5-2014

The Role of Obesity, Diabetes, and Hypertension in Cleft Lip and Cleft Palate Birth Defects

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THE ROLE OF OBESITY, DIABETES, AND HYPERTENSION IN CLEFT LIP

AND CLEFT PALATE BIRTH DEFECTS

by

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A dissertation submitted in partial fulfillment
of other requirements for the degree

of

DOCTOR OF PHILOSOPHY

in

Nutrition and Food Sciences

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UTAH STATE UNIVERSITY
Logan, UT
2014

ABSTRACT

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and Cleft Palate Birth Defects

by

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Utah State University, 2014

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Orofacial clefts (OFCs) are among the most common structural birth defects and a public health problem. Several studies suggest that maternal obesity pre-existing diabetes mellitus (DM), and the underlying metabolic abnormalities, may be involved in the pathogenesis of cleft lip (CL) and cleft palate (CP) birth defects. Although hypertension and gestational diabetes mellitus (GDM) have been associated in a few studies with congenital birth defects, studies examining the risk associated with OFCs are limited. The overall objective of this dissertation was to examine the association between maternal obesity, DM, GDM, and hypertension and the risk of OFCs in case-control studies.

Analyses of data from an international consortium revealed that maternal obesity (pre-pregnancy BMI >30), compared to normal weight (18.5<BMI>25), was associated with an increased risk of cleft palate with or without cleft lip (CP/L) (adjusted odds ratio (aOR) =1.13 [95% confidence intervals (CI) 1.01-1.25]). We also found a marginal association between maternal underweight and CP/L (1.0 [reference]; aOR=1.14 [0.97-1.34]. CL only was not associated with maternal bodyweight. Interestingly, among college-graduates, there was no increased risk of

CP, but mothers with less than a completed college education had an increased risk of CP for underweight and obesity.

Investigation of the Utah OFC data provided evidence that maternal GDM is significantly associated with isolated (aOR=2.63 [1.30-5.34]) and non-isolated clefts (aOR=2.66 [1.02-6.97]). Maternal hypertension is significantly associated with non-isolated clefts (aOR=6.56 [2.18-19.77]). We found a further elevated risk of OFCs among GDM mothers and those with hypertension who were also obese.

The analyses of data from an international consortium revealed significant associations between maternal diabetes and the risk of OFCs. The estimated relative risk of DM for isolated OFCs was 1.33 [1.14-1.54] and was slightly higher for multiple OFCs (aOR=1.86 [1.44-2.40]). Diabetic mothers with abnormal body-mass-index had an increased risk for having inborn with OFCs.

Throughout the dissertation, we demonstrated the extent in which maternal obesity, pre-existing DM, GDM, and maternal hypertension may increase the risk of OFC birth defects. The results highlight the need for pre-conceptional program planning for the prevention of OFCs with screening for abnormal glucose tolerance and hypertension.

(157 pages)

PUBLIC ABSTRACT

The Role of Obesity, Diabetes, and Hypertension in Cleft Lip and

Cleft Palate Birth Defects

Hebah Kutbi

Orofacial clefts (OFCs) are birth defects characterized by immediately recognizable disruption of normal facial structure caused by abnormal facial development during the first six to eight weeks of gestation, causing a cleft in the lip or the palate. OFCs are among the most common structural birth defects and a public health problem. Some studies have found that maternal obesity, diabetes, hypertension, or the underlying metabolic abnormalities known as the metabolic syndrome, might be associated with the risk of OFCs, though other studies have been inconsistent. Data of mothers who have had children with OFCs were compared to those of children without OFCs to assess the association between maternal obesity, diabetes or gestational diabetes, or hypertension and the risk of OFCs.

Results of studies conducted in this dissertation indicated an increased risk of OFCs when abnormal maternal weight is present. Both maternal obesity and underweight were found to be associated with increased risk of having children with orofacial clefts. This effect however was only present among mothers with lower maternal education levels. Maternal diabetes mellitus and gestational diabetes increased the risk for having a child with OFC birth defects, as well as maternal hypertension. When maternal diabetes or hypertension was combined with obesity or underweight, the risk of OFC increased compared to normal weight mothers.

With the increased prevalence of obesity, diabetes, and hypertension and the association of these syndromes with OFCs, it is recommended that mothers planning

to become pregnant to follow healthy habits, maintain healthy weight, and be

screened for possible diabetes or hypertension prior to conception and early in

pregnancy.

ACKNOWLEDGMENTS

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CHAPTER 1

INTRODUCTION

Each year an estimated 150,000 babies are born with birth defects in the United States [1]. According to a 1998 report of the National Center for Health Statistics, birth defects cause one in five infant deaths, making them the leading cause of infant mortality [1]. The National Vital Statistics Report indicated that in 2010, infant mortality rate due to congenital malformations was 127.7 per 100,000 live births, accounting for 20.8% (n=5,107) of total infant deaths [2]. Clefts of the lip and palate, collectively termed orofacial clefts (OFCs), are among the most common structural birth defects and are therefore a public health problem [3, 4]. Between 1998 and 2001, the Centers for Disease Control and Prevention (CDC) reported that 6,800 infants in the United States were affected by OFCs annually [5]. In 2010, an estimated 4,437 live births per year had cleft lip or cleft palate [6]. Several studies suggest that maternal obesity, diabetes, or the underlying metabolic abnormalities known as Metabolic Syndrome, may be involved in the pathogenesis of cleft lip and cleft palate [7-9]. Yet, further studies are needed for a more complete understanding of the etiology of this disorder [10].

Obesity is defined as having a body-mass-index (BMI; weight in kg/height in M^2) of ≥ 30.0. Among adults, age-adjusted prevalence of obesity in 2007-2008 was 33.8%, with an overall 32.2% among men and 35.5% among women [11]. However, it was expected that by 2015, 41% of adults in the United States would be obese [12]. Increased adiposity is associated with an increased incidence of a number of conditions, including diabetes mellitus (DM) [13] and hypertension [14]. An increased risk for DM begins to rise at a BMI of >30 [13], whereas BMI above the normal range is associated with a number of adverse reproductive health outcomes, including

gestational diabetes mellitus (GDM) [15], pregnancy induced hypertension [16], and birth defects [17].

Maternal DM before pregnancy (pre-gestational diabetes) has been associated with congenital malformations, including OFCs, in the offspring. Poor glycemic control in very early pregnancy may increase the malformations rate [18]. However, pre-pregnancy care of mothers with existing diabetes may reduce the malformation risk [19]. There is less evidence on the teratogenic risk of GDM, although this disorder has been suggested to be a human teratogenic factor [20]. In 1985, congenital malformations represented the largest single cause of mortality in infants of diabetic mothers [21]. Schaeffer et al. studied 3743 pregnancies diagnosed with GDM and found an association between maternal blood glucose levels and the risk for major–but not minor–congenital malformations in the offspring. Women with GDM were identified in a screening program while birth defects were identified by intense pediatric examinations at the time of discharge from the delivery unit [22].

Metabolic syndrome is a cluster of metabolic and physical characteristics that raise the risk of developing heart disease, diabetes, and other diseases. These include insulin resistance, hypertension, obesity, central body fat deposition, low HDL cholesterol, and hypertriglyceridemia [23]. In 2009, approximately 34% of adults met the criteria for metabolic syndrome and its prevalence increases with age and BMI [24].

Hypertension, which complicates approximately 10% of all pregnancies, remains a major cause of morbidity and mortality for both mother and fetus [25]. Blood pressure normally decreases early in pregnancy, and by the mid-trimester, diastolic levels are often 10 mmHg lower than postpartum measurements. Pressures then increase gradually, approaching pre-pregnant levels near term, and some have even recorded transient rises in the immediate puerperium [26]. Because cardiac output is

also elevated, the decrease in blood pressure is primarily related to a marked decrease in peripheral vascular resistance [25]. Infants born to women who have hypertension early in pregnancy have an increased risk of birth defects. In 2011, researchers at the Kaiser Foundation Research Institute in California collected health information on 465,000 mother-infant pairs in the Kaiser Permanente Northern California health care system and compared the risk of birth defects in infants born to mothers with hypertension using antihypertensive drugs to that of infants born to mothers with hypertension but not taking any antihypertensive drugs. Results indicated an increased risk of major non-chromosomal congenital malformations in all mothers with hypertension and the risk remained elevated even with the use of hypertensive drugs during pregnancy [27].

Maternal diabetes, or the underlying metabolic abnormalities known as the metabolic syndrome, was hypothesized to be involved in the pathogenesis of cleft lip and cleft palate, while it was debated whether this is true also at maternal GDM. With the rising rates of excess weight among pregnant women, even a modest effect of maternal obesity may result in an increased population burden of OFC. Maternal weight gain increases the risk for DM and hypertension. Although hypertension has been associated in a few studies with congenital birth defects, studies examining the risk associated with OFC are limited. Given the aforementioned information, this dissertation is a step towards a comprehensive analyses of the effect of maternal obesity, diabetes, GDM, and hypertension on the risk of OFC birth defects. Further analyses were performed to describe possible potential confounders that may interact with these risk factors. The work outlined in chapters one through six can be useful in determining the associations between maternal obesity, diabetes, GDM, and hypertension on the risk of OFC birth defects.

Dissertation Hypotheses and Objectives

The overall objective of this dissertation was to examine the associations between maternal obesity, diabetes, and hypertension and the risk of orofacial clefts. The specific objectives and hypotheses of this dissertation are:

1. To determine whether maternal obesity is associated with the risk of cleft lip and cleft palate. Maternal obesity is hypothesized to cause cleft lip and cleft palate via metabolic abnormalities that affect fetal development. This hypothesis was examined in analyses of data from a large international consortium of case-control studies from Utah, Iowa, Norway, Denmark, and the U.S. National Birth Defects Prevention Study.

2. To investigate whether maternal gestational diabetes and hypertension are associated with risk of cleft lip and cleft palate. These two factors are hypothesized to cause cleft lip and cleft palate via metabolic abnormalities that affect fetal development. This set of related hypotheses was examined in analyses of data from the Utah case-control cleft study.

3. To examine the association between maternal diabetes and the risk of cleft lip and cleft palate. This hypothesis was examined in analyses of data from the international consortium of case-control studies from Utah, Iowa, Norway, Denmark, and the U.S. National Birth Defects Prevention Study.

Dissertation Structure

This dissertation is divided into six chapters.

Chapter 1 provides an introduction to the research along with outlines covering study objectives and hypotheses.

Chapter 2 is titled "Obesity, Diabetes, and Hypertension and Cleft Lip and

Cleft Palate Birth Defects: A Review." This chapter provides literature review of each of these three modifiers and evidence that they are related to the risk of orofacial clefts.

Chapter 3 is titled "Maternal Obesity and Underweight and the Risk of Orofacial Clefts." Chapter 3 undertakes analyses of data from an international consortium, including case-control studies from the U.S and Norway, to test whether an association between maternal obesity and underweight and the risk of OFCs exist after adjusting for potential confounders. The demographic characteristics for each study site were explored. The risk of maternal body weight groups on OFC subtypes (cleft lip only (CLO), cleft lip with or without cleft palate (CL/P), and cleft palate with or without cleft lip (CP/L)) was tested among each study site. The association between maternal education levels and the risk of each OFC subtype (CLO, CLP, cleft palate only (CPO), CP/L, and all cleft subtypes) was also tested. Given the known association between maternal education level and risk of orofacial clefts, the risk of maternal body weight groups stratified by maternal education levels was examined.

Chapter 4 is titled "The Role of Gestational Diabetes Mellitus and Hypertension on the Risk of Orofacial Clefts in Utah." This chapter describes the main characteristics of the Utah population sample and examines the independent effect of maternal GDM and hypertension on the risk of cleft. Given that maternal obesity is a risk factor for OFC, the effect of maternal GDM and hypertension is assessed after stratifying data for maternal weight categories.

Chapter 5 is titled "The Association Between Maternal Diabetes and Orofacial Clefts in an International Consortium of Case-Control Studies." This chapter examines the association between maternal diabetes and each type of OFC

(isolated, multiple, and isolated and multiple clefts combined), and subtype (CLO,

CL/P, CPO, and all clefts) using data from an international consortium that includes

case-control studies from the U.S., Norway, and Denmark. The risk of maternal

diabetes was also tested within each maternal body weight category and obesity

levels.

Chapter 6 wraps up with a discussion on the findings and provides

conclusions and recommendation for further research directions and for practitioners.

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CHAPTER 2

OBESITY, DIABETES, AND HYPERTENSION AND CLEFT LIP

AND CLEFT PALATE BIRTH DEFECTS: A REVIEW

Birth Defects

Birth defects remain an important public health issue and the leading cause of infant mortality and disabilities in the United States. The National Vital Statistics Report indicated that in 2010, infant mortality rate due to congenital malformations was 127.7 per 100,000 live births, accounting for 20.8% (n=5,107) of total infant deaths [1]. Children who survive and live with birth defects are faced with an increased risk of developing life-long physical, cognitive, and social challenges concerning which medical intervention and other supportive services have little impact [2]. Parental consanguineous marriages, advanced maternal age, maternal smoking, poverty, poor nutrition, or alcohol and drug use are some of the risk factors that have been reported to cause birth defects [3]. The National Birth Defects Prevention Network (NBDPN) provided an update of the national estimates of 21 selected birth defects. Chromosomal anomalies were the most common birth defects, with a prevalence of 17.48 per 10,000 live births and accounting for 14.47 for Down syndrome, followed by orofacial defects, cardiovascular, musculoskeletal, gastrointestinal, and central nervous system defects, with prevalences of 16.98, 14.73, 14.13, 6.85, and 6.38 per 10,000 live births, respectively [4].

The Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based, active birth defects surveillance system operating in the five central counties of metropolitan Atlanta, examined the prevalence of birth defects among racial and ethnic subpopulations. Compared to births of non-Hispanic white women,

births to non-Hispanic black women had a significantly higher prevalence of five

birth defects and a lower prevalence of 10 birth defects, while births to Hispanic

women had a higher prevalence of four birth defects and a lower prevalence of six

birth defects. However, the reasons for racial and ethnic variations in the prevalence

of birth defects are not well understood [5]. Disparities in the prevalence of birth defects

may result from different underlying etiologies [5]. Some birth defects are inherited,

while others are a product of harmful environmental factors or multifactorial,

resulting from a complex interaction of genetic and environmental influences.

Nevertheless, in about 50% of all birth defect cases, the causes remain unknown [6, 7].

Many birth defects occur due to abnormalities of the genetic material before

the conception [7]. For instance, the chromosomal abnormalities, which are changes in

the number or structure of chromosomes and result in a gain or loss of genetic

material, account for approximately 6.0% of birth defects in industrialized countries [8].

Down syndrome, caused by an extra chromosome 21 (trisomy 21), is the most

common chromosomal abnormality [7]; single gene defects that are caused by

alterations in gene structure (mutations) result in abnormal cell functioning and

accounts for 7.5% of birth defects; and multifactorial disorders, alternately called

congenital malformations, caused by the interaction of genes and the environment

compose 20-30% of all causes of birth defects. However, birth defects originating

after conception are largely non-genetic in origin. Intrauterine environmental factors,

such as congenital infections, maternal illness and altered maternal metabolism as

well as recreational and therapeutic drugs may cause the birth defects through the

process of interfering with the normal growth and development of the embryo and

deforming the fetus [7]. Those birth defects compose 5-10% of the causes. Examples of

these three categories include rubella and toxoplasmosis, maternal insulin-dependent

diabetes mellitus and iodine deficiency, and alcohol and antiepileptic drugs, respectively. Unknown causes lead to 50% of the birth defects [7].

Birth defects are multifactorial occurring due to a combination of genes that place the fetus at risk in the presence of specific environmental factors. A few examples are congenital heart disease, neural tube defects, and OFCs. Multifactorial inheritance can also be the cause of the many common systemic diseases with a genetic predisposition presenting later in life. Examples are hypertension, diabetes, stroke, mental disorders, and cancer [9].

Cleft Lip and Cleft Palate Birth Defects

Orofacial clefts (OFCs) are congenital malformations characterized by immediately recognizable disruption of normal facial structure caused by abnormal facial development during the first six to eight weeks of gestation, causing a cleft—a gap. A cleft lip (CL) is a physical split or separation of one or both sides of the upper lip and appears as a narrow opening in the skin of the upper lip. This rupture often extends beyond the base of the nose and includes the alveolus, the bony structure of the maxilla containing the gums and dentition. A cleft palate (CP) is a split or gap in the palate, the roof of the mouth. A cleft palate can involve the hard palate (the bony front portion of the roof of the mouth), and/or the soft palate (the soft back portion of the roof of the mouth) [10].

It is important to distinguish between non-syndromic (isolated) and syndromic CL/P in order to determine management and recurrence risk for patients and families [11]. Non-syndromic OFCs, are those that occur with no other major anomaly or one or two minor anomalies [12] with an average prevalence of about 1/700 live births [13]. Major anomalies usually include those of functional significance requiring some

degree of medical intervention. Minor anomalies, however, are those of minimal or no functional significance [14]. CL can occur on one or both sides of the mouth. Because the lip and the palate develop separately, it is possible to have a CLO, a CPO, or both together [15]. Thus, it is reasonable to limit the definition of non-syndromic OFCs to those associated with no additional malformations and one or two minor anomalies. Affected individuals may have CL and CP (CLP), CP only (CPO), or CL only (CLO) [15].

There appears to be a greater chance of clefting in a newborn if a sibling, parent, or relative has had the defect. OFCs may cause complications in feeding, dental problems, and speech, hearing, and social integration. However, OFCs can be corrected to varying degrees by surgery, dental care, speech psychotherapy and psychosocial intervention [16].

Epidemiology of Cleft Lip and Cleft Palate by Gender

Orofacial clefting is the most common craniofacial anomaly. Therefore, it is important to analyze the distribution of this defect and describe its characteristics [17]. Using data from three registries of congenital anomalies based on a total of more than 5 million births, some epidemiological characteristics were studied for 8,315 infants mainly with non-chromosomal CL/P. Robert et al. have observed a higher distribution of CL/P among males than females, while gender ratio was lower when multiple OFCs existed. The distribution of Pierre Robin type CP, which is a posterior U-shaped CP, was similar among males and females, while other types of CP had the usual excess of females [18]. Similarly, Mossey et al. have reported a higher frequency of CL/P among males than females, while isolated CP was more commonly observed among females [19]. Gender ratio varied with severity of the cleft [19], presence of additional malformations, number of affected siblings in a family, ethnic origin, and

possibly paternal age [20]. For instance, the gender ratio for CL/P in white populations was about 2:1 (male: female). The male predominance in CL/P became more apparent with increasing severity of cleft and less apparent when more than one sibling is affected in the family [21, 22]. By contrast, the male excess in CL/P is smaller when the infant has malformations of other systems [20]

Epidemiology of Cleft Lip and Cleft Palate Birth Defects by the Geographical Variation

The birth frequency of CLO, CLP, and CPO is not known in some parts of the world. Comparability of data related to the prevalence of OFCs among regions can be affected considerably by the differences in sample source (hospital vs population), duration, method of ascertainment, inclusion criteria, and sampling fluctuation [11].

The United States

Data from the California registry in the period 1983-1992 was used to estimate the prevalence of CL/P among Native Americans. The prevalence of CL/P was reported to be as high as 1.99 per 1000 births [23]. The National Birth Defects Prevention Network (NBDPN) examined the prevalence of OFCs by U.S. state. The highest reported was for New Mexico in the period 1995-1996, with a prevalence of 1.73 per 1000 live births and the stillbirths combined. In Wisconsin 1989-1995, the prevalence was 1.56 per 1000 live births and stillbirths combined. The lowest recorded prevalence rate for CL/P was 0.59 per 1000 live births in Alaska, for 1996 only, and Illinois, for the period 1989-1996 [11].

Latin America

The Latin American Collaborative Studies of Congenital Malformations reported the prevalence of CL/P across Central and South America. The highest CL/P prevalence recorded was for Bolivia (2.28 per 1000), followed by Argentina (1.16 per

1000) and Chile (1.13 per 1000). These are geographically in the southern parts of South America and are generally less developed than the U.S. and Canada [11]. At the lowest end of the scale was the geographically different population in Central America and the Caribbean, reporting a prevalence of 0.42/1000, followed by Venezuela (0.77 per 1000) [24].

Europe

The highest prevalence of CL/P from all European countries was 1.46 [25]. Overall, the highest frequencies of CL/P were found in Norway, Denmark, Sweden, Iceland, and the northern Netherlands, while the lowest levels were in Southern Europe [11]. In 2013, an epidemiological study conducted in Australia reported the prevalence of OFCs among the Australian populace. The birth prevalence of CL/P reported was 12.05 per 10,000 births (1 in 833 births). For CP, the prevalence was 10.12 per 10,000 births or 1 in 990 births. CL/P rates were significantly higher in males than females; while for CP, the prevalence rate in females was significantly higher than for males. Compared with non-Aboriginal Australians, birth prevalence rates for Aboriginal Australians were 1.89 times higher for CL/P and 1.30 times higher for CP. Birth prevalence of all forms of OFC did not differ by geographic location or by socioeconomic status. From 1980 to 2009, there was no significant change in annual rates for CL/P but rates for CP increased by an average of 1.97% per year [26].

The Middle East

In the Middle East, the highest record of CL/P was 1.89 per 1000 live births in a Saudi Arabian Hospital-based [27], followed by a reported non-syndromic prevalence of OFCs in Kuwait) in the period 1985-1987 (1.06 per 1000 live births[28]. In Turkey, studies of OFCs are limited. However, it has been reported that 194 cases were

identified with an age range of 1 to 65 years. Among the cases, 127 subjects (65.5%) had isolated CP, including 63 females and 64 males; 42 (21.6%) subjects had CL, including 17 females and 25 males; and 25 subjects (12.9%) had CLP, including 12 females and 13 males [29].

The Far East

The highest prevalence rate of OFCs in the Far East was reported from a hospital-based Japanese data between 1948-1954, revealing a prevalence of 2.13 per 1000 live births [30]. In the Philippines, a prevalence of 1.94 per 1000 live births was reported for OFCs in a 7-year survey of hospital records in the period 1989-1996 [31], while in Taiwan, the prevalence of OFCs between 2002-2009 was 0.1% for CL/P and 0.04% for CP [32].

Environmental Risk Factors for Orofacial Clefts

Although the literature on OFCs is extensive, the exact etiology and the unique risk factors remain unknown [11]. Several studies suggested a multifactorial etiology for OFC, with both genetic predisposition and environmental influence playing a role [11]. A meta-analysis investigated the potential maternal factors associated with OFCs in the offspring. Data suggested that maternal socioeconomic status, smoking, alcohol consumption, medications, caffeine, and lead exposure are the most environmental risk factors associated with OFCs [33, 34], while folic acid intake by the mother was found to reduce the risk of CL/P in offspring in several studies [33, 34]. In a Case-Control Study of non-syndromic OFCs in Maryland conducted to examine both environmental and genetic risk factors for OFCs, and to test for possible interactions, researchers could not find a statistically significant association with any of the following: maternal smoking, vitamin use, urinary tract infection, or recreational drug use. This could be explained by the small sample size in the study

(n=171) [35].

