2014

Gestational and Pregestational Diabetes in the Eastern Mediterranean Region: A Meta-analysis of Maternal and Fetal Outcomes

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

February 2014

Abstract

Pregestational diabetes mellitus (PGDM) and gestational diabetes mellitus (GDM) are associated with adverse pregnancy outcomes including increased caesarean section rates, macrosomia, and perinatal mortality. Despite the high prevalence of GDM and PGDM in the Eastern Mediterranean Region (EMR), most of the published studies examining the association between GDM/PGDM and adverse pregnancy outcomes have small sample sizes, low statistical power, and few adverse outcomes with conflicting results. The purpose of this study was to determine the association of GDM/PGDM with adverse pregnancy outcomes among women in the EMR, by using a meta-analysis research design. Following the conceptual model of the epidemiologic triangle, the research questions for this study tested whether an association existed between GDM/PGDM and delivery by cesarean section, macrosomia, and perinatal mortality among women in the EMR. A random effects model was used for merging the weighted average of the odds ratios in the 33 primary studies. Pooling of the data showed that, in the EMR, odds of undergoing caesarean section, of having a macrosomic baby, and of perinatal death among women with GDM/PGDM were higher than those without GDM/PGDM. This study contributes to social change by providing a better picture of magnitude and severity of GDM/PGDM, in creating awareness of the seriousness of the problem, and in helping inform public health interventions in the EMR. Women with GDM/PGDM receiving proper health care can have decreased adverse outcomes which, in turn, results in healthy mothers and children forming a healthy family and leading to a healthy, productive community.

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Dedication

I dedicate this dissertation to the memory of my beloved late parents who believed in the value of women's education and provided me invaluable educational opportunities.

Acknowledgments

The writing of this doctoral dissertation has been a long journey and an excellent learning experience. I wish to acknowledge that the completion of this journey was possible with the support of several people. I would like to express my sincere gratitude to all of them. First of all, I would like to thank my committee chair, Dr. Cassandra Arroyo, for her support, guidance, and suggestions that were extremely helpful and appropriate. My special thanks to Professor Peter Anderson who has been a source of encouragement and support throughout the dissertation process. He provided his invaluable support at the final stages of my dissertation when, after departure of Dr. Cassandra Arroyo, he took the responsibility as the Chair of my dissertation committee. I would like to express my gratitude to the members of my dissertation committee, Dr. Frank Besag and Dr. Xianbin Li, for their valuable guidance and scholarly inputs. I would like to thank the University Research Reviewer, Dr. James Rohrer, for offering thorough, constructive and encouraging feedback on the proposal of my dissertation.

Finally, I owe my deepest gratitude to members of my family. I am much indebted to my husband, Dr. Amjad Ali, who supported me throughout this process and constantly encouraged me when the tasks seemed insurmountable. I would like to thank him for reminding me of the blessings in our life and making my mind relax during the hard times of my dissertation. I also would like to thank my son, Rafay Omar Syed, and my daughter, Aliba Omar Syed, for being patient and understanding over the years. Their constant prayers and continued support eased this journey for me. I owe my achievements to my family.

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Chapter 1: Introduction to the Study

Introduction

Globally, researchers are concerned about an increase in the prevalence of gestational diabetes mellitus (GDM) and pregestational diabetes (PGDM; Carolan, Davey, Biro, & Kealy, 2011). Middle Eastern countries are reported to have a high prevalence of GDM and PGDM, ranging from 4.7% in Iran (Hossein-Nezhad, Maghbooli, Vassigh, & Larijani, 2007) to 24.9% in the United Arab Emirates (Agarwal, Dhatt, & Shah, 2010) in comparison to the United States, where the prevalence ranges from 3.47% to 7.15% (Bardenheier et al., 2013). PGDM and GDM are associated with adverse fetal and maternal outcomes (Crowther et al., 2005; Metzger et al., 2008). Adverse fetal outcomes include congenital anomalies, trauma during birth, macrosomia, and perinatal mortality (Ayaz, Saeed, Farooq, Ali Bahoo, & Hanif, 2009; Ornoy, 2011; Rosenberg, Garbers, Lipkind, & Chiasson, 2005; Thorpe et al., 2005). Adverse maternal outcomes include increased rates of caesarean section and increased lifetime risk of developing type 2 diabetes (Bellamy, Casas, Hingorani, & Williams, 2009; Langer, Yogev, Most, & Xenakis, 2005; Rosenberg et al., 2005). Cesarean deliveries may be associated with a range of morbidities, with complications ranging from mild to serious (Silver et al., 2006). Wound infection and wound rupture associated with prolonged hospital stay may follow a caesarean section. Injuries to bowel, urinary bladder or urethra may occur during the surgical procedure. Repeated caesarean sections may result in placenta accreta, a serious obstetric complication resulting from deep attachment of the placenta. Deep venous thrombosis, pulmonary embolism—and in rare cases maternal

death—may occur (Silver et al., 2006). Generally, maternal morbidity increases with repeated caesarean sections. The complications of repeated caesarean sections are especially important in the context of those cultures where large families are a norm, as is the custom in most countries of the Middle Eastern Region.

There are a few small-scale published studies examining the association between GDM/PGDM and maternal and fetal outcomes among women in the EMR; many of these studies do not have adequate sample size and have only a few adverse outcomes (Abdelgadir, Elbagir, Eltom, Eltom, & Berne, 2003; Al-Dabbous, Owa, Nasserallah, & al-Qurash, 1996; Misra, Rashid, Grundsell, & Sedagathian, 2001). Due to the rare occurrence of adverse outcomes and small sample sizes in the published studies, the estimates of association may not be stable. Because of the increasing prevalence of PGDM and GDM and the extent of morbidity caused by them, research efforts need to focus on the magnitude of the problem in the EMR. Determining the magnitude of association between GDM/PGDM and adverse pregnancy outcomes is an important initial step in understanding the epidemiology of adverse pregnancy outcomes as they relate to PGDM and GDM in the EMR.

In this Chapter, I provide the background of the study, problem statement, purpose of the study, research questions and hypotheses, nature of the study, conceptual model, assumptions and limitations of the study, delimitations, and significance of the study. I end the chapter with a summary of the chapter and transition to the next.

Background

Diabetes mellitus is a chronic condition characterized by increased glucose levels in the body. The long-term increased levels of glucose, called hyperglycemia, result in various health complications (International Diabetes Federation [IDF], 2011; Maraschin, 2012). There are three main types of diabetes mellitus; type 1 diabetes mellitus, type 2 diabetes mellitus, and GDM (IDF, 2011). Diabetes during pregnancy can be classified into two categories; PGDM and GDM (Lawrence, Contreras, Chen, & Sacks, 2008). Type 1 or type 2 diabetes diagnosed in pregnant women before pregnancy is called pregestational diabetes mellitus (Lawrence et al., 2008). Women diagnosed with diabetes for the first time, during pregnancy, are diagnosed with gestational diabetes mellitus (Bentley-Lewis, Levkoff, Stuebe, & Seely, 2008; Black, Sacks, Xiang, & Lawrence, 2010; Kim et al., 2010; Luoto et al., 2011; Reece, Leguizamón, & Wiznitzer, 2009). PGDM and GDM are common medical conditions during pregnancy.

There is an increasing trend in the prevalence of PGDM and GDM (Bell et al., 2008; Carolan et al., 2011; Jiwani et al., 2012; Lawrence et al., 2008). This increase in prevalence is seen globally, as well as in the EMR. According to the World Health Organization [WHO], the Eastern Mediterranean Regional Office [EMRO] consists of a group of WHO member states in one of its six geographical regions and includes 22 Middle Eastern countries, such as Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon and Libya. Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates [UAE], and Yemen (WHO, n.d.). Middle Eastern countries have a high prevalence of GDM and PGDM in

comparison to other countries of the world (Agarwal et al., 2010; Hossein-Nezhad et al., 2007). Depending on the diagnostic criteria, the prevalence of GDM in UAE ranged from 7.9% to 24.9% (Agarwal, Dhatt, Punnose, & Koster, 2005). Researchers have also reported high incidence of GDM. In Yazd, Iran, the incidence of GDM was shown to be 10.2% among 1,071 pregnant women screened for GDM (Soheilykhah et al., 2010). In a large retrospective cohort study, in Bahrain, the incidence of GDM was found to increase from 7.2% in 2002 to 12.5% in 2010 (Rajab, Issa, Hasan, Rajab, & Jaradat, 2012). With this increasing incidence, the burden of adverse pregnancy outcomes is also expected to increase.

Adverse maternal and fetal outcomes in women having pregnancy with diabetes have been documented in the EMR. Bener, Saleh, and Al-Hamaq (2011) studied a cohort of 1,608 pregnant women in Qatar. There was an increased incidence of maternal complications, such as preeclampsia and cesarean section, in women with GDM. Gasim (2012) compared pregnancy outcomes in 220 Saudi women with GDM/PGDM and 220 without GDM/PGDM. The researcher found a significantly higher incidence of cesarean section ($p = 0.0019$) and macrosomia ($p = 0.0186$) among women with GDM/PGDM in comparison to those without GDM/PGDM. However, the difference between congenital anomalies and perinatal mortality rates was not statistically significant between the two groups. Several researchers found that GDM/PGDM increased rates of caesarean section (Badakhsh et al., 2012; Barakat, Youssef and Al-Lawati, 2010; Hossein-Nezhad et al., 2007; Misra et al., 2001). Additionally, researchers have suggested that GDM/PGDM increases risk for macrosomia (Al-Khalifah, Al-Faleh, Al-Subaihin, Al-Kharfi, & Al-

Alaiyan, 2012; Barakat et al., 2010; Hossein-Nezhad et al., 2007; Keshavarz et al., 2005; Nasrat et al., 1993) and perinatal mortality (Hossein-Nezhad et al., 2007; Keshavarz et al., 2005; Misra et al., 2001). Contradictory results regarding the association of adverse outcomes and GDM/PGDM in the EMR have also been documented.

While a positive association of GDM/PGDM and delivery by cesarean section was seen in some studies (Bener et al., 2011; Gasim, 2012), a non-statistically significant association between GDM/PGDM and delivery by cesarean section has also been seen (Nasrat, Augensen, Abushal, & Shalhoub, 1994). Similarly, there is evidence that the association between GDM/PGDM and macrosomia is not statistically significant. (Al-Khalifah et al., 2012; Shirazian et al., 2008). Due to a low number of perinatal deaths in any single study, estimates of the association between GDM/PGDM and perinatal mortality were underpowered and unstable (Abdelgadir et al., 2003; Gasim, 2012). Overall, most studies have had a limited number of participants resulting in low precision for estimating the association with GDM/PGDM. For example, Abolfazl, Hamidreza, Narges, and Maryam (2008) included 70 women with GDM and Keshavarz et al. (2005) were able to include 63 women with GDM in their studies. Many studies conducted to determine the effect of GDM/PGDM on pregnancy outcomes had low power. For example, the study conducted by Sobande, Al-Bar, and Archibong (2000) had a power of 41.7% at an alpha level of 0.05, to determine a statistically significant difference of perinatal deaths between women with GDM/PGDM and those without GDM/PGDM. Synthesizing the results of these studies by meta-analysis served to increase the sample size and thus improve the precision of the desired associations to be estimated (The

Cochrane Collaboration, 2008). Meta-analysis is considered one of the best methods to inform evidence-based decisions for health care (Lavis et al., 2005; Wallace, Nwosu, & Clarke, 2012). Meta-analysis is also helpful in planning future research for delivering optimal health care (Cook, Mulrow, & Haynes, 1997; Roloff, Higgins, & Sutton, 2013). There is a need for precise and valid estimates of the true association between adverse pregnancy outcomes and GDM/PGDM among women in EMR.

Problem Statement

Despite the reported high prevalence of GDM and PGDM in Middle Eastern countries (Agarwal et al., 2010; Hossein-Nezhad et al., 2007), most of the published studies examining the association between GDM/PGDM and adverse outcomes in this region are conducted on a small scale with varied and sometimes conflicting results (Al-Hakeem, 2006; Al-Khalifah et al., 2012; Barakat et al., 2010; Bener et al., 2011; Gasim, 2012; Keshavarz et al., 2005; Nasrat et al., 1994; Shirazian et al., 2008). The true underlying association may not be well estimated due to small sample sizes, low statistical power, and few adverse outcomes in any given study. The number of caesarean sections and macrosomic babies born is low in any given study. Similarly, perinatal mortality is an uncommon occurrence, and there are nil or few perinatal deaths in any given study. Studies including multiple countries of the EMR have not been conducted, thus resulting in a lack of information regarding a broader perspective of the situation in the EMR. To date, there has not been an attempt to statistically synthesize studies from countries in the EMR, by meta-analysis, to quantify complications related to pregnancy

with GDM/PGDM with greater precision or to provide insight into the magnitude of the association and extent of the problem in the EMR.

Purpose of the Study

The purpose of this study was to determine the association of GDM/PGDM with adverse pregnancy outcomes among women in the EMR. Measuring the association of GDM and PGDM with adverse pregnancy outcomes would help in providing a better picture of magnitude and severity of the problem in the EMR. Given the rising prevalence of GDM and PGDM in Middle Eastern countries, it is important to be aware of the severity and seriousness of the problem. Determining the magnitude of association between GDM/PGDM and adverse pregnancy outcomes is an important initial step for developing appropriate interventions.

In this meta-analysis, independent variables were PGDM and GDM. The dependent variable for maternal outcomes was delivery by cesarean section. The dependent variables for neonatal outcomes were macrosomia/large for gestational age and perinatal mortality.

Research Questions and Hypotheses

1. Is there an association between GDM/PGDM and delivery by cesarean section among women in the EMR?

   H_{01} - There is no association between GDM/PGDM and delivery by cesarean section among women in the EMR

   H_{A1} - There is an association between GDM/PGDM and delivery by cesarean section among women in the EMR

2. Is there an association between GDM/PGDM and adverse fetal outcomes among women in the EMR?

2a. Is there an association between GDM/PGDM and macrosomia among women in the EMR?

H_{02a} - There is no association between GDM/PGDM and macrosomia among women in the EMR

H_{A2a} - There is an association between GDM/PGDM and macrosomia among women in the EMR

2b. Is there an association between GDM/PGDM and perinatal mortality among women in the EMR?

H_{02b} - There is no association between GDM/PGDM and perinatal mortality among women in the EMR

H_{A2b} - There is an association between GDM/PGDM and perinatal mortality among women in the EMR

Conceptual Model

The conceptual model for this study is the epidemiologic triangle— a traditional model examining the agent, the host, and the environmental factors for an association in causation of infectious disease (Centers for Disease Control and Prevention [CDC], 2009). The epidemiologic triangle explains disease causation by using a simple paradigm. It states that the disease is caused by an imbalance among the factors related to host, agent, and environment. The epidemiologic triangle was originally designed to explain the cause of infectious diseases, but it has also been applied to noncommunicable

diseases and other health problems (Huerta & Leventhal, 2002; Peller, LaPlante, & Shaffer, 2008; Ramirez & Peek-Asa, 2005). The components of the epidemiologic triangle include host factors related to humans making them susceptible to the agent or causative factors, agent factors necessary for the causation of disease or health condition, and environmental factors that are external to the host and agent (CDC, 2012).

The key elements of this study are related to the components of epidemiologic triangle. The agent factor for GDM/PGDM is the hormone insulin. Adverse outcomes of GDM/PGDM such as macrosomia, delivery by caesarean section, and perinatal mortality are associated with insulin resistance during pregnancy (Young & Ecker, 2013). The host factors consist of both nonmodifiable and modifiable factors including age, race, family history of diabetes, and lifestyle factors, including diet and physical activity. Regarding the association of adverse outcomes of GDM/PGDM with host factors, an association between caesarean delivery and race/ethnicity has been documented (Esakoff, Caughey, Block-Kurbisch, Inturrisi, & Cheng, 2011). An association between increasing age and increased prepregnancy BMI with macrosomia as well as cesarean delivery is reported (Beucher, Viaris de Lesegno, & Dreyfus, 2010; Gutaj, Wender-Ozegowska, Mantaj, Zawiejska, & Brazert, 2011). Environmental factors that contribute to GDM/PGDM may be physical, social, and economic. The availability and affordability of healthy food, cultural values, and accessibility to health care facilities are some of the environmental factors. In turn, these environmental factors are also related to obesity and maternal and fetal outcomes of GDM/PGDM, including macrosomia, caesarean delivery, and perinatal

mortality (El-Chaar et al., 2013; Yogev & Visser, 2009). I discuss the conceptual model in more detail in Chapter 2.

Nature of the Study

To determine an association between GDM/PGDM and adverse pregnancy outcomes among Eastern Mediterranean women, quantitative research was conducted. For the purpose of this study, I used a meta-analysis research design. Meta-analysis is an appropriate technique for this quantitative research because magnitude of association was determined by combining results of studies from most countries of the region, conducted over various periods of time in varied settings. An original study of this extent would have been resource-intensive and difficult to conduct because of the adverse social, economic, and political situation of many member countries. Meta-analysis is appropriate as it statistically combines quantitative estimates from various primary studies (Sutton et al., 2000). Moreover, meta-analysis may identify gaps in the existing literature (Garg, Hackam, & Tonelli, 2008). In this meta-analysis, the independent variables were GDM/PGDM. The dependent variable for maternal outcome was delivery by cesarean section while the dependent variables for neonatal outcomes were macrosomia and perinatal mortality.

Search Strategy for Relevant Studies

A review of studies conducted on GDM/PGDM in the EMR was conducted to systematically identify the relevant literature. A comprehensive literature search was conducted in several research databases. Explicit criteria for inclusion or exclusion were

used for meta-analyses. Detailed search strategy, inclusion and exclusion criteria, are explained in Chapter 3.

Details of the study included in the meta-analysis. The guidelines for reporting a meta-analysis of observational studies was followed (Stroup et al., 2000). A summary table was created to record the main elements of each study, such as relevant bibliographic information, the studies' design, type(s) of diabetes mellitus, age group/ mean age of women, and outcome data (Glasziou, Irwig, Bain, & Colditz, 2001). To assess individual observational studies, quality criteria were laid down by selecting elements from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (Von Elm et al., 2007). The details of these criteria are stated in Chapter 3.

Statistical Procedures

The software, Comprehensive Meta Analysis (Version 2) , was used to conduct the meta-analysis. Statistical procedures included effect size computation, random effects model, heterogeneity assessment, sensitivity analysis, sub-group analysis, moderator analysis and publication bias assessment.

An effect size is a number that expresses the magnitude of the association between two variables (Cooper & Hedges, 2009). To calculate effect sizes in this study, odds ratio (OR) was the primary metric, because the OR has certain statistical properties that make it the best index for a meta-analysis (Borenstein, Hedges, Higgins, & Rothstein, 2009, p. 36). For merging effect sizes, a random effects model was used because of the presence of a heterogeneous population and potential diversity among the

studies (Cooper & Hedges, 2009; Petticrew & Roberts, 2006). Statistical significance of heterogeneity was assessed by Cochrane's *Q* statistic and *I*-squared (Borenstein et al., 2009). The details of these statistics are provided in Chapter 3.

Sensitivity analyses were performed to assess variation in effect size caused by study design, sample size, and country of study (Borenstein et al., 2009). The influence of outliers was also evaluated to determine the affect of their omission on overall results (Tobias et al., 2010). The possible presence of publication bias was evaluated by funnel plot (Egger, Smith, Schneider, & Minder, 1997) and Egger's test (Crombie, & Davies, 2009; Wendland et al., 2012).

Definitions of the Variables

In this study, the independent variables were GDM and PGDM, while the dependent variables were caesarean section, macrosomia, and perinatal mortality. The definitions of independent variables and dependent variables are as follows:

GDM - Glucose intolerance leading to hyperglycemia, diagnosed first time in pregnancy is labeled as gestational diabetes mellitus (Bentley-Lewis et al., 2008; Black et al., 2010; Kim et al., 2010; Luoto et al., 2011; Reece et al., 2009). In this research, the study participants labeled by the authors as gestational diabetes was accepted as GDM cases, irrespective of the diagnostic criteria used.

PGDM - Type 1 or type 2 diabetes diagnosed in pregnant women before pregnancy is called PGDM (Lawrence et al., 2008). The study participants labeled by the authors as PGDM were accepted as PGDM cases.

Cesarean section - Cesarean section is a surgical technique for delivering a baby by incision through the abdominal wall and uterus of the mother (Mayo Clinic, 2012). For the sake of this study, the birth labeled by authors as cesarean delivery was accepted as birth by cesarean section.

Macrosomia or large for gestational age - Macrosomia signifies a newborn with an excessive birth weight. There are different ways of defining fetal macrosomia. A birth weight of 4000-4500 g (8 lb 13 oz to 9 lb 15 oz) or more than 90% for gestational age is labeled macrosomia (Medscape, 2012). For this meta-analysis, macrosomia and large for gestational age births were included as defined by the authors of the primary study.

Perinatal mortality - Perinatal mortality refers to fetal (20 or more weeks of gestation) deaths as well as neonatal deaths (MacDorman, Kirmeyer, & Wilson, 2012). Perinatal mortality included intrauterine fetal death, stillbirth, and early neonatal death.

Assumptions

The assumptions in this study were mostly related to the primary studies included in the meta-analysis. It was assumed that the primary studies were conducted rigorously, taking care of quality measures during study design and data collection. It was assumed that appropriate statistical analysis was conducted, and that the authors made sound decisions to reduce the role of bias and confounding in their studies. It was also assumed that, in spite of different diagnostic criteria used for GDM diagnosis, the effects on the frequency of adverse outcomes would have been minimal. All of these assumptions were

necessary in the context of this study because the results of meta-analysis depend on the scientific rigor of the primary studies from which the data will be drawn (Garg et al., 2008). Limitations of the primary studies—such as biases, weaknesses in methodology, and inherent problems in the execution of the primary studies—cannot be rectified in meta-analysis.

Scope and Delimitations

In this study, I focused on adverse pregnancy outcomes related only to PGDM/GDM in the EMR women. Specifically, delivery by cesarean section, macrosomia, and perinatal mortality were the adverse pregnancy outcomes of interest. This focus was chosen due to the limited number of primary studies conducted in the EMR that had small sample sizes with few adverse outcomes. The small sample sizes are primarily due to the uncommon occurrence of macrosomia and perinatal mortality in the EMR. The low incidence of macrosomia and perinatal mortality in the EMR supported the use of meta-analysis to estimate the associations between delivery by cesarean section, macrosomia, and perinatal mortality with increased statistical power, greater precision, and improved internal validity. As a result, other adverse pregnancy outcomes that have been linked to GDM/PGDM, as well as their causative factors, could not be determined by this study.

This study was delimited to the population of the EMR countries in which the primary studies were conducted. Thus, the results are valid and generalizable to the specific set of countries in which the primary studies were conducted. The results may not be generalized to other populations, such as Europeans or Americans.

Limitations

This study has limitations which correspond with the limitations of meta-analyses in general (Garg et al., 2008). The study includes diverse studies with different settings, designs, and participants. The quality and reliability of the overall effect size and conclusions of the study depend on the reliability and appropriateness of the methods used by the primary studies. Meta-analysis of observational studies has certain specific limitations, which are also reflected in this study. The role of chance, confounding factors, or biases, may affect the results in primary observational studies which cannot be rectified in the meta-analysis (Egger, Smith, & Schneider, 2008, pp.213-220). Another limitation specific to this study is the variability in defining the dependent and independent variables in primary studies. Variable diagnostic criteria were used for GDM in various studies. Similarly, the definition of macrosomia/large for gestational age also varied in primary studies. Variability in these definitions in primary studies might have affected the results of meta-analysis.

To address the limitations in this study, the following steps were taken: a comprehensive search strategy was used to avoid bias in study identification and selection; the quality of the primary studies was assessed; the statistical methods for calculation of combined effect size were appropriate; the test for heterogeneity and the assessment for publication bias were carried out(Crombie & Davies, 2009). Standard guidelines for reporting of meta-analysis including MOOSE (Stroup et al., 2000) and PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009) were followed in this study.

Significance

The present study is significant as it provides a broader perspective of adverse pregnancy outcomes associated with GDM/PGDM among women in the EMR. Filling gaps in the literature helps in creating positive social change which is an important aspect of this study. Measuring the association of GDM/PGDM with adverse pregnancy outcomes helps in providing a better picture of magnitude and severity of the problem in the EMR, creating awareness about its severity and seriousness. Determining the magnitude of association between GDM/PGDM and adverse pregnancy outcomes constituted an important initial step for developing appropriate interventions. Disseminating the results of this study can lead to measures that policy makers and health care workers can take to develop intervention strategies for preventing complications related to GDM/PGDM. Healthy mothers and children form a healthy family leading to a healthy, productive community.

Summary

The prevalence of GDM/PGDM is rising globally and in the EMR, specifically. Various studies have been conducted to determine the association of GDM/PGDM and adverse pregnancy outcomes in this region. However, studies conducted on a large scale to get a broader perspective of the region are lacking. This study determined a broader perspective of these outcomes in the EMR by combining the findings of various studies conducted on a small scale. Determining the magnitude and severity of association was a necessary step before developing appropriate interventions to deal with the rising problem of pregnancy with GDM/PGDM in the EMR.

In this chapter, I discussed the background of the study, problem statement, and purpose of the study. I identified the research questions, the related hypotheses, and conceptual model for the study. A brief overview of the assumptions, scope and limitations was provided. Finally, I concluded with a brief discussion of the significance of the current study and implications for positive social change. A review of the literature is presented in Chapter 2. It supports the planned research, including relevant studies on adverse pregnancy outcomes in women with GDM/PGDM in the EMR.

Chapter 2: Literature Review

Introduction

Globally, an increase in the prevalence of GDM and PGDM is reported (Carolan et al., 2011). Middle Eastern countries are reported to have a high prevalence of GDM and PGDM ranging from 4.7% in Iran (Hossein-Nezhad et al., 2007) to 24.9% in the United Arab Emirates (Agarwal et al., 2010). PGDM and GDM are associated with adverse maternal and fetal outcomes (Crowther et al., 2005; Metzger et al., 2008). Adverse maternal outcomes include increased caesarean section rates and increased lifetime risk of type 2 diabetes (Bellamy et al., 2009; Langer et al., 2005; Rosenberg et al., 2005). Adverse fetal outcomes include congenital anomalies, trauma during birth, macrosomia, and perinatal mortality (Ayaz et al., 2009; Ornoy, 2011; Rosenberg et al., 2005; Thorpe et al., 2005).

Despite the reported high prevalence of GDM and PGDM in Middle Eastern countries (Agarwal et al., 2010; Hossein-Nezhad et al., 2007), most of the published studies examining the association between adverse outcomes and GDM/PGDM in this region, were conducted on a small scale and showed varied results. These studies may not depict the true, underlying association because of small sample sizes, low statistical power. and few adverse outcomes in any given study. Synthesizing these studies statistically, by meta-analysis, quantified complications related to pregnancy with diabetes and provide insight regarding the magnitude of association and the extent of the problem in the EMR.

The purpose of this study was to determine the association between GDM/PGDM and adverse pregnancy outcomes among women in the EMR. Measuring the association of GDM/PGDM with adverse pregnancy outcomes helps in providing a better picture of magnitude and severity of the problem in the EMR. Given the rising prevalence of PGDM and GDM in Middle Eastern countries, it is important to be aware of the severity and seriousness of the problem. Determining the magnitude of association between GDM/PGDM and adverse pregnancy outcomes is an important initial step for developing appropriate interventions.

This chapter will cover the literature search strategy, conceptual model of the study, description of diabetes mellitus and its complications, followed by description of pregnancy with diabetes (PGDM and GDM), risk factors and adverse maternal and fetal outcomes of GDM/PGDM. The chapter also includes an overview of screening, management, and prevention of GDM. The final section constitutes a review of the methodologies of research and a rationale for using meta-analysis for this study, followed by a summary of this chapter and transition to the next.

Literature Search Strategy

Information for the literature review was obtained by searching electronic databases, journals' websites, theses and dissertations available electronically, and reference lists of relevant articles and research documents. The electronic databases included ABI/INFORM, Academic Search Premier, CINAHL, Cochrane Database of Systematic Reviews (CDSR), Dissertations and Abstracts, Educational Resource Information Center (ERIC), Emrmedex, Journals at Ovid, Library Information Science

and Technology Abstract (LISTA), MEDLINE, Proquest, PsycINFO, and publishers' databases, such as Elsevier and Springer. Google Scholar was also used to supplement the research databases. The databases were searched from inception to January 2013 to identify relevant citations. The following keywords were used to search the databases: *diabetes mellitus*, *type I diabetes*, *type 2 diabetes mellitus*, *NIDDM*, *pregnancy, pregestational diabetes*, *gestational diabetes*, *diabetic pregnancy*, *diabetes in pregnancy*, *pregnancy complications*, *outcome*, *macrosomia*, *cesarean*, *cross-sectional*, *case control*, and *cohort studies*. These terms were also searched in combination and with the names of individual member countries of EMR. These countries included Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates, and Yemen.

I restricted my search to articles published in the English language. The search limit start-date was chosen as the earliest date the database had been available. These dates varied for various databases. For example, PubMed included articles published since 1961 while research databases such asAcademic Search Complete, CINAHL Plus with Full Text, Cochrane Database of Systematic Reviews, ERIC, Library, Information Science & Technology Abstracts, MEDLINE with Full Text, SocINDEX with Full Text, CINAHL Complete included articles published only since 1989. This list provided access to numerous bibliographic resources on the topic which were examined, reviewed, and included in this chapter. In addition to electronic database searches, articles cited in meta-analyses and systematic reviews on PGDM and GDM, were reviewed. The

reference lists of published literature on PGDM and GDM were also examined to identify studies eligible for inclusion in this literature review.

Various sources of literature specific for EMR were searched and reviewed. The medical journals of EMR such as *Eastern Mediterranean Health Journal* by World Health Organization, *Annals of Saudi Medicine*, *Saudi Medical Journal*, and *Saudi Journal of Family and Community Medicine* were hand-searched in the local libraries. Internet searches were conducted using the keywords mentioned above, through search engines such as Google Scholar. Websites such as World Health Organization Eastern Mediterranean Regional Office (WHO EMRO), and websites of Ministry of Health of member countries of EMRO were also searched for relevant researches. Individual websites of medical journals of the EMR were explored for relevant articles. A thorough literature review was conducted to determine the appropriate conceptual model for this study which is described in the next section.

Conceptual Model

The epidemiologic triangle is a traditional model examining the agent, the host, and the environmental factors to examine causation of infectious disease (CDC, 2009). The epidemiologic triangle explains disease causation by using a simple paradigm. It states that the disease is caused by an imbalance among the factors related to agent, host and environment. The epidemiologic triangle has also been applied to non-communicable diseases and health problems. Researchers have applied this model to earthquake-related traumatic injuries (Ramirez & Peek-Asa, 2005), bio-terrorism (Huerta & Leventhal, 2002), and gambling behavior (Peller et al., 2008). Merrill (2010) suggested an advanced

model of the epidemiologic triangle for chronic diseases. The advanced model includes the causes of chronic diseases in addition to the factors related to communicable diseases. The advanced model recognizes the complex etiology of chronic diseases. The components of the model include causative factors, the population group and their characteristics, the environment, behavior, culture, physiological factors, and ecological elements (Merrill, 2010). The components of epidemiologic triangle are explained as follows:

- Agent factors are those which are necessary for the causation of disease or health condition. These factors may include a living or non-living substance, or a force responsible for the event. The agent factors include biological agents such as bacteria, virus and parasites; chemical substances such as poisons, pesticides, medications; and physical factors including radiation, noise and heat (CDC, 2012; Ferng, n.d.).
- Host factors are related to humans making them susceptible to the agent or causative factors. These include factors such as age, socioeconomic status, physiologic factors, psychological factors, and behavioral factors (CDC, 2012).
- Environmental factors stand for all those factors which are external to the host and agent. Environmental factors are external factors which influence the agent and the chances for exposure. These include geologic factors, such as climate; biologic factors such as plants, animals, parasites,and viruses; and socioeconomic factors, such as population distribution, housing, and health services availability (CDC, 2012; Ferng, n.d.).

For GDM and its outcomes, the epidemiologic triangle can be applied as follows:

Agent. The agent is the cause of the condition. The agent for GDM is insulin. During pregnancy, some hormones (human placental lactogen, estrogen, and cortisol) produced by placenta can affect the functions of insulin, causing "insulin resistance." If the insulin production is not adequate to counter the effect of the placental hormones, GDM results (Ohio State University, n.d.). Adverse outcomes of GDM/PGDM such as macrosomia, delivery by caesarean section and perinatal mortality are associated with insulin resistance during pregnancy (Young & Ecker, 2013).

Host. The host factors comprise of non-modifiable and modifiable factors. Non-modifiable factors include age (women more than 25 years age are at a higher risk for developing GDM than younger women); race (Asian American, American Indian, African-American, or Pacific Islander have a greater risk); family history of diabetes; having given birth previously to macrosomic baby, a stillbirth, or a child with a birth defect. Modifiable factors include overweight/obesity; lifestyle factors including diet and physical activity. Regarding the association of adverse outcomes of PGDM/GDM with host factors, studies have demonstrated lower odds of caesarean delivery in Asian women (adjusted odds ratio (aOR) =0.86, 95% CI [0.77–0.96]) as compared to European American and African-Americans (Esakoff et al., 2011). Asians are also shown to have lower odds (aOR=0.58, [95% CI 0.48–0.70]) of macrosomia and perinatal mortality as compared to African-Americans (Esakoff et al., 2011). An association between increasing age and increased pre-pregnancy BMI with macrosomia as well as cesarean delivery is reported (Beucher et al., 2010; Gutaj et al., 2011).

Environment. Environmental factors that contribute to GDM may include physical, social and economic environment. Availability and affordability of healthy food; cultural values and accessibility to health care facilities are some of the environmental factors playing their role in the etiology of gestational diabetes. In turn, these environmental factors are also related to maternal and fetal outcomes of PGDM/GDM including macrosomia, caesarean delivery and perinatal mortality.

To sum up, the conceptual model for this study is epidemiologic triangle. Agent, host and environment play an important role in the causation of diabetes mellitus, PGDM/GDM, and their adverse maternal and fetal outcomes. The following section of the chapter discusses burden of diabetes mellitus and its complications.

Burden of Diabetes Mellitus

Diabetes mellitus is a chronic condition characterized by increased glucose levels in the body due to reduced production of insulin in the body or difficulty in utilizing insulin effectively (International Diabetes Federation [IDF], 2011d; Maraschin, Murussi, Witter, & Silveiro, 2010). There are three main types of diabetes mellitus; type 1 diabetes mellitus, type 2 diabetes mellitus and GDM (IDF, 2011d; Maraschin, 2012). Type 2 diabetes mellitus is considered a global epidemic (Tovar, Chasan-Taber, Eggleston, & Oken, 2011). Globally, 366 million people had diabetes in 2011. It is projected to rise to 552 million by 2030. Low- and middle-income countries bear the main brunt of the problem having 80% of people with diabetes. In 2011, a total of 4.6 million deaths occurred because of diabetes (IDF, 2011c). Rising incidence of diabetes mellitus has been reported from various parts of the world. In the United States, the prevalence of diabetes

mellitus is expected to rise from 16.2 million in 2005 to 48.3 million in 2050 (Feig, Zinman, Wang, & Hux, 2008). Other parts of the world are also reporting rising incidence of diabetes.

By 2020, an estimated 438 million people are predicted to have diabetes globally; half of these will be residents of Asia (Hirst, Tran, Do, Morris, & Jeffery, 2012). In South-East Asia, seven countries occupy almost one-fifth of people with diabetes, worldwide (IDF, 2011b). The EMR includes six out of the world's top 10 countries for highest prevalence of diabetes. These countries are Kuwait, Lebanon, Qatar, Saudi Arabia, Bahrain and the United Arab Emirates. A notable increase in the prevalence of diabetes in these countries is attributed to rapid economic development and increased life expectancy resulting in ageing populations. Moreover, rapid urbanization in wealthy oil-producing countries has caused lifestyle changes such as poor dietary habits and decreased physical activity leading to obesity which is an important risk factor for diabetes (IDF, 2011a). The countries with rapid socioeconomic changes have a greater increase in prevalence of diabetes (Hirst et al., 2012).

In 2011, the prevalence of diabetes in the Middle East and North Africa region was 9.1%, comprising of 32.8 million people with diabetes in this region (IDF, 2011a). It is estimated that, in less than 20 years, this number will double reaching approximately 60 million. Majority of these persons have type 2 diabetes. In this region, the prevalence of diabetes among younger persons is higher as compared to the prevalence recorded globally. Moreover, 6.7% (24 million people) of the population have impaired glucose tolerance (IGT) and are at high risk of having diabetes in the future. It is estimated that

the number will by doubled by 2030. A total of 65,200 children have type 1 diabetes in the region; Saudi Arabia has the highest number of children with type 1 diabetes (IDF, 2011a). During 2011, an estimated 280,000 deaths in the region, were attributed to diabetes, which is approximately 10% of all deaths in adults in the region. The number of deaths is almost similar in both genders; 141,000 in males while 138,000 in females (IDF, 2011a). In addition to higher mortality, diabetes is also associated with increased morbidity because of a host of diabetes complications.

Complications of Diabetes Mellitus

Diabetes mellitus results in a number of complications due to continuously increased blood glucose levels. The complications may affect the heart and blood vessels, nerves, kidneys or eyes. Heart disease, blindness, renal failure, and amputations may occur as a result of complications of diabetes. Cardiovascular complications include stroke, myocardial infarction, heart failure, and peripheral vascular disease (IDF, 2011d). Diabetes doubles the risk of suffering from heart attack or a stroke. The risk of dying due to coronary heart disease is 50% greater in women as compared to men (Anna, Ploeg, Cheung, Huxley, & Bauman, 2008). Chronic kidney disease leading to renal failure is another serious complication of diabetes mellitus. Diabetic retinopathy can damage vision and may lead to blindness (IDF, 2011d). Diabetic neuropathies may cause problems in gastrointestinal, genitourinary systems and the extremities. The extremities may have pain, tingling or loss of sensation due to nerve damage. Loss of sensation leads to unnoticed injuries which may result in gangrene leading to amputations. Persons with

diabetes have an increased risk of gingivitis and a possible enhanced risk of obstructive sleep apnea (IDF, 2011d). Women with diabetes face special risks during pregnancy.

