

Relationship between Family History of Diabetes Mellitus and Gestational Diabetes Mellitus: A Meta-Analysis

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ABSTRACT

Background: Gestational Diabetes Mellitus (GDM) is the most common metabolic disorder first diagnosed during pregnancy. According to the American Diabetes Association (ADA) in 2006, GDM occurred in 7% of pregnancies each year. Family history of diabetes is an important risk factor for GDM. The relationship between family history of DM and GDM has been investigated in several primary studies with several contradictions in the outcome. Therefore, this study aimed to determine the relationship between family history of diabetes and GDM using a meta-analysis method.

Subjects and Method: The meta-analysis was conducted by systematically reviewing articles published from 2007 to 2020 from the Pubmed, Google Scholar, Science Direct, and ResearchGate databases. The keywords were "Risk factor" OR "family history" OR "family history DM") AND "GDM" AND "cross sectional". The article search was carried out using PICO: the study population was pregnant women, the intervention/exposure was family history of DM, the comparison was no family history of DM, and the outcome was GDM. The

article search was carried out for one month. The articles included in this study were full-text articles with a cross-sectional design. The articles were reviewed using the PRISMA flow diagram guidelines. This study used Revman 5.3 Software to analyze the articles.

Results: Family history of DM increased the risk of Gestational Diabetes Mellitus (aOR= 2.02; 95% CI= 1.54 - 2.67; p<0.001). This study used 11 articles from Ethiopia, Cameroon, Peru, Iran, Pakistan, Malaysia, Kuwait, Saudi Arabia, and India.

Conclusion: Family history of diabetes mellitus increases the risk of gestational diabetes mellitus.

Keywords: Gestational diabetes mellitus, Family history of diabetes

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Cite this as:

Ammutammima UF, Tamtomo DG, Murti B (2021). Relationship between Family History of Diabetes Mellitus and Gestational Diabetes Mellitus: A Meta-Analysis. *Indones J Med.* 06(01): 71-81. <https://doi.org/10.26911/theijmed.2021.06.01.08>.



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BACKGROUND

Gestational Diabetes Mellitus (GDM) is defined as glucose intolerance identified during pregnancy (Sugianto, 2016). This situation usually occurs at 24 weeks of gestation and some of the patient's blood glucose levels will go back to normal after delivery (Ministry of Health RI, 2008). How-

ever, in almost half of the incidence, diabetes will recur (Nurrahmani, 2012).

GDM in mothers can increase the risk of having diabetes by 3-5% in the future. This can affect the unborn baby, namely the fetus who died in the womb, macrosomia, late lung maturation, birth trauma, growth retardation, congenital malformation, and neonatal death. Newborns were also at high

risk of obesity, glucose intolerance, and diabetes as adolescents (Bilous et al, 2014).

GDM has become a global problem based on the rate and its impact (Osgood et al, 2011). According to the American Diabetes Association (ADA) in 2006, GDM occurred in 7% of pregnancies each year. The prevalence of GDM varied from 1%-14%. This rate depended on the population studied and the screening criteria used (ADA, 2006).

High blood sugar levels in pregnant women can be caused by several factors such as age, genetics, smoking habits, or exercise, sex and age, anatomy or constitution, physical, chemical, biological, psychological, socio-cultural conditions, and behavioral and nutrition (Begum et al, 2017).

Family history of DM is one of the genetic factors affecting a person to have GDM. A person who has a family of Diabetes Mellitus has a 3 times risk of having Diabetes Mellitus. A family history of DM has a risk of having DM by 15%. If both parents have diabetes mellitus, the risk of having diabetes mellitus is 75%. The risk of having DM from the mother was 10-30% greater than the father (Zhang et al, 2015).

Based on the result of the previous study conducted by Sulistiyah, the medical factor of GDM in pregnant women is a family history of DM (49%). Some other literature added that a family history of DM was also likely related to GDM in pregnant women (Sulistiyah, 2015).