Socioeconomic status (SES)

Several studies in the United States and other countries revealed possible associations between parental socioeconomic status and the risks for birth defects, including OFCs, though findings were inconsistent [36-39]. For instance, a case-control study conducted in France between 1985 and 1989 reported an increased risk for OFCs among mothers with low SES measured by household income [40]. The National Birth Defects Prevention Study (NBDPS), an ongoing case-control study of about 30 different birth defects, started in 1997, examined individual and household SES in relation to phenotypes of selected birth defects, including OFCs, based on 2,551 normal-formed live born controls and 1,841 cases delivered in 1997–2000. The individual SES was measured by parental education, occupation, and household income. Household SES index was defined by combining all individual SES measures. Elevated risk of CPO in the offspring of fathers with lower education levels and maternal operator/laborer occupation was observed [41]. Mossey and colleagues (2003) conducted a population-based case-control study in Scotland to investigate the association between SES according to household income and OFCs. Results revealed a strong association between OFC and SES, with a stronger pattern for CL/P than for CPO [42]. In a case-control study conducted in Philippines and included two separate sites, maternal lower education level was significantly associated with an increased risk of OFCs in Negros Occidental but not in Davao sample [43]

In contrast, a population-based case-control study consisted of 696 case mothers and 734 control mothers found no significant effect of SES on increasing the risk for OFCs [39]. Another population-based Hungarian case-control study included 1,374 cases with CL/P, 601 with posterior CP, and 38,151 controls and found no

difference in SES status, measured by maternal employment, between mothers of these two types of OFC cases and controls [44]. In Sweden, Kallen reported no association between low maternal education levels and the risk of OFCs [45]. Different measures of SES and different prevalences of birth defects across geographic populations may have contributed to the inconsistent findings to some extent.

Smoking

Several studies investigating the association between maternal smoking and the risk of OFCs have found positive associations with dosage effects [46-49], while others had conflicting results [50-53]. Population and sampling variations in addition to the variation in inherited pharmacogenetic susceptibilities may contribute to the disparities in cigarette smoking effects [54]. For example, a meta-analysis that included data from 24 case-control and cohort studies found a statistically significant association between CL/P and maternal smoking. It was suggested that smoking during pregnancy would increase the risk of having a child with CL/P and CP by 30% and 20%, respectively [55]. However, this association was significant for non-Hispanic Whites, but not for non-Hispanic Blacks and Hispanics [56]. Maternal passive smoking has been also associated with increased risk of CL/P. A study conducted in Tehran, Iran found a positive association between the environmental tobacco smoke exposure and OFCs [57]. Similarly, based on a study included 88 infants with CL/P and 651 infants without any major external birth defects, the odds ratio for CL/P associated with maternal passive smoking was 1.8. After the adjustment for maternal occupation, periconceptional flu or fever, and infant gender, the risk increased to 2.0.

Since the mid-1990s a number of epidemiological studies have investigated interactions between various genes (transforming growth factor alpha (TGFa), transforming growth factor beta-3 (TGFb3), retinoic acid receptor alpha (RARA),

msh homeobox-1 (MSX1), cytochrome P (CYP), glutathione S-transferase (GST) and epoxide hydrolase-1 (EPHX1)) [58] and markers in the glutathione s-transferase-1 (GSTT1) or nitric oxide synthase-3 (NOS3) gene [54, 59-61] and smoking by women during pregnancy in relation to the development of CL/P in their offspring [58]. Case-triads have suggested an association between a NAT2 haplotype and isolated CL but with little evidence of interaction with smoking, but the other genes related to detoxification of compounds of cigarette smoke (NAT2, CYP1A1, GSTP1, GSTT1, and GSTM1) were not confirmed [62]. Smoking has also been recently associated with a joint risk with variants in IRF6, while the same study reported interactions between multivitamins (MVIs) and IRF6 variants [63]. These findings have been inconsistent, suggesting that any interaction would probably explain only a small proportion of OFCs. Such studies are still preliminary [55].

Alcohol consumption

Several studies have shown an association between prenatal alcohol exposure and OFCs [64, 65], but the evidence has been more inconsistent [66]. Studies also suggest that 'binge' drinking patterns increase the risk of OFCs [67], which is supported by associations with variation in the ADH1C alcohol dehydrogenase gene. However, these links to alcohol consumption remain to be confirmed [68].

Maternal alcohol consumption was also examined in some studies in relation to OFC in the offspring. For example, Werler et al. explored the association between maternal alcohol use and the risk of birth defects in the offspring. Three measures of alcohol exposures were used: (1) maximum number of drinks in any day (maximum intensity), (2) average daily frequency, and (3) average intensity of drinking per day. The only statistically significant increased risk was observed among CL/P cases in the highest intake category, five or more drinks per day (odds ratio (OR)=3.0 [95%

confidence intervals (CI) 1.1-8.5]) [69].

In a population-based case-control study conducted in Iowa between 1987 and 1991, cases were obtained from the Iowa Birth Defects Registry. Alcohol use was categorized as 1-3, 4-10, or >10 drinks per month within the three months prior to conception. CL/P risk was significantly associated with increasing alcohol exposure [64]. Another population-based case-control study of California births from 1987 to 1989, investigated the association between maternal alcohol use and the risk of OFCs. Data on alcohol use was categorized as never, 1-3 during the four months critical window period, 1-3 per month, 1-4 per week, or daily. The only significant associations were found among mothers reporting five or more drinks per drinking occasion, with ORs of 3.4 [95% CI 1.1-9.7] for isolated CL/P, 4.6 [95% CI 1.2-18.8] for multiple CL/P, and 6.9 [95% CI 1.9-28.6] for syndromic OFCs [70]. Romitti and colleagues (1999) conducted a study in Iowa and found a significant increased risk for CL/P among mothers reporting ≥4 drinks per month during the periconceptional period [71]. Yet, in a multicenter case-control study in four European countries where alcohol use was defined as <70grams or >70 grams per week found a statistical significant increased risk only for isolated and non-isolated CP. This finding was inconsistent with the studies listed above, which showed no significant association between maternal alcohol use and CP [65].

Medications

Inconsistent associations have been found when looking at OFCs and anticonvulsant seizure medications, corticosteroids, or benzodiazepines, the anti-depressant drugs [72-75]. Epileptic women are at increased risk of having offspring with OFCs [76-79]. It was unclear whether the epilepsy or the drug therapy used to treat the epilepsy that account for the increased clefting in epileptic women [11]. Several studies

reported the increased risk of congenital malformations, including OFCs, with the anticonvulsant use to treat the epilepsy [78, 80-82]. Smith has reported that more than 80% of pregnant women exposed to trimethadion in utero as the only anticonvulsant medication during pregnancy have either been spontaneously aborted or malformed at birth. The most frequent major malformations reported were CL/P and cardiac defects [83]. Using data from a population-based case-control study, maternal epilepsy and anticonvulsant drug therapy were both associated with increased risk of non-syndromic CLP, but not with CPO [84].

Hashmi et al. used data from the NBDPS to evaluate the association of maternal report of febrile illnesses in early pregnancy and the risk of OFCs. Mothers reporting febrile illness during pregnancy were stratified by fever grade and antipyretic use. The dataset included 5821 controls, 1567 cases of CL/P and 835 cases of CPO. A modestly increased risk was observed for isolated CL/P. Stratification by fever grade (body temperature <101.58 or 101.58F) did not yield significant differences in risk. Risk estimates were higher among women who reported a fever but did not take antipyretics to control their fever, particularly for non-isolated compared with isolated OFCs. The authors suggested that adequate control of fever may diminish the deleterious effects of fever in cases of OFC [85].

Corticosteroids are mainly used to treat asthma, lupus, and rheumatoid disorders. Several studies reported a significant association between maternal use of the corticosteroids during the first trimester of pregnancy and the risk of having offspring with CL/P [74, 86, 87]. It was theorized that the steroids act directly on the fetus, resulting in the loss of amniotic fluids [88]. It was also suggested that receptors of glucocorticoids are more common in palatal mesenchymal cells, affecting the palatal formation when corticosteroids are used in the first trimester of pregnancy [89, 90]

Caffeine

Bille et al. examined the association between the maternal lifestyle factors during the first trimester and OFCs based on prospective data from the Danish National Birth Cohort. Information on risk factors including tea, coffee, and cola consumption was obtained during pregnancy for 192 mothers who gave birth to children with an OFC while 828 mothers were selected as controls. The investigators found no association with maternal coffee or cola drinking among the mothers of affected infants. However, they found associations, although insignificant, with maternal drinking of more than 11 colas per week as well as drinking five or more cups of tea per day during the first trimester of pregnancy [91].

Another population based case-control study evaluated the association between maternal consumption of coffee and caffeine from other types of beverages in early pregnancy and the risk of delivering an infant with an OFC. Coffee consumption during the first trimester was associated with an increased risk of CLP, but not CLO, in a dose dependent manner. However, no evidence was found for an association between other caffeinated beverages and the risk of CLP [92]. Further, Collier and colleagues (2009) investigated whether an association between maternal intake of coffee, teas, sodas, chocolate, and medications containing caffeine in the year before pregnancy and the risk of having a child with CL/P and CPO. The only significant association was between Isolated CL/P and the use of medications containing at least 100 mg of caffeine per dose [93].

Other environmental pollutants

A few epidemiological studies investigated the relationship between exposure to environmental lead and birth defects and yielded inconsistent results [94]. No effect on prevalence at birth of major or minor anomalies has been noted in some studies,

while other investigations reported an association between lead exposure and birth defects [95]. Vinceti et al. observed an excess risk of cardiovascular defects, OFCs, and musculoskeletal anomalies in the lead polluted area [96]. Additional environmental exposures include some specific teratogens [66, 97] such as stress [98] and ionizing radiation [99-101]. Nonetheless, the harmful effects of these factors are still inconsistent [100]. Studies of gene-environment interaction may provide the understanding required to explain such effects [58]. However, the interaction between the studies of the environmental risks and genes related to clefting require large prospective cohort studies and access to genetic material to measure effects on clefting. Attempts at identifying susceptibility loci via family and case-control studies have proved inconsistency [102]. Yet, this is a promising area of research that can be expected to expand [103, 104]. Thus, identification of the environmental risk, particularly if they can be adapted with genetic modifiers, can be more flexible and provide the best short-term opportunities to provide more insight into better understanding and prevention [58, 100].

Maternal Vitamin and Mineral Nutrition

Observational studies suggest a role for maternal nutrition in OFC, even though assessments of dietary intake or biochemical measures of nutritional status are demanding and often not available in many of the impoverished populations with the highest rates of OFCs [105].

Folate and nutrients related to one-carbon metabolism.

Case-control studies of folic acid-containing multivitamin (MVI) supplements [106-109], maternal dietary folate intake [57, 107, 110-112], and red cell and plasma folate [43, 112-114] are inconsistent. Bille et al. have found that supplementation use of folic acid with ≥400-mcg daily during the entire first trimester would have an inverse association

with OFC [91]. Furthermore, in a 2011 case-control study in Utah, even though there were no differences in MVI use during pregnancy, case-mothers had significantly lower plasma and red cell folate levels than did control mothers, and the mean differences in folate levels between cases and controls widened years after the affected pregnancy, suggesting that progressive disorder of folate metabolism may be more common in case mothers compared to control mothers [34].

Smits and Hukkelhoven reported an increased risk of adverse birth outcome at both ends of the interpregnancy interval spectrum, and a lower risk between 12 and 23 months. The authors hypothesized the increased risks associated with short interpregnancy intervals are partly attributable to maternal depletion of micronutrients, particularly folate [115]. Pregnancy places a burden on maternal micronutrient reserves and, if a new conception occurs before these reserves are sufficiently restored, growth and development of the conceptus may be compromised. Pregnancies accomplished shortly after the preceding delivery, in addition, are more likely than others to be unintended [116], which decrease the probability of periconceptional folic acid supplements (or MVI) use. However, Villamor et al., Krapels et al. and Wyszynski et al. suggested the risk of OFCs to be dependent on periconceptional intake of folate and other micronutrients [111, 117, 118].

Other specific nutrients

Strong evidence suggests an association between OFCs and other nutritional factors, including vitamin A, riboflavin, folic acid, panthothenic acid, vitamin B12, vitamin B6, and zinc [111, 119, 120]. Mothers of infants with CL/P have been reported to have higher mean serum homocysteine levels [113, 114, 121]. Vitamin B-6 (pyridoxine and related compounds) is also a co-factor in homocysteine metabolism and reduces the occurrence of CL/P in animal studies [114]. Biomarkers of poor vitamin B-6 status were

associated with an increased risk of CL/P in the Netherlands [113] and in the Philippines [43].

Zinc is important during pregnancy for the fetal development; and zinc deficiency causes CP and other malformations in animal studies [122]. Mothers of children with CL/P in the Netherlands had lower erythrocyte zinc levels than control mothers. In Philippines, zinc deficiency is widespread, and higher maternal plasma zinc levels were associated inversely with the risk of CL/P [120]. However, in a case-control study in Utah, Munger et al. found no difference in plasma zinc levels between case and control mothers [123].

Iron intake during pregnancy was also found to decrease the risk for OFCs [57]. Other nutrients that may be involved in the etiology of CL/P include vitamin B2 and vitamin A [101]. Bille et al., however, found no effect for vitamin A, B6 or B12 on the occurrence of cleft [91].

According to a meta-analysis conducted in 2008 [112], maternal use of MVI supplements in early pregnancy may attenuate the birth prevalence of clefts by 25%. A potential interaction between maternal hyperthermia during pregnancy and MVI supplement use was indicated by two previous studies, suggesting that supplement use reduces the increased risk of CL/P associated with hyperthermia [124, 125]. On the other hand, Czeizel et al. indicated that daily supplementation with MVI does not have the inverse effect on the risk of clefts [126]. It is difficult to determine whether this reduction is due to the consumption of a specific nutrient or other healthy behaviors confounded these results [112].

Additionally, several studies investigated whether the risk for birth defects associated with maternal diabetes is attenuated by use of multivitamin supplements during the periconceptional period. Mothers with diabetes were having an increased

risk of having offspring with selected birth defects. However, the effect appeared only within mothers who had diabetes but were not taking MVIs, suggesting that MVI use during the periconceptional period may reduce the risk for birth defects among offspring of mothers with diabetes [127, 128]

Maternal Obesity and Underweight

Obesity is a health condition in which excess body fat has accumulated, leading to increased health problems such as heart disease and type 2 diabetes and reduced life expectancy [129]. Several factors including higher food energy intake with reduced energy expenditure (sedentary life style) [130] and genetic susceptibility are involved in obesity. In addition, pregnancy, in itself, is considered a risk factor for obesity as the mother gain weight during pregnancy and become increasingly obese with the frequent pregnancies, increasing the risk of congenital malformation and stillbirth [131]. Maternal underweight is associated with several adverse outcomes, including low birth weight, anemia, and an increased mortality rate [132]. Nevertheless, it remains an understudied health problem [133].

A study intended to estimate the overall prevalence of overweight and obesity in the world and in various regions in 2005 and to project the global burden in 2030. Overall, 23.2% of the world's adult population in 2005 was overweight with a higher rate in men (24.0%) than women (22.4%). The overall prevalence of obesity in the world, yet, was lower (9.8%) with a higher rate in women (11.9%) than obese men (7.7%). The total number of overweight adults was projected to increase during the period 2005 to 2030 from 937 million to 1.35 billion, while the number of obese adults was expected to increase from 396 million to 537 million without adjusting for secular trends [134]. In addition, the incidence of obesity in pregnancy has increased

over the past 2 decades; with nearly 50% of U.S. women aged 15-49 years classified as overweight or obese [135].

Body-mass-index (BMI) is a screening tool calculated from an individual's weight and height and defines people as overweight (pre-obese) if their BMI is between 25 and 29.9 kg/m^2, obese when it is greater than 30 kg/m^2, and underweight when it is less than 18.5 kg/m^2 [136]. The BMI was originally invented by Adolphe Quetelet in 1832, as the relation between body weight and mortality, particularly cardiac disease and diabetes, gradually became a medical concern following the Second World War, and thus, a quest for a reliable and practical index of relative weight began to be increasingly important. Quetelet proposed that in adults, in exploring various indices combining weight and height, normal body weight in kilograms was proportional to the square of the height in meters [137, 138]. Ancel Keys (1904–2004) confirmed the validity of the Quetelet Index and named it the BMI [139]. Since then, as evidence of the association of obesity with various diseases continues to increase, the BMI has been used as an expression to report the link of excess relative weight to morbidity and mortality. Even though the generalizability and applicability of the BMI and its cut-off points to other populations has been questioned and its sensitivity as a measure of excess fat queried, it remains a dependable value and the basis of much of the associations reported heretofore with obesity [140].

Maternal obesity and DM have been hypothesized to act synergistically in the pathogenesis of craniofacial abnormalities [141-143], and both maternal obesity [143, 144] and underweight [145] have been found to be associated with CL/P, but these issues are still insufficiently studied in OFC research [105].

The prevalence of obesity is currently rising worldwide. The epidemic is especially pronounced in women of reproductive age [146]. A study conducted in 2012 aimed to estimate the prevalence of adult obesity from the 2009-2010 National Health and Nutrition Examination Survey (NHANES) and compare adult obesity and the distribution of BMI with data from 1999-2008. The age-adjusted prevalence of obesity was 35.5% among adult men and 35.8% among adult women. Obesity showed no significant increase among women overall through 1999-2010 (adjusted odds ratio aOR=1.01 [95% CI 1.00-1.03]), but increases were statistically significant for non-Hispanic black women and Mexican American women. Men presented a significant linear trend through the period 1999-2010. For both men and women, the most recent 2 years (2009-2010) did not differ significantly from the period 2003-2008. The prevalence of obesity was 35.5% among males and 35.8% among females; and BMI trends were similar to trends in obesity [147]. When the future prevalence and BMI distribution was projected for 2010 to 2030, it was estimated that if the trends continue, in only 15 years, 80% of all American adults would be overweight or obese [148].

Maternal undernutrition is highly prevalent in low-income and middle-income countries, resulting in significant increases in mortality and overall disease burden. Undernutrition involves deficiencies of essential vitamins and minerals (micronutrients) as one form of malnutrition, with obesity or over-consumption of specific nutrients as another form [149] For instance, it has been reported that in many areas of India people suffer from an under-nutrition problem [150]. Nevertheless, Garg et al. recommended immediate attention for the higher rate of obesity among Indian women. Between the periods 1998–1999 to 2005–2006, the prevalence of obesity increased by 24.52%. 23.7% of women aged between 40-49 years were reported to be

obese. 23.5% of the obese residents reside in cities and 30.5% of them are wealthy. Several life style factors, such as sedentary lifestyle and junk food habits contributed to the increased prevalence in India [150]. Another study comparing the prevalence of obesity between men and women in Shahjahanpur City, India found the highest rate to be in women at age 41-50 years (41.2%) and men at age 61-70 years (37.0%) [151].

A longitudinal prospective study conducted in 2011 has revealed that in comparison to normal weight pregnant women, obese pregnant women were at increased risk of gestational diabetes mellitus, pregnancy induced hypertension, pre-eclampsia, and postpartum infection morbidities. These women were more prone to develop diabetes and chronic hypertension in the future as well [152].

As the prevalence of obesity has risen in developed countries, overweight among pregnant women has become increasingly common [153]. In the United States, the incidence of obesity among pregnant women ranges from 18.5% to 38.3%, according to the cohort studies and cutoff points used to define overweight [154, 155]. In Sweden, the prevalence of obesity among pregnant women was 26.1% [156, 157], while in Netherlands and France, the prevalence reported to be 17% [158]. Compared with normal weight, maternal overweight is related to a higher incidence of premature birth, congenital malformations, and infant mortality [158].

Maternal Obesity and Underweight and Cleft Lip and Cleft Palate Birth Defects

Maternal obesity is associated with an increased risk of several congenital birth defects. The association is most pronounced for neural tube defects [159-163], cardiac defects [141, 160, 162, 164], and orofacial cleft (OFC) defects [117, 141, 143, 162, 165-167]. However, many studies of maternal obesity and OFC risk were limited by the small sample sizes. For instance, Waller et al. has investigated the association between

maternal obesity, overweight, and underweight with distinct types of structural birth defects. The results suggested a borderline increased risk of isolated cleft palate only (CPO) within obese mothers (n=86; adjusted odds ratio (aOR)=1.27 [95% confidence intervals (CI) 0.98-1.66]) and a significant increase in cleft lip with or without palate (CL/P) within underweight mothers (aOR= 1.35 [1.04-1.76]) [162]. A recent a population-based case-control study conducted in Florida found obese women to experience increased odds of having a child with CL/P after controlling for maternal race, education, smoking, marital status, nativity, and maternal age (OR=1.25 [95% CI 1.05-1.48] and CP, OR=1.32 [1.07-1.62]). However, in this same study, the offspring of underweight mothers were not at a higher risk of OFCs [168].

Obese women were also reported by other studies to have high incidences of birth injuries and congenital malformations particularly OFCs [152, 169]. Mothers who were underweight were reported to have no significant increase or decrease in the risk for heart defects, hypospadias, omphalocele, or craniosynostosis birth defects, but did not have a significant increase in risk for CL/P (adjusted OR1.35 [95% CI 1.04-1.76]) [162].

In a study consisting of 1,049,582 infants born in Sweden from January 1, 1995 through December 31, 2007, maternal overweight and obesity were associated with an increased risk OFCs and the risk was increasing with the increased degree of obesity [170]. Another study conducted in Sweden consisted of 988,171 infants, where OFCs were divided into: isolated CPO, CLO, and CL/P. The subjects were also divided into isolated (without any other major malformation present) or non-isolated (with other major malformations). In the maternal underweight group, no change in the risk for an infant with cleft was observed. In the overweight group, the risk was above one for CPO, CLO, CLP, and all CLs as well as for isolated and non-isolated

defects separately. In the group of obese mothers, there was an overall increased risk for infants with OFCs. The increased risk was higher when the OFCs were associated with other major malformations than when they were isolated [171].

In Saudi Arabia in 2012, a study aimed at detecting the predictors of isolated structural birth defects in live births. Out of 37,168 live births, isolated structural birth defects were found in 318 cases. Obesity was a significant predictor for increased facial defects (aOR=5.92 [95% CI 2.8–12.4]) [172].

In contrast to the studies described, Oddy and collegues reported an insignificant increased risk of OFC associated with obesity (n=6; aOR=1.41 [0.85-2.34]) [173]. Stott-Miller et al. also evaluated the effect of maternal obesity in relation to the risk of non-syndromic orofacial clefting. Regardless of the type of cleft, obese women had a small, non-significant increase risk of isolated OFCs in their offspring compared with normal-body mass index women [174].

