized 10% of the data a second time. The variables that had more than 5% mismatches were recollected and the data re-entered for all study subjects. If the data for a health center had more than 5% mismatches, all data were recollected and re-entered for the center. For example, date of last menstrual period was recollected and re-entered for three health centers.

For the first and second studies, all identified singleton stillbirths in rural areas of the Golestan province from 2007 to 2010 (N=501) were selected as cases. Thereafter, we determined each region as a block and calculated block sample size based on the population growth rate of the region. All pregnancies during the study period in the region were listed and numbered based on date of delivery. So as to have at least five controls per case, we randomly selected 3,000 pregnancies by using random digits created by a computer. Finally, after

excluding births before 28 gestational weeks, multiple births and stillbirths, the control group included 2,888 live singleton births with a gestational age of at least 28 completed weeks.

For Study III and Study IV, the exposed groups included randomly selected women with a self-reported history of using any variety of opiates during the index pregnancy. The unexposed group included women who did not have any positive history of opium use before or during pregnancy. We randomly selected a total of 920 opium users during pregnancy ("exposed" women) and 920 non-opium users ("unexposed" women) using stratified randomization sampling. Exposed and unexposed pregnancies were selected by using computer-created random digits. Women exposed and unexposed to opium during pregnancy were frequency matched by residential area (village). We excluded 10 exposed and 11 unexposed women due to multiple births, miscarriages and stillbirths. We also excluded 18 (exposed) mothers who gave up using opium in early pregnancy, two mothers who were unexposed to opium but exposed to tobacco, and mothers who used alcohol during pregnancy (2 unexposed and 5 exposed mothers). Finally, our study included 887 opium users (of whom 133 also smoked tobacco and 633 only used opium) and 905 non-opium users (all non-smokers) with live births. All studies were restricted to singleton pregnancies.

2.4 STUDY DESIGN

We conducted four population-based studies with different designs to study risk factors (including novel and rarely studied factors, such as parental consanguinity and opium use) for adverse pregnancy outcomes (stillbirth, preterm birth and fetal growth restriction) using prospectively collected information from pre-pregnancy.

In these studies, maternal Body Mass Index (BMI) was calculated based on maternal body weight and height which were measured at pre-pregnancy visits (weight in kilograms divided by height in meters squared). Gestational age was calculated based on date of the first day of the last menstrual period and date of delivery. Preterm delivery was defined as a delivery before 37 completed gestational weeks. Information on socioeconomic circumstances was based on husband's occupation, categorized as unskilled manual worker, skilled manual worker, self-employed, farmer, other occupation, and unemployed (Table 2-1).

Table 2-1. Some examples of occupations in each category.

Unskilled manual worker	Simple worker, seasonal farm worker
Skilled manual worker	Car craftsman, carpenter, clerk, driver
Self-employed	Shop owner
Farmer	Land owner
Other occupation	Student

2.4.1 Design of study on consanguinity

We investigated associations between parental consanguinity, maternal pre-pregnancy characteristics, and risk of stillbirth in a population-based case-control study. Therefore, we included cases and controls who had a record of pre-pregnancy visits. Due to the small number of exposed individuals, it was not possible to estimate the association for smoking (no smokers among cases and 1.2% among controls), opium use (1.8% and 2.4% respectively), or maternal chronic diseases (1.1% and 1.5%, respectively). To reduce confounding and increase internal validity, we excluded them from the main analysis. Our aim in this study was to investigate association between maternal pre-pregnancy characteristics and risk of stillbirth. Therefore, we included 283 cases and 2,120 controls from all stillbirths (n=501) and 2,918 randomly selected singleton live births who had received a pre-pregnancy visit in this study. Finally, from all stillbirths (n=501) and 2,888 randomly selected singleton live births, we included 283 cases and 2,120 controls into the study.

In this study, parental consanguinity was defined as a marriage between first cousins, as recorded in the health files. In Iran, particularly in villages, marriage between relatives is culturally accepted and the overall rate of first cousin marriage is relatively high (255). Moreover, the rest of population may include second or third cousin couples. A self-reported previous miscarriage was defined as a miscarriage before onset of the index pregnancy. Infertility was defined as the inability to achieve pregnancy naturally within one year. A preterm birth was defined as a live birth before 37 completed weeks of pregnancy. SGA was defined as a birth weight below the 10th percentile (in the control group) for gestational age (week) and sex and was used as a proxy for fetal growth restriction.

2.4.2 Design of study on hemoglobin concentration

In this population-based case control study, we evaluated the association of maternal hemoglobin concentration and maternal hemoglobin dilution before and during pregnancy and risk of stillbirth. We selected all (n=501) singleton stillbirths and excluded 6 stillbirths without any maternal blood hemoglobin concentration records during pregnancy as cases. We randomly selected 2,888 live singleton births with a gestational age of at least 28 completed weeks as controls.

All pregnant women undergo laboratory testing during the year before pregnancy and twice during pregnancy. In addition, all anemic women are treated with a therapeutic dose of iron and all pregnant women are given iron supplements after the 16th gestational week of pregnancy. The mean gestational ages for the first and second hemoglobin concentration measurements were 9 weeks and 28 weeks for both cases and controls. We estimated hemoglobin dilution during the second trimester of pregnancy as the difference between blood hemoglobin concentration at the first and last measurement during pregnancy divided by the time period (completed weeks) between the two measurements (mean change in hemoglobin concentration per gestational week). Observations with a time interval of less than three weeks between two hemoglobin measurements were excluded from the analysis of hemoglobin

dilution (n=3). We also estimated hemoglobin dilution during pregnancy, defined as the difference between the pre-pregnancy and the last pregnancy measurement of blood hemoglobin concentration divided by gestational age (in completed weeks) at the last measurement among all cases (n=158) and controls (n=1,225) who had a recorded blood hemoglobin concentration during the year before pregnancy.
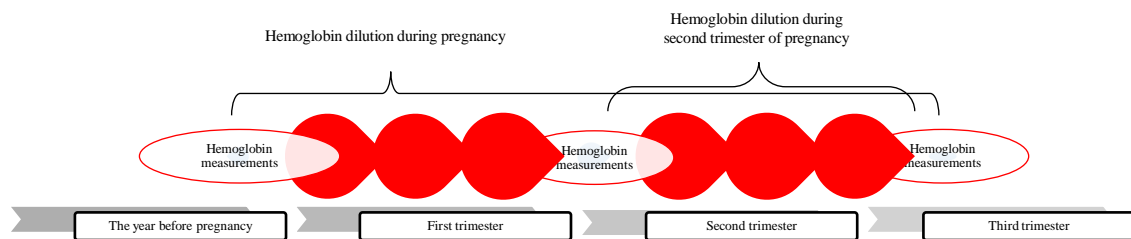

Figure 2-3: Maternal hemoglobin measurements before and during pregnancy.

Maternal blood pressure was measured before pregnancy, at least 8 times during pregnancy, and after delivery. Hypertension was defined as a measured systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 during each trimester of pregnancy. Self-reported information on current or previous smoking and opium use was also collected. The measurement of socioeconomic circumstances was based on husband's occupation (Table 2-1).

2.4.3 Design of studies on maternal opium use

We performed two population-based cohort studies investigating association between maternal opium use during pregnancy and risk of adverse pregnancy outcomes. Exposure was defined as self-reported history of using any variety of opiates during the index pregnancy. We included 887 opium users and 905 non-opium users in the analysis. The outcomes of the studies comprised preterm birth (Study III), short crown-heel length, small head circumference, and SGA (Study IV) which was defined as a birth weight below the 10th percentile for gestational age, based on a sex-specific global reference for birth weight (197). We considered crown-heel length and head (Occipito-frontal) circumference below the 5th percentile curve of unexposed and term pregnancies as short crown-heel length (shorter than 47 cm) and small head circumference (smaller than 33 cm), respectively (194).

2.5 STATISTICAL METHODS

Univariate and multivariate logistic regression models were used for estimating Odds Ratios (OR) and 95% Confidence Intervals (CI) of the associations between exposures and stillbirth in the first and second case-control studies. The multivariate models were adjusted for potential confounding factors (see sections 2.5.1 and 2.5.2 below for details). As the outcome is rare in both exposed and unexposed mothers, the Odds Ratio approximates the Risk Ratio.

Univariate and multivariate logistic regression models were also used to analyze the data for the third and fourth cohort studies (see sections 2.5.3 and 2.5.4 below for details). The multiple imputations method was used to deal with missing data and provide estimates for the missing values of father's occupation (7 among cases and 45 among controls) and mother's height (70 among cases and 64 in controls). The MI procedure (SAS software) with five imputations was used for this purpose. In the cohort studies, the multiple imputations method was also used to impute data for missing values of maternal age (6 among mothers unexposed to opium and 5 among exposed mothers), infant sex (15 among mothers unexposed to opium and 10 among exposed mothers), husband's occupation (4 among unexposed and 9 among exposed), and mother's height (39 among unexposed and 17 among exposed) (256). To investigate if missing data had a major impact on the results, we also performed a sensitivity analysis by restricting the analysis to observations without any missing data. SAS software version 9.3 was used for analyzing the data.