Pregnancy with Diabetes Mellitus

Diabetes during pregnancy can be classified into two categories: PGDM and GDM (Lawrence et al., 2008). A brief description of PGDM and GDM is provided as follows:

Pregestational Diabetes Mellitus

Type 1 or type 2 diabetes diagnosed in pregnant women before pregnancy is called PGDM (Lawrence et al., 2008). An increasing trend in the prevalence of PGDM is reported by various studies. In a retrospective study of 175,249 pregnancies, the prevalence of PGDM increased from 0.81 percent in 1999 to 1.82% in 2005. The study included 209,287 deliveries with 20 or more weeks of gestation. These deliveries took place during 1999 to 2005 in Kaiser Permanente hospitals, in southern California. Rising prevalence was observed among all ages and all ethnic groups. Among all deliveries to women with diabetes, 10% were due to PGDM in 1999, increasing to 21% in 2005 (Lawrence et al., 2008). Similar trend of increasing prevalence is reported from the United Kingdom. A regional population-based survey in all maternity units in the North of England included 1,258 pregnancies in women with PGDM delivered between 1996 and 2004. The study revealed that the prevalence of PGDM increased from 3.1 per 1,000 births in 1996-98 to 4.7 per 1,000 in 2002-04 (test for linear trend, $p < 0.0001$) (Bell et al., 2008). Eastern Mediterranean Region is also reported having an increasing trend in the prevalence of PGDM (Wahabi, Alzeidan, Bawazeer, Alansari, & Esmaeil, 2010).

Pregestational diabetes has various adverse maternal and fetal outcomes. Poor glycemic control during early pregnancy results in an increased incidence of spontaneous abortions and congenital abnormalities (American Diabetes Association, 2004). It also results in increased risk of macrosomia if hyperglycemia persists later in pregnancy. The risk of preterm delivery and perinatal death is reported to be higher in women with type 1 diabetes (American Diabetes Association, 2004). PGDM is found to be associated with disturbances of intrauterine growth and post-natal neurobehavioral abnormalities in the offspring. In some studies, delayed brain maturity, inattention or hyperactivity is observed in newborns of women with diabetes (Ornoy, 2005). Thus, PGDM may result in substantial morbidity among women and their newborns.

Gestational Diabetes Mellitus

Glucose intolerance leading to hyperglycemia, diagnosed for the first time in pregnancy is labeled as gestational diabetes mellitus (Bentley-Lewis et al., 2008; Black et al., 2010; Kim et al., 2010; Luoto et al., 2011; Reece et al., 2009). Generally GDM resolves after pregnancy. It is the most commonly diagnosed medical condition during pregnancy (Moses & Cheung, 2009). Several risks are associated with GDM. Women diagnosed with GDM are at higher risk of developing diabetes later in life. It is associated with increased perinatal morbidity and mortality. Metabolic disorders may occur in the children of mothers with GDM (Moses & Cheung, 2009). It is the most common pregnancy complication leading to fetal mortality and perinatal morbidity (Kautzky-Willer et al., 2008).

An increasing prevalence of GDM is reported worldwide (Carolan et al., 2011). In a survey administered in 173 countries, GDM prevalence estimates ranged from <1% to 28% (Jiwani et al., 2012)**.** Middle Eastern countries are reported to have a high prevalence of GDM and PGDM ranging from 4.7% in Iran (Hossein-Nezhad et al., 2007) to 24.9% in the United Arab Emirates (Agarwal et al., 2010). In Yazd, Iran, the incidence of GDM was 10.2% among 1,071 pregnant women screened for GDM at 24-28 weeks of gestation (Soheilykhah et al., 2010). In Bahrain, an increase in the incidence of GDM from 7.2% in 2002 to 12.5% in 2010 ($p < 0.01$), was observed (Rajab et al., 2012). Because of higher birth rates in Middle Eastern countries, this increasing incidence of GDM has more implications on the burden of GDM and its complications. While comparing burden of GDM between various regions or various periods of time, it is important to take into account the diagnostic criteria used for GDM.

Diagnosis of GDM. The basis for diagnosis of GDM is to identify the women at risk of both adverse obstetrical outcomes, and the future development of type 2 diabetes mellitus. In 1964, O'Sullivan and Mahan suggested the initial glycemic thresholds for diagnosis of GDM on oral glucose tolerance test (OGTT) to identify women at risk of developing type 2 diabetes mellitus (O'Sullivan & Mahan, 1964). Since then, there has been a debate on the diagnostic criteria for GDM. The debate mainly focuses on the identification of fetal overgrowth and its associated obstetrical complications, resulting in different sets of diagnostic criteria proposed by various organizations such as the National Diabetes Data Group, the American Diabetes Association, and the WHO (Retnakaran et al., 2009).

Currently, international consensus is lacking about the diagnostic criteria for GDM. Although OGTT is commonly used, the dosages of glucose challenge vary, and there are different diagnostic thresholds. GDM is diagnosed either on the basis of 100 gram 3-hour test (used in the USA) or the 75 gram 2-hour WHO test (IDF, 2009). In some countries, a two-stage diagnostic procedure is conducted comprising of a non-fasting glucose challenge test (GCT) followed by OGTT for women who test positive for GCT (IDF, 2009). According to American Diabetes Association (ADA) guidelines, GDM is diagnosed if at least two 75-g or 100-g OGTT values meet the following thresholds: ≥95 mg/dl FPG, 1-h glucose ≥180 mg/dl, 2-h glucose ≥155 mg/dl, and 3-h glucose ≥140 mg/dl (Black et al., 2010). Various international organizations have tried to develop a consensus on GDM diagnostic criteria.

After discussions in 2008–2009, the International Association of Diabetes and Pregnancy Study Groups (IADPSG), an international professional group with representatives from several obstetrical and diabetes institutions produced revised recommendations for the diagnosis of GDM. The primary focus of IADPSG Consensus Panel was to recommend diagnostic threshold values that identified clinically significant risk for adverse pregnancy outcome (Metzger et al., 2010). The group recommended that all women not having a history of diabetes undergo a 75-g OGTT at 24–28 weeks of gestation ("Standards of Medical Care in Diabetes--2012," 2011). The diagnostic criteria proposed for the 75-g, 2-hour OGTT are that any of these following thresholds be met or exceeded: fasting plasma glucose 92 mg/dL (5.1 mmol/L); one-hour plasma glucose 180 mg/dL (10 mmol/L); or two-hour plasma glucose 153 mg/dL (8.5 mmol/L) (Coustan et

al., 2010; Royal College of Obstetricians and Gynaecologists, 2011; Mahdavian et al., 2010).

As various international organizations have recommended different criteria for diagnosis of GDM, epidemiologic studies have been conducted to compare and determine the appropriateness of these criteria. Agarwal et al. (2010) conducted a study to compare IADPSG criteria with the ADA criteria and the fasting plasma glucose (FPG) to predict GDM. A total of 10,283 pregnant women were studied including 80.1% Arab and 15.5% South Asian women. The researchers found that the IADPSG and ADA criteria identified GDM in 3,875 (37.7%) women and 1,328 (12.9%) women, respectively ($p < 0.0005$). FPG thresholds of ≥5.1 mmol/l diagnosed GDM in 2,975 (28.9%) women with a specificity of 100% while <4.4 mmol/l excluded GDM in 2,228 (21.7%) women with 95.4% sensitivity. The authors concluded that IADPSG criteria increased the prevalence of GDM almost threefold (Agarwal et al., 2010). In contrast, on investigating the impact of IADPSG guidelines in a cohort of pregnant women from the general population, Mahdavian and colleagues (2010) concluded that these guidelines offered a unique opportunity for a unified and global approach to GDM. Thus, an international consensus on diagnosis of GDM is still lacking. Risk factors for GDM play an important role in the diagnostic criteria. The following section elaborates the risk factors for GDM.

Risk Factors for GDM

Risk factors for GDM can be classified into modifiable and non-modifiable risk factors. The non-modifiable risk factors include age, ethnicity, family history of diabetes and past obstetric history (Ferrara, 2007). The modifiable risk factors include obesity,

weight gain during pregnancy, diet and physical activity (Iqbal, 2005). A description of modifiable and non-modifiable risk factors is provided in the following sections.

Non-Modifiable Risk Factors

The risk for GDM rises with age, and incidence rates differ by race/ethnicity (Anna et al., 2008; Ben-Haroush, Yogev, & Hod, 2004; Hunt & Schuller, 2007). In a prospective cohort study, The Nurses' Health Study II, 14,613 women without previous GDM or other known diabetes were included. The researchers found that the risk for GDM increased significantly with increasing maternal age (p for trend < 0.01) and family history of diabetes mellitus (Relative Risk [RR] = 1.68; 95% confidence interval [CI] [1.39-2.04]). African-American, Hispanic or Asian women had significantly increased age-adjusted relative risk for GDM in comparison to white women (Solomon et al., 1997). Similarly, in a study of 4,566 parous women participating in the National Health and Nutrition Examination Survey III, women with a maternal (Odds Ratio [OR] = 3.0; 95% confidence interval [CI] [1.2-7.3]), paternal (OR = 3.3; 95% CI [1.1-10.2]), or sibling (OR = 7.1; 95% CI [1.6-30.9]) history of diabetes had higher odds of having GDM in comparison to women without a family history of diabetes (Kim, Liu, Valdez, & Beckles, 2009). A hospital-based case-control study of 6,032 women in Australia, revealed statistically significant association of GDM with age ≥ 25 years (OR = 1.9; 95% CI [1.3-2.7]), family history of diabetes mellitus (OR = 7.1; 95% CI [5.6-8.9]) and ethnicity (high-risk racial heritage) (OR = 2.5; 95% CI [2.0-3.2]) (Davey & Hamblin, 2001). Thus, age, family history of diabetes, and ethnicity are found to be associated with GDM in various studies.

Studies have reported ethnic differences in the prevalence of GDM. In the U.S., Native Americans, Asians, Hispanics, and African-American women were found to be at higher risk for GDM than non-Hispanic white women. Similarly, in Europe, GDM was reported to be more prevalent among Asian women than among European women (Ferrara, 2007). In a systematic review of 13 studies, non-White race/ethnicity was the most important predictor for recurrence of GDM in future (Kim, Berger, & Chamany, 2007). Similar results were shown in a cohort study conducted among members of the Northern California Kaiser Permanente Medical Care Program, including 267,051 pregnancies screened for GDM. The women diagnosed with GDM were more likely to be from ethnic groups such as African American, Asian and Hispanic (Ferrara, Kahn, Quesenberry, Riley, & Hedderson, 2004). High prevalence of GDM is reported in South Asian, black Carribean and Middle Eastern including women from Saudi Arabia, Kuwait, United Arab Emirates, Qatar, Oman, Egypt, Jordan, Syria, Lebanon, or Iraq (National Collaborating Centre for Women's and Children's Health, 2008).

Previous history of GDM and family history of diabetes are important risk factors for GDM. The probability of recurrence of GDM is reported as 30–84% (National Collaborating Centre for Women's and Children's Health, 2008). A prospective population-based study conducted in Sweden included 3,616 women. Along with other risk factors, important risk factors were history of GDM (OR = 23.6; 95% CI [11.6 - 48.0]) and family history of diabetes (OR = 2.74; 95% CI [1.47 - 5.11]) (Ostlund & Hanson, 2003). Similarly, in a cohort of 3,950 Italian women, GDM diagnosis was significantly associated with age ($p < 0.0001$), and family history of diabetes ($p < 0.01$;

(Di Cianni et al., 2003). These findings were supported in a case- control study including 510 pregnant women with GDM (cases) and 1,160 pregnant women with normal glucose tolerance (controls), where age (30.1 vs. 27.2 years; $p < 0.0001$) and family history of diabetes (40.0 vs. 25.7%; $p < 0.01$) were significantly associated with GDM (Cypryk, Szymczak, Czupryniak, Sobczak, & Lewiński, 2008). Thus, age, family history of diabetes, and previous history of GDM are important non-modifiable risk factors identified in research studies conducted globally.

Various studies conducted in Middle Eastern countries have revealed similar risk factors. A prospective cohort study of 1,310 pregnant Iranian women revealed age more than 30 years, family history of diabetes, and previous macrosomia as statistically significant ($p < 0.001$) risk factors for GDM (Keshavarz et al., 2005). In a prospective study carried out among 2,000 Kashmiri women, the researchers found increasing rate of GDM with increasing age; from 1.7% in women below 25 years to 18% in women 35 years or older. In this study, GDM occurred more frequently in women who had GDM during previous pregnancies, had given birth to a macrosomic baby, or had a family history of diabetes mellitus (Zargar et al., 2004). In Bahrain, in a study of 4,982 women with GDM, maternal age was associated with GDM (OR = 1.094; 95% CI [1.081-1.107]) (Rajab et al., 2012). Similar risk factors were found in a cross-sectional study at primary health care centers in Qatar, including 4,295 pregnant women. Age 35 years or more (OR = 3.8; 95% CI [2.4-6.4]) and multigravida with 4 or more pregnancies (OR = 2.7; 95% CI [1.7-4.2]) were found to be significant predictors of GDM in this study (Al-Kuwari & Al-Kubaisi, 2011). Among Iranian women, a significant association between incidence of

GDM and age, family history of diabetes, history of GDM, parity, macrosomic baby and still birth during previous pregnancies was identified (Garshasbi, Faghihzadeh, Naghizadeh, & Ghavam, 2008; Rahimi, Dinari, & Najafi, 2010; Soheilykhah et al., 2010). Thus, studies in Middle Eastern countries have demonstrated maternal age, parity, family history of diabetes, and previous history of GDM as important risk factors of GDM. In addition to the non-modifiable factors, modifiable factors also play an important role in occurrence of GDM.

Modifiable Risk Factors

Overweight and obesity are recognized risk factors for diabetes (Lawrence et al., 2008; Kim et al., 2010; Narayan, Boyle, Thompson, Gregg, & Williamson, 2007), and are designated as the major modifiable risk factors of GDM (Bowers et al., 2011). A systematic review conducted to assess and quantify the risk for GDM according to pre-pregnancy maternal body mass index (BMI) included observational studies published in the last 30 years. Compared with women with a normal BMI, the unadjusted pooled OR of an underweight woman developing GDM was 0.75 (95% CI [0.69 - 0.82]). The OR for overweight, moderately obese and morbidly obese women were 1.97 (95% CI [1.77 - 2.19]), 3.01 (95% CI [2.34 - 3.87]) and 5.55 (95% CI [4.27 - 7.21]) respectively (Torloni et al., 2009).

Various studies conducted in developed countries have demonstrated an association between overweight/obesity and GDM. In a hospital-based case-control study of 6,032 women in Australia; the researchers found statistically significant association between GDM and body mass index (BMI) $\geq 27 kg/m^2$ (OR = 2.3; 95% CI [1.6-3.3];

Davey & Hamblin, 2001). In Sweden, a prospective population-based study including 3,616 women found that weight ≥ 90 kg or more (OR = 3.33; 95% CI [1.56 - 7.13]) and BMI ≥ 30 kg/m^2 (OR = 2.65; 95% CI [1.36 - 5.14]) had statistically significant association with GDM (Ostlund & Hanson, 2003). Similarly, a cohort study including women with pregnancies between 16 and 18 weeks, classified women as underweight (BMI<18.5), normal (BMI 18.5–25), overweight (BMI 25–30), and obese (BMI>30) women. Compared to other groups, obese women were more likely to develop GDM (p<0.001; Doherty, Magann, Francis, Morrison, & Newnham, 2006). A case- control study comprising of 510 pregnant women with GDM and 1,160 pregnant women as controls also showed an association between BMI and GDM. The study found BMI > 25 kg/m^2 (OR = 4.14) a risk factor for GDM (Cypryk et al., 2008). In The Nurses' Health Study II, relative risks for GDM were 2.13 (95% CI [1.65-2.74]) for pregravid BMI of 25 to 29.9 kg/m^2 and 2.90 (95% CI [2.15-3.91]) for BMI of 30 kg/m^2 when compared to BMI of <20 kg/m^2. Risk for GDM rose with greater weight gain (RR = 3.56; 95% CI [2.70 - 4.69]) for weight gain of 20 kg or more] (Solomon et al., 1997). Thus, increased BMI, overweight, obesity and extent of weight gain during pregnancy are found to be important modifiable risk factors of GDM in studies conducted in the developed world.

Association of overweight and obesity with GDM is also found in research studies from other regions of the world. Out of a total of 9,471 pregnant Chinese women screened for GDM, 174 women were confirmed to have GDM. Pre-pregnancy BMI and weight gain in pregnancy before screening were found as risk factors for GDM in this population (Yang et al., 2002). In a prospective study carried out in 2,000 Kashmiri

women, the researchers found that women with obesity and hypertension had a higher prevalence of GDM (Zargar et al., 2004). In a study of 1,720 Iranian pregnant women, obesity was one of the risk factors for GDM (Rahimi et al., 2010)**.** In another study from Iran, screening for GDM was performed on 1,804 women. GDM diagnosis was significantly associated with pre-pregnancy BMI ($p = 0.005$) (Garshasbi et al., 2008). Overweight and obesity are closely related to the dietary habits and physical activity of an individual. Increased physical activity may also play a role in prevention of GDM.

The role of physical activity during pregnancy in reduction of risk of GDM has been explored in various studies. Data from the 1988 National Maternal and Infant Health Survey was analyzed for 4,813 women, reporting physical inactivity before pregnancy. GDM was diagnosed in 3.5 percent of this group. Among previously inactive women, 11.8 percent became physically active during pregnancy. These women had 57 percent lower adjusted odds of developing GDM than those who continued to be physically inactive (OR = 0.43; 95% CI [0.20–0.93]). Brisk walking during pregnancy resulted in a reduced risk of GDM (OR = 0.44; 95% CI [0.19–1.02]) (Liu, Laditka, Mayer-Davis, & Pate, 2008)**.** Therefore, physical activity is found to be an important factor in the occurrence as well as prevention of GDM.

In addition to obesity and lack of physical activities, various studies have demonstrated other risk factors. Twin pregnancies are found to be a risk factor for GDM. In a cohort of 23,056 pregnant women who gave birth to a live infant; 553 women had twin pregnancy. Patients with twin pregnancies had a higher rate of GDM when compared with singleton pregnancies (3.98% vs. 2.32%; $p = 0.01$) (Rauh-Hain et al.,

2009). Another risk factor for GDM is periodontal disease. An association of periodontal diseases with GDM is demonstrated in some studies. A total of 53 pregnant women with GDM and 106 pregnant women without GDM were studied at Woman's Hospital, Baton Rouge, Louisiana. The adjusted OR for association of periodontal diseases and GDM was 2.6 (95% CI [1.1 - 6.1]; Xiong et al., 2009). On literature search, researches exploring association of periodontal disease and GDM in Eastern Mediterranean countries could not be found. However, certain other risk factors such as polycystic ovarian syndrome are explored by researchers in Eastern Mediterranean countries.

Polycystic ovarian syndrome (PCOS) is a pathological condition signified by anovulation, resistance to insulin, and excess of androgen. The women with PCOS have a higher risk of glucose intolerance and type 2 diabetes (Lo et al., 2006). Commonly the affected women have insulin resistance and hyperinsulinaemia and consequently, may, have a higher risk of GDM (Mikola, Hiilesmaa, Halttunen, Suhonen, & Tiitinen, 2001). Some studies suggest the risk of GDM is higher among PCOS versus non-PCOS women (Lo et al., 2006). However, in a retrospective case-control study, the researchers found no statistically significant difference in the prevalence of GDM between the PCOS (22%) and the controls (17%; Vollenhoven, Clark, Kovacs, Burger, & Healy, 2000). In a study conducted to determine the impact of PCOS on glucose tolerance during pregnancy, the researchers compared the pregnancy records of 38 PCOS patients retrospectively with 136 non-PCOS patients. The prevalence of GDM was similar in both groups (Turhan, Seçkin, Aybar, & Inegöl, 2003). Similarly, a case-control study included 188 pregnant women; 94 women had GDM (cases) while the other 94 were women without GDM

(controls). The results of the study showed that the women with GDM had a history of PCOS more often than the control group of women (15 cases of PCOS in GDM group vs. 6 cases of PCOS in the control group, $p = 0.03$) (Kashanian, Fazy, & Pirak, 2008). In another study of the pregnancies of 66 women with PCOS and 66 age- and weight-matched controls, no statistically significant difference was found in the prevalence of GDM between the group of PCOS patients and the controls (Haakova et al., 2003). In contrast, in a total of 99 pregnancies retrospectively evaluated in women with PCOS and compared with the control population, GDM developed in 20% of the PCOS patients and in 8.9% of the controls ($p < 0.001$) (Mikola et al., 2001). Although some studies have shown an association between GDM and PCOS, the results are inconclusive. Some other risk factors of GDM such as levels of ferritin are explored by few studies.

Some epidemiological studies have documented a positive association of circulating levels of ferritin (a marker of body iron stores) with circulating levels of glucose and insulin, and risk of type 2 diabetes mellitus and GDM (Bowers et al., 2011). In a case-control study, 34 women with diagnosed GDM were compared with 34 non-GDM women in the control group at 24-28 weeks of pregnancy. The results of the study showed that concentration of serum ferritin, iron and transferrin saturation was significantly higher in the GDM group ($p < .05$; Afkhami-Ardekani & Rashidi, 2009). Similarly, a prospective study suggested an association between increased iron stores and glucose intolerance in non-anemic women at the third trimester (Lao, Chan, & Tam, 2001).

To sum up, many modifiable and non-modifiable risk factors are related to GDM. Some of these factors such as age, family history of diabetes are well-researched while other factors such as ferritin levels need to be further researched to reach a definitive conclusion. Information about risk factors of GDM is important not only for the prevention of GDM but also for reduction in adverse outcomes of GDM/PGDM.

Outcomes of Pregnancy with Diabetes

Pregnancy with diabetes is associated with increased perinatal morbidity (Reece et al., 2009). It has been associated with maternal, fetal, and infant complications, including cesarean section, infant macrosomia and birth trauma (Kim et al., 2010). GDM has many effects on fetal outcomes, maternal outcomes and also there are long-term health effects on women with a history of GDM (Hedderson, Gunderson, & Ferrara, 2010; Hsu-Hage & Yang, 1999). Epidemiological research suggests that women who have GDM have an increased risk of type 2 diabetes later in life (Bellamy et al., 2009; Buchanan & Xiang, 2005; Horvath et al., 2010). To determine the effects of GDM/PGDM on maternal and fetal outcomes, population databases of all women and their infants, discharged from hospital following birth in New South Wales (NSW) between July 01, 1998 and December 31, 2002, were studied. A total of 370,703 women and their newborns were included. Out of these 1,248 women (0.3%) had PGDM and 17,128 (4.5%) had GDM. The researchers found that, in comparison with women without diabetes, maternal morbidity or mortality was more frequent in women with PGDM (7.9%; OR = 3.2; 95% CI [2.6 - 3.9]) and in women with GDM (3.1%) (OR = 1.2; 95% CI [1.1 - 1.4]). Infant morbidity or mortality was more common in newborns of women

with PGDM compared with those without diabetes (13.6% vs. 3.1%; OR = 5.0; 95% CI [4.2 - 5.8]) and in newborns of women with GDM compared with women without diabetes (3.2% vs. 2.3%; OR = 1.4; 95% CI [1.3 - 1.5]; Shand, Bell, McElduff, Morris, & Roberts, 2008). Although in general maternal and fetal morbidity are increased, certain specific adverse fetal and maternal outcomes are associated with PGDM/GDM.

Adverse fetal outcomes include complications such as macrosomia, shoulder dystocia, birth injuries, neonatal hyperbilirubinemia, while adverse maternal outcomes include caesarean section, and pre-eclampsia (Metzger et al., 2008). There are certain factors associated with the adverse maternal and fetal outcomes including racial/ethnic differences and type of maternal diabetes.

Racial/ ethnic differences have been found in perinatal outcomes, in women with GDM. Esakoff and colleagues (2011) in a retrospective cohort study included singleton pregnancies with GDM receiving health care from California Diabetes and Pregnancy Program (CDAPP) between 2001 and 2004. A total of 26,411 women with gestational diabetes sub-grouped by four races/ethnicities (Caucasian, African-American, Latina, and Asian) were included in the study. The results of the study showed that Asians had lower odds (aOR = 0.58; 95% CI [0.48 - 0.70]) of birthweight > 4000 g. African-Americans had highest odds of intrauterine fetal death (aOR = 5.93; 95% CI [1.73- 20.29]) as compared to other races/ethnicities (Esakoff et al., 2011). Other adverse pregnancy outcomes are also shown to vary in different races or ethnicities and according to the type of maternal diabetes.

Type of diabetes during pregnancy influences adverse maternal and fetal outcomes. In a population-based study conducted in Sweden between 1991 and 2003, data were obtained from the Medical Birth Registry, including more than 98% of all pregnancies in Sweden. A total of 5,089 pregnancies with type 1 diabetes and 1,260,207 pregnancies without diabetes were included. The results of the study showed that, in type 1 diabetes, preeclampsia was significantly more frequent (OR = 4.47; 95% CI [3.77-5.31]) as was delivery by cesarean section (OR = 5.31; 95% CI [4.97-5.69]) compared with results for the general population. Stillbirth (OR = 3.34; 95% CI [2.46-4.55]), perinatal mortality (OR = 3.29; 95% CI [2.50-4.33]), and major malformations (OR = 2.50; 95% CI [2.13-2.94]) were more common in women with type 1 diabetes than in women without diabetes. The incidence of fetal macrosomia was increased in the group with diabetes (OR = 11.45; 95% CI [10.61-12.36]; Persson, Norman, & Hanson, 2009). Individual adverse maternal and fetal outcomes are discussed in the following sections.

Adverse Maternal Outcomes

Cesarean Section

Studies from various parts of the world have reported a higher rate of cesarean section in women having pregnancy with diabetes as compared to those without diabetes. A study was conducted among women with pregestational type 2 diabetes during the period between 1992 and 2006 from one center in the Netherlands. Sixty-six singleton pregnancies were analyzed. Delivery occurred by cesarean section in 42.9% cases (de Valk, van Nieuwaal, & Visser, 2006). Similarly, in a 12 years' (1990 -2002) outcome analysis of pregnancies in 182 women with type 2 diabetes, 161 (88%) resulted in a live

outcome. Fifty-three percent were delivered by caesarean section in this study population (Dunne, Brydon, Smith, & Gee, 2003).

Higher rate of caesarean section in women having pregnancy with diabetes is reported by various studies from Eastern Mediterranean countries. Various studies conducted in this region has demonstrated the rate of cesarean section ranging from 22% to 84%. In an observational cross-sectional study conducted among infants of women with diabetes in Pakistan, 40 infants were included. Twenty-two (55%) newborns were delivered by cesarean section (Alam, Raza, Sherali, Akhtar, & Akhtar, 2006). Another hospital-based study in Pakistan included 42 pregnant women with diabetes; 45% of these women were delivered by cesarean section (Hussain, Irshad, Khattak, & Khan, 2011). In a study of 8,000 pregnant women, in Saudi Arabia, 685 women were diagnosed with GDM, between January 2000 - December 2001. A total of 148 (21.6%) were delivered by cesarean section (Al-Hakeem, 2006). High rate of cesarean section was reported in a prospective observational study in Sudan which included 50 infants of women with diabetes; 42 (84%) infants were delivered by caesarean section (Kheir, Berair, Gulfan, Karrar, & Mohammed, 2012). In addition to determining the proportion of deliveries by caesarean section in women with GDM/PGDM, researchers have also compared these proportions between women with GDM/PGDM and those without GDM/PGDM.

Epidemiological studies have shown a statistically significant association between delivery by cesarean section in women with diabetes when compared to women without diabetes. In a prospective cohort study conducted in Iran, 1,310 pregnant women were

included in the study. The researchers found that women with GDM had a higher rate of caesarean section ($p < 0.001$) as compared to those without GDM (Keshavarz et al., 2005). Similarly, Hossein-Nezhad et al. (2007) studied 2,416 Iranian pregnant women and identified 114 women (4.7%; 95% CI [3.9-5.6%]) with GDM in this cohort. The odds ratio for cesarean section (OR = 2.28, $p = 0.0002$) was significantly higher in women with GDM as compared to those without GDM. In another study including 420 Iranian women referred to Shiraz hospitals in 2006, seventy were pregnant women with diabetes and 350 were those without diabetes. There was a significant difference between the two groups in delivery by cesarean section (RR = 1.96, $p < 0.05$; Abolfazl et al., 2008). In Qatar, a prospective cohort study included a representative sample of 2,056 pregnant women attending the antenatal clinics of the Women's Hospital. From this sample, 1,608 women (78.2%) expressed their consent to participate in the study. Cesarean section rate (27.9% vs 12.4%; $p < 0.001$) was significantly higher in women with GDM as compared to those without GDM (Bener et al., 2011)**.** In a study of 228 pregnant women, higher rate of cesarean section (68%) was noted among women with GDM as compared to 46.8% ($p = 0.009$) in those without diabetes (Tahir, Zafar, & Thontia, 2011).

Women with PGDM are reported to have higher rates of caesarean section as compared to those with GDM. In a one year retrospective review of registry records, of the 5,394 women registered, 225 had GDM and 56 had PGDM. A statistically significant greater rate of cesarean delivery was found among women with GDM (OR = 2.70; 95% CI [1.17-4.03]) and PGDM (OR = 4.39; 95% CI [1.68-11.49]) as compared to those without diabetes (Barakat et al., 2010)**.** A prospective hospital-based study conducted

among 100 women with diabetes (27 women with GDM and 73 women with PGDM) compared fetal/neonatal complications of GDM and PGDM. Women with PGDM had a higher rate of cesarean section as compared to those with GDM (Akhlaghi & Hamedi**,** 2005). In another hospital-based study conducted in Abu Dhabi, 129 records of women with diabetes delivered over a two year period were reviewed. Of these, 82 had GDM, and 47 had PGDM. Patients with PGDM had a significantly higher rate of caesarean sections ($p = 0.0147$) as compared to those with GDM (Misra et al., 2001). Thus, higher rates of caesarean section is an important adverse outcome in women having pregnancy with diabetes. Among women having pregnancy with diabetes, women with PGDM are more at risk of having the delivery by caesarean section than women with GDM. In addition to higher rates of caesarean section, other adverse maternal outcomes also occur in pregnancy with diabetes and may also differ in frequency among women with PGDM and those with GDM.

Other Adverse Maternal Outcomes

Other adverse maternal outcomes of pregnancy with diabetes include pregnancy induced hypertension, development of type 2 diabetes mellitus and hypertension in the long term. Hypertension occurring because of pregnancy is called pregnancy-induced hypertension (PIH), which has two groups: gestational hypertension and pre-eclampsia (Hossein-nezhad, Mirzaei, Ahmadi, Maghbooli, & Karimi, 2011). In a retrospective analysis of the record of 1,813 women with GDM, preeclampsia was diagnosed in 9.6% (174/1,813) women with diabetes (Yogev, Xenakis, & Langer, 2004). In a prospective observation of pregnancy outcomes among 462 women with PGDM, 92 (20%) had

preeclampsia. The frequency of preeclampsia increased significantly with increasing severity of diabetes (Sibai et al., 2000). In another study including women having singleton births in Victoria during 1996, women with GDM had increased rates of hypertension and pre-eclampsia [adjusted OR = 1.6, 95% CI, 1.4-1.9; Stone, McLachlan, Halliday, Wein, & Tippett, 2002). Similarly, in a study of 749 women from the randomized controlled Diabetes and Pre-eclampsia Intervention Trial (DAPIT), pre-eclampsia and gestational hypertension occured in 17% and 11% of pregnancies, respectively. Women with pre-eclampsia had statistically significant higher levels of HbA1C before and during pregnancy in comparison to the women who did not have pre-eclampsia (Holmes et al., 2011).

An association between pregnancy induced hypertension and GDM/PGDM is demonstrated in various studies of the Eastern Mediterranean Region. A prospective cohort study in Iranian population among 1,310 pregnant women, demonstrated a higher rate of gestational hypertension (OR = 6; 95% CI [2.3-15.3]) in women having pregnancy with diabetes (Keshavarz et al., 2005). In another cohort study of 615 Iranian pregnant women including 293 GDM patients and 322 women without GDM, a significant higher prevalence of pregnancy induced hypertension (RR = 1.03; 95% CI [1.004-1.06]) was demonstrated (Hossein-nezhad et al., 2011). Similarly, a significantly higher incidence of pre-eclampsia ($p < 0.0001$) is demonstrated in Saudi women with GDM when compared with those without GDM (Gasim, 2012). In most cases, pregnancy induced hypertension is a short-term effect and resolves after pregnancy; however, there are also certain long-term effects of GDM such as the occurrence of type 2 diabetes.

Women with GDM are at increased risk of developing type 2 diabetes later in life. GDM is found to be a strong predictor of type 2 diabetes. Women with GDM are approximately six times more prone to develop type 2 diabetes in comparison to women with normal glucose tolerance in pregnancy (Anna et al., 2008; Cheung & Byth, 2003). In a systematic review of 675,455 women with 10,859 having type 2 diabetes, women with GDM had an increased risk of developing type 2 diabetes compared with those who had a normoglycaemic pregnancy (RR = 7.43; 95% CI [4.79 -11.51]) (Bellamy et al., 2009). To conclude, adverse maternal outcomes of GDM/PGDM include higher rate of delivery by caesarean section, pregnancy induced hypertension, and occurrence of type 2 diabetes later in life. Next section will discuss various adverse fetal outcomes associated with GDM/PGDM.

Adverse Fetal Outcomes

Macrosomia

Macrosomia signifies a newborn with an excessive birth weight. There are different ways of defining fetal macrosomia. Birth weight of 4,000-4,500 g (8 lb 13 oz to 9 lb 15 oz) or more than 90% for gestational age is labeled as macrosomia (Medscape, 2013). The most frequent and significant morbidity in pregnancy with diabetes is fetal macrosomia, which in turn is associated with increased risk of birth injuries and asphyxia (Persson & Hanson, 1998). A retrospective cohort study was performed on 111,563 pregnancies delivered in 39 hospitals in northern and central Alberta, Canada. Infants born to mothers with GDM were at higher risk of being macrosomic or large-for-gestational-age (Xiong, Saunders, Wang, & Demianczuk, 2001). Svare, Hansen, &

Mølsted-Pedersen (2001) examined the outcome of pregnancy in 327 women with GDM and 295 women without GDM. Although not statistically significant, the incidence of macrosomia was higher, (8% *vs.* 2%, $p = 0.07$), in the group with GDM. Incidence of macrosomia varies according to the type of diabetes in pregnancy. A prospective cohort study comprising of 682 consecutive pregnancies with diabetes in East Anglia included 408 (59.8%) pregnancies with type 1 and 274 (40.2%) with type 2 diabetes. Women with type 2 diabetes had fewer large-for-gestational-age infants (37.6 vs. 52.9%, $p < 0.0008$) as compared to those with type 1 diabetes (Murphy et al., 2011). Variations in incidence of macrosomia are also reported in studies conducted in different parts of the world.

Research studies from EMR have shown high proportion of infants with macrosomia in women with GDM/PGDM. In Pakistan, a hospital-based study of 42 infants of women with diabetes found macrosomia (40.4%) the most common complication in this study population (Hussain et al., 2011). Haider, Zehra, Anjum, and Munir (2009) studied 110 pregnant women with diabetes in Pakistan and found macrosomia in 41.8% newborns. In another study in Pakistan, 50 pregnant women with GDM were identified among 1,429 delivered women. Most frequent fetal complication was macrosomia identified in 18 (36%) newborns (Farooq, Ayaz, Ali, & Ahmed, 2007). Similarly, among 50 infants of Sudanese women with diabetes, 14 (28%) newborns were macrosomic (Kheir et al., 2012). In Bahrain, in a cohort of 3,443 pregnant women with GDM, 6.5% newborns had a birth weight of more than 4000 g (Al Mahroos, Nagalla, Yousif, & Sanad, 2005).