A family history of type 2 DM would have a 15% possibility of having DM and the risk of having glucose intolerance (the inability to metabolize carbohydrates normally) by 30% (Damayanti, 2015).

Therefore, the researcher was interested in investigating the relationship between family history of DM and GDM. The data obtained would be analyzed using a meta-analysis by synthesizing the results.

SUBJECTS AND METHOD

1. Study Design

This was a systematic review and a meta-analysis. The meta-analysis was carried out by systematically reviewing articles published from 2007 to 2020 from the Pubmed, Google Scholar, Science Direct, and Research Get databases. The keywords were "Risk factor" OR "family history" OR "family history DM") AND "GDM" AND "cross sectional".

2. Inclusion Criteria

The author developed inclusion criteria: full-text articles in English and Indonesian languages with a cross-sectional study design. The study subjects were pregnant women aged >28 years old and pregnant women with a BMI of >27 kg/m². The outcome analyzed was Gestational Diabetes Mellitus. The study used multivariate analysis with an adjusted Odds Ratio. The outcome was Gestational Diabetes Mellitus.

3. Exclusion Criteria

The exclusion criteria were non-cross-sectional study, non-full-text articles, published before 2007, non-English and Indonesian languages, non-multivariate analysis study.

4. Operational Definition of Variables

The article search was carried out by considering the eligibility criteria defined using the PICO model. The population of this study was pregnant women. The intervention was a family history of DM. The comparison was no family history of DM. The outcome was Gestational Diabetes Mellitus.

Family history of DM was the main risk factor in women for having GDM. This study used a questionnaire with a categorical scale as the measurement instrument.

Gestational Diabetes Mellitus was a carbohydrate intolerance condition that developed first diagnosed during pregnancy. This study used a glucose test with a continuous scale as the measuring instrument.

5. Data Analysis

The articles were collected using a PRISMA diagram. The data analysis was conducted using RevMan 5 published by the Cochrane Collaboration. RevMan was used to calculate the overall adjusted Odds Ratio (aOR), configured the 95% confidence interval (CI) using the effects model, and I² or heterogeneity of the data.

RESULTS

The article review process is in the PRISMA flow diagram in Figure 1. This meta-analysis analyzed 11 primary studies conducted in Ethiopia, Cameroon, Peru, Iran, Pakistan, Malaysia, Kuwait, Saudi Arabia, and India.