Villamor and Cnattingius have examined the associations between change in pre-pregnancy BMI from the first to the second pregnancies, and the risk of adverse outcomes during the second pregnancy in a nationwide Swedish study of 151,025 women who had their first two consecutive singleton births between 1992 and 2001. The results supported the causal relation between being overweight or obese and risks of adverse pregnancy outcomes. Additionally, they suggested that modest increases in BMI before pregnancy could result in perinatal complications, even if a woman does not become overweight [175]. Similarly, Guelinckx reported a higher incidence of premature birth, congenital malformations, and infant mortality among mothers with increased BMI [153]. Cedergren and Kallen have regarded the positive association between maternal obesity and OFCs risk to the undetected type-2-diabetes mellitus within obese mothers [171].

Maternal Diabetes

Diabetes mellitus (DM) is a group of metabolic diseases resulting from defects in insulin secretion, insulin action, or both and characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. Three main types of diabetes have been defined: type-1, type-2, and gestational diabetes mellitus (GDM) [176]. Type-1 diabetes mellitus or insulin-dependent diabetes mellitus (IDDM) is partly inherited and then triggered by certain infections. It results from a T-cell mediated autoimmune destruction of the pancreatic beta cells in genetically predisposed individuals [177]. Type-2 diabetes or non-insulin-dependent diabetes mellitus (NIDDM) is due primarily to lifestyle factors and genetics [178]. Type-1 and -2 are both conditions that usually cannot be reversed. Hence, adherence to healthy diet, exercise, and use of appropriate medications is very important to keep blood sugar levels as close to normal "euglycemia" and avoid diabetes complications [179].

Gestational diabetes mellitus (GDM) is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels (particularly during third trimester of pregnancy) when their bodies do not secrete the adequate insulin required during pregnancy [180]. Yet, mothers with GDM are at high risk for having or developing diabetes after their pregnancy [181]. There is a very close relationship between GDM and Type 2 diabetes; GDM is considered to be a transient unmasking of an underlying predisposition to Type 2 diabetes, induced by the metabolic changes of pregnancy [182]

Diagnoses of Diabetes

According to the American Diabetes Association (ADA), an individual can be diagnosed with DM in any one of the four methods: (1) Glycosylated hemoglobin, or hemoglobin A1C, of $\geq 6.5\%$; (2) Fasting Plasma Glucose (FPG) of ≥ 126 mg/dL; (3)

two-hour plasma glucose of ≥ 200 mg/dL during an Oral Glucose Tolerance Test (OGTT); or (4) classic symptoms of hyperglycemia or hyperglycemic crisis (polydipsia, polyuria, and unexplained weight loss) accompanied by a random plasma glucose of ≥ 200 mg/dL. However, different diagnoses criteria of GDM have been identified [183]. For instance, the World Health Organization (WHO) in 2006 has developed a different diagnostic criteria with lower glucose cut-off values for GDM than the ones reported by the ADA and demonstrated that GDM should be diagnosed at any time in pregnancy if one or more of the following criteria are met: (1) FPG of 92 -125 mg/dl); (2) one-hour plasma glucose of 180 mg/dL following a 75g OGTT; or (3) 2-hour plasma glucose 153 -199 mg/dL following a 75g OGTT. These guidelines are based on the association of plasma glucose and adverse maternal and neonatal outcomes during pregnancy, at birth and immediately following it [184].

Diabetes first onset during pregnancy was recognized and termed "GDM" in the 1950s [185]. GDM was originally defined to identify pregnant women who are at a higher risk for developing Type-2 diabetes later in life. The diagnosis is now being used to predict many potential neonatal and maternal complications in pregnancy [186]. The prevalence of GDM varies greatly from 1 to 16% depending on the population studied and the diagnostic criteria used [187]. For several years, the diagnosis of GDM at the local hospitals was made by a 100-g oral glucose tolerance test (OGTT) using the ADA criteria based on the "selective screening," which is a selective strategy to detect GDM among older or obese women [188]. However, the 100-g glucose load caused vomiting in nearly 10% of the women undergoing the OGTT [189]. Therefore, after the ADA endorsed the 75-g OGTT for the diagnosis of GDM, it was decided to screen all women not previously known to have diabetes using the 75-gram OGTT between 24 and 28 weeks of gestation and using diagnostic cut points of greater than

92 mg/dl for the fasting glucose test; greater than 180 mg/dl one hour after drinking the 75-gram glucose solution; and greater than 153 mg/dl two hours after drinking the glucose solution [183].

Epidemiology of Diabetes

Diabetes mellitus is one of the most common chronic diseases in nearly all countries, and continues to increase in numbers and significance, as changing lifestyles lead to reduced physical activity, and increased obesity [190]. The current estimate of diabetes prevalence worldwide was reported by the World Health Organization (WHO) to be 171,000,000, while it is projected that in 2030, the prevalence will increase to 366,000,000 [191]. Compared to estimates reported by previous studies, the prevalence of diabetes worldwide is significantly increasing. In 1995, one worldwide study has projected the number of people with diabetes in all countries of the world for three points in time, the years 1995, 2000, and 2025. The prevalence of diabetes in adults worldwide was expected to be 4.0% (135 million) in 1995, with a higher prevalence within females than males with diabetes (73 vs. 62 million). However, the prevalence of diabetes was expected to rise to 5.4% (300 million) by the year 2025, showing a 35% increase in the worldwide prevalence of diabetes, with a somewhat reduced excess within females than males (159 vs. 141 million) [192, 193]. Another study projected that in 50 years the number of American with diagnosed diabetes will increase 165%, from 11 million in 2000 to 29 million in 2050 with a higher prevalence in females than in males after the age of 64. This study predicted that 37% of the 18 million increase in 2025 would be due to changes in demographic composition, 27% due to population growth, and 36% are due to increasing prevalence rates [194]. Another study projected an increase of diagnosed diabetes prevalence from 4.4% (12.0 million) in 2000 to 9.7% (39.0 million) in 2050

[195]. In 2011, a follow-up epidemiological study evaluated the current prevalence of NIDDM in Saudi Arabia. The age-adjusted prevalence of NIDDM was 31.6% with a significantly higher prevalence in men (34.7%) than in women (28.6%) [196].

The frequency of GDM usually reflects the frequency of NIDDM in the underlying population [197, 198]. Established risk factors for GDM include advanced maternal age, obesity, and family history of diabetes [180]. Xiong et al. estimated the prevalence, risk factors, and maternal and infant outcomes of mothers with GDM in a retrospective cohort study, based on 111,563 pregnancies delivered between 1991 through 1997 in 39 hospitals, in northern and central Alberta, Canada. The prevalence of GDM was 2.5%. Risk factors for GDM included age over 35 years, obesity, history of prior neonatal death, and prior cesarean section. Teenage mothers and women who consumed alcohol were less likely to have GDM. Mothers with GDM were at increased risk of presenting with pre-eclampsia, premature rupture of membranes, cesarean section, and preterm delivery. Infants born to mothers with GDM were at a higher risk of being large-for-gestational-age [199].

Maternal Diabetes and Cleft Lip and Cleft Palate Birth Defects

Animal Studies

Abundant clinical evidence indicated that diabetic mothers are at a high risk of having malformed offspring [200, 201] and that congenital malformations contribute to the high neonatal loss among infants born to diabetic mothers [202]. Watanabe and collegues conducted an experiment to study the teratogenic effects of alloxan diabetes upon the mouse embryo. CP was found to be induced in embryos of alloxan-diabetic females, with the type and frequency of deformities being dependent upon the timing of alloxan injection [203].

Ejdesjo et al. investigated the influence of parental transgenerational genetics

and maternal metabolic state on fetal deformity in diabetic rat pregnancy. Rats from an inbred malformation-resistant (W) strain, and an inbred malformation-prone (L) strain, were cross-mated to produce two different F_1 hybrids, WL and LW. Normal (N) and manifestly diabetic (MD) WL and LW females were mated with normal males of the same F_1 generation to obtain WLWL and LWLW F_2 hybrids. Maternal diabetes increased malformation and resorption rates in both F_2 generations. MD-WLWL offspring had higher resorption rate but a similar malformation rate compared with the MD-LWLW offspring. Such results imply a possible teratological mechanism in diabetic pregnancies that are influenced by maternal metabolism and parental strain epigenetics [204]. In contrast, an experiment was conducted to investigate whether congenital malformations in offspring of alloxan-diabetic mice can be prevented by insulin injections of 80 mg per kg of bodyweight during pregnancy. In 50 successful pregnancies treated with insulin, only one fetus (0.2%) of 472 was malformed with a cleft palate; in 50 successful pregnancies given alloxan alone, 14 (28%) of mice had one or more malformed fetuses. Altogether, six of 437 fetuses had CP. The difference between the alloxan group and insulin treated group in the number of mothers having malformed fetuses, and in the number of malformed fetuses produced was statistically significant according to the chi-square test with a probability level of less than 0.01. However, no significant correlation was observed between the magnitude of hyperglycemia of mother mice and the frequency of fetuses with congenital malformations [205].

Human Studies

Diabetes Mellitus (DM) has been identified as independent risk factors for several birth defects, providing support for a mechanism that involves hyperglycemia and hyperinsulinemia in the development of malformations [206, 207]. Mothers who

develop GDM later in pregnancy may have had undiagnosed type-2 DM and are susceptible to acquire DM later in life [208]. However, it is debated whether this is true also at gestational diabetes [209].

A population-based case-control study was conducted to investigate the association between maternal DM and the risk of OFCs in the offspring using the 1996 National Center for Health Statistics United States Natality database. The sample consisted of 2,207 live births with CL/P and 4,414 randomly selected live births controls. Results indicated an increased risk for CL/P among diabetic mothers compared to non-diabetic mothers (adjusted odds ratio (aOR)=1.35 [95% confidence interval (CI) 1.00–1.82]) [210]. In a retrospective cohort study consisted of 126 non-syndromic cleft cases, the association between maternal diabetes mellitus and the risk of OFCs was evaluated. Results indicated a significant increased risk of isolated CP within diabetic mothers [211]. CP has been also reported by Arteaga to have a higher frequency in congenital malformation than in the rest of malformed newborns of non-diabetic mothers [212].

Data from the National Birth Defects Prevention Study from 1997 to 2007 were used to investigate the association between maternal Dietary Glycemic Index (DGI) and the risk of birth defects among non-diabetic women. Among the 53 birth defects analyzed, high DGI was significantly associated with encephalocele and atrial septal defect. Using quartiles to categorize DGI, the authors identified associations with CLP and anorectal atresia/stenosis. The joint effect of high DGI and obesity provided evidence of a synergistic effect on the risk of selected birth defects. High DGI was associated with an increased risk of a number of birth defects. Obesity coupled with high DGI appeared to further increase the risk for some birth defects [213]. Additionally, using dietary data collected in the Boston University Slone

Epidemiology Birth Defects Study, Yazdy et al. examined the effect of a high dietary

glycemic index (dGI) or load (dGL) on the risk of birth defects. High DGL intakes

were more common than controls for OFC case groups, but the Odds Ratio (OR)

estimates were unstable due to small population size [214].

In 2002, a study was conducted to investigate the frequency of hyperglycemia

in pregnant women who were without health benefits and did not receive prenatal

specialist care. Clinical characteristics of newborns show statistically significant

increased risk of CLP in offspring whose mothers had inadequate prenatal care

compared to of infants whose mothers had regular prenatal care, suggesting a

necessity to start establishing new programs and ways of making health information

available to women in primary care clinics to educate the general population and

stress the importance of regular visits to a prenatal care specialist [215].

Goldman et al. investigated whether arachidonic acid is involved in processes

analogous to neural tube folding and fusion in diabetic mothers. This hypothesis was

raised by the role of arachidonic acid in palatal elevation and fusion. The study

suggested that the mechanism of mediating the teratogenic effect of an increased

glucose concentration involves a functional deficiency of arachidonic acid at a critical

stage of organogenesis [216].

Furthermore, a Turkish congenital malformation survey revealed a

significantly frequent incidence of CPO. Abnormal ultrasonographic findings and

disorders such as DM and GDM were found to be valuable indicators for the presence

of congenital malformations in the fetus [217].

Janssen et al. investigated the association between GDM and the development

of congenital malformations from a populations-based retrospective study. Data for

births to mothers with established diabetes were also available. Newborns of mothers

with established diabetes were more likely to have a congenital malformation than newborns of non-diabetic mothers. On the other hand, there was only a slightly higher prevalence of congenital malformations among newborns of mothers with GDM. The association with maternal established diabetes was greater for neonates with multiple malformations than for single malformations. Four to seven fold associations were observed with skeletal, neural tube and heart abnormalities, and CL/P. The association of established diabetes with congenital malformations was nearly twice as strong among female neonates than among male neonates and no such variation was observed for associations with GDM [218]. In addition, based on a cohort study of 2,060 infants to mothers with GDM, congenital malformations, including CL/P, have been correlated to pre-pregnancy BMI and to the severity of diabetes [142].

The risk of birth defects was investigated by Correa et al. (2012) in relation to DM and the lack of use of periconceptional vitamins or supplements containing folic acid using a population-based case-control study. Among 14,721 cases and 5,473 controls, the risk of OFCs associated with DM in the absence of periconceptional use of MVIs containing folic acid increased significantly (ratio of 11:2 (cases: controls) and aOR of 13.84 [95% CI 3.01-63.68]) compared to mothers with DM and reported periconceptional MVI use (ratio of 23:27 and aOR of 2.17 [95% CI 1.20-3.93]). This result suggests that the periconceptional use of MVI may reduce the risk for birth defects among offspring of mothers with diabetes [127, 128].

Abdominal obesity, aberrant glycemic control, hypertension, and hyperlipidemia are variably defined as a co-occurrence of metabolic syndrome [219]. Some of the common co-morbidities of this diagnosis include increased oxidative stress and inflammation and compromised immune function [220]. Investigation of this

syndrome, with the presence of obesity, DM, and hypertension may provide useful clues regarding birth defects associations [98].

Previous studies have suggested an increased risk for having newborns with OFCs in diabetic mothers compared to non-diabetic mothers [207, 211, 221, 222]. Although GDM has been also reported by previous studies to increase the risk for congenital birth defects [223-225], studies of the association between GDM and OFC are limited. Investigating the effect of maternal DM and GDM on the risk of OFC specific types may provide useful clues regarding the risk factors associated with the etiology of OFCs.

Hypertension

Hypertension is a chronic medical condition in which the systemic arterial blood pressure is elevated to a level that may induce adverse effects such as cardiovascular damage. Normal blood pressure is 120/80 mm/Hg. High blood pressure is anything more than 140/90 mm/Hg. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of associated health complications [226]. Although no direct cause has been identified, there are many factors such as sedentary lifestyle, smoking, stress, hypokalemia [227], salt (sodium) sensitivity [228], alcohol intake [229] and vitamin D deficiency that increase the risk of developing hypertension [230]. Hypertension is also caused by other conditions such as obesity [231]. Lifestyle modification including dietary changes, physical exercise, and weight loss has been proven to significantly reduce blood pressure in people with hypertension [232].

Epidemiology of Hypertension

Hypertension affects millions of persons in the United States, and less

than half of those with hypertension have their condition controlled. Using the National Health and Nutrition Examination Survey (NHANES) data, several studies have been conducted to estimate the prevalence of hypertension in the United States. A study has used the NHANES Survey 1999–2004 database, and found the overall prevalence of hypertension to be 29.3%. When compared with the 1999–2000 data set, there were non-significant increases in the overall prevalence of hypertension [233]. A more recent study reported the prevalence of hypertension in the United States. During 2005-2008, approximately 68 million (31%) U.S. adults aged ≥18 years were having hypertension, and this prevalence has shown no improvement in the past decade and of these adults, 86% had their condition uncontrolled [234].

In 2012, a study was conducted to examine the prevalence and outcomes of primary and secondary chronic hypertension using a population-based sample of deliveries. During 1995-2008, the prevalence of primary and secondary hypertension increased significantly from 0.90% in 1995-1996 to 1.52% in 2007-2008 and from 0.07% to 0.24%, respectively. Primary and secondary chronic hypertension were considerable for many maternal adverse outcomes, including acute renal failure, pulmonary edema, and preeclampsia, and accounted for a significant fraction of pregnancy complications [235].

Maternal Hypertension and Cleft Lip and Cleft Palate Birth Defects

Pregnancy in women with hypertension has various neonatal complications [236]. However, the effect of maternal hypertension of the risk of congenital malformations, including OFCs, has been understudied [237]. In a study conducted to explore possible maternal factors associated with OFCs in the US population, the prevalence of pregnancy-associated hypertension was significantly higher in OFC

group compared to controls. After adjustment for maternal age and tobacco smoking, multivariate models found Non-Hispanic Blacks with pregnancy-associated hypertension to be at lower risk for having a child with an OFC (aOR=0.09 [95% CI 0.02-0.42]) as well as Hispanics (OR=0.79 [95% CI 0.63-0.98]). Researchers in this study suggested a role of the epigenetic DNA modification resulted from the non-inherited (modifiable) factor, the pregnancy-associated hypertension, in determining whether the genes that direct the proper formation of the lip and palate are properly expressed [56].

A case-control study conducted in Thailand sought to identify the risk factors for congenital malformations between May 1987 to April 1988. CLPs were among the most common types of malformations. Risk factors significantly associated with malformations included maternal hypertension during pregnancy, maternal age > 35 years, low maternal education levels, separated or divorced marital status, family history of similar abnormalities, an accident during pregnancy, and maternal illness during pregnancy [238].

Although hypertension has been associated in a few studies with congenital malformations, maternal hypertension and the risk of having offspring with OFCs have been relatively understudied. Further investigation of this association may help in reducing the risk of OFCs.

Metabolic Syndrome

Metabolic syndrome is a combination of medical disorders that, when co-occurring together, increase the risk of developing cardiovascular disease and diabetes [239, 240]. In 2001, the Third Report of the U.S. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood

Cholesterol in Adults (NCEP/ATP III) provided a working definition of the metabolic syndrome based on five commonly measured clinical criteria and it requires at least three of the risk factors to be present: 1) central obesity: waist circumference ≥ 102 cm or 40 inches (male), ≥ 88 cm or 36 inches (female); 2) dyslipidemia: TG ≥ 1.7 mmol/L (150 mg/dl); 3) dyslipidemia: HDL-C < 40 mg/dL (male), < 50 mg/dL (female); 4) blood pressure ≥ 130/85 mmHg; 5) fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dl) [241]. In 2004, the American Heart Association intended to update the NCEP ATP III definition as follows: 1) Elevated waist circumference: > 40 inches or 102 cm (male), > 35 inches or 88 cm (female); 2) Elevated triglycerides: ≥ 150 mg/dL (1.7 mmol/L); 3) Reduced HDL ("good") cholesterol: < 40 mg/dL (1.03 mmol/L) (male), < 50 mg/dL (1.29 mmol/L) (female); 4) Elevated blood pressure: ≥ 130/85 mm Hg or use of medication for hypertension; 5) Elevated fasting glucose: ≥100 mg/dL (5.6 mmol/L) or use of medication for hyperglycemia [242]. The most recent definitions, though, are from the International Diabetes Federation (IDF) and from the American Heart Association/National Heart, Lung and Blood Institute AHA/NHLBI [243-245]. The differences between these definitions are essentially the threshold for the parameters to define a syndrome abnormality, the number of abnormalities before the syndrome is deemed to be present, and whether there is a compulsory abnormality that is required to be present [246].

Since 1947, several studies suggested that early onset of obesity, hyperplasia of normal adipocytes, and normal quantities of visceral abdominal fat may be associated with a favorable metabolic response in obese subjects [247, 248]. Keyes suggested that obesity for some was not a risk factor and might even be healthy [249]. Bonora et al. concluded that a subgroup of obese individuals with a normal metabolic response is evident [250]. Brochu et al. have also suggested that obese metabolically

normal subgroups must be taken into consideration in both clinical and research work. In fact, attempts at weight loss may be counterproductive [251]. Kip et al. conducted a study to assess whether the contribution of obesity to cardiovascular risk is independent of the presence of metabolic syndrome. Data revealed that metabolic syndrome, but not BMI, predicts future cardiovascular risk in women. Results also indicated that normal-weight women with the metabolic syndrome have a significantly higher cardiovascular risk. However, overweight and obese women with normal metabolism have a relatively low cardiovascular risk. A possible explanation suggested by Kip et al. was that the measurement of BMI to define overweight and obesity does not quantify the magnitude or ratio of subcutaneous to visceral fat or muscle in an individual. The visceral fat area appears to be an important link between many components of the metabolic syndrome, such as dyslipidemia and hypertension. For a better precise clinical measurement, it is important to assess whether the participants with normal BMI and the metabolic syndrome have relatively high levels of visceral fat or, conversely, whether obese individuals with normal metabolic status have relatively low levels of visceral fat [252].

Epidemiology of Metabolic Syndrome

Many reports were undertaken to explore the prevalence of the metabolic syndrome around the world. However, the prevalence rates of the metabolic syndrome reported in the different studies have varied widely, mainly because of differences in the criteria used for defining the syndrome and the differences in the characteristics of the populations studied [253].

Metabolic Syndrome in United States and Canada

Between NHANES 1988 to 1994, more than 25% of the population in the United States had metabolic syndrome by NCEP criteria. A similar prevalence was

described for Canada. By the age of 60, the percentage affected in the United States increased to 40% [219].

In 2003 to 2006, 34% of adults met the criteria for metabolic syndrome. Males and females between 40-59 years of age were about three times as likely as those 20-39 years of age to meet the criteria for metabolic syndrome. By the age of 60, males were four times as likely as the youngest group to meet the criteria, while females were more than six times as likely. Non-Hispanic black males were about 50% as likely as non-Hispanic white males to meet the criteria for metabolic syndrome, while non-Hispanic black and Mexican-American females were about 150% as likely as non-Hispanic white females to meet the criteria. Overweight males were six times as likely while obese males were 32 times as likely as normal weight males to meet the criteria. Overweight females were about five times as likely as normal weight females to meet the criteria and obese females were more than 17 times as likely [254].

Metabolic Syndrome in Europe

Several studies on the occurrence of the metabolic syndrome in Europe have been reported and the criteria used to define the metabolic syndrome varied across the studies [255-265]. However, it can be estimated that approximately 25% of the adult European population had the metabolic syndrome. Prevalence varied across the age group studied and geographic location. When NCEP and IDF criteria were compared, the IDF criteria usually gave a higher prevalence [253].

Metabolic Syndrome in Latin America

According to a meta-analysis [253], the prevalence of the metabolic syndrome, as defined by NCEP or WHO, is relatively high. Approximately 25% of the adult population had the metabolic syndrome, with the highest prevalence contributing to the Brazilian population (53%) [266].