Researchers from Middle Eastern countries have studied the association between pregnancy with diabetes and macrosomia. In Iran, a cohort of 1,801 pregnant women, was classified into four groups according to the results of GCT and OGTT. The groups included: normal GCT (<130 mg/dl); GCT ≥ 130 mg/dl but normal OGTT; impaired glucose test (IGT); and GDM. The results of the study showed that the prevalence of macrosomia in patients with GDM, IGT, only abnormal GCT and normal GCT was 15.8% , 6%, 3.6% and 1.1%, respectively (Khoshniat nikoo et al., 2010). Similarly, in Iran a prospective cohort of 1,310 Iranian pregnant women demonstrated that women with GDM had a higher rate of macrosomia (OR = 3.2; 95% CI [1.2-8.6]) as compared to those without GDM (Keshavarz et al., 2005). In another study in Iran, Hossein-Nezhad et al. (2007) studied 2,416 Iranian pregnant women including 114 women with GDM in this group. The odds ratio for macrosomia (OR = 1.93, $p = 0.0374$) was significantly higher in women with GDM as compared to those without GDM. Bener et al. (2011) studied a cohort of 1,608 pregnant women in Qatar. Newborns of women with GDM were at increased risk of macrosomia (10.3% vs 5.9%; $p = 0.01$) than those of women without GDM**.** In a historical cohort study including 420 Iranian women (70 women with diabetes and 350 without diabetes), the newborns of women with GDM were seven times more at risk of being macrosomic [RR = 7.38, $p < 0.05$] as compared to those born to women without GDM (Abolfazl et al., 2008). On comparing the strength of association of macrosomia in women having pregnancy with diabetes, women with PGDM were found to be more prone to have a macrosomic baby. In a 1-year retrospective review of records of 5,394 pregnant women registered, 225 had GDM and 56 had PGDM. The risk of

macrosomia was three-fold among women with GDM (OR =3.03; 95% CI [1.36-6.75]) and approximately seven-fold among those with PGDM (OR =7.20; 95% CI [2.30-22.61]) (Barakat et al., 2010). In contrast, some studies have shown statistically non-significant association between macrosomia and pregnancy with diabetes. In Saudi Arabia, 424 pregnant women were studied. Infants of women with diabetes were found to be heavier than those without diabetes, however, the proportion of babies with birth weight ≥ 2 standard deviations above the mean, were equal in both groups (Nasrat et al., 1994). In another study of 185 pregnant women with diabetes in Saudi Arabia, there were 27(14.6%) with type 1 diabetes forming group 1; 19 (10.2%) with type 2 diabetes constituting group 2 and 139 (75.2%) with GDM making up group 3. The results of the study showed no statistically significant differences in the three groups regarding the mean birth weight ($p > 0.05$) of newborns (Sobande, Eskander, & Archibong, 2005). Another retrospective cohort study among pregnant women with GDM in Saudi Arabia including 766 women (419 women with GDM and 347 without GDM), was also not able to demonstrate statistically significant association between macrosomia and GDM (Al-Khalifah et al., 2012). To sum up, macrosomia is one of the most common adverse outcomes of pregnancy with diabetes. High incidence of macrosomia is reported in infants of women with GDM/PGDM globally as well as in the EMR. Macrosomia results in perinatal morbidity and some of its complications may lead to perinatal mortality.

Perinatal Mortality

Perinatal mortality refers to fetal (20 or more weeks of gestation) deaths as well as neonatal deaths (MacDorman et al., 2012). The Confidential Enquiry into Maternal

and Child Health in UK reported that perinatal mortality was approximately four-fold in women with diabetes as compared to the general population (Confidential Enquiry into Maternal and Child Health [CEMACH], 2005). On a review of pregnancy outcome in 116,303 pregnancies, at the Mercy Hospital for Women, GDM was found to be associated with an increased risk of perinatal mortality (OR = 1.53; 95% CI [1.13-2.06]; Beischer, Wein, Sheedy, & Steffen, 1996). An analysis of outcomes of pregnancies among women with type 2 diabetes mellitus, was performed. From a regional computerized database, data were obtained about 182 women delivered between 1990 and 2002. Infants of women with type 2 diabetes had a twice higher risk of stillbirth, a 2.5 times higher risk of perinatal death, a 3.5 times higher risk of neonatal death and a 6-times higher risk of infant death when compared with regional/national statistics (Dunne et al., 2003). The researchers compared outcomes of pregnancy in women with type 1 diabetes with those in the general population in a prospective multicenter study conducted in eight Danish centers. The study included 990 women with 1,218 pregnancies. The results of the study showed that the perinatal mortality rate was 3.1% in pregnancies with type 1 diabetes compared with 0.75% in the general population (RR = 4.1; 95% CI [2.9-5.6]), and the stillbirth rate was 2.1% compared with 0.45% (RR = 4.7; 95% CI [3.2-7.0]) in the general population (Jensen et al., 2004).

The incidence of perinatal mortality is shown to vary according to the type of diabetes. Data for a duration of 12 years (1985–1997), from a population in Auckland, revealed 434 pregnancies in women with type 2 diabetes, 160 pregnancies in women with type 1 diabetes and 932 in women with GDM. The results of the study showed that the

perinatal mortality in type 2 diabetes was 46.1/1000, significantly ($p < 0.0001$) higher than the rates for type 1 diabetes (12.5/1000) and GDM (8.9/1000). A seven-fold greater rate of late fetal death and 2.5-fold greater rate of neonatal death was also shown in this study (Cundy et al., 2000). Some studies have reported a worse perinatal outcome in women with type 2 DM as compared to type 1 diabetes. In a study conducted to compare the maternal and fetal outcomes in pregnant women with type 2 and type 1 DM, the researchers found that women with type 2 DM had a higher risk of perinatal mortality (OR = 1.50; 95% CI [1.15-1.96]; Balsells, García-Patterson, Gich, & Corcoy, 2009). In a population- based cohort study in 231 maternity units in England, Wales, and Northern Ireland, 2,359 pregnancies to women with type 1 or type 2 diabetes were studied. Of 2,359 women with diabetes, 652 had type 2 diabetes and 1,707 had type 1 diabetes. Perinatal mortality in infants of women with diabetes was 31.8/1000 births. Perinatal mortality was almost similar among women with type 1 (31.7/1000 births) and type 2 diabetes (32.3/1000) and was approximately four times greater than that in the general population (Macintosh, 2006).

An increased perinatal mortality rate is especially important in settings where appropriate obstetric care is not accessible to the whole population (IDF, 2009; Schmidt et al., 2001). Because of poor socioeconomic conditions, some countries of EMR such as Afghanistan and Pakistan, are not able to provide access to obstetric care to a substantial proportion of their population. Thus, it is important to determine the perinatal mortality attributed to pregnancy with GDM/PGDM.

Studies from Middle Eastern region have shown an increased perinatal mortality rate in women with GDM/PGDM. A study conducted in Benghazi Diabetic Clinic during the period from 1984 to 1991 included 988 pregnant women with diabetes. Twelve women had type 1 diabetes mellitus while 976 women had type 2 diabetes mellitus. Rates of intra-uterine death and still birth were 3.28% and 2.6%, respectively. Perinatal mortality was 11.44% (Kadiki, Reddy, Sahli, Shawar, & Rao, 1993)**.** Approximately similar perinatal mortality rate of 7.5% was found in a cross-sectional study of 40 infants born to women with diabetes in Pakistan (Alam et al., 2006). In another hospital-based study, in Pakistan, the mortality rate was 4.7% among 42 infants born to women with diabetes (Hussain et al., 2011)**.** In Iran, in a prospective cohort study of 1,310 Iranian pregnant women, babies born to women with GDM had a higher rate of stillbirth (OR = 17.1; 95% CI [4.5-65.5]; Keshavarz et al., 2005). In another cohort study including 420 Iranian pregnant women (70 women with diabetes and 350 without diabetes), statistically significant difference in still births [RR= 8.87, $p < 0.05$] between the two groups was observed (Abolfazl et al., 2008). Misra et al., (2001) reviewed records of 129 women with diabetes in a hospital-based study in Abu Dhabi. Perinatal mortality rate was 2.5 times higher in the pregnancies with diabetes than in the general population. In a case-control study conducted in Sudan, the perinatal mortality rate was significantly higher among women with diabetes (80.2%) than the total hospital population (23.7%) ($p < 0.01$). The overall perinatal mortality rate in women with diabetes was 3.5 times more than that for women without diabetes. Unexplained intrauterine deaths were more common in PGDM (RR = 18.4; 95% CI [3.9 - 85.7]) than in GDM (RR = 13.4; 95% CI

[29- 61.6]; Dafallah & Yousif, 2004)**.** Thus, many studies have shown an association between increased perinatal mortality rate and GDM/PGDM, however, considering the improvement in health care generally and improved management of GDM/PGDM in many countries of the world, it is important to look at the trends of perinatal mortality in women with GDM/PGDM.

Some studies have shown a decreasing trend in perinatal mortality rate among women having pregnancy with diabetes. A review of 1,528 pregnancies in women with diabetes mellitus between 1968 and 1987 at National Women's Hospital showed that 571 had PGDM and 957 had GDM. During this period, the perinatal mortality rate for women with PGDM fell from 15.2% to 2% and for those with GDM from 6.7% to 0.5% (Roberts & Pattison, 1990). Similar trend was shown in a retrospective survey conducted to examine changes in perinatal mortality in babies born to mothers with pregestational type 1 diabetes over 40 years in Edinburgh, Scotland. Perinatal mortality were ascertained from 643 babies born after 28 gestational weeks to mothers with pregestational type 1 diabetes between 1960 and 1999. The results of the study showed that there was a remarkable improvement in perinatal mortality rate, decreasing from 225 per 1,000 total births in the 1960s to 102 in the 1970s. It further decreased to 21 in the 1980s, and then 10 per 1,000 total births in the 1990s ($p < .001$; Johnstone, Lindsay, & Steel, 2006). Studies showing the trend of perinatal mortality in Eastern Mediterranean countries could not be found on literature search, however, this meta-analysis will be able to demonstrate changes in perinatal mortality rates in various countries in different periods of time. In addition to perinatal mortality, certain other adverse fetal outcomes may occur in

pregnancy with GDM/PGDM. These adverse fetal outcomes are discussed in the next section.

Other Adverse Fetal Outcomes

Other adverse fetal outcomes in pregnancy with diabetes include congenital malformations and long term effects such as increased BMI in adulthood. The excess risk for birth defects among babies of women with diabetes mellitus is well documented. In the Atlanta Birth Defects Case-Control Study, 4,929 live and stillborn babies with major malformations, were included. The study also included 3,029 non-malformed live babies. The relative risk for major malformations among infants of mothers with type 1 diabetes mellitus (n = 28) was 7.9 (95% CI [1.9- 33.5]) compared with infants of women without diabetes. Infants of mothers with GDM who required insulin during the third trimester of pregnancy were 20.6 (95% CI [2.5-168.5]) times more likely to have major cardiovascular system defects than infants of women without diabetes (Becerra, Khoury, Cordero, & Erickson, 1990). The percentage of pregnancies with congenital abnormalities (12.3% in type 2 vs. 4.4% in type 1; $p = 0.002$) was found higher in women with type 2 diabetes as compared to type 1 diabetes in a study of pregnancies with PGDM (389 type 1 diabetes and 146 type 2 diabetes) from 10 UK hospitals (Roland, Murphy, Ball, Northcote-Wright, & Temple, 2005). In contrast, in a hospital- based study at the Gulf Medical College Hospital and Research Center, Ajman, records of 1,222 consecutive live births, the researchers found no statistically significant association of GDM with congenital anomalies (Aryasinghe et al., 2012). In addition to congenital

anomalies, certain long term consequences have also been observed in infants of women with GDM/PGDM.

Maternal diabetes mellitus may have long-term consequences for greater BMI in offspring. A record-linkage prospective cohort study of 280,866 singleton-born Swedish men from 248,293 families was conducted to determine the effect of maternal diabetes mellitus on the body mass index (BMI) of the offspring in early adulthood. It was found that GDM/PGDM was associated with higher mean BMI in their sons at age 18 (Lawlor, Lichtenstein, & Långström, 2011). Thus, GDM/PGDM are associated with many adverse maternal and fetal outcomes. Some outcomes such as macrosomia and perinatal mortality occur in short-term while other adverse outcomes such as higher BMI in adulthood are long-term consequences of GDM/PGDM. Considering the magnitude of adverse outcomes in GDM/PGDM, it is important to manage these conditions optimally. Screening for GDM/PGDM and appropriate treatment of GDM/PGDM are the cornerstones of optimal management.

Screening for GDM

The objective of screening for GDM is to identify women at risk of adverse maternal and fetal outcomes (Rey, 1999). There is continuing debate about whether all pregnant women should be screened (universal screening), or whether screening should be done only if risk factors are present (selective screening). Main risk factors for GDM include increasing maternal age, overweight or obesity, previous GDM, previous macrosomic baby, family history of diabetes, and belonging to an ethnic group having a high prevalence of diabetes (Griffin et al., 2000). The pros and cons of selective and

universal screening are debated (Moses & Cheung, 2009). It is argued that with selective screening based on risk factors, a substantial proportion of GDM cases might be overlooked. Studies have found 22% to 53% missed cases of GDM when screening is conducted through risk factors. However, studies examining broader criteria for risk factor screening observed that only 3–9% of GDM cases would be missed but it would require to screen 80–90% of women (Moses, Moses, & Davis, 1998; Moses & Cheung, 2009; Williams et al., 1999). Selective screening has also been found to be challenging and complex (Moses & Cheung, 2009). Studies have revealed that even well-trained health care workers may face difficulty in conducting selective screening. A survey conducted in New Zealand showed that even experienced midwives had difficulty recalling the recognized risk factors for GDM (Simmons, Devers, Wolmarans, & Johnson, 2009). The current recommendations for screening of GDM include:

- Screening for undiagnosed type 2 diabetes at the first prenatal visit in those with risk factors, using standard diagnostic criteria.
- In pregnant women not previously known to have diabetes, screening for GDM at 24–28 weeks' gestation, using a 75-g OGTT, with plasma glucose measurement fasting and at 1 and 2 hours.
- The OGTT should be performed in the morning after an overnight fast of at least 8 hours.

Women identified of having GDM on screening need to be managed appropriately to prevent the occurrence of adverse maternal and fetal outcomes.

Management of GDM/PGDM

It is well-documented that women with GDM/PGDM are at higher risk of adverse pregnancy outcomes (Crowther et al., 2005; Landon et al., 2009; Kwik, Seeho, Smith, McElduff, & Morris, 2007). Proper management of women with GDM/PGDM can decrease the risk of these adverse outcomes (IDF, 2009). The primary intervention for women with GDM/PGDM is lifestyle modification, however, medications may be needed to achieve adequate glycaemic control. Oral hypoglycaemic agents or insulin may be required (Royal College of Obstetricians and Gynaecologists, 2011). Women should be made aware of the risk of hypoglycemia, and information about prevention and treatment should be provided to them (National Collaborating Centre for Women's and Children's Health, 2008). Continuous glucose monitoring should be emphasized, and pregnant women with diabetes should be encouraged to self-monitor blood glucose levels. In addition to self-monitoring of blood glucose, the HbA1c level should also be measured at intervals of 4 to 8 weeks (IDF, 2009). In addition to management of glucose levels, lifestyle modifications especially appropriate diet plays an important role in management of GDM/PGDM.

All pregnant women with diabetes should receive advice about appropriate nutrition. In most cases, previous nutritional advice for women with PGDM needs to be revised and altered according to pregnancy requirements. Women who develop GDM should be provided with nutritional advice. Healthcare professionals should provide individualized and culturally sensitive nutritional advice. To help control glucose levels, the carbohydrate intake needs to be regulated, and a change in the types of the

carbohydrates consumed may prove beneficial (IDF, 2009). Lifestyle modifications include not only changes in diet but also changes in physical activity. Physical activity plays an important role in the management of pregnancy with diabetes. A moderate amount of exercise is beneficial for women with diabetes in pregnancy. A minimum of 30 minutes exercise on most days of the week is recommended (IDF, 2009). Appropriate communication strategies are needed to convey proper advice about diet and physical activity in women with GDM/PGDM.

Healthcare professionals should play their role by providing information and support that will help to decrease the risks of adverse pregnancy outcomes. Healthcare professionals should provide information about the importance of appropriate diet, body weight and physical activity; the risks of hypoglycemia; the higher risk of having a large for gestational age baby which raises the risk of birth trauma, induction of labor and caesarean section; the importance of appropriate feeding of the newborn; and the chances of metabolic disturbances during the neonatal period (National Collaborating Centre for Women's and Children's Health, 2008). The management of pregnancy with diabetes continues after pregnancy. Women with GDM should have a postpartum OGTT. Women belonging to high-risk group should have an annual OGTT while those in the low-risk group may have tests for fasting glucose levels every two to three years (IDF, 2009). Thus, management of GDM does not stop at the completion of pregnancy rather it continues to follow- up to identify women at risk of developing long term consequences of GDM. Provision of information to women for prevention of GDM in subsequent pregnancies is also an important step in the management of GDM.

Prevention of GDM

In spite of increasing incidence of GDM, there is lack of evidence on effective approaches to prevent it. It is suggested that a combined dietary and exercise intervention may have an impact on insulin resistance leading to prevention of GDM (Callaway et al., 2010). Some studies have shown that restricting energy and carbohydrates could minimize gestational weight gain. Thus, weight management through nutritional prevention strategies could prove successful in reducing the risk for GDM (Morisset et al., 2010). In contrast, a cluster-randomized trial conducted to examine whether GDM can be prevented by lifestyle counseling in pregnant women at high risk of GDM, could not demonstrate positive results (Luoto et al., 2011). Studies conducted to determine the role of physical activity on prevention of GDM have also shown inconclusive results (Callaway et al., 2010). Wolff, Legarth, Vangsgaard, Toubro, & Astrup (2008) found that restriction of gestational weight gain in obese women is achievable through limited energy intake. Although studies have identified maternal weight and physical activity as important factors in prevention of GDM, further studies are needed to determine the influence of these factors as preventive measures.

Review of Methodologies Used in Determining Maternal and Fetal Outcomes of PGDM/GDM among women in Eastern Mediterranean Region

The literature reviewed includes research addressing the effect of GDM/PGDM on maternal and fetal outcomes of pregnancy. These studies are observational and quantitative in nature and are mostly hospital-based. The study designs include cross-sectional studies, retrospective review of administrative records, case- control studies,

and cohort studies. The strengths and limitations of these research designs in the context of determining maternal and fetal outcomes among women with GDM/PGDM are discussed below:

Cross-sectional studies

A cross-sectional study describes the health status and the presence or absence of exposure of a specified population at a defined point in time (Ressing, Blettner, & Klug, 2010). It determines the association between an outcome and an exposure among individuals in a specified population at a specific point in time (Aschengrau & Seage III, 2008). Thus, the researcher observes the exposure and outcome in the study population, simultaneously. The strength of this design is that the prevalence of disease or health outcome in a population can be assessed. Furthermore, these studies are less resource and time- intensive. However, the cross-sectional design has certain limitations which make it less scientifically rigorous than case-control and cohort studies (Aschengrau & Seage III, 2008). These studies cannot determine the temporal sequence of exposure and disease, thus, it is difficult to establish the association between exposure and disease (Aschengrau & Seage III, 2008). However, temporal sequence is not an issue in the studies for determining association between PGDM/GDM and pregnancy outcomes, as exposure always precedes the outcomes. Hossein-Nezhad et al. (2007) conducted a cross-sectional study and determined the prevalence of GDM and its association with various adverse pregnancy outcomes in the study population.

Case- Control Studies

The case-control study compares the individuals with the disease or health outcome (case) to those without the disease or health outcome (control) (Ressing et al., 2010). A case–control study examines a single disease in relation to exposure to risk factors (Aschengrau & Seage III, 2008). The strengths of case- control studies include their cost-effectiveness and time- efficiency. They are appropriate to study rare diseases and diseases with long latent periods. Moreover, multiple risk factors can be examined to determine their association with the outcome. Limitations of case-control studies include the inability to calculate incidence rates, confounding and bias. Bias may occur due to inappropriate selection of the control group in the case-control studies (Aschengrau & Seage III, 2008). Another limitation is the information bias as the study is dependent on the medical records or study participant's ability to recall events. For example, Diejomaoh et al. (2009) stated the limitation of inability to calculate body mass index (BMI) of study participants as height of the pregnant women were not recorded in their medical records. This may have affected the association of GDM/PGDM with macrosomia as the confounding effect of obesity could not be ruled out.

Cohort Studies

Cohorts are groups of similar individuals such as all pregnant women registered in a health care facility during a specified period of time. In cohort studies, the cohort is followed over a period of time to determine the outcomes in relation to certain risk factor (Aschengrau & Seage III, 2008). The cohort study begins with the observation of study participants without outcomes who are either exposed or non-exposed to certain risk

factor (Ressing et al., 2010). Thus, the cohort under investigation is divided into two groups on the basis of their exposure status such as women with GDM/PGDM and those without GDM/PGDM. The researchers observe the study population and follow them over time to determine the outcome in the exposed and unexposed group. Cohort studies can be either prospective or retrospective (Lounds Taylor et al., 2012). In a prospective cohort study, the study population is defined prospectively before outcome occurrence. A prospective study allows for a more accurate measure of exposure and outcome. In a retrospective cohort study, the outcome occurs before the start of the study; however, the study population is classified on the basis of exposure status. The cohort studies are useful in studying several possible outcomes from a single exposure. Incidence rate of a disease can be calculated. The prospective cohort studies are time consuming and resource intensive. The study participants may be lost to follow up resulting in attrition bias. In case of retrospective cohort studies, information bias may occur. Al-Khalifah et al. (2012) have discussed the limitations of their retrospective cohort study as information regarding nutritional status of pregnant women and adherence to treatment regimen was not available in the medical records. Thus, the confounding effect of these factors on the association between GDM and adverse pregnancy outcomes could not be controlled.

Summary of Methodological Issues

Most studies of GDM/PGDM in the EMR were case-control studies (Abdelgadir et al., 2003; Dafallah & Yousif, 2004; Diejomaoh et al., 2009) and cohort studies (Abolfazl et al., 2008; Al-Khalifah et al., 2012; Bener et al., 2011; Hossein-nezhad et al., 2011; Keshavarz et al., 2005). Some Eastern Mediterranean studies determined maternal

and fetal outcomes of GDM/PGDM by using administrative data. Thus, retrospective review of the administrative records to determine an association between adverse pregnancy outcomes and GDM/PGDM was conducted (Al Najashi & Al Umran, 1997; Barakat et al., 2010; Misra et al., 2001). Many of these studies had limited sample sizes (Abdelgadir et al., 2003; Abu-Heija, Jallad, & Abukteish, 1999; Al-Dabbous et al., 1996). For example, Abu-Heija et al. (1999) only identified 11 women with PGDM out of their total sample of 114 women.

Many studies conducted in the EMR have used medical records for data collection (Barakat et al., 2010; Gasim, 2012; Misra et al., 2001). Use of administrative data is cost-effective and time-efficient but has certain methodological limitations. The number of variables available for analysis is limited in administrative data. For example, information about certain risk factors which may affect the outcomes of pregnancy such as age of onset or duration of PGDM may not be available in the administrative records. Some women with GDM/PGDM may choose to use private health care facilities. Any single study based on administrative data from public hospital may not represent the complications in those who got health care services from private institutions; who had severe complications or those who had complications during home delivery.

An important design issue among the studies reviewed was the duration of the study. For example, Al-Khalifah et al. (2012) reviewed hospital records of women with GDM for the duration of one year while other studies reviewed the records for a duration of two years (Misra et al., 2001; Sobande et al., 2000; Tahir et al., 2011). Data of many studies were limited because the data were collected from a single health care facility

(Al-Khalifah et al., 2012; Mazhar et al., 2003; Misra et al., 2001; Sobande et al., 2000). Some of the above mentioned methodological limitations can be overcome by conducting meta-analysis. Meta-analysis combines the data from various studies. Combining data of these studies provided a better perspective by having larger sample size; longer duration of study; data from multiple countries and multiple health care facilities.

Meta-analysis

Meta-analysis is a statistical method for synthesizing the results of relevant primary studies (Crombie, & Davies, 2009). While reviewing the literature for my dissertation, I reviewed various studies in which meta-analysis was conducted on the topic of PGDM and GDM. Researchers have addressed a variety of topics related to PGDM and GDM. Purposes of these meta-analyses, number of studies included in the meta-analysis, publication years of included studies, and the outcomes discussed in these meta-analysis are illustrated in Table 1. The number of studies included in the meta-analysis ranged from a minimum of seven (Poel et al., 2012) to a maximum of 22 studies (Mao, Li, & Gao, 2012). The span of time for studies included in meta-analysis varied; ranging from 3 years (Lepercq et al., 2012) to more than 20 years (Chu et al., 2007; Horvath et al., 2010; Wahabi, Alzeidan, & Esmaeil, 2012). To synthesize the effects of treatments on women with GDM, Horvath et al. (2010) included studies conducted over a span of around 40 years, from 1966 to 2005.

In addition to variation in the time span and number of studies included in meta-analysis, a variety of topics are addressed in these meta-analyses. Associations of various adverse outcomes with GDM/PGDM are studied, as well. Balsells et al. (2012)

performed a meta-analysis to determine the association of major congenital malformations in women with GDM/PGDM in comparison to the general population. Bellamy and colleagues (2009) determined the strength of association between GDM and risk of developing type 2 diabetes later in life. However, I could not find a meta-analysis addressing adverse pregnancy outcome among women with GDM/PGDM in the EMR. As most of the countries in this region have high birth rate and also prevalence of GDM/PGDM is higher in comparison to rest of the world, it was important to conduct a meta-analysis by including studies conducted in this region. Such a meta-analysis provided a better picture of gravity of the situation in EMR.

This dissertation is a meta-analysis of observational studies conducted on adverse maternal and fetal outcomes among women with GDM/PGDM in the EMR. Meta-analysis was appropriate for this research because I have tried to explore existence and magnitude of association between adverse pregnancy outcomes and GDM/PGDM in the EMR. The meta-analysis included studies from most countries of the Region, conducted in various periods of time in varied settings. It utilized scientific literature search strategies and statistical methods for quantitatively summarizing the results of relevant primary studies addressing a particular research question (Cook et al., 1997). The quantitative summary provides a broader perspective of relevant findings from research on a specific topic. Statistical synthesis of data from several primary studies results in a more precise estimate of the effect size, in comparison to any single primary study. On combining the samples of primary studies, the overall sample size was enhanced, leading to increased statistical power, thus reducing the size of the confidence interval and

increasing the precision of the results. Moreover, systematic reviews and meta-analysis may identify gaps in the existing literature (Garg et al., 2008). Meta-analysis provides evidence to make informed decisions for health care. They are also helpful in planning future research for delivering optimal health care (Cook et al., 1997).

Table 1

Characteristics of Published Meta-analysis on Various Issues related to Pregestational/ Gestational Diabetes Mellitus

Author	Purpose	Number of studies included in meta-analysis	Publication years of studies included in meta-analysis	Type of diabetes	Outcome	
					Maternal	Fetal
Balsells, García-Patterson, Gich, & Corcoy, 2012	To perform a systematic review and meta-analysis of major congenital malformations in women with GDM as compared to general population.	17 studies	1988-2008	GDM and PGDM		Congenital Malformation
Bellamy, Casas, Hingorani, & Williams, 2009	To assess the strength of association between GDM and risk of developing type 2 diabetes	20 studies	1991-2008	GDM	Type 2 Diabetes Mellitus	
Chu et al., 2007	To determine the magnitude of association between risk of GDM with increasing weight or BMI	20 studies	1980-2006	GDM	GDM	
Horvath et al., 2010	To summarize the benefits and harms of treatments for women with GDM	Pool A: 5 studies Pool B: 13 studies	1966-2005	GDM	Pre-eclampsia	Shoulder dystocia; Large for Gestational Age

Author	Purpose	Number of studies included in meta-analysis	Publication years of studies included in meta-analysis	Type of diabetes	Outcome	
					Maternal	Fetal
Lepercq et al., 2012	To compare use of insulin glargine with human NPH insulin for efficacy and safety-related outcomes during pregnancy.	8 studies	2007-2010	GDM and PGDM	Weight at delivery, weight gain, 1st/3rd trimester HbA1c, severe hypoglycemia, gestation/new-onset hypertension, preeclampsia, and cesarean section	Congenital malformations, gestational age at delivery, birth weight, macrosomia, LGA, 5 minute Apgar score >7, NICU admissions, respiratory distress syndrome, neonatal hypoglycemia, and hyperbilirubinemia
Mao, Li, & Gao, 2012	To derive a more precise estimation of the association between common type 2 diabetes (T2D) risk gene polymorphisms, hence achieve a better understanding to the relationship between T2D and GDM.	22 studies	1994-2012	GDM		
Poel et al., 2012	To examine association between vitamin D and glucose metabolism in women with GDM compared with normal glucose tolerance (NGT)	7 studies	2007-2011	GDM		

Author	Purpose	Number of studies included in meta-analysis	Publication years of studies included in meta-analysis	Type of diabetes	Outcome	
					Maternal	Fetal
Tobias, Zhang, Dam, Bowers, & Hu, 2010	To synthesize the current evidence on the relation between physical activity and the development of GDM	8 studies	2004-2010	GDM		
Wahabi, Alzeidan, & Esmaeil, 2012	To evaluate the effectiveness and safety of pre-pregnancy care in improving the rate of congenital malformations and perinatal mortality for women with PGDM	21 studies	1983-2010	PGDM	HbA1c in the first trimester of pregnancy	Congenital malformation; perinatal mortality;
Wendland et al., 2012	To systematically review the evidence for the associations between GDM and adverse outcomes	8 studies	1994-2010	GDM	Preeclampsia; cesarean delivery	Macrosomia; large for gestational age; perinatal mortality

Summary and Transition

Chapter 2 presented a literature review for GDM/PGDM and their adverse maternal and fetal outcomes. GDM and PGDM are associated with adverse maternal and fetal outcomes and may result in serious health complications (Crowther et al., 2005; Metzger et al., 2008). Increased caesarean section rates, high blood pressure, and increased lifetime risk of occurrence of type 2 diabetes are adverse maternal outcomes (Langer et al., 2005; Bellamy et al., 2009). Adverse fetal outcomes include perinatal complications, still birth, macrosomia, and trauma during birth (Ayaz et al., 2009; Ornoy, 2011; Thorpe et al., 2005).

Middle Eastern countries are reported to have a high prevalence of GDM and PGDM (Agarwal et al., 2010; Hossein-Nezhad et al., 2007). There are a limited number of published studies examining the association between adverse outcomes and GDM/PGDM among women in Middle Eastern countries. Most of the published studies are hospital-based and tend to have small sample sizes. Since adverse fetal outcomes, such as still births are not common occurrences and the number of cases in any given study is few, the measure of association may not be significant statistically for these outcomes. These non-significant results are due to smaller sample size and low statistical power of the study. Synthesizing these studies statistically, by meta-analysis, quantified complications related to pregnancy with diabetes and provided insight regarding the extent of the problem in the EMR. This study determined the existence of association as well as strength of association of adverse pregnancy outcomes with GDM and PGDM among women in EMR. Measuring the association of adverse pregnancy outcomes with GDM and PGDM helped in providing a better picture of magnitude and severity of the problem in EMR. Given the rising prevalence of PGDM and GDM in Middle Eastern countries, it is important to be aware of the severity and seriousness of the problem. Determining the magnitude of association between adverse pregnancy outcomes filled the gap in the existing literature regarding this important topic related to maternal and child health.

In Chapter 3, I provide the details of the study, including the research design and its rationale. Description of the population, dependent and independent variables,

literature search strategy, inclusion and exclusion criteria for studies, and data analysis techniques will also be described in Chapter 3.

Chapter 3: Research Method

Introduction

Given the rising prevalence of PGDM and GDM in the EMR ,.determining the magnitude of association between GDM/PGDM and adverse pregnancy outcomes is an important initial step that will help provide a better picture of magnitude and severity of the problem. The purpose of this study was to determine the association between GDM/PGDM and adverse pregnancy outcomes among women in the EMR. Studies on pregnancy with diabetes and its outcomes are generally conducted at a smaller scale; however, this meta-analysis combines the sample sizes of studies from various countries and analyzes their results to provide an idea about this public health issue at a regional level .

The first section of this chapter describes the research design and rationale. After restating the research questions, I describe what is meta-analysis. I then describe the population used for the study. In the subsequent sections, I describe the independent and dependent variables, the literature search strategy for identifying studies for inclusion in the meta-analysis, the inclusion and exclusion criteria for various studies used in this project, and the data analysis techniques and sensitivity analysis.

Research Questions and Hypotheses

This study was based on two main research questions, each of which generated related hypotheses:

1. Is there an association between GDM/PGDM and delivery by cesarean section among women in the EMR?

H_{01} - There is no association between GDM/PGDM and delivery by cesarean section among women in the EMR

H_{A1} - There is an association between GDM/PGDM and delivery by cesarean section among women in the EMR

2. Is there an association between GDM/PGDM and adverse fetal outcomes among women in the EMR?

2a. Is there an association between GDM/PGDM and macrosomia among women in the EMR?

H_{02a} - There is no association between GDM/PGDM and macrosomia among women in the EMR

H_{A2a} - There is an association between GDM/PGDM and macrosomia among women in the EMR

2b. Is there an association between GDM/PGDM and perinatal mortality among women in the EMR?

H_{02b} - There is no association between GDM/PGDM and perinatal mortality among women in the EMR

H_{A2b} - There is an association between GDM/PGDM and perinatal mortality among women in the EMR

Research Design and Rationale

The purpose of this study was to determine whether GDM/PGDM, as independent variables, had any association with the adverse pregnancy outcomes among women in the EMR. Quantitative research is an appropriate methodology as the study is designed to test

a hypothesis using quantitative data. In order to find any association between the independent and dependent variables as well as their strengths of association, primary studies on GDM/PGDM among women in the EMR were collected to conduct a meta-analysis. Generally, a single study cannot answer important questions, and combination of results from multiple primary studies provides more compelling evidence as compared to result from a single study (Wilson, 2012). Moreover, combination of results of studies conducted in different regions with varied populations is expected to be more generalizable as compared to the results of a single study (Wilson, 2012). Meta-analysis is a statistical method used for synthesizing the results of relevant primary studies (Crombie & Davies, 2009). It uses scientific literature search strategies and statistical methods for quantitatively summarizing the results of relevant primary studies addressing a particular research question (Cook et al., 1997). The quantitative summary provides a broader perspective of research findings on a specific topic. Statistical synthesis of data from several primary studies results in a more precise estimate of the results, in comparison to any single primary study. On combining the samples of primary studies, the overall sample size is enhanced, leading to increased statistical power thus reducing the size of the confidence interval (CI) and increasing the precision of the results (Garg et al., 2008). Moreover, meta-analysis may identify gaps in the existing literature (Garg et al., 2008). For example, it was revealed during the literature search for this meta-analysis that the studies examining the association between GDM/PGDM and perinatal deaths in the EMR were few with inconsistent results. The reasons for gaps in the research

identified during meta-analysis include insufficient information, biased information or inconsistent results (Robinson et al., 2013).

Meta-analysis is an appropriate method for this research because I tried to explore if there is any association and the strength of that association between GDM/PGDM and adverse pregnancy outcomes in the EMR. The meta-analysis included studies from most countries of the region, conducted in various periods of time in varied settings addressing the research questions of this dissertation. An original study of this extent would have been resource- intensive and difficult to conduct because of adverse social, economic and political situation of many member countries in the EMR. Meta-analysis is appropriate as it statistically combines quantitative estimates from various primary studies (Sutton et al., 2000). Therefore, my study provided a broader picture of the gravity of the situation in Middle Eastern countries by combining quantitative estimates from various countries. The estimates from various studies were combined to provide a pooled estimate.

Meta-analysis of epidemiological studies and the integration of observational data has become increasingly popular in medicine and health care (Egger, Smith, & O'rourke, 2008). Systematic reviews and meta-analysis can result in the identification of an important research question, and may help in appropriate sample size calculation for future studies (Egger et al., 2008, p.12). They are also helpful in planning future research for delivering optimal health care (Cook et al., 1997). My study provides scientific information for informed decision by the policy makers in the EMR. Moreover, it helps in identifying gaps in the available literature and in planning future research in this important area of maternal and child health care.

Time and Resource Constraints

There were certain time and resource constraints in conducting this study. Acquiring all relevant research documents was not possible within the available time frame. It was difficult and time consuming to get access to unpublished researches related to the study topic. Thus, only published journal articles were included. Although there were resource constraints in accessing all relevant articles, Walden library and its document delivery system were quite helpful in this context. This meta-analysis included research published only in English. Although some related researches are published in languages other than English, such as Arabic, Persian, and other native languages, because of resource constraints, translations of these researches could not be obtained.

Methodology

Population of Study

This meta-analysis included the population of countries of the EMR. Although there are variations in socioeconomic conditions, these countries share many cultural practices and lifestyle patterns (Jahan, 2008). The WHO Eastern Mediterranean Region comprises 22 countries with a population of approximately 583 million (WHO, n.d.a). The Eastern Mediterranean Regional Office (EMRO) comprises a group of WHO member states in one of its six geographical regions. The 22 Middle Eastern countries of EMRO include Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon and Libya. In addition, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates, and Yemen are also included in the WHO EMRO (World Health Organization, n.d.b).

The population size and health indicators of Middle Eastern countries are variable and differ from country to country. During 2011, the population of the member countries of WHO EMRO ranged from 865,000 in Djibouti to 177,100,000 in Pakistan which has the largest population in the region (WHO, 2012). During the same period, crude birth rate in the region varied from as low as 11.9 per thousand in Qatar to as high as 44 per thousand in Somalia while total fertility rate was 0.9 per woman in Kuwait which was the lowest while it was 6.4 per woman in Somalia which was the highest in the region (WHO, 2012). My dissertation included available relevant published studies in English from the member countries, and the results of the study reflected the situation in the above mentioned population.

Sampling and Sampling Procedures

All original research studies conducted to determine the association between GDM/PGDM and pregnancy outcomes among women in the Eastern Mediterranean countries were searched by a comprehensive search strategy, stated in the next section. Many studies conducted to determine the effect of GDM/PGDM on pregnancy outcomes had small sample size and few adverse outcomes. These studies might be having low power to detect the association of GDM/PGDM with adverse outcomes. For example, the study conducted by Sobande et al. (2000) had a power of 41.7% at an alpha level of 0.05, to determine statistically significant difference between women with GDM/PGDM and those without GDM/PGDM and perinatal deaths. Synthesizing the results of these studies by meta-analysis increased the sample size which lead to increased precision of the results (The Cochrane Collaboration, 2008). I combined all the sample sizes of all the

published relevant and eligible research in English from the EMR which helped in increasing the precision of the results and in identifying statistically significant associations.