2.5.1 Study I: Maternal pre-pregnancy characteristics and risk of stillbirth

The multivariate models were adjusted for maternal age, BMI, height, parity, history of miscarriage, history of infertility, region of residence and husband's occupation. We also performed an analysis stratified by preterm and term birth because of possible differences in causes of stillbirth in relation to gestational age. We also analyzed term stillbirths stratified into SGA and non-SGA stillbirths.

We estimated ORs for established risk factors of stillbirth, including maternal age (≤19, 20-24, 25-29, 30-34 and ≥35 years), BMI (<18.5, 18.5 to <25, 25 to <30, 30 to <35 and ≥35), and mother's height (<150, 150-154, 155-159, 160-164, and ≥165 cm), parity (nulliparous, 1-2 and ≥3 previous births), and history of miscarriage (yes, no) as categorical variables.

Restricting the study to those who had data from pre-pregnancy visits may potentially cause selection bias. Therefore, we performed a sensitivity analysis using information of all singleton stillbirths (N=501) and live births (N=2,918). We estimated the association for some variables that were available for all mothers (with or without a pre-pregnancy visit), including maternal age, maternal BMI, height, age, parity, and, history of miscarriage and infertility.

2.5.2 Study II: Maternal hemoglobin concentration and risk of stillbirth

We used univariate and multivariate logistic regression models to estimate ORs and 95% CIs for the associations between maternal hemoglobin concentration and hemoglobin dilution with stillbirth risk. The multivariate models were adjusted for maternal age, pre-pregnancy BMI, height, gestational age at the first hemoglobin measurement, parity (0, 1-2, >2), smoking status, region of residence, and husband's occupation. We also investigated possible non-linear effects of age and BMI by introducing age squared and BMI squared into the adjusted models. However, these variables had no notable effects and were therefore not included in the final models.

This study examined associations between maternal hemoglobin concentration before pregnancy, in the first trimester, and in the second trimester of pregnancy with respect to stillbirth risk. We estimated the risk of stillbirth using both maternal hemoglobin concentration as a continuous variable (gram per liter [g/l]), and as a four-category measure (<110, 110-120, 120-139, and ≥140 g/l). We also calculated ORs for stillbirth associated with the average hemoglobin dilution in each gestational week during pregnancy (>0.78, 0.78-0.01, and ≤ 0.00 g/l), and also during the second trimester of pregnancy. We categorized hemoglobin dilution values based on tertiles of the distribution in the control group into three categories (>0.69, 0.69-0.01, and ≤0.00). Information on preeclampsia or eclampsia, a possible confounding factor, was not available.

We also performed a sensitivity analysis excluding all subjects with a record of hypertension during pregnancy to tackle concern about the possible confounding effect of pregnancy-induced hypertensive diseases which are related to both hemoglobin concentration during pregnancy and stillbirth risk (2).

2.5.3   Study III: Maternal opium use and risk of preterm birth

We used univariate and multivariate logistic regression models to estimate ORs and 95% CIs for the association between maternal opium use and risk of preterm birth. The multivariate models were adjusted for place of residence, maternal age, BMI, height, parity, husband's occupation, and infant sex (model A). Due to a lack of specific information on spontaneous and medically indicated preterm delivery, we stratified preterm delivery into vaginal preterm delivery (predominantly including spontaneous preterm deliveries) and caesarean section preterm delivery (including both medically indicated preterm deliveries and emergency caesarean deliveries). The main indications for elective caesarean delivery are maternal (usually due to hypertensive diseases) or fetal concern (due to fetal growth restriction or fetal asphyxia). In an additional model of opium use and preterm delivery, we therefore also adjusted for hypertension and birth of an SGA infant (model B). Additional stratified analyses were performed to investigate the risks of preterm delivery among opium-using mothers who smoked or did not smoke tobacco during pregnancy.

2.5.4   Study IV: Maternal opium use and infant size at birth

We estimated Odds Ratios (ORs) and 95% Confidence Intervals (CIs) of the associations between opium use during pregnancy and SGA, short birth length and small head circumference using univariate and multivariate logistic regression models. The models were adjusted for potential confounding factors, including place of residence, maternal age, height, BMI, husband's occupation and infant sex.

Due to insufficient data, we could not construct gestational age specific curves for birth length and head circumference. Analyses of birth length and head circumference were therefore restricted to term births (>37 weeks), where we also adjusted for gestational age (in weeks). Stratified analyses were performed to investigate the risks of growth restriction among opium-using mothers who smoked or did not smoke tobacco during pregnancy.

2.6 ETHICAL CONSIDERATIONS

The project included four epidemiological observational studies using already recorded data and there was no intervention which could be harmful to study subjects. All patient data were anonymous which ensured the full data protection of patients. We identified all study participants in the rural part of the Golestan province, using the records kept at the District Health Centers. Patients were not contacted at any phase of the investigation. Each file, including information on the mother, children and spouse, received a unique code at the time of data collection (extracting data from family health files and entering the data in writing on paper data collecting forms). The codes were used during data entry into the access table and analysis which made it possible to analyze the data anonymously. Only the research team had access to the data and no one will be able to trace results back to individual persons. Only aggregated data were analyzed and presented in the final results, which makes it impossible to identify individuals.

We applied for ethical permission from the ethical committee at Golestan University of Medical Sciences, Gorgan, Iran and the regional ethical committee at Karolinska Institutet before the start of the project. Both committees approved the study (Golestan University of Medical Sciences, Iran (35/2633-p/g, 17 January 2011) and Karolinska Institutet, Sweden (2011/1657-31/3)).

3 RESULTS

In summary, the main findings of the project were.

- Study I: Consanguineous marriage is associated with an increased risk of stillbirth. Findings for other maternal risk factors for stillbirth including maternal age, BMI, history of infertility, positive history of pregnancy complications and adverse outcomes in rural Iran are consistent with previously reported findings from high-income countries.
- Study II: Hemoglobin concentration before pregnancy is not associated with stillbirth risk. High hemoglobin levels at the end of the first and second trimesters of pregnancy and absence of hemoglobin dilution during pregnancy are associated with stillbirth risk and can be considered as indicators of a high-risk pregnancy.
- Study III: Opium use during pregnancy among non-tobacco smokers is associated with an increased risk of preterm caesarean delivery, which may indicate an increased risk of a compromised fetus before or during labor. Women who both use opium and smoke during pregnancy have an increased risk of preterm vaginal delivery, indicating an increased risk of spontaneous preterm delivery.
- Study IV: Maternal opium use during pregnancy is associated with an increased risk of Small for Gestational Age at birth and a higher risk of short crown-heel length and small head circumference among term neonates.

3.1 STUDY I

Pre-pregnancy characteristics of cases and controls stratified by the main exposure of the study, consanguineous marriage, are demonstrated in Table 3-1.

Table 3-1. Characteristics of the cases and controls by consanguineous marriage.

