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The Risk Factors of Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis Study

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Abstract

Objectives: Gestational diabetes mellitus (GDM) is the most common medical complication of pregnancy. If remains uncontrolled, it can cause lots of complications for both mother and fetus. The aim of this study is to investigate the risk factors of GDM in Iran using a meta-analysis study.

Methods: Different databases including all national scientific (Iranmedex, SID, Magiran, Irandoc, and Medlib) and international (PubMed/Medline, Scopus, and ISI Web of Knowledge) databases were searched for published data on GDM risk factors in Iran. A total of 21 relevant articles from 2001 to 2015 were finally analyzed. Data synthesis was performed based on the random effects model. Data were analyzed using R software and STATA.

Results: A total of 1658 pregnant women with average age of 29.15 years old were investigated. The mean body mass index (BMI) of the subjects was 27.53. The most common risk factors for GDM were: high age 64% (95% CI: 53–76), excess weight and obesity 47% (95% CI: 40–54), family history of diabetes 31% (95% CI: 26–36), history of abortion 22% (95% CI:16–27), history of glycosuria 12% (95% CI: 4–19), history of macrosomia 10% (95% CI: 6 –13), delivery ≥5 case 10% (95% CI: 2–17), history of gestational hypertension 5% (95% CI: 1–8), history of preeclampsia 4% (95% CI:2 –7), history of diabetes in pregnancy 4% (95% CI:1–8), history of stillbirths 3% (95% CI: 2–5), delivery <37 weeks 3% (95% CI: 0–6), previous congenital malformations 1% (95% CI: 0–2) and previous neonatal death 1% (95% CI: 0-2).

Conclusion: Considering that approximately 40% of pregnancy diabetes cases will turn into diabetes over the coming years, controlling the risk factors can reduce the incidence of diabetes in pregnancy.

Keywords: Gestational diabetes, risk factors, meta-analysis, Iran

Introduction

Gestational diabetes mellitus (GDM) refers to elevated blood sugar level that is firstly diagnosed during pregnancy (1). GDM is the most common metabolic disorder in pregnancy (2) which leads to severe complications for mother and fetus such as preeclampsia, premature membrane rupture, preterm delivery, cesarean, fetal macrosomia and poly hydramnios or damages during delivery including dislocation of the shoulder, bone fractures, nerve paralysis, low birth weight and fetal metabolic disorders (3-9). Results of studies on children of mothers with gestational diabetes indicate that these children are exposed to greater risk levels of obesity, increased body mass index (BMI), excess weight, insulin resistance, hypertension, renal disease, and type 2 diabetes (5,10-13). Some investigations revealed that GDM are more common in the communities with a higher prevalence of type 2 diabetes; however, the risk and onset of the disease are quite variable (14-16). In addition, the risk of cardiovascular diseases and type 2 diabetes have been proven in women with history of gestational diabetes (10,17).

The most important risk factors for gestational diabetes include age, high BMI, previous history of gestational diabetes, positive family history in first degree relatives, family history of diabetes, history of disorders in previous pregnancies (such as miscarriage, stillbirth, macrosomia, preterm delivery, eclampsia, preeclampsia, etc), belonging to a particular race, smoking, and short stature of mothers (8,9). GDM is one of the most common complications of pregnancy in the United States occurring in about 7% (more than 200 000 each year) of all pregnancies (18). Despite numerous studies on risk factors for gestational diabetes in American and European populations, limited studies have been conducted in this field in Iran (19). Considering the numerous and serious complications of this disease, lack of appropriate measures for the prevention, control and treatment, leads to countless limitations and problems for individuals at risk (20). Therefore, this investigation aims to assess risk factors associated with gestational diabetes by various studies in Iran using the meta-analytical method.

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Methods

Search Strategy

We conducted a systematic literature search for published papers on gestational diabetes risk factors in Iran in the national and international journals and students' theses. The databases include national scientific (Iranmedex, SID, Magiran, Irandoc, and Medlib) and international (PubMed/Medline, Scopus, and ISI Web of Knowledge) databases. Searching was done using keywords like gestational diabetes mellitus, gestational age, high age, overweight and obese, stillbirth, abortion, family history of diabetes, fetal macrosomia, preeclampsia, gestational diabetes history, Glycosuria, gestational hypertension, Iran, and their combinations and their corresponding Persian keywords. For any of the risk factors, relevant keywords were searched in women of reproductive age. The study was limited to papers in English and Persian languages published between 1990 and 2015. To expand the search, wildcard symbol '*' was used and the search words or phrases were combined using Boolean operators. We also searched bibliographies of retrieved articles for additional references. In addition, the references from selected articles were examined as a further search tool. A manual search for additional studies was carried out using references cited in the reviewed articles.