Meta-analysis increases the statistical power by reducing the standard error of the weighted average effect size. It also decreases the confidence interval, representing increased precision, around effect size (Cohn & Becker, 2003). Effect size is defined as the magnitude of a difference measured on a standardized scale. It is a metric-free measure and can be used for comparison of results of different studies (Sun, Pan, & Wang, 2010). As small sample sizes from primary studies are pooled into a large one, statistical power is higher in meta- analyses as compared to primary studies (Cohn & Becker, 2003). Statistical power of a study refers to the chances of identifying an underlying association within the population. By pooling the samples of primary studies, a meta-analysis can increase the likelihood of detecting true estimates of effect size in the underlying population (Cohn & Becker, 2003).

At the planning stage of meta-analysis, it is important to estimate the chances of detecting a significant effect by that meta-analysis (Cafri, Kromrey, & Brannick, 2009). This estimation can be done by conducting a power analysis prior to the study (Cafri et al., 2009). Theoretically, statistical power in meta-analysis and in primary studies is similar, as it is a function of sample size, an estimation of population effect size, and the Type I error rate in both cases (Valentine, Pigott, & Rothstein, 2010). Increasing any one of these variables without changing the others increases power of the study (Valentine et al., 2010). Table 2 shows the estimation of power of a meta-analysis with a random

effects model, under various assumptions regarding different factors of the meta-analysis. The calculations in Table 2 assume $\alpha = 0.05$ for Type I error.

Table 2

Illustration of the Random Effects of Statistical Power (One-Tailed) as a Function of Different Assumptions About Review Parameters

Within-study sample size (per group)	Number of studies to be included	Effect size to detect	Degree of heterogeneity	Power
20	40	0.15	Moderate	0.68
30	40	0.15	Moderate	0.75
40	40	0.15	Moderate	0.79
20	25	0.15	Moderate	0.51
20	40	0.15	Moderate	0.68
20	65	0.15	Moderate	0.83
20	40	0.05	Moderate	0.18
20	40	0.25	Moderate	0.97
20	40	0.35	Moderate	~ 1.00
20	40	0.15	Large	0.44
20	40	0.15	Small	0.83

Note. Adapted with permission of the author from "How Many Studies Do You Need? A Primer on Statistical Power for Meta-Analysis" by J. C. Valentine, T. D. Pigott, and H. R. Rothstein, 2010, *Journal of Educational and Behavioral Statistics*, *35*(2), p. 221. Copyright 2010 by the American Educational Research Association.

While reviewing the literature for this dissertation, I found within study sample size (per group) of more than 40, in most of the studies conducted for determining the association between GDM/PGDM and pregnancy outcomes among women in the EMR. Based on the criteria stated in Table 2, a meta-analysis of 40 studies with moderate heterogeneity, will have a power of 0.79 to detect an effect size of 0.15 in my study.

All relevant studies conducted for determining the association between GDM/PGDM and pregnancy outcomes among women in the EMR were considered for

possible inclusion in meta-analysis, based on inclusion and exclusion criteria listed in the following section.

Criteria for Inclusion and Exclusion of Studies in the Meta-analysis

It is important to set explicit criteria for the inclusion and exclusion of studies in the meta-analysis. Inclusion criteria for studies can be based on various characteristics of the research studies. The following criteria were used for the inclusion of studies in the meta-analysis for estimating the association of GDM/PGDM with adverse maternal and fetal outcomes.

Types of Studies. The observational studies regarding pregnancy outcomes in women with diabetes were systematically reviewed. I included studies with a prospective or retrospective cohort, case-control, and cross- sectional designs. Cohort and case-control studies, which examined pregnancy outcomes in women with diabetes, were included. Those cross-sectional studies were included where pregnant women with diabetes were compared with those without diabetes and measures of association were calculated or there is data available for these calculations.

Types of participants. Pregnant women with GDM and/or PGDM.

Types of settings. Population-based as well as hospital- based studies were included in this meta-analysis.

Types of outcomes measures. The research study should provide information on at least one outcome included in the meta-analysis. Fetal outcomes including macrosomia and perinatal death, ascertained through registry review, birth/medical records, and physical examination of the newborn, were accepted.

Geographical context. This dissertation included studies conducted in countries of the EMR as classified by WHO (n.d.b). The meta-analysis was limited to articles written in English.

Timeframe. Publication period ranged from the inception of the research database to November 2013.

Exclusion Criteria

I excluded the studies with following attributes:

- case report or case series;
- review articles;
- studies from countries other than members of the EMR;
- not published in English;
- a conference proceeding or abstract, letter to the editor, or commentary;
- no assessment of an outcome relevant to the research questions;
- animal studies.

Procedures for Data Collection

Review of the Literature. A meta-analysis identifies, evaluates, and combines relevant studies on a specific topic (Petticrew & Roberts, 2006, p.2). This meta-analysis included all stages of research synthesis including problem statement, literature search, data evaluation, data analysis, data interpretation and writing of the results (Cooper & Hedges, 2009). The background, research questions and methods of meta-analysis; inclusion and exclusion criteria for primary studies; search strategy for finding relevant research; and statistical procedures were stated (Victor, 2008). Background of the study,

and inclusion and exclusion criteria for primary studies are stated in the above sections while rest of the components are described in the sections below.

Independent and Dependent Variables

In this meta-analysis, independent variables were GDM/PGDM. The dependent variable for maternal outcome was delivery by cesarean section. The dependent variables for neonatal outcomes were (a) macrosomia, which means that the birth weight was greater than 4000 g (large for gestational age or LGA) or that the (birth weight was greater than the 90th percentile for their gestational age), and (b) perinatal mortality. I defined the outcomes as follows:

- Cesarean delivery was defined according to the primary study definition.
- Large for gestational age births and macrosomia were included as defined by the authors of the primary study.
- Perinatal mortality included stillbirth and early neonatal death.

To identify relevant literature including the above mentioned independent and dependent variables, a comprehensive literature search strategy was developed which is described in the next section.

Search Strategy for Relevant Studies

A review of studies conducted on GDM/PGDM in the EMR was conducted to assess the relevant literature. For meta-analyses, it is important to conduct a literature search in a systematic manner to identify all available relevant research. It requires a comprehensive literature search in several research databases, such as ProQuest Family Health, ProQuest Health & Medical, ProQuest Health Management, ProQuest Nursing & Allied Health

Source, ProQuest Science Journals, Academic Search Complete, CINAHL Plus, and MEDLINE. Moreover, relevant journals and the reference lists of relevant papers should also be hand searched (Crombie, & Davies, 2009). Explicit criteria for inclusion or exclusion of studies must be used for meta-analyses (Crombie, & Davies, 2009). Important keywords capable of identifying relevant research should be used as search terms.

Search Terms. A comprehensive search for relevant studies using important keywords was conducted. The index terms for search were *diabetes mellitus*, *type I diabetes, type 2 diabetes mellitus, NIDDM, pregnancy, pregestational diabetes, gestational diabetes, diabetic pregnancy, diabetes in pregnancy, pregnancy complications, outcome, macrosomia, cesarean, cross- sectional, case control,* and *cohort* studies. The search terms were combined using the term "AND" to create a complete list of articles for this meta-analysis. These terms were also searched with the names of individual member countries of the EMR. These countries include *Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon; Libya*, *Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates, and Yemen*. The limitation applied was the English language. The search limit start-date was chosen by the earliest date the database had been available.

Electronic databases. The electronic databases searched included ABI/INFORM, Academic Search Premier, CINAHL, Cochrane Database of Systematic Reviews (CDSR), Educational Resource Information Center (ERIC), Emrmedex, Journals at Ovid, Library Information Science and Technology Abstract (LISTA), Medline, Proquest,

PsychINFO, and publishers' databases such as Elsevier and Springer. The databases were searched from inception to November 2013 to identify relevant citations.

Hand searching. The medical journals of EMR such as Eastern Mediterranean Health Journal by World Health Organization, Annals of Saudi Medicine, Saudi Medical Journal and Saudi Journal of Family and Community Medicine were hand-searched. These journals are likely to publish articles relevant to the topic of this meta- analysis. Hand searching was performed by scanning the table of contents of the journals most likely to publish articles on the topic and scanning reference lists from included articles and review articles on GDM/PGDM.

Internet searching. Internet searches were conducted using the keywords mentioned above, through search engines such as googlescholar.com and google.com. Websites such as WHO EMRO, and websites of Ministry of Health of member countries of EMRO were also searched for relevant researches. Individual websites of journals of the EMR such as Eastern Mediterranean Health Journal by World Health Organization, Annals of Saudi Medicine, Saudi Medical Journal and Saudi Journal of Family and Community Medicine were explored for relevant articles.

Reference lists. In addition to electronic database searches, articles cited in meta-analyses and systematic reviews on GDM and PGDM, were reviewed. The reference lists of relevant literature were also examined, to identify studies eligible for inclusion in the present study.

Documenting the Search Process

A complete record of literature search and data collection process was maintained. The record included information about search time periods; research databases; search engines; keywords; and search results. Studies were searched mainly through the Walden University library system. If electronic copies were not available, print copies of the journal articles were obtained. A record of excluded studies along with the reason for exclusion was maintained.

Details of Study Included in the Meta-analysis

For maintaining details of studies included in the meta-analysis, the guidelines for reporting meta- analysis of observational studies (Appendix A) was followed (Stroup et al., 2000). A summary table helps in displaying individual study characteristics in an organized manner. A summary table (Appendix B) was created to record the main elements of each study such as relevant bibliographic information, the studies' design, type(s) of diabetes mellitus, age group/ mean age of women and outcome data (Glasziou et al., 2001). In addition, any other pertinent information about the study was also included.

Steps in Search Strategy

- All titles and abstracts were considered for eligibility.
- I screened the title and abstract of each study identified by the search and apply the inclusion and exclusion criteria.

- Whenever an abstract seemed that the journal article may meet the inclusion criteria, the corresponding full-text article was reviewed and the inclusion and exclusion criteria applied.
- References of review articles were searched for additional relevant studies.
- Bibliographies of relevant retrieved studies were hand-searched for additional publications.
- Studies identified through additional search activities were reviewed to identify duplicates of articles retrieved earlier.
- Data on characteristics of study participants and outcomes (caesarean section, macrosomia and perinatal mortality) listed in research questions were abstracted.

Data Abstraction

Articles were selected by reviewing the abstract and assessing if it met the selection criteria for meta-analysis. When an abstract potentially fulfilled the criteria, the corresponding full text was reviewed to find out if it fitted into the designated criteria. The citations of all identified articles were entered into an electronic database for record keeping and for removing the duplicates. I reviewed each article that met the selection criteria and abstracted the data by using data abstraction form (Appendix C). I extracted information about the general study characteristics (study design, study period, country of study, and year of publication), study participants (number of study participants, maternal age, type of diabetes); and designated maternal and fetal outcomes.

The relative risks (RRs) and odds ratios (ORs) for the association with adverse pregnancy outcomes were abstracted, if stated. The unadjusted and adjusted RRs or ORs

and 95% confidence intervals (CIs) were extracted as reported by authors. If not stated, then the RRs and ORs were calculated from information stated in each study. When raw quantitative data were not reported, values were obtained from the provided information. Dichotomous data reported as percentages were converted to counts and OR and RR were calculated. For each study, I constructed separate two-by-two tables to compute the ORs or RRs and 95% CIs of each outcome. Association of caesarean section with GDM/PGDM was observed for maternal outcome while macrosomia and perinatal mortality (stillbirths and neonatal deaths) were focused for fetal outcome. All information from the article review process was entered and analyzed in Comprehensive Meta Analysis (CMA) software, Version 2.

It is important to write the report of meta-analysis according to standard international guidelines. For reporting of meta- analysis, I followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000), attached as Appendix A and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) included as Appendix D. An important component mentioned in the guidelines for meta-analysis is the assessment of quality of the included studies. In this meta-analysis, quality of studies was assessed by various criteria. Quality assessment of the studies is discussed in the next section.

Quality Assessment of Studies

Quality assessment of the studies (Appendix E) included in meta-analysis was done. To assess individual observational studies, quality criteria were laid down by organizations such as the Agency for Healthcare Research and Quality (AHRQ) (Myers

et al., 2008). These criteria addressed issues related to the methods employed to select the study population, the appropriateness of the sample size, the methods for determining outcomes, and the appropriateness of the statistical analysis.

Researchers have argued the utility of assigning a summary quality score to individual observational studies. There is lack of evidence regarding substantial impact on the results of meta-analysis by using a quality scoring system (Jüni, Witschi, Bloch, & Egger, 1999). It is reported that instead of determining a cumulative quality score, identifying quality issues such as inadequate sample size or inappropriate statistical methods may be more helpful in guiding future research (Agency for Health Care Research and Quality [AHRQ], 2010; Myers et al., 2008). Thus, quality scoring was not done in my study, however, to assess the quality of the included studies various criteria were observed and reported (Appendix E).

I conducted quality assessment of the studies by selecting elements from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (Von Elm et al., 2007). For quality assessment, STROBE guideline (Appendix F) includes different criteria for various study designs. I used the following criteria for various study designs to assess the quality of the studies (Myers et al., 2008; Von Elm et al., 2007).

Cohort study:

- Appropriate cohort selection
- Appropriate sample size
- Properly described cohort

- Clear description of diagnostic criteria for GDM/PGDM
- Clear definition of the outcomes
- Description of the methods for ascertaining outcomes
- Description of lost to follow up
- Appropriateness of statistical analyses

Case-control study:

- Selection of cases in an appropriate and unbiased manner
- Selection of controls in an appropriate manner
- Matching of cases and controls regarding potential confounders
- Description of diagnostic criteria
- Clear definition of outcomes
- Address the potential sources of bias
- Appropriateness of statistical analyses

Cross-sectional study:

- Adequate sample size
- Appropriate methods of selection of participants
- Description of diagnostic criteria
- Clear definition of outcomes
- Appropriate sources of data and methods of assessment for outcomes
- Address the potential sources of bias
- Appropriateness of statistical analyses

Data Analysis Plan

Meta- analysis was conducted using the software Comprehensive Meta Analysis, v2. Various statistical procedures were conducted in this software. This section describes statistical procedures including effect size computation, random effects model and fixed effects model, subgroup analysis, assessing heterogeneity, sensitivity analysis, publication bias, and a brief description of software used for computation of data in the meta- analysis. The description of each of these components is as follows:

Effect Size Computation

Most meta-analyses focus on relationships between variables (Borenstein et al., 2009; p. 17). These relationships or associations are expressed as indices such as relative risk (RR) or odds ratio (OR). Both OR and the RR can be given as the summary measure. Although technically different, usually the ORs and the RRs have the same interpretation (Davies, Crombie, & Tavakoli, 1998). In meta-analysis, the results from primary studies are combined by statistical technique. There are different techniques for combining relative risks, odds ratios and other effect estimates, but the basic principle is the same. An estimate, weighted by the precision of the estimate is obtained from each study (Crombie, & Davies, 2009). For some indices that are similar such as ORs and the RRs, it is acceptable to combine them under certain conditions. ORs and the RRs are approximately equal and can readily be combined, if the event is rare (Borenstein et al., 2009; p. 21). In my study ORs and the RRs were combined to calculate the effect size as the outcomes of interest such as perinatal death are rare.

An effect size is a number that expresses the magnitude of the association between two variables (Cooper & Hedges, 2009). There are various types of effect size measures; *r* type in which effect size measured in terms of strength of association when both the independent and dependent variables are ordered; and *d* type when the independent variable is dichotomous and the dependent variable is ordered (Kraemer et al., 2003). In meta-analysis, computation of effect size is the cornerstone as it synthesizes the results related to outcomes of interest (Borenstein, 2009). The effect size computation depends on three factors: (a) the measures for variables of outcomes of interest, (b) the study designs of primary studies included in meta-analysis, and (c) the data analyses of the primary studies (Lipsey & Wilson, 2001). In my dissertation, the studies included in meta-analysis were observational studies with cohort, case-control and cross-sectional designs. Thus, RRs and ORs were the indices measuring outcomes of interest in these studies, both of which could be used for calculation of effect size in meta-analysis.

For the calculation of effect sizes in this study, OR is the primary metric, as the OR has certain statistical properties which make it the best index for a meta-analysis (Borenstein et al., 2009, p. 36). A weighted average of the ORs in the studies was computed. In meta-analysis, odds ratios need to be transformed, followed by computation of a weighted mean for the transformed values and then conversion of this mean back into an odds ratio to report the combined value. Log scale is used for computations. The log odds ratio, and the standard error of the log odds ratio, are computed and are used for all calculations in the meta-analysis (Borenstein et al., 2009, p. 36). For my study, all these statistical procedures were conducted by using the data analysis software.

Odds ratios are analyzed in log units. Following is the computational formula for the odds ratio (Borenstein et al., 2009; p. 36):

$$\text{Odds ratio} = AD/BC$$

log odds ratio: LogOddsRatio = ln(OddsRatio)

With approximate variance: $V_{LogOddsRatio} = 1/A + 1/B + 1/C + 1/D$

An important step in conducting meta-analysis is to select the method for merging effect sizes. Two types of models, fixed effects model and random effects model, can be used for merging effect sizes. Selection of the model depends on certain characteristics of primary studies such as heterogeneity. Decision about model selection should be taken before conducting meta-analysis. A brief description of both these models along with the decision about selection of model for this study follows in the next section.

Random Effects Model and Fixed Effect Model

Random effects model is a technique for merging effect sizes. It assumes that reported effect sizes among studies may vary, due to both sampling error as well as actual difference in population parameters (Cooper & Hedges, 2009). In contrast, the fixed-effect model takes an average of the primary study estimates and computes a pooled effect estimate. It weights each study estimate by the inverse of its variance. The fixed-effect model assumes that there is no heterogeneity between studies. On the other hand, some aspects of heterogeneity are incorporated in random effect models, and are preferred to the fixed effect method when the studies are heterogeneous. Both models give almost similar results, except that the confidence interval is generally wider in the random effect model as compared to the fixed-effect model (Sutton et al., 2000, p. 360).

In this meta-analysis, random effects model is used because of potential diversity among the studies. Comprehensive Meta-Analysis (Version 2) software provided options for analyzing data both by fixed-effect model and random effects model.

Random effects model is appropriate when the primary studies belong to different populations. In my dissertation, the population of various studies included in meta-analysis was heterogeneous and differed from one another. Thus, random effects model was the choice for calculating effect sizes. I prespecified use of the random effects model because the studies were from different populations and had different designs such as cohort and case-control studies (Flenady et al., 2011). Random effects model addresses variation in study effects, due to variation in the effect sizes across primary studies as a result of various factors such as ages and ethnicities of the study population. Moreover, a random effects model balances weights across large and small primary studies in a more appropriate manner (Borenstein et al., 2009). Various researchers have used random effects models for meta-analysis on similar topics (Chu et al., 2007; Poel et al., 2012; Wendland et al., 2012). Thus, random effects model was the most appropriate choice for this study. Effect estimates were combined with random effects method in the software, which yielded pooled adjusted odds ratios (aOR) and associated 95% CIs. I pooled outcomes from primary studies calculating the OR for each outcome, and statistical significance for overall effect was tested by *Z* test with the conventional significance level of $p < 0.05$. CMA software has the option of calculating *Z* test according to specified significance levels.

Subgroup Analysis

Some studies included in the meta-analysis reported outcome measures according to various sub-groups such as outcome measures according to type of diabetes. Thus, sub-group meta-analyses for the main outcomes was performed. For each outcome, the sub-groups were defined as those with different types of diabetes. The results were considered statistically significant at the conventional value of $p < 0.05$.

Assessing Heterogeneity

Heterogeneity is the extent of variation of effect sizes among primary studies (Peticrew & Roberts, 2006). A meta-analysis addresses a broader question than those addressed by the included primary studies. Thus, there is expected diversity among the included studies. It is important to anticipate this diversity and interpret the findings of the meta-analysis accordingly (Borenstein et al., 2009, p.358). For this purpose, statistical tests such as Cochrane's *Q* statistic and *I*-squared are used to assess heterogeneity.

Cochrane's *Q* statistic tests the statistical significance of the inconsistency among studies. If the results are statistically significant, the studies are considered heterogeneous. The *Q* statistic determines the sum of the between-studies variance relative to within-studies variance. If the effects are homogeneous, that is, if the total variance is no more than expected on the basis of the variance within-studies, then the expected value of *Q* would equal the degrees of freedom (the number of studies minus 1; Borenstein et al., 2009). For a statistically non-significant *Q* statistic, studies are considered homogeneous. Although *Q* statistic is commonly used for assessment of heterogeneity among studies, the test has certain limitations.

Experts have expressed reservations about the use of *Q* statistic because of both technical and conceptual problems (Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006). One technical problem is the fact that the *Q* statistic is not intuitive. A *Q* value of 10 could represent a high amount of dispersion in a meta- analysis with fewer studies, and little or no dispersion in another with a greater number of studies. Therefore, *Q* does not lend itself to simple interpretation. Moreover, the *Q* statistic serves as a test of the null, and like other tests of significance, it may not be significant because of low statistical power. In contrast, it may be statistically significant if many studies are included in the meta-analysis even if the dispersion is minimal (Borenstein et al., 2009). Because of these limitations, certain alternative for assessing heterogeneity among studies may also be considered.

An alternative statistic for assessment of heterogeneity is *I*-squared (Borenstein et al., 2009). It measures the extent of total variation across primary studies because of heterogeneity. It describes the heterogeneity in percentage. *I*-squared is an index, defined as variance (between studies) /variance (total). This is equivalent to true/total variance. The strength of this index is that the number of studies in the meta-analysis do not directly affect it. The index is multiplied by 100 and reported on a scale of 0 to 100 (Borenstein et al., 2009). Various researchers have used *Q* statistic as well as *I*-squared to assess heterogeneity in the meta-analysis (Balsells, García-Patterson, Gich, & Corcoy, 2012; Flenady et al., 2011; Horvath et al., 2010; Poel et al., 2012; Tobias et al., 2010; Wendland et al., 2012). In the current study, to assess heterogeneity in the meta-analysis, I used both *Q* statistic and *I*-squared, computed by the data analysis software. The *Q*

statistic tests the existence of heterogeneity while *I*-squared also determines the extent of heterogeneity and quantifies its magnitude. It is crucial to assess heterogeneity in meta-analysis because the decision to select the fixed or random-effects model in a meta-analysis may be based on the result of a homogeneity test (Huedo-Medina et al., 2006). For this meta-analysis, the decision to use random-effects model was made apriori because of the diversity of the population studied, however, assessment of heterogeneity helped in providing statistical support to this decision. Moreover, quantification of magnitude of heterogeneity by *I*-squared was helpful in interpreting the results of the meta-analysis. For example, a value of 50% for *I*-squared means that sampling error is responsible for half of the total variability among effect sizes while half of it is caused by true heterogeneity between studies.

Sensitivity Analysis

A sensitivity analysis is a technique employed to examine the robustness of the results of analysis of data (Borenstein et al., 2009). In a meta-analysis, study design and sample size should be taken into account as potential sources of biased results. Extremely large or small sample sizes or effect size on extremes can lead to skewed results (Borenstein et al., 2009). Sensitivity analysis is carried out to explore the ways in which selection of the studies and synthesis of data may have affected the overall results. It also explores the effect of excluding various categories of studies. It may also examine the extent of consistency of the results across various subgroups (Crombie & Davies, 2009). Thus, sensitivity analysis is an important component of meta-analysis, to assess the robustness of the results.

Sensitivity analysis can be used to examine the changes in results by using varied study inclusion rules. An outlier study may be examined to see its effects on the results of meta-analysis. Thus, it can show the variation in results on omitting a single study or some studies. Sensitivity analysis may also examine the effect of selection of the statistical methods used on the overall results of the analysis. For example, examining the difference in the overall result on using a different effect size measure such as a risk ratio in comparison to an odds ratio. Sensitivity analysis may also examine if the overall results would be the same if fixed-effect models had been used instead of random-effects models (Borenstein et al., 2009). In this study, sensitivity analyses was performed to assess variation in effect size caused by study design, sample size and country of study. The influence of outliers was also evaluated to determine the affect of their omission on overall results (Tobias et al., 2010).

Assessment of Publication Bias

A key concern in meta-analysis is publication bias, as the researches with non-significant or negative findings are less likely to be accepted for publication (Palma & Delgado-Rodriguez, 2005). Possible presence of publication bias can be evaluated by funnel plot (Egger et al., 1997). In funnel plot, the studies included in the meta-analysis are displayed in a plot of effect size against sample size. Funnel plot should display the picture of a symmetrical inverted funnel as chance variability is more in smaller studies as compared to studies with larger sample size. If the plot is asymmetric, this suggests that some studies might have been missed in the meta-analysis. The funnel plot has some limitations, such as difficulty in visual detection of asymmetry (Terrin, Schmid, & Lau,

2005). Certain statistical methods are also available to test for heterogeneity. Egger's regression test is commonly used to test for publication bias (Crombie & Davies, 2009).

In this study, publication bias was assessed using both funnel plot and Egger's test (Wendland et al., 2012). For publication bias, a visual inspection of the funnel plot was performed, looking for an asymmetric picture (Tobias et al., 2010). Funnel plot asymmetry was assessed with statistical methods (Balsells et al., 2012; Mao, Li, & Gao, 2012). Egger's test, using a significance level of $p < 0.05$, was used to determine significant asymmetry.

Software

Comprehensive Meta-analysis (CMA) [Version 2] was used for computation of effect sizes as well as for computation of statistics such as *p*-values, confidence intervals, *Q* statistics and *I*-squared. Forest plot and funnel plots were also created utilizing this software.

Data Analysis Plan for Individual Research Questions

Data analysis plan for each research question along with the hypothesis is described below:

Research Question 1. Is there an association between the presence of GDM/ PGDM and delivery by cesarean section among women in the EMR?

H_{01} - There is no association between the presence of GDM/ PGDM and delivery by cesarean section among women in the EMR

H_{A1} - There is an association between the presence of GDM/PGDM and delivery by cesarean section among women in the EMR

***Data analysis plan*.** Odds ratio was the primary metric for the calculation of effect size regarding the association between GDM/PGDM and delivery by cesarean section among women in the EMR. A weighted average of the ORs in the studies was computed. For combining effect sizes of primary studies, random effects model was used because of potential diversity among the studies. Effect estimates were combined with random effects method in Comprehensive Meta Analysis (CMA) software [Version 2], which yielded pooled adjusted odds ratios (aOR) and associated 95% CIs. I will pool outcome regarding caesarean section from primary studies calculating the OR, and statistical significance for overall effect was tested by Z test with significance level at $p < 0.05$.

Some studies included in the meta-analysis reported occurrence of caesarean section according to type of diabetes (GDM and PGDM). Sub-group meta-analyses for the occurrence of caesarean section according to the type of diabetes was performed. The results were considered statistically significant at $p < 0.05$. A sensitivity analysis was employed to examine the robustness of the results. Sensitivity analyses was performed to assess variation in effect size caused by study design, sample size and country of study. The influence of outliers was also be evaluated to determine the affect of their omission on overall results.

Research Question 2. Is there an association between GDM/PGDM and adverse fetal outcomes among women in the EMR?

Research Question 2a. Is there an association between GDM/PGDM and macrosomia among women in the EMR?

H_{02a} - There is no association between GDM/PGDM and macrosomia among women in the EMR

H_{A2a} - There is an association between GDM/PGDM and macrosomia among women in the EMR

***Data analysis plan*.** Odds ratio was the primary metric for the calculation of effect size regarding the existence of association between GDM/PGDM and macrosomia among women in the EMR. Random effects model was used for merging effect sizes because of potential diversity among the studies. Effect estimates were combined with random effects method in the data analysis software, which yielded pooled adjusted odds ratios (aOR) and associated 95% CIs. I pooled outcome regarding macrosomia from primary studies calculating the OR, and statistical significance for overall effect will be tested by *Z* test with significance level at $p < 0.05$.

Sub-group meta-analyses for the occurrence of macrosomia according to the type of diabetes was performed. The sub-groups were defined as those with different types of diabetes. The results were considered statistically significant at $p < 0.05$. A sensitivity analysis was employed to examine the robustness of the results, and to assess variation in effect size caused by study design and sample size.

Research Question 2b. Is there an association between GDM/PGDM and perinatal mortality among women in the EMR?

H_{02b} - There is no association between GDM/PGDM and perinatal mortality among women in the EMR

H_{A2b} - There is an association between GDM/PGDM and perinatal mortality among women in the EMR

***Data analysis plan*.** Odds ratio was the primary metric for the calculation of effect size regarding the existence of association between GDM/PGDM and perinatal mortality among women in the EMR. Random effects model was used for merging effect sizes. Pooled adjusted odds ratios (aOR) and associated 95% CIs were obtained by combining effect estimates with random effects method in the data analysis software. The statistical significance for overall effect was tested by Z test with significance level at $p < 0.05$.

Sub-group meta-analyses for the occurrence of perinatal mortality according to the type of diabetes was performed. The sub-groups were defined as those with different types of diabetes. The results were considered statistically significant at $p < 0.05$. Sensitivity analyses was performed to assess variation in effect size caused by study design, sample size and country of study. The influence of outliers was also evaluated to determine the affect of their omission on overall results.

Threats to Validity

Meta-analyses have limitations like all other types of research (Garg et al., 2008). There are threats to the validity by factors that might lead to incorrect inferences (Cooper, Hedges, & Valentine, 2009). There may be threats to construct validity, internal validity, statistical conclusion validity, and external validity. These threats to validity are discussed as follows:

Construct Validity

It is important for meta-analysis that the effect sizes calculated from various measures can be compared directly (Nugent, 2009). For this purpose, definitions of variables should be consistent in the primary studies and meta-analysis. In my study, there were certain threats to construct validity, as the definitions used in the primary studies were not consistent. For example, the criteria for diagnosis of GDM were not consistent in primary studies. This is because of lack of consensus on the diagnostic criteria and due to changing criteria for GDM in different periods of time. Similarly, definition of macrosomia varied in primary studies; some studies using the cut-off weight of 4,000 grams while others using 4,500 grams for defining macrosomia. These threats to construct validity were addressed by discussing various definitions stated in primary studies while writing results in chapter 4, and while discussing the results in chapter 5.

Internal Validity

Internal validity refers to the validity of associations inferred from the results of the primary studies. Meta-analysis includes diverse studies differing in their designs and study participants. The meta-analysis cannot rectify issues with the design and implementation of the primary studies. It also cannot correct the biases in the primary studies (Garg et al., 2008). In addition to these general limitations of meta-analysis, there are certain specific limitations related to the types of study designs included in the meta-analysis. Meta-analysis of observational studies have certain specific limitations which are threats to internal validity. Estimates of association in observational studies may not depict true association because of various factors. In addition to the role of chance,

confounding factors, biases, or both may affect the results in observational studies. The exposed study participants may be different in various ways which are related to the risk of developing the outcome of interest (Egger, Smith, & Schneider, 2008). The effect of residual confounding is another threat to the validity of meta-analysis of observational studies (Flenady et al., 2011). This study included observational studies in meta-analysis. Thus, it had threats to internal validity because of general limitations related to meta-analysis as well as limitations specific to the meta-analysis of observational studies.

To address the threats to internal validity, it is important to adopt comprehensive search strategy to avoid bias in study identification and selection; and to assess the quality of the primary studies using appropriate criteria (Crombie & Davies, 2009). Following standard guidelines for reporting of meta-analysis such as MOOSE (Appendix A) and PRISMA (Appendix D) guidelines is important in addressing the threats to internal validity. All these measures were taken into consideration for my dissertation to address the threats to internal validity. Specific discussions relating to internal validity will be presented in chapter 5.

Statistical Conclusion Validity

Statistical conclusion validity refers to the application of appropriate statistical tests in primary studies (Cooper et al., 2009). The quality and reliability of the overall effect size and conclusions of meta-analysis depends on the reliability and appropriateness of methods used by the primary studies. The statistical results of the meta-analysis depend upon the statistical analysis conducted in primary studies. The statistical conclusion validity also implies correct application of analytic procedures in

meta-analysis, such as control of confounding factors by using logistic regression. To address the threat to statistical conclusion validity, it is important to assess the quality of the primary studies using appropriate criteria including statistical tests used for analysis. It is also important to use appropriate statistical methods for calculation of the combined effect size, and to consider and test for heterogeneity (Crombie & Davies, 2009). All these measures were taken into consideration for my dissertation to address the threat to statistical conclusion validity.

External Validity

External validity refers to the generalization of the results of meta-analysis (Cooper et al., 2009). Meta-analysis includes diverse studies differing in their study participants enrolled from various geographical regions. This study generalizes the results to the population of the EMR. The studies selected for inclusion in meta-analysis did not include studies from all countries in the EMR, leading to the threat to the external validity. To address this issue, an exhaustive literature search was conducted to include available studies from different countries of the region. In addition to electronic searches, local libraries were contacted. When required, the authors of relevant journal articles were also contacted to obtain the relevant article.

Ethical Procedures

This study is a meta-analysis which provides an opportunity to learn more from the published data and increase the benefits of conducted studies. Thus, time and efforts of the human participants involved in the primary studies entering into the meta-analysis are said to be more justified when their data enter into a meta-analysis (Rosenthal, 1994).

The meta-analysis increases the utility of the primary studies. Other costs of primary studies such as those of funding, researcher time and effort, and other resources are also said to be more justified because the utility of primary studies is enhanced by the strength obtained by combining the results from other studies (Rosenthal, 1994).

This study used data obtained from previously published studies. Thus, the issues of confidentiality and anonymity were not relevant as these issues were already addressed by the authors, reviewers and editors of the published articles. There were no associated conflicts of interest. Although ethical concerns were minimal, ethical review board approval was obtained before proceeding with data management. I obtained Walden Institutional Review Board approval (number: 11-11-13-0137511) for my study.

Summary

This chapter contained an explanation of the research study, research questions and hypotheses, and other pertinent issues related to the meta-analysis. Meta-analysis is a statistical method for synthesizing the results of relevant primary studies by utilizing scientific literature search strategies. This meta-analysis included studies from most countries of the EMR, conducted in various periods of time in varied settings. A comprehensive search strategy with explicit criteria for the inclusion and exclusion of studies was used. Several research databases, such as MEDLINE, ProQuest and EBSCOhost, were used to obtain primary studies for inclusion in meta-analysis. Journal articles were selected by reviewing the abstract and assessing if it meets the selection criteria for meta-analysis. When an abstract potentially met the criteria, the full text article was reviewed to find out if it fitted into the designated criteria. The data were

abstracted by using data abstraction form. For reporting of meta- analysis, I followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000) and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

Description of literature search strategy, selection criteria for the studies, data abstraction, and quality assessment of studies for inclusion in the meta-analysis were provided in this chapter. Important statistical aspects including effect size computation, assessment of heterogeneity, sub-group analysis, and sensitivity analysis were explained. Furthermore, limitations of meta-analysis and various measures to address these limitations were also discussed. Chapter 4 will discuss the data analysis and results of the study.

Chapter 4: Results

Introduction

The purpose of this study was to determine the association of GDM/PGDM with adverse pregnancy outcomes among women in the EMR. Given the rising prevalence of PGDM and GDM in the Middle Eastern countries, it is important to be aware of the severity and seriousness of the problem. Determining the magnitude of association between adverse pregnancy outcomes and GDM/PGDM is an important initial step for developing appropriate interventions. Proper interventions for improvement of outcomes in GDM/PGDM will result in healthier mothers and children in Middle Eastern countries and thus leading to a healthier and more productive community. To determine the magnitude of association between adverse pregnancy outcomes in GDM/PGDM, certain outcomes were specified, and the research questions were constructed around them.

There were two research questions for this study First question was related to adverse maternal outcome and determined an association between GDM/PGDM and birth by caesarian section among women in the EMR. Second question was whether there is an association between GDM/PGDM and adverse fetal outcomes among women in the EMR. Two adverse fetal outcomes were explored for association with GDM/PGDM among women in EMR. These adverse fetal outcomes included macrosomia and perinatal mortality.

This chapter presents findings on the pregnancy outcomes of 118,652 women, including (a) 9,288 women with GDM/PGDM and (b) 109,364 without GDM/PGDM, all of whom were participants in 33 observational studies that examined the pregnancy

outcomes of women with GDM/PGDM in the Eastern Mediterranean countries. This chapter explains the procedures for data collection, describes studies included in the meta-analysis, and discusses the results of the meta-analysis, including sub-group analysis, moderator analysis, and public bias.

Data Collection

Procedures for Data Collection

I conducted a systematic review of published journal articles providing original data on pregnancy outcomes in GDM/PGDM among women in the EMR. According to the standard protocol outlined by MOOSE (Stroup et al., 2000) and PRISMA guidelines (Moher et al., 2009), the background; research questions and methods of meta-analysis; inclusion and exclusion criteria for primary studies; search strategy for finding relevant research; and statistical procedures were stated in chapter 3.

In this meta-analysis, independent variables are GDM and PGDM. The dependent variables for maternal outcome are delivery by cesarean section. The dependent variables for neonatal outcomes are macrosomia (birth weight > 4000 g)/large for gestational age (LGA; birth weight > 90th percentile for their gestational age), and perinatal mortality. To identify relevant literature including these independent and dependent variables, I followed a comprehensive literature search strategy which is described in the next section.

Search Strategy for Relevant Studies

To identify all available relevant research, I conducted a comprehensive literature search in several research databases in a systematic manner, for studies published on

GDM/PGDM in the EMR. Moreover, relevant journals and the reference lists of relevant papers were also hand searched. Explicit criteria for inclusion or exclusion of studies were used for meta-analyses. Important keywords capable of identifying relevant research were used as search terms. As discussed in detail in Chapter 3, important keywords were used to search electronic databases, search engines and relevant websites. The medical journals of the EMR such as Eastern Mediterranean Health Journal by World Health Organization, Annals of Saudi Medicine, Saudi Medical Journal and Saudi Journal of Family and Community Medicine were hand-searched in the local libraries. The reference lists of relevant literature were also examined, to identify studies eligible for inclusion in the present meta-analysis.