	Cases		Controls	
	Consanguineous marriage	Non Consanguineous marriage	Consanguineous marriage	Non Consanguineous marriage
	n (%)	n (%)	n (%)	n (%)
All pregnancies	55 (100)	228 (100)	283 (100)	1805 (100)
Mother's age, year				
≤19	10 (18.2)	38 (16.7)	47 (16.6)	231 (12.8)
20-24	17 (30.9)	51 (22.4)	84 (29.7)	584 (32.3)
25-29	16 (29.1)	59 (25.9)	70 (24.7)	486 (26.9)
30-34	11 (20.0)	37 (16.2)	57 (20.1)	354 (19.6)
≥35	1 (1.8)	43 (18.9)	25 (8.8)	150 (8.3)
Mean (SD)	25.7 (5.7)	25.9 (5.7)	25.7 (5.8)	25.9 (5.7)
Median (Range)	25 (14-41)	25 (13-46)	25 (14-41)	25 (13-46)
Body Mass Index				
<18.5	5 (10.9)	16 (9.6)	16 (5.7)	137 (7.8)
18.5-24.9	26 (56.5)	66 (39.5)	155 (55.6)	993 (56.8)
25-29.9	11 (23.9)	48 (28.7)	77 (27.6)	428 (24.5)
30-34.9	3 (6.5)	27 (16.2)	24 (8.6)	150 (8.6)
≥35	1 (2.2)	10 (6.0)	7 (2.5)	39 (2.2)
Mother's height, cm				
<150	7 (15.2)	15 (9.0)	18 (6.4)	118 (6.7)
150-154	11 (23.9)	40 (23.5)	59 (21.1)	396 (22.7)
155-159	18 (39.1)	69 (41.3)	105 (37.6)	638 (36.5)
160-164	6 (13.1)	21 (12.6)	47 (16.8)	338 (19.3)
≥165	4 (8.7)	22 (13.2)	50 (17.9)	257 (14.7)
Mean (SD)	158.9 (6.0)	158.5 (5.7)	159.0 (6.0)	158.5 (5.7)
Median (Range)	160 (141-185)	158 (139-199)	160 (141-185)	158 (139-199)
Parity				
Nulliparous	36 (65.4)	107 (46.9)	121 (42.7)	839 (46.5)
1-2	18 (32.7)	100 (43.9)	141 (49.8)	863 (47.8)
≥3	1 (1.8)	21 (9.2)	21 (7.4)	103 (5.7)
History of miscarriage				
No	49 (89.1)	176 (77.2)	238 (84.1)	1549 (85.8)
Yes	6 (10.9)	52 (22.8)	45 (15.9)	256 (14.2)
History of infertility				
No	53 (96.4)	218 (95.6)	275 (97.2)	1772 (98.2)
Yes	2 (3.6)	10 (4.4)	8 (2.8)	33 (1.8)
Father's occupation				
Unskilled manual	21 (39.6)	91 (41.7)	130 (47.4)	822 (46.6)
Skilled manual	7 (13.2)	24 (11.0)	24 (8.8)	171 (9.7)
Self-employed	8 (15.1)	42 (19.3)	25 (9.1)	222 (12.6)
Farmer	8 (15.1)	35 (16.1)	69 (24.4)	306 (17.4)
Other occupation	9 (17.0)	16 (7.3)	26 (9.5)	181 (10.3)
Unemployed	0 (0.0)	10 (4.6)	2 (0.7)	60 (3.4)

Among all regions in the Golestan province, a crude analysis showed that, compared with Gorgan, the risk of stillbirth was higher in the rural parts of Gonbad, Aliabad, Galikesh and Gomishan. However, these differences were not statistically significant after adjusting for maternal BMI, age and husband's occupation.

Consanguinity, the main exposure of the study, was associated with a 50% increased risk of stillbirth in the adjusted analysis (OR: 1.53, 95% CI; 1.10-214). For further investigation, we stratified the analysis of consanguinity into term or preterm stillbirths and among term stillbirths into Small for Gestational Age and non-Small for Gestational Age stillbirths. In the analysis of preterm and term stillbirths, we found that consanguinity was associated with a more than twofold increased risk for preterm stillbirth (OR: 2.43, 95% CI [1.46-4.04]). Among term deliveries (68.2% and 89.7% of cases and controls, respectively), the OR (95% CI) for the association of consanguinity with SGA stillbirth and with non-SGA stillbirth was 1.40 (0.72-2.72) and 1.01 (0.54-1.88), respectively.

Table 3-2. Maternal pre-pregnancy characteristics and risk of stillbirth in Golestan, Iran.

	Cases	Controls	Odds Ratio (95% CI)	
	n (%)	n (%)	Crude	Adjusted[1]
Consanguineous marriage				
No	228 (80.6)	1,805 (86.4)	Reference	
Yes	55 (19.4)	283 (13.6)	1.54 (1.12-2.12)	1.53 (1.10-2.14)
Mother's age, year				
≤19	48 (17.0)	278 (13.3)	1.70 (1.14-2.52)	1.74 (1.15-2.62)
20-24	68 (24.0)	668 (32.0)	Reference	
25-29	75 (26.5)	556 (26.6)	1.32 (0.94-1.87)	1.26 (0.87-1.83)
30-34	48 (17.0)	411 (19.7)	1.15 (0.78-1.69)	1.09 (0.70-1.69)
≥35	44 (15.5)	175 (8.4)	2.47 (1.63-3.74)	2.61 (1.61-4.22)
Body Mass Index				
<18.5	21 (9.9)	153 (7.5)	1.55 (0.96-2.48)	1.74 (1.05-2.87)
18.5 to <25	92 (43.2)	1,148 (56.7)	Reference	
25 to <30	59 (27.7)	505 (24.9)	1.46 (1.07-2.00)	1.31 (0.94-1.82)
30 to <35	30 (14.1)	174 (8.6)	1.95 (1.27-3.01)	1.75 (1.12-2.75)
≥35	11 (5.2)	46 (2.3)	2.81 (1.51-5.20)	2.29 (1.18-4.44)
Mother's height, cm				
<150	22 (10.3)	136 (6.7)	1.37 (0.84-2.23)	1.28 (0.77-2.13)
150-154	51 (23.9)	455 (22.5)	0.98 (0.70-1.37)	1.02 (0.72-1.44)
155-159	87 (40.8)	743 (36.7)	Reference	
160-164	27 (12.7)	385 (19.0)	0.82 (0.57-1.19)	0.81 (0.55-1.19)
≥165	26 (12.2)	307 (15.1)	0.77 (0.49-1.22)	0.84 (0.52-1.34)
Parity				
0	143 (50.5)	960 (46.0)	1.27 (0.98-1.64)	1.48 (1.09-2.00)
1-2	118 (40.7)	1,004 (48.1)	Reference	
≥3	22 (7.8)	124 (5.9)	1.51 (0.92-2.47)	1.26 (0.74-2.14)
History of miscarriage				
No	225 (79.5)	1,787 (85.6)	Reference	
Yes	58 (20.5)	301 (14.4)	1.53 (1.12-2.09)	1.41 (1.01-1.98)
History of infertility				
No	271 (95.8)	2,047 (98.0)	Reference	
Yes	12 (4.2)	41 (2.1)	2.21 (1.15-4.26)	2.33 (1.18-4.60)
Father's occupation				
Unskilled manual	112 (41.3)	952 (46.8)	Reference	
Skilled manual	31 (11.4)	195 (9.6)	1.35 (0.88-2.07)	1.12 (0.59-2.12)
Self-employed	50 (18.4)	247 (12.1)	1.70 (1.18-2.44)	1.51 (0.86-2.66)
Farmer	43 (15.9)	373 (18.3)	0.99 (0.68-1.43)	0.90 (0.52-1.56)
Other occupation	25 (9.2)	207 (10.2)	1.06 (0.68-1.67)	0.78 (0.38-1.58)
Unemployed	10 (3.7)	62 (3.0)	1.47 (0.74-2.93)	2.17 (0.89-5.30)
Missing	12	52		

[1]Adjusted for all variables in the table and place of residence.

Table 3-2 presents the associations between maternal pre-pregnancy characteristics and risk of stillbirth. This study showed that teenage pregnancy and especially mothers who were 35 years or older had an increased risk of stillbirth compared with mothers aged 20 to 24 years. Maternal underweight (BMI<18.5), mild obesity (BMI 30.0 to <35), and especially mothers with severe obesity (BMI >35) had an increased risk of stillbirth. Nulliparity, a history of infertility, and a positive history of miscarriage were also associated with increased stillbirth risks.

We also investigated the association for some risk factors available among all singleton stillbirths (n=501) and 2,918 randomly selected live birth pregnancies for sensitivity analysis. There were no notable differences between the two analyses (with pre-pregnancy visit or all pregnancies). Among all pregnancies, both a history of miscarriage and a history of infertility were associated with increased risks of stillbirth (OR=1.41, 95% CI [1.08-1.84] and OR=2.40, 95% CI [1.40-4.13], respectively). Compared with 20 to 24-year-old mothers, the risk of stillbirth for younger mothers and those who were 35 years or older was OR=1.34, 95% CI [0.95-1.89] and OR=2.64, 95% CI [1.79-3.89], respectively (data not shown in table).

The associations of characteristics of previous pregnancies with risk of stillbirth among parous women are shown in Table 3-3. This study showed that a positive history of preeclampsia was associated with an almost fourfold increased stillbirth risk. A history of preterm delivery was associated with a more than fourfold increase in risk and a previous stillbirth was associated with a more than tenfold increase in risk.

Table 3-3. Odds Ratio (OR) and 95% Confidence Interval (CI) for the associations between previous obstetric history and stillbirth in parous mothers.