Metabolic Syndrome in Asia

The prevalence of metabolic syndrome was reported by several studies in Central Asia, Southeast Asia, China, and Japan. In India, A cross-sectional population based study reported the prevalence of metabolic syndrome in a local population in India. Out of 1,568 patients were referred to High Tech Hospital, 33.17% of males and 27.04% of females were diagnosed to have metabolic syndrome [267]. Furthermore, a population-based survey of cohort of subjects in the Metropolitan city of Mumbai reported that 19.52% out of 548 subjects to have Metabolic syndrome. The overall prevalence of BMI (>23 kg/m2) was 79.01% [268]. In Southeast Asia, less than one-fifth of the studied population in Southeast Asia had the metabolic syndrome [269, 270]. In China, the general population had a relatively low prevalence, possibly because of the high waist circumference cut-off value of NCEP that was used for abdominal obesity criterion. In older Chinese subjects with type-2 diabetes, the prevalence was much higher [271-273]. Finally, in Japan, the reported prevalence varied substantially from one study to another. Surprisingly, two reports in men indicated a prevalence up to 25% of the population [274, 275]

Metabolic Syndrome in the Middle East

In the Eastern Mediterranean region, a study of adult female Saudi subjects found the prevalence of metabolic syndrome to be 16.1% and 13.6% according to IDF and ATP III definitions, respectively [276]. The prevalence of metabolic syndrome in the Arab Gulf countries was 10%–15% higher than in most developing countries, with a higher prevalence among women. The proportion of metabolic syndrome in the Arab Gulf countries ranged from 20.7% to 37.2% using ATP III definition, and from 29.6% to 36.2% using the IDF definition [277].

In conclusion, the overall prevalence of the metabolic syndrome

demonstrates that metabolic syndrome is prevalent worldwide and that it increases with age and with BMI. The prevalence varied by race and ethnicity but the pattern was different for males and females.

Metabolic Syndrome: The Underlying Causal Mechanism Linking Maternal Obesity, Diabetes, and Hypertension to OFCs?

There is a common link between hypertension, diabetes, and obesity illustrated by the causal relationship between the level of circulating insulin and diastolic pressure caused by obesity [278]. Abdominal obesity, glucose intolerance, hypertension, and dyslipidemia are risk factors that comprise metabolic syndrome [279]. The increasing global prevalences of NIDDM and hypertension are a result of rising rates of obesity [280], as well as hypertension [231] and have all been implicated in the development of congenital defects [141, 238]. Obese women are at higher risk for developing NIDDM and, through pregnancy, at higher risk of developing GDM. Women who develop GDM later in pregnancy may also have had undetected metabolic problems earlier in the pregnancy [208]. Since 1970, Navarrete et al. indicated a definitive relation between a maternal glucose metabolic disorder and congenital malformations and suggested research into the early phases of diabetic states in mothers pregnant of a deformed infant [281]. However, obese women, even in the absence of diabetes, have been found to have impaired glucose metabolism [208]. Forest et al. have revealed that among white women in their mid-30s, the prevalence of the metabolic syndrome is 3- to 5-fold increase in those with a history of pregnancy-induced hypertension in their first pregnancy [282].

McCarthy [130] has suggested that NIDDM results when pancreatic beta cells are unable to secrete sufficient insulin to maintain normoglycemia, typically in the context of increasing peripheral insulin resistance. The beta-cell abnormalities

fundamental to type-2 diabetes are thought to include both reduced beta-cell mass and disruptions of beta-cell function. Insulin resistance can be the consequence of obesity or of obesity-independent abnormalities in the responses of muscle, fat, or liver to insulin. Examples of susceptibility factors, given current evidence, that are likely to influence predisposition to OFCs by means of each of these mechanisms are shown (Figure 2-1).

Abdominal obesity, aberrant glycemic control, and hypertension are variably defined as a co-occurrence of metabolic syndrome [219] and are substantially interrelated, reflecting substantial overlap in their etiology and mechanisms [283]. Studies of the association between maternal bodyweight categories, DM and GDM, and hypertension and the risk of specific OFC types may substantially reduce the risk of OFCs associated with these conditions.

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Figure 2-1. Pathways to Type-2 Diabetes Implicated by Identified Common Variant Associations [130]
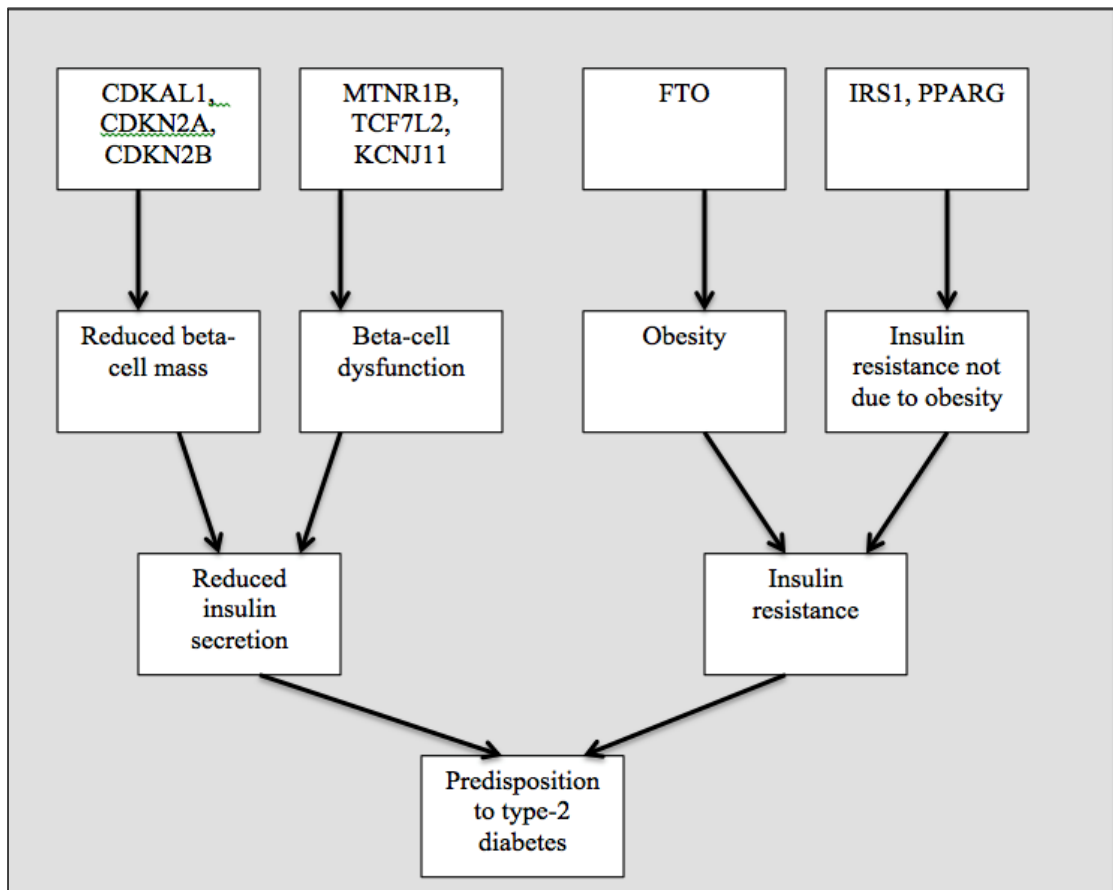
CHAPTER 3

MATERNAL OBESITY AND UNDERWEIGHT AND THE RISK OF

OROFACIAL CLEFTS[1]

Abstract

Objective To evaluate whether maternal underweight and obesity are independently

associated with risk of orofacial clefts.

Design Pooled analyses of population-based case–control studies.

Setting A unique and large international consortium of case-control studies from

Utah, Iowa, Norway (two studies 1996-2001 and (2000-2009)), and the U.S. National

Birth Defects Prevention Study.

Participants Mothers of 2,162 infants with cleft palate and cleft lip (CLP); 1,161

infants with cleft lip only (CLO); 1,774 infants with cleft palate only (CPO); and

10,633 controls.

Main outcome measures Association of orofacial clefts with maternal pre-pregnancy

weight classified by the body-mass index (BMI, kg/m^2) for underweight, normal

weight, overweight, and obesity.

Results Maternal obesity (pre-pregnancy BMI >30), compared to normal weight

(18.5<BMI>25), was associated with an increased risk of cleft palate with or without

cleft lip (CP/L) (aOR=1.13 [95%CI 1.01-1.25]), after adjusting for maternal age,

multivitamin use, smoking during pregnancy, alcohol use, and education level. We

also found a marginal association between maternal underweight and CP/L (1.0

[reference]; aOR=1.14 [95%CI 0.97-1.34]. CLO was not associated with underweight

or obesity. Among college-graduates, there was no increased risk of cleft palate for

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[1] Coauthored by Hebah A. Kutbi and Ronald G. Munger.

either underweight (aOR= 0.84 [95% CI 0.58-1.21]) or obesity (aOR =1.01 [95% CI 0.79-1.28]), but mothers with less than a completed college education had an increased risk of cleft palate for underweight (aOR =1.26[95% CI [1.05-1.51]) and obesity (aOR=1.17 [95% CI 1.05-1.32]).

Conclusions Maternal obesity and underweight are both similarly associated with increased risk of orofacial clefts. These deviations from normal weight likely represent diverse metabolic, dietary, socioeconomic, and lifestyle factors that may be related to the causes of orofacial clefts. Interestingly, we found significant modification of the associations between maternal underweight and obesity and cleft risk by maternal education levels. Further analyses are needed to identify the pathways leading to the increased risk for orofacial clefts and more detailed assessment of socioeconomic status is needed. Our findings suggest that BMI may be an imprecise indicator of risk and there is a need to assess mothers for hyperglycemia and other underlying metabolic abnormalities early in pregnancy to reduce the risk of orofacial cleft in their offspring.

Introduction

Clefts of the lip and palate are among the most common structural birth defects and a public health problem [1, 2]. In 2010 in the United States, an estimated 4,437 live births per year had cleft lip or cleft palate [3]. Several studies suggest that obesity, diabetes, or the underlying metabolic abnormalities known as the metabolic syndrome, may be involved in the pathogenesis of cleft lip and cleft palate [4-6]. However, further studies are needed for a more complete understanding of the etiology of this disorder [7].

Maternal obesity in early pregnancy has been associated with an increased risk

of orofacial clefts (OFCs) in some studies. Yet, the magnitude of effect has varied across studies and the question remains unresolved [8-12]. This question is especially relevant as obesity is leading global public health problem. Thus, even a modest effect of maternal obesity may be linked to a significant burden of OFCs. The role of maternal underweight is relatively understudied although it has potential adverse perinatal outcomes [13]. While underweight is a lesser problem in industrialized countries, a better understanding of the role of underweight may help in understanding the causes of OFCs in both industrialized and developing countries.

Obesity is usually defined as having a body-mass-index (BMI; weight in kg/height in M^2) of $\geq$30.0 kg/m^2 [14]. Among adults, age-adjusted prevalence of obesity in 2007-2008 was 33.8%, with an overall 32.2% among men and 35.5% among women [14]. It is expected that by 2015, 41% of adults in the United States will be obese [15]. An increased bodyweight is associated with increased incidence of a number of conditions, including diabetes mellitus and cardiovascular disease. An increased risk for diabetes mellitus begins to rise at a BMI of greater than 30 kg/m^2 [16]. Other risk factor that may contribute to a higher obesity risk is low educational attainment of mothers [17]. We assessed the relationship between maternal BMI and the risk of clefts in a consortium of studies from Utah, Iowa, Norway, and the U.S. National Birth Defects Prevention Study.

Methods

Study Design & Data Collection

This study is a combined, unique, and large international consortium of population-based case-control studies from two separate studies from Iowa, Utah, the U.S. National Birth Defects and Prevention Study (NBDPS), and two Norwegian studies. The combined sample includes 15,726 women including 5,093 mothers of

children with OFCs and 10,633 mothers of unaffected children. Table 3-1 summarizes the types of clefts, the numbers, and the sources of samples. Data were available on self-reported pre-pregnancy maternal weight and height and other perinatal and demographic factors, which are used as covariates to control for potential confounding. Body-mass index (BMI) was computed as weight (kg)/height (m^2) and used to define body weight categories as underweight (BMI<18.5 kg/ m^2), normal weight (18.5-<25 kg/ m^2), overweight (25-<30 kg/ m^2) and obese (≥30 kg/ m^2). Studies included in this current study are as follows:

(1) Utah Study: A state-wide case-control study of clefts was conducted in Utah during 1995 to 2004 in collaboration with the Utah Birth Defects Network (UBDN) involving 561 cases with CL/P and 660 randomly selected unaffected births (from birth certificates) matched cases by month, year of birth, and gender of the child. The UBDN staff members attempted to contact potential case and control mothers by mail to obtain consent for release of their names to USU investigators. Address updates were sought using available Internet services. If no mailing address was available, attempts were made to locate the mothers in person by field tracing that included visits to the last known home address and inquiries with neighbors. The UBDN later joined the National Birth Defects Prevention Study (NBDPS) described below. A detailed description of data collection is provided elsewhere [18].

(2) Norway Facial Cleft Study: The Norway Facial Clefts Study (NCL) is a population survey of infants born with CL/P in Norway in 1996 through 2001. Data included 570 cases and their parents and a randomly selected control sample of 736 infants born without birth defects in the same period [19]. Extensive data on maternal behaviors, household factors and socioeconomics were available. The data collection is described elsewhere [20].

(3) Norway National Mother and Child Cohort Study: The Norwegian Mother and Child Cohort Study (MoBa), conducted by the Norwegian Institute of Public Health (NIPH, Oslo, Norway), is a cohort consisting of pregnancies recruited beginning in 1999 to 2008 [21]. Identified were 164 cases of C/P and 551 control mothers of which were randomly selected with matching to the case sample by year and state of birth. Data on maternal health behaviors, demographic and socioeconomic characteristics, health problems and food behaviors were obtained during pregnancy between weeks 15 and 30 (data on risk and health behaviors is collected between 15 and 18 weeks). The study also involved follow-up interviews with the mother and child until the child is three years old.

(4) Iowa Case-Control Sample: The Iowa Registry of Congenital and Inherited Disorders (IRCID) case-control sample consisted of about 287 cases with CL/P and 302 controls born between 1987 through 1996. The control sample was randomly selected from all unaffected live births and matched to the affected sample by birth month, year and gender. Data on risk behaviors, socioeconomic characteristics and other relevant data, were obtained through telephone-based interviews and self-administered forms were sent by mail [22].

(5) National Birth Defects Population Studies: NBDPS samples with CL/P and control samples included multiple participating States. These include Arkansas, California, Georgia, Massachusetts, New Jersey, New York, North Carolina, Iowa, Texas, and Utah. NBDPS sample provided 3,491 CL/P cases and 8,357 control mothers, matched by State and birth year to the CL/P sample [23].

Table 3-1. Number of Controls and Orofacial Cleft Cases by Cleft Type and Study Site

Site and Birth years	Number of study participants by cleft type				
	Controls	Cleft Lip Only	Cleft Lip and Palate	Cleft Palate Only	All Clefts
Utah, USA (1995-2004)	660	142	232	187	561
Norway Case-Control Study (1996-2001)	763	140	234	196	570
Norway Mother-Baby (MoBa) Study (2000-2009)	551	31	94	63	184
Iowa, USA (1987-1991)	302	56	111	120	287
U.S. National Birth Defects Prevention Study (1997-2008)	8357	792	1491	1208	3491
Total sample	10633	1161	2162	1774	5093

Statistical Analyses

SPSS statistical analysis version 20.0 was used to describe the characteristics of study population. Descriptive analysis was conducted in SPSS to examine the association between obesity and other factors, such as maternal age, smoking during pregnancy, multivitamin use, education (college graduate, high school graduate only, and less than high school graduate) and socioeconomic status.

Analysis of variance was used to examine the association between body mass index (BMI) and each selected covariates, such as maternal age, study site, smoking during pregnancy, multivitamin use, education, and socioeconomic status.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the relative risk for CL/P across the weight categories defined by BMI levels. Multiple logistic regression analysis was used to adjust for differences in maternal age, educational level of mother (college graduate, high school graduate only, and

less than high school graduate), multivitamin use during the first trimester of

pregnancy, and history of smoking and alcohol use during the first trimester of

pregnancy (yes versus no for each) and model the effect of body weight on OFC risk.

Results

Among the case and control children, 58.6% (n=2,933) and 51.9% (n=5,480)

respectively were boys. Among the case children, cleft lip only (CLO) accounted for

22.8% (n=1,161), cleft palate only (CPO) 34.8% (n=1,774), and cleft lip with cleft

palate (CLP) accounted for 42.5% (n=2,162) of cases. Within CLO cases, 1,053 and

108 children cases were reported to have isolated and multiple birth defects,

respectively. 1,809 cases had isolated CLP and 353 cases had multiple CLP. Within

CPO cases, 1,313 and 461 CPO cases had isolated and multiple birth defects,

respectively.

Demographic characteristics of the sample appear in table 3-2. The mean ages

of mothers of cases and controls and the maternal BMI were not significantly

different at any site. Smoking during the index pregnancy period was common and

associated significantly with the risk of OFCs among Utah subjects (p-value=0.002),

Norway (p-value <0.001), and NBDPS studies (p-value <0.001). Use of alcohol by

the mother during the index pregnancy was significantly more frequent (p-

value=0.011) among the case versus control mothers in Norway study; no significant

associations were seen in the other studies. Maternal caffeine use during the first

trimester was associated significantly with the risk of OFCs in MoBa study only (p-

value=0.023). Maternal employment was significantly associated with the risk of

OFC in the Norway sample (p-value=0.019) and NBDPS sample (p-value=0.018), but

was not among any other study sites. Maternal folic acid intake was significantly

associated with the risk of OFCs within Iowa (p-value=0.055) and NBDPS (p-value=0.024) samples only. Maternal education was associated with the risk of OFC within NBDPS sample (p-value <0.001).

The distribution of body weight categories varied considerably across study sites. However, in subgroup analyses maternal body weight categories were only significantly associated with the risk of OFCs within NBDPS sample group, where higher percent of cases among underweight and obese mothers were observed (6.6% and 20.6%) compared to controls (5.5% and 18.1%), respectively.

Logistic regression models were used to evaluate the association between maternal BMI, maternal weight categories, and isolated and multiple OFCs combined (CLO, CLP, CPO, and all clefts). In a multiple logistic regression analysis that controlled for maternal age groups, maternal smoking during pregnancy, alcohol drinking, multivitamin use, and education (college graduate, high school graduate, and less than high school) shown in table 3-3, the estimated relative risk (adjusted OR (aOR) and 95% confidence intervals (CIs)) for having cleft lip and cleft palate (CLP) (aOR=1.15 [95%CI 1.00-1.32]), cleft palate with or without cleft lip (CP/L) (aOR=1.13 [95%CI 1.01-1.25]), and all clefts combined (aOR=1.12 [95%CI 1.01-1.23]) increased significantly with maternal obesity. No effect of maternal obesity on CLO was observed (aOR=1.06 [95%CI 0.89-1.27]). Associations between maternal bodyweight categories and the risk of isolated clefts, including CLO, CLP, CPO, CP/L, and all isolated cleft types combined were similar but were on the margins of statistical significance.

Table 3-4 illustrates the risk of isolated OFCs by maternal BMI categories by cleft types. Maternal body weight appeared not to be associated with any of the isolated cleft types.

Table 3-2. Demographic Characteristics of Mothers of Children with OFC Cases and Controls by Study Sites

Characteristics	Study Site											
	Utah		Norway CC[1]		Norway-MoBa[2]		Iowa CC[3]		NBDPS[4]		Total	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Maternal age in years $\pm$ standard deviation (SD)	27.0 $\pm$5.7	26.8$\pm$5.2	28.9$\pm$5.0	29.23$\pm$4.8	29.9$\pm$5.0	30.0$\pm$4.6	26.7$\pm$5.3	27.1$\pm$4.9	26.9$\pm$6.2	26.9$\pm$6.1	27.2$\pm$6.0	27.2$\pm$5.9
Paternal age in years $\pm$ SD	29.4$\pm$6.4	28.9$\pm$5.6	28.9$\pm$5.0	31.8$\pm$5.5	32.9$\pm$6.0	32.9$\pm$5.6	26.7$\pm$5.3	27.1$\pm$4.9	30.0$\pm$6.9	29.8$\pm$6.8	29.9$\pm$7.0	29.9$\pm$6.8
Body-mass index (BMI; kg/M[2]) $\pm$ SD	24.3$\pm$5.0	24.2$\pm$5.3	23.7$\pm$4.4	23.4$\pm$3.7	23.9$\pm$4.2	24.1$\pm$4.2	23.5$\pm$5.2	23.0$\pm$4.4	25.3$\pm$6.2	25.0$\pm$5.8	24.9$\pm$5.8	24.8$\pm$5.5
Maternal BMI categories												
Underweight[5] %	6.6	6.8	3.3	3.7	5.0	4.4	6.3	8.0	6.7	5.5	6.3	5.4
Normal Weight[6] %	55.3	59.5	3.3	3.7	63.6	62.6	65.4	65.4	49.1	51.4	53.4	54.3
Overweight[7] %	25.3	21.5	19.5	18.8	19.0	23.1	19.7	17.6	23.6	25.1	23.0	24.0
Obesity[8] %	12.8	12.1	8.1	7.0	12.4	9.9	8.7	9.0	20.7	18.1	17.3	16.2
Smoker %	13.5	8	41.6	31.8	27.6	23.8	25.1	22.2	21.2	16.2	23.1	17.4
Alcohol use in 1st trimester %	7.5	6.4	38.1	30.5	12.7	14	34.5	34.8	22.9	22.5	23.3	22.0
Maternal employment %	88.1	85.6	80.2	85.1	78.6	79.2	N/A	N/A	69.5	71.7	73.3	74.0
Maternal caffeine use in 1st trimester %	98.6	98.3	89.6	89.8	86.2	92.4	85.0	83.8	70.9	69.8	78.4	75.3
Multivitamin use %	75.8	75.6	37.2	40.6	70.7	74.6	63.6	71.1	82.2	83.9	75.0	79.5
Education $\leq$ High School %	8.0	6.5	16.1	11.4	5.7	2.6	9.8	7.6	19.9	17.3	17.1	15.2
Education $\geq$ College %	26.7	30.5	39.6	40.9	62.7	62.4	18.1	22.5	26.0	31.6	28.3	33.4
High School graduate %	65.2	63.0	44.2	47.7	31.6	34.9	72.1	69.9	54.2	51.1	54.6	51.4
Male %	59.2	60.6	60.3	53.3	58.2	55.2	53.8	54.0	58.6	50.9	58.6	51.9

[1]Norway case-control study.
[2]Norway mother-baby study.
[3]Iowa case-control study.
[4]National Birth Defect Prevention study.
[5]Underweight defined as BMI <18.5.
[6] Normal weight defined as =>18.5, <25 BMI.
[7]Overweight defined as =>25, <30 BMI.
[8]Obesity defined as BMI=>30.