Studies were included if they fulfilled the inclusion criteria. The criteria used for the exclusion and inclusion of studies in the meta-analysis for estimating the association of GDM/PGDM with adverse maternal and fetal outcomes were discussed in Chapter 3. The steps in literature search strategy are listed as follows:

Steps in Search Strategy

- All titles were considered for eligibility.
- I screened the abstract of relevant title identified by the search for possible inclusion in the meta-analysis.
- Whenever an abstract seemed that the journal article may meet the inclusion criteria, the corresponding full text was reviewed, and the inclusion and exclusion criteria applied.

- References of review articles and bibliographies of relevant retrieved studies were searched for additional relevant studies.
- Studies identified through additional search activities were reviewed to identify duplicates of articles retrieved earlier.
- Data on characteristics of study participants and outcomes (caesarean section, macrosomia and perinatal mortality) listed in research questions were abstracted.

Documenting the Search Process

I maintained a complete record of literature search and data collection process. The record included information about search time periods; research databases; search engines; keywords; and search results. Studies were searched mainly through the Walden University library system. Journal articles not available in Walden Library were requested by document delivery system. If electronic copies were not available, print copies of the journal articles were obtained from local libraries or by personal request to the authors of that journal article. Two articles (Al Teheawt & Farida, 1995; Denguezli et al., 2007) could not be obtained by document delivery system. One of them (Al Teheawt & Farida, 1995) was obtained by personal request, from the local library in Egypt. The other (Denguezli et al., 2007) was obtained by requesting the author via e- mail. The author emailed scanned copy of the requested journal article.

The search strategy retrieved 12,188 records. I considered all titles for eligibility. The abstracts of all relevant titles were reviewed. Whenever an abstract seemed that the journal article could meet the inclusion criteria, I assessed the corresponding full text, to find out if it fits into the designated criteria. On title review, 170 abstracts were eligible

for review. On reviewing the abstracts, 69 full-text journal articles seemed to meet inclusion criteria. Thus, 69 full-text journal articles were examined for inclusion criteria. Of these studies, 36 (52.2%) did not qualify for the meta-analysis and were excluded. The search strategy is summarized in Figure 1.

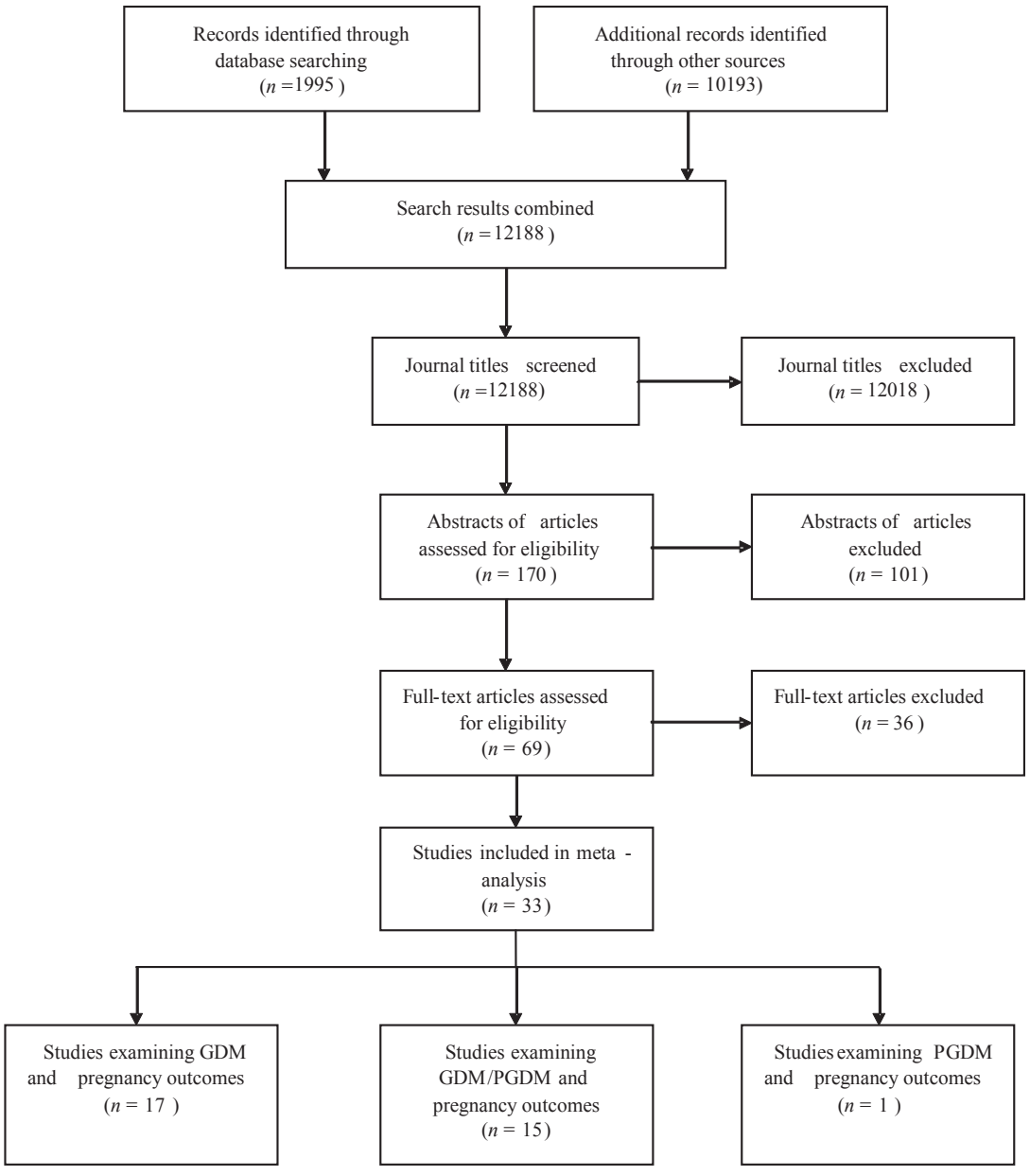

Figure 1. Flow chart of article elimination for journal articles in meta-analysis.

I maintained a record of excluded studies along with the reason for exclusion. Table 3 shows brief information about each article and the reasons for exclusion of that article. The most common reason of exclusion of articles (18 or 50%) was that they did not have a control or comparison group. Other reasons were that the articles discussed the prevalence and/or incidence of PGDM/GDM and their risk factors, or the specific outcomes of interest were not measured or were excluded from the study. For some excluded articles, abstract was available in English while the full text was only available in Persian language.

Table 3

Thirty Six Studies of GDM/PGDM Outcome Excluded from Meta-Analysis

Study	Data of interest	Reason excluded
Akhlaghi & Hamedi, 2005	Studied maternal and fetal outcomes in 73 women with GDM and 27 women with PGDM.	Compared pregnancy outcome of women with GDM with those of PGDM; did not have a control/ comparison group of women without GDM/PGDM
Al Busaidi, Al-Farsi, Ganguly, & Gowri, 2012	Caesarean section as an obstetric outcome, was studied ; one of the risk factors for caesarean section was PGDM.	Case-control study with cases as women delivered by caesarean section while controls as women who did not deliver by caesarean section.
Al Mahroos, Nagalla, Yousif, & Sanad, 2005	Studied birth weight of children and macrosomia born to women with GDM.	Did not have a control/ comparison group of women without GDM.
Al Najashi & Al Umran, 1997	466 women with GDM/PGDM were studied; fetal outcome (congenital anomalies among infants of diabetic mothers) was studied.	Did not study outcomes of interest included in this dissertation.
Al-Dabbous, Owa, Nasserallah, & al-Qurash, 1996	Studied perinatal mortality in 133 women with GDM and PGDM.	Compared perinatal mortality in the study population with perinatal mortality of the hospital during the same duration of study, however, the sample size for control group (total number of deliveries in the hospital) was not available.
Al-Hakeem, 2006	685 women with GDM were studied; maternal outcome (caesarean section) and fetal outcome (still birth) reported.	Did not have a control/ comparison group of women without GDM.
Almarzouki,	78 women with GDM were studied;	Did not have a control/ comparison group

Study	Data of interest	Reason excluded
2012	maternal outcome (caesarean section) and fetal outcome (macrosomia and perinatal mortality) reported.	of women without GDM.
Al-Sultan, Anan, & Ahmed, 2004)	76 women with GDM were studied; risk factors for GDM and reasons for hospital admission were studied	Did not study outcomes of interest included in this dissertation
Ayaz, Saeed, Farooq, Ali Bahoo, & Hanif, 2009	76 women with GDM were studied; maternal and fetal outcomes according to the gestational age at the time of diagnosis studied.	Study population divided into three groups according to the gestational age at the time of diagnosis; these three groups were compared in terms of pregnancy outcomes; did not have a control/ comparison group of women without GDM.
Beigi, Yazdani, & salehi, 2007	70 women with GDM were studied; maternal and fetal outcomes were studied and compared with women without GDM.	Full text article in Persian language.
El-Gilany & Hammad, 2010	787 pregnant women (normal weight, overweight and obese) were studied; GDM and caesarean section as outcomes of body mass index (BMI) were stated.	GDM and caesarean section in relation to BMI were studied.
Elnour & McElnay, 2010	165 women with GDM were studied; caesarean section and macrosomia was studied.	Effect of various values of diagnostic criteria on pregnancy outcomes discussed; did not have a control/ comparison group of women without GDM.
Garshasbi, Faghihzadeh, Naghizadeh, & Ghavam, 2008	1804 pregnant women were screened for GDM; and 124 women with GDM were studied.	Prevalence and risk factors of GDM were studied; outcomes of interest in relation to women with GDM and those without GDM was not studied.
Hindi, Gazzaz, Barhamin, Dhafar, & Farooq, 2012	118 women with GDM and PGDM were studied. Caesarean section rate was studied.	Caesarean section rate among women with GDM and PGDM was studied. Did not have a control/comparison group of women without GDM and PGDM.
Hossein-nezhad et al., 2011	293 women with GDM were studied. Pregnancy-induced hypertension was studied as maternal outcome.	Comparison of incidence of hypertensive disorders in pregnant women with GDM and those without GDM. Did not study outcomes of interest included in this dissertation.
Hussain, Irshad, Khattak, & Khan, 2011	42 women with GDM and PGDM were studied; caesarean section, macrosomia and perinatal mortality rate were studied.	Did not have a control/comparison group of women without GDM and PGDM.
Jaber, 2006	47 newborns of women with GDM and PGDM were studied; caesarean section rates and plasma leptin level of the newborns were the outcome of interest.	Study population was newborns admitted in nursery according to the diabetic status of the mother. The study discussed caesarean section rates in this group but the enrollment is of children admitted in

Study	Data of interest	Reason excluded
		the neonatology ward.
Kadiki, Reddy, Sahli, Shawar, & Rao, 1993	988 women with GDM and PGDM were studied. Caesarean section rates and perinatal mortality discussed in relation to level of control of diabetes.	Women with GDM and PGDM were divided into two groups of well- controlled diabetes and poorly controlled diabetes. Did not have a control/comparison group of women without GDM and PGDM.
Kamali, Shahnam, Poormemari, 2003	13 women with GDM were studied. Macrosomia and still birth were studied.	Full text article in Persian language.
Keshavarz & Babaei, 2004	63 women with GDM were studied. Caesarean section rates, macrosomia and still birth were studied.	Full text article in Persian language.
Khan, 2012	229 newborns with birth weight $\geq$ 3,500 grams born to women with GDM/PGDM (72) and those without GDM/PGDM (157) were studied. Caesarean section rates and perinatal mortality were studied.	Caesarean section rates and perinatal mortality in relation to macrosomia were studied.
Kheir, Berair, Gulfan, Karrar, & Mohammed, 2012	50 newborns born to women with GDM/PGDM were studied. Caesarean section rates were studied.	Did not have a control/ comparison group of women without GDM and PGDM.
Marssussi & Darban Hosseini, 1999	56 women with GDM/PGDM were studied. Macrosomia was studied.	Full text article in Persian language.
Mazhar, Saleh, & Rennie, 2003	386 women were studied (17 with type 1 diabetes; 86 with type 2 diabetes; and 116 with GDM). Discussed caesarean section rate and perinatal mortality rate in the study population.	The article had no comparison group but had given the background figures for hospital, however, the denominator for total number of deliveries in the hospital was not available. Thus, the sample size for control group was not available.
Meher-un-nisa, Aslam, Ahmed, Rajab, & Kattea, 2009	1000 pregnant women divided into 5 groups depending upon their BMI (< 18.5, 18.5-24.9, 25-29.9, 30-39.9 &>40, classified as underweight, normal weight, overweight, obese & morbidly obese respectively), were studied. Caesarean section rates and macrosomia were studied.	Effect of various values of BMI on pregnancy outcomes discussed. Did not have a control/ comparison group of women without GDM/PGDM.
Misra, Rashid, Grundsell, & Sedagathian, 2001	129 women were studied (82 with GDM and 47 with PGDM). The article compared GDM and PGDM outcomes including caesarean section, macrosomia and perinatal mortality	The article compared GDM and PGDM outcomes. A table illustrated comparison of all diabetic pregnancies with normal pregnancies, however, the denominator for total number of deliveries in the hospital was not available. Thus, the sample size for control group was not available.

Study	Data of interest	Reason excluded
Najafian & Cheraghi, 2012	1800 newborns with macrosomia were studied.	Macrosomic infants as cases and non-macorosomic infants as controls, were studied. Association of macrosomia with diabetes mentioned but diabetes was considered a risk factor for macrosomia.
Narchi & Kulaylat, 1997	1870 infants born to women with GDM/PGDM were studied; Down's syndrome was studied as fetal outcome.	Down's syndrome and its association with diabetes was studied. Did not study outcomes of interest included in this dissertation.
Nasrat, Augensen, Abushal, & Shalhoub, 1994	212 women with impaired glucose tolerance test were studied. macrosomia was studied.	Outcomes of pregnancy in patients with impaired glucose tolerance test were studied.
Nili & Mahdaviani, 2004	107 infants born to women with GDM/PGDM were studied. Macrosomia was studied.	Did not have a control/ comparison group of women without GDM/PGDM.
Rajab & Mehdi, 1998	725 pregnant women with raised blood glucose level (>7.7 mmol/l) were studied. Pregnancy outcomes such as macrosomia was discussed .	Macrosomia was discussed in relation to various categories of raised blood glucose levels.
Rajab, Issa, Hasan, Rajab, & Jaradat, 2012	4982 pregnant women with GDM were studied.	Incidence and risk factors of GDM were studied; Did not study outcomes of interest included in this dissertation.
Randhawa, Moin, & Shoaib, 2003	50 women with GDM/PGDM were studied; still births and neonatal deaths discussed.	Did not have a control/ comparison group of women without GDM/PGDM.
Saleh et al., 2008	766 newborns with macrosomia were studied.	Study population was newborns with macrosomia. Newborns with macrosomia were grouped according to being born to women with GDM/PGDM or women without GDM/PGDM.
Sobande, Eskandar, Eskander, & Archibong, 2005	155 women with GDM/PGDM were studied. Pregnancy outcomes such as caesarean section and perinatal mortality rate was compared between women with Type 1, type 2 and GDM.	Did not have a control/ comparison group of women without GDM/PGDM.
Yaseen et al., 1999	188 newborns of women with GDM/PGDM were studied. Macrosomia was studied.	Did not have a control/ comparison group of women without GDM/PGDM; determined the predictive factors of morbidity in infants of women with GDM/PGDM.

Details of the Studies Included in the Meta-analysis

For maintaining details of studies included in the meta-analysis, the guidelines for reporting meta- analysis of observational studies was followed (Stroup et al., 2000). A summary table was created to record the main elements of each study such as relevant bibliographic information, the studies' design, type(s) of diabetes mellitus, age group/ mean age of women and outcome data. In addition, any other pertinent information about the study was also included (Table4).

Description of Included Studies

Thirty three articles fulfilled the inclusion criteria and were included in the meta-analysis. Countries of origin of included journal articles were Egypt, Iran, Jordan, Kuwait, Oman, Pakistan, Qatar, Saudi Arabia, Sudan, Tunisia, and United Arab Emirates. A total of 17 studies included women with GDM while 15 included women with GDM/PGDM and one study included women with PGDM only. Out of the 15 studies including women with both GDM and PGDM, 8 studies discussed and analyzed the outcomes in GDM and PGDM separately while 7 studies did not differentiate between GDM and PGDM, and mentioned the participants as women with diabetes. A total of 118,652 pregnant women were included in these studies. The studies including women with GDM had a total of 53,744 pregnant women while those including women with GDM/PGDM included 62,320 pregnant women. There were 2,588 pregnant women in the study including women with PGDM. A total of 27 studies examined the association of GDM/PGDM with caesarean section while 26 studied macrosomia and 24 studies observed perinatal deaths.

Table 4 illustrates the information on authors and year of article publication, country of study, duration of study; maternal characteristics (age and type of diabetes); and selected maternal and fetal outcomes described in the study. All 33 studies included in this meta-analysis were published in scholarly, peer-reviewed journals. Their publication year ranged from 1988 to 2013. The attributes of the studies included in the meta-analysis are described as follows:

Country of origin. Twelve (37%) studies were conducted in Saudi Arabia, five (15%) in Iran, five (15%) in Pakistan, two (6%) in Kuwait, two (6%) in Qatar, two (6%) in Sudan, one (3%) in Egypt, one (3%) in Jordan, one (3%) in Oman, one (3%) in Tunisia, and one (3%) in UAE. Thus, out of a total of 22 countries in the EMR,11(50%) countries are represented in this meta-analysis.

Duration of study. The duration of the studies ranged from a minimum of 3 months (Diejomaoh et al., 2009) to a maximum of 30 years (Badakhsh et al., 2012). In two studies (Abolfazl et al., 2008; Al Teheawt & Farida, 1995) year in which study was conducted was mentioned, however, the duration of the study was not mentioned. One of the studies (Ezimokhai, Joseph, & Bradley-Watson, 2006) was conducted for two 18-month periods, 5 years apart.

Research design. A total of 33 studies were included in this meta-analysis, of which 14 (42.4%) case- control, 10 (30.3%) cross-sectional including retrospective review of the hospital/ medical records and 9 (27.3%) cohort studies were included in the meta-analysis. All studies were hospital-based. All studies except one (Fadwa, Shawqi, Asma, Nabil, Adel, & Kamel, 2013) collected data from hospital records. Fadwa et al.

(2013) collected data from women with diabetes and those without diabetes through structured questionnaires.

Study participants. There were a total of thirty three studies, and 118,652 participants were included in this meta-analysis. Minimum number of participants in any single study was 138 (Abdelgadir et al., 2003) while the maximum number was 37,997 women (Badakhsh et al., 2012). A total of 28 studies mentioned the sample size for GDM patients. Total number of women with GDM in these studies was 6,192 with a minimum number of women with GDM as 19 (Abdelgadir et al., 2003) while the maximum number of women with GDM was 972 women (El Mallah, Narchi, Kulaylat, & Shaban, 1997). A total of 11 studies stated the sample size for PGDM patients. Total number of women with PGDM in these studies was 929, with a minimum number of women with PGDM as 18 (Jawad & Irshaduddin, 1996) while 161 women was the maximum number of women with PGDM (Johnstone, Nasrat, & Prescott, 1990). Four studies did not differentiate between GDM and PGDM and labeled the study participants as women with diabetes and those without diabetes. These studies included 1,026 women in the study by Al-Mejhim & Al-Najashi, 1998; while Fadwa et al. (2013) included 750 women with diabetes; Denguezli et al., (2007) studied 200 women; and Nasrat et al. (1993) had a total of 193 women with diabetes in their study.

Majority of the studies had mentioned the mean age of study participants. The mean age of women without GDM/PGDM ranged from 25.2 ± 5.1 to 33.2 ± 6.8 years. The mean age of women with GDM ranged from 29.3 ± 5.7 to 33.5 ± 5.7 years. Two studies stated the age of women with PGDM. Wahabi et al. (2012) stated the mean age of

women with PGDM as 34.95 ± 5.66 years, while Abdelgadir et al. (2003) mentioned the mean age of women with Type I diabetes as 28.8 ±5.8; while those with Type II diabetes as 34.4 ±4.0 years. Fadwa et al. (2013) did not differentiate between PGDM and GDM and mentioned the mean age of women with diabetes as 34.7 ± 4.67 years in comparison to those without diabetes as 32.9 ± 5.26 years.

Table 4

Characteristics of Observational Studies of Pregestational/Gestational Diabetes and Adverse Pregnancy Outcomes in Eastern Mediterranean Region Included in Meta-Analysis

Author	Country	Study Design	Time Period	Sample size(n)	Type of Maternal Diabetes	Outcome	
						Maternal	Fetal
Abdelgadir, Elbagir, Eltom, Eltom, & Berne, 2003	Sudan	Case-control study	Duration 2 years; year of study not mentioned	138 women; 88 with diabetes (19 with GDM; 38 with type 1 diabetes; and 31 with type 2 diabetes); 50 without diabetes	Gestational Diabetes Mellitus (GDM) and Pregestational Diabetes Mellitus (PGDM)	C-section	Macrosomia (Large for gestational age) Perinatal mortality (Intrauterine fetal death and neonatal death)
Abolfazl, Hamidreza, Narges, & Maryam, 2008	Iran	Cohort study	2006	420 women; 70 with diabetes and 350 without diabetes	GDM	C-section	Macrosomia Perinatal mortality (Still births)
Al-Khalifah, AlFaleh, Al-Subaihin, Al-Kharfi, & Al-Alaiyan, 2012	Saudi Arabia	Case-control Study	January 2007-December 2007	766 women; 419 GDM and 347 without GDM	GDM	C-section	Macrosomia (Large for gestational age)

Author	Country	Study Design	Time Period	Sample size(n)	Type of Maternal Diabetes	Outcome	
						Maternal	Fetal
Almarzouki, 2013	Saudi Arabia	Case-control Study	June 01, 2008 - November 30, 2008	GDM = 69; High risk without GDM = 80	GDM	C-section	Macrosomia Large for gestational age Perinatal mortality
Al-Mejhim & Al-Najashi, 1998	Saudi Arabia	Cross-sectional Study	January 1987 - December 1996	28,507 women; 1026 with GDM/PGDM	GDM and PGDM		Perinatal mortality
Al-Shawaf, Moghraby, & Akiel, 1988	Saudi Arabia	Cross-sectional Study	June 1984 - December 1986	218 women; 177 with impaired glucose tolerance; 41 with GDM	GDM & Impaired Glucose Tolerance Test	C-section	Macrosomia
Al Teheawt & Farida, 1995	Egypt	Case - Control Study	1992	406 women; 203 cases (132 PGDM; 71 GDM); and 203 controls	GDM and PGDM	C-section	Macrosomia Perinatal mortality
Badakhsh et al., 2012	Iran	Cohort study	January 01, 1980 - December 31, 2009	37,997 women; 312 with GDM	GDM	C-section	
Barakat, Youssef, & Al-Lawati, 2010	Oman	Case - Control Study	January 1, 2004- December 31, 2004	5394 women; 225 with GDM; 56 with PGDM	GDM and PGDM	C-section	Macrosomia (High birth weight) Perinatal mortality (Still birth)
Bener et al., 2013	Qatar	Cross-sectional Study	January 2010- April 2011	1432 women; 227 with GDM	GDM	C-section	
Bener, Saleh, & Al-Hamaq, 2011	Qatar	Cohort study	January 2010 - April 2011	1608 women; 262 with GDM and 1346 without GDM	GDM	C-section	Macrosomia

Author	Country	Study Design	Time Period	Sample size(n)	Type of Maternal Diabetes	Outcome	
						Maternal	Fetal
Dafallah & Yousif, 2004	Sudan	Case - Control Study	January 1998 - December 2001	1280 women; 660 cases (130 PGDM; 230 GDM; 330 impaired glucose tolerance test); 620 controls	GDM and PGDM		Perinatal mortality (Still birth, Early Neonatal deaths)
Denguezli et al., 2007	Tunisia	Case-Control Study	January 01, 1999 - December 31, 2003	400 women; 200 with diabetes and 200 without diabetes	GDM and PGDM	C-section	Macrosomia
Diejomaoh et al., 2009	Kuwait	Case - Control Study	April 2005 – June 2005	177 with DM (128 with GDM; 49 PGDM) and 177 controls	GDM and PGDM	C-section	Macrosomia Perinatal mortality (Intrauterine fetal death)
El Mallah, Narchi, Kulaylat, & Shaban, 1997	Saudi Arabia	Cross-sectional Study	January 1991 - April 1994	972 women with GDM; 71 women PGDM	GDM and PGDM	C-section	Macrosomia Perinatal mortality (Still births)
Ezimokhai, Joseph, & Bradley-Watson, 2006	United Arab Emirates	Cross-sectional Study	Two 18-month periods; 5 years apart (June 1996 - December 1997 and June 2001 - December 2002)	11738 women; 905 with diabetes (802 with GDM; 103 PGDM)	PGDM and GDM	C-section	Macrosomia Perinatal mortality (Intrauterine fetal death)

Author	Country	Study Design	Time Period	Sample size(n)	Type of Maternal Diabetes	Outcome	
						Maternal	Fetal
Fadwa, Shawqi, Asma, Nabil, Adel, & Kamel, 2013	Jordan	Cross-sectional Study	September 2007 - January 2008	1500 women; 750 with diabetes	PGDM and GDM	C-section	Macrosomia Perinatal mortality (Intrauterine fetal death; Still birth; Neonatal Death)
Gasim, 2012	Saudi Arabia	Case - Control Study	January 2001 - December 2008	440 women; 220 with GDM and 220 without GDM	GDM	C-section	Macrosomia Perinatal mortality
Hossein-Nezhad, Maghbooli, Vassigh, & Larijani, 2007	Iran	Cross sectional study	2 years: study years not mentioned	2,416 women; 114 with GDM	GDM	C-section	Macrosomia Perinatal mortality (Still births)
Jawad & Irshaduddin, 1996	Pakistan	Cross sectional study	January 1990 - December 1992	5559 women; 192 with GDM	GDM		Perinatal mortality
Johnstone, Nasrat, & Prescott, 1990	Kuwait	Case - control study	1984 - 1986	731 cases and 731 controls	GDM and PGDM		Macrosomia Perinatal mortality (Still birth, early neonatal death, perinatal death and intrauterine fetal death)
Keshavarz et al., 2005	Iran	Cohort Study	December 1999 - January 2001	1310 women; 63 with GDM and 1247 without GDM	GDM	C-section	Macrosomia Perinatal mortality (Still birth)
Khan, Ali, & Khan, 2013	Pakistan	Cohort Study	February 2012 to December 2012	200 women; 103 with GDM and 97 without GDM	GDM	C-section	Macrosomia Perinatal mortality (Still birth)

Author	Country	Study Design	Time Period	Sample size(n)	Type of Maternal Diabetes	Outcome	
						Maternal	Fetal
Khan, Hashmi, & Rizvi, 1995	Pakistan	Case-control study	June 1988-June 1992	1292 women; 292 women with abnormal GTT ; 177 with GDM and 115 with Impaired Glucose Tolerance Test	GDM	C-section	Macrosomia
Khoshniatnikoo et al., 2010	Iran	Cohort study	July 2004 - September 2005	1801 women; 412 abnormal GCT/normal OGTT; 67 with Impaired Glucose Tolerance Test; 133 with GDM	GDM		Macrosomia
Nasrat, Abalkhail, Fageeh, Shabat, & el Zahrany, 1997	Saudi Arabia	Cross-sectional study	January 1991 - December 1992	51 newborns of women with GDM; 501 newborns of women without GDM	GDM and PGDM		Macrosomia
Nasrat, Fageeh, Abalkhail, Yamani, & Ardawi, 1996	Saudi Arabia	Case - control study	January 1991 to December 1992	510 women; 173 with GDM; 337 without diabetes	GDM	C-section	Macrosomia (fetal weight > the 90th centile of weight for gestational age) Perinatal mortality

Author	Country	Study Design	Time Period	Sample size(n)	Type of Maternal Diabetes	Outcome	
						Maternal	Fetal
Nasrat, Salleh, Ardawi, & Ghafouri, 1993	Saudi Arabia	Case - control study		384 newborns; 191 of women with diabetes and 193 of women without diabetes	GDM and PGDM	C-section	Macrosomia Perinatal mortality (neonatal death)
Rizvi, Rasul, Malik, Rehamatullh, & Khan, 1992	Pakistan	Case - control study	January 01, 1988-December 31,1989	2,230 women; 780 with GDM and 424 with impaired glucose tolerance test	GDM	C-section	Perinatal mortality
Sobande, Al-Bar, & Archibong, 2000	Saudi Arabia	Case-Control Study	January 1991-December 1992	166 women; 83 with diabetes (26 with PGDM and 57 with GDM); 83 without diabetes	GDM and PGDM	C-section	Perinatal mortality (Still birth, Early Neonatal deaths)
Tahir, Zafar, & Thontia, 2011	Pakistan	Cross-sectional study	August 2007 - August 2009	228 women; 111 without diabetes; 42 with mild gestational hyperglycemia, 75 with GDM	GDM	C-section	Macrosomia Perinatal mortality (Neonatal deaths and intrauterine fetal death)
Wahabi, Esmaeil, Fayed, Al-Shaikh, & Alzeidan, 2012	Saudi Arabia	Cohort Study	January 01, 2008-December 31, 2008	3,157 women; 116 women with PGDM	PGDM	C-section	Macrosomia Perinatal mortality (intrauterine fetal death)
Wahabi, Esmaeil, Fayed, & Alzeidan, 2013	Saudi Arabia	Cohort Study	January 01, 2010-December 31, 2010	3,041 women; 569 women with GDM	GDM	C-section	Macrosomia Perinatal mortality (intrauterine fetal death)

Data Abstraction

I reviewed each selected article that met the inclusion criteria and abstracted the data by using data abstraction form (Appendix C). I extracted information about the general study characteristics (study design, study period, country of study, and year of publication), study participants (number of study participants, maternal age, type of diabetes); the diagnostic criteria for GDM; and designated maternal and fetal outcomes. The study characteristics of included studies were entered and analyzed in Epi Info version 3.5.4.

The relative risks (RRs) and odds ratios (ORs) for the association with adverse pregnancy outcomes were abstracted, if stated. The unadjusted and adjusted RRs or ORs and 95% confidence intervals (CIs) were extracted as reported by authors. If not stated, then the RRs and ORs were calculated from information stated in each study. When raw quantitative data was not reported, values were obtained from the provided information. Dichotomous data reported as percentages were converted to counts and OR and RR were calculated. For each study, I constructed separate two-by-two tables to compute the ORs or RRs and 95% CIs of each outcome. Association of GDM/PGDM with caesarean section was observed for maternal outcome while macrosomia and perinatal mortality (intrauterine fetal deaths, stillbirths and neonatal deaths) were focused for fetal outcome. All information from the article review process were entered and analyzed in the data analysis software.

Issues during Data Abstraction

Several special situations arose while data abstraction. For this meta-analysis, subtypes of diabetes were classified as PGDM and GDM. However, various studies had used different classifications for diabetes, such as "Type I diabetes," or "insulin-dependent diabetes mellitus" "adult onset diabetes," "type II diabetes," or "noninsulin-dependent diabetes mellitus. All these categories were classified as PGDM for this meta-analysis. Some studies reported outcome data on women with type 2 DM and type 1 DM (Abdelgadir et al., 2003; Wahabi et al., 2012). In these cases, I merged the data of women with type 2 DM and type 1 DM and analyzed as PGDM. Some studies included women with impaired glucose tolerance test as cases (Al-Shawaf et al., 1988; Dafallah & Yousif, 2004; Johnstone et al., 1990; Khoshniat nikoo et al., 2010; Rizvi, Rasul, Malik, Rehamatuallh, & Khan, 1992), however, the analysis of these cases was presented separately. So women with IGTT were not included in this meta-analysis. Tahir et al. (2011) stated a category of mild hyperglycemia in 42 cases, but the data were analyzed separately and were not included in this meta-analysis. However, in two studies (Diejomaoh et al., 2009; Khan, Hashmi, & Rizvi, 1995) it was not possible to exclude the data of women with IGTT as the data analysis was not presented separately for these groups. In the study of Diejomaoh et al. (2009), among 177 cases with diabetes mellitus, 25 cases of IGTT were also included. Khan et al. (1995) had included 292 women with abnormal GTT in their study; out of which 177 were with GDM while 115 were with IGTT.

Some issues were faced regarding study participants. Researchers in a case-control study (Almarzouki, 2013) had included women with GDM as cases while the controls were high- risk women without GDM. Another special situation was noted in the study by Nasrat, Abalkhail, Fageeh, Shabat, & El Zahrany (1997). The aim of this study was to examine the clinical significance of subcutaneous deposition of fat in fetuses of mothers with gestational diabetes, however, the study stated the proportion of macrocosmic children in women with diabetes as well as those without diabetes in pregnancy. The data were extracted from that information.

The method of diagnosis of GDM varied across the studies. Various studies used different criteria for diagnosing GDM. Out of 32 studies including women with GDM, 6 (18.8%) had used WHO criteria; 4 (12.5%) had used Carpenter and Coustan criteria; 3 (9.4%) used O'sullivan's criteria; 2 (6.3%) used American Diabetes Association criteria; 2 6.3%) National Diabetes Data Group (NDDG) criteria; while one (3.1%) had used O'sullivan and Mahan criteria. Nine studies had given details of the diagnosis of GDM mentioning the cut-off points but did not name the criteria; while five studies did not state details of diagnosis.

Discrepancies in Definition of Outcome

Out of the total 33 studies, 26 had included macrosomia as fetal outcome. Twenty four studies stated definition of macrosomia. Various studies used different definitions of macrosomia. Ten studies defined macrosomia as birth weight more than 4 kg while six studies defined it as more than or equal to 4 kg. Two studies had defined macrosomia as more than 4.5 kg (Barakat et al., 2010; Johnstone et al., 1990). Some studies had used the

term of large for gestational age (Abdelgadir et al., 2003; Al-Khalifah et al., 2012; Almarzouki, 2013). Most studies defined large for gestational age as birth weight more than 90th percentile.

Out of the total of 33 studies, 24 studies discussed perinatal deaths. Twenty studies included a description of perinatal deaths. Various studies used different descriptions for perinatal deaths. Only one study (Almarzouki, 2013) defined perinatal mortality as fetal or neonatal death from 22 weeks of pregnancy to 4 weeks after birth. Al-Mejhim & Al-Najashi (1998) defined perinatal deaths as all stillbirths and all live babies who weighed 500 g or more and died in the first week of life. Still births/intrauterine fetal deaths and early neonatal deaths were described in 7 studies (Abdelgadir et al., 2003; Dafallah & Yousif, 2004; Fadwa et al., 2013; Jawad & Irshaduddin, 1996; Johnstone et al., 1990; Sobande et al., 2000; Tahir et al., 2011). Ten studies (Abolfazl et al., 2008; Barakat et al., 2010; Diejomaoh et al., 2009; El Mallah et al., 1997; Ezimokhai et al., 2006; Hossein-Nezhad et al., 2007; Keshavarz et al., 2005; Khan, Ali, & Khan, 2013; Wahabi et al., 2012; Wahabi, Esmaeil, Fayed, & Alzeidan, 2013) had included only still births/intrauterine fetal deaths. Nasrat et al. (1993) had included only neonatal deaths.

An important step in conducting meta-analysis is the assessment of quality of the included studies. In this meta-analysis, quality of studies was assessed by various criteria, outlined in Chapter 3. These criteria address issues related to the methods employed to select the study population, the appropriateness of the sample size, the methods for determining outcomes, and the appropriateness of the statistical analysis (Appendix E).

Quality Assessment of the Studies

Quality assessment of individual studies was performed using criteria based on various aspects of the study related to methods and results of the study. Quality scores were not generated as assigning quality score is largely an arbitrary and subjective process. Generally, quality scoring is based on reported information which may not be an accurate measure of the truth about an element of quality. Moreover, the reliability and validity of the quality rating scales have not been well evaluated (Taylor, 2005).

In this meta-analysis, the included studies were assessed for quality, however, no study was rejected on the basis of quality criteria. Separate criteria were laid down for case-control, cohort and cross- sectional study designs. Criteria such as adequate sample size; description of diagnostic criteria; clear definition of outcomes; appropriate statistical analyses; and power of the study were common for all study designs, and had similar definitions as described below:

Description of Diagnostic Criteria

The description of diagnostic criteria was considered appropriate if the author had provided the name of the method used for diagnosis of GDM such as WHO Criteria or American Diabetes Association Criteria. The description was also considered appropriate if the authors mentioned the procedure and cut-off values for diagnosing GDM even if the name of the diagnostic criteria were not mentioned. However, if the details were not provided clearly, then the description was considered “partially” appropriate. The description was considered inappropriate if no description for diagnosing GDM were provided.

Clear Definition of Outcomes

Out of the three outcomes studied in this meta-analysis, macrosomia and perinatal death were examined for a clear definition in the article. If one of these outcomes was defined, then it was considered to meet the criteria "partially", and if both the outcomes were clearly defined then this criterion was labeled as yes. If none of these outcomes was defined in the article then the criterion was labeled as no.

Power of the Study

Power of the study to detect statistically significant association of adverse outcomes among women with GDM/PGDM was calculated by using G-Power software. The power of each study was calculated by using the sample size of the smallest group for an outcome. If the sample size was similar in more than one outcome, then the group having the smallest number of events was used to calculate the power of the study. The criteria used in G-Power software, for calculation of power were as follows:

- type of power analysis: 'Post hoc: compute achieved power - given alpha, sample size and effect size;
- test family: z-test;
- statistical test: 'Proportions: Difference between two independent proportions'; and
- alpha: 0.05.

Adequate Sample Size

If the power of the study was $\geq$ 80%, then the sample size was labeled as adequate; for 60-80% power, sample size was considered 'partially' adequate while for power <60% the sample size was considered inadequate.