	Cases	Controls	Odds Ratio (95% CI)	
	n (%)	n (%)	Crude	Adjusted[1]
History of neonatal death				
No	131 (93.6)	1,100 (97.5)	Reference	
Yes	9 (6.4)	28 (2.5)	2.66 (1.18-6.00)	2.31 (0.98-5.44)
History of preeclampsia				
No	128 (91.4)	1,099 (97.4)	Reference	
Yes	12 (8.6)	29 (2.5)	3.35 (1.63-6.87)	3.82 (1.79-8.18)
History of preterm delivery				
No	124 (88.6)	1,100 (97.5)	Reference	
Yes	16 (11.4)	28 (2.5)	5.07 (2.67-9.63)	4.66 (2.29-9.45)
History of stillbirth				
No	105 (75.0)	1,092 (96.8)	Reference	
Yes	35 (25.0)	36 (3.2)	10.11 (6.09-16.78)	10.67 (6.05-18.82)

[1]Adjusted for all maternal characteristics (provided in Table 4-3)

3.2   STUDY II

This study showed that maternal hemoglobin concentration before pregnancy was not associated with a risk of stillbirth. Compared with normal maternal hemoglobin concentrations (110-120 g/l) measured at the end of the first trimester, high hemoglobin values (≥140 g/l) were associated with a 36% increased risk of stillbirth. Compared with normal hemoglobin values at the second trimester of pregnancy, high maternal hemoglobin values were associated with a more than twofold increased risk of stillbirth, and low hemoglobin concentration (≤ 110 g/l) was associated with a reduced stillbirth risk. Associations of maternal hemoglobin concentrations with risk of stillbirth are presented in Table 3-4.

Table 3-4. Hemoglobin concentration and the risk of stillbirth

	Cases	Controls	Odds Ratio (95% Confidence Interval)	
	n (%)	n (%)	Crude	Adjusted[1]
Hemoglobin concentration before pregnancy (g/l)				
< 110	4 (2.5)	31 (2.5)	1.04 (0.36-3.04)	1.23 (0.39-3.84)
110-120	72 (45.6)	582 (47.5)	Reference	
121-139	49 (31.0)	360 (29.4)	1.10 (0.75-1.61)	0.97 (0.64-1.47)
≥140	33 (20.9)	252 (21.0)	1.06 (0.68-1.64)	0.83 (0.52-1.34)
Continuous	158 (100)	1,225 (100)	1.00 (0.99-1.02)	1.00 (0.98-1.01)
Hemoglobin concentration at first trimester (g/l)				
< 110	26 (5.3)	181 (6.5)	0.91 (0.59-1.40)	0.87 (0.55-1.37)
110-120	223 (46.1)	1,411 (50.5)	Reference	
121-139	152 (31.4)	834 (30.0)	1.45 (0.92-1.44)	1.18 (0.94-1.49)
≥140	83 (17.1)	366 (13.1)	1.43 (1.09-1.89)	1.36 (1.01-1.81)
Continuous	484 (100)	2,792 (100)	1.01 (1.00-1.02)	1.01 (1.00-1.02)
Hemoglobin concentration at end of second trimester(g/l)				
< 110	37 (14.0)	523 (21.2)	0.64 (0.44-0.92)	0.63 (0.43-0.92)
110-120	180 (65.2)	1,618 (65.6)	Reference	
121-139	40 (14.4)	268 (10.9)	1.34 (0.93-1.93)	1.19 (0.81-1.74)
≥140	18 (6.4)	59 (2.4)	2.74 (1.58-4.75)	2.31 (1.30-4.10)
Continuous	275 (100)	2,468 (100)	1.03 (1.02-1.04)	1.03 (1.01-1.04)

[1]Adjusted for maternal age, height, BMI, parity, smoking status, husband's occupation, place of residence and gestational age at hemoglobin measurement.

We also investigated the associations between maternal hemoglobin concentrations and risk of stillbirth stratified by gestational age (preterm and term stillbirth), which had no notable differences in the results.

During the second trimester of pregnancy, mothers with a decreased hemoglobin concentration had a reduced risk of stillbirth compared with those who did not have any change in hemoglobin concentration (Table 3-5). We also estimated hemoglobin dilution during pregnancy (from before pregnancy to last measurement during pregnancy) where information on pre-pregnancy hemoglobin concentration was available. Mothers with a decreased hemoglobin concentration during pregnancy had a reduced risk of stillbirth compared with those who did not have any change in hemoglobin concentration. We also found a dose-

response association between hemoglobin dilution and risk of stillbirth, both in the analysis of the second trimester and in the analysis of pregnancy.

Table 3-5. Hemoglobin dilution and the risk of stillbirth

	Cases	Controls	Odds Ratio (95% Confidence Interval)	
	n (%)	n (%)	Crude	Adjusted[1]
Hemoglobin dilution during second trimester of pregnancy (g/l)				
> 0.78	70 (26.7)	765 (33.8)	0.57 (0.42-0.78)	0.54 (0.39-0.74)
0.78-0.01	73 (27.9)	750 (33.2)	0.61 (0.45-0.83)	0.62 (0.45-0.85)
0.00 ≤	119 (45.4)	745 (33.0)	Reference	
P for trend				<0.0001
Continuous	262 (100)	2,260 (100)	0.76 (0.63-0.92)	0.75 (0.62-0.90)
Hemoglobin dilution during pregnancy (g/l)				
> 0.69	31 (20.0)	392 (33.1)	0.33 (0.21-0.51)	0.33 (0.21-0.52)
0.69-0.01	38 (24.5)	430 (36.3)	0.37 (0.25-0.56)	0.42 (0.27-0.66)
0.00 ≤	86 (55.5)	361 (30.5)	Reference	
P for trend				<0.0001
Continuous	155 (100)	1,183 (100)	0.58 (0.45-0.74)	0.61 (0.46-0.80)

[1]Adjusted for maternal age, height, BMI, parity, gestational age at first hemoglobin measurement, smoking status, husband's occupation, and place of residence.

The associations of average weekly blood hemoglobin concentration change with stillbirth risk stratified by term and preterm delivery are demonstrated in Table 3-6. There were no significant differences between risks for term and preterm stillbirth. We observed a statistically significant 25% risk reduction for an average of one g/l weekly change in hemoglobin during the second trimester among term stillbirths.

Table 3-6. Hemoglobin dilution and risks of preterm and term stillbirth

	Preterm stillbirth			Term stillbirth		
	Cases (n=81)	Controls (n=2,260)	Odds Ratio[1] (95% CI)	Cases (n=181)	Controls (n=2,105)	Odds Ratio[1] (95% CI)
	n (%)	n (%)		n (%)	n (%)	
Hemoglobin dilution during second trimester of pregnancy (g/l)						
> 0.78	22 (27.6)	765 (33.8)	0.49 (0.28-0.84)	48 (26.5)	716 (34.0)	0.55 (0.38-0.81)
0.78-0.01	20 (24.7)	750 (33.2)	0.50 (0.28-0.87)	53 (29.3)	701 (33.3)	0.67 (0.46-0.97)
0.00 ≤	39 (48.1)	745 (33.0)	Reference	80 (44.2)	688 (32.7)	Reference
P for trend			<0.01			<0.01
Continuous	81 (100)	2,260 (100)	0.75 (0.54-1.06)	181 (100)	2,105 (100)	0.75 (0.61-0.93)

[1]Adjusted for maternal age, height, BMI, parity, gestational age at first hemoglobin measurement, history of smoking, husband's occupation, and place or residence.

In the next step, we categorized term deliveries into SGA stillbirths and non-SGA stillbirths. We found a 40% reduced risk for SGA stillbirth for every g/l weekly hemoglobin dilution during the second trimester (OR= 0.59, 95% CI [0.36-0.97]). Hemoglobin dilution was

not associated with a reduced risk of non-SGA term stillbirth. Restricting analyses to observations without any missing data did not notably change the results.

We also performed a sensitivity analysis after excluding all pregnancies with a record of hypertension (systolic blood pressure $\geq$140 and/or diastolic blood pressure $\geq$90) during pregnancy. After excluding 36 cases and 102 controls with hypertensive disorders, the results were virtually unchanged.

3.3   STUDY III

Maternal characteristics of exposed (opium users) and unexposed (non-opium users) cohorts are presented in Table 3-7. Compared with unexposed mothers, exposed mothers were more often parous and slightly older. Otherwise, there were no discernible differences between the two groups.