Study Selection

Titles and abstracts related to GDM risk factors in Iran were screened and when decision could not be made based the abstract alone, full articles were acquired for the other stage of screening. When necessary, authors were contacted for additional information. Studies presenting insufficient data, meta-analyses or systematic reviews and duplicate publication of the same study were omitted.

Data Extraction

The main information of the included articles was summarized by 2 authors into the data collection forms, and then these data were entered into Microsoft Excel. For all studies, the following data were extracted: first author, year of publication, location, sample size, mean age of the patients and the risks factors of diabetes during pregnancy. Data in this review were obtained only from studies that had used random sampling and a standard measurement technique for data collection.

Statistical Analysis

Variance of each study was calculated according to the binomial distribution. Studies were combined based on their sample sizes, mean and standard deviation. The difference between the average variance of the normal distribution was calculated using the formula of two integrated variance. Due to the heterogeneity in the studies, random effect model was employed in combining studies; and heterogeneity assessment was carried out by Cochrane Q test and I^2 statistics. *P* value less than 0.05 was considered as a significant heterogeneity test. Depending on the analyzed data, there was not a need to determine publication bias and drawing the funnel plot. Statistical analyses were performed by STATA version 12.

Results

According to initial search keywords related to risk factors of GDM in Iran in different sources, 106 articles were found. In a secondary screening, 17 of them were excluded based on title and abstract evaluation, 8 of them were excluded because of duplication and 81 were retained for detailed full-text evaluation. So, finally 81 relevant articles containing original data were fully examined. After full-text evaluation, we excluded another 60 articles (Of these, thirty-nine did not report the risk factors of GDM, nine were retrospective and review studies, twelve presented quantitative data that could not be analyzed). Finally 21 articles published from 2001 to 2015 met the inclusion criteria of the study (Figure 1). The characteristics of the 21 studies included (21-41) in this meta-analysis are summarized in Table 1.

A total of 1658 pregnant women with average age of 29.15 years old were investigated. Their mean BMI were 27.53 which are located at the overweight range. Table 1 presents the risk factors of GDM and the prevalence each of them in included articles. The estimated prevalence of the GDM risk factors in the country according to meta-analysis is shown in Table 2. As it can be seen, the prevalence of high age was calculated as 64% (with a confidence interval of 95.3%: 53–76) (Figure 2). In seven studies (23,25-27,33,34,36) ages ≥ 25 were considered as risk factors of gestational diabetes, whereas four studies (24,28,29,32) suggested ages ≥30 as the risk factor of gestational diabetes. The prevalence of overweight and obesity in our female subjects were 47% (with a CI of 78.6%: 40–54) (Figure 3). Meta-analysis showed a 3% prevalence of stillbirths (with a CI of 43%: 2–5), 22% history of abortion (with a CI of 78.3%:16–27) (Figure 4), 31% family history of diabetes (with a CI of 75.6%: 26–36) (Figure 5), 5% history of gestational hypertension (with a CI of 70.6%: 1–8), 4% history of preeclampsia (with a CI of 78.5%:2 –7), 4% history of diabetes in pregnancy (with a CI of 51.4%:1–8), 10% history of macrosomia (with a CI of 83.4%: 6 –13), 12% glycosuria (with a CI of 93%: 4–19), 1% previous congenital malformations (with a CI of 0.0%: 0–2), 1% previous neonatal death (with a CI of 0.0%: 0-2), 3% delivery <37 weeks (with a Ci of 65%: 0–6) and 10% delivery ≥5 case (with a Ci of 643%: 2–17 (Table 2).

The relationship between GDM risk factors and year of study was calculated based on the Meta regression model. Interpretation of meta-regression showed that there was no significant relationship between GDM risk factors and the year of study ($P \geq 0.05$). For example in Figure 6 the prevalence of history of abortion was checked with its year. As it can be seen, there was no significant relationship in this regard ($P = 0.59$).