Table 3-3. Risk of Orofacial Clefts by Maternal Body Weight Categories and Cleft Types.

Maternal Body Mass Index (BMI[2]) Group	Adjusted odds ratios (aORs)[3] and 95 percent confidence intervals (CIs) by Type of Clefts				
	Cleft Lip Only	Cleft Lip and Palate	Cleft Palate Only	Cleft Palate with or without Cleft Lip	All Clefts
Underweight BMI <18.5	1.05 [0.80-1.38]	1.11 [0.90-1.36]	1.18 [0.95-1.48]	1.14 [0.97-1.34]	1.13 [0.97-1.31]
Normal weight BMI $\geq$18.5, < 25	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Overweight BMI $\geq$25, <30	1.01 [0.92-1.10]	0.99 [0.88-1.12]	1.04 [0.91-1.18]	1.01 [0.92-1.11]	1.01 [0.92-1.10]
Obese BMI $\geq$30	1.06 [0.89-1.27]	1.15 [1.00-1.32]	1.10 [0.95-1.27]	1.13 [1.01-1.25]	1.12 [1.01-1.23]

[1]Include isolated orofacial clefts and those with multiple birth defects.
[2]Body mass index, weight in kg/height in M[2.]
[3]Covariates in multiple logistic regression models include study site, maternal age, maternal smoking during pregnancy, alcohol drinking, multivitamin use, and education level.

Table 3-4. Risk of Isolated Orofacial Clefts by Maternal Body Weight Categories by Cleft Types

Maternal Body Mass Index (BMI[1]) Group	Adjusted odds ratios (aORs)[2] and 95 percent confidence intervals (CIs) by Cleft Types				
	Isolated Cleft Lip Only	Isolated Cleft Lip and Palate	Isolated Cleft Palate Only	Isolated Cleft Palate with or without Cleft Lip	All Isolated Clefts
Underweight BMI <18.5	1.02 [0.76-1.37]	1.11 [0.89-1.39]	1.10 [0.85-1.43]	1.11 [0.93-1.34]	1.09 [0.93-1.29]
Normal weight BMI ≥18.5, < 25	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Overweight BMI ≥25, <30	1.00 [0.85-1.18]	1.00 [0.87-1.13]	1.01 [0.87-1.17]	1.00 [0.90-1.11]	1.00 [0.91-1.10]
Obese BMI ≥30	1.06 [0.88-1.28]	1.11 [0.96-1.29]	1.12 [0.94-1.32]	1.11 [0.99-1.25]	1.10 [0.99-1.23]

[1]Body mass index, weight in kg/height in M^2
[2]Covariates in multiple logistic regression models include study site, maternal age, maternal smoking during pregnancy, alcohol drinking, multivitamin use, and education level.

The association between OFC and maternal education level, shown in table 3-5, revealed that the risk of OFCs was significantly higher in mothers who were not high school graduates compared to high school graduate mothers, with having college graduate group as a reference. The risk in high school graduate only for CLP, CPO, CP/L, and all cleft cases increased significantly (aORs of 1.36 [95% CI 1.20-1.54], 1.26 [95% CI 1.11-1.44], 1.32 [95% CI 1.20-1.45], and 1.24 [95%CI 1.14-1.35], respectively).

Adjusted odds ratios by cleft type related to maternal body weight was stratified by two levels of maternal education (less than college graduate versus college graduate) (table 6). Because overweight seemed similar to normal weight in that no effect on increased risk was observed, maternal overweight and normal weight were combined in the reference group. This is also important because the data become sparse when split into many subgroups. After controlling for maternal age, maternal smoking during pregnancy, alcohol drinking, and multivitamin use, the risk of OFC was higher for all body weight categories, including maternal underweight (aOR=1.23 [95% CI 1.02-1.49]), obesity among those with lower education levels (aOR=1.16 [1.03-1.31]). No significant associations were found with BMI among mothers who were college graduates (table 3-6).

Table 3-5. Risk of Orofacial Clefts[1] by Maternal Education Level by Cleft Type

Education Level	Adjusted odds ratios (aOR)[2] and 95 percent confidence intervals (CI) by Cleft Types				
	Cleft Lip Only	Cleft Lip and Palate	Cleft Palate Only	Cleft Palate with or without Cleft Lip	All Clefts
College graduate	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
High School graduate only	1.02 [0.87-1.19]	1.36 [1.20-1.54]	1.26 [1.11-1.44]	1.32 [1.20-1.45]	1.24 [1.14-1.35]
< High School graduate	0.94 [0.72-1.22]	1.85 [1.52-2.25]	1.28 [1.02-1.59]	1.46 [1.23-1.73]	1.40 [1.21-1.62]

[1]Isolated orofacial clefts and those with multiple birth defects
[2]Covariates in multiple logistic regression models include study site, maternal age, maternal smoking during pregnancy, alcohol use, multivitamin use, and body weight categories.

Adjusted odds ratios by cleft type were determined within each study site after controlling maternal age, maternal smoking during pregnancy, alcohol drinking, and multivitamin use, using CIs of 95% (table 3-7). In the Utah study, maternal underweight appeared to be protective against the risk of having a child with CLO (1.0 [reference]; aOR=0.16 [0.04-0.70]), while it appeared to increase the risk for all CL (aOR=1.66 [95% CI 1.01-2.72]).

The total sample indicated a significant high risk for all cleft lip and all cleft palate associated with maternal obesity (1.0 [reference]; aOR=1.13 [95% CI 1.00-1.26]) and 1.13 [1.01-1.25]). Other maternal categories did not show any effect on the risk of cleft.

Table 3-6. Adjusted[1] Odds Ratio (aORs) and 95% Confidence Intervals (CI) of Cleft Palate, with or Without cleft lip, Isolated or With Multiple Birth Defects By Maternal Body Mass Index (BMI)[2] Group, Stratified by Two Levels of Maternal Education.

Maternal level of education	Adjusted odds ratios (aOR) and 95 percent confidence intervals (CI) by Cleft Types	
	Maternal BMI	Cleft Palate with or without Cleft Lip
< College Graduate	Underweight BMI <18.5	1.23 [1.02-1.49]
	Normal Weight BMI $\geq$18.5, < 25; and Overweight BMI $\geq$25, <30	1.00 [reference]
	Obese BMI $\geq$30	1.16 [1.03-1.31]
College Graduate	Underweight BMI <18.5	0.85 [0.59-1.23]
	Normal Weight BMI $\geq$18.5, < 25; and Overweight BMI $\geq$25, <30	1.00 [reference]
	Obese BMI $\geq$30	1.00 [0.79-1.27]

[1]Covariates in multiple logistic regression models include study site, maternal age, maternal smoking during pregnancy, alcohol use, and multivitamin use.
[2]Body mass index, weight in kg/height in M.^{2}

Table 3-7. Adjusted Odds Ratios (aORs)[1] and 95 Percent Confidence Intervals (CIs) of Isolated and Multiple OFCs Combined by maternal Body Mass Index group by cleft type and study site

Study site	Maternal Body Weight Category	Adjusted odds ratios by cleft type			
		Cleft lip only	All Cleft palate[2]	All Cleft Lip	All Clefts
Utah	Underweight BMI <18.5	0.16 [0.04-0.70]	1.13 [0.68-1.86]	0.56 [0.30-1.04]	0.85 [0.52-1.37]
	Normal weight BMI ≥18.5, < 25	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Overweight BMI ≥25, <30	1.03 [0.65-1.63]	1.12 [0.82-1.52]	1.15 [0.84-1.58]	1.09 [0.82-1.46]
	Obese BMI ≥30	1.06 [0.61-1.85]	1.19 [0.81-1.76]	1.13 [0.76-1.69]	1.16 [0.81-1.66]
Norway CC	Underweight BMI <18.5	0.66 [0.22-2.00]	1.28 [0.70-2.34]	0.95 [0.49-1.86]	1.11 [0.63-1.97]
	Normal weight BMI ≥18.5, < 25	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Overweight BMI ≥25, <30	1.10 [0.67-1.80]	1.16 [0.85-1.58]	0.99 [0.70-1.38]	1.13 [0.85-1.50]
	Obese BMI ≥30	1.85 [0.95-3.60]	1.14 [0.72-1.83]	1.42 [0.89-2.25]	1.26 [0.82-1.92]
MoBa	Underweight BMI <18.5	0.00	0.52 [0.17-1.59]	0.32 [0.07-1.45]	0.46 [0.15-1.41]
	Normal weight BMI ≥18.5, < 25	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Overweight BMI ≥25, <30	0.729 [0.26-2.61]	0.73 [0.42-1.27]	0.88 [0.49-1.59]	0.74 [0.44-1.25]
	Obese BMI ≥30	0.30 [0.04-2.47]	1.07 [0.56-2.06]	0.687 [0.30-1.56]	0.96 [0.51-1.80]
Iowa CC	Underweight BMI <18.5	1.15 [0.40-3.28]	1.05 [0.53-2.05]	0.99 [0.46-2.11]	1.09 [0.59-2.03]
	Normal weight BMI ≥18.5, < 25	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Overweight BMI ≥25, <30	1.46 [0.67-3.185]	1.34 [0.85-2.08]	1.66 [1.01-2.72]	1.35 [0.88-2.07]

Continued

Study site	Maternal Body Weight Category	Adjusted odds ratios by cleft type			
		Cleft lip only	All Cleft palate[2]	All Cleft Lip	All Clefts
	Obese BMI ≥30	0.892 [0.24-3.31]	1.09 [0.58-2.04]	1.38 [0.69-2.74]	1.02 [0.56-1.88]
NBDPS	Underweight BMI <18.5	1.27 [0.94-1.74]	1.16 [0.96-1.41]	1.23 [1.01-1.51]	1.19 [0.99-1.41]
	Normal weight BMI ≥18.5, < 25	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Overweight BMI ≥25, <30	0.98 [0.81-1.18]	0.99 [0.88-1.11]	0.96 [0.85-1.08]	0.99 [0.89-1.09]
	Obese BMI ≥30	1.05 [0.85-1.29]	1.15 [1.02-1.30]	1.12 [0.99-1.28]	1.13 [1.01-1.27]
Total sample	Underweight BMI <18.5	1.05 [0.80-1.38]	1.14 [0.97-1.34]	1.10 [0.92-1.31]	1.13 [0.97-1.31]
	Normal weight BMI ≥18.5, < 25	1.00 [reference]	1.00 [reference]	1.00 [reference]	1.00 [reference]
	Overweight BMI ≥25, <30	1.01 [0.92-1.10]	1.01 [0.92-1.11]	0.99 [0.90-1.10]	1.01 [0.92-1.10]
	Obese BMI ≥30	1.06 [0.89-1.27]	1.13 [1.01-1.25]	1.13 [1.00-1.26]	1.12 [1.01-1.23]

[1]Covariates in multiple logistic regression models include study site, maternal age, maternal smoking during pregnancy, alcohol use, maternal education (3-levels), and multivitamin use.
[2] Cleft palate with or without cleft lip.

Discussion

Statement of Principal Findings

This study provides evidence that maternal obesity increases the risk of having

a child with a cleft palate with or without cleft lip (CP/L). Maternal underweight

appears to increase the risk of CP/L in the offspring. The association between low

level of maternal education level and increased risk of CLP, CPO, CP/L, and all clefts

was significant, while among mothers with higher education, underweight and obese

were not associated with an elevated risk for orofacial clefts (OFCs).

Strengths of the Study

The current study has several strengths. It represents the largest international

consortium of case-control study to date with multiple countrywide sites in Europe

and statewide sites in the US. The study is population-based and relatively robust

against selection bias. OFC cases were drawn from birth defects registries. Controls

were randomly selected from centralized birth records. Data obtained from the birth

defect registries and birth records are rich data sources with respect to information on

potential confounders. However, information on potential confounders were collected

from participants' interview. The study was designed to use well-defined procedures

for case definition and careful classification of OFCs and associated conditions by

clinical specialists.

In some studies, conclusions about the association between maternal obesity

and orofacial clefting were limited by small number of cases [5, 9, 12, 24]. The present

study was designed to test maternal weight hypotheses in relation to OFCs. High

quality data were available on several relevant covariates to control for potential

confounding. Statistical analyses were conducted for both isolated and non-isolated

clefts combined and cleft type. The effects of maternal underweight, overweight, and obesity on the risk of orofacial cleft were all evaluated. As obesity is an epidemic health problem, a modest effect of maternal obesity can be linked to a significant burden of OFCs. Maternal underweight is associated with several adverse outcomes. Nevertheless, it remains an understudied problem. Results of this study confirmed that maternal obesity increases the risk of having a child with a CLP, CP/L, and all OFC types combined, while no effect of obesity on CLO was observed. Maternal underweight appeared to increase the risk of CP/L in the offspring. The association between low level of maternal education level and the risk of all OFC types was significant, while among mothers with higher education, underweight and obesity were not associated with risk of OFCs.

Limitations of the Study

Potential limitations of this study include the use of self-reported pre-pregnancy weight and height and the possibility of recall bias among underweight and obese women [25]. Data on exposures to smoking, multivitamin intake and socioeconomic status were limited to dichotomous exposure levels, thus residual confounding related to these factors is a possibility. As in all case-control studies, recall bias is a concern. Additionally, weight association with orofacial clefts was modified by the socioeconomic status as indicated by mother's level of education, which is a limited measure of socioeconomic status.

Strength and Weaknesses in Relation to Other Studies

With the rising rates of excess weight among pregnant women [26], the current findings of an association between maternal obesity and OFCs in the offspring is a major public health concern. Studies of the association between pre-pregnancy maternal weight and risk of OFCs have produced inconsistent findings that may be

related to variations in population sample size, definitions of OFC subtypes, lack of consideration of maternal underweight, and inadequate control of potential confounding factors.

In the present study, a positive association was found between both maternal underweight and obesity in early pregnancy and isolated and multiple OFC groups combined in the offspring. Similarly, Waller et al. reported that mothers who were underweight had no significant increase or decrease in the risk for birth defects, except for a significant increase in risk for cleft lip with or without cleft palate (aOR=1.35 [95% CI 1.04-1.76] [11]. A meta–analysis conducted to assess current evidence of the association between maternal overweight, maternal obesity, and congenital anomaly also reported increased risks for CP (aOR=1.23 [95% CI 1.03-1.47]) and CLP (aOR=1.20 [95% CI 1.03-1.40]) [6]. Rankin et al. (2010) found an overall increased risk of congenital anomalies in women who were obese and underweight compared with women of recommended weight, but no association between maternal underweight and OFCs was found, OR=1.84 [95% CI 0.55–6.25]. This study included only 44 infants with OFCs [27].

The association of obesity with clefts has been observed in a few other studies, although low numbers of cases limited their statistical power [5, 27, 28]. Cedergren and Kallen (28) observed modest increases in the risk of CP and CL/P associated with pre-pregnancy BMI of >29, while another case-control study reported an increase in the birth prevalence of all OFCs among women with BMI of $\geq$ 30 as compared with those with a BMI of < 30, OR=1.7 [95% CI 1.1-2.8] [9]. Oddy et al. found twofold increased odds of having infants with OFCs in mothers with a BMI of $\geq$ 30, aOR=1.97 [95% CI 0.73-5.32], where only 6 mothers out of 48 were classified as obese [24]. Recently, a population-based case-control study conducted in Florida found

obese women to experience increased odds of having a child with CL/P after
controlling for maternal race, education, smoking, marital status, nativity, and
maternal age (OR=1.25 [95% CI 1.05-1.48] and CP, OR=1.32 [1.07-1.62]). However,
in this same study, the offspring of underweight mothers were not at a higher risk of
OFCs [29]. One limitation of their study is the lack of information on intake of vitamin
supplement, which might have confounded the associations between pre-pregnancy
maternal underweight/obesity and clefts.

Similar to our findings, there was a strong association between CP/L and
obesity but not with CLO [11]. We also found a significant positive association when we
combined CP with CL and all cleft palate. A previous study indicated a possible effect
of maternal obesity on cleft palate malformation through the indirect influence of
excess adiposity related to the bioaccumulation and release of dioxins, causing cleft
palate in mice [30]. Thus, our results suggest the associations with maternal bodyweight
are specific to cleft palate and not to cleft lip.

A case-control study reported an increased risk of isolated and multiple birth
defects by maternal GDM in the presence of maternal obesity after adjusting for
potential confounders [31]. Marengo et al. reported a positive association between BMI
and CPO among non-diabetic mothers (p< 0.05). For cleft lip, however, the
prevalence was statistically elevated only among the non-diabetic mothers with class-
3 obesity (BMI ≥40), aOR=1.55 [95 % CI 1.14 -2.07]. Authors of this study found
that smoking and education were not confounders of the association between BMI
and birth defects. Therefore, they adjusted for maternal race/ethnicity and maternal
age only [32] . In addition, the percentage of obese mothers reported in their sample was
22.70%, but the prevalence of obesity within mothers of OFC cases was not
described. Stott-Miller et al. reported a very modest elevation in risk of OFCs in

relation to maternal obesity. This could be due to residual confounding related to data collection, imprecision of primary exposure that may have biased the results, and/or the considerable amount of missing data for maternal BMI and pre-pregnancy weight [8].

Elevated risks for OFCs with increasing BMI were not observed in some other studies. Shaw et al. (2000) reported insignificant ORs for the risk isolated CL/P, aOR=1.0 [95% CI 0.6-1.6]; isolated CP, aOR=1.1 [0.6-2.0]; multiple CL/P, aOR=1.0 [0.5-2.1]; and multiple CP, aOR=1.6 [0.8-3.4] [33]. However, there were too few cases with maternal pre-pregnancy obesity studies to obtain valid adjusted estimates of the ORs. Villamor et al. (2008) evaluated the risk of OFCs in relation to pre-pregnancy weight change and interpregnancy interval. Data revealed an increased risk of isolated CP 2.3 times [95% CI 1.4-4.0] within women whose second-pregnancy BMI was ≥ 3 units higher than their first-pregnancy BMI as compared with women whose BMI did not change significantly, while the BMI change was not related to the risk of cleft lip [10].

Implications for Clinicians and Policymakers

What mechanisms could link maternal underweight and obesity to OFCs in the offspring? Whatever the underlying mechanism behind the observed associations is, maternal underweight and obesity appear to increase the risk for CP/L malformations but only in the less educated mothers. It is possible that the educated mothers have the characteristic of being "obese but metabolically healthy" or "underweight but metabolically healthy." These terms describe a subset of people who seem to be protected against obesity- and underweight-related metabolic complications [34-39]. As the association between maternal bodyweight and the risk of CP/L was significant,

while no association with CLO existed, further investigation may yield insight into lip-palate-specific mechanisms of development.

A possible explanation for the association between maternal obesity and OFCs is undetected type-2 diabetes with hyperglycemia and insulin resistance. A previous study reported that even in the absence of gestational diabetes, obese women were found to have an impaired glucose metabolism [40], which may be associated with an elevated risk for OFCs [5, 41, 42]. Another possibility is that cases involved in the current study included "obese but metabolically healthy" or "underweight but metabolically unhealthy" individuals. These terms describe a subset of people who seem to be protected against obesity-related metabolic complications and individuals who are underweight but, like people with overt obesity, are insulin resistant and predisposed to type-2 diabetes and hypertriglyceridemia, respectively. Maternal body size, both underweight and obesity, appears to be an indirect measure of cleft risk. Up to one-third of obese persons are "metabolically healthy" [34-39] and this state of "metabolically healthy obesity" was correlated with higher educational status in the present study. Likewise, a substantial proportion of underweight persons might be "metabolically unhealthy."

Another possible explanation for the association between maternal obesity and OFCs could be improper nutrition. Shaw et al. (1995) and Itikala et al. (2001) suggested a possible role of folic acid deficiency on increasing the risk for OFCs [43, 44], while other studies reported inconsistent findings [45, 46]. Additionally, high dietary glycemic load intake was found to be more common among mothers of OFC cases [47, 48]. Hendricks et al. (2001) have suggested a possible role of maternal poor glycemic control, independent of diabetes diagnosis, on the risk of OFCs [49]. Previous findings provide evidence for higher levels of insulin resistance among obese patients [50-52].

Thus, the joint effect of abnormal glucose metabolism and obesity provide evidence of a synergistic effect on the risk of OFCs. Although the development of facial structure occurs within the first trimester of pregnancy, there are only a few data on glucose screening tests before 24 weeks of gestation. Further studies on appropriate methods for diabetes testing in early pregnancy are recommended.

Our results also revealed significant associations between maternal education levels and the risk of CLP and all cleft palates, with a significant higher risk in CLP and all cleft cases, while Cedergren & Kallen [28] produced inconsistint finding of a weak association between maternal education levels, and maternal obesity and infant clefts. This may relate to the limited number of subjects with a known BMI in their study. However, authors suggested a possible indirect association through the effect of maternal obesity at low maternal education.

Conclusions

Maternal underweight and obesity are significantly associated with the risk of CPs but not CLO. The metabolic abnormalities underlying the increased risk are unknown and require further study. Surprisingly, a strong modification of the association was found by maternal education. It is possible that the BMI is just an indirect measure for the risk and college educated mothers who are obese are more fit and metabolically healthy than obese mothers with lower education levels. A more detailed assessment of socioeconomic status is needed. In addition, our findings highlight the need to assess the obese mothers for hyperglycemia early in pregnancy to reduce the risk of OFCs in their offspring.

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CHAPTER 4

THE ROLE OF GESTATIONAL DIABETES MELLITUS AND

HYPERTENSION ON THE RISK OF OROFACIAL CLEFTS IN UTAH [1]

Abstract

Objective: To evaluate whether maternal gestational diabetes mellitus (GDM) and

hypertension are independently associated with risk of orofacial clefts.

Methods: A statewide case-control study of clefts in Utah during 1995 to 2004, in

collaboration with the Utah Birth Defects Network (UBDN) involved mothers of 562

infants with cleft, in which 430 cases were classified as isolated cleft cases and 133 as

all multiples, syndromic, or chromosomal clefts, matched with 658 controls randomly

selected unaffected births (from birth certificates) matched to cases by month, year of

birth, and gender of the child. Descriptive analysis was conducted in SPSS to examine

the association between GDM, hypertension, and orofacial clefts (OFCs). Odds ratios

(ORs) and 95% confidence intervals (CIs) were calculated to estimate the relative risk

for cleft lip with or without cleft palate (CL/P), cleft palate only (CPO), and all clefts

(isolated and non-isolated clefts combined) according to the presence of diabetes or

hypertension. Adjusted ORs (aORs) include control for potential confounding due to

factors such as maternal smoking, periconceptional multivitamin use, maternal

education level, body-mass-index (BMI), and maternal age.

Results: Maternal GDM was significantly associated with isolated clefts (aOR=2.63

[CI 95% 1.30-5.34]) and non-isolated clefts (aOR=2.66 [95% CI 1.015-6.97]).