Table 3-7. Characteristics of study participants.

| | Unexposed[1] | Opium user | | |
		All	Opium user only	Tobacco and opium user
	N(%)	N(%)	N(%)	N(%)
Maternal age (Years)				
≤ 19	134(14.8)	49(5.5)	40(5.9)	9(4.3)
20-24	250(27.6)	161(18.2)	133(19.6)	28(13.3)
25-29	260(28.7)	278(31.3)	210(31.0)	68(32.4)
30-34	187(20.7)	251(28.3)	181(26.7)	70(33.3)
≥ 35	68(7.5)	143(16.1)	108(16.0)	35(16.7)
Maternal height (cm)				
≤ 149	68(7.5)	66(7.4)	47(6.9)	19(9.0)
150-155	198(21.9)	193(21.8)	152(22.5)	41(19.5)
156-160	380(42.0)	399(45.0)	295(43.6)	104(49.5)
161-164	120(13.3)	109(12.3)	84(12.4)	25(11.9)
≥ 165	100(11.0)	103(11.6)	86(12.7)	17(8.1)
Maternal Body Mass Index				
< 18.5	63(7.0)	52(5.9)	34(5.0)	18(8.6)
18.5 to < 25	439(48.5)	474(53.4)	356(52.6)	118(56.2)
25 to < 30	245(27.1)	231(26.0)	184(27.2)	47(22.4)
30 to < 35	91(10.1)	91(10.3)	72(10.6)	19(9.0)
≥ 35	28(3.1)	21(2.4)	18(2.7)	3(1.4)
Parity				
Nulliparous	372(41.1)	199(22.4)	155(22.9)	44(21.0)
Multiparous	533(58.9)	688(77.6)	522(77.1)	169(79.0)
Delivery method				
Vaginal delivery	559(61.8)	572(64.5)	428(63.2)	144(68.6)
Caesarean section	320(35.4)	292(32.9)	234(34.6)	58(27.6)
Husband's occupation				
Unemployed	25(2.8)	56(6.3)	37(5.5)	19(9.0)
Unskilled manual	400(44.2)	419(47.2)	312(46.1)	107(51.0)
Skilled manual	91(10.1)	70(7.9)	58(8.6)	12(5.7)
Self-employed	111(12.3)	101(11.4)	89(13.1)	12(5.7)
Farmer	179(19.8)	163(18.4)	123(18.2)	40(19.0)
Other occupation	95(10.5)	69(7.8)	52(7.7)	17(78.1)
Hypertension during pregnancy				
Yes	28(3.1)	26(2.9)	19(2.8)	7(3.3)
No	877(96.9)	861(97.1)	658(97.2)	203(96.7)
Birth of a Small for Gestational Age infant				
Yes	105(11.6)	164(18.5)	125(18.5)	39(18.6)
No	785(86.6)	713(80.2)	543(80.2)	170(81.0)

[1]Unexposed includes mothers who used neither opium nor tobacco.

The frequencies of preterm delivery among unexposed and exposed mothers were 6.1% and 10.0%, respectively. Compared with unexposed mothers (unexposed to both opium and tobacco smoking), mothers exposed to opium use during pregnancy had a 74% higher risk of preterm delivery. Compared with unexposed mothers, non-smoking mothers who used opium had an increased risk of preterm delivery (OR=1.56, 95% CI [1.05-2.32]) and the odds of having a preterm birth among mothers exposed to both opium and tobacco during pregnancy were OR=2.40, 95% CI [1.43-4.04]). We also adjusted for hypertension during pregnancy and SGA in model B but the results remained unchanged (Table 3-8).

Table 3-8. Odds Ratios (OR) and 95% Confidence Intervals (CI) for association between opium and tobacco use during pregnancy and risk of preterm delivery.

	Pregnancies N	Events N	(%)	Crude OR (95% CI)	Model A[1] OR (95% CI)	Model B[2] OR (95% CI)
Opium						
Unexposed	905	55	(6.1)		Reference	
Exposed	887	89	(10.0)	1.73 (1.22-2.45)	1.74 (1.21-2.45)	1.69 (1.16-2.44)
Tobacco and opium						
Unexposed	905	55	(6.1)		Reference	
Exposed to opium only	677	61	(9.0)	1.53 (1.05-2.23)	1.56 (1.05-2.32)	1.51 (1.01-2.24)
Exposed to opium and tobacco	210	28	(13.3)	2.38 (1.47-3.85)	2.40 (1.43-4.04)	2.37 (1.40-3.99)

[1]Adjusted for maternal age, height, BMI, parity, husband's occupation, sex of infant, delivery method, and place of residence.
[2]Adjusted for all covariates which are included in Model A plus hypertension during the pregnancy and Small for Gestational Age.

We stratified the outcome of the study into vaginal preterm deliveries and caesarean section preterm deliveries. Compared with unexposed mothers, the risk of vaginal preterm delivery was not significantly higher among opium-using mothers. Compared with unexposed mothers, mothers who were exposed to both opium and tobacco during pregnancy had a 2.5 times increased risk (Table 3-9).

Table 3-9. Odds Ratios (OR) and 95% Confidence Intervals (CI) for association between opium and tobacco use during pregnancy and risk of vaginal preterm delivery.[1]

	Pregnancies N	Events N	(%)	Crude OR (95% CI)	Model A[2] OR (95% CI)	Model B[3] OR (95% CI)
Opium						
Unexposed	887	37	(4.2)		Reference	
Exposed	853	55	(6.4)	1.59 (1.03-2.43)	1.45 (0.91-2.31)	1.49 (0.93-2.37)
Tobacco and opium						
Unexposed	887	37	(4.2)		Reference	
Exposed to opium only	649	33	(5.1)	1.23 (0.76-1.99)	1.25 (0.75-2.07)	1.28 (0.77-2.13)
Exposed to opium and tobacco	204	22	(10.8)	2.78 (1.60-4.82)	2.58 (1.41-4.71)	2.69 (1.47-4.97)

[1] Those with caesarean section preterm delivery are excluded
[2]Adjusted for maternal age, height, BMI, parity, husband's occupation, sex of infant and place of residence.
[3]Adjusted for all covariates which are included in Model A plus hypertension during the pregnancy and Small for Gestational Age.

Opium use during pregnancy was associated with a twofold risk of caesarean section preterm delivery. Compared with unexposed mothers, mothers who only used opium had a twofold risk of caesarean section preterm delivery. The corresponding risk related to dual use of opium and tobacco was not statistically significantly increased, but the analysis was limited by a small number of events. After adjusting for hypertension during pregnancy and SGA, we observed that the risk of preterm delivery was attenuated and did not reach statistical significance (Table 3-10).

Table 3-10. Odds Ratios (OR) and 95% Confidence Intervals (CI) for association between opium and tobacco use during pregnancy and risk of caesarean section preterm delivery.[1]

	Pregnancies	Events		Crude	Model A[2]	Model B[3]
	N	N	(%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Opium						
Unexposed	868	18	(2.1)		Reference	
Exposed	832	34	(4.1)	2.02 (1.13-3.60)	1.99 (1.09-3.64)	1.69 (0.92-3.13)
Tobacco and opium						
Unexposed	868	18	(2.1)		Reference	
Exposed to opium only	644	28	(4.3)	2.15 (1.18-3.92)	2.05 (1.10-3.82)	1.75 (0.93-3.29)
Exposed to opium and tobacco	188	6	(3.2)	1.56 (0.61-3.98)	1.75 (0.65-4.70)	1.46 (0.53-4.01)

[1]Those with preterm vaginal delivery are excluded.
[2]Adjusted for maternal age, height, BMI, parity, husband's occupation, sex of infant and place of residence.
[3]Adjusted for all covariates which are included in Model A plus hypertension during the pregnancy and Small for Gestational Age.

3.4 STUDY IV

The frequencies of SGA births among infants of exposed and unexposed cohorts were 10.9% and 17.9%, respectively. When we restricted the analysis to term pregnancies, 6.5% of infants of unexposed and 13.0% of infants of exposed cohorts were shorter than 47 cm at birth and the corresponding percentages for a small head circumference (<33 cm) were 6.2% and 13.4%, respectively.

Compared with non-use of opium and tobacco, using opium during pregnancy was associated with a 76% increased risk of birth of an SGA infant after adjusting for potential confounders. After restricting the analysis to term pregnancies, the risk of SGA was slightly lower in offspring of mothers who only used opium (OR=1.67, 95% CI [1.22-2.29]) than in offspring of mothers who were dual users of opium and tobacco during pregnancy (OR=1.81, 95% CI [1.15-2.84]) (Table 3-11).

Table 3-11. Odds Ratios (OR) and 95% Confidence Intervals (CI) for association between opium and tobacco use during pregnancy and risk of Small for Gestational Age at birth

	Pregnancies	SGA[1]	Crude	Adjusted[2]
	N	N (%)	OR OR	OR (95% CI)
Opium				
Unexposed	905	99 (10.9)	Reference	
Exposed	887	154 (17.4)	1.70 (1.30-2.23)	1.76 (1.32-2.34)
Tobacco and opium				
Unexposed	905	99 (10.9)	Reference	
Exposed to opium only	677	115 (17.0)	1.66 (1.24-2.22)	1.79 (1.32-2.42)
Exposed to opium and tobacco	210	39 (18.6)	1.83 (1.22-2.57)	1.67 (1.08-2.59)
Restricted to term pregnancies				
Opium				
Unexposed	850	93 (10.9)	Reference	
Exposed	798	132 (16.5)	1.61 (1.21-2.14)	1.70 (1.27-2.29)
Tobacco and opium				
Unexposed	850	93 (10.9)	Reference	
Exposed to opium only	616	97 (15.7)	1.52 (1.12-2.06)	1.67 (1.22-2.29)
Exposed to opium and tobacco	182	35 (19.2)	1.92 (1.25-2.94)	1.81 (1.15-2.84)

[1] Small for Gestational Age was defined as a birth weight below the 10th percentile for appropriate gestational age, based on a sex-specific global reference for birth weight (197).
[2] Adjusted for maternal age, height, BMI, parity, husband's occupation and place of residence.