Appropriate Statistical Analyses

If the authors used appropriate statistical tests such as logistic regression or x^2 test for comparing proportions and had also adjusted for confounding factors, then the statistical analysis was considered appropriate. If statistical tests were appropriate, but no adjustment for confounding factors was done, then the statistical analysis was considered "partially" appropriate.

Above mentioned criteria were used for all study designs, however, some criteria were specific to a single study design. These criteria are discussed in the following section under discussion of quality assessment of studies according to their study designs.

Case-control studies. Quality criteria specific to case-control studies included appropriate selection of cases and controls, and description of matching criteria. If the eligibility criteria and the sources of cases and controls were stated properly, it was considered 'appropriate' selection of cases and controls. For matched studies, describing matching criteria and stating the number of controls per case was examined and noted down. Table 5 displays the findings of quality assessment of case-control studies. Most of the studies did not have an adequate sample size and the power to detect statistically significant association was low. All studies had used appropriate statistical tests, but the majority of them had reported crude odds ratio and had not adjusted odds ratio for the confounding factors (Table 5).

Table 5

Quality Assessment of Case-Control Studies Included in the Meta-analysis

Author	Appropriate selection of cases	Appropriate selection of controls	Adequate sample size	Matching of cases and controls	Description of diagnostic criteria	Clear definition of outcomes	Address potential sources of bias	Appropriate statistical analyses	Power of the Study (%)
Abdelgadir et al., 2003	Yes	Yes	No	Yes	Yes	Yes	Yes	Partially	39.30
Al-Khalifah et al., 2012	Yes	Yes	No	No	Yes	Yes	Partially	Partially	28.02
Almarzouki, 2013	Yes	Partially	No	No	Yes	Yes	No	Partially	5.00
Al Teheawt & Farida, 1995	Yes	Yes	No	No	No	Partially	Yes	Partially	28.15
Barakat et al., 2010	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	13.37
Dafallah & Yousif, 2004	Yes	Yes	Yes	No	Yes	Yes	Yes	Partially	97.54
Denguezli et al., 2007	Yes	Yes	Yes	No	Yes	Yes	Partially	Yes	99.97
Diejomaoh et al., 2009	Yes	Yes	No	Yes	No	Yes	Yes	Partially	12.07
Gasim, 2012	Yes	Yes	No	Yes	Yes	Partially	Yes	Yes	0.05
Johnstone et al., 1990	Yes	Yes	Yes	No	Yes	Yes	Yes	Partially	98.62
Nasrat et al., 1996	Yes	Yes	No	Yes	Yes	Partially	Yes	Yes	9.95
Nasrat et al., 1993	Yes	Yes	No	No	Yes	Yes	Yes	Partially	9.55
Rizvi et al., 1992	Yes	Yes	No	Yes	Yes	Partially	Yes	Partially	18.25
Sobande et al., 2000	Yes	Yes	Partially	Yes	Yes	Yes	Yes	Partially	66.72

Cohort studies. Quality criteria specific to cohort studies included appropriate selection of cohorts, description of methods of ascertaining outcomes and description of lost to follow-up. Cohort selection was considered appropriate if the authors described eligibility criteria, and the sources, methods of selection of participants. If matching criteria and number of exposed and unexposed were stated, it was considered a properly described cohort. Table 6 displays the findings of quality assessment of cohort studies included in the meta-analysis. An important finding was regarding the description of lost

to follow-up. As most of the studies were retrospective cohort studies, description of lost to follow up was not provided in most of them.

Table 6

Quality Assessment of Cohort Studies Included in the Meta-analysis

Author	Appropriate cohort selection	Adequate sample size	Properly described cohort	Clear description of diagnostic criteria	Clear definition of the outcomes	Description of the methods for ascertaining outcomes	Description of lost to follow up	Appropriateness of statistical analyses	Power of the Study (%)
Abolfazl et al., 2008	Yes	Partially	Yes	No	Partially	Yes	No	Partially	78.26
Badakhsh et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	100.00
Bener et al., 2011	Yes	Partially	Yes	Yes	Yes	Yes	No	Yes	63.98
Keshavarz et al., 2005	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	88.62
Khan et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partially	81.29
Khan et al., 1995	Yes	Partially	Yes	Yes	Yes	Yes	No	Partially	64.31
Khoshniatnikoo et al., 2010	Yes	Yes	Yes	Yes	Yes	Yes	No	Partially	99.99
Wahabi et al., 2012	Yes	No	Yes	Not Applicable	Yes	Yes	No	Yes	52.36
Wahabi et al., 2013	Yes	No	Yes	Yes	Yes	Yes	No	Partially	5.00

Cross-sectional studies. Quality criteria specific to cross-sectional studies included appropriate method of selection of participants, and appropriate sources of data and methods of assessment for outcomes. If the authors described the eligibility criteria, and the sources and methods of selection of participants, it was considered appropriate methods of selection of participants. All of these studies were hospital-based and in all studies except one (Fadwa et al., 2013) the source of data for outcomes were medical

records, which are considered credible sources of information. Table 7 displays the findings of quality assessment of cross-sectional studies included in the meta-analysis.

Table 7

Quality Assessment of Cross-sectional Studies Included in the Meta-analysis

Author	Adequate sample size	Appropriate methods of selection of participants	Description of diagnostic criteria	Clear definition of outcomes	Appropriate sources of data and methods of assessment for outcomes	Address the potential sources of bias	Appropriateness of statistical analyses	Power of the Study (%)
Al-Mejhim & Al-Najashi, 1998	Yes	Yes	No	Yes	Yes	No	Partially	100.00
Al-Shawaf et al., 1988	Yes	Yes	Yes	Yes	Yes	No	Partially	95.10
Bener, A. et al., 2013	No	Yes	No	Yes	Yes	Yes	Partially	54.30
El Mallah et al., 1997	No	Yes	Yes	Yes	Yes	Yes	Partially	44.92
Ezimokhai et al., 2006	Partially	Yes	Yes	Partially	Yes	Yes	Partially	73.63
Fadwa et al., 2013	Yes	Yes	No	Yes	Partially	Yes	Yes	100.00
Hossein-Nezhad et al., 2007	Yes	Yes	Yes	Yes	Yes	No	Yes	100.00
Jawad & Irshaduddin, 1996)	Yes	Yes	Yes	Yes	Yes	No	Partially	85.82
Nasrat et al., 1997	No	Yes	Yes	Yes	Yes	No	Partially	43.32
Tahir et al., 2011	No	Yes	Yes	Yes	Yes	Yes	Partially	26.30

To sum up, quality assessment of studies included in the meta-analysis revealed important findings. In many studies, the cases (women with GDM/PGDM) and comparison groups (women without GDM/PGDM) differed not only in the type of DM but also in some associated characteristics, such as age of the women. Most of the studies had not mentioned matching criteria of the two groups, however, all of these studies were hospital-based, and in most cases the researchers had mentioned some criteria for

selection. For example, woman without GDM/PGDM delivered next to the enrolled woman with GDM/PGDM was included in the study for comparison. All outcomes of interest were not defined in some studies (Ezimokhai et al., 2006; Abolfazl et al., 2008; Al Teheawt & Farida, 1995; Gasim, 2012; Nasrat et al., 1996; Rizvi et al., 1992). Few studies adjusted for the potential confounding factors in their analysis (Badakhsh et al., 2012; Barakat et al., 2010; Bener et al., 2011; Denguezli et al., 2007; Fadwa et al., 2013; Gasim, 2012; Hossein-Nezhad et al., 2007; Keshavarz et al., 2005; Nasrat et al., 1996; Wahabi et al., 2012). In spite of the above mentioned issues with the quality of the studies, none of the selected articles fulfilling inclusion/exclusion criteria was rejected because of quality assessment. The next section presents the results of meta-analysis of these studies.

Meta-Analysis Results

This meta-analysis investigated adverse maternal and fetal outcomes in women with GDM/PGDM in comparison to women without GDM/PGDM. Caesarean section was studied as the adverse maternal outcome, which was reported in 27 (81.8%) out of the total 33 studies. Out of these 27 studies, 16 (59.3%) examined the association of GDM with caesarean section, 10 (37.0%) examined the association of both GDM and PGDM while one (3.7%) study examined the association of PGDM with caesarean section. Adverse fetal outcomes studied in this meta-analysis included macrosomia and perinatal death. Macrosomia was reported in 26 (78.8%) studies; out of which 14 (53.8%) examined the association of GDM with macrosomia, 11 (42.3%) examined the association of both GDM and PGDM with macrosomia while one (3.8%) study examined

the association of PGDM with macrosomia. Perinatal death was reported in 24 (72.7%) studies. Out of the total 24 studies, 13 (54.2%) studied the association of both GDM and PGDM with perinatal death, 10 (41.7%) examined the association of GDM with perinatal death while one (4.2%) study examined the association of PGDM with perinatal death.

Measures of association (odds ratios, or relative risks) and their 95% confidence intervals (CIs) were abstracted or derived from published data. The maternal and fetal outcomes were expressed as odds ratios and 95% confidence intervals were calculated for individual study. Comprehensive Meta-Analysis software (CMA) [Version 2] was used to calculate individual effect sizes for each study. I pooled outcomes from primary studies calculating the odds ratio of an outcome occurring, and significance for combined effect was tested with a *z*- test. Because of expected statistical heterogeneity within primary studies, random-effects model was employed to combine the data, setting statistical significance at a p value <0.05. The random effects model was selected a priori as it allows for variation of the different effect sizes in each study (Borenstein et al., 2009). It allows for the difference in the observed effect sizes due to both sampling error and true variability in population parameters (Cooper & Hedges, 2009). Factors varying from study to study included sample size, method of GDM diagnosis, definition of outcome measures, study design, as well as the country of origin of study.

A test of heterogeneity, Cochran's Q test, was performed for each outcome. It was conducted to assess the variance of the true effect sizes using the Q statistic, a measure of weighted standard deviations. To express the percentage of total variation among studies

attributable to heterogeneity, I used the I^2 statistic, which explains the proportion of total variation in study estimates due to heterogeneity.

Subgroup analysis involves calculating a summary estimate for subgroups of studies (The Cochrane Collaboration, 2008). In this meta-analysis, the outcomes among women with GDM and PGDM were analyzed as sub-groups.

Sensitivity analysis tests the robustness of the overall findings of the meta-analysis with respect to different assumptions or inclusion of certain studies. It is an important tool for investigating heterogeneity (Taylor, 2005). I assessed the influence of individual studies by estimating the summary estimate of effect in the absence of each study.

Moderator analysis examines heterogeneity by observing the influence of various differences in studies such as study design and year of publication (Huedo-Medina et al., 2006). Heterogeneity was examined by classifying studies according to potential sources of variation and analyzing these subgroups of studies. Three moderators were analyzed to determine their influence on the pooled odds ratio. These moderators included publication period, study design and country of origin of the study. Regarding publication period, the studies were divided into two groups; those published before the year 2000 and those published in the year 2000 and after.

Various methods were used to assess the publication bias for association between GDM/PGDM and adverse outcomes, including funnel plot, Duval and Tweedie trim and fill procedure, Egger's regression test, fail safe N, and Orwin's fail safe N tests (Borenstein, 2005). Association of each of the maternal and fetal outcome among women

with GDM/PGDM in comparison to women without GDM/PGDM is discussed in the next sections.

Association Between GDM/PGDM and Delivery by Cesarean Section Among Women in the Eastern Mediterranean Region

The analysis for examining the association of caesarean section and GDM/PGDM included 27 studies with a total of 7,102 women with GDM/PGDM. Out of these, 5,341 had GDM, 620 had PGDM while 1,141 women were labeled as diabetics having either GDM or PGDM. The study was used as the unit of analysis for overall pooling of data for the groups GDM, PGDM and those labeled as diabetics. Thus, the data analysis software was used to calculate a pooled estimate for association of caesarean section in each of those studies where the researchers had reported separate odds ratios for women with GDM and for women with PGDM. This overall pooling of the data showed that odds of undergoing caesarean section in women with GDM/PGDM were 2.56 times more than those without GDM/PGDM (OR = 2.56, 95% CI [2.13 - 3.07], $p < 0.0001$; Figure 2). The Q statistic was statistically significant ($Q = 150.78$, $df = 26$, $p < 0.0001$, $I^2 = 82.76\%$), and variance in effect sizes can be attributed to both sampling error and heterogeneity among studies (Borenstein et al., 2009). Figure 2 shows effect sizes across 27 studies and a corresponding forest plot visually depicting the effect sizes and weight of each of the studies. The size of the squares on the plot indicate the weight assigned to the study based on sample size, with a smaller square representing smaller weights and a larger square representing larger weights. The central vertical line is at the null value (OR = 1.0).

Figure 2 displays that virtually all studies except one (Nasrat et al., 1996) reported increased odds of caesarean section in women with GDM/PGDM as compared to those without GDM/PGDM, although the associations were not always statistically significant. However, 24 studies found a significantly increased rate of caesarean section among women with GDM/PGDM compared with those without GDM/PGDM, with significant odds ratios ranging from 1.44 (Bener et al., 2013) to 10.01 (Badakhsh et al., 2012).

Study name	Statistics for each study			
	Odds ratio	Lower limit	Upper limit	p-Value
Nasrat, 1996	0.97	0.57	1.64	0.9094
Al-Khalifah, 2012	1.32	0.93	1.87	0.1232
Bener, 2013	1.44	1.03	2.00	0.0328
Wahabi, 2013	1.49	1.20	1.84	0.0003
Al-Shawaf, 1988	1.72	0.70	4.22	0.2341
Diejomaoh, 2009	1.98	1.22	3.21	0.0059
Abolfazl, 2008	2.06	1.12	3.80	0.0203
Khan, 2013	2.15	1.01	4.59	0.0474
Gasim, 2012	2.27	1.37	3.77	0.0016
Hossein-Nezhad, 2007	2.28	1.48	3.50	0.0002
Fadwa, 2013	2.30	1.79	2.96	0.0000
Tahir, 2011	2.41	1.31	4.45	0.0048
Almarzouki, 2013	2.47	1.05	5.80	0.0377
El Mallah, 1997	2.52	2.12	2.99	0.0000
Khan, 1995	2.60	1.88	3.60	0.0000
Ezimokhai, 2006	2.66	2.25	3.14	0.0000
Denguezli, 2007	2.72	1.80	4.11	0.0000
Abdelgadir, 2003	2.91	1.36	6.23	0.0059
Al Teheawt, 1995	3.02	2.12	4.28	0.0000
Rizvi, 1992	3.14	1.25	7.88	0.0150
Bener, 2011	3.25	2.39	4.42	0.0000
Barakat, 2010	3.33	1.77	6.26	0.0002
Wahabi, 2012	3.50	2.34	5.24	0.0000
Nasrat, 1993	4.39	2.29	8.44	0.0000
Keshavarz, 2005	5.07	2.39	10.72	0.0000
Sobande, 2000	5.22	2.01	13.59	0.0007
Badakhsh, 2012	10.01	7.27	13.78	0.0000
Overall	**2.56**	**2.13**	**3.07**	**0.0000**

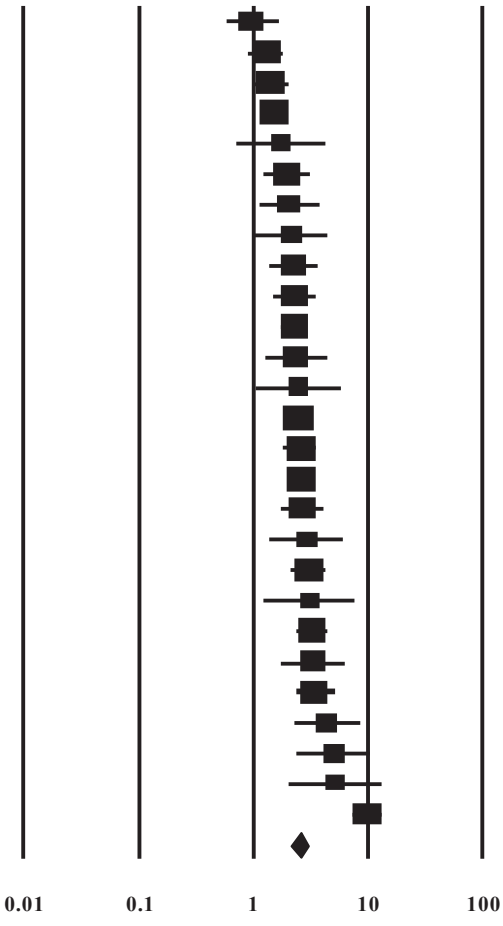

Figure 2. Forest plot of the odds ratio (OR) of delivery by caesarean section among women with GDM/PGDM in the Eastern Mediterranean Region. The odds ratio for delivery by caesarean section is reported for each study (black square) along with its 95% confidence interval (horizontal lines). The size of the square is proportional to the statistical weight of the study based on random effects model. Summary line represents the overall pooled estimate and its 95% CI. The diamond represents the summary odds ratios obtained from random effects pooled analysis with 95% confidence interval demonstrated by its width.

Subgroup Analysis

The pooled odds ratio for women with GDM and the outcome of caesarean section showed that in women with GDM, the odds of being delivered by caesarean section were 2.39 times in comparison to those without GDM (OR = 2.39, 95% CI [1.84-3.1], $p < 0.0001$; Figure 3). Out of 20 studies analyzing the association of GDM with caesarean section, four studies (Nasrat et al., 1996; Al-Khalifah et al., 2012; Al-Shawaf et al., 1988; Abdelgadir et al., 2003) had statistically non-significant association. Nasrat et al. (1996) reported the lowest odds ratio of 0.97 (95% CI, 0.57 - 1.64, $p = 0.91$) while Badakhsh et al. (2012) reported the highest odds ratio of 10.01 (95% CI, 7.27 - 13.78, $p < 0.0001$). As random effects model was used, the relative weight of the studies was balanced. The lowest relative weight for a single study was 2.44% (Abdelgadir et al., 2003) while the highest relative weight was 6.42% (El Mallah et al., 1997). The Q statistic was statistically significant ($Q = 137.05$, $df = 19$, $p < 0.0001$, $I^2 = 86.14\%$) and variance in effect sizes can be attributed to both sampling error and heterogeneity among studies (Borenstein et al., 2009).

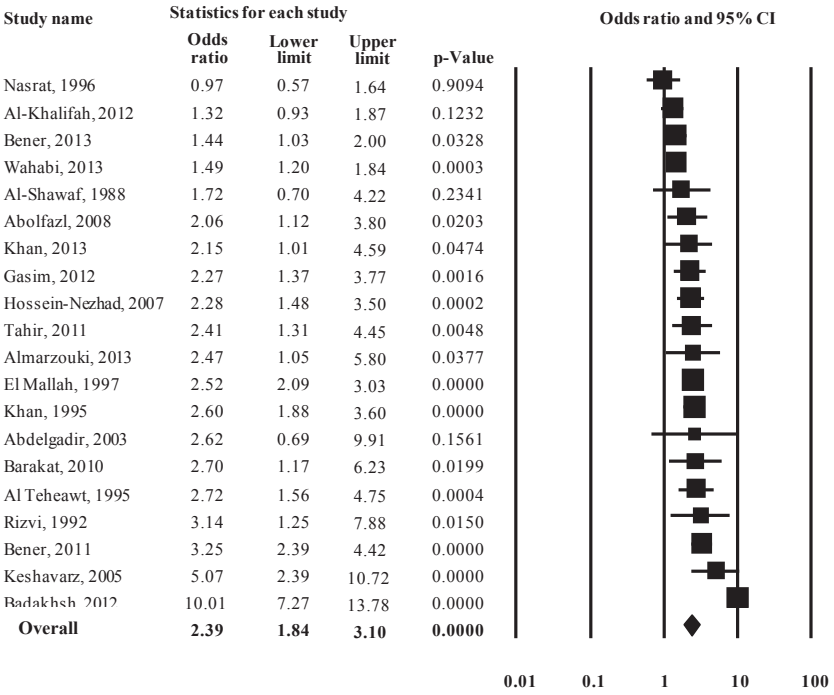

Figure 3. Forest plot of the odds ratio of delivery by caesarean section among women with GDM in the Eastern Mediterranean Region. The odds ratio for delivery by caesarean section is reported for each study (black square) along with its 95% confidence interval (horizontal lines). The size of the square is proportional to the statistical weight of the study based on random effects model. Summary line represents the overall pooled estimate and its 95% CI. The diamond represents the summary odds ratios obtained from random effects pooled analysis with 95% confidence interval demonstrated by its width.

Five studies reported association of PGDM with delivery by caesarean section. The pooled estimate for women with PGDM and the outcome of caesarean section was 3.24 (95% CI, 2.51 - 4.17, $p < 0.0001$; Figure 4). All studies had statistically significant

association. El Mallah et al. (1997) reported the lowest odds ratio of 2.51 (95% CI, 1.34-4.69, $p = 0.004$) while Barakat et al. (2010) reported the highest odds ratio of 4.39 (95% CI, 1.68-11.48, $p = 0.003$). The lowest relative weight for a single study was 6.45% (Abdelgadir et al., 2003) while the highest relative weight was 39.62% (Wahabi et al., 2012). The Q statistic was not significant statistically ($Q = 1.197$, $df = 4$, $p = 0.879$, $I^2 = 0.0\%$) and variance in effect sizes can be attributed to sampling error only (Borenstein et al., 2009).

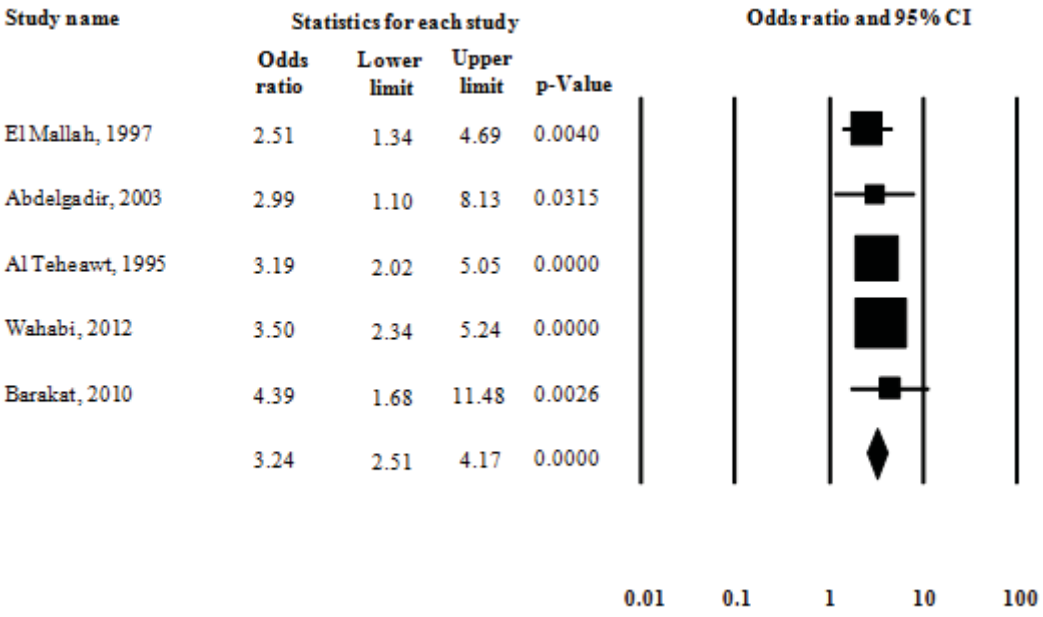

Figure 4. Forest plot of the odds ratio of delivery by caesarean section among women with PGDM in the Eastern Mediterranean Region. The odds ratio for delivery by caesarean section is reported for each study (black square) along with its 95% confidence interval (horizontal lines). The size of the square is proportional to the statistical weight of the study based on random effects model. Summary line represents the overall pooled estimate and its 95% CI. The diamond represents the summary odds ratios obtained from random effects pooled analysis with 95% confidence interval demonstrated by its width.

Sensitivity Analyses

I performed a sensitivity analysis investigating whether the results are influenced by the effect of certain specific studies. Sensitivity analyses indicated that none of the studies seemed to contribute more to the analysis. I assessed the relative influence of each study by omitting one study at a time from the pooled analysis. Excluding individual studies did not substantially affect the estimates. The pooled odds ratio for association between GDM/PGDM and delivery by caesarean sections after leaving out one study at a time ranged from 2.37 to 2.65 which is close to the pooled estimate of 2.56. Sensitivity analyses, excluding the study with the highest odds ratio (Badakhsh et al., 2012), produced results [OR = 2.38, 95% CI (2.08-2.72)] similar to the pooled odds ratio estimated for all included studies.

Moderator Analysis

Three moderators were analyzed to determine their influence on the pooled odds ratio for caesarean section. These moderators included; publication period, study design and country of origin of the study.

Regarding publication period, the studies were divided into two groups; those published before the year 2000 and those published in the year 2000 and after. By random effects analysis, the pooled odds ratio for the studies published before the year 2000 was 2.4 (95% CI, 1.64-3.52, $p < 0.0001$), while those published in the year 2000 and after had a pooled odds ratio of 2.62 (95% CI, 2.1-3.27, $p < 0.0001$). Although the studies published in the 2000s showed a higher pooled odds ratio, the difference was not statistically significant ($p = 0.702$).

To assess the relationship between study design and odds ratio, I analyzed differences in effect sizes between three subgroups representing cross-sectional, case-control and cohort study designs. The pooled odds ratio for cross-sectional studies was 2.18 (95% CI, 1.53-3.12, $p < 0.0001$), for case control studies 2.44 (95% CI, 1.8-3.29, $p < 0.0001$) and for the cohort studies 3.17 (95% CI, 2.25-4.46, $p < 0.0001$). Although pooled odds ratio varied between three study design, the differences were not statistically significant ($p = 0.308$).

The studies were assessed for differences in effect sizes according to the country of origin of study. A total of 11 countries were represented in this meta-analysis. Although pooled odds ratio varied among countries between the lowest of 1.98 (95% CI, 0.69-5.62, $p < 0.0001$) from Kuwait to the highest of 4.05 (95% CI, 2.38-6.9, $p = 0.201$) from Iran, the differences among countries were not statistically significant ($p = 0.917$).

Publication Bias

Various methods were used to assess the publication bias for association between GDM/PGDM and delivery by caesarean section, including funnel plot, Duval and Tweedie trim and fill procedure, Egger's regression test, fail safe N, and Orwin's fail-safe N tests were applied. A funnel plot was generated to evaluate the potential for publication bias. On visual inspection, the funnel plot (Figure 5) depicts a mostly symmetrical diagram of studies about the effect size, resembling a funnel shape. This depiction implies an absence of publication bias (Borenstein et al., 2009). In case of publication bias, the bottom of the plot would display a greater concentration of studies on one side of the mean as compared to the other. A tendency of the studies to congregate towards

the bottom of the plot reflects the fact that the chances of publication of smaller studies are higher if they have greater than average effects, and hence a greater likelihood of yielding statistical significance. The Duval and Tweedie trim and fill procedure showed no indication of publication bias (Duvall and Tweedie adjusted OR = 2.48, 95% CI, 2.32-2.66, number of imputed studies = 0). Egger's regression test also showed no indication of publication bias (Egger test intercept = 0.42; *SE* = 0.99; *p* = .67).

This meta-analysis incorporated data from 27 studies, which yield a *z*-value of 23.35 and corresponding 2-tailed *p* value of less than 0.0001. The fail-safe N is 3,807. This means that we would be required to find and include 3,807 'null' studies for the pooled 2-tailed *p* value to exceed 0.05. Thus, 141.0 missing studies would be required for every observed study for the effect to be nullified. The Orwin's fail safe N is the number of missing studies that, when added to the analysis, will bring the pooled odds ratio below a specified threshold (Borenstein, 2005). On specifying threshold of OR equal to 1.2, the Orwin's fail-safe N is 108. This means that we would be required to find 108 studies with mean odds ratio of 1 to bring the combined odds ratio under 1.2. To sum up, all tests applied for the assessment of publication bias did not provide evidence of publication bias.

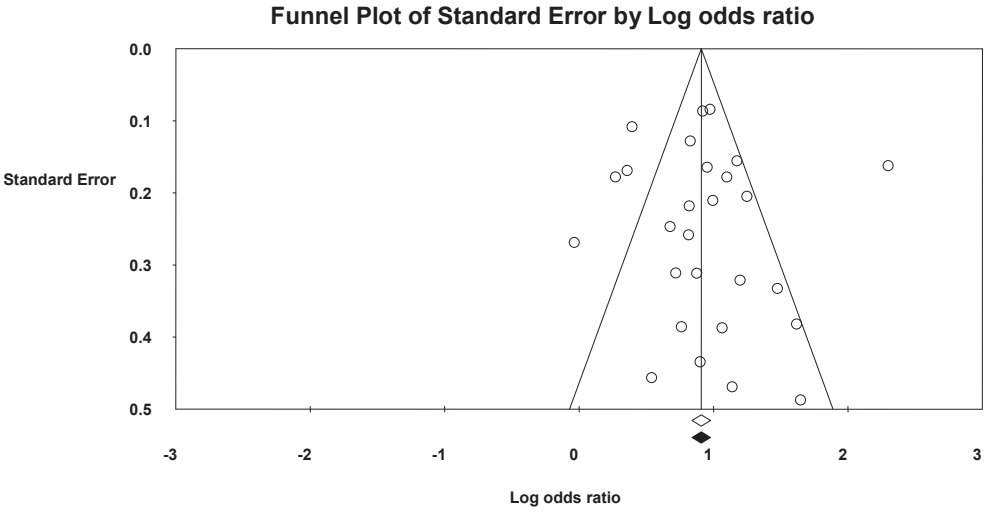

Figure 5. Funnel plot of studies included in meta-analysis on association of delivery by Caesarean section and GDM/PGDM among women in Eastern Mediterranean Region. The diagonal lines represent the 95% confidence interval (CI) around the overall effect estimate, which is indicated by the vertical line. The effect of each study is marked by a circle. Observed and adjusted pooled estimates are calculated using Duval and Tweedie's trim and fill method. The observed pooled estimate is shown in an open diamond, while pooled estimate adjusted for publication bias is shown in filled diamond. The summary of estimates obtained before (open diamond) and after the adjustment (filled diamond) indicates that there are no missing studies.

Association Between Macrosomia and GDM/PGDM Among Women in the Eastern Mediterranean Region

The analysis for examining the association of macrosomia and GDM/PGDM included 26 studies with a total of 7,000 women with GDM/PGDM. Out of these, 5,104 had GDM, 755 had PGDM while 1,141 women were labeled as diabetics having either GDM or PGDM. The study was used as the unit of analysis for overall pooling of data for

the groups GDM, PGDM and those labeled as diabetics. Thus, the data analysis software was used to calculate a pooled estimate for association of macrosomia in each of those studies where the researchers had reported separate odds ratios for women with GDM and for women with PGDM. Overall pooling of all data for macrosomia showed the odds of having a macrosomic baby in women with GDM/PGDM 3.5 times as compared to those without GDM/PGDM. The pooled odds ratio for macrosomia and GDM/PGDM among women was 3.51 (95% CI, 2.73-4.51, $p < 0.0001$; Figure 6). Six studies had statistically non-significant association. Nasrat et al. (1993) reported the lowest odds ratio of 1.72 (95% CI, 0.79- 3.75.69, $p = 0.171$) while Khoshniat nikoo et al. (2010) reported the highest odds ratio of 16.96 (95% CI, 8.27-34.79, $p < 0.0001$). The Q statistic was statistically significant ($Q = 148.41$, $df = 25$, $p < 0.0001$, $I^2 = 83.15\%$) and variance in effect sizes can be attributed to both sampling error and heterogeneity among studies.

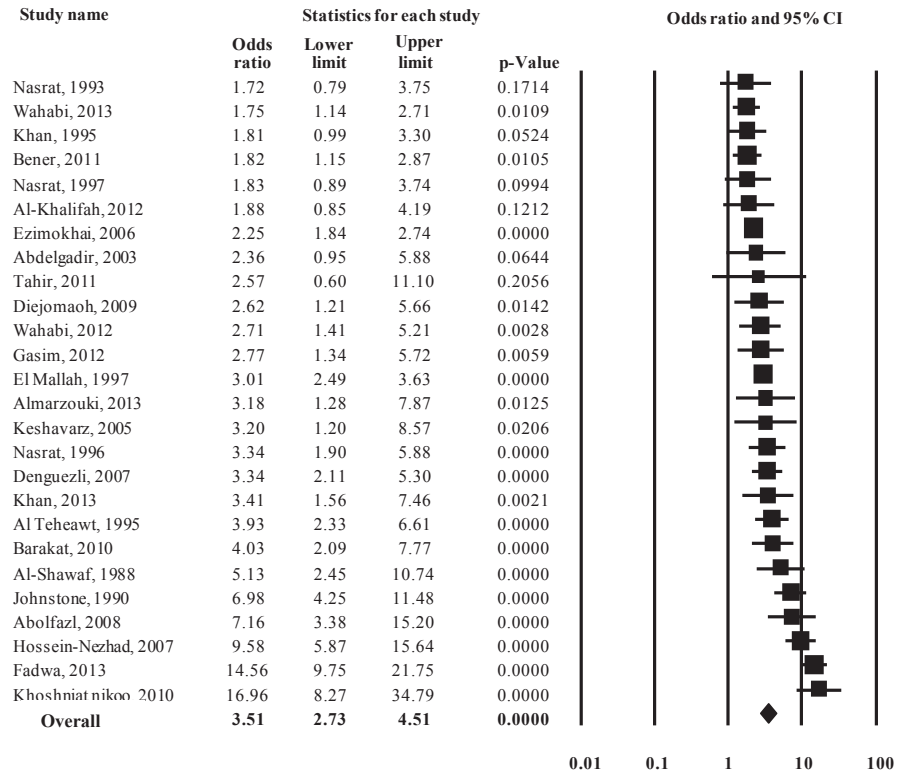

Figure 6. Forest plot of the odds ratio of macrosomia among women with GDM/PGDM in the Eastern Mediterranean Region. The odds ratio for macrosomia is reported for each study (black square) along with its 95% confidence interval (horizontal lines). The size of the square is proportional to the statistical weight of the study based on random effects model. Summary line represents the overall pooled estimate and its 95% confidence interval. The diamond represents the summary odds ratios obtained from random effects pooled analysis with 95% confidence interval demonstrated by its width.

Subgroup Analysis

Analysis according to diabetes type showed that in women with GDM, the odds of having a macrosomic baby is 3.8 times in comparison to those without diabetes. The pooled odds ratio for women with GDM and the outcome of macrosomia was 3.83 (95%

CI, 2.83 - 5.18, $p < 0.0001$; Figure 7). Out of 19 studies analyzing the association of GDM with macrosomia, four studies (Khan et al., 1995; Al-Khalifah et al., 2012; Tahir et al., 2011; Abdelgadir et al., 2003) had statistically non-significant association. Wahabi et al. (2013) reported the lowest odds ratio of 1.75 (95% CI, 1.14-2.71, $p = 0.011$) while Khoshniat nikoo et al. (2010) reported the highest odds ratio of 16.96 (95% CI, 8.27-34.79, $p < 0.0001$). As random effects model was used, the relative weight of the studies was balanced. The lowest relative weight was 2.65% (Abdelgadir et al., 2003) while the highest relative weight was 7.40% (El Mallah et al., 1997). The Q statistic was statistically significant ($Q = 80.51$, $df = 18$, $p < 0.000$, $I^2 = 77.64\%$), and variance in effect sizes can be attributed to both sampling error and heterogeneity among studies.

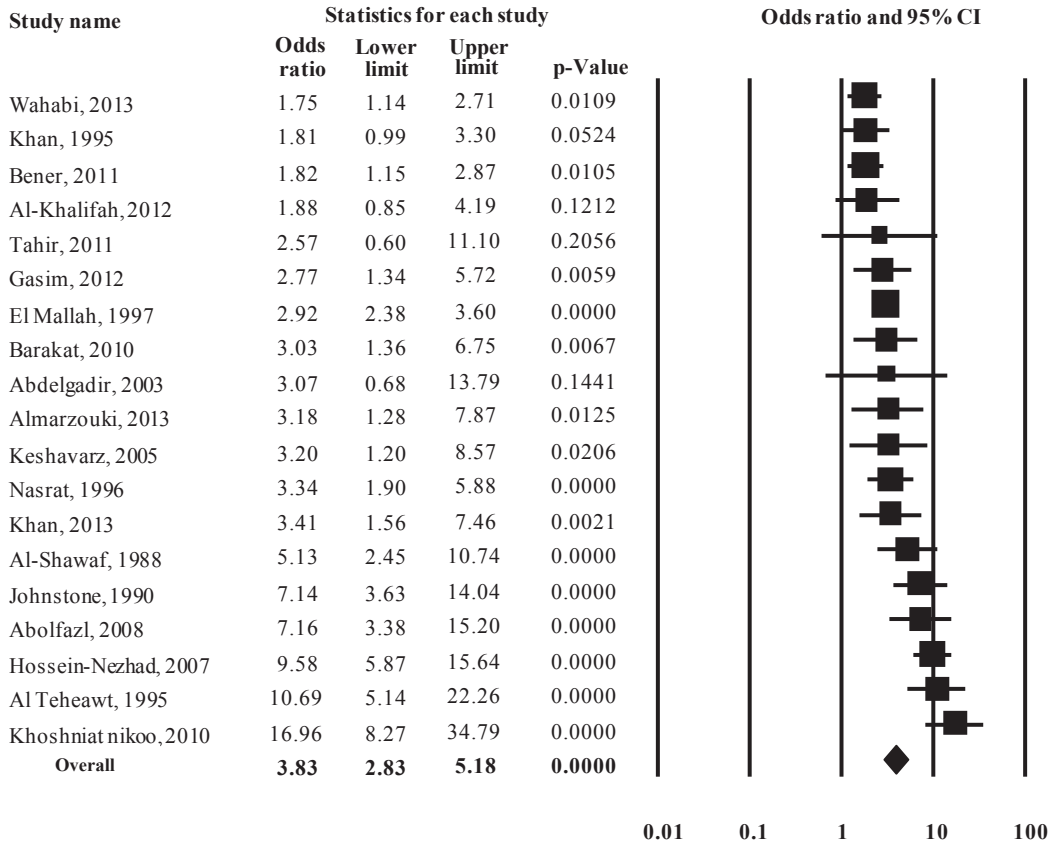

Figure 7. Forest plot of the odds ratio of macrosomia among women with GDM in the Eastern Mediterranean Region. The odds ratio for macrosomia is reported for each study (black square) along with its 95% confidence interval (horizontal lines). The size of the square is proportional to the statistical weight of the study based on random effects model. Summary line represents the overall pooled estimate and its 95% confidence interval. The diamond represents the summary odds ratios obtained from random effects pooled analysis with 95% confidence interval demonstrated by its width.