Maternal hypertension was significantly associated with non-isolated clefts

(aOR=6.56 [95% CI 2.12-19.77]) and results were suggestive for isolated clefts

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[1] Coauthored by Hebah A. Kutbi and Ronald G. Munger.

(aOR=2.56 [95% CI 0.91-7.15]). We found a further increased risk of OFCs among GDM vs. non-GDM mothers who were obese (Body Mass Index (BMI>30) for isolated clefts (aOR=4.96 [1.26-19.51]) and for non-isolated clefts (aOR=14.21 [2.52-80.21]). Mothers with hypertension who were also obese had an elevated risk for non-isolated OFCs only (aOR=29.88 [95% CI 2.45-363.83]).

Conclusions: Both GDM and hypertension were associated with OFCs, suggesting a possible existence of underlying abnormalities related to metabolic syndrome prior to pregnancy. Screening for diabetes and hypertension earlier in the periconceptional period may be needed to reduce the risk of OFCs in the offspring.

Introduction

Maternal diabetes mellitus (DM) [1-3] and hypertension [4, 5] have been implicated in several studies as possible etiological factors of various infant congenital malformations. Orofacial clefts (OFCs) are among the most frequent congenital birth defects in human [6]. However, further studies are needed for a more complete understanding of the etiology of this disorder [7].

Diabetes mellitus is a group of metabolic diseases results from defects in insulin secretion, insulin action, or both and characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. Three main types of diabetes have been defined: type-1, type-2, and gestational diabetes [8]. Type-1 diabetes mellitus or insulin-dependent diabetes mellitus (IDDM) is partly inherited and then triggered by certain infections. It results from a T-cell mediated autoimmune destruction of the pancreatic beta cells in genetically predisposed individuals [9]. Type-2 diabetes or non-insulin-dependent diabetes mellitus (NIDDM) is due primarily to lifestyle factors and genetics [10]. Type 1 and 2 are both conditions that can be treated

but not cured. Hence, diet, exercise, and use of appropriate medications to keep blood sugar levels as close to normal "euglycemia" can be achieved [11]. Since 1970, Navarrete et al. indicated a definitive relation between a maternal glucose metabolic disorder and congenital malformations and suggested research into the early phases of diabetic state in mothers of malformed infants [12].

Gestational diabetes mellitus (GDM) is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels (particularly during third trimester of pregnancy) when their bodies do not secrete excess insulin required during pregnancy [13]. However, women with GDM are at high risk for having or developing diabetes when they are not pregnant [14]. It has been predicted that women who develop GDM later in pregnancy may also have had undetected metabolic problems earlier in the pregnancy [15].

Hypertension is a chronic medical condition in which the systemic arterial blood pressure is elevated, increasing the blood pressure to a level that induces some adverse effects such as the cardiovascular damage. Normal blood pressure is 120/80 mmHg, while high blood pressure is anything more than 140/90 mmHg [16]. A case-control study conducted in Thailand sought to identify the risk factors for congenital malformations from May 1987 to April 1988. Cleft lip or cleft palate was among one of the most common types of malformations. Maternal age >35 years, low maternal education levels, separated/divorced marital status, family history of similar anomalies, an accident during pregnancy, maternal illness during pregnancy, and maternal hypertension during pregnancy were significantly associated with the risk of orofacial clefts (OFCs) [4].

There is a substantial overlap between diabetes and hypertension, reflecting substantial overlap in their etiology and mechanisms. Among all diabetics,

hypertension is found in over 70% [17]. Common pathways shared by DM and hypertension include Sympathetic Nervous System, Renin-Angiotensin-Aldosterone System, oxidative stress, adipokines, and insulin resistance (Fig. 4-1). These pathways may interact and influence each other.

Abdominal obesity, aberrant glycemic control, hyperlipidemia, or hypertension is variably defined as co-occurrence of metabolic syndrome [18]. Mothers who develop GDM later in pregnancy may have had undiagnosed type-2 DM and are susceptible to acquire DM later in life [15]. Some of the common co-morbidities of GDM include increased oxidative stress and inflammation and immune dysfunction [19]. Investigation of metabolic syndrome, with the presence of diabetes, hypertension, and other more serious physiologic consequences, may provide useful clues regarding birth defects associations [20]. We assessed the relationship between maternal gestational diabetes and hypertension and the risk of OFC. These two risk factors are hypothesized to cause cleft lip and cleft palate via metabolic abnormalities that affect fetal development. This set of related hypotheses was examined in analyses of data from the Utah cleft study.

Materials and Methods

A statewide case-control study of clefts was conducted in Utah during 1995 to 2004 in collaboration with the Utah Birth Defects Network (UBDN). The UBDN staff members attempted to contact potential case and control mothers by mail to obtain consent for release of their names to USU investigators. Address updates were sought using available Internet services. If no mailing address was available, attempts were made to locate the mothers in person by field tracing that included visits to the last known home address and inquiries with neighbors. Interviews with mothers were

Figure 4-1. Summary of Putative Pathophysiologic Mechanisms in the Development of Hypertension in Diabetes Mellitus. RAAS_Renin- Angiotensin-Aldosterone System; SNS_Sympathetic Nervous System; VSMC_Vascular Smooth Muscle Cell [21].
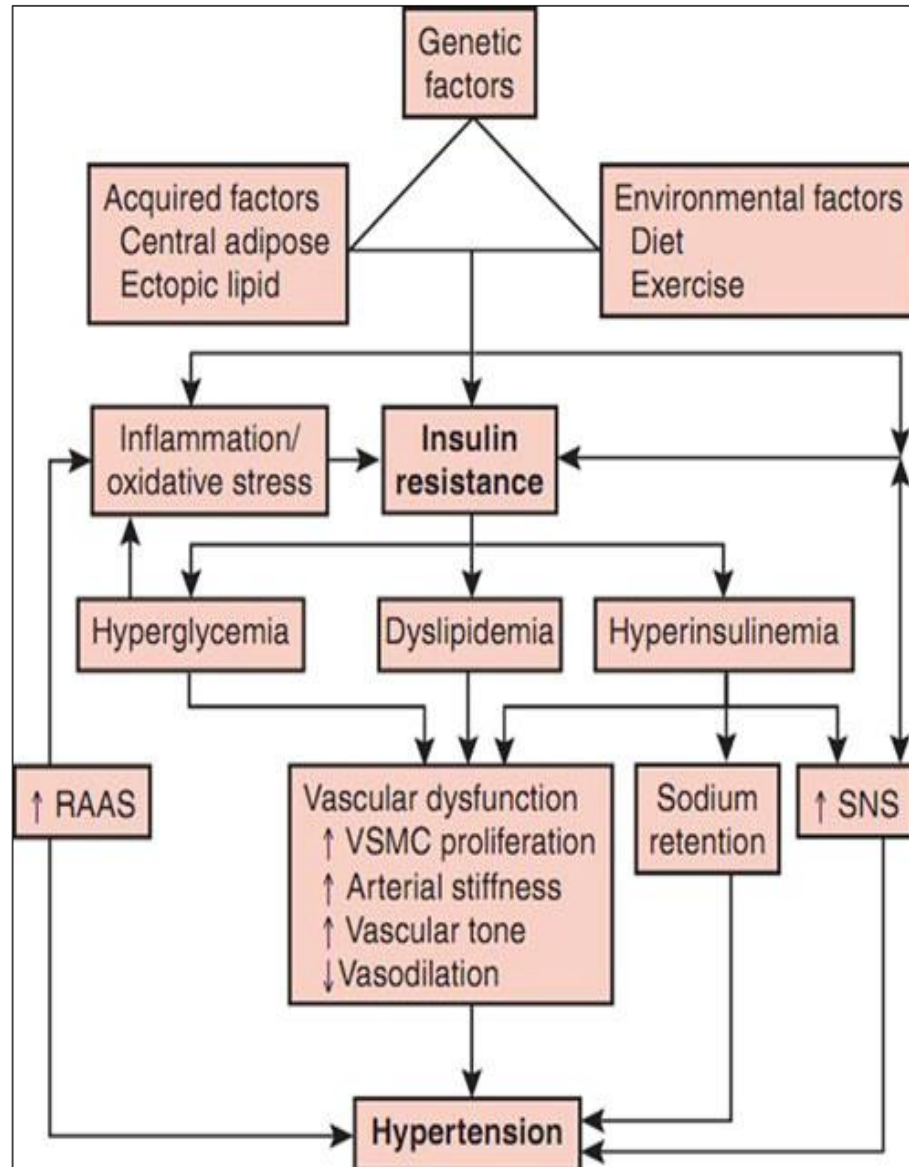
conducted primarily by telephone; however, personal interviews were completed if no telephone was available. The interview included questions on demographic characteristics of the biologic parents, a reproductive health and pregnancy history, supplement use, medications, medical conditions, and smoking and alcohol use. Each mother received an individualized, color-coded pregnancy calendar that was generated based on the date of delivery of her index child and the self-reported gestational length. This visual aid was intended to assist mothers in recalling activities and timing of events during various periods referred to. Color-coding of the calendars indicated the reference periods including the 3-month period before the estimated date of conception and three trimesters. Interview materials were translated into Spanish, and a bilingual interviewer contacted mothers speaking Spanish only. The UBDN later joined the National Birth Defects Prevention Study (NBDPS). A detailed description of data collection is provided elsewhere [22].

Combined samples involved 375 cases with cleft lip with or without cleft palate (CL/P), 187 cases with cleft palate only (CPO), and 658 randomly selected unaffected births matched cases by month, year of birth, and gender of the child. Data were available on pre-pregnancy maternal weight and height and other perinatal and demographic factors, which were used as covariates to control for potential confounding. Body-mass-index (BMI) was computed as weight kilograms (kgs)/height (m^2) and used to define body weight categories as underweight (BMI<18.5 kg/ m^2), normal weight (18.5- <25 kg/ m^2), overweight (25-<30 kg/ m^2) and obese ($\geq$30 kg/ m^2).

SPSS statistical analysis version 20.0 was used to describe the characteristics of study population. Descriptive analysis was conducted in SPSS to examine the association between maternal GDM and hypertension and other factors, such as

maternal age, history of smoking (three months prior to conception), multivitamin use during the first trimester of pregnancy, and education level (college graduate, high school graduate only, and less than high school graduate) and alcohol consumption.

Simple Chi-square analysis of contingency tables for categorical analysis was used to examine the association between each independent variable and selected covariates, such as maternal educational level, multivitamin (MVI) use during the first trimester of pregnancy, smoking, and alcohol consumption.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the relative risk for CLO, CL/P, and all OFCs according to the presence of diabetes and hypertension. Multiple logistic regression analysis was used to adjust for differences in maternal age, multivitamin use, and history of smoking and model the effect of diabetes and hypertension on CPO, CL/P, and all OFC risk.

Results

Table 4-1 shows the demographic characteristics of study participants. Among the case and control children, 60.3% (n=339) and 60.9% (n=401) respectively were boys. Among the case children, CL/P accounted for 66.7% (n=375) and CPO accounted for 33.3% (n=187) of cases. Maternal age, mean BMI, and alcohol drinking three months prior to pregnancy were not significantly different between mothers of cases and controls. Maternal smoking three months prior to pregnancy was significantly higher among mothers of cases (15.5%; n=85) than controls (10.0%; n=64). Maternal use of MVI was not statistically different between cases (33.8%; n=186) and controls (29.9%; n=192). Maternal education was significantly different among mothers of cases and controls (p-value=0.017), with a higher percent of mothers of controls holding a college degree (31.1%; n=200) or completed some

college (44.2%; n=248) compared to mothers of cases (27.5%; n=151 and 40.4%; n=222), respectively. Mothers of cases were more frequent to be high school graduate or less (32.2%; n=177) compared to mothers of controls (24.7%; n=159).

The prevalence of maternal GDM and hypertension was significantly higher (p-value=0.004) among mothers of cases (5.2%; n=29 and 3.20%; n=18) than controls (2.1%; n=14 and 0.9%; n=6), respectively. GDM was also associated with the higher BMI value (p-value=0.004), but not with older maternal age (p-value=0.134). Maternal hypertension, however, was not significantly associated with maternal BMI at conception (p-value=0.088), while appeared more frequent among mothers with older age (p-value=0.042). Maternal GDM and hypertension were not associated with maternal smoking (p-value=0.383 and 0.459), MVI use (p-value=0.941 and 0.321), or education level (p-value=0.752 and 0.677), respectively.

Table 4-2 illustrates the crude and adjusted Odds Ratios (aORs) for GDM on isolated, non-isolated OFC subtypes and both types combined. GDM appears to increase the risk for isolated CPO (aOR=3.36 [95% CI 1.28-8.81]), CL/P (aOR=2.49 [95% CI 1.15-5.36]), and all isolated clefts (aOR=2.63 [95% CI 1.30-5.34]); non-isolated CPO (aOR=3.65 [1.12-11.86]) and all non-isolated OFC (aOR=2.66 [1.02-6.97]), but not for non-isolated CL/P (aOR=2.12 [0.57-7.87]). Overall, GDM increased the risk for isolated and non-isolated CPO (aOR=3.42 [95% CI 1.48-7.91]), CL/P (aOR=2.33 [95% CI 1.11-4.87]), and all OFCs (aOR=2.58 [95% CI 1.31-5.06]).

Table 4-3 illustrates the crude and aORs for maternal hypertension on isolated, non-isolated, and both isolated and non-isolated OFC types and subtypes. Maternal hypertension increases the risk for non-isolated CPO (aOR=5.76 [95% CI 1.35-24.59]), CL/P (aOR=7.87 [95% CI 2.21-27.94]), and all non-isolated OFCs (aOR=6.56 [95% CI 2.18-19.77]); and all CPO (aOR=3.78 [95% CI 1.18-12.07]),

Table 4-1. Demographic Characteristics of Orofacial Cleft Cases and Controls; Utah Child and Family Health Study

Characteristics	Controls (n=658)	Cases		
		CL/P (n=375)	CPO (n=187)	All Clefts (n=562)
Mean Maternal Age ± standard deviation (SD)	26.2± (5.3)	26.3± (5.3)	26.8± (5.9)	26.5 ± (5.7)
Mean BMI± (SD)	24.3± (5.4)	25.2± (11.7)	25.1± (12.9)	25.1± (12.1)
Pre-existing Diabetes (%)	2 (0.3)	1 (0.3)	0 (0.0)	1 (0.2)
Gestational Diabetes Mellitus (%)	14 (2.1)	18 (4.8)	11 (5.9)	29 (5.2)
Hypertension (%)	6 (0.9)	12 (3.2)	6 (3.2)	18 (3.20)
Gestational Diabetes Mellitus and Hypertension Combined (%)	1 (0.2)	4 (1.1)	2 (1.1)	6 (1.1)
Average month of Diagnosis of GDM ± (SD)	6.2± (1.2)	5.3± (1.8)	5.7 ± (2.0)	5.4 + (1.8)
Maternal Smoking 3-Months Prior to Pregnancy (%)	64 (10.0)	58 (15.7)	27 (15.0)	85 (15.5)
Maternal Alcohol Consumption 3-Months Prior to Pregnancy (%)	145 (22.6)	100 (27.0)	40 (22.2)	140 (25.5)
Supplement use during first trimester of pregnancy (%)	192 (29.9)	118 (31.9)	68 (37.8)	186 (33.8)
College Graduate (%)	200 (31.1)	92 (24.9)	59 (32.8)	151 (27.5)
Male Cleft Cases (%)	401 (60.9)	244 (65.1)	95 (50.8)	339 (60.3)

Table 4-2. Risk of Orofacial Clefts by Maternal Gestational Diabetes Mellitus by Cleft Types

Cleft Group		Odds Ratios and 95% Confidence Intervals by Cleft Subtype		
		CL/P[1]	CPO[2]	CL/P and CPO
Isolated	Crude	2.36 [1.13-4.96]	2.78 [1.10-7.03]	2.48 [1.26-4.90]
	Adjusted[3]	2.49 [1.15-5.36]	3.36 [1.28-8.81]	2.63 [1.30-5.34]
Non-Isolated	Crude	2.12 [0.60-7.58]	3.07 [0.98-9.61]	2.56 [1.01-6.46]
	Adjusted[3]	2.12 [0.57-7.87]	3.65 [1.12-11.86]	2.66 [1.02-6.97]
Isolated and	Crude	2.32 [1.14-4.72]	2.88 [1.28-6.44]	2.50 [1.31-4.79]
Non-Isolated	Adjusted[3]	2.33 [1.11-4.87]	3.42 [1.48-7.91]	2.58 [1.31-5.06]

[1] Cleft lip, with or without cleft palate; n=15 (4.9%) isolated, 3 (4.4%) non-isolated.
[2] Cleft palate only; n= 7 (5.7%) isolated, 4 (6.3%) non-isolated.
[3] Covariate in logistic regression model include maternal age, body-mass-index, education, multivitamin use, and smoking.

CL/P (aOR=3.50 [95% CI 1.28-9.55]), and all OFCs (aOR=3.42 [95% CI 1.34-8.74]). However, no effect for maternal hypertension on isolated OFCs was observed. Crude and adjusted ORs of Maternal GDM by maternal body weight categories (normal weight, overweight, and obesity) for isolated, non-isolated, and all clefts appear in table 4-4. Underweight category was skipped, as no participants appeared to be underweight with GDM. The aORs of GDM imply the increased risk for isolated (aOR=4.96 [1.26-19.51]), non-isolated (aOR=14.21 [2.52-80.21]), and all clefts (aOR=6.30 [1.71-23.21]) among obese mothers only.

Crude and adjusted ORs of Maternal hypertension by maternal body weight categories (normal weight, overweight, and obesity) for isolated, non-isolated, and all clefts appear in table 4-5. Maternal hypertension increases the risk for non-isolated OFCs among obese mothers only (aOR=29.88 [2.45-363.83]).

Table 4-3. Risk of Orofacial Clefts by Maternal Hypertension by Cleft Types

Cleft Group		Odds Ratios and 95% Confidence Intervals by Cleft Subtype		
		CL/P[1]	CPO[2]	CL/P and CPO
Isolated	Crude	2.54 [0.85-7.61]	2.71 [0.67-10.98]	2.59 [0.93-7.17]
	Adjusted[3]	2.54 [0.84-7.73]	2.82 [0.68-11.69]	2.56 [0.91-7.15]
Non-Isolated	Crude	8.60 [2.55-28.97]	5.33 [1.30-21.83]	6.93 [2.37-20.33]
	Adjusted[3]	7.87 [2.21-27.94]	5.76 [1.35-24.59]	6.56 [2.18-19.77]
Isolated and	Crude	3.59 [1.34-9.65]	3.59 [1.14-11.27]	3.59 [1.42-9.11]
Non-Isolated	Adjusted[3]	3.50 [1.28-9.55]	3.78 [1.18-12.07]	3.42 [1.34-8.74]

[1] Cleft lip, with or without cleft palate; n=7 (2.3) isolated, 5 (7.4%) non-isolated.
[2] Cleft palate only; n= 3 (2.4%) isolated, 3 (4.7%).
[3] Covariate in logistic regression model include maternal age, body-mass-index, education, multivitamin use, and smoking.

Table 4-4. Risk of Orofacial Clefts by Maternal Gestational Diabetes Mellitus by Cleft Types Stratified by Maternal Body-Mass-Index (BMI) Categories

Maternal BMI Group[1]		Odds Ratios and 95% Confidence Intervals by Cleft Type		
		Isolated Clefts n=430	Non-Isolated Clefts n=133	All Clefts n=562
Normal weight[2]	Crude	1.64 [0.57-4.73]	0.71 [0.09-5.84]	1.41 [0.51-3.94]
	Adjusted[5]	1.78 [0.57-5.53]	0.72 [0.08-6.52]	1.46 [0.48-4.39]
Overweight[3]	Crude	1.31 [0.32-5.37]	1.69 [0.18-15.87]	1.37 [0.36-5.23]
	Adjusted[5]	1.38 [0.32-5.93]	1.73 [0.17-17.61]	1.36 [0.34-5.36]
Obesity[4]	Crude	5.73 [1.50-21.87]	8.78 [1.89-40.70]	6.48 [1.79-23.38]
	Adjusted[5]	4.96 [1.26-19.51]	14.21 [2.52-80.21]	6.30 [1.71-23.21]

[1] Data for underweight mothers not included as it was too sparse for analysis.
[2] BMI $\geq$18.5, < 25; n=7 isolated, 1 non-isolated clefts.
[3] BMI $\geq$25, <30; n=4 isolated, 1 non-isolated clefts.
[4] BMI $\geq$30; n=10 isolated, 5 non-isolated clefts.
[5] Covariates in logistic regression model include maternal age, body-mass-index, education, multivitamin use, and smoking.

Table 4-5. Risk of Orofacial Clefts by Maternal Hypertension by Cleft Types Stratified by Maternal Body Weight Categories

Maternal BMI Group[1]	Odds Ratios (ORs)	Odds Ratios and 95% Confidence Intervals by Cleft Type		
		Isolated Clefts n=430	Non-Isolated Clefts n=133	All Clefts n=562
Normal weight[2]	Crude	4.11 [0.79-21.34]	2.51 [0.23-27.97]	3.73 [0.75-18.58]
	Adjusted[5]	4.16 [0.78-22.04]	2.24 [0.19-25.80]	3.63 [0.72-18.37]
Overweight[3]	Crude	0.86 [0.14-5.26]	4.77 [0.75-30.42]	1.462 [0.32-6.66]
	Adjusted[5]	0.81 [0.13-5.19]	5.11 [0.66-39.64]	1.41 [0.29-6.88]
Obesity[4]	Crude	4.53 [0.46-44.70]	20.00 [2.10-190.91]	8.12 [0.97-67.61]
	Adjusted[5]	3.56 [0.35-36.66]	29.88 [2.45-363.83]	6.99 [0.81-60.27]

[1]Data for underweight mothers not included as it was too sparse for analysis.
[1] BMI $\geq$18.5, < 25; n=5 isolated, 1 non-isolated clefts.
[2]BMI $\geq$25, <30; n=2 isolated, 2 non-isolated clefts.
[3]BMI $\geq$30; n=3 isolated, 4 non-isolated clefts.
[4]Covariates in logistic regression model include maternal age, body-mass-index, education, multivitamin use, and smoking.

Discussion

This study provides evidence that maternal GDM increases the risk of having a child with isolated CPO, CL/P, and all isolated clefts; all CPO, CL/P, and all clefts; and non-isolated CPO and all non-isolated OFCs significantly. Maternal hypertension increases the risk for non-isolated and all CPO, CL/P, and all non-isolated and all OFCs significantly, but not for isolated OFCs.

An association between maternal GDM by obesity and increased risk of isolated, multiple, and isolated and multiple clefts combined found to be statistically significant, while maternal hypertension by obesity increases the risk for non-isolated OFCs only.

