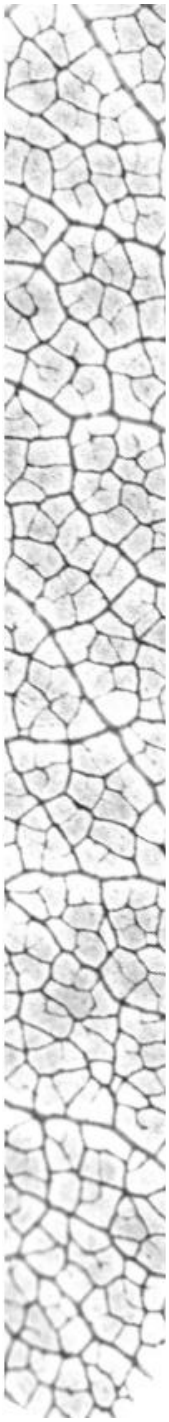

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Determine the association between a broader array of pregnancy complications and the future risk of cardiovascular: a systematic review and meta-analysis

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Abstract

Background and aim: the aim of present systematic review and meta-analysis was determine the association between a broader array of pregnancy complications and the future risk of cardiovascular.
Method: From the electronic databases, PubMed, Cochrane Library, Embase, ISI have been used to perform a systematic literature between 2015 and 2020. Therefore, a software program (Endnote X8) has been utilized for managing the electronic titles. Searches were performed with mesh terms. Odds ratio between two groups with 95% confidence interval (CI), random effect model and restricted maximum-likelihood method were calculated. Random effects were used to deal with potential heterogeneity and I^2 showed heterogeneity. The Meta analysis and forest plots have been evaluated with the use of a software program Stata V16.
Result: A total of 486 potentially relevant titles and abstracts were found during the electronic and manual search. Finally, a total of 21 publications fulfilled the inclusion criteria required for this systematic review. Pooled results of nine studies examining gestational hypertension suggest a 40% (95% ICI, -0.09, and 0.90) higher risk of subsequent CVD in women with gestational hypertension compared to women without. The odds ratio was (OR, 0.40 95% CI -0.09, 0.90. P= 0.11), and heterogeneity found (I2 = 82.35%)
Conclusion: Women with a history of gestational hypertension, gestational diabetes, preterm birth, and stillbirth are at higher risk for CVD than other women.

Keywords: pregnancy complications, cardiovascular, hypertensive disorders of pregnancy

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INTRODUCTION

Gestational diabetes mellitus, preterm birth, and hypertensive disorders of pregnancy (HDP) occur in 1 to 2% of pregnancies and are associated with maternal and fetal mortality and mortality (Kessous, et al. 2013. Robbins, et al. 2014. Grandi, et al. 2019- Auger, et al. 2020). The results of studies show that women with ≥1 pregnancy complications or multiple pregnancies have high risk of maternal and fetal mortality (Auger, et al. 2017. Auger, et al. 2018- Riise, et al. 2017). Also studies have shown that women with a history of preeclampsia, gestational hypertension, gestational diabetes mellitus, and preterm birth are at higher risk for cardiovascular disease (CVD)(Grandi, et al. 2019, Kessous, et al. 2013. Minissian, et al. 2018- Tanz, et al. 2017). On the other hand, other studies show that the increased risk of CVD after pregnancy complications may continue for a long time (Umesawa, & Kobashi, 2017, Løkke, et al. 2014; Bulgakov et al., 2018). Other evidence suggests a link between some pregnancy complications and CVD. It is recommended that CVD be evaluated long-term in women. Also, according to the guidelines of the American College of Obstetricians and Gynecologists and the American Heart Association, women with a history of gestational hypertension, gestational diabetes

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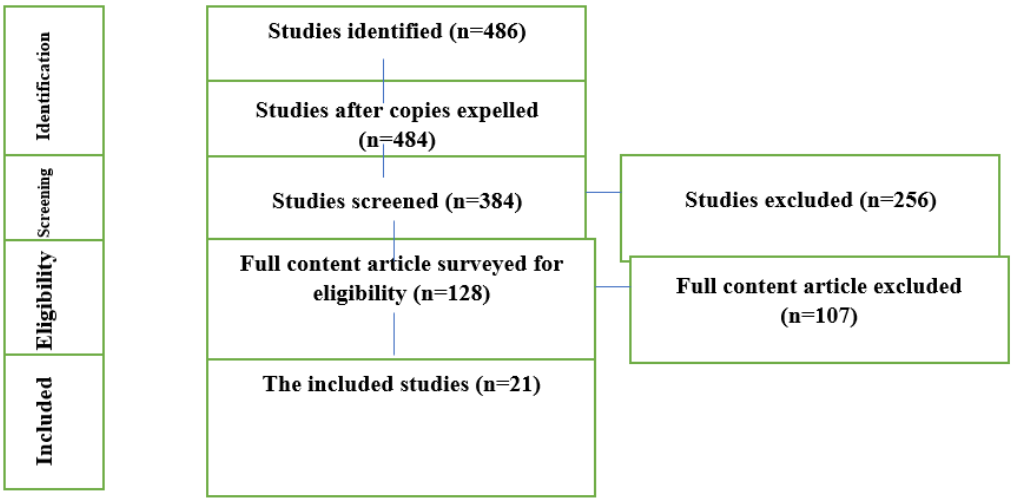