According to the publication bias figure, the effect of bias in these studies was not significant. For example Figure 7 presents the funnel plot of the included trials related to prevalence of fetal macrosomia. Regression analysis of this plot indicated no significant asymmetry (*P*

Table 1. The Characteristics of different Studies Related to Risk Factors of Gestational Diabetes

Study location (Ref)	Year of study	Sample size	The risk factors of GDM and the its prevalence, 95% CI [Lower - Upper]													
			High age	Overweight and obese	History of stillbirth	History of abortion	Family history of diabetes	History of hypertension	History of preeclampsia	History of Gestational diabetes	Previous foetal macrosomia	History of Glycosuria	Delivery ≥5 case	Delivery <37 wk	Previous congenital malformations	Previous neonatal death
Tehran (21)	1992-1994	27		15% [1,28]			22% [7,38]	11% [-1,23]				11% [-1 ,23]				
Tehran (22)	1997-2001				5 % [-5,15]	42% [20,64]	232% [11,53]				16% [-1,32]		10% [-3,24]			
Bushehr (23)	1998-2000	64	84% [76,93]	72% [61,83]	10% [3,17]		31% [20,43]	10% [2,17]		3% [-1,8]	16% [7,25]				3% [-1,8]	3% [-1,8]
Shahrood (24)	1999-2000	63	41% [29,53]	43% [31,55]	2% [-1,5]	6% [0,12]	43% [31,55]	0% [-3,3]	3% [-1,8]		21% [11,31]	19% [9,29]			2% [-1,5]	2% [-1,5]
Tehran (25)	2000-2001	107	89% [87,90]	44% [42,46]	1% [-1,3]	14% [7,21]	28% [26,30]		0.0% [-2,2]		3% [2,4]				1% [-1,3]	
Tehran (26)	2001-2002	114	27% [19,35]	37% [28,46]		25% [17,33]	33% [25,42]		4% [1,8]		25% [17,33]	34% [25,43]	15% [8,21]	8% [3,13]		
Bandarabbas (27)	2002-2003	62	73% [61,84]	50% [38,62]	2% [-2,5]	18% [8,27]	13% [5,21]	2% [-2,5]	3% [-1, 8]		5% [-1,10]	5% [-1 ,10]	5% [-1,10]	2% [-2,5]		
Esfahan (28)	2002-2003	73	53% [42,65]	59% [48,70]			13% [5,20]									
Ardebel (29)	2003	8	50% [15,85]	38% [4,71]												
Tehran (30)	2003-2006		57% [50,64]													
Ahvaz (31)	2004-2006	50			2% [-2,6]	30% [17,43]				10% [2,18]	6% [-1, 13]				0% [-4,4]	
Tehran (32)	2007-2008		48% [43,53]	49% [44,54]	4% [2,5]		38% [33,43]		8% [5,11]		17% [13,21]	7% [4,9]			1% [0,2]	2% [0,3]

Table 1. Continued

Kermanshah (33)	2008	59		44% [31,57]	5% [-1,11]	32% [20,44]	37% [25,50]	5% [-1,11]	2% [-2,5]	7% [0,13]	5% [-1 ,11]					
Karaj (34)	2008	124	79% [72,86]			18% [11,24]	32% [24,41]				9% [4, 14]					
Tehran (35)	2008-2009	20		45% [31,57]							5% [-5, 15]					
Babol (36)	2010-2011	191	76% [67,86]	52% [45,59]	9% [3,16]	37% [30,43]	45% [34,55]	12% [5,19]	17% [9,24]		8% [4, 12]					
Esfahan (37)	2011				4% [0.0,8]	17% [9,25]	30% [20,40]		3% [-1,6]	0.0% [-2,2]	1% [-1,4]	0.0% [-2,2]	1% [-1,4]	3% [-1,6]	0% [-2,2]	
Gorgan (38)	2011-2012	62			10% [3,17]	11% [3,19]	35% [24,47]	0.0% [-3,3]		5% [-1,10]	10% [2, 17]					
Rafsanjan (39)	2012-2013						37% [19,55]	19% [4,33]	4% [2,7]	7% [-2,17]	15% [1,28]					
Hamedan (40)	2014		70% [58,82]													
Zabol (41)	2014		82% [64,100]	65% [42,87]	6% [-5,17]	35% [13,58]	29% [8,51]			12% [-4,27]	6% [5,17]					