Six studies reported association of PGDM with macrosomia. The pooled estimate for women with PGDM and macrosomia was 3.51 (95% CI, 2.22-5.57, $p < 0.0001$) (Figure 8). Two studies had statistically non-significant association (Abdelgadir et al., 2003; Al Teheawt & Farida, 1995). Al Teheawt and Farida (1995) reported the lowest odds ratio of 1.60 (95% CI, 0.72-3.56, $p = 0.253$) while Barakat et al. (2010) reported the highest odds ratio of 7.20 (95% CI, 2.3-22.57, $p < 0.0001$). The lowest relative weight was 10.34% (Abdelgadir et al., 2003) while the highest relative weight was 22.03% (El Mallah et al., 1997). The Q statistic was not significant statistically ($Q = 9.66$, $df = 5$, $p = 0.085$, $I^2 = 48.262\%$) and variance in effect sizes can be attributed to the sampling error, and heterogeneity among studies is low.

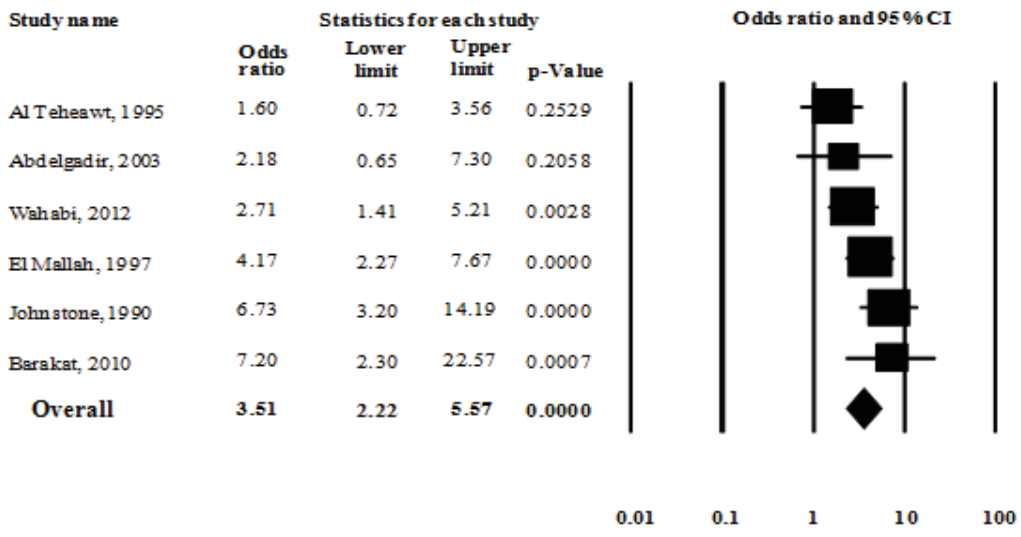

Figure 8. Forest plot of the odds ratio of macrosomia among women with PGDM in the Eastern Mediterranean Region. The odds ratio for macrosomia is reported for each study (black square) along with its 95% confidence interval (horizontal lines). The size of the square is proportional to the statistical weight of the study based on random effects model. Summary line represents the overall pooled estimate and its 95% confidence interval. The diamond represents the summary odds ratios obtained from random effects pooled analysis with 95% confidence interval demonstrated by its width.

Sensitivity Analyses

I performed a sensitivity analysis investigating whether the results are influenced by the effect of certain specific studies. Sensitivity analyses indicated that none of the studies seemed to contribute more to the analysis. I assessed the relative influence of each study by omitting one study at a time from the pooled analysis. Excluding individual studies did not substantially affect the estimates. The pooled estimates after leaving out one study at a time ranged from 3.27 (95% CI, 2.65-4.05, $p < 0.0001$) to 3.63 (95% CI,

2.81- 4.69, $p < 0.0001$) which is close to the pooled estimate of 3.5 (95% CI, 2.73-4.51, $p < 0.0001$). Sensitivity analyses, excluding the study with the highest odds ratio (Khoshniat nikoo et al., 2010), produced results (OR = 3.18, 95% CI, 2.89-3.49) similar to the pooled estimated of all included studies.

Moderator Analysis

Three moderators were analyzed to determine their influence on the pooled odds ratio for macrosomia. These moderators included; publication period, study design and country of origin of the study.

Regarding publication period, the studies were divided into two groups; those published before the year 2000 and those published in the year 2000 and after. By random effects analysis, the pooled odds ratio for the studies published before the year 2000 was 3.13 (95% CI, 1.95-5.00; $p < 0.0001$), while those published in the year 2000 and after had a pooled odds ratio of 3.71 (95% CI, 2.68-5.13; $p < 0.0001$). Although the studies published in the 2000s showed a higher pooled odds ratio, the difference was not statistically significant ($p = 0.560$).

To assess the relationship between study design and odds ratio for macrosomia, I analyzed differences in effect sizes between three subgroups representing cross-sectional, case-control and cohort study designs. The pooled odds ratio for cross-sectional studies was 4.37 (95% CI, 2.65-7.21, $p < 0.0001$), for case- control studies 3.14 (95% CI, 2.08-4.74, $p < 0.0001$) and for the cohort studies 3.33 (95% CI, 2.06-5.37, $p < 0.0001$). Although pooled odds ratio varied between three study design, the differences were not statistically significant ($p = 0.585$).

The studies examining macrosomia as an adverse fetal outcome were assessed for differences in effect sizes according to the country of origin of study. A total of 11 countries were represented in this meta-analysis. The pooled odds ratio varied among countries between the lowest of 1.82 (95% CI, 0.93-3.56, $p = 0.082$) from Qatar to the highest of 14.56 (95% CI, 7.71-27.49, $p < 0.0001$) from Jordan. The differences among countries was statistically significant ($p < 0.0001$).

Publication Bias

Various methods were used to assess the publication bias for association between GDM/PGDM and macrosomia, including funnel plot, Duval and Tweedie trim and fill procedure, Egger's regression test, fail safe N, and Orwin's fail safe N tests. A funnel plot was generated to evaluate the potential for publication bias. On visual inspection, the funnel plot (Figure 9) depicts a mostly symmetrical diagram of studies about the effect size, resembling a funnel shape. This depiction implies an absence of publication bias. The Duval and Tweedie trim and fill procedure showed no indication of publication bias (Duvall and Tweedie adjusted OR = 3.24 [95% CI, 2.96-3.56]), number of imputed studies = 0]). Egger's regression test also showed no indication of publication bias (Egger test intercept = 0.85; $SE = 0.96$; $p = 0.39$).

The meta-analysis for macrosomia incorporated data from 26 studies, which yield a z-value of 22.74 and corresponding 2-tailed *p*-value of less than 0.0001. The fail-safe N is 3,474. This means that we would be required to find and include 3,474 "null" studies in order for the pooled 2-tailed *p*-value to exceed 0.050. In other words, 133.6 missing studies would be required for every observed study for the effect to be nullified. The

Orwin fail-safe N is the number of missing studies that, when added to the analysis, will bring the pooled odds ratio below a specified threshold (Borenstein, 2005). On specifying threshold of OR equal to 1.2, the Orwin's fail-safe N is 142. This means that we would need to locate 142 studies with mean odds ratio of 1 to bring the combined odds ratio under 1.2.

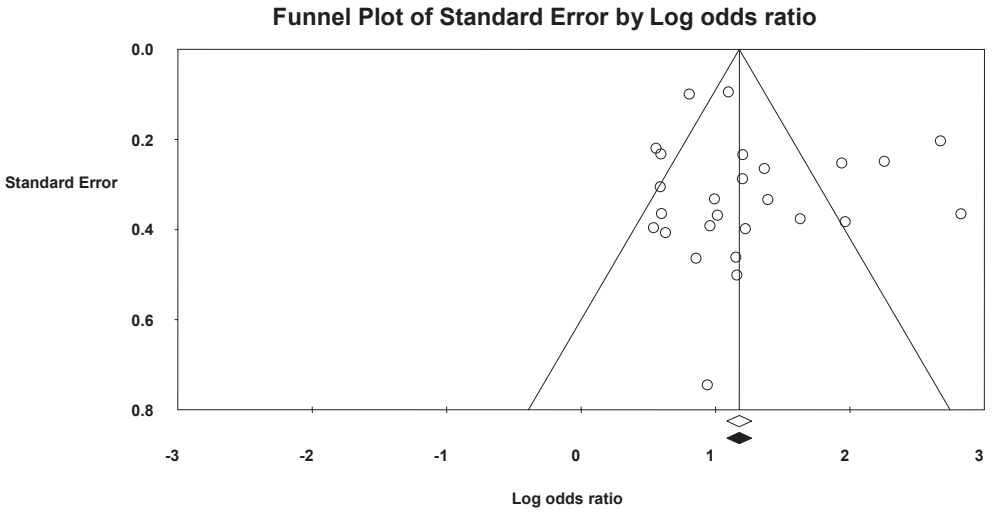

Figure 9. Funnel plot of studies included in meta-analysis on association of macrosomia and GDM/PGDM among women in Eastern Mediterranean Region. The diagonal lines represent the 95% confidence interval (CI) around the overall effect estimate, which is indicated by the vertical line. The effect of each study is marked by a circle. Observed and adjusted pooled estimates are calculated using Duval and Tweedie's trim and fill method. The observed pooled estimate is shown in an open diamond, while pooled estimate adjusted for publication bias is shown in filled diamond. The summary of estimates obtained before (open diamond) and after the adjustment (filled diamond) indicates that there are no missing studies.

Association Between Perinatal Death and GDM/PGDM Among Women in the Eastern Mediterranean Region

The analysis for examining the association of perinatal death and GDM/PGDM included 24 studies with a total of 7,352 women with GDM/PGDM. Out of these, 4,456 had GDM, 929 had PGDM while 1,967 women were labeled as diabetics having either GDM or PGDM. The study was used as the unit of analysis for overall pooling of data for the groups GDM, PGDM and those labeled as diabetics. Thus, CMA software [Version 2] was used to calculate a pooled estimate for association of caesarean section in each of those studies where the researchers had reported separate odds ratios for women with GDM and for women with PGDM. This overall pooling of the data showed that odds of perinatal death in women with GDM/PGDM was 2.46 times more than those without GDM/PGDM (OR = 2.46, 95% CI [1.81-3.34], $p < 0.0001$; Figure 10). The Q statistic was statistically significant ($Q = 65.257$, $df = 23$, $p < 0.0001$, $I^2 = 64.75\%$) and variance in effect sizes can be attributed to both sampling error and heterogeneity among studies. Figure 10 shows effect sizes across 24 studies and a corresponding forest plot visually depicting the effect sizes and weight of each of the studies. The size of the squares on the plot indicate the weight assigned to the study based on sample size, with a smaller square representing smaller weights and a larger square representing larger weights. The central vertical line is at the null value (OR = 1.0). Thirteen studies showed statistically non-significant association. Diejomaoh et al. (2009) reported the lowest odds ratio of 0.33 (95% CI, 0.03-3.2, $p = 0.338$) while Khan et al. (2013) reported the highest odds ratio of 19.60 (95% CI, 1.13-341.57, $p = 0.041$). As random effects model was used, the relative

weight of the studies was balanced. The lowest relative weight was 0.83% (Nasrat et al., 1993) while the highest relative weight was 8.66% (Al-Mejhim & Al-Najashi, 1998).

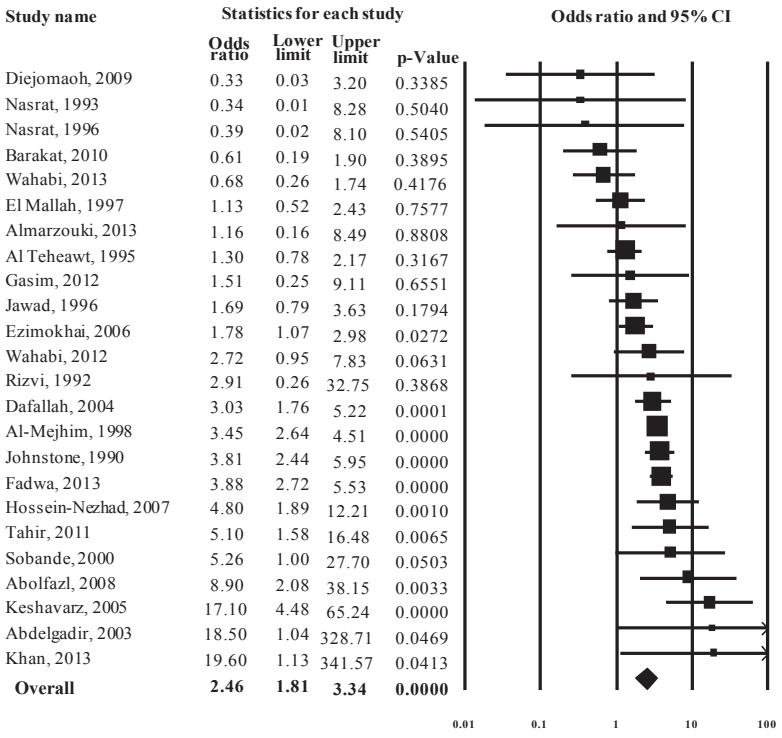

Figure 10. Forest plot of the odds ratio of perinatal death among women with GDM/PGDM in the Eastern Mediterranean Region. The odds ratio for perinatal death is reported for each study (black square) along with its 95% confidence interval (horizontal lines). The size of the square is proportional to the statistical weight of the study based on random effects model. Summary line represents the overall pooled estimate and its 95% confidence interval. The diamond represents the summary odds ratios obtained from random effects pooled analysis with 95% confidence interval demonstrated by its width.

Subgroup Analysis

The pooled odds ratio for women with GDM and the outcome of perinatal death was 2.23 [(95% CI (1.40-3.54), $p = 0.0007$] (Figure 11). Out of 18 studies analyzing the association of GDM with perinatal death, 12 studies had statistically non-significant association. Nasrat et al. (1996) reported the lowest odds ratio of 0.39 [95% CI (0.02-8.1), $p = 0.540$] while Khan et al. (2013) reported the highest odds ratio of 19.60 (95% CI [1.125 - 341.568], $p = 0.041$). As random effects model was used, the relative weight of the studies was balanced. The lowest relative weight for a single study was 1.73% (Abdelgadir et al., 2003) while the highest relative weight was 9.47% (Johnstone et al., 1990). The Q statistic was statistically significant ($Q = 39.647$, $df = 17$, $p < 0.001$, $I^2 = 57.12\%$) and variance in effect sizes can be attributed to both sampling error and heterogeneity among studies.

Study name	Statistics for each study: Odds ratio	Lower limit	Upper limit	p-Value
Nasrat, 1996	0.39	0.02	8.10	0.5405
Barakat, 2010	0.57	0.14	2.30	0.4294
Wahabi, 2013	0.68	0.26	1.74	0.4176
El Mallah, 1997	0.86	0.34	2.17	0.7544
Jawad, 1996	1.04	0.38	2.86	0.9358
Almarzouki, 2013	1.16	0.16	8.49	0.8808
Al Teheawt, 1995	1.40	0.61	3.25	0.4300
Gasim, 2012	1.51	0.25	9.11	0.6551
Dafallah, 2004	2.03	0.92	4.50	0.0793
Rizvi, 1992	2.91	0.26	32.75	0.3868
Sobande, 2000	2.98	0.26	33.69	0.3772
Johnstone, 1990	3.00	1.60	5.63	0.0006
Hossein-Nezhad, 2007	4.80	1.89	12.21	0.0010
Tahir, 2011	5.10	1.58	16.48	0.0065
Abdelgadir, 2003	8.19	0.32	210.07	0.2040
Abolfazl, 2008	8.90	2.08	38.15	0.0033
Keshavarz, 2005	17.10	4.48	65.24	0.0000
Khan, 2013	19.60	1.13	341.57	0.0413
Overall	**2.23**	**1.40**	**3.54**	**0.0007**

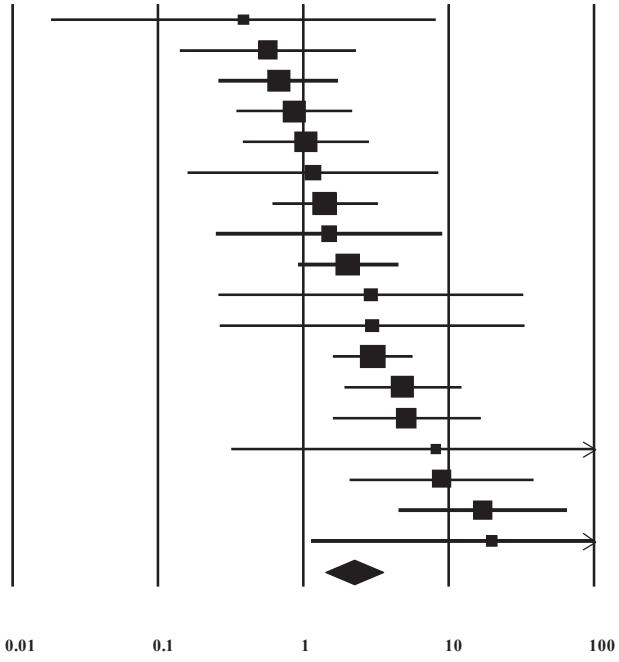

Figure 11. Forest plot of the odds ratio of perinatal death among women with GDM in the Eastern Mediterranean Region. The odds ratio for perinatal death is reported for each study (black square) along with its 95% confidence interval (horizontal lines). The size of the square is proportional to the statistical weight of the study based on random effects model. Summary line represents the overall pooled estimate and its 95% CI. The diamond represents the summary odds ratios obtained from random effects pooled analysis with 95% confidence interval demonstrated by its width.

Nine studies reported association of PGDM with perinatal death. The pooled odds ratio for women with PGDM and perinatal death was 3.71 (95% CI [2.09-6.57], $p <$ 0.0001; Figure 12). Four studies had statistically non-significant association. Barakat et al. (2010) reported the lowest odds ratio of 0.75 (95% CI [0.09-6.37], $p = 0.793$) while Sobande et al. (2000) reported the highest odds ratio of 10.70 (95% CI [1.06-107.75], $p =$ 0.044). The lowest relative weight was 3.33% (Abdelgadir et al., 2003) while the highest relative weight was 18.22% (Johnstone et al., 1990). The Q statistic was statistically significant ($Q = 18.294$, $df = 8$, $p = 0.019$, $I^2 = 56.27\%$). Thus, the studies included in this sub-group meta-analysis were shown to be heterogeneous, and variance in effect sizes can be attributed to both sampling error and heterogeneity among studies.

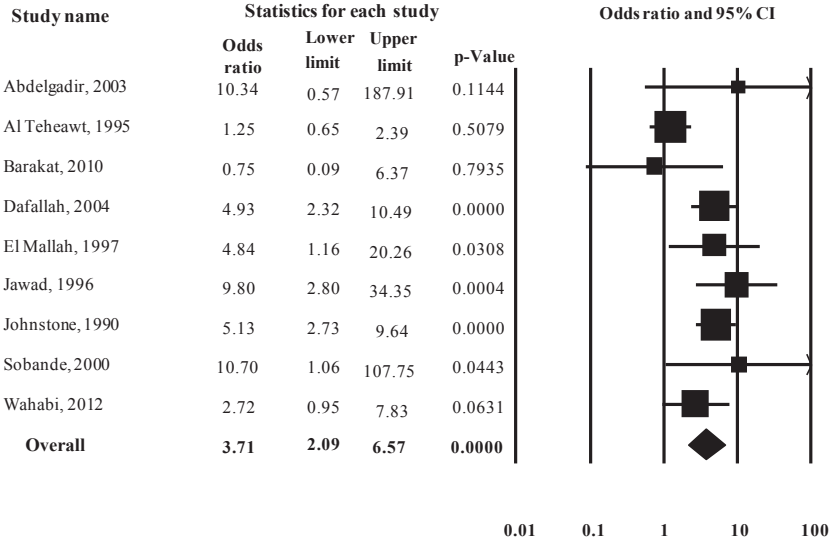

Figure 12. Forest plot of the odds ratio of perinatal death among women with PGDM in the Eastern Mediterranean Region. The odds ratio for perinatal death is reported for each study (black square) along with its 95% confidence interval (horizontal lines). The size of the square is proportional to the statistical weight of the study based on random effects model. Summary line represents the overall pooled estimate and its 95% CI. The diamond represents the summary odds ratios obtained from random effects pooled analysis with 95% confidence interval demonstrated by its width.

Sensitivity Analyses

I performed a sensitivity analysis investigating whether the results were influenced by the effect of certain specific studies. Sensitivity analyses indicated that

none of the studies seemed to contribute more to the analysis. I assessed the relative influence of each study by omitting one study at a time from the pooled analysis. Excluding individual studies examining perinatal deaths did not substantially affect the estimates. The pooled estimates after leaving out one study at a time ranged from 2.46 (95% CI [1.86-3.24], $p < 0.0001$) to 2.74 (95% CI [2.08-3.61], $p < 0.0001$) which is close to the pooled estimate of 2.59 (95% CI [1.95-3.43], $p < 0.0001$). Sensitivity analyses, excluding the study with the highest odds ratio (Khan et al., 2013), produced results (OR = 2.54, 95% CI [1.91-3.37]) similar to the pooled estimated of all included studies.

Moderator Analysis

Three moderators were analyzed to determine their influence on the pooled odds ratio. These moderators included; publication period, study design and country of origin of the study.

Regarding publication period, the studies were divided into two groups; those published before the year 2000 and those published in the year 2000 and after. By random effects analysis, the pooled odds ratio for the studies published before the year 2000 was 2.67 (95% CI [2.20-3.24], $p < 0.0001$), while those published in the year 2000 and after had a pooled odds ratio of 2.91 (95% CI [2.35-3.60], $p < 0.0001$). Although the studies published in the 2000s showed a higher pooled odds ratio, the difference was not statistically significant ($p = 0.28$).

To assess the relationship between study design and odds ratio, I analyzed differences in effect sizes between three subgroups representing cross-sectional, case-control and cohort study designs. The pooled odds ratio for cross-sectional studies was

3.03 (95% CI [2.53-3.63], $p < 0.0001$), for case- control studies 2.27 (95% CI [1.75-2.95], $p < 0.0001$) and for the cohort studies 2.97 (95% CI [1.69-5.21], $p = 0.0001$). Although pooled odds ratio varied between three study design, the differences were not statistically significant ($p = 0.315$).

The studies were assessed for differences in effect sizes according to the country of origin of study. A total of 9 countries were represented in this meta-analysis. The pooled odds ratio varied among countries with the lowest of 0.61(95% CI [0.11-3.36], $p = 0.567$) from Oman to the highest of 8.39 (95% CI [3.02-23.33], $p < 0.0001$) from Iran. The difference among countries was statistically non-significant ($p = 0.145$).

Publication Bias

Various methods were used to assess the publication bias for association between GDM/PGDM and perinatal death, including funnel plot, Duval and Tweedie trim and fill procedure, Egger's regression test, fail safe N, and Orwin's fail safe N tests were applied.

A funnel plot was generated to evaluate the potential for publication bias. On visual inspection, the funnel plot (Figure 13) depicts a mostly symmetrical diagram of studies about the effect size, resembling a funnel shape. This depiction implies an absence of publication bias (Borenstein et al., 2009). The Duval and Tweedie trim and fill procedure showed no indication of publication bias (Duvall and Tweedie adjusted *OR* = 2.78; 95% *CI*, 2.41-3.20; number of imputed studies = 0). Egger's regression test also showed no indication of publication bias (Egger test intercept = -0.53; *SE* = 0.57; $p = 0.36$).

This meta-analysis for perinatal deaths incorporated data from 24 studies, which yielded a *z*-value of 10.17 and corresponding 2-tailed *p* value of less than 0.0001. The fail safe N is 623. This means that we would be required to find and include 623 'null' studies in order for the pooled 2-tailed *p* value to exceed 0.050. Put another way, 26.0 missing studies would be required for every observed study for the effect to be nullified. The Orwin's fail safe N is the number of missing studies that, when added to the analysis, will bring the pooled odds ratio below a specified threshold (Borenstein, 2005). On specifying threshold of OR equal to 1.2, the Orwin's fail safe N is 111. This means that we would need to locate 111 studies with mean odds ratio of 1 to bring the combined odds ratio under 1.2.

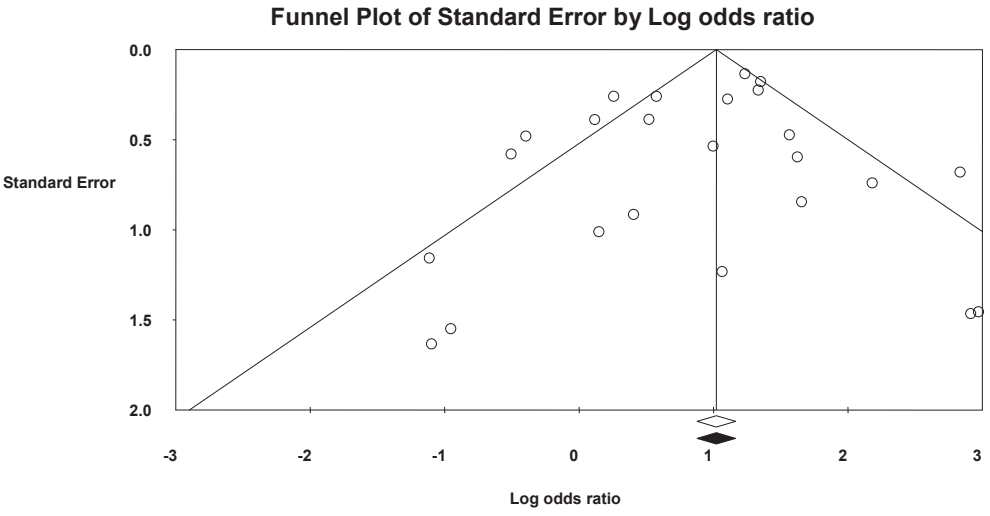

Figure 13. Funnel plot of studies included in meta-analysis on association of perinatal death and GDM/PGDM among women in Eastern Mediterranean Region. The diagonal lines represent the 95% confidence interval (CI) around the overall effect estimate, which is indicated by the vertical line. The effect of each study is marked by a circle. Observed and adjusted pooled estimates are calculated using Duval and Tweedie's trim and fill

method. The observed pooled estimate is shown in an open diamond, while pooled estimate adjusted for publication bias is shown in filled diamond. The summary of estimates obtained before (open diamond) and after the adjustment (filled diamond) indicates that there are no missing studies.

Summary and Transition

This chapter contained a description of the meta-analysis results. It included a summary of research questions and hypotheses, details of literature search and data collection procedures, quality assessment of studies, data abstraction, attributes of the studies included in the meta-analysis, and findings of the meta-analysis. The meta-analysis included sub-group analysis, sensitivity analysis, moderator analysis, and tests for publication bias.

Scientific literature search strategies were utilized for synthesizing the results of relevant primary studies. A comprehensive search strategy with explicit criteria for the inclusion and exclusion of studies was used. The full text articles were selected on meeting the designated criteria. The data was abstracted by using data abstraction form. For reporting of meta- analysis, I followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000) and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

The search strategy retrieved 12,188 records. On title review, 170 abstracts were eligible for review. On reviewing the abstracts, 69 full-text journal articles seemed to meet inclusion criteria. On examining full-text journal, 33 articles fulfilled the inclusion criteria and were included in the meta-analysis. These articles represented 11 (50%) countries of the Middle Eastern Region with the highest number of studies from Saudi

Arabia [12 (37%)] followed by Iran and Pakistan each of which contributed five (15%) studies in this meta-analysis. Out of the total 33 studies included in this meta-analysis, 17 studies included women with GDM, while 15 included women with GDM/PGDM and one study included women with PGDM only. A total of 118,652 pregnant women were included in these studies. The studies including women with GDM had a total of 53,744 pregnant women while those including women with GDM/PGDM included 62,320 pregnant women. There were 2,588 pregnant women in the study including women with PGDM. This meta-analysis investigated caesarean section as the adverse maternal outcome while macrosomia and perinatal death as adverse fetal outcome. A total of 27 (81.8%) studies examined the association of GDM/PGDM with caesarean section while 26 (78.8%) studied macrosomia and 24 (72.7%) studies observed perinatal deaths.

In this meta-analysis, the association of GDM/PGDM with adverse maternal and fetal outcomes were expressed as odds ratios and 95% confidence intervals. Comprehensive Meta-Analysis software (CMA) [Version 2] was used to calculate individual effect sizes for each study. Because statistical heterogeneity was expected within included studies, a random-effects model was employed to pool the data, setting statistical significance at a p value < 0.05. To assess the variance of the true effect sizes the Q statistic and I^2 statistic were computed. Subgroup analysis for the outcomes among women with GDM and PGDM was conducted to calculate a summary estimate for subgroups of studies. Sensitivity analysis was done to assess the influence of individual studies on the results of the meta-analysis. Moderator analysis examined heterogeneity by observing the influence of differences in study design, year of publication and country of

origin of the studies. Funnel plot, Duval and Tweedie trim and fill procedure, Egger's regression test, fail safe N, and Orwin's fail safe N tests were applied to assess the publication bias.

The pooling of the data showed that odds of undergoing caesarean section in women with GDM/PGDM was 2.56 times more than those without GDM/PGDM [OR = 2.56, 95% CI (2.13-3.07), $p < 0.0001$)]. The pooled estimate for women with PGDM and the outcome of caesarean section (OR = 3.24 95% CI [2.51-4.17], $p < 0.0001$) was greater as compared to those with GDM (OR = 2.39, 95% CI [1.84-3.1], $p < 0.0001$). Overall pooling of all data for macrosomia showed the odds of having a macrosomic baby in women with GDM/PGDM 3.5 times as compared to those without GDM/PGDM (OR = 3.51, 95% CI [2.73-4.51], $p < 0.0001$). The pooled odds ratio for women with GDM and the outcome of macrosomia (OR = 3.83, 95% CI [2.83-5.18], $p < 0.0001$) was more as compared to women with PGDM (OR = 3.51 95% CI [2.22-5.57], $p < 0.0001$). The overall pooling of the data showed that odds of perinatal death in women with GDM/PGDM was 2.46 times more than those without GDM/PGDM (OR = 2.46, 95% CI [1.81-3.34], $p < 0.0001$). The pooled odds ratio for women with PGDM and perinatal death 3.71 (95% CI [2.09-6.57], $p < 0.0001$) was more as compared to those with GDM (OR = 2.23, 95% CI [1.40 -3.54], $p = 0.0007$).

The tests for heterogeneity were statistically significant showing moderate heterogeneity in most cases. However, there were statistically non-significant results, on assessing the studies examining delivery by caesarean section and perinatal death, for the differences in effect sizes according to study design, publication period and country of

origin of the study. In case of macrosomia, statistically significant differences in effect sizes were not found for study design and publication period; however, the results were statistically significant for the difference in effect sizes according to the country of origin of study. Chapter 5 will include the interpretation of the meta-analysis results, limitations of this meta-analysis, recommendations and implications for positive social change of this study.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

To determine the association of GDM/PGDM with adverse pregnancy outcomes among women in the EMR, I performed a meta-analysis of the research studies conducted in the EMR. Maternal and fetal outcomes were specified to determine the magnitude of association between adverse pregnancy outcomes in GDM/PGDM. In this meta-analysis, caesarean section was studied as adverse maternal outcome while macrosomia and perinatal mortality were studied as adverse fetal outcomes.

The odds of having an adverse maternal outcome was greater in women with GDM/PGDM as compared to those without GDM/PGDM. This meta-analysis indicated that the odds of undergoing caesarean section in women with GDM/PGDM was 2.56 times more than those without GDM/PGDM. The odds of undergoing caesarean section in women with PGDM was 3.24 times as compared to those without GDM/PGDM while it was 2.39 times more in women with GDM in comparison to those without GDM/PGDM.

The odds of having adverse fetal outcomes was greater in women with GDM/PGDM as compared to those without GDM/PGDM. The odds of having a macrosomic baby in women with GDM/PGDM was 3.5 times as compared to those without GDM/PGDM. On subgroup analysis, the odds of having a macrosomic baby in women with GDM was 3.83 times as compared to those without GDM/PGDM while it was 3.51 times in women with PGDM as compared to those without GDM/PGDM. On examining the association of perinatal deaths with GDM/PGDM, the odds of perinatal

death in women with GDM/PGDM was 2.46 times more than those without GDM/PGDM. The odds of having perinatal death was higher in women with PGDM being 3.71 times more as compared to those without GDM/PGDM, while it was 2.23 times more in women with GDM in comparison to those without GDM/PGDM.

Interpretation of the Findings

The findings of this meta-analysis are in accordance with the findings of most of the studies conducted worldwide as well as in the EMR. However, the results are more precise and stable as compared to any single study conducted in the EMR. The interpretation of findings of this meta-analysis and their comparison with the international literature is discussed according to the 2 research questions, as follow.

Research Question 1

RQ1 asks the following question: Is there an association between delivery by cesarean section and GDM/PGDM among women in the EMR?

In this meta-analysis, the odds of undergoing caesarean section in women with GDM/PGDM was 2.56 times greater than those without GDM/PGDM (OR = 2.56, 95% CI [2.13-3.07], $p < 0.0001$). This is in accordance with a case-control study conducted in Kuwait where women with GDM/PGDM had significantly higher rate of caesarean section ($p = 0.008$) as compared to those without GDM/PGDM (Diejomaoh et al., 2009). Sobande et al. (2000) also found a statistically significant association between GDM/PGDM and delivery by caesarean section. The researchers reported an odds ratio of 5.22; however, the confidence intervals were wide with a 95% confidence interval of 1.90 to 16.48 (Sobande et al., 2000). To determine the association of GDM and PGDM

with delivery by cesarean section among women in the EMR, I also conducted subgroup analysis.

On subgroup analysis, among women with GDM, the odds of being delivered by caesarean section was 2.39 times as compared to those without GDM (OR= 2.39, 95% CI [1.84-3.1], $p < 0.0001$). This strength of association of caesarean section with GDM is higher as compared to that found in a study from Sweden which was conducted to determine maternal and neonatal outcomes for women with GDM during 1991-2003. It was a population-based cohort study using the Swedish Medical Birth Register data. In this study adjusted odds ratio for caesarean section was 1.46 (95% CI, 1.38-1.54; Fadl, Östlund, Magnuson, & Hanson, 2010). The finding of this meta-analysis is supported by various studies in the EMR. In Qatar, the cesarean section rate was significantly higher in women with GDM as compared to those without GDM (27.9% vs. 12.4%; $p < 0.001$;Bener et al., 2011)**.** Similarly, in a study of 228 pregnant women higher rate of cesarean section (68%) was noted among women with GDM as compared to 46.8% ($p = 0.009$) in those without diabetes (Tahir et al., 2011). The findings of this meta-analysis are also in accordance to the study by Hossein-Nezhad et al. (2007) in which the odds for cesarean section were 2.28 times more in women with GDM as compared to those without GDM. The results were statistically significant at $p = 0.0002$. In another study including 420 Iranian women, there was a significant difference between women with GDM and those without GDM in delivery by cesarean section (RR= 1.96, $p < 0.05$; Abolfazl et al. 2008). In contrast to the above studies, certain studies did not show

statistically significant association between GDM and delivery by caesarean section (Al-Khalifah et al., 2012; Nasrat et al., 1997; Al-Shawaf et al., 1988).

In this meta-analysis, the pooled estimate of odds ratio for women with PGDM and the outcome of caesarean section was 3.24 (95% CI, [2.51-4.17], $p<0.0001$), which was higher as compared to those with GDM (OR = 2.39, 95% CI [1.84-3.1], $p < 0.0001$). Other studies have also shown that women with PGDM have higher rates of caesarean section as compared to those with GDM. Shand et al., (2008) studied outcomes of pregnancies in 370,703 Australian women; out of which 1,248 women had PGDM while 17,128 had GDM. The odds of having delivery by caesarean section was reported in two categories; caesarean before labor and caesarean after labor. Among women with PGDM, the odds ratio for caesarean before labor was 4.83 (95% CI, 4.25-5.48) while for caesarean after labor, it was 3.18 (95% CI, 2.72-3.71). Among women with GDM, the odds ratio for caesarean before labor was 1.77 (95% CI, 1.70-1.85), while for caesarean after labor, it was 1.48 (95% CI, 1.41-1.55). Similar results are reported by researchers from the EMR. A prospective hospital-based study conducted among 100 women with diabetes (27 women with GDM and 73 women with PGDM) showed that women with PGDM had higher rate of cesarean section as compared to those with GDM (Akhlaghi & Hamedi**,** 2005). In another hospital-based study conducted in Abu Dhabi, 129 records of women with diabetes delivered over a two year period were reviewed. Of these, 82 had GDM, and 47 had PGDM. Patients with PGDM had a significantly higher rate of caesarean sections ($p = 0.0147$) as compared to those with GDM (Misra et al., 2001). Similarly, Barakat, et al. (2010) observed a higher strength of association for cesarean

delivery among women with PGDM (OR = 4.39; 95% CI [1.68-11.49]) as compared to those with GDM (OR = 2.70; 95% CI [1.17-4.03])**.** Thus, this meta-analysis showed that delivery by caesarean section is an important adverse outcome in women having pregnancy with diabetes. Moreover, among women having pregnancy with diabetes, the odds of having delivery by caesarean section are greater in women with PGDM as compared to those with GDM. In addition to higher rates of caesarean section, adverse fetal outcomes also occur in pregnancy with diabetes and are discussed as follows:

Research Question 2

RQ2 asks the following question: Is there an association between adverse fetal outcomes and GDM/PGDM among women in the EMR?