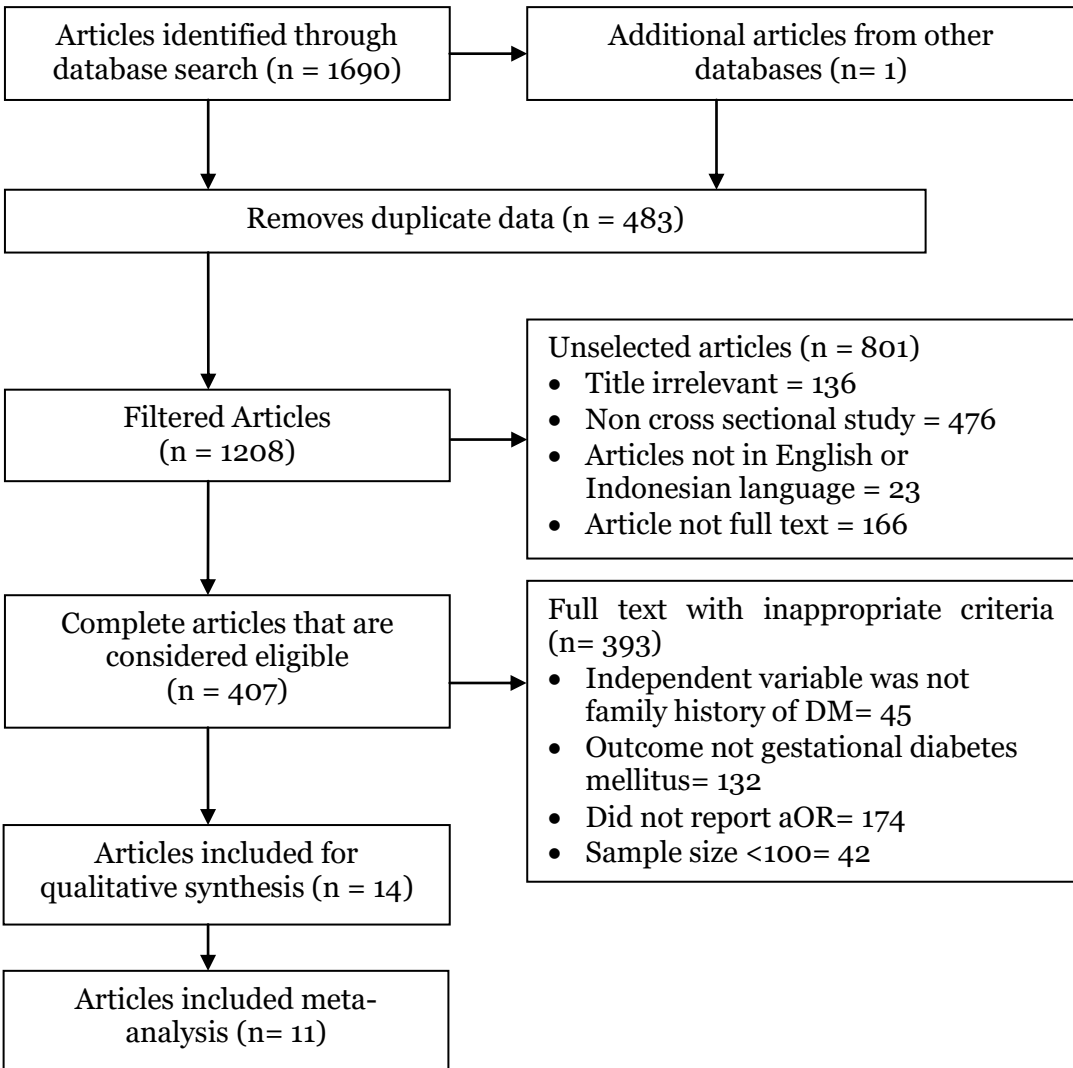


Figure 1. PRISMA flow diagram

**Table 2. The description of the primary study included in the meta-analysis
The relationship between family history of DM and Gestational Diabetes Mellitus**

Author (Year)	Location	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome
Muche et al, 2019	Northwest Ethiopia (Africa)	Cross-sectional	1027	Pregnant Women	Maternal age (> 25 years), marital status (Married), education level(Senior High School), obesity (MUAC ≥28), had a history of GDM, had a history of macrosomic infants, had a history of abortion, had a history of stillbirth, *had a family history of DM*	Maternal age(< 25 years), marital status (Single), education level(elementary school, obesity (MUAC <28), no history of GDM, no history of macrosomic infants, no history of abortion, no history of stillbirth, *no family history of DM*	Gestational Diabetes Mellitus (GDM)
Wolka et al, 2018	Southern Ethiopia (Africa)	Cross-sectional	518	Pregnant Women	Maternal age (> 35 years), marital status (Married), obesity (MUAC ≥30), had a history of GDM, had a history of stillbirth/ miscarriage, had a history of abortion, *had a family history of DM*	Maternal age(16-20 years), marital status (Single), obesity(MUAC <30), had the history of GDM, had a history of stillbirth/ miscarriage, no history of abortion, *no family history of DM*	Gestational Diabetes Mellitus (GDM)
Egbe et al, 2017	Cameroon (Africa)	Cross-sectional	200	Pregnant Women	Age (>19 years), Type 2 DM, Duration of diabetes (>6 years), normal systolic blood pressure level (>140mmhg), *had a family history of DM*	Age (<19 years), Type 1 DM, Duration of diabetes (<6 years), Normal systolic blood pressure level (<140 mmhg), *no family history of DM*	Gestational Diabetes Mellitus (GDM)
Torrealva et al., 2018	Peru (America)	Cross-sectional	1300	Pregnant Women	Maternal age (≥ 35 years), marital status (Married), maternal education (>12 years), maternal BMI ≥30 kg/m ² , had depression,	Maternal age (< 19 years), marital status (Single), maternal education (<9 years), maternal BMI < 25 kg/m ² , no depression,	Gestational Diabetes Mellitus (GDM)