Fig. 1. Study Attrition

mellitus, preeclampsia, or preterm birth should be screened for CVD(American College of Obstetricians and Gynecologists. 2013, Mosca, et al. 2011). Nevertheless, the mechanism of action between several pregnancy complications, including preeclampsia, placental abruption, and low birth weight, and age for small pregnancies (SGA), birth weight should be considered. According to importance of subject the aim of present systematic review and meta-analysis was determine the association between a broader array of pregnancy complications and the future risk of cardiovascular.

METHOD

Search strategy

From the electronic databases, PubMed, Cochrane Library, Embase, ISI have been used to perform a systematic literature between 2015 and 2020. Therefore, a software program (Endnote X8) has been utilized for managing the electronic titles. Searches were performed with mesh terms:

("Pregnancy"[Mesh]) OR "Pregnancy Complications"[Mesh]) OR ("Pregnancy Complications, Parasitic"[Mesh] OR "Pregnancy Complications, Neoplastic"[Mesh] OR "Pregnancy Complications, Infectious"[Mesh] OR "Pregnancy Complications, Hematologic"[Mesh] OR "Pregnancy Complications, Cardiovascular"[Mesh])) AND "Cardiovascular Diseases/adverse effects"[Mesh]. This systematic review has been conducted on the basis of the key consideration of the PRISMA Statement–Preferred Reporting Items for the Systematic Review and Meta-analysis(Liberati, et al. 2009).

Selection criteria

Inclusion criteria

1. Randomized controlled trials studies, controlled clinical trials, and prospective and retrospective cohort studies.
2. Indication of a pregnancy complication
3. in English

Exclusion criteria

1. In vitro studies, case studies, case reports and reviews.
2. Studies of cardiovascular outcomes in infants born to mothers with a history of pregnancy complications

Data Extraction and method of analysis

The data have been extracted from the research included with regard to the study, years, study design, sample size, mean/ range of age, follow-up period. For Data extraction, two reviewers blind and independently extracted data from abstract and full text of studies that included. Moreover, Odds ratio between two groups (case and control) with 95% confidence interval (CI), Random effect model and restricted maximum-likelihood method were calculated. Random effects were used to deal with potential heterogeneity and I^2 showed heterogeneity. The Meta analysis and forest plots have been evaluated with the use of a software program available in the market (i.e., Comprehensive Meta-Analysis Stata V16).

RESULTS

According to the research design, 486 potentially important research abstracts and titles have been discovered in our electronic searches. At the first phase of the study selection, 384 research have been with regard to the topics and abstracts. Therefore, we fully assessed the complete full-text papers of the rest 128 studies in the second stage so that we excluded 107 publications due to the lack of the defined inclusion criteria. Then, 21 papers remained in agreement with our inclusion criteria required (**Fig. 1**).

Study Characteristics

21 studies (cohort studies) have been included with sample sizes ranging from 242 to 1,515,387 women.

Table 1. Characteristics of Studies selected for systematic review and meta-analysis (Hypertensive Disorders in Pregnancy)