RQ2a. Is there an association between macrosomia and GDM/PGDM among women in the EMR?

The odds of having a macrosomic baby in women with GDM/PGDM was 3.5 times more as compared to those without GDM/PGDM. The pooled odds ratio for macrosomia and GDM/PGDM among women was 3.51 (95% CI, 2.73-4.51, $p < 0.0001$). Diejomaoh et al. (2009) found the incidence of fetal macrosomia in women with GDM/PGDM double than those without GDM/PGDM (13.6 vs. 5.7%). The odds of having a macrosomic baby in women with GDM/PGDM was 2.62 (95% CI, 1.213–5.657) as compared to those without GDM/PGDM (Diejomaoh et al., 2009).

On sub-group analysis, in women with GDM, the odds of having a macrosomic baby is 3.8 times in comparison to those without diabetes. The pooled odds ratio for women with GDM and the outcome of macrosomia was 3.83 (95% CI, 2.83-5.18, $p <$

0.0001). Other authors have also reported similar association between macrosomia and GDM. The finding of this meta-analysis is comparable to the study using the Swedish Medical Birth Register data for the period 1991-2003, in which the adjusted odds ratios for large for gestational age newborns among women with GDM was 3.43 (95% CI, 3.21-3.67; Fadl et al., 2010). In another study, live-born infants of Australian women with GDM were 1.6 times more likely to have a birth weight greater than the 90th percentile (OR = 1.65, 95% CI, 1.57-1.72; Shand et al., 2008). Similar results were demonstrated in a cohort study in Iran in which women with GDM had a higher rate of macrosomia (OR = 3.2; 95% CI [1.2-8.6]) as compared to those without GDM (Keshavarz et al., 2005). In another study in Iran, Hossein-Nezhad et al. (2007) found that the odds ratio for macrosomia (OR = 1.93, $p = 0.0374$) was significantly higher in women with GDM as compared to those without GDM. Bener et al. (2011) studied a cohort of 1,608 pregnant women in Qatar, and found that the newborns of women with GDM were at increased risk of macrosomia (10.3% vs. 5.9%; $p = 0.01$) than those of women without GDM**.** In a cohort study including 420 Iranian women, the newborns of women with GDM were seven times more at risk of being macrosomic (RR = 7.38, $p < 0.05$) as compared to those born to women without GDM (Abolfazl et al., 2008).

In this meta-analysis, the pooled estimate of odds ratio for women with PGDM and the outcome of macrosomia was 3.51 (95% CI, 2.22-5.57, $p < 0.0001$), which was lower as compared to those with GDM (OR = 3.83, 95% CI [2.83-5.18], $p < 0.0001$). This is in contrast to certain studies where on comparing the strength of association of macrosomia, women with PGDM were found to be more prone to have a macrosomic

baby. In a one-year retrospective review of records of 5,394 pregnant women registered in Oman, 225 had GDM and 56 had PGDM. The risk of macrosomia was three-fold among women with GDM (OR = 3.03; 95% CI [1.36-6.75]) and approximately seven-fold among those with PGDM (OR = 7.20; 95% CI [2.30-22.61]; Barakat et al., 2010). Shand et al., (2008) found that the infants of Australian women with PGDM were 4.6 times more likely to have a birth weight greater than the 90th centile (OR = 4.6, 95% CI 4.1-5.2) compared with infants of mothers without diabetes. In the same study the odds of having a newborn > 90th percentile among women with GDM was 1.65 (95% CI, 1.57-1.72; Shand et al., 2008).

In contrast to the findings of above studies, some researchers have reported statistically non-significant association between macrosomia and pregnancy with diabetes. In a study of 424 pregnant women in Saudi Arabia, infants of women with diabetes were found to be heavier than those without diabetes, however, the proportion of babies with birth weight ≥ 2 standard deviations above the mean, were equal in both groups (Nasrat et al., 1994). In another study of 185 pregnant women with diabetes in Saudi Arabia, there were 27 (14.6%) with type 1 diabetes forming group 1; 19 (10.2%) with type 2 diabetes constituting group 2 and 139 (75.2%) with GDM making up group 3. There were no statistically significant differences in the three groups regarding the mean birth weight ($p > 0.05$) of newborns (Sobande et al., 2005). Another retrospective cohort study among pregnant women with GDM in Saudi Arabia including 766 women (419 women with GDM and 347 without GDM), was also not able to demonstrate statistically significant association between macrosomia and GDM (Al-Khalifah et al., 2012). To

sum up, although researchers of primary studies have reported conflicting results regarding association between macrosomia and GDM/PGDM, there is a clear positive association between macrosomia and GDM/PGDM among women in the EMR, in this meta-analysis.

RQ 2b: Is there an association between perinatal mortality and GDM/PGDM among women in the EMR?

The odds of perinatal death in women with GDM/PGDM was 2.46 times more than those without GDM/PGDM (OR = 2.46, 95% CI [1.81-3.34], $p < 0.0001$). The Confidential Enquiry into Maternal and Child Health in the United Kingdom reported that perinatal mortality was nearly four-fold in women with diabetes as compared to the general population (Confidential Enquiry into Maternal and Child Health [CEMACH], 2005). In a cohort study including 420 Iranian pregnant women (70 women with diabetes and 350 without diabetes), statistically significant difference in still births [RR = 8.87, $p < 0.05$] between the two groups was observed (Abolfazl et al., 2008). Misra et al. (2001) reviewed records of 129 women with diabetes in a hospital-based study in Abu Dhabi. Perinatal mortality rate was 2.5 times higher among women with diabetes than in the general population. In a case-control study conducted in Sudan, the perinatal mortality rate was significantly higher ($p < 0.01$) among women with diabetes than the total hospital population. The overall perinatal mortality rate in women with diabetes was 3.5 times more than that for women without diabetes (Dafallah & Yousif, 2004). Unexplained intrauterine deaths were more common in PGDM (RR = 18.4; 95% CI [3.9-85.7]) than in GDM (RR = 13.4; 95% CI [29-61.6]; Dafallah & Yousif, 2004).

In this meta-analysis, the pooled odds ratio for women with GDM and the outcome of perinatal death was 2.23 (95% CI [1.40-3.54], $p = 0.0007$). This finding is consistent with the results of various studies. On a review of pregnancy outcome in 116,303 pregnancies, at the Mercy Hospital for Women, GDM was found to be associated with an increased risk of perinatal mortality (OR = 1.53, 95% CI [1.13-2.06]; Beischer et al., 1996). Similarly, Shand et al. (2008) found that Australian women with PGDM and GDM were at increased risk of mortality in infants as compared to those without diabetes. They found the odds of having a still birth among women with GDM as 1.17 (95% CI, 0.88-1.54). Studies from Middle Eastern region have also shown an increased perinatal mortality rate in women with GDM/PGDM. In Iran, in a prospective cohort study of 1,310 Iranian pregnant women, babies born to women with GDM had a higher rate of stillbirth (OR = 17.1, 95% CI [4.5-65.5]; Keshavarz et al., 2005). Because of less number of events in any single study, most of the studies from EMR did not have statistically significant association between GDM and perinatal deaths (Almarzouki, 2013; Barakat et al., 2010; El Mallah et al., 1997; Gasim, 2012; Nasrat et al., 1996; Wahabi et al., 2013). However, combining results of these studies by meta-analysis showed statistically significant association of perinatal deaths and GDM.

In this meta-analysis, the pooled odds ratio for women with PGDM and perinatal death was 3.71 (95% CI [2.09 - 6.57], $p < 0.0001$). Shand et al. (2008) found an odds ratio of 2.90 (95% CI, 1.81-4.60) for still birth among Australian women with PGDM. In an attempt to explore major risk factors for still births in high income countries, a meta-analysis of five studies showed that the odds of stillbirth increased nearly three times for

women with PGDM (OR = 2.90, 95% CI, 2.05-4.09)**,** however, the same study did not demonstrate an increased risk of still birth among women with GDM (Flenady et al., 2011)**.** Because of few numbers of perinatal deaths in any single study, most of the primary studies from the EMR did not report a statistically significant association between perinatal deaths and PGDM (Abdelgadir et al., 2003; Al Teheawt& Farida, 1995; Barakat et al., 2010; Wahabi et al., 2012). However, merging the results of these studies by meta-analysis lead to a statistically significant association found between perinatal deaths and PGDM.

Researchers have compared outcomes of pregnancy in women with type 1 diabetes, type 2 diabetes and GDM. Greater risk of perinatal deaths, among women with type 2 diabetes as compared to those with type 1 diabetes or GDM, are reported (Cundy et al., 2000; Dunne et al., 2003; Jensen et al., 2004; Macintosh, 2006). In a meta-analysis conducted to compare maternal and fetal outcomes in pregnant women with type 2 and type 1 DM, the researchers found that women with type 2 DM had a greater risk of perinatal mortality (OR = 1.50, 95% CI [1.15-1.96]; Balsells et al., 2009). Although incidence of perinatal mortality is shown to vary according to the type of diabetes, in this meta-analysis because of limited available data perinatal mortality could not be analyzed according to the types of diabetes.

An increased perinatal mortality rate is especially important in settings where appropriate obstetric care is not accessible to the whole population (IDF, 2009; Schmidt et al., 2001). Because of poor socioeconomic conditions, some countries of the EMR such as Somalia, Afghanistan and Pakistan, are not able to provide access to obstetric

care to a substantial proportion of their population. Thus, it is important to determine the perinatal mortality attributed to pregnancy with GDM/PGDM.

Meta-analysis Findings in Context of Conceptual Model

For this meta-analysis, epidemiologic triangle was used as the conceptual model. The epidemiologic triangle is a traditional model examining the agent, the host, and the environmental factors to examine causation of infectious disease (CDC, 2009). However, it has also been used for chronic diseases and other health problems.

Agent

For GDM and its outcomes, the agent which is the cause of the condition, is insulin. During pregnancy, some hormones (human placental lactogen, estrogen, and cortisol) secreted by placenta can have a blocking effect on insulin, named as "insulin resistance." GDM results if the insulin secretion is not adequate to counter the effect of the placental hormones (Ohio State University, n.d.). Generally production of insulin increases during pregnancy, however, there is less insulin secretion in women with GDM as compared to those without GDM (Abayomi, Wood, Spelman, Morrison, & Purewal, 2013). Adverse outcomes of GDM/PGDM such as macrosomia, delivery by caesarean section and perinatal mortality are associated with insulin resistance during pregnancy (Young & Ecker, 2013).

Host

The host factors comprise of non-modifiable and modifiable factors. Non-modifiable factors include age (women more than 25 years age are at a higher risk for developing GDM than younger women); race (Asian American, American Indian,

African-American, Hispanic/Latino, or Pacific Islander have a greater risk); having given birth previously to macrosomic baby, or a still birth (Ben-Haroush et al., 2006; Ferrara, 2007). Modifiable factors include overweight/obesity; lifestyle factors including diet and physical activity (Iqbal, 2005)..

Perinatal outcomes among women with GDM differ by ethnicity. These variations may occur due to genetic factors as well as cultural traditions and diet during pregnancy influencing glycemic control. Another factor is variation in prenatal care accessibility and quality of available prenatal care (Nguyen et al., 2012). In the Middle Eastern region, various important demographic, lifestyle, and health transitions have occurred during previous decades. However, these transitions vary in different countries as the ethnicity, socio-cultural conditions, and economic situation varies among the member countries (Zabetian, Keli, Echouffo-Tcheugui, Narayan, & Ali, 2013). These variations could also be seen among the studies included in this meta-analysis. Strength of association with various adverse outcomes varied from country to country. The studies were assessed for differences in effect sizes according to the country of origin of study. The pooled odds ratio for adverse maternal and fetal outcomes varied among countries, however the differences among countries were not significant statistically for delivery by caesarean section and perinatal deaths while the differences among countries was statistically significant ($p < 0.0001$) in case of macrosomia.

Environment

Environmental factors that contribute to GDM may include physical, social and economic environment. Availability and affordability of healthy food; cultural values and

accessibility to health care facilities are some of the environmental factors playing their role in the etiology of GDM. In turn, these environmental factors are also related to maternal and fetal outcomes of PGDM/GDM including macrosomia, caesarean delivery and perinatal mortality (El-Chaar et al., 2013; Yogev & Visser, 2009).

GDM and PGDM are becoming more prevalent in pregnancy, however, it is observed that women with diabetes often do not receive optimal pre-conception care and antenatal care (Abayomi et al., 2013). The high incidence of some adverse pregnancy outcomes associated with GDM in low- and middle-income countries may signify inadequate care for women with GDM in these countries (Zabetian et al., 2013). It is estimated that 98% of all perinatal deaths occur in low-income countries where perinatal mortality rate is approximately five times higher than high-income countries (Cloke & Pasupathy, 2013). In my meta-analysis study, there is greater strength of association for perinatal deaths as compared to the findings of the studies conducted in developed nations, as the EMR comprises both middle-income and low- income countries. One of the reasons for higher perinatal death rate in low-income countries is that only around 40% of births in low-income countries are attended by trained health care workers in comparison to almost 100% in the high income countries (Cloke & Pasupathy, 2013).

To sum up, the conceptual model for this study is epidemiologic triangle. Agent, host and environment play an important role in the causation of diabetes mellitus, PGDM/GDM, and their adverse maternal and fetal outcomes.

Limitations of the Study

This study has limitations which correspond with the limitations of meta-analyses in general (Garg et al., 2008). This meta-analysis includes diverse studies with different settings, designs, and study participants. The quality and reliability of the overall effect size and conclusions of this meta-analysis depends on the reliability and appropriateness of methods used by the primary studies. Meta-analysis of observational studies has certain specific limitations which are also reflected in my study. The role of chance, confounding factors, or biases, may affect the results in primary observational studies which could not be rectified in this meta-analysis (Egger et al., 2008). Another limitation specific to this meta-analysis is the variability in defining the dependent and independent variables in primary studies. Different diagnostic criteria were used for GDM in various studies. Similarly, definition of macrosomia/large for gestational age also varied in primary studies. In some studies, women with impaired glucose tolerance test (IGTT) were also included along with women with GDM/PGDM. In most of these studies, data for women with IGTT were separately analyzed. However, in two studies (Diejomaoh et al., 2009; Khan et al., 1995), it was not done and women with IGTT were also included in this meta-analysis. In the study of Diejomaoh et al. (2009), among 177 cases with diabetes mellitus, 25 cases of IGTT were also included and the data were not analyzed separately. Khan et al. (1995) had included 292 women with abnormal GTT in their study; out of which 177 were with GDM while 115 were with IGTT. Data analysis was not presented separately for these groups. As women with IGTT are less prone to have adverse pregnancy outcomes, this inclusion of women with IGTT might have decreased

the strength of association between exposure and outcome, observed in this meta-analysis.

Other limitations related to selection of participants in the primary studies might have affected the results of this meta-analysis. Researchers in a case- control study (Almarzouki, 2013) had included women with GDM as cases while the controls were high risk women without GDM. This inclusion might have decreased the strength of association between exposure and outcome as the high risk women are more prone to have adverse pregnancy outcomes. Fadwa et al. (2013) collected data from women with diabetes and those without diabetes through structured questionnaires. Women were asked about history of various adverse pregnancy outcomes. The data collected in this study may have limitations because of recall bias. Because of limitations of the primary studies, this meta-analysis has certain threats to validity which are discussed in the next section.

Threats to Validity

This meta-analysis has threats to the validity by factors that might lead to incorrect inferences (Cooper et al., 2009). There are threats to construct validity, internal validity, statistical conclusion validity, and external validity. These threats to validity are discussed as follows:

Construct Validity

It is important for meta-analysis that the effect sizes calculated from various measures can be compared directly (Nugent, 2009). For this purpose, definitions of variables should be consistent in the primary studies and meta-analysis. In my study, the

definitions used in the primary studies were not consistent. The criteria for diagnosis of GDM were not consistent in primary studies. Some studies used WHO criteria; while others used Carpenter and Coustan criteria; O'sullivan's criteria; American Diabetes Association criteria; or National Diabetes Data Group (NDDG) criteria. Similarly, definition of macrosomia varied in primary studies; some studies used the cut-off weight of 4,000 grams (Bener et al., 2011; El Mallah et al., 1997; Khan, Ali, & Khan, 2013), some used 4,500 grams (Barakat et al., 2010; Johnstone et al., 1990) for defining macrosomia; while others used the term large for gestational age (Abdelgadir et al., 2003; Al-Khalifah et al., 2012; Almarzouki, 2013). Similarly, various studies used different descriptions for perinatal deaths. Only one study (Almarzouki, 2013) defined perinatal mortality as fetal or neonatal death from 22 weeks of pregnancy to four weeks after birth. Al-Mejhim & Al-Najashi (1998) defined perinatal deaths as all stillbirths and all live babies who weighed 500 g or more and died in the first week of life. Some studies reported still births/intrauterine fetal deaths and early neonatal deaths while others had included only still births/intrauterine fetal deaths. Nasrat et al. (1993) had included only neonatal deaths. The discrepancies in various variable definitions might have pushed toward or pulled away the results from the null value.

Internal Validity

Internal validity refers to the validity of associations inferred from the results of the primary studies. Meta-analysis of observational studies has certain specific limitations which are threats to internal validity. Estimates of association in observational studies may not depict true associations because of various factors. In addition to the role of

chance, confounding factors, biases, or both may affect the results in observational studies. The exposed study participants may be different in various ways which are related to the risk of developing the outcome of interest (Egger et al., 2008). The effect of residual confounding is another threat to validity of meta-analysis of observational studies (Flenady et al., 2011). Many case- control studies in this meta-analysis had not matched the cases and controls for important confounding factors, which may have affected the results of those primary studies (Al-Khalifah et al., 2012; Almarzouki, 2013; Al Teheawt & Farida, 1995; Barakat et al., 2010), in turn reflecting on the results of this meta-analysis.

Statistical Conclusion Validity

Statistical conclusion validity refers to the application of appropriate statistical tests in primary studies (Cooper et al., 2009). The quality and reliability of the overall effect size and conclusions of meta-analysis depends on the reliability and appropriateness of methods used by the primary studies. The statistical results of the meta-analysis depend upon the statistical analysis conducted in primary studies, such as control of confounding factors by using logistic regression. Most of the primary studies in this meta-analysis did not use logistic regression or other statistical test to control confounding factors which may have affected the results of this meta-analysis.

External Validity

External validity refers to the generalization of the results of meta-analysis (Cooper et al., 2009). Meta-analysis includes diverse studies differing in their study participants enrolled from various geographical regions. My study generalizes the results

to the population of EMR. The studies selected for inclusion in meta-analysis did not include studies from all countries in the EMR, leading to threats to the external validity. None of the studies could be found from low-income countries such as Afghanistan, Yemen and Somalia which may have a different picture of adverse pregnancy outcomes among women with GDM/PGDM.

Recommendations

This meta-analysis has generated questions for future research beyond the scope of this study. These questions concern five areas: (a) reasons for higher magnitude of association of adverse pregnancy outcomes among women in the EMR as compared to other parts of the world, (b) magnitude of association of adverse pregnancy outcomes among women in those countries of EMR from where no studies were available, (c) research to get a broader picture of the situation in the EMR by a multi-country study, (d) population-based research for determining adverse pregnancy outcomes among women deprived of care by an appropriate health care facility, and (e) research to determine the health seeking patterns of women with GDM/PGDM, as in many countries of the EMR, home deliveries are common. A large scale study with uniform definitions for macrosomia and perinatal mortality may also be conducted in the Region so that valid comparisons are possible and real picture of this important public health problem is gained.

Implications

Filling gaps in the literature helps in creating positive social change which is an important aspect of this study. This meta-analysis provides a broader perspective of

adverse pregnancy outcomes associated with GDM/PGDM among women in the EMR. By combining the results of small-scale published studies with small sample sizes and few adverse outcomes among women in the EMR, this meta-analysis has filled the literature gap through providing stable and statistically significant estimates of association. This meta-analysis has also demonstrated the magnitude of association between GDM/PGDM and adverse pregnancy outcomes among women in the EMR, which is an important initial step prior to research efforts focusing on the epidemiology of adverse pregnancy outcomes as they relate to PGDM and GDM in the EMR. Information about the strength of association of GDM/PGDM with adverse pregnancy outcomes is helpful in creating awareness about the severity and seriousness of the problem. Disseminating the results of this study can lead to measures taken by the policy makers and health care workers to develop intervention strategies for prevention of complications related to GDM/PGDM. Thus, an implication for social change resulting from this meta-analysis includes making health care providers aware of the magnitude of problem related to GDM/PGDM. Awareness of the problem can enhance the ability of the health care providers to identify, diagnose and properly manage the women with GDM/PGDM.

In light of the findings of this meta-analysis, I suggest three recommendations. The first recommendation is for health care workers to follow the guidelines for screening and managing the pregnant women with GDM/PGDM. The second recommendation is for health education workers to create awareness among women with GDM/PGDM to follow the instructions by health care providers. Traditionally, home

deliveries are practiced in some countries of the EMR. Encouraging women with GDM/PGDM to receive antenatal check ups and delivery in a well-equipped health care facility can play vital role in reducing adverse pregnancy outcomes and associated complications (Koyanagi et al., 2013). The third recommendation is for the decision makers to keep updating the policies and guidelines related to GDM/PGDM and to assure implementation of these guidelines. Pre-conception care for women with PGDM is associated with better outcomes (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee et al., 2013). Therefore, optimal pre-conception care may be provided to women with PGDM. The policy makers should also consider providing specialized health care for women with GDM/PGDM, during pregnancy and in the postpartum period to reduce adverse maternal and fetal outcomes. These intervention will also help women in making changes to their lifestyle, thus, improving their health in the long term (Abayomi et al., 2013)

Conclusion

GDM/PGDM is associated with significant maternal and fetal morbidity, including delivery by caesarean section, macrosomia and perinatal deaths (Carolan, 2013; Cho, 2013). The number of women with GDM is increasing steadily, which may be attributed to higher maternal age, increasing prevalence of obesity, and sedentary lifestyles (Cho, 2013). In the EMR, these demographic and lifestyle changes have occurred during previous decades (Zabetian et al., 2013). In this meta-analysis study there was a strong association between adverse maternal and fetal outcomes and GDM/PGDM and I recommend that health care providers and policy makers design

intervention measures to create awareness among women. Moreover, guidelines and protocols for care of women with diabetes should be developed and implemented to decrease the adverse outcomes. Interventions during pregnancy provide important opportunities to improve the health of mothers and children (Cho, 2013). Healthy mothers and children are vital for a healthy and productive community, and for a prosperous world.

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Appendix A: MOOSE Guidelines

MOOSE: (Meta-analysis of observational studies in epidemiology): A checklist for authors, editors, and reviewers of meta-analyses of observational studies.

Reporting background should include

- Problem definition
- Hypothesis statement
- Description
- Type of exposure or intervention used
- Type of study designs used
- Study population

Reporting of search strategy should include

- Qualifications of searches (e.g. librarians and investigators)
- Search strategy, including time period included in the synthesis and keywords
- Effort to include all available studies, including contact with authors
- Databases and registries searched
- Search software used, name and version, including special features
- Use of hand searching (e.g. reference lists of obtained articles)
- List of citations located and those excluded including justification
- Method of addressing articles published in languages other than English
- Method of handling abstracts and unpublished studies
- Description of any contact with authors

Reporting methods should include

- Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested
- Rationale for the selection and coding of data (eg, sound clinical principles or convenience)
- Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)
- Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)
- Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results
- Assessment of heterogeneity
- Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated
- Provision of appropriate tables and graphics
- Table giving descriptive information for each study included

Reporting of results should include

- Graphic summarizing individual study estimates and overall estimate
- Results of sensitivity testing (eg, subgroup analysis)
- Indication of statistical uncertainty of findings

Reporting of discussion should include

- Assessment of quality of included studies
- Justification for exclusion (eg, exclusion of non–English-language citations)
- Quantitative assessment of bias (eg, publication bias)

Reporting of conclusions should include

- Consideration of alternative explanations for observed results
- Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)
- Guidelines for future research
- Disclosure of funding source

Note: Adapted with permission of the author from "Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group" by,. D. F. Stroup, J. A. Berlin, S. C. Morton, I. Olkin, G. D.Williamson, D. Rennie, … S. B. Thacker, 2000, *JAMA: The Journal of the American Medical Association*, *283*(15), p.2010. Copyright 2000 by the American Medical Association

Appendix B: Dummy Table for Summary of Research Studies Included in Meta-Analysis

Characteristics of observational studies of Pregestational/ Gestational Diabetes and Adverse Pregnancy Outcomes in Eastern Mediterranean Region

Study No	Author	Country	Study Design	Time Period	Sample size(n)	Type of Maternal Diabetes	Outcome	
							Maternal	Fetal

Appendix C: Data Abstraction Form

Sr. No:

Author:

Journal Article Title:

Country:

Study Design:

Time Period during which study was conducted:

Sample Size:

Mean Maternal Age:

Type of Diabetes:

Pregnancy Outcomes

Fetal Outcome:

Macrosomia ☐

Perinatal mortality ☐

Maternal Outcome:

C-section ☐

Comments:-

_____

_____

Quality Assessment:

_____

_____

_____

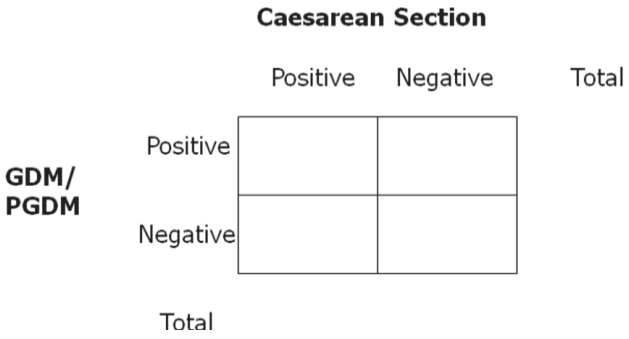
Reported Measures of Effect and Confidence Intervals

Caesarean Section:_____

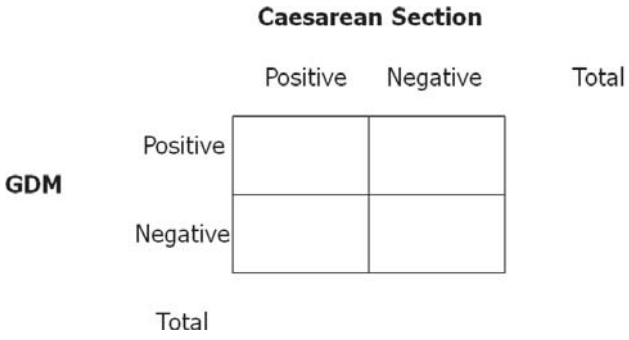
Macrosomia: _____

Perinatal Mortality:_____

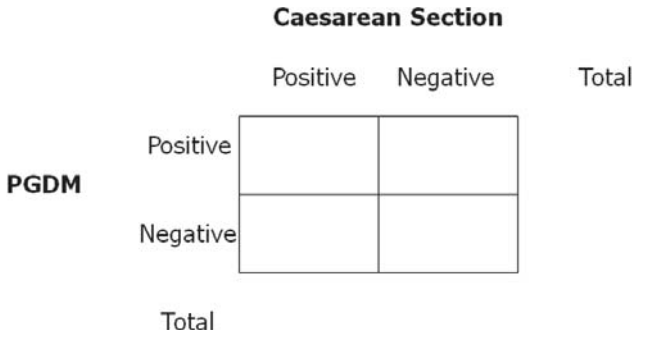
Dummy 2X2 Tables for calculation of Measures of Effect and Confidence Intervals

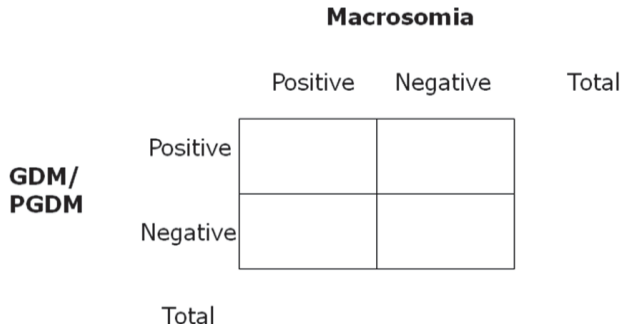


Odds Ratio (95% Confidence Interval)=

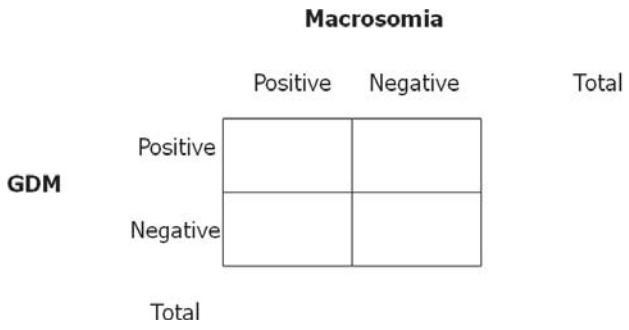


Odds Ratio (95% Confidence Interval)=





Odds Ratio (95% Confidence Interval)=



Odds Ratio (95% Confidence Interval)=

		Macrosomia		
		Positive	Negative	Total
PGDM	Positive			
	Negative			
	Total			

Odds Ratio (95% Confidence Interval)=

		Perinatal Deaths		
		Positive	Negative	Total
GDM/ PGDM	Positive			
	Negative			
	Total			

Odds Ratio (95% Confidence Interval)=

		Perinatal Deaths		
		Positive	Negative	Total
GDM	Positive			
	Negative			
	Total			

Odds Ratio (95% Confidence Interval)=

		Perinatal Deaths		
		Positive	Negative	Total
PGDM	Positive			
	Negative			
	Total			

Odds Ratio (95% Confidence Interval)=

Appendix D: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
Results		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
Discussion		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
Funding		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

Note. Adapted from "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement" by D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman, & The PRISMA Group, 2009. *PLoS Med*, *6*(7), e1000097. doi:10.1371/journal.pmed.1000097

Appendix E: Form for Quality Assessment of Studies

Cohort study

• Appropriate cohort selection

(The eligibility criteria, and the sources and methods of selection of participants are mentioned. Methods of follow-up are described)

Yes Partially No Can't tell

• Appropriate sample size

Yes Partially No Can't tell

• Properly described cohort

(For matched studies, matching criteria and number of exposed and unexposed are stated)

Yes Partially No Can't tell

• Clear description of diagnostic criteria for GDM/PGDM

Yes Partially No Can't tell

• Clear definition of the outcomes

Yes Partially No Can't tell

• Description of the methods for ascertaining outcomes

Yes Partially No Can't tell

• Description of lost to follow up

Yes Partially No Can't tell

• Appropriateness of statistical analyses

(Analysis with control for confounding factors taken into account)

Yes Partially No Can't tell

Case-control study

• Selection of cases in an appropriate and unbiased manner

(The eligibility criteria, and the sources and methods of case ascertainment are stated)

Yes Partially No Can't tell

• Selection of controls in an appropriate manner

Yes Partially No Can't tell

• Matching of cases and controls regarding potential confounders

(For matched studies, matching criteria and the number of controls per case are stated)

Yes Partially No Can't tell

• Description of diagnostic criteria

Yes Partially No Can't tell

• Clear definition of outcomes

Yes Partially No Can't tell

• Address the potential sources of bias

Yes Partially No Can't tell

• Appropriateness of statistical analyses

(Analysis with control for confounding factors taken into account)

Yes Partially No Can't tell

Cross-sectional study

- Adequate sample size

(Calculation of sample size is explained)

Yes Partially No Can't tell

- Appropriate methods of selection of participants

(Eligibility criteria, and the sources and methods of selection of participants are stated)

Yes Partially No Can't tell

- Description of diagnostic criteria

Yes Partially No Can't tell

- Clear definition of outcomes

Yes Partially No Can't tell

- Appropriate sources of data and methods of assessment for outcomes

(For each outcome, sources of data and methods of assessment for outcome is described)

Yes Partially No Can't tell

- Address the potential sources of bias

(Efforts to address potential sources of bias are described)

Yes Partially No Can't tell

- Appropriateness of statistical analyses

(Analysis with control for confounding factors taken into account)

Yes Partially No Can't tell

Appendix F: STROBE Guidelines

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias

Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Source: University of Bern. (2009). STROBE Statement: STROBE checklists. Retrieved from http://www.strobe-statement.org/?id=available-checklists

Appendix G: Permissions

Permission for Table 2

SAGE

Title: How Many Studies Do You Need?:A Primer on Statistical Power for Meta-Analysis

Author: Jeffrey C. Valentine, Therese D. Pigott, Hannah R. Rothstein

Publication: JOURNAL OF EDUCATION AND BEHAVIORAL STATISTICS

Publisher: SAGE Publications

Date: 04/01/2010

Logged in as:
saulat jahan

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Permission for Appendix A: MOOSE Guidelines

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Licensed content publication	JAMA
Licensed content title	Meta-analysis of Observational Studies in Epidemiology: A Proposal for Reporting
Licensed content author	Stroup, Donna F., Berlin, Jesse A. et al
Licensed content date	Apr 19, 2000
Volume number	283
Issue number	15
Type of Use	Dissertation/Thesis
Requestor type	student
Format	electronic
Portion	figures/tables/images
Number of figures/tables/images	1
List of figures/tables/images	
Will you be translating?	no
Circulation/distribution	1
Distributing to	North America
Order reference number	
Title of your thesis / dissertation	Gestational and Pre-gestational Diabetes in Eastern Mediterranean Region: A Meta- analysis of Maternal and Fetal Outcomes

Curriculum Vitae

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Experience	2011- Present Head of Research and Information Unit.	Research and Information Unit. Public Health Administration.	Qassim. Saudi Arabia.
	2004 - 2011 Public Health Specialist.	Health Education and Training Department.	Qassim. Saudi Arabia.
	2000- 2002 Assistant Professor.	Community Medicine Department. Islamic International Medical College.	Rawalpindi. Pakistan.
	1999-2001 Senior Public Health Officer.	Heartfile (Non-Governmental Organization for prevention of Heart diseases).	Islamabad. Pakistan
	1993-2000 Lady Medical Officer.	Capital Hospital.	Islamabad. Pakistan
	1989-1991 General Duty Medical Officer.	Pakistan Ordnance Factories Hospital.	Wah Cantonment. Pakistan.
Education	2008- Present PhD in Public Health (Epidemiology)	Walden University	Minneapolis, MN. USA.
	1996 -2001 FCPS in Community Medicine.	College of Physicians and Surgeons.	Karachi. Pakistan

1998- 1999 Master of Public Health	Health Services Academy.	Islamabad. Pakistan
1982-1987 M.B.B.S.	King Edward Medical College.	Lahore. Pakistan

Publications

Jahan, S., & Henary, B. (2012). Attitudes of primary health care physician managers toward research: a pre-experimental study. *Australian Journal of Primary Health*. Retrieved from http://dx.doi.org/10.1071/PY11146

Jahan, S. (2012). Health Promotion: Opportunities and Challenges. *Journal of Biosafety and Health Education*, 1:e105. doi:10.4172/jbhe.1000e105

Jahan, S. (2012). Epidemiology of Foodborne Illness. In B. Valdez (Ed.). *Scientific, Health and Social Aspects of the Food Industry.* InTech, ISBN: 978-953-307-916-5, Available from: http://www.intechopen.com/articles/show/title/epidemiology-of-foodborne-illness

Al-Goblan, A. S., & Jahan, S. (2010). Surveillance for foodborne illness outbreaks in Qassim, Saudi Arabia, 2006. *Foodborne Pathogens and Disease*, *7*(12), 1559–1562. doi:10.1089/fpd.2010.0638

Jahan, S., & Al Saigul, A. M. (2009). Response to: Measles outbreak in Qassim, Saudi Arabia 2007. *Journal of Public Health*. doi:10.1093/pubmed/fdp021

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Jahan, S., Al Saigul, A. M., Abu Baker, M. A. M., Alataya, A. O., & Hamed, S. A. R. (2008). Measles outbreak in Qassim, Saudi Arabia 2007: epidemiology and evaluation of outbreak response. *Journal of Public Health*, *30*(4), 384–390. doi:10.1093/pubmed/fdn070

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Jahan, S., Mohammed Al Saigul, A., & Abdul Rahim Hamed, S. (2007). Scorpion stings in Qassim, Saudi Arabia--a 5-year surveillance report. *Toxicon: Official Journal of the International Society on Toxinology*, *50*(2), 302–305. doi:10.1016/j.toxicon.2007.03.013

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Nishtar, S., Mirza, Y. A., Jahan, S., Hadi, Y., Badar, A., Yusuf, S., & Shahab, S. (2004). Newspaper articles as a tool for cardiovascular prevention programs in a developing country. *Journal of Health Communication*, *9*(4), 355–369. doi:10.1080/10810730490468603

Nishtar, S., Zoka, N., Nishtar, S. S., Khan, S. Y., Jahan, S., & Mirza, Y. A. (2004). Posters as a tool for disseminating health related information in a developing country: a pilot experience. *JPMA. The Journal of the Pakistan Medical Association*, *54*(9), 456–460.

Sultana, A., Jahan, S., & Ahmad, I. (2001). Knowledge, Attitude and Practice of Immunization in an Urban Population. *Pakistan Armed Forces Medical Journal*, *51*(2), 177-81.