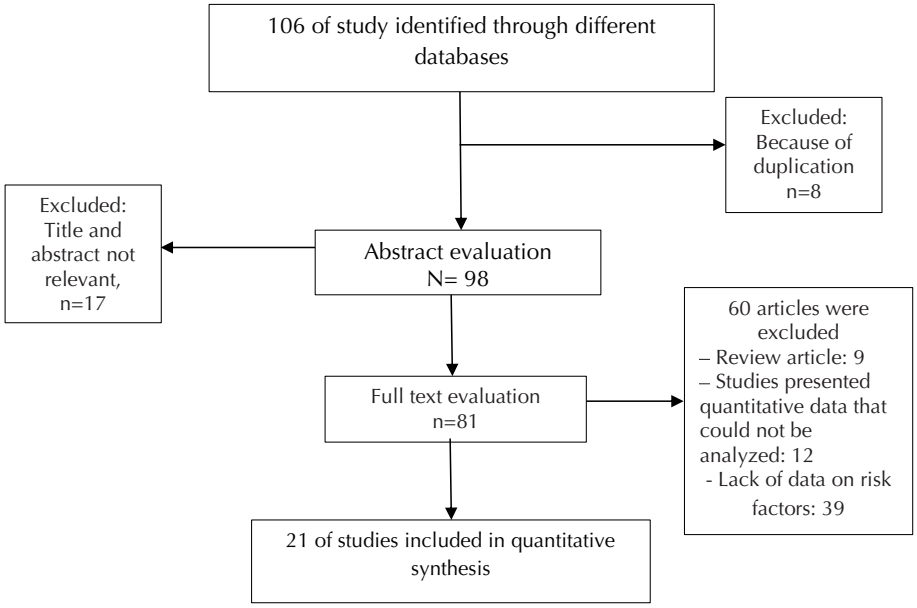

Figure 1. The Flowchart of Selected Articles for Final Analysis.

= 0.862) and thus no evidence of bias. In fact, most studies were located inside the funnel plot, thus demonstrating that the results of most relevant studies performed in Iran were included in the analysis (Figure 7).

Discussion

The relationship between some kind of risk factors such as high age, increase in body fat, race, and family history of diabetes, history of delivering a macrosomic infant, and previous history of impaired glucose tolerance with gestational diabetes has been proven (42,43). Despite the numerous studies in this area field in different countries, a few studies have investigated the risk factors of gestational diabetes in Iran. In the present study, some of these risk factors were evaluated. The mean age of women with gestational diabetes was determined 29.15 which was similar to findings of Pirc et al, Hjelm et al and Seshiah et al (44-46). Another investigation in India reported the highest incidence of gestational diabetes in women older than 25 (47). Age of mother, is one of the factors contributing to the risk of pregnancy so that in two reproductive age ranges (less than 20 years and more than 35 years), problems and consequences of pregnancy are exacerbated (48-50). Age is a risk factor even in normal pregnancies and frequency of gestational diabetes increases with age, so that being older than 25 or 30 years old has been recognized as a risk factor for gestational diabetes (26). Results of the present investigation showed that the women in this study were at the gestational diabetes-risky age range. Variables of age and BMI have been reported

Table 2. The Risk Factors Prevalence of GDM in the Country According to the Included Study

Risk Factors of GDM	No of Studies	Sample Size	Prevalence (%) (Random Effects Model)	95% CI	I^2 (%)	*P* Value
High age	13	483	64	53-76	95.3%	0.000
Overweight and obese	13	780	47	40-54	78.6%	0.000
History of stillbirth	12	658	3	2-5	43.0%	0.000
History of abortion	12	832	22	16-27	78.3%	0.000
Family history of diabetes	16	692	31	26-36	75.6%	0.000
Previous foetal macrosomia	16	916	10	6-13	83.4%	0.000
History of preeclampsia	9	489	4	2-7	78.5%	0.000
Gestational diabetes history	7	235	4	1-8	51.4%	0.006
History of glycosuria	6	266	12	4-19	93.0%	0.000
History of gestational hypertension	8	466	5	1-8	70.6%	0.001
Previous congenital malformations	6	272	1	0-2	0.00%	0.855
Previous neonatal death	4	171	1	0-2	0.00%	0.524
Delivery <37 weeks	3	119	3	0-6	65.0%	0.058
Delivery ≥5 cases	3	127	10	2-17	64.1%	0.062