Author (Year)	Location	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome
Nezhad et al, 2007	Iran (Asia)	Cross-sectional	2416	Pregnant Women	*had a family history of DM* Maternal age (35–45 years), BMI (>27kg/m ²), had the history of macrosomic infants, had a history of abortion, had a history of stillbirth,	*no family history of DM* Maternal age (15–24 years), BMI (≤27 kg/m ²), no history of macrosomic infants, no history of abortion, no history of stillbirth,	Gestational Diabetes Mellitus (GDM)
Mohammad zadeh et al, 2015	Iran (Asia)	Cross-sectional	1276	Pregnant Women	*had a family history of DM* Maternal age (> 30 years), Height (< 158 Cm), Weight (> 73kg), BMI (29 kg/m ²), Systolic Blood Pressure (107.6 mmHg), Diastolic Blood Pressure (66.8 mmHg), had a history of GDM, had a history of hypertension during pregnancy, had a macrosomia, had a history of abortion and stillbirth, had congenital malformation, *had a family history of DM*	*no family history of DM* Maternal age (< 27 years), Height (>159 Cm), Weight (< 64kg), BMI (25 kg / m ²), Systolic Blood Pressure (104.7 mmHg), Diastolic Blood Pressure (66.2 mmHg), no history of GDM, no history of hypertension during pregnancy, no history of macrosomia, no history of abortion and stillbirth, no congenital malformation, *no family history of DM*	Gestational Diabetes Mellitus (GDM)
Hossain et al, 2017	Pakistan (Asia)	Cross-sectional	1030	Pregnant Women	Maternal age (> 26 years), BMI (>25kg/m ²), had the history of macrosomic infants, had a history of GDM, *had a family history of DM*	Maternal age (< 26 years), BMI (<25kg/m ²), no history of macrosomic infants, no history of GDM, *no family history of DM*	Gestational Diabetes
Lee et al, 2020	Malaysia (Asia)	Cross-sectional	526	Pregnant Women	Maternal age (19–45 years), marital status (Married), education level (Tertiary), BMI during pregnancy (16–	Maternal age (< 19 years), marital status (Single/ others), education level (Primary), BMI during	Gestational Diabetes Mellitus (GDM)

Author (Year)	Location	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome
Groof et al, 2019	Kuwait (Asia)	Cross-sectional	947	Pregnant Women	58.5), had a family history of depression/anxiety, had a history of hypertension, had a history of GDM, had a history of stillbirth/ miscarriage, had a family history of hypertension, *had a family history of DM* Maternal age (> 25 years), marital status (Married), education level (College or university), obesity (MUAC ≥30), had a history of GDM, had a history of stillbirth/ miscarriage, *had a family history of DM*	pregnancy (<16), no family history of depression/anxiety, no history of hypertension, no history of GDM, no history of stillbirth/ miscarriage, no family history of hypertension, *no family history of DM* Maternal age (< 25 years), marital status (Single/others), education level (Middle school), obesity (MUAC <30), no history of GDM, no history of stillbirth/miscarriage, *no family history of DM*	Gestational Diabetes Mellitus (GDM)
Wahabi, 2018	Saudi Arabia (Asia)	Cross-sectional	316	Pregnant Women	Maternal age (> 30 years), BMI at pre-pregnancy (≥ 30 kg/m ²) *had a history of T2DM*	Maternal age (< 30 years), BMI at pre-pregnancy (≥ 25kg/m ²) *no history of T2DM*	Gestational Diabetes Mellitus (GDM)
Begum et al, 2017	India (Asia)	Cross-sectional	303	Pregnant Women	Maternal age (> 30 years), education level (Graduate), education >60 kg, BMI (≥25), had a family history of GDM, *had a family history of DM*	Maternal age (< 30 years), education level (Primary), weight <60 kg, BMI (<25), no family history of GDM, *no family history of DM*	Gestational Diabetes Mellitus (GDM)

Variables included in the meta-analysis study

a. Forest plot

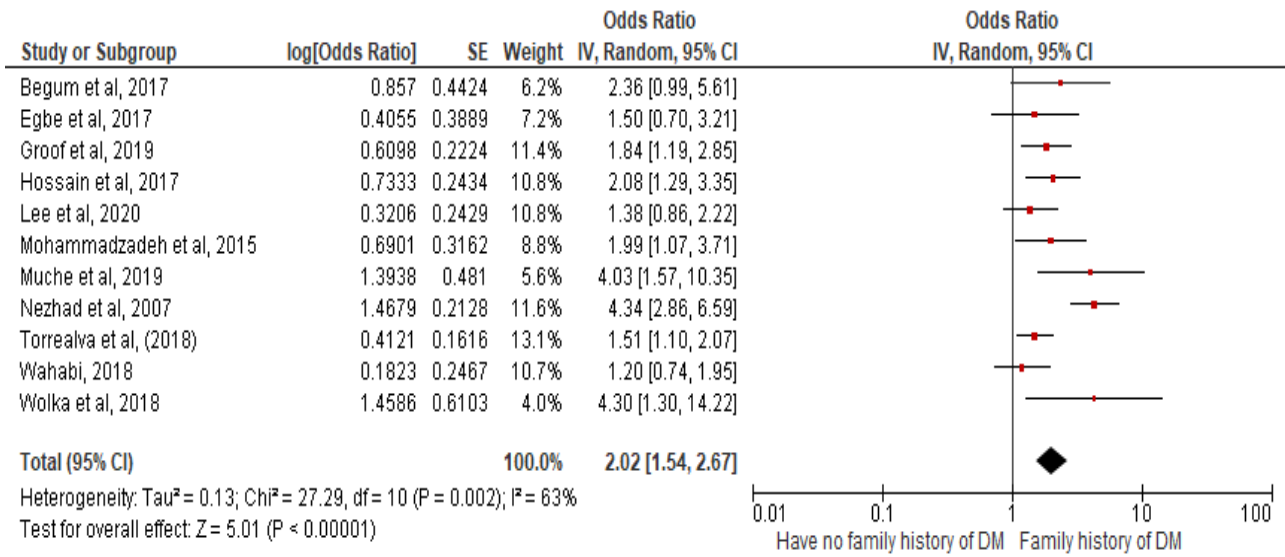


Figure 3. The forest plot of the relationship between family history of DM and Gestational Diabetes Mellitus

b. Funnel plot

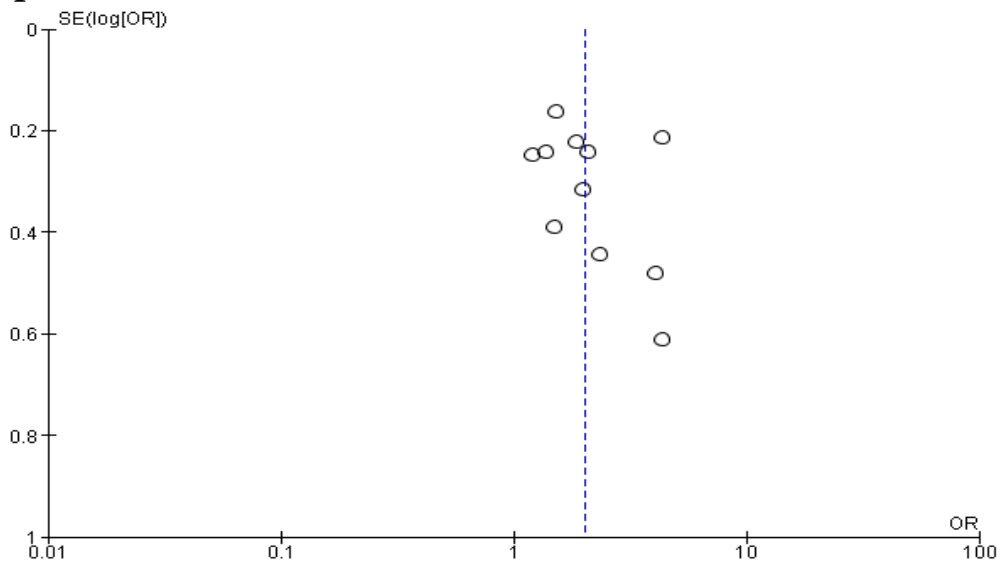


Figure 4. The funnel plot of the relationship between family history of DM and gestational diabetes mellitus

The forest plot showed that pregnant women with a family history of DM could increase the risk of Gestational Diabetes Mellitus 2.02 times compared to pregnant women who did not have a history of DM ($p < 0.001$). The heterogeneity of the study data showed that $I^2 = 63\%$. Therefore, the

distribution of the data was heterogeneous (random effect model).

The funnel plot showed a publication bias characterized by an asymmetry of the right and left plots where 4 plots were on the right and 4 plots were on the left. The plot on the left of the graph had a standard

error between 0 and 0.4. Besides, the plot on the right had a standard error between 0.2 and 0.6. Bias occurred from the imbalance among the distances of each study on both the right and left of the funnel plot where 2 plots were on the right and 3 plots were on the left. The plot on the left of the graph had a standard error between 0.4 and 1. Besides, the plot on the right had a standard error between 0.6 and 0.8. Bias occurred from the imbalance among the distances of each study on both the right and left of the funnel plot.

DISCUSSION

DM develops slowly and progressively so that there is no early detection due to clinical figures had by sufferers such as the triad of diabetes mellitus, namely polyuria (frequent urination), drinking and eating a lot. Diabetes control efforts aimed to prevent microvascular and macrovascular complications (Prasetyowati, 2018)

The development of DM could also be seen from the DM risk group. DM did not only attack the elderly but also the productive age. In many cases, DM attacked pregnant women. Insulin disorders in pregnant women were called Gestational Diabetes Mellitus.

This study was a systematic study and a meta-analysis. It focused on the relationship between family history of Diabetes Mellitus and Gestational Diabetes Mellitus. The results of the systematic review and a meta-analysis on the primary study showed an epidemiological study design with a larger sample and different demographic characteristics in both developed and developing countries, thus providing a basis for concluding that family history of DM was statistically related to the incidence of Gestational Diabetes Mellitus.

This systematic review and meta-analysis study used studies that controlled

confounding factors. It could be seen from the inclusion criteria of the primary study. It was the result of multivariate analysis in the form of adjusted Odds Ratio (aOR). According to Murti (2018), the confounding factor was the combination of the estimated relationships between exposure and the disease studied, by other factors associated, both with disease and exposure. Confounding factors affected the relationship or effect of exposure to the occurrence of the disease estimated by the study. It was not the same as the relationship or effect that occurred in the target population (invalid study result).

The estimation of the combination between family history of DM and GDM was processed using the RevMan 5.3 application with the generic inverse variance method. This method aimed to analyze the data in the form of rate, time-to-event, hazard ratio, ordinal scale, adjusted estimate, difference of mean, or ratio of mean.

The results of the systematic study and meta-analysis were presented in the form of a forest plot and a funnel plot. The forest plot provided an overview of the information from each of the studies examined in the meta-analysis and the estimation of the overall results (Murti, 2018). The forest plot showed visually the amount of variation (heterogeneity) among study results (Akobeng in Murti, 2018).

A funnel plot was a diagram in a meta-analysis that aimed to demonstrate possible publication bias. The funnel plot showed the relationship between the effect size of the study and the sample size or standard error of the effect size of the various studies examined (Murti, 2018). The funnel plot showed visually the amount of variation (heterogeneity) (Akobeng, 2005 in Murti, 2018). The funnel plot showed the relationship between the effect size of the study and the sample size of the

various studies examined which could be measured in several different ways (Murthi, 2018).

Family history of DM and Gestational Diabetes Mellitus

The results of the meta-analysis of 11 articles regarding the relationship between family history of DM and GDM were summarized in a forest plot. The forest plot in Figure 4.1 showed that pregnant women with a family history of DM increased the risk of GDM by 2.02 times compared to pregnant women who did not have a family history of DM. The statistical result was statistically significant (aOR= 2.02; 95% CI= 1.51 to 2.70; $p < 0.001$).

Family history of DM was an important factor in most diabetics from the same family who were autosomal dominant. This is in line with a study conducted by Budiarti (2018) that there was a relationship between family history and an increased risk of type 2 DM and it was statistically significant. Family history of DM was associated with the occurrence of preeclampsia. This was proven in a study conducted by Sari (2019) that the factors affecting preeclampsia were related to the mother's medical history, including a family history of hypertension, history of hypertension, and family history of DM.

Family history of DM was associated with GDM. This is in line with a study conducted by Sulistiyah (2015) that pregnant women with a family history of DM (49%) were a risk factor for diabetes mellitus in pregnancy compared to other risk factors such as a history of recurrent miscarriage (25%), a history of preeclampsia (14%), Polyhydramnios (11%), and IUFD (7%).

Women who had diabetes during pregnancy had normal glucose homeostasis in the first half of pregnancy. It progressed

to relative insulin deficiency during the second half, thus causing hyperglycemia.

A study conducted by Moosazadeh (2017) showed that a family history of diabetes was the main risk factor for Gestational Diabetes Mellitus in Iran. This result was statistically significant aOR 3.46 (95% CI= 2.80 to 4.27; $p = 0.001$). In addition, Ali et al, (2016), in their study stated that a family history of diabetes was an independent risk factor for the prevalence of GDM.

The study conducted by Fuji Rachmawati (2016) stated that there was a significant relationship between the family history of DM and GDM in pregnant women at Simpang Timbangan Community Health Center, South Sumatra, Indonesia. The results of the correlation test showed that the p-value was ≤ 0.050 , namely 0.002. It showed that there was a significant relationship between the family history of DM and GDM in pregnant women.

The result is in line with a study carried out by Choi et al. in Korea (2016). This study was conducted by surveying Korean nurses through an independent interview with a web-based computer. It was developed in consultation with cardiologists, gynecologists, and statisticians. This study showed that family history was a cardiovascular risk factor associated with pregnancy medical disorders such as GHD and GDM in a survey of nurses in Korea. Family history of DM was one of the main risk factors in this study; the results were statistically significant; aOR 2.68 (95% CI: 1.86-3.86).

Groof et al, (2019) and Njete et al, (2017) examined the risk factors and prevalence of GDM. The result of a study conducted by Groof et al, (2019) estimated that 12.6% of pregnancies in Kuwait were affected by GDM. Based on national self-reporting, elderly, obesity before pregnancy, family history of T2 DM/GDM, and

a history of stillbirth/miscarriage were associated with an increased risk of GDM in this study. Njete et al, (2017) stated that the prevalence of GDM was significantly related to the family history of DM (aOR 2.14).

Based on the discussion above, a family history of DM could increase GDM.

The limitation of this study was that there was a publication bias showed in the funnel plot. Language bias occurred because the selected articles were only published in the the English language, thus ignoring articles using other languages. Besides, the researchers used 4 databases only (PubMed, Research Get, Science Direct, and Google Scholar), thus ignoring other search sources.

AUTHOR CONTRIBUTION

Ummu was the main researcher who selected the topic, investigated, and collected the data. Didik Tamtomo and Bhisma Murti played roles in guiding the writing and reviewing the documents.

CONFLICT OF INTEREST

This study did not have any conflict of interest.

FUNDING AND SPONSORSHIP

This study used personal funds from the main researcher.

ACKNOWLEDGEMENT

We would like to thank the databases provider of PubMed, ResearchGate, Science Direct, Google Scholar.

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