Research

Meta-Analysis: Effects of Obesity and Family History of Diabetes Mellitus on the Risk of Gestational Diabetes Mellitus

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ABSTRACT

Background: Gestational diabetes mellitus is a serious complication of pregnancy, this is due to impaired carbohydrate tolerance which results in increased blood sugar levels and was first noticed during pregnancy. Gestational diabetes mellitus is a global problem in terms of its incidence and impact. Studies suggest that obesity and a family history of diabetes mellitus are important risk factors for gestational diabetes mellitus. This study aimed to analyze the influence of obesity and family history of diabetes mellitus on the incidence of gestational diabetes mellitus by meta-analysis.

Subjects and Method: This was a systematic review and meta-analysis carried out by following the PRISMA flow diagram. The electronic database for article searches is as follows: Pub-Med, Science Direct, Springer Link, Scopus, and Google Scholar. The search for articles was carried out on articles published from 2010 to 2020. The keywords used were "gestational diabetes mellitus AND obesity", "gestational diabetes mellitus AND family history. The inclusion criteria were full text articles, used English, cross-sectional study design, and results reported in adjusted odds ratio (aOR). P= Pregnant mother. I= Obesity and family history of diabetes mellitus. C= No obesity and no family history of diabetes mellitus. O= gestational diabetes mellitus. Articles that meet the requirements are analyzed using the Revman 5.3.

Results: Nine articles were reviewed in this study with a total of 11,657 subjects. The results of the meta-analysis showed that obesity increased the risk of gestational diabetes mellitus 1.81 times compared with non-obese (aOR= 1.81; 95% CI= 1.53 to 2.15; p <0.001). Having a family history of diabetes mellitus increased the risk of gestational diabetes mellitus 2.08 times compared with those without a family history of diabetes mellitus (aOR= 2.08; 95% CI= 1.34 to 3.22; p <0.001).

Conclusion: Obesity and a family history of diabetes mellitus increase the risk of gestational diabetes mellitus.

Keywords: obesity, family history of diabetes mellitus, gestational diabetes mellitus

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BACKGROUND

Gestational diabetes mellitus is a disease caused by impaired carbohydrate tolerance which results in increased blood sugar levels and occurs or is known for the first time during pregnancy (Soelistijo et al., 2015). This condition usually occurs at 24 weeks of gestation and some sufferers will return to normal after giving birth, but in some cases they will still become diabetes mellitus or become impaired glucose tolerance (Anazawa, 2015).

Based on research by the International Diabetes Federation (IDF), 90% of diabetes cases in pregnant women are gestational diabetes mellitus cases that affect approximately 14% of pregnancies worldwide, representing about 18 million births each year (Plows et al., 2018). According to the American Diabetes Association (ADA), gestational diabetes occurs in 7% of pregnancies each year (ADA, 2014). Gestational diabetes mellitus is a global problem and a public health problem in terms of the incidence and impact on maternal and fetal health (Mahtab and Bhowmik, 2016).

The prevalence of gestational diabetes mellitus varies, namely 1% -14%. This figure depends on the population studied and the screening criteria used (Yeung et al., 2016). Gestational diabetes mellitus accounts for approximately 4% of all pregnancies in the United States, and 3–5% in the UK. The prevalence of gestational diabetes mellitus in Europe is 2-6% (Zhu and Zhang, 2016). The prevalence of gestational diabetes mellitus in Indonesia is 1.9% - 3.6% in general pregnancies. In pregnant women with a family history of diabetes mellitus, the prevalence of gestational diabetes mellitus is 5.1%. This figure is much lower than the prevalence in Britain and the United States (Fitriani, 2017).

The risk factors for gestational diabetes mellitus include being overweight/ obese, an unhealthy lifestyle, a westernized diet, micronutrient deficiency, elderly mothers, and a family history of insulin resistance and/or diabetes (Plows et al., 2018).

Research conducted by Hartling et al. (2014) states that the impact caused by mothers with gestational diabetes mellitus is that they are at high risk of preeclampsia, eclampsia, cesarean section, and cardiovascular complications to death. After childbirth occurs, the patient is at risk of conti-nuing to develop type-2 diabetes or recurrent gestational diabetes in the future, while babies born to mothers who have gestational diabetes are at high risk of developing macrosomia (Mirghani Dirar and Doupis, 2017).