Compared with unexposed term infants, term infants who were prenatally exposed to opium had a more than doubled risk of short birth length (<47 cm). The risk of short birth length was essentially similar between those only exposed to opium (OR=2.05, 95% CI [1.40-2.99]) and those exposed to both opium and tobacco during pregnancy (OR=2.19, 95% CI [1.29-3.72]) (Table 3-12).

Table 3-12. Odds Ratios (OR) and 95% Confidence Intervals (CI) for association between opium and tobacco use during pregnancy and risk of short birth length at term birth

	Pregnancies	Short birth length[1]	Crude	Adjusted[2]
	N	N (%)	OR (95% CI)	OR (95% CI)
Opium				
Unexposed	850	50 (5.9)	Reference	
Exposed	798	92 (11.5)	2.08 (1.45-2.98)	2.08 (1.45-2.98)
Tobacco and opium				
Unexposed	850	50 (5.9)	Reference	
Exposed to opium only	616	70 (11.4)	2.05 (1.40-2.99)	2.05 (1.40-2.99)
Exposed to opium and tobacco	182	22 (12.2)	2.18 (1.28-3.69)	2.19 (1.29-3.72)

[1] Birth length less than 47 cm (2 SD less than mean birth length of unexposed and term live births).
[2] Adjusted for maternal age, height, BMI, parity, gestational age in weeks, sex of infant, husband's occupation and place of region.

Compared with unexposed term infants, term infants who were prenatally exposed to opium had a 2.6 times higher risk of small head circumference at birth. The risk of a small head circumference was similar in infants prenatally exposed only to opium and in infants exposed to both opium and tobacco (Table 3-13).

Table 3-13. Odds Ratios (OR) and 95% Confidence Intervals (CI) for association between opium and tobacco use during pregnancy and risk of small head circumference at term birth

	Pregnancies	Small head circumference[1]	Crude	Adjusted[2]
	N	N (%)	OR (95% CI)	OR (95% CI)
Opium				
Unexposed	850	45 (5.3)	Reference	
Exposed	798	99 (12.4)	2.53 (1.75-3.65)	2.57 (1.78-3.71)
Tobacco and opium				
Unexposed	850	45 (5.3)	Reference	
Exposed to opium only	616	76 (12.3)	2.52 (1.71-3.70)	2.59 (1.76-3.81)
Exposed to opium and tobacco	182	23 (12.6)	2.56 (1.51-4.35)	2.52 (1.48-4.29)

[1] Small head circumference less than 33 cm (2 SD less than mean head circumference of unexposed and term live births).
[2] Adjusted for maternal age, height, BMI, parity, husband's occupation, sex of infant, gestational age in weeks and place of residence.

4 DISCUSSION

4.1 METHODOLOGICAL CONSIDERATIONS

A gold standard examination can only be achieved when all study participants have identical characteristics expect for the factor under investigation but this is rarely if ever the case. The two main types of epidemiological studies are experimental studies, such as randomized controlled trials, and observational (non-experimental) studies. The level of accuracy of results in either observational or experimental studies are evaluated based on their precision and validity. Findings of all studies are affected by a varying degree of errors and an immaculate epidemiological study only exists in theory. However, describing the appropriate design and addressing the possible limitations is useful for both planning and interpreting the findings of a study.

A cohort study is a study in which participants are followed over time. You can use a population-based cohort, where comparisons are made within the cohort. You can also use an exposed and an unexposed cohort; the exposed cohort includes participants with a certain characteristic (exposure) which is compared with a group of individuals who do not have the characteristic in question (unexposed group). Cohort studies are generally known to have a higher validity than other observational studies. Following an exposed and an unexposed cohort are deemed appropriate for investigating rare exposures. However, they are often impractical and time and cost-consuming. Studies III and IV have a cohort design.

The case-control design is more cost-efficient and suitable for estimating the association of one or more exposure(s) with a rare outcome. Designing a case control study begins by identifying cases, controls and a precisely defined study population. Individuals who developed the outcomes of interest are included as cases and controls are those who do not have the outcome and should be truly representative of the study population regarding the exposure in question. The validity of case-control studies is strongly dependent on whether the controls represent the study population or not. Studies I and II have a case-control design.

4.1.1 Internal validity

Inaccuracy in epidemiological studies is divided into systematic and random errors. Systematic errors commonly refer to any kind of biases which can cause a deviation from accuracy. This can happen when inappropriate study participants are selected (selection bias), or as a result of the method of measuring exposure(s) and outcome(s) (information bias), and/or the existence of some uncontrolled factors in the analysis (confounding). Random error (observational or measurement error) is the difference between a measured value and the real quantity of that value due to unknown and unpredictable changes.

4.1.2 Selection bias

Selection bias has been defined as distortions due to methods which influence participation in the study. It is caused by initial differences between participants and those who are eligible but do not participate in the study (257).

In Studies I and II, all registered singleton stillbirths in the study population during the study period were selected as cases. In Study I, we selected all pregnancies who received pre-pregnancy visits in order to investigate the association between maternal pre-pregnancy characteristics and risk of stillbirth. Thus, we excluded pregnancies with missing information on pre-pregnancy visits. Given a possible difference between eligible samples who were excluded and those who were included in the study, we performed a sensitivity analysis for all pregnancies, whether or not there had been a pre-pregnancy visit. We found no noteworthy difference between the two results.

4.1.3 Information bias

Information bias arises when incorrect measurement of the exposure(s) or outcome(s) enters into the study. It can lead to bias in the estimation of the association between exposures and outcomes and usually causes misclassification. Misclassification is defined as the incorrect assignment of an observation (exposure or outcome) to a category other than the true one. Misclassification may be non-differential or differential. As long as the measurement error (misclassification) occurs independently of other variables, misclassification will be considered as non-differential. In contrast to differential misclassification, the probability of misclassified exposure is associated with outcome and vice versa. It is often stated that non-differential misclassification leads to a diluted observed estimation of the true Odds Ratio which is not always a correct speculation (258-261).

In this project, we used prospectively collected information from medical records produced at pre-pregnancy and antenatal visits by Iran's public health organization. In addition, information in the medical records from the archives was of high quality and the variables of interest appeared to be accurate with very little missing information. However, some non-differential misclassification is feasible. For example, since induced abortion is illegal in Iran, some women may have not reported a history of induced abortion correctly. Consanguinity was defined as marriage between first cousins in Study I. Therefore, the unexposed group includes both second cousin and non-cousin couples which will minimize the association between consanguinity and outcome. In Studies III and VI, we selected an exposed group (use of opioids during pregnancy) based on mothers' disclosure to their care providers, and unwillingness to admit the use of drugs may have caused some disturbance in selecting the unexposed group. However, a validation study in northern Iran had reasonably confirmed high sensitivity (91%) and specificity (89%) of self-reporting opium use with a urine opium laboratory detection test (255). Finally, estimation of gestational age and in consequence preterm birth (outcome of Study III) was based on the first day of last maternal menstrual period, which can be a subject of misclassification of outcome (262).

4.1.4 Confounding

Confounders constitute a third factor which is associated with both exposure and outcome, without being an intermediate step in the causal pathway from the exposure to the outcome. Confounding factors influence or confuse the risk estimation with the effect of another factor (257). The degree of confounding effect depends on the magnitude of the association between confounder, outcome and exposure, and prevalence of the confounder factor, and magnitude of the real (true) relative risk.

Confounders can lead to overestimation or underestimation of real association or even change the association from positive to negative. There are different strategies for dealing with confounders in an epidemiological study. The most effective way is randomization. By randomizing the exposure, we guarantee that there are no systematic differences between the exposed and unexposed groups. In an ideal randomized controlled trial (RCT), there is no confounding effect which is often unfeasible in practice due to cost and ethics. An observed statistical association can only truly be interpreted as a causal relation by adjusting (controlling) for all confounding factors. However, we can only adjust for confounders that we have been informed about and measured. There are different methods for dealing with confounding including stratification, matching, standardization, propensity score, regression modeling, and inverse probability weighting. These methods are often combined as we have done in our projects (a combination of randomization, matching, stratification and, finally, regression models).

The identification of real confounders is an important step in employing adjusting methods. One strategy would be to adjust for all measured possible confounding factors but this is not optimal because some covariates may not be confounders, model misspecification, measurement errors, and reducing statistical power. Directed Acyclic Graphs (DAGs) are a well-known tool for identifying potential confounding factors relying on published information, our priori knowledge, and statistical analyses of observed data. We only adjusted for covariates that were selected in a stepwise regression procedure and changed the point estimate of interest by more than 10%.