Study. Years	Sample size	Age (years)	Follow-up	Source of data
Auger et al. 2017	1,108,581	Not reported	15.5 (Median)	Hospital discharge records*
Grandi et al. 2017	146,748	29.5 (6.1)	4.7 (IQR 1.9-9.1)	Administrative database
Behrens et al. 2016	1,075,763	Not reported	17.9 (Mean)	National patient and birth registries
Cain et al. 2016	302,686	Exposed: 24.9 (6.1) Unexposed: 25.1 (6.0)	4.9 (Median)	Hospital discharge record
Canoy et al. 2016	1,105,568	Exposed: 55.9 (4.7) Unexposed: 56.0 (4.8)	11.6 (2.3)	Self-report
Cirillo et al.2015	14,062	26	Not reported	Medical record
Heida et al,2015	22,265	Exposed: 54.1 (8.9) Unexposed: 51.2 (10.4)	Not reported	Self-report
Kessous et al. 2015	96,370	Exposed: 28.3 (6.0) Unexposed: 28.8 (6.0)	Not reported	Perinatal database
Lin et al. 2016	141,730	GHTN: 31.2 (5.0) PE: 30.9 (5.1) Unexposed: NR	Not reported	National health insurance database
McDonald, et al. 2016	242	GHTN: 48 (8) PE: 47.5 (9.5) Unexposed: 50 (6)	Not reported	Self-report
Nelander et al, 2016	3,232	Exposed: 71 (5.1) Unexposed: 71.8 (5.6)	Not reported	Self-report
Riise et al. 2017	342,421	Exposed: 28.1 (5.6) Unexposed: 27.5 (5.7)	Not reported	Birth registry
Soh et al. 2015	3,977	Exposed: 29 (IQR 23 -31) Unexposed: 27 (IQR 23 - 30)	Not reported	Birth registry
Theilen et al. 2016	83,720	Exposed: 26 (5.9) Unexposed: 26 (5.9)	Not reported	Birth certificate
Tooher et al. 2017	31,656		20 (range: 3-29)	Hospital record

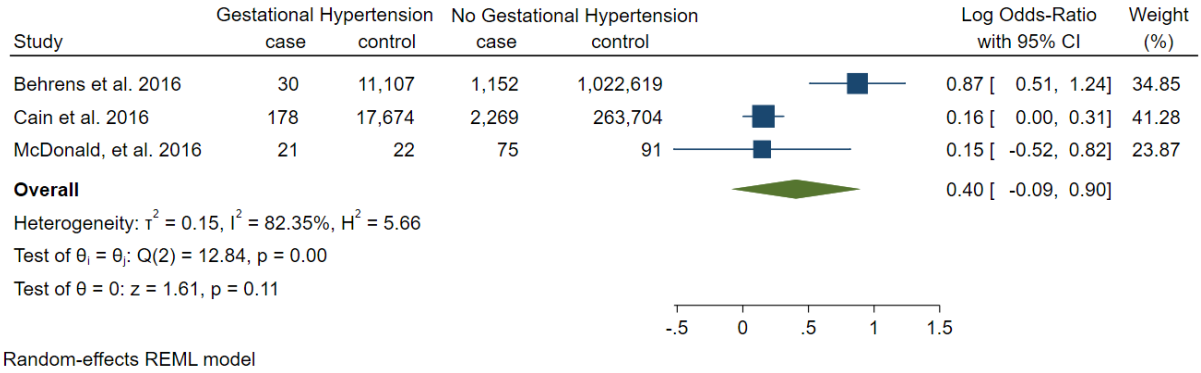

Fig. 2. Gestational Hypertension and CVD-Related Morbidity

Table 2. Characteristics of Studies selected for systematic review and meta-analysis (Gestational Diabetes Mellitus)

Study. Years	Sample size	Age (years)	Follow-up	Exposure – Source of data
Cirillo et al.2015	14,062	26	Not reported	Medical record
Goueslard et al. 2016	1,515,387	Not reported	3.8 (1.8)	Medico administrative database
Heida et al,2015	22,265	Exposed: 54.1 (8.9) Unexposed: 51.2 (10.4)	Not reported	Self-report
Kaul et al. 2015	222,496	28.7 (5.6)	5.3 (IQR 2.2-8.4)	Administrative claims database
Kessous et al. 2015 (22)	96,370	Exposed: 28.3 (6.0) Unexposed: 28.8 (6.0)	Not reported	Perinatal database

Data sources used to ascertain the exposure of pregnancy complications in these studies included self-report, hospital records, maternity files, birth and patient registries, administrative databases, and health insurance claims databases (**Table 1** to **5**).

Gestational Hypertension and CVD-Related

Table 1 showed Characteristics of Studies selected for systematic review and meta-analysis. 15 studies (cohort studies) have been included with sample sizes ranging from 242 to 1,108,581women. Pooled results of nine studies examining gestational hypertension suggest a 40% (95% ICI, -0.09, and 0.90) higher risk of subsequent CVD in women with gestational hypertension compared to women without. The odds ratio was (OR, 0.40 95% CI -0.09, 0.90. P= 0.11), and heterogeneity found (I2 = 82.35%) (**Fig. 2**).