The present study was designed to test maternal GDM and hypertension hypotheses in relation to OFCs. High quality data were available on several conceptually relevant covariates to control for potential confounding. Statistical analyses were conducted for isolated, multiple, and isolated and multiple cleft groups combined and cleft subtypes (CPO, CL/P, and all clefts). The effects of maternal GDM and hypertension and maternal BMI categories on the risk of OFC were all evaluated. Although DM has been reported by previous studies to be correlated with the risk of congenital birth defects [23, 24], and some reported to have an effect on increasing the risk of OFC [25, 26], studies of the association between maternal GDM and OFC are limited. Similarly, studies of the association between maternal hypertension and OFC are limited.

We also conducted a pooled analysis using individual data on GDM and hypertension and potential confounding factors (age, smoking three months prior to pregnancy, multivitamin use, education level, and BMI categories). The risk of orofacial clefting by maternal GDM and hypertension by maternal BMI categories was also evaluated.

The presence of GDM and hypertension were determined based on maternal self-reports of diagnosed GDM that were similar to approaches used in previous population-based case-control studies of birth defects [27, 28]. Hypertension status was also determined based on self-reports. Self-reported GDM may lead to misclassification as some women who reported having no DM may have had undiagnosed type-2 DM. However, there is no reason to believe that the subsequent misclassification of GDM status occurred differently for case and control mothers in this study, so the net effect was probably of an attenuation of associations of diabetes mellitus with OFC birth defects.

Other potential limitations of this study include the use of self-reported pre-gestational weight and height and the possibility of recall bias for these variables. Data on exposures to smoking, and multivitamin intake were limited to dichotomous exposure levels, thus residual confounding related to these factors is a possibility. As in all case-control studies, recall bias is a concern.

In the present study, a positive association was found between maternal GDM and OFCs in the offspring. Navarrete et al. indicated a definitive relation between a maternal glucose metabolic disorder and congenital malformations [12]. Several other studies reported an increased risk for having newborns with OFCs in diabetic mothers compared to non-diabetic mothers [26, 29-31]. Although GDM has been also reported by previous studies to increase the risk for congenital birth defects [27, 32, 33], including OFC [2], studies of the association between GDM and OFC are limited. In our study, we found a significant positive association between GDM and isolated, non-isolated, and all clefts.

Hypertension has been reported to be associated with congenital malformations [4], while Lebby et al. indicated no effect of the presence or absence of hypertension on OFC risk [5]. In fact, there is a lack of published studies examining the association between maternal hypertension and the risk of OFC. In the present study, we found an increased risk of non-isolated and all CPO, CL/P, all clefts. It is possible that hypertension during pregnancy alters the perfusion in the placenta, causing urogenital malformations. However, the exact teratogenic effect of hypertension is still unknown [34].

A case-control study reported an increased risk of isolated and multiple birth defects by maternal GDM in the presence of maternal obesity after adjusting for maternal BMI, age, race/ethnicity, entry into prenatal care, study center, and

household income (aOR=1.42 [95% CI 1.17-1.73] and 1.50 [95% CI 1.13-2.00], respectively) [2]. Similarly, our results show a higher risk of GDM for isolated (aOR=4.473 [95% CI 1.13-17.76]), non-isolated (aOR=16.35 [95% CI 2.71-98.62]), and all clefts (aOR=6.07 [95% CI 1.64-22.47]) among obese mothers, while maternal hypertension increased the risk for non-isolated OFC only among obese mothers (aOR=22.21 [95% CI 2.22-334.23]).

While maternal GDM appears to be associated with cleft risk, pregnant mothers are not usually tested for hyperglycemia until 26-28 weeks of gestation, after formation of the lip and palate. Thus, we highlight the importance of early screening of all pregnant women for hyperglycemia at the time of conception. This may alleviate the risk of GDM and reduce the prevalence of OFC associated with GDM. Maternal hypertension is associated with the risk of OFC. However, studies are limited. Further research on the relationship between maternal hypertension, GDM and DM, and other metabolic syndrome factors might be warranted.

Our findings expand on the body of literature of OFC among infants of women with GDM or hypertension. Given that both maternal GDM and hypertension were associated with an increased risk of OFCs, both CL/P and CPO, the importance of identifying and implementing effective detection, control, and prevention strategies for metabolic abnormalities, including maternal GDM and hypertension, among women of childbearing age is a necessity.

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CHAPTER 5

THE ASSOCIATION BETWEEN MATERNAL DIABETES AND OROFACIAL

CLEFTS IN AN INTERNATIONAL CONSORTIUM OF

CASE-CONTROL STUDIES[1]

Abstract

Objective: To evaluate whether maternal diabetes mellitus (DM) is independently

associated with risk of orofacial clefts (OFCs).

Methods: Pooled analyses of population-based case–control studies from a unique

and large international consortium including Utah, Iowa, Norway (two studies 1996-

2001 and 2000-2009, Denmark, and the U.S. National Birth Defects Prevention Study

was conducted. Subjects included mothers of 5,280 infants with OFCs and 11,461

controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to

estimate the relative risk for cleft subtypes associated with diabetes. Multiple logistic

regression analysis was used to adjust for the potential confounding effects of

maternal age, multivitamin use, maternal body-mass-index (BMI) categories, and

history of smoking.

Results: Maternal DM was associated with an increased risk of all types of OFCs

after adjustment for maternal age, multivitamin use, smoking during the first trimester

of pregnancy, and BMI. The estimated relative risk of DM for isolated OFCs was 1.33

[95% CI 1.14-1.54] and was slightly higher for multiple OFCs (aOR=1.86 [95% CI

1.44-2.40]). No excess risk was observed among diabetic mothers with normal body

weight. However, diabetic mothers who were also overweight or obese had an

increased risk for having children with isolated, multiple, and isolated and multiple

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[1] Coauthored by Hebah A. Kutbi and Ronald G. Munger

OFC groups combined (aOR=1.33 [95% CI 1.02-1.73], 2.61 [95% CI 1.71-3.97], and 1.52 [95% CI 1.19-1.93]), respectively. We also found an elevated risk of OFCs among mothers with diabetes who were underweight (aOR=2.63 [95% CI 1.26-5.49].

Conclusions: Maternal DM was significantly associated with an elevated risk of all types of OFCs. Mothers of normal bodyweight however had no increased risk of OFCs if they were diabetic; the elevated risk among diabetics only occurred among underweight, overweight, and obese mothers. Further studies are needed to identify diabetes related pathways leading to the increased risk of OFCs and to understand how this risk is modified by risk factors related to both underweight and overweight. Our findings also highlight the need to assess all mothers for hyperglycemia and other metabolic abnormalities in the periconceptional period to reduce the risk of OFC in their offspring.

Introduction

Maternal diabetes mellitus (DM) has been implicated in several studies as a possible etiological factor of various infant congenital malformations [1-3]. Orofacial clefts (OFCs) are among the most frequent congenital birth defects [4]. In 2006, Centers for Disease Control and Prevention (CDC) reported that from 1999 through 2001, nearly 4,209 infants each year in the United States are born with OFCs [5]. These estimates have been increased in 2010 to 4,437 live births per year [6]. Several studies suggest that maternal diabetes or the underlying metabolic abnormalities known as the metabolic syndrome may be involved in the pathogenesis of cleft lip and cleft palate [7-9]. However, further studies are needed for a more complete understanding of the etiology of this disorder [10].

DM is a group of metabolic diseases resulting from defects in insulin secretion, insulin action, or both, and characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. Three main types of diabetes have been defined: type-1, type-2, and GDM [11]. Type-1 diabetes mellitus or insulin-dependent diabetes mellitus (IDDM) is partly inherited and then triggered by certain infections. It results from a T-cell mediated autoimmune destruction of the pancreatic beta cells in genetically predisposed individuals [12]. Type-2 diabetes or non-insulin-dependent diabetes mellitus (NIDDM) is due primarily to lifestyle factors and genetics [13]. GDM is a condition in which women without previously undiagnosed diabetes exhibit high blood glucose levels (particularly during third trimester of pregnancy) when their bodies do not secrete excess insulin required during pregnancy [14].

Type-1 and type-2 are both conditions that can be treated but not cured [15]. GDM may increase the risk for developing diabetes when they are not pregnant [16]. It has been predicted that mothers who develop GDM later in pregnancy may also have had undetected metabolic problems earlier in the pregnancy [17]. Hence, diet, exercise, and use of appropriate medications to keep blood sugar levels as close to normal "euglycemia" can be achieved [15].

In 1970, Navarrete et al. found an association between congenital malformation of infants and the development of diabetes in their mothers later in life and suggested research into the early phases of diabetic state in mothers pregnant of malformed infants [18]. Several studies reported an increased risk for having newborns with OFCs in diabetic mothers compared to non-diabetic mothers [19-22] with a higher statistical significant rate of cleft palate only (CPO) [20].

Thus, investigation of DM may provide useful clues regarding birth defects associations [23]. We assessed the relationship between maternal DM and the risk of OFC birth defects. DM is hypothesized to cause OFCs via metabolic abnormalities that affect fetal development. This hypothesis was examined in analyses of data from the international consortium of case-control studies from Utah, Iowa, Norway, Denmark, and the U.S. National Birth Defects Prevention Study.

Materials and Methods

This study is a combined, unique, and large international consortium of case-control studies from the U.S. (two separate studies from Iowa, Utah, and the U.S. National Birth Defects and Prevention Study-NBDPS), Denmark, and Norway. The combined sample includes 16,741 women including 5,280 mothers of children with OFCs and 11,461 mothers of unaffected children. Data were available on the presence of DM, pre-pregnancy maternal weight and height, in addition to other perinatal and demographic factors, which are used as covariates to control for potential confounding. Body-mass-index (BMI) was computed as weight kilograms (kgs)/height (m^2) and used to define body weight categories as underweight (BMI<18.5 kg/ m^2), normal weight (18.5 <25 kg/ m^2), overweight (25 <30 kg/ m^2) and obesity (≥30 kg/ m^2). Studies included in this current study are as follows:

(1) Iowa Case-Control Sample: The Iowa Registry of Congenital and Inherited Disorders (IRCID) case-control sample consists of about 287 cases with CL/P and 302 controls born between 1987 through 1996. The control sample was randomly selected from all unaffected live births and matched to the affected sample by birth month, year and gender. Data on risk behaviors, socioeconomic characteristics and other relevant data, were obtained through telephone-based interviews and self-

administered forms sent by mail [24].

(2) Utah Study: A state-wide case-control study of clefts was conducted in Utah during 1995 to 2004 in collaboration with the Utah Birth Defects Network (UBDN) involves 561 cases with CL/P and 660 randomly selected unaffected births (from birth certificates) matched cases by month, year of birth, and gender of the child. The UBDN staff members attempted to contact potential case and control mothers by mail to obtain consent for release of their names to USU investigators. Address updates were sought using available Internet services. If no mailing address was available, attempts were made to locate the mothers in person by field tracing that included visits to the last known home address and inquiries with neighbors. The UBDN later joined the National Birth Defects Prevention Study (NBDPS) described below. A detailed description of data collection is provided elsewhere [25].

(3) National Birth Defects Population Studies: NBDPS samples with CL/P and control samples multiple participating States were included. These include Arkansas, California, Georgia, Massachusetts, New Jersey, New York, North Carolina, Iowa, Texas and Utah. NBDPS sample provided 3491 CL/P cases and 8357 control mothers, matched by State and birth year to the CL/P sample [26].

(4) Danish Study: The data were extracted from the Danish National Birth Cohort study between 1997 and 2003 and involved a sample of 828 mothers of affected cases with CL/P and 156 randomly selected mothers of unaffected births. The women were typically enrolled in the study at the first visit to general practitioners (usually in the first trimester). Participated mothers were interviewed about a broad range of health related information, such as health and risk behaviors, potential fetal risk factors, socioeconomic and other relevant characteristics. Further follow-up with

mothers of children with congenital anomalies was conducted after birth and until the child is 18 months of age.

(5) Norway Facial Cleft Study: The Norway Facial Clefts Study, or Norway Case-Control study (Norway CC), is a population survey of infants born with CL/P in Norway in 1996 through 2001. Data included 570 cases and their parents and a randomly selected control sample of 736 infants born without birth defects in the same period [27]. Extensive data on maternal behaviors and household factors and socioeconomics were available. The data collection is described elsewhere [28].

(6) Norway National Mother and Child Cohort Study: The Norwegian Mother and Child Cohort Study (MoBa), conducted by the Norwegian Institute of Public Health (NIPH, Oslo, Norway), is a cohort consisting of pregnancies recruited beginning in 1999 to 2008 [29]. Identified were 164 cases of CL/P and 551 control mother of which were randomly selected with matching to the case sample by year and state of birth. Data on maternal health behaviors, demographic and socioeconomic characteristics, health problems and food behaviors were obtained during pregnancy between weeks 15 and 30 (data on risk and health behaviors was collected between 15 and 18 weeks). The study also involved follow-up interviews with the mother and child until the child is three years.

SPSS statistical analysis version 20.0 was used to describe the characteristics of study population. Descriptive analysis was conducted in SPSS to examine the association between maternal DM and other factors, such as maternal age, history of smoking (three months prior to conception), multivitamin use during the periconceptional period, and education level (college graduate, high school graduate only, and less than high school graduate) and alcohol consumption.

Simple Chi-square analysis of contingency tables for categorical analysis was used to examine the association between each independent variable and selected covariates, such as maternal educational level, multivitamin use during the first trimester of pregnancy, smoking, and alcohol consumption.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the relative risk for cleft lip only (CLO), cleft lip with or without cleft palate (CL/P), cleft lip and cleft palate (CLP), cleft palate only (CPO), and all orofacial clefts (OFCs) according to the presence of diabetes. Multiple logistic regression analysis was used to adjust for differences in maternal age, multivitamin use, maternal BMI categories, and history of smoking, and model the effect of diabetes on OFC risk.

Results

Table 5-1 summarizes the types of clefts, the numbers, and the sources of samples. Among the case children, CL accounted for 23.09% (n=1,219), CL/P accounted for 65.36% (n=3,451), and CP accounted for 34.68% (n=1,831) of cases. Within CL cases, 1,107 (90.8%) and 112 (9.2%) children cases were reported to have isolated and multiple birth defects, respectively. Isolated CL/P accounted for 2,976 (86.2%) cases and 475 (13.8%) cases had multiple CL/P. Within CP cases, 1345 (73.5%) and 486 (26.5%) CP cases had isolated and multiples, respectively (table 5-2).

Table 5-1. Number of Controls and Orofacial Cleft Cases by Cleft Type and Study Site

Site and Birth years	Number of study participants by cleft type				
	Controls	CLO	CPL	CPO	All OFCs
Iowa, USA (1987-1991)	302	56	111	120	287
Utah, USA (1995-2004)	660	142	232	187	561
U.S. National Birth Defects Prevention Study (1997-2008)	8357	792	1491	1208	3491
Danish National Birth Cohort (1998-2001)	828	58	72	57	187
Norway Case-Control Study (1996-2001)	763	140	234	196	570
Norway Mother-Baby (MoBa) Study (2000-2009)	551	31	94	63	184
Total sample	11461	1219	2234	1831	5280

Table 5-2. Number of Orofacial Cleft Cases by Cleft Type; International Consortium of Orofacial Cleft Case-Control Study

Cleft Type	Cleft Lip Only	Cleft Lip with or without Cleft Palate	Cleft Palate Only
Isolated Clefts	1107	2976	1345
Multiple Clefts	112	475	486
All Clefts	1219	3451	1831

Demographic characteristics of the sample appear in table 5-3. The mean ages of mothers of cases and controls were significantly different at Iowa (p-value=0.002) and NBDPS (p-value<0.001) study sites. Smoking during the first trimester of pregnancy was common and associated significantly with the risk of OFCs among Utah (p-value=0.002), Danish (p-value=0.035), Norway (p-value<0.01) and NBDPS studies (p-value<0.05). Maternal BMIs of mothers of cases and controls were significantly different among NBDPS sample group, but not at other study sites. Use of alcohol by the mother during the first trimester of pregnancy was significantly

more frequent (p-value=0.004) among the case versus control mothers in Norway study; no significant associations were seen in the other studies. Maternal caffeine use during the first trimester was associated significantly with the risk of OFCs in MoBa study only (p-value=0.023). Maternal employment was significantly associated with the risk of OFC among Norway sample (p-value=0.019) and NBDPS sample (p-value=0.018), but was not among any other study sites. Maternal multivitamin (MVI) use was significantly associated with the risk of OFC within NBDPS (p-value=0.024) sample only. Maternal education was associated with the risk of OFC within Norway sample (p-value=0.040) and NBDPS samples (p-value <0.001).

The prevalence of DM was 5.3% among control mothers and 7.2% among case mothers. The prevalence of DM varied considerably across study sites and generally higher in the U.S. sites compared to the European sites. In subgroup analyses, maternal DM was significantly associated with the risk of OFCs in the Utah and NBDPS samples, where higher percent of cases among diabetic mothers were observed (5.7% and 9.3%) compared to controls (2.6% and 6.6%), respectively. Maternal age of mothers of cases and controls were significantly different among Iowa (p-value=0.004) and NBDPS (p-value<0.001) study sites. Maternal smoking during the first 3 months of pregnancy differed between case and control mothers in Utah (p-value=0.006), Norway (p-value=0.016), and Iowa (p-value=0.026). Maternal BMIs of mothers of cases and controls were significantly different among Utah (p-value<0.001), Norway (p-value=0.021), and NBDPS (p-value<0.001). Maternal alcohol and caffeine use were not significantly associated with maternal DM of cases and controls at any study site. Maternal education level was significantly associated with maternal DM in NBDPS sample, but not at other study sites.

Table 5-3. Demographic Characteristics of Mothers of Children with Orofacial Cleft Cases and Controls by Study Sites

| Characteristics | Utah | | Norway CC | | Moba | | Iowa CC | | NBDPS | | Danish | |
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Maternal age in years ± standard deviation (SD)	27.0 ±5.7	26.8 ±5.2	28.9 ±5.0	29.2 ±4.8	29.9 ±5.0	30.0 ±4.6	26.7 ±5.3	27.1 ±4.9	26.9 ±6.2	26.9 ±6.1	29.5 ±4.5	30.0± 4.12
Mean maternal body mass index (BMI; kg/M2) ± SD	24.3 ±5.0	24.2 ±5.3	23.7 ±4.4	23.4 ±3.7	23.9 ±4.2	24.0 ±4.2	23.5 ±5.2	23.0 ±4.4	25.3 ±6.2	25.0 ±5.8	24.3 ±4.6	23.6 ±4.2
Smoker %	13.5	8	41.6	31.8	27.6	23.8	25.1	22.2	21.2	16.2	6.2	21.9
Alcohol use in 1st trimester %	7.5	6.4	38.1	30.5	12.7	14	34.5	34.8	22.9	22.5	43.3	42.6
Maternal employment %	88.1	85.6	80.2	85.1	78.6	79.2	N/A	N/A	69.5	71.7	NA	NA
Maternal caffeine use in first Trimester %	98.6	98.3	89.6	89.8	86.2	92.4	85.0	83.8	70.9	69.8	95	92.4
Multivitamin use %	75.8	75.6	37.2	40.6	70.7	74.6	63.6	71.1	82.2	83.9	56.2	61.3
Education ≤ High school %	8.0	6.5	16.1	11.4	5.7	2.6	9.8	7.6	19.9	17.3	N/A	N/A
College Graduate %	26.7	30.5	39.6	40.9	62.7	62.4	18.1	22.5	26	31.6	N/A	N/A
High School graduate %	65.2	63	44.2	47.7	31.6	34.9	72.1	69.9	54.2	51.1	N/A	N/A
Male %	59.2	60.6	60.3	53.3	58.2	55.2	53.8	54	58.6	50.9	N/A	N/A
Diabetes (%)	32 (5.7)	17 (2.6)	2 (0.4)	4 (0.5)	1 (0.5)	7 (1.3)	21 (7.3)	15 (5.0)	325 (9.3)	555 (6.6)	0(0.0)	5 (0.6)

Because crude and adjusted ORs (aOR) were very similar, only aORs are presented. The estimated relative risk for having offspring with isolated clefts, multiple clefts, and all clefts increased significantly with maternal DM (aOR=1.33 [CI 95% 1.14-1.55], aOR=1.86 [CI 95% 1.44-2.40], and aOR=1.41 [CI 95% 1.23-1.62]), respectively (table 5-4). Maternal DM was associated with significantly increased risk for having CL, CL/P, and CP among the isolated OFC, with aORs ranging from 1.29 to 1.39; among multiple CL/P and CPO, with aORs of 1.74 [CI 95% 1.22-2.49] and 2.00 [CI 95% 1.42-2.82] respectively, and among isolated and multiple cleft groups combined, with aORs ranging from 1.35 to 1.52.

Table 5-4. Adjusted Odds Ratios (aORs)[1] and 95 Percent Confidence Intervals (CIs) of Orofacial Cleft Types and Subtypes by Maternal DM

Cleft Types	Cleft Lip Only	Cleft Lip with or without Cleft Palate	Cleft Palate Only	All Clefts
Isolated Clefts	1.37 [1.06-1.79]	1.29 [1.09-1.55]	1.40 [1.11-1.75]	1.33 [1.14-1.55]
Multiple Clefts	1.08 [0.43-2.70]	1.74 [1.22-2.49]	2.00 [1.42-2.82]	1.86 [1.44-2.40]
Isolated and non-isolated Clefts Combined	1.35 [1.05-1.74]	1.35 [1.15-1.60]	1.53 [1.25-1.86]	1.41 [1.23-1.62]

[1] Covariates in logistic regression models include study site, maternal age, education levels, multivitamin use, maternal BMI categories, and history of smoking

Statistical analyses were used to evaluate the possibility of effect modification of the association between maternal DM and OFCs by maternal weight categories (table 5-5). In a multiple logistic regression analysis that controlled for maternal age groups, maternal smoking during the first trimester of pregnancy, multivitamin use, and education (college graduate vs. not college graduate) shown in table 9, the estimated relative risk for having isolated and all clefts increased significantly with maternal underweight (1.0 [reference]; OR= 2.76 [95% CI 1.29-5.93] and 2.63 [95% CI 1.26-5.49]), respectively. Maternal overweight and obesity increased the risk of having isolated, multiple, and isolated and multiple clefts combined significantly, with aOR ranging from 1.33 to 2.61. DM was not associated with OFCs among normal weight mothers.

Table 5-5. Adjusted Odds Ratios (aORs)[1] and 95 Percent Confidence Intervals (CIs) of Orofacial Cleft Types by Maternal Diabetes Stratified by Maternal Body Weight Categories

Maternal Body Mass Index (BMI) Group	Isolated Clefts n=4319	Non-isolated Clefts n=961	All Clefts n=5280
Underweight BMI <18.5	2.76 [1.29-5.93]	2.13 [0.56-8.05]	2.63 [1.26-5.49]
Normal weight BMI >18.5, < 25	1.11 [0.85-1.44]	1.13 [0.67-1.92]	1.11 [0.87-1.43]
Overweight BMI >25, <30	1.45 [1.10-1.91]	1.81 [1.13-2.91]	1.51 [1.17-1.96]
Obese BMI >30	1.33 [1.02-1.73]	2.61 [1.71-3.97]	1.52 [1.19-1.93]

[1] Covariates in logistic regression models include study site, maternal age, education levels, multivitamin use, and history of smoking.