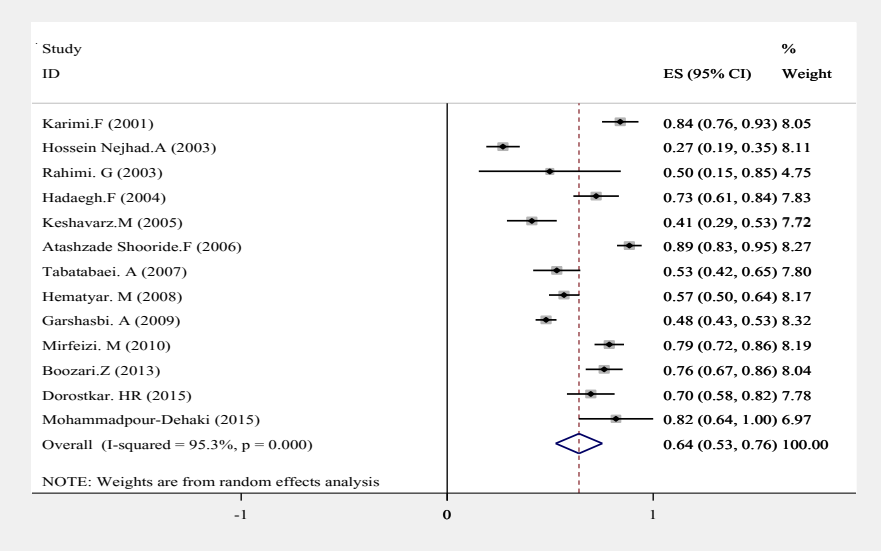

Figure 2. Prevalence of High Age and its 95% CI. Midpoint of each line segment represents the estimated prevalence in the study. Rhombic mark shows the prevalence n Iran extracted from all studies.

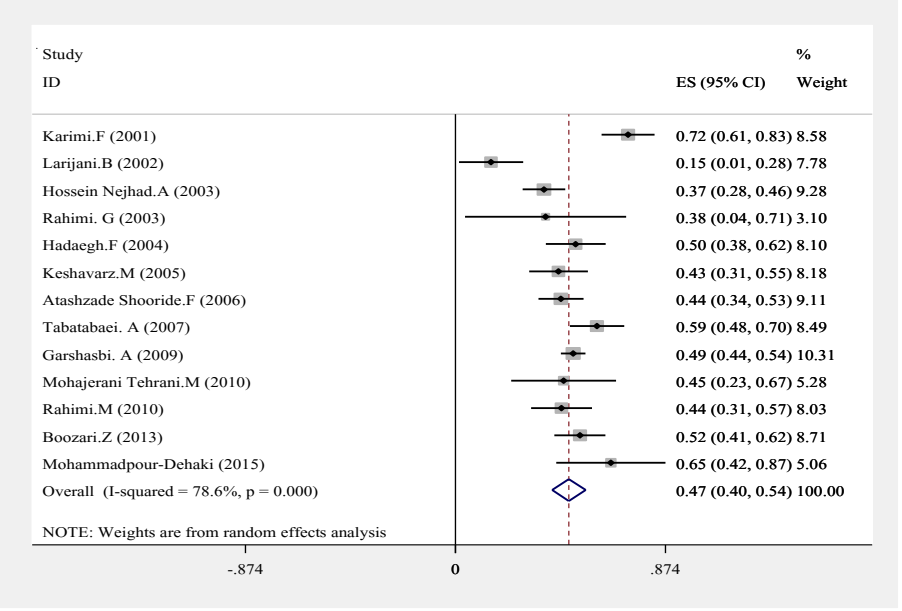

Figure 3. Prevalence of Overweight and Obese and its 95% CI. Midpoint of each line segment represents the estimated prevalence in the study. Rhombic mark shows the prevalence in Iran extracted from all studies.

as two risk factors involved in gestational diabetes in a study conducted in Nigeria (51), which is similar with our findings. The relationship between maternal age and the prevalence of GDM has been also shown in Zargar et al study in Kashmir (52).