4.1.5 Random error

Another type of error in epidemiological studies is random error or chance. The concept of random error reflects the statistical power of calculation in the study which will be estimated by Confidence Interval. The Confidence Interval of 95% has been arbitrarily specified and indicates that if the examination were repeated 100 times, 95 of those point estimates would be between the lower and higher limit of Confidence Interval. The P-value is defined as the probability of obtaining an effect at least as extreme as the one in the sample data, presuming the truth of the null hypothesis. The studies in this thesis had a reasonable statistical power for estimation of the main association. Still, the results of each analysis, either positive or null findings, may be due to chance. Statistical methods have been used to speculate the precision of the results. Random error can be limited by increasing the study size and thereby increasing

the precision. However, stratified analyses reduced the number of subjects in certain subcategories, thereby reducing statistical power.

4.1.6   External validity

External validity is defined as the extent to which the findings of the study are generalizable to populations outside the study target population. The limitation of the project to the rural part of the Golestan province is a potential threat to generalizability. However, the age and BMI distributions in our control group are similar to previously reported age and BMI distributions among pregnant women in other parts of Iran (263).

4.2   GENERAL DISCUSSION

4.2.1   Pre-pregnancy maternal characteristics and risk of stillbirth

4.2.1.1   Main finding

This population-based case-control study showed that parental consanguinity is associated with a higher risk of stillbirth. The association was only statistically significant for preterm stillbirths. This study also showed that pre-pregnancy maternal characteristics, including low and high maternal age, underweight, obesity, infertility, previous adverse pregnancy outcomes (a history of abortion, preterm delivery, and stillbirth, and a positive history of preeclampsia) were risk factors for stillbirth.

This study suggested that a significant reduction in stillbirth rate is possible in theory, since many of these risk factors for stillbirth are preventable. These results may help health providers to identify a high-risk group for more intense supervision during pregnancy.

4.2.1.2   Previous research

Our finding of a positive association between consanguineous marriage and stillbirth risk is in line with results of previous studies (67, 68, 70). An Egyptian study investigating 84 cases of stillbirth and 1,978 controls reported a strong association between consanguineous marriage and stillbirth (OR=10.6) (68). A high risk of pregnancy loss and self-reported pregnancy wastage (including both abortion and stillbirth) among Palestinian mothers was also reported in two independent studies (70, 71). Other studies have also demonstrated that consanguineous marriage is associated with increased risks of low birth weight (74), preeclampsia (264) and congenital anomalies (75) which in turn are associated with a higher risk of stillbirth, particularly preterm stillbirth (77, 133). Lethal genes have been identified in associations between consanguinity and diseases in offspring, including hearing loss (80), familial Mediterranean fever (81), intellectual disability (82) and other disorders. Thus, the positive association between consanguineous marriages and preterm stillbirth risk found in our study may be due to either culprit recessive alleles leading to poor placentation (giving a higher risk of fetal growth restriction and preeclampsia) or fetal congenital anomalies, or both.

The results from our study also showed that pre-pregnancy maternal characteristics, including low and high maternal age, underweight, obesity, a history of miscarriage or infertility, were associated with stillbirth risk. A meta-analysis of 96 population-based studies reported similar results for association between maternal age, BMI, and primiparity and stillbirth risk in high-income nations (23). Our study also indicates that previous obstetric history (a history of preeclampsia, miscarriage, preterm delivery, stillbirth or neonatal death) is associated with a higher risk of stillbirth in the index pregnancy, which is supported by previous findings (23, 63).

4.2.2 Maternal hemoglobin concentrations and dilution and risk of stillbirth

4.2.2.1 Main finding

This study indicated that a low concentration of hemoglobin throughout the whole pregnancy or during the second trimester was associated with reduced stillbirth risk. This study also suggested that elevated maternal hemoglobin levels during pregnancy is a risk factor for stillbirth, while a low hemoglobin level is inversely associated with stillbirth risk. In addition, this study reported that maternal blood hemoglobin concentration before pregnancy was not associated with a risk of stillbirth.

4.2.2.2 Previous research

Our findings are consistent and extend on results of previous studies showing associations between high maternal blood hemoglobin concentrations in early (85, 89) and late pregnancy (90) and increased risks of stillbirth and other adverse outcomes (91-93, 246). During pregnancy, plasma renin activity increases (265, 266) and the atrial natriuretic peptide levels decrease to meet higher blood volume demands of new vascular beds (267, 268). In addition, maternal erythropoietin secretion during pregnancy causes an increase in red blood cell mass. Consequently, at the end of the second trimester of normal pregnancy, the plasma hemoglobin concentration decreases by about 10 to 20 grams per liter because the plasma volume increases relatively higher than the red blood cell mass (269).

However, this was the first study investigating the possible role of hemoglobin concentration before pregnancy. In Iran, women of reproductive age undergo screening before pregnancy to identify and treat iron deficiency anemia which may to a large extent eliminate the possible effects of iron deficiency in our study (21). The lack of association between hemoglobin concentration before pregnancy and stillbirth in this study could be due to the fact that women with low hemoglobin concentration receive pharmacological treatment before pregnancy.

This practice also provided evidence that regardless of initial hemoglobin level, decreasing hemoglobin concentration during pregnancy was associated with a lower stillbirth risk. This protective effect was also observed in previous studies on stillbirth (85), preeclampsia (270) and low birth weight (270, 271).

On the other hand, preeclampsia is associated with both stillbirth risk and hemoglobin concentration during pregnancy and this disorder could be an intermediate factor (23, 93). As information on preeclampsia or eclampsia was not available, we reanalyzed the data after excluding all subjects with a record of hypertension during pregnancy. We observed no noticeable change in the results. That was in contrast with the results of a previous Swedish study in which the stillbirth-related risks due to a high hemoglobin concentration increased when women with preeclampsia or eclampsia were excluded (85).

There is an inconsistency in the benefit of taking iron supplements for women with normal blood values (272). Iron deficiency can be a major contributing factor for both hemoglobin dilution and serious maternal anemia which might increase risks of adverse pregnancy outcomes such as preterm birth and low birth weight (84, 269). However, other studies showed that prenatal iron use is associated with a significant increase in birth weight and reduction in risk of low birth weight (273). In addition, daily iron supplement intake during pregnancy might also cause a higher risk of hemoglobin concentration during pregnancy (274).

4.2.3   Opium use during pregnancy and risk of preterm delivery

4.2.3.1   Main finding

This study provides evidence that opium use during pregnancy is associated with an increased risk of preterm delivery. The risk was evident in non-tobacco smoking, opium exposed mothers during pregnancy and was even higher among those who were exposed to both opium and tobacco during pregnancy. Among mothers who were only exposed to opium, the risk was apparent for caesarean section preterm delivery. This group included both elective (pre-labor) preterm caesarean deliveries (medically indicated due to concern about maternal or fetal wellbeing) (275) and emergency caesarean section deliveries, probably predominantly due to fetal asphyxia and lack of labor progress (276). After controlling for maternal hypertensive disorders and SGA, we observed that the risk of caesarean preterm delivery among opium-exposed pregnancies was attenuated. Therefore, we speculate that opium use during pregnancy may increase the risk of caesarean preterm delivery by inducing fetal stress before or during labor (168).

This study also demonstrated that using opium and tobacco during pregnancy was associated with a twofold increased risk of vaginal preterm delivery. Smoking is associated with increased risks of premature rupture of membranes, (277) intrauterine infection, prostaglandin activity in fetal membranes, and an increased systemic inflammatory response, which can lead to spontaneous preterm labor and in consequence preterm delivery (169). Thus, we speculate that the observed higher risk of spontaneous preterm delivery among women who use opium and tobacco during pregnancy might be due to additive or interactive effects of the two risk factors (179, 220).

4.2.3.2 Previous research

The results of this study are compatible with findings of studies reporting positive associations of opioids use, such as heroin, with higher risk of preterm delivery (179, 218). The association between uses of opiates (heroin or methadone) during pregnancy and an increased risk of preterm delivery has been shown by several studies (179, 220, 278). However, most of these studies suffer from confounding effects of the high-risk lifestyle of drug abusing mothers (218).

Previous studies proposed different hypothetical explanations for the associations between use of opiates and risks of adverse pregnancy outcomes. The first theory assumes that intrauterine hypoxic stress may be imposed to the fetus by fluctuating cycles of intoxication and withdrawal due to use of opioids during pregnancy. Accordingly, this recurrent hypoxic stress during withdrawal can lead to intrauterine growth restriction and preterm delivery (279). Furthermore, some studies showed that opioid abuse during pregnancy is associated with higher risks of preeclampsia, premature labor, premature rupture of membranes, placental abruption and insufficiency, and intrauterine death (280, 281). The other explanation is the epiphenomena of drug use and chaotic lifestyle, including multiple drug abuse, poor prenatal care, dietary restriction and disadvantaged socioeconomic circumstances (282).