Gestational Diabetes Mellitus and CVD-Related

Table 2 showed Characteristics of Studies selected for systematic review and meta-analysis. Four studies (cohort studies) have been included with sample sizes ranging from 14,062 to 1,515,387 women. None of the studies were included in the meta-analysis. The odds ratio was (OR, 1.12 95% CI 1.01, 1.23. P= 0.00) (**Fig. 3**). The odds of subsequent CVD in women with gestational diabetes mellitus was 12% (95% CI,.01, 1.23) higher

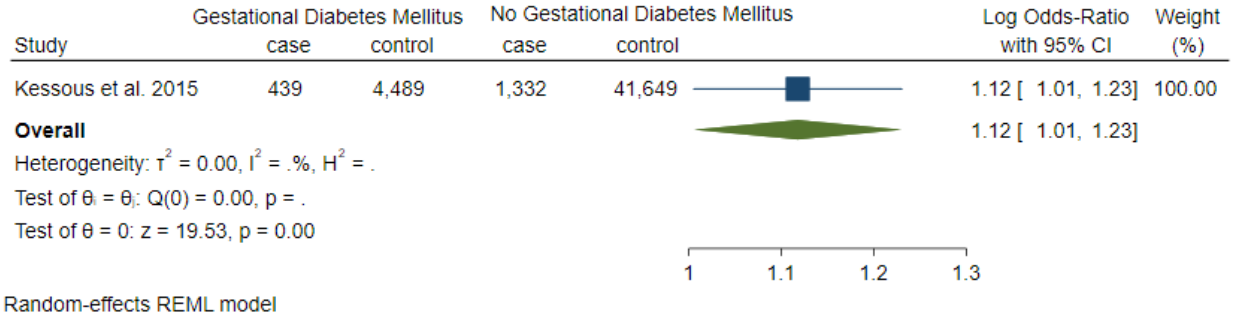

Fig. 3. Gestational Diabetes Mellitus and CVD-Related Morbidity and Mortality

Table 3. Characteristics of Studies selected for systematic review and meta-analysis (Preterm Birth)

Study. Years	Sample size	Age (years)	Follow-up	Exposure – Source of data
Cirillo et al.2015	14,062	26	Not reported	Medical record
Ngo et al. 2015	797,056	31 (IQR 27-35) at last birth	7.5 (IQR 3-13)	Administrative database
Ngo et al. 2016	902,008	Administrative database	31 (IQR 27-35) at last birth	7.3 (IQR 3.0-12.8)
Tanz et al. 2017	70,182	Term: 27 (4.7), Moderate preterm: 27.8 (5.1), vey preterm: 27.5 (5.6)	32 (IQR 2-50)	Self-report

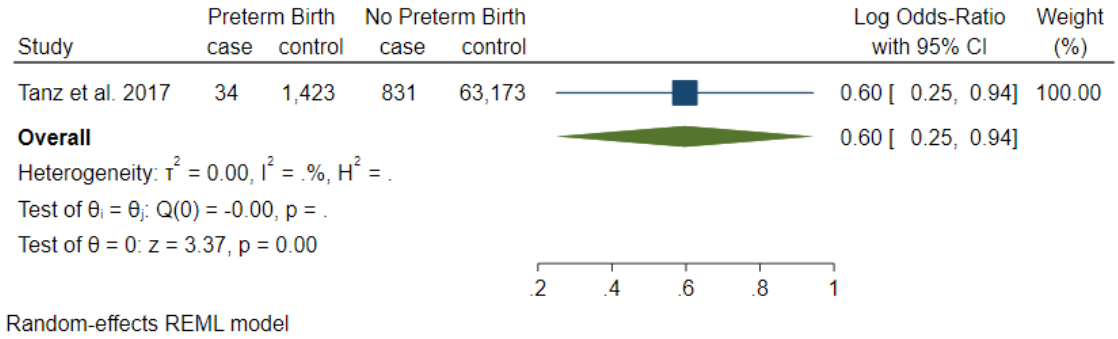

Fig. 4. Preterm Birth and CVD-Related Morbidity

Table 4. Characteristics of Studies selected for systematic review and meta-analysis (Miscarriage)

Study. Years	Sample size	Age (years)	Follow-up	Exposure – Source of data
Peters et a. 2017	282,797	57.0	7.1 (IQR 6.2-8.1)	Self-report
Yamada et al. 2017	52,289	Exposed: 55.8 (SE 0.1) Unexposed: 58.0 (SE 0.1)	Exposed: 16.8 Unexposed: 16.6	Self-report

Table 5. Characteristics of Studies selected for systematic review and meta-analysis (Stillbirth)