In the present study, the mean BMI of subjects was 27.53 which belongs to the overweight range. The investigation of O'Sullivan et al in Ireland highlighted high age and obesity as the contributing factors in increasing the prevalence of gestational diabetes (53). Also, Hisrt et al (4), in an investigation conducted on Vietnamese women, showed that increase in BMI leads to higher degrees of gestational diabetes which is consistent with our results. In several studies it has been found that there is a significant relationship between BMI and gestational diabetes (54), and they all suggest that weight gain is associated with development of diabetes. Relative insulin resistance and diabetes risk increase in obese individuals (55), and the impact of obesity on undesirable pregnancy outcome, such as history of stillbirth, abortion, macrosomia and preeclampsia, hypertension in pregnancy, and caesarean section have been reported in numerous studies (56-60). Considering this scientific fact that changes in BMI at the end of pregnancy is related to pre-pregnancy BMI and the weight gain of the mother during pregnancy, it has been accepted that weight gain and obesity are among the

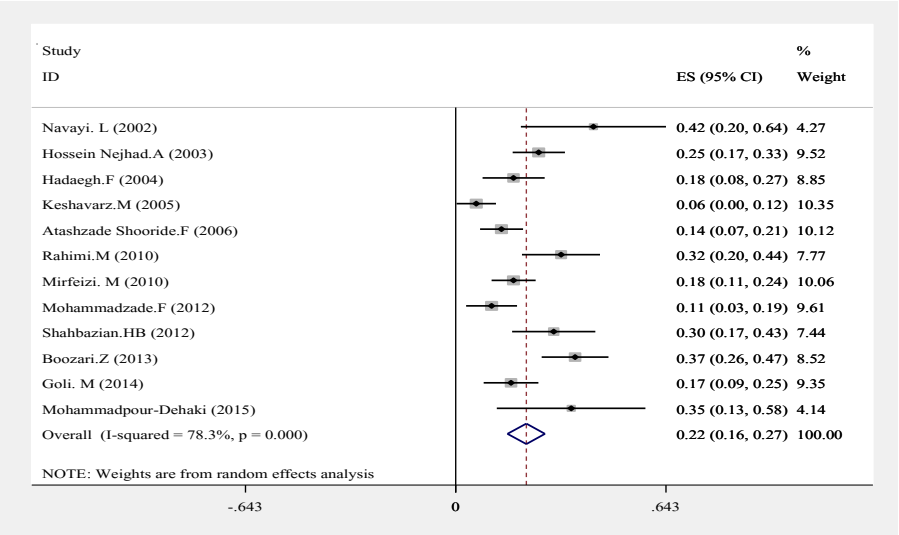

Figure 4. Prevalence of History of Abortion and its 95% CI. Midpoint of each line segment represents the estimated prevalence in the study. Rhombic mark shows the prevalence in Iran extracted from all studies.