4.2.4   Opium use during pregnancy and infant size at birth

4.2.4.1 Main finding

Our study demonstrated that prenatal exposure to opioids was associated with increased risk of SGA at birth. In addition, we found that risk of SGA for infants who were prenatally only exposed to opium was similar to that for those exposed to both opium and tobacco. This cohort study also showed that among infants born at term, those whose mothers used opium during pregnancy had shorter birth length and smaller head circumference after adjustment for gestational age, sex of infant and other potential confounders.

4.2.4.2 Previous research

The results of this study are in line with findings of other studies investigating the risk among infants of mothers using heroin, methadone, or other opiates during pregnancy. Previous studies have reported that prenatally opioids exposed neonates tend to have a higher risk of low birth weight (218, 219, 283-285). Meta-analyses of several observational studies confirmed that the use of opioids during pregnancy is associated with a more than fourfold higher risk of low birth weight and threefold higher perinatal mortality rate (221, 222). On the other hand, maternal narcotic abuse and addiction are associated with multiple drug abuse, parental psychopathology, poor prenatal care, dietary restriction, and disadvantaged socioeconomic circumstances (282, 286). However, use of drugs during pregnancy was associated with a higher risk of low birth weight despite comprehensive antenatal care (220).

Other investigations on maternal heroin or methadone use during pregnancy also reported an increased risk of short birth length (284, 287, 288). Visconti et al. observed that infants who

were prenatally exposed to opium or methadone had shorter femur and humerus lengths compared with infants who were unexposed during pregnancy (289).

The association of opioid abuse and risk of small head circumference reported in our study is also consistent with results of previous investigations on maternal heroin or methadone use during pregnancy (223, 284, 287, 290). Arlettaz et al. reported that neonates prenatally exposed to opiates had a fourfold higher risk of small head circumference at birth (291). Previous studies also demonstrated that psycho-behavioral dysfunctions, impaired motors and cognitive functions, intentional disorders and Attention Deficit Hyperactivity Disorder (ADHD) at school age were associated with intrauterine opioids exposure (224, 290, 292-297). In addition, experimental studies on animals observed a neurotoxicity effect of opioids during fetal life (298, 299).

4.3 STRENGTHS AND LIMITATIONS

4.3.1 Strengths

The strengths of this project include using prospectively collected population-based information from medical records of pre-pregnancy and antenatal visits and delivery from family health files. This provides a unique possibility to investigate effects of different factors on adverse pregnancy outcomes with a minimal risk of selection and recall bias. This study was conducted in rural parts of the Golestan province in northern Iran where most pregnancies are planned and women have a scheduled pre-pregnancy visit, several pregnancy visits and an "after delivery visit". Some 97% of pregnant women are in contact with the primary healthcare system and receive nutritional supplements including iron during pregnancy (21).

There is only limited information on the incidence of adverse pregnancy outcomes in low/middle income countries, and this study adds important population-based data from rural areas in Iran. To the best of our knowledge, this is the first study of traditional opium use during pregnancy and risk of preterm delivery and fetal size at birth. Most previous studies are derived from investigations of mothers exposed to heroin or methadone in high-income countries, while information from traditional opium use in low or middle-income countries is lacking (224).

A general issue in studies in which the effects of illicit drugs are investigated is confounding caused by factors related to lifestyle, such as multiple drug abuse, alcohol consumption, tobacco smoking, and even blood-borne infectious diseases (220, 300). Opium has traditionally been used in southern Asia and middle-eastern countries such as Iran as a sedative and for pleasure (248). In Iran, the socioeconomic profile of opium users is almost identical with the general population (128). It has been shown that opium users have less psychiatric comorbidity, unemployment, homelessness, and criminal behaviors compared with users of other narcotic drugs (301, 302). This study provides an exceptional possibility to investigate the risk of adverse pregnancy outcomes among opium exposed mothers who otherwise lived a normal life and had an acceptable level of care during pregnancy.

4.3.2 Limitations

This project also has some potential limitations. There may be concern regarding generalizability of the results as we only used information from the family health files in rural areas of the Golestan province. However, the age and BMI distributions in our control group are similar to previously reported age and BMI distributions among pregnant women in other parts of Iran (263).

The exclusion of those with missing hemoglobin values or missing pre-pregnancy visits might cause selection bias in the first and second study. In addition, we performed a sensitivity analysis in both studies and we found that there were no differences in stillbirth risks related to maternal age, a history of miscarriage, and a history of infertility among included observations compared with all mothers.

Moreover, maternal blood profile was tested in different laboratories which may have had different methods and accuracy. Moreover, values of serum hemoglobin were rounded to the nearest half; thus, we did not have information on exact values of serum hemoglobin concentration.

Medical information from family health files had some deficiencies, including lack of information on extremely preterm birth deliveries (before 28 weeks of gestational age). Gestational age was estimated based on the first day of last maternal menstrual period, which can be subject to inaccuracy (262).

In addition, consanguinity was registered as a first cousin marriage in the health files. Therefore, the unexposed group includes both second cousin and non-cousin couples. This misclassification of consanguinity may cause an underestimation of the association between consanguinity and stillbirth risk.

As induced abortion is illegal in Iran, some women may not have reported a history of induced abortion. This non-differential misclassification might shift the association towards the null. There was also a lack of information on malformations which made it impossible to investigate the association between exposures and malformed/non-malformed stillbirths.

Furthermore, the misclassification of maternal smoking and residual confounding by opium use could be of potential concern. Tobacco smoking is not accepted culturally in rural parts of Iran and some women may not have correctly reported their smoking history. In this study, information on mothers' opium use during pregnancy was also based on mothers' disclosure to their care providers, and unwillingness to admit drugs use may have pushed our estimates towards to the null. However, a validation study of self-reported opium use with a urine opium detection laboratory test from northern Iran reported reasonably high sensitivity (91%) and specificity (89%) (255).

Finally, a lack of specific information on mothers' socioeconomic circumstances, including the mothers' educational level, was also an important potential limitation of this project. Controlling for husband's occupation and place of residence as a measure of socioeconomic

circumstances for the families may not have been sufficiently discriminatory, and we can therefore not rule out effects of residual confounding.

4.4 CONCLUSIONS

Consanguineous marriage is a risk factor for stillbirth, especially for preterm stillbirth. Pre-pregnancy maternal characteristics, such as maternal underweight, obesity, teenage pregnancy, high maternal age, and having a positive history of adverse pregnancy outcomes also increased the risk of stillbirth in our target population.

An elevated maternal hemoglobin level during pregnancy is a risk factor for stillbirth, and low hemoglobin level is inversely associated with stillbirth. A high hemoglobin value and absence of hemoglobin dilution during pregnancy can be considered as indicators of a high-risk pregnancy, regardless of measured hemoglobin concentration. Hemoglobin concentration before pregnancy was not associated with stillbirth risk.

The risk of preterm delivery is increased by opium exposure. Opium use alone may be associated with an increased risk of medically indicated preterm delivery, while dual use of opium and tobacco during pregnancy may increase the risk of spontaneous preterm delivery.

Opium use during pregnancy is associated with a higher risk of SGA at birth. It is unlikely that the observed associations are confounded by other factors related to high-risk behaviors, such as use of other harmful substances. Among term pregnancies, infants of opium-exposed mothers have a higher risk of short birth length and small head circumference.

5   FUTURE STUDIES

Despite the wide range of improvements in public health and increasing attention to maternal and child health, the rate of many adverse pregnancy outcomes has remained stable during recent decades (23). This thesis suggests that maternal characteristics such as consanguineous marriage, use of opioids, and maternal anthropometric indexes are associated with a higher risk of adverse pregnancy outcomes.

The first study suggests that the association between consanguinity and preterm stillbirth could be due to lethal recessive alleles. A study with a larger sample size would make it possible to investigate the association for different types of stillbirth, e.g. early vs late stillbirth, SGA and non-SGA stillbirths, and it would be of even greater importance to investigate stillbirths by causes. Investigating possible exposure-response relationships for first and second cousin marriage and risk of stillbirth considering genetic disorders and congenital anomalies of fetus could be helpful to find possible mechanisms.

It has now been reported in both Sweden and Iran that high hemoglobin concentrations are associated with increased stillbirth risk and that hemoglobin dilution during pregnancy has a protective effect. The next step could be an attempt to quantify the value of dilution for creating a practical guideline for risk assessment during pregnancy. Based on the Iranian primary health service's guidelines, anemic women are given iron in therapeutic doses during pregnancy. Moreover, all pregnant women are given iron supplements during pregnancy. Conducting an investigation on the effectiveness and cost benefits of iron supplements and therapy during and before pregnancy would be valuable.

Future research needs to further investigate effects of maternal opium use during pregnancy. An investigation of dose-response relationships of tobacco smoking and use of opioids during different trimesters of pregnancy and risks of adverse pregnancy outcomes is warranted.

6 ACKNOWLEDGEMENTS

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