The estimated relative risk of DM with maternal underweight for having isolated and all CPO (OR=4.26 [1.58-11.48] and 4.00 [1.59-10.04]) respectively appeared to be higher than in the other body weight groups. Maternal overweight increased the risk for isolated, multiple, and all CL/P in addition to isolated and all CPO. Maternal obesity increased the risk for isolated and all CLO; isolated, multiple, and all CL/P; and multiple and all CPO. Diabetic normal weight mothers had no increased risk for any OFC type (table 5-6).

Table 5-7 shows the aORs of OFCs types and subtypes by maternal DM stratified by maternal periconceptional multivitamin (MVI) use vs. non-multivitamin use. The results demonstrate a slightly decreased risk of isolated (aOR=1.30 [95% CI 1.01-1.54]) and isolated and non-isolated OFC groups combined (aOR=1.35 [95% CI 1.15-1.57]) among MVI users compared to non-MVI users (aORs=1.48 [95% CI 1.05-2.09] and 1.72 [95% CI 1.26-2.35], respectively). However, the effect of MVI use in attenuating the risk of OFCs among mothers with DM appeared to be stronger for OFCs with multiple birth defects (aOR=1.62 [95% CI 1.19-2.20]) compared to non-multivitamin users (aOR=2.73 [95% CI 1.67-4.46]).

Table 5-6. Adjusted Odds Ratios (aORs)[1] and 95 Percent Confidence Intervals (CIs) of Orofacial Cleft Types and Subtypes by Maternal Diabetes Stratified by Maternal Body Weight Categories

Orofacial Cleft Type	Maternal Body Weight Category	Cleft Lip Only	Cleft Lip with or without Cleft Palate	Cleft Palate Only	All Clefts
Isolated Clefts	Underweight BMI <18.5	2.01 [0.53-7.55]	2.16 [0.89-5.20]	4.26 [1.58-11.48]	2.76 [1.29-5.93]
	Normal Weight BMI>18.5, <25	0.92 [0.55-1.52]	1.01 [0.74-1.39]	1.29 [0.87-1.91]	1.105 [0.85-1.44]
	Overweight BMI>25, <30	1.58 [0.99-2.53]	1.39 [1.00-1.92]	1.53 [1.01-2.32]	1.45 [1.10-1.91]
	Obesity BMI >30	1.68 [1.07-2.65]	1.43 [1.06-1.94]	1.15 [0.75-1.75]	1.33 [1.02-1.73]
Multiple Clefts	Underweight BMI <18.5	4.56 [0.47-44.33]	1.34 [0.17-10.81]	3.35 [0.66-16.86]	2.13 [0.56-8.05]
	Normal Weight BMI>18.5, <25	0.61 [0.08-4.44]	0.98 [0.45-2.12]	1.27 [0.64-2.53]	1.13 [0.67-1.92]
	Overweight BMI>25, <30	0.85 [0.11-6.48]	2.09 [1.10-3.96]	1.60 [0.82-3.09]	1.81 [1.13-2.91]
	Obesity BMI >30	1.27 [0.28-5.86]	2.19 [1.23-3.91]	3.21 [1.81-5.69]	2.61 [1.71-3.97]
Isolated and Multiple Clefts Combined	Underweight BMI <18.5	2.37 [0.73-7.71]	2.02 [0.86-4.74]	4.00 [1.59-10.04]	2.63 [1.26-5.49]
	Normal Weight BMI>18.5, <25	0.89 [0.54-1.46]	1.01 [0.75-1.37]	1.29 [0.91-1.83]	1.11 [0.865-1.43]
	Overweight BMI>25, <30	1.53 [0.96-2.41]	1.47 [1.09-1.99]	1.54 [1.07-2.22]	1.51 [1.17-1.96]
	Obesity BMI >30	1.64 [1.06-2.55]	1.53 [1.15-2.02]	1.53 [1.08-2.17]	1.52 [1.19-1.93]

[1] Covariates in logistic regression models include study site, maternal age, education levels, multivitamin use, and history of smoking.

Table 5-7. Adjusted Odds Ratios (aORs) and 95% Confidence Intervals (CIs) of Orofacial Cleft Types and Subtypes by Maternal Diabetes Stratified by Maternal Multivitamin (MVI) Use

Status of Multivitamin Use	Orofacial Cleft Type	Cleft Lip Only	Cleft Lip with or without Cleft Palate	Cleft Palate Only	All Clefts
MVI Users	Isolated Clefts	1.27 [0.94-1.72]	1.24 [1.02-1.51]	1.41 [1.10-1.82]	1.30 [1.10-1.54]
	Multiple Clefts	0.85 [0.26-2.75]	1.35 [0.86-2.13]	1.91 [1.28-2.83]	1.62 [1.19-2.20]
	Isolated and Multiple Clefts Combined	1.24 [0.92-1.67]	1.25 [1.04-1.51]	1.41 [1.10-1.82]	1.34 [1.15-1.57]
Non-MVI Users	Isolated Clefts	1.89 [1.10-3.26]	1.57 [1.07-2.31]	1.30 [0.76-2.22]	1.48 [1.05-2.09]
	Multiple Clefts	1.83 [0.41-8.10]	3.20 [1.72-5.94]	2.19 [1.08-4.45]	2.73 [1.67-4.46]
	Isolated and Multiple Clefts Combined	1.87 [1.11-3.15]	1.83 [1.29-2.59]	1.30 [0.76-2.22]	1.72 [1.26-2.35]

[1] Covariates in logistic regression models include study site, maternal age, maternal BMI categories, education levels, and history of smoking.

Discussion

This study provides evidence that maternal DM significantly increases the risk of having a child with OFC. An association between maternal DM among obese mothers and increased risk of isolated, multiple, and isolated and multiple clefts combined found to be statistically significant. Interestingly, the risk of maternal DM among underweight mothers appeared to be higher than among obese mothers in isolated and isolated and multiple cleft groups combined, while no excess risk was found among diabetic mothers with normal weight.

This is the largest international consortium of case-control study to date with multiple countrywide sites in Europe and statewide sites in the US. The study is population-based and relatively robust against selection bias. OFC cases were drawn from birth defects registries. Data on potential confounders were obtained through the process of interviewing participants. The study was designed to use well-defined procedures for case definition and careful classification of OFCs and associated conditions by clinical specialists.

The present study was designed to test the maternal DM hypothesis in relation to OFCs. High-quality data were available on several conceptually relevant covariates to control for potential confounding. Statistical analyses were conducted for isolated, multiple, and isolated and multiple cleft groups combined and cleft subtypes. The effects of maternal DM and maternal BMI categories on the risk of OFC were all evaluated. As DM is an epidemic health problem, a modest effect of maternal DM can be linked to a significant burden of OFCs. We also conducted a pooled analysis using individual data on DM and potential confounding factors (age, smoking during the first trimester of pregnancy, multivitamin use, education level,

and BMI categories). The risk of orofacial clefting by maternal DM by maternal BMI categories was also evaluated.

The presence of DM was determined based on maternal self-reports of diagnosed DM that were similar to approaches used in previous population-based case-control studies of birth defects [30, 31]. This is subject to DM status misclassification as some women who reported having no DM may have had undiagnosed type-2 DM. However, there is no reason to believe that the subsequent misclassification of DM status occurred differently for case and control mothers in this study, so the net effect was probably of an attenuation of associations of diabetes mellitus with OFC birth defects.

Other potential limitations of this study include the use of self-reported pre-gestational weight and height and the possibility of recall bias for these variables. Data on exposures to smoking, and multivitamin intake were limited to dichotomous exposure levels, thus residual confounding related to these factors is a possibility. As in all case-control studies, recall bias is a concern.

With the rising rates of DM [32], the current findings of the association between maternal DM and OFCs in the offspring is a major public health concern. Studies of the association between maternal DM and risk of OFCs have produced somewhat consistent findings for the positive effect of DM, although an inconsistency related to the effect on the type of cleft has been observed [19, 20, 22, 33, 34]. This may be related to variations in population sample size, definitions of OFC subtypes, lack of consideration of maternal underweight, and inadequate control of potential confounding factors.

In the present study, a positive association was found between maternal DM and OFCs in the offspring. This is similar to results reported by previous studies [19, 20,

[22, 33, 34]. However, Carinci et al., and Arteaga et al. reported a higher correlation between DM and isolated clefts [20, 34], while Tantbirojnet al. indicated a higher risk of CL/P among diabetic mothers . Our results indiated an increased risk for isolated, non-isolated, and both cleft groups combined when maternal DM is present, with a higher aOR for multiple clefts than in isolated clefts (aOR=1.86 [95%CI 1.44-2.40] and 1.33 [95%CI 1.14-1.55]), respectively. Yet, the aOR of isolated and non-isolated cleft groups combined was the highest compared to each separate group (aOR=1.41 [95%CI 1.23-1.62]). This result is consistent with the one reported by Correa et al. in which the association between maternal DM and multiple defects is stronger than with isolated defects [2]. Possible explanation for the stronger associations with multiple OFC includes an increased underlying susceptibility and/or exposure to a more adverse metabolic environment in utero. Further research is warranted to elucidate the basis for the variation in the ORs by OFC subtype and to identify the reasons for the stronger associations of DM with multiple defects.

DM has been found in earlier studies to be associated with various birth defects including OFCs. The consistent finding of the associations between maternal DM and birth defects suggest the hypothesis that complex underlying metabolic disorders that are associated with DM increase the likelyhood that signal transduction pathways and morphogenic processes might be distrubed [35-37].

The association of DM in the presence of obesity with OFC has been observed in a few other studies [8, 22, 38]. Similarly, our results indicate that pregnancies of women who were both obese and diabetic increase the risk for having an offspring with OFC, with ORs ranging from 1.33 to 2.61 for isolated, multiple, and both groups combined. However, pregnancies of women who were underweight and diabetic also appeared to have a higher risk for OFC compared to obese mothers, with an estimated relative risk

of 2.8 [95% CI 1.29-5.93] for having offspring with isolated cleft, 2.6 [95% CI 1.26-5.49] for any type of cleft, and 4.3 fold increased risk [95% CI 1.58-11.48] for isolated CPO. Rao, 1984 reported an association between maternal undernutrition and DM. Maternal underweight is a form of undernutrition and can be an important determinant of DM in an individual through a process of impairing beta cells progressively or by increasing the susceptibility of the individual to other genetic and environmental diabetogenic influence [39]. Thus, mothers characterized by being lean can be at a similar risk for developing DM as obese individuals. However, mothers who are both lean and diabetic may be at an even higher risk to have an infant with OFC compared to obese mothers.

Multiple CPO represented the highest risk when maternal DM is present (aOR= 1.98 [95% CI 1.40-2.80]). Maternal obesity combined with DM was also associated with a higher risk for CPO. On the other hand, women with DM and normal weight had no excess risk of having offspring affected by OFC. This is similar to the study reported by Moore et al. [8], suggesting that obesity and DM may act synergistically in the pathogenesis of congenital abnormalities. Maternal obesity on cleft palate malformation was reported to have an indirect influence of excess adiposity due to bioaccumulation and release of dioxins, which have been shown to cause cleft palate in mice [40]. Both obesity and DM are indicators for metabolic syndrome and are also associated with conditions known as "diabesity" [32], implying a possible role of metabolic syndrome on palate formation in the embryo [41].

What mechanisms could link maternal DM to OFCs in the offspring? Whatever the underlying mechanism behind the observed associations is, maternal DM appears to be associated with the risk of all types of OFC. While no excess risk of OFCs within diabetic normal weight mothers was found, mothers who were

diabetic and underweight, overweight, or obese had an increased risk for having

inborn with any type of OFCs. Diabetic underweight mothers showed a higher risk

than that of obese diabetic mothers to have a child with OFC. Thus, maternal DM

combined with obesity or underweight appear to be an indirect measure of cleft risk,

suggesting that the state of mothers being underweight does not reduce or protect

against the risk of OFC. Further studies are needed to understand how this risk is

modified by risk factors related to both underweight and overweight.

DM can be caused by various environmental and genetic factors, including

obesity, sedentary lifestyles, and overnutrition [32]. Previous studies reported that even

in the absence of maternal diabetes, obese women have been found to have an

impaired glucose metabolism [42], which may be associated with an elevated risk for

OFCs [8, 19, 22]. Multivitamin use appeared to attenuate the risk of OFCs due to DM.

Although OFC deformities occur within the first trimester of pregnancy, and given

that DM is associated with an increased risk for OFC, there is only a few data on

screening tests before 24 weeks' gestation. Therefore, further studies on appropriate

methods for diabetes testing in the periconceptional period for all mothers, including

underweight mothers, are recommended.

This is the largest study to date to test the association between maternal DM

and risk of having a newborn with an OFC. Maternal type-1 DM is significantly

associated with the risk of OFCs. Diabetic women who are also obese have a higher

risk to have an offspring with OFC compared to diabetic mothers with normal weight.

Underweight mothers who are also diabetic have a doubled increased risk to have

inborn with OFC. Multivitamin use appeared to attenuate the risk of OFCs due to

GDM. To prevent this devastating craniofacial anomaly, our findings highlight the

need of obstetricians and gynecologists to assess all mothers for hyperglycemia in the

periconceptional period to reduce the risk of OFC in their offspring.

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CHAPTER 6
SUMMARY, CONCLUSIONS, AND FUTURE DIRECTIONS

Summary

The overall objective of this dissertation was to determine whether maternal obesity, diabetes and gestational diabetes, and maternal hypertension are independently associated with the risk of orofacial cleft (OFC) birth defects. OFCs are among the most common structural birth defects and a public health problem. There is a strong evidence of an etiologic role for both genetic and environmental factors. Environmental factors that have been associated with the risk of cleft include maternal smoking, multivitamin use, alcohol drinking, socioeconomic status, and body weight. Several studies suggest that maternal obesity, diabetes mellitus (DM), or the underlying metabolic abnormalities known as the metabolic syndrome, may be involved in the pathogenesis of cleft lip and cleft palate, and it is unclear whether this is true also for maternal gestational diabetes mellitus (GDM). With the rising rates of excess weight among pregnant women, even a modest effect of maternal obesity may result in excess risk of OFC. Maternal weight gain increases the risk for DM and hypertension. Although hypertension has been associated in a few studies with congenital birth defects, studies examining the risk associated with OFC are limited. Investigation of metabolic syndrome, with the presence of obesity, diabetes, hypertension, and other more serious physiologic consequences, may provide useful clues regarding birth defects associations.

The results of the studies conducted in this dissertation support the roles of abnormal maternal weight- both underweight and obesity- and gestational diabetes and hypertension on increasing the risk of OFC. A pooled analysis of population-based case–control studies conducted using the international consortium of case-

control studies from Utah, Iowa, Norway, and the U.S. National Birth Defects Prevention Study confirmed the independent association between maternal obesity and underweight and the risk of cleft palate. The effect of maternal education level on the risk of OFC was also tested. Interestingly, an increased risk for cleft lip with palate, cleft palate only, cleft palate with or without cleft lip, and all clefts was observed among mothers with lower education levels, while no effect on cleft lip only was seen. This may suggest a possible indirect effect of maternal education level on cleft palate risk. Thus, maternal body weight categories association with the risk of all cleft palate was tested after stratifying by maternal education level. The results showed an increased risk for cleft palate with or without cleft lip in obese and underweight mothers when mothers were less educated, with a highest risk observed among the underweight mothers. Such effect can be related to a combination of maternal underweight with lifestyle with behavioral factors associated with lower maternal education. In some previous studies, conclusions about the association between maternal obesity and orofacial clefting were limited by small number of cases, while this study represented the largest international consortium of case-control study to date with multiple countrywide sites in Europe and statewide sites in the U.S.

In a statewide case-control study of clefts conducted in Utah in collaboration with the Utah Birth Defects Network (UBDN), an increased risk for isolated and non-isolated clefts was observed among mothers diagnosed with GDM; while hypertension increased the risk for non-isolated and the results were suggestive for isolated clefts. As maternal obesity has been reported to be associated with both maternal GDM and hypertension, the risk of isolated and non-isolated OFC was tested within the different maternal body weight groups. Results indicated an increased risk for isolated and non-isolated clefts when the GDM is present among obese mothers.

Hypertension appeared to increase the risk for OFCs and this seems more pronounced for multiple OFCs and obese mothers.

Lastly, the analyses of the international consortium data revealed an association between DM on the risk of OFCs across all types (isolated, non-isolated, and all clefts) and subtypes (cleft lip only, cleft lip with or without cleft palate, and cleft palate only). When data were stratified by maternal body weight categories, maternal overweight and obesity combined with the presence of DM appeared to increase the risk of isolated, non-isolated, and all cleft groups combined. Maternal underweight status with the presence of DM also increased the risk of isolated and all cleft groups combined and the risk appeared to be stronger compared to that of obesity and overweight when combined with DM. Notably, diabetic mothers with normal weight did not have a significant elevated risks for OFCs.

<div align="center">Limitations and Future Directions</div>

The dissertation described here provides evidence of the roles of maternal obesity, DM, and GDM, and hypertension on OFC risk after adjusting for potential confounders. There are some limitations that must be discussed and addressed in future work. One limitation was the self-reported pre-gestational weight and height collected in the international consortium data. It is common among obese women to underreport their weights and overestimate their heights [1], resulting in an underestimation and misclassification of body-mass-index (BMI). However, even with the possibility of maternal underestimation of BMI, a significant increase in the risk of having a child with OFC birth defects was observed among the obese mothers and that effect could be stronger if the prevalence of obesity in the study sample was have accurately assessed.

In addition to the limitations of use of self-reported pre-pregnancy weight and height and the possibility of recall bias, in the study examining the role of maternal DM on the risk of OFC, the DM was determined based on maternal self-reports of diagnosed DM. This is subject to DM status misclassification as some women who reported having no DM may have had undiagnosed DM. However, there is no reason to believe that the subsequent misclassification of DM status occurred differently for case and control mothers in this study, so the net effect was probably of an attenuation of associations of diabetes mellitus with OFC birth defects.

The role of maternal GDM and hypertension was based on Utah OFC study. Due to the small number of participants with GDM and hypertension, the confidence intervals were wide. However, the detection for the increased risk even with this small sample size was suggestive and should encourage further research.

Although the potential confounders in the analyses of studies in this dissertation were adjusted for, it is possible that residual confounding exists. To better understand the underlying etiology of OFCs and whether genes and environmental risk factors play a causal role for OFCs, future studies are needed. The following recommendations are also offered for related research on OFC:

1. Given that maternal obesity, DM, and hypertension are all risk factors of metabolic syndrome, and appeared to have strong effects on increasing the risk of OFC, further studies on the exact pathophysiology of this syndrome may help in understanding the causal mechanisms for OFCs.

2. Research related to other potential environmental factors and genes and how they interact with maternal metabolic abnormalities would be of value to help better understand the etiology of OFCs.

3. Based on the results of the dissertation, maternal underweight and obesity may both have severe effects on the offspring. As it is unclear whether the cause is related to mothers' weight or other factors related to body composition, further research on the difference between obese, but metabolically healthy individuals and lean, but metabolically unhealthy people may justify why some people present to have higher risk for metabolic disorders than others, independently of body weight.

Recommendations for Practitioners

The following recommendations are offered for related research on OFC:

1. Based on the results of this dissertation, it is recommended to modify the guidelines of maternal screening for abnormal glucose tolerance to be performed in pre-conceptional and early prenatal visits of all women, highlighting that underweight mothers should be also tested for as they may have a higher risk for having offspring with congenital anomalies.

2. Given that obesity, DM, and hypertension are modifiable diseases and can be prevented through the application of healthy behaviors, it is recommended to inform and educate mothers planning for pregnancy on distinct practices to remain healthy and avoid pregnancy complications.

Conclusions

In conclusion, this dissertation presents additional insight into the possible etiologies associated with OFCs. The findings indicate that maternal obesity and underweight increase the risk of cleft palate in the offspring significantly; the risk increases further among mothers with lower education levels, while higher maternal

education levels protect against the effect of maternal underweight and obesity against the risk of OFCs. Additionally, the results support the hypotheses that maternal GDM and hypertension are independently associated with the risk of OFCs. Maternal DM increases the risk of all types (isolated, non-isolated, and all clefts) and subtypes (cleft lip only, cleft lip with or without cleft palate, and cleft palate only) of OFCs; and the risk increases further when maternal obesity is present among diabetic mothers. Normal weight mothers who were diabetic had no increased risk.

The findings demonstrated here can pose an important role for guiding further studies to identify risk factors associated with OFCs. Additional studies will be helpful in elucidating the pathophysiology behind these associations with OFCs.

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CURRICULUM VITAE

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(June 2014)

RESEARCH INTERESTS

Birth defects epidemiology, nutritional epidemiology, clinical epidemiology, and genetic epidemiology and statistical genetics.

EDUCATION

2009-2014	Ph.D.	Utah State University Logan, UT, United States Department of Nutrition and Food Science Emphasis: Nutrition science Dissertation: *The role of obesity, diabetes, and hypertension in cleft lip and cleft palate birth defects.* Major Professor: Ronald Munger, PhD.
2012-2013	B.S.	Utah State University Logan, UT, United States Emphasis: Dietetics

2013-2014	Dietetic Internship	Utah State University
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		    DaVita Dialysis Center (Outpatient Clinical)
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		    Women, Infants, and Child program (WIC), PHFE (Community nutrition)

2008	M.S.	King Abdulaziz University Jeddah, Saudi Arabia Food and Nutritional Sciences
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PROFESSIONAL EXPERIENCE

09/2007-   Clinical Dietitian, King Abdulaziz University Hospital.

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Translated the physician written diet order in terms of foods or nutritional products & formulas; assessed, developed, implemented and evaluated nutritional care plans and provided follow up; designed meal patterns individualized according to patients food habits and modified according to therapeutic needs; counseled patients and family of home diet if needed; recommended appropriate formulas for enteral feeding (intravenous); documented patients nutritional care during their hospitalization; participated in evaluation and monitoring of food service system and made recommendation as needed.

PROFESSIONAL MEMBERSHIP AND CREDENTIALS

2014-Present   Registered Dietitian

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PROFESSIONAL PRESENTATIONS

Kutbi HA, Munger R, Moreno LM, Romitti P, Christensen K, DeRoo L, Wilcox A, Lie RT, Murray JC, Wehby GL. *Maternal Obesity and Underweight both Associated with Increased Risk of Oral Clefts.* Presented at the 12th International Congress on Cleft Lip and Cleft Palate and Related Craniofacial Anomalies. Miami, FL. May 2013