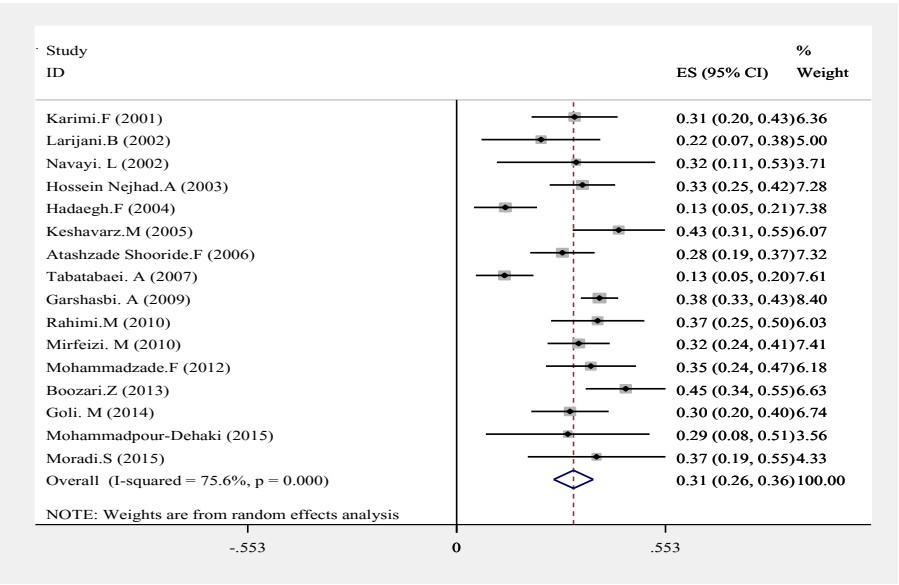

Figure 5. Prevalence of Family History of Diabetes and its 95% CI. Midpoint of each line segment represents the estimated prevalence in the study. Rhombic mark shows the prevalence in Iran extracted from all studies.

risk factors for type 1 and 2 diabetes and also gestational diabetes (61,62).

Also, history of abortion has been always considered as a risk factor for carbohydrate intolerance. This factor, at all levels of this disorder, shows a significant relationship, especially in gestational diabetes (63). The results of our study showed a high prevalence of abortion in women with gestational diabetes which is in agreement with previous studies (64,65).

History of gestational diabetes or carbohydrate intolerance increases the likelihood of recurrence of this disease in future pregnancies. Some studies estimated approximately 30% to 70% of recurrence for this disease in future pregnancies (26). In the present study, prevalence of family history of diabetes were calculated as 31%, which is higher than the results of Irving et al (66); they calculated 12% prevalence of gestational diabetes in women with a family history of diabetes (66). Our results suggest that family history of diabetes is a risk factor for gestational diabetes, which is in line with results of Johns et al (67). Also, Hisrt et al (4) reported a high prevalence of diabetes in the immediate family members of women with gestational diabetes which is consistent with the results of the present study. Family history of diabetes in first degree relatives is one of the most significant risk factors for gestational diabetes which further emphasizes the role of genetics in susceptibility toward this disease (68). On the other hand, Chan et al have suggested an independent role for this factor, especially in those older than 30 (69).

History of macrosomia was among the risk factors

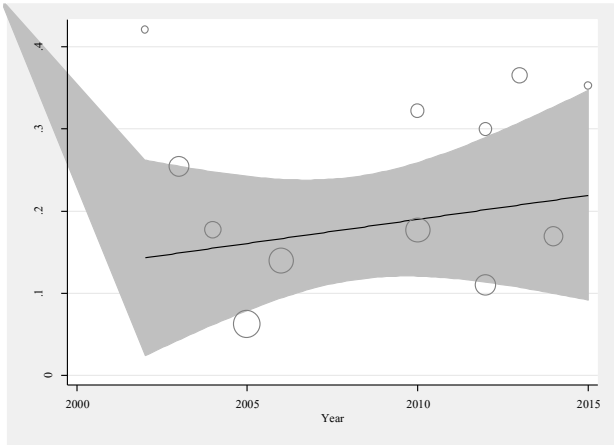

Figure 6. The Association Between Prevalence of History of Abortion and Year of Study Using Meta Regression

examined in this investigation. The incidence of neonatal macrosomia in patients with gestational diabetes is 20%-30% which is one of the most common complications of this disease. Some studies show that almost half of all cases of macrosomia were due to gestational diabetes. Therefore, delivery of a macrosomic infant appears to be a risk factor for developing the disease in subsequent pregnancies (70,71). Saldana et al in a study conducted in North Carolina, reported high prevalence of macrosomia in women with gestational diabetes (72). Also, Hernández-Herrera et al conducted an investigation in Spain on 85 infants of diabetic mothers; 31.7% of infants were macrosomic (73). 23.7% prevalence of macrosomia has been reported in the general population and in the group with gestational diabetes, macrosomia of 23.58% has been reported which is significantly higher than the normal. In the group with gestational diabetes, macrosomia of 23.58% has been reported which is significantly higher than the normal (74). Therefore, given the high prevalence of macrosomia in pregnancy outcome of patients with gestational diabetes, it seems that the history of previous macrosomia can be considered as a risk factor in women with gestational diabetes. Although the macrosomia is a major fetal complication, but due to the possible obstetrics involvement and cesarean in these mothers, is also considered as one of the high risk factors for mothers (75).

One of the main problems in women with gestational diabetes is their high blood pressure during pregnancy (76,77). Gestational hypertension can be found in 10% of pregnant women and is associated with various fetal complications such as premature delivery, intrauterine growth retardation, asphyxia, embryos dying, placental abruption, acute liver and kidney failure, hemorrhage before and after delivery, and maternal mortality (78-80). Women with gestational hypertension are at risk of seizures during pregnancy, metabolic syndrome, cardiovascular diseases, and strokes (78).

In the present study, the prevalence of glycosuria was 12%. Glycosuria is a common finding in pregnancy. Increased glomerular filtration, along with impaired capacity for tubular reabsorption for the refined glucose, could be responsible for the emergence of glycosuria during pregnancy. Studies have shown that approximately 1 in 6 pregnant women was diagnosed with glycosuria (81). Glycosuria has shown an independent association with this disorder in many of the studies that have been conducted about gestational diabetes and impaired glucose tolerance (82).

Risk factors associated with gestational diabetes have been investigated in various studies. For example, in the studies of Hisrt et al (4), or Xiong et al (83), stillbirth, macrosomia, preeclampsia, family history of hypertension, and history of death at the birth have been proposed as risk factors of gestational diabetes. According to studies conducted in Australia and America, general risk factors for the gestational diabetes are similar and include high

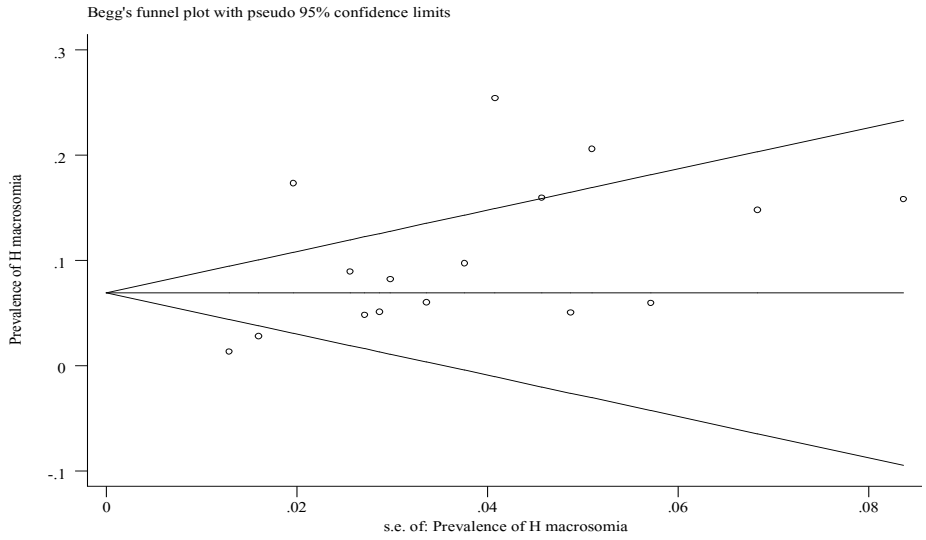

Figure 7. Funnel Plot for Publication Bias in the Risk Difference Analysis.

BMI, positive family history of diabetes, history of macrosomia and glycosuria and high parity, and short stature of mothers (9,84). Characteristics such as race, age, obesity, history of macrosomia and unexplained stillbirth puts women at the risk of gestational diabetes (85). Recently, in a review study, the necessity of conducting discussions regarding the risk factors such as number of pregnancies, history of hypertension, and other causes, has been further emphasized (42). Cheung et al, in a study conducted in Australia on the Asian pregnant women, showed that the risk factors of GDM in the Asian race are similar to Western countries (86).

Conclusion

The relationship between risk factors such as high age, increased body fat, race, family history of diabetes, history of delivering a macrosomic infant, history of impaired glucose tolerance etc in women with gestational diabetes have been proven in various studies. Given that about 40 percent of gestational diabetes cases can be converted to diabetes over the coming years, controlling these risk factors can reduce the incidence of diabetes during pregnancy. Therefore, the need to review and identify these risk factors seems necessary.

Ethical Issues

Not applicable.

Conflict of Interests

None to be declared.

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