Gestational diabetes mellitus is the main cause of maternal and infant mortality and causes serious complications in the delivery process (Lekva et al., 2016). As many as 3 million babies are stillborn each year due to gestational diabetes mellitus. Pregnancy accompanied by gestational DM is also at risk of causing maternal death up to 4 times (Buchanan et al., 2012). Pregnant women with gestational diabetes generally experience complications during the delivery process and tend to give birth to babies who are overweight, or give birth to premature babies or with physical disabilities (Alberico et al., 2014).

The phase of progression from gestational diabetes to type 2 diabetes generally occurs 5-10 years after delivery. Not only that, babies of women who suffer from gestational diabetes are also at high risk of developing type-2 diabetes, being overweight and obese when they are children and adolescents (Busta et al., 2017). Not optimal prevention and treatment of gestational diabetes mellitus is a bad threat for pregnant women. Gestational diabetes mellitus can contribute to a bad intergenerational red circle due to an unhealthy lifestyle, obesity, family history, and other risk factors that have an impact on the overall health of the population (Kurniawan, 2016).

The aim of this study was to draw conclusions by conducting a systematic review and meta-analysis through collecting and combining all relevant and pre-existing research results on the effect of obesity and family history of diabetes mellitus on the risk of gestational DM.

SUBJECTS AND METHOD

1. Study Design

This was a systematic review and meta-analysis carried out by following the PRISMA flow diagram. The article search databases are as follows: PubMed, Science Direct, Springer Link, Scopus, and Google Scholar. The keywords used in the search for the article were "gestational diabetes mellitus AND obesity", "gestational diabetes mellitus AND family history".

2. Inclusion Criteria

The inclusion criteria in this study were full-text articles and in English. The articles are published from 2010 to 2020. The study design is an observational, cross-sectional study. Articles that discuss the effect of obesity and family history of DM on the risk of gestational DM. The sample in this study were pregnant women. His research articles are those that use multivariate analysis and report results in adjusted odds ratio (aOR).

3. Exclusion Criteria

The exclusion criteria in this study were RCT research articles, case control, quasi experiment, protocol study and pilot study. Articles are those published in a language other than English. His research articles are those with reported results not adjusted odds ratio (aOR).

4. Operational Definition of Variables

Gestational Diabetes Mellitus is a disorder of carbohydrate tolerance which results in increased blood sugar levels. This situation tends to occur during the 2nd trimester of pregnancy, but is usually found at 24-28 weeks of gestation.

Obesity is the accumulation of excess fat due to an imbalance between energy intake and energy use for a long time.

Family History Diabetes Mellitus is a condition in which both the father and mother have or have had diabetes and this can increase the risk of developing diabetes.

5. Instruments

The research stages followed the PRISMA flow diagram and the assessment of the quality of research articles, using the Critical Appraisal Check List For Study from the Center for Evidence Based Management, (2014) for a cross-sectional study.

6. Data Analysis

The data analysis process in this study was carried out using the Review Manager application (RevMan 5.3), to determine the effect size and heterogeneity of the study. The results of meta-analysis data processing are presented in the form of a forest plot and a funnel plot.

RESULTS

The process of searching for articles on an electronic database according to PRISMA flow diagrams can be seen in Figure 1.

Nine articles out of 1,127 were reviewed in this study. Three research articles on the Asian continent, one research article on the continent of Europe, one research article on the American continent, three research articles on the African continent and one research article on the Oceania continent. Furthermore, the researchers conducted an assessment of the quality of the articles (Table 1).

1. Effect of obesity on the risk of gestational diabetes mellitus

Table 2 provides information on 6 articles with a cross-sectional study design as a source of meta-analysis of the effect of obesity on the risk of gestational DM.
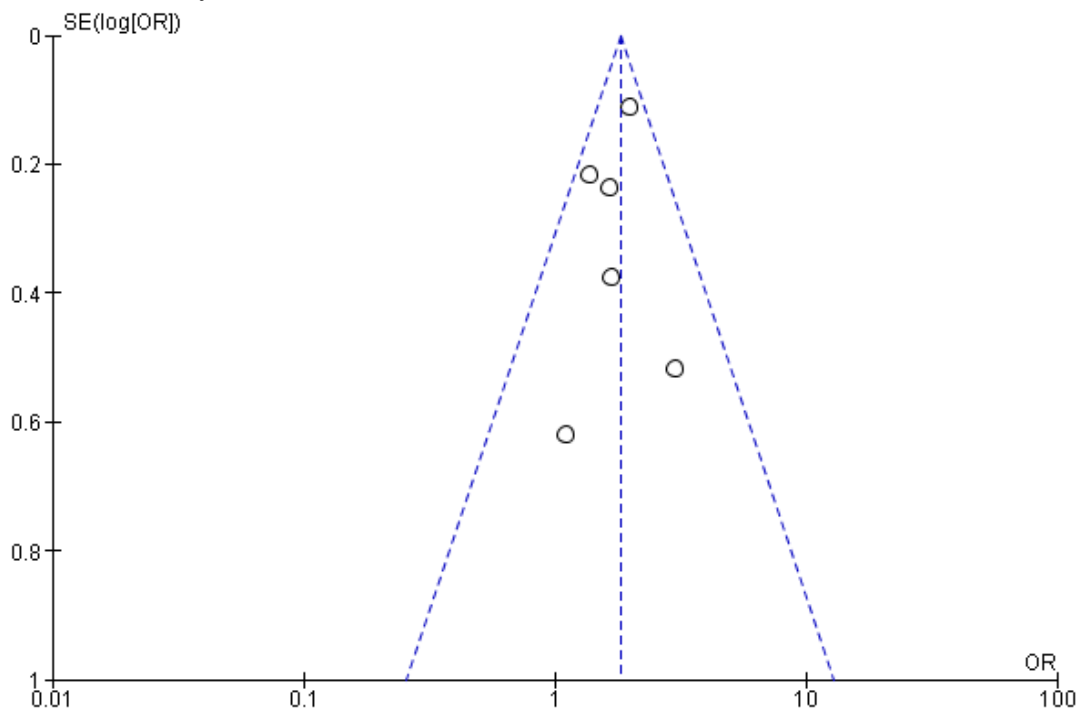
a. Forest Plot

Figure 2, forest plot shows that obesity increases the risk of gestational diabetes mellitus by 1.81 times compared with non-obese, statistically significant (aOR= 1.81; 95% CI= 1.53 to 2.15). Low heterogeneity between experiments (I^2= 0%; p <0.001) so that the fixed-effect model (FEM) was used.
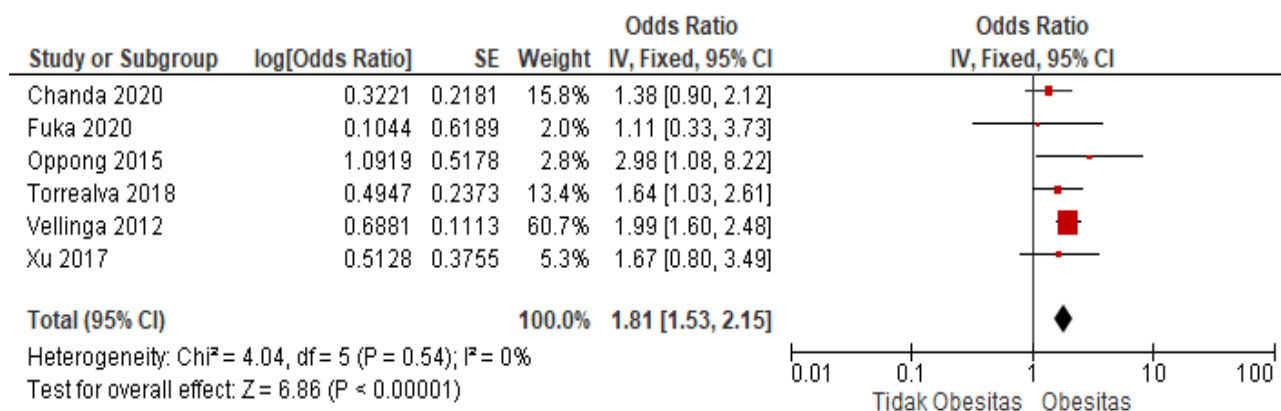
b. Funnel Plot

Figure 3, funnel plot of the effect of obesity on the risk of gestational diabetes mellitus there is publication bias, the plots on the right and left are not symmetrical with each other and do not form an inverted funnel. The left plot has a standard error of 0.6 while the plot on the right has a standard error of <0.6.

Figure 3. Funnel Plot of the Effect of Obesity on the Risk of Gestational Diabetes Mellitus

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Chanda 2020	0.3221	0.2181	15.8%	1.38 [0.90, 2.12]
Fuka 2020	0.1044	0.6189	2.0%	1.11 [0.33, 3.73]
Oppong 2015	1.0919	0.5178	2.8%	2.98 [1.08, 8.22]
Torrealva 2018	0.4947	0.2373	13.4%	1.64 [1.03, 2.61]
Vellinga 2012	0.6881	0.1113	60.7%	1.99 [1.60, 2.48]
Xu 2017	0.5128	0.3755	5.3%	1.67 [0.80, 3.49]
Total (95% CI)			100.0%	1.81 [1.53, 2.15]

Heterogeneity: Chi² = 4.04, df = 5 (P = 0.54); I² = 0%
Test for overall effect: Z = 6.86 (P < 0.00001)

Figure 2. Forest Plot of the Effect of Obesity on the Risk of Gestational Diabetes Mellitus

Effects of Obesity and Family History of Diabetes Mellitus on the Risk of Gestational Diabetes Mellitus

Table 1. Assessment of Research Quality

Publication	The study objective / focus is clear	Cross-sectional	Method	Selection bias	Sample represents	Sample Size	Response reached	Instrument	Statistical significance	Confidence interval	Confound-ing	Results can be applied	Total
(Chanda et al., 2020)	2	2	2	1	2	2	2	2	2	2	1	2	22
(Fuka et al., 2020)	2	2	2	1	2	2	2	2	2	2	1	1	21
(Lim-Uy et al., 2010)	2	2	2	1	2	2	2	1	2	2	1	2	21
(Muche et al., 2019)	2	2	2	1	2	2	2	2	2	2	1	2	22
(Mwanri et al., 2014)	2	2	2	1	2	2	2	2	2	2	1	1	21
Oppong et al., 2018)	2	2	2	1	2	2	2	2	2	2	1	2	22
(Toreealva et al., 2018)	2	2	2	1	2	2	1	2	2	2	1	2	21
(Vellinga et al., 2012)	2	2	2	1	2	2	1	2	2	2	1	1	20
(Xu et al., 2017)	2	2	2	1	2	2	2	1	2	2	1	2	21

Note
Yes = 2
Unexplained= 1
No = 0

Table 2. Summary Sources of the Effect of Family History of Diabetes Mellitus on the Risk of Gestational Diabetes Mellitus

| Author, year	Location	Study Design and Number of Subjects	Inclusion Criteria	Outcome	aOR	CI (95%)
(Chanda et al., 2020)	India	Cross-sectional dan 1410	Full paper articles, observational research, multivariate analysis (aOR)	Gestational diabetes mellitus	1.82	1.08-3.06
(Fuka et al., 2020)	Fijian	Cross-sectional dan 255	Full paper articles, observational research, multivariate analysis (aOR)	Gestational diabetes mellitus	0.95	0.47-1.95
(Lim-Uy et al., 2010)	Philipine	Cross-sectional dan 668	Full paper articles, observational research, multivariate analysis (aOR)	Gestational diabetes mellitus	6.27	2.63-14.96
(Muche et al., 2019)	Gondar	Cross-sectional dan 1027	Full paper articles, observational research, multivariate analysis (aOR)	Gestational diabetes mellitus	4.03	1.57-10.35
(Mwanri et al., 2014)	Tanzania	Cross-sectional dan 910	Full paper articles, observational research, multivariate analysis (aOR)	Gestational diabetes mellitus	2.10	1.10-4.20
(Torrealva et al., 2019)	Peru	Cross-sectional dan 1300	Full paper articles, observational research, multivariate analysis (aOR)	Gestational diabetes mellitus	1.51	1.10-2.07

2. The Effect of family history of DM on the risk of gestational DM

Table 3 provides information on 6 articles with a cross-sectional study of the effect of family history of DM on the risk of gestational DM.

a. Forest Plot

Figure 4, forest plot shows that a family history of diabetes mellitus increases the risk of gestational DM by 2.08 times compared to those without a family history of DM, which is statistically significant (aOR= 2.08; 95% CI= 1.34 to 3.22). High heterogeneity between experiments (I^2= 67%; p <0.001) so that the random-effect (REM) model was used.
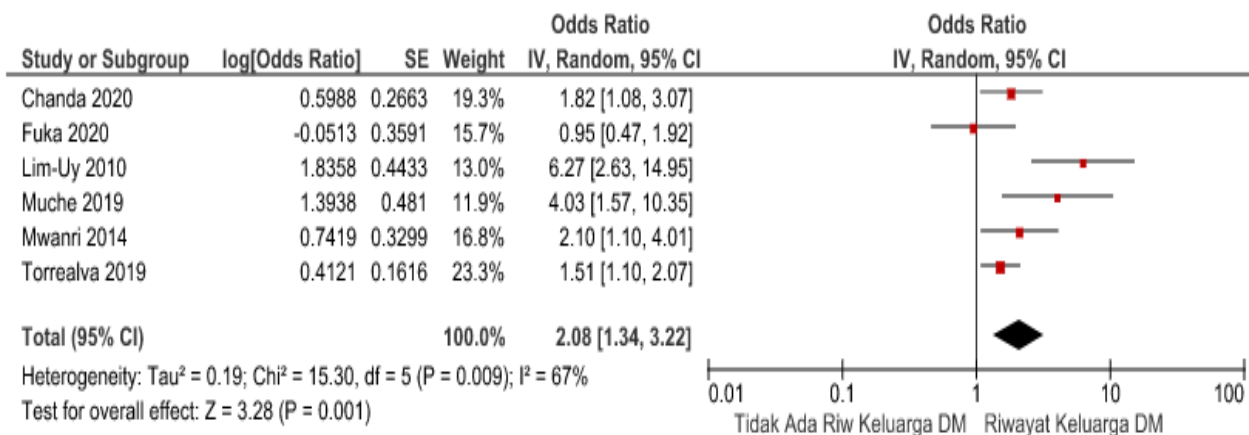
Figure 4. Forest Plot of the Effect of Family History of DM on the Risk of Gestational dm

b. Funnel Plot

Figure 4. Funnel plot the effect of family history of diabetes mellitus on the risk of gestational diabetes mellitus, there is publication bias, the plots on the right and left are not symmetrical with each other and do not form an inverted funnel. The left plot has a standard error of 0.4 while the plot on the right has a standard error of >0.4.
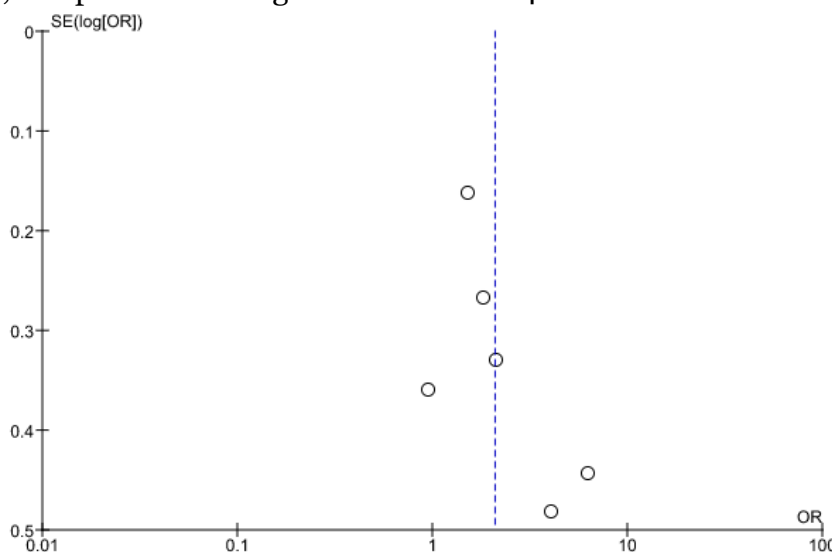
Figure 5. Funnel Plot The Effect of Family History of DM on the Risk of Gestational DM

DISCUSSION

This study is a systematic review and meta-analysis of risk factors for gestational DM. The independent variables in this study were obesity and a family history of DM.

The aim of this study was to draw conclusions from the results of similar studies examining the risk factors that can influence the development of gestational DM. The primary studies involved in this research are those conducted in various countries and races, in order to obtain conclusions that can be generally applied as a basis for intervention.

Most of the primary studies only report the results of statistical analysis in the crude odds ratio (cOR), this shows that the results of these studies have not controlled for confounding factors..

Confounding factor according to Murti (2018) is a mixture of estimated relationships between exposure and the disease under study, by other factors that are related, both to disease and exposure. In accordance with the inclusion criteria, this study was conducted using the results of primary studies that have controlled for confounding factors as indicated by multivariate data analysis and the size of the relationship reported in the form of Adjusted Odds Ratio (aOR).

Estimates of the combined association of the association of each risk factor with the incidence of gestational DM were processed using the RevMan 5.3 application with the generic inverse-variance method. This method is used to analyze data in the form of: rate, time-time-to-event, hazard ratio, ordinal scale, adjusted estimate, difference of mean ratio of mean (Anulus et al., 2019). The results of the systematic review and meta-analysis of this study are presented in the form of forest plots and funnel plots.

The forest plot is a graphical representation of the meta-analysis results that includes information related to the incorporation of the results from the primary study. Then, on the right side there is a line representing each study carried out by the meta-analysis plotted according to its weighting. Visually, the forest plot can also show the amount of heterogeneity between study results (Akobeng, 2005 in Murti, 2018).

A funnel plot is a diagram in a meta-analysis that illustrates the possibility of publication bias. In this case, the funnel plot shows the relationship between the effect size of the study and the sample size or standard error of the effect size of each study studied. The bias shown by the funnel plot can be seen by assessing the asymmetry of the study (the number of points on the right and left sides) compared to the standard error and the imbalance of the number of studies on the right and left (Murti, 2018).

1. Effect of obesity on the risk of gestational diabetes mellitus

The results of a meta-analysis of 6 articles on the effect of obesity on the risk of gestational DM were summarized in a forest plot. The forest plot shows that the effect of obesity can increase 1.81 times the risk for developing gestational DM compared to non-obese people, which is statistically significant.

These results are supported by Teh et al. (2011) in their study reported that obesity is a significant risk factor for gestational DM. It was explained that to assess a person's weight is still within normal limits or not, it is necessary to calculate the body mass index (BMI). The formula for BMI is your weight (kg) divided by your height (m²). In his study, it was reported that adults are said to be obese if the BMI is ≥30.

This study is reinforced by Mwanri et al. (2015). In the study, it was explained that a person who is obese becomes less sensitive to insulin over time (insulin resistance). Insulin is a hormone produced by pancreatic beta cells which functions to absorb sugar or glucose in the blood, so that blood sugar levels remain normal. Visceral fat in obese people will increase the release of free fatty acids which cause insulin resistance. Pancreatic beta cells work harder to produce insulin. Over time, the pancreatic beta cells become exhausted and are no longer able to produce sufficient amounts of insulin. As a result, blood sugar levels increase. Uncontrolled blood sugar can lead to coma and death. Even if controlled, gestational diabetes mellitus is still at risk of causing organ damage and causing various complications.

The results of the meta-analysis that the researchers conducted are in line with several studies on the effect of obesity on the risk of gestational DM, so obesity is an important risk factor that greatly influences the incidence and complications of gestational DM. This situation should get more attention, so it is necessary to do prevention and early detection in order to minimize the risks and complications of gestational DM that occur.

2. The Effect of family history of DM on the risk of gestational DM

The results of a meta-analysis of 6 articles regarding the effect of family history of DM on the risk of gestational DM were summarized in a forest plot. The forest plot shows that the effect of a family history of DM can increase 2.08 times the risk for developing gestational DM compared to those without a family history of DM, which is statistically significant.

Moosazadeh et al. (2017) reported that family history of DM is a significant predictor of gestational DM. It was explained that a pregnant woman who has a family history of DM develops gestational diabetes mellitus in her current pregnancy.

This study was in line with Sulistiyah (2015). In his study, it was explained that the medical risk factor for gestational diabetes mellitus in pregnant women was a family history of DM by 49%. Family history of DM is an important factor in most diabetics from the same family who are autosomal dominant. These inherited disorders can directly affect beta cells and alter their ability to recognize and disperse secretory stimuli or a complex series of steps that are part of insulin synthesis or release. This condition increases the individual's susceptibility to environmental factors that can alter the integrity and function of pancreatic beta cells.

Family history of diabetes is thought to be autosomonal dominant, recessive, and mixed. The results showed that gestational diabetes mellitus was more prevalent in pregnant women with a family history of diabetes mellitus (Nct, 2018).

A series of factors associated with the incidence of gestational diabetes mellitus are age, history of miscarriage, history of gestational DM in previous pregnancies, history of giving birth to children weighing >4 kg and PCOS syndrome. Thus, the best way to prevent and minimize risk factors and complications of gestational diabetes mellitus is to do comprehensive prevention and early detection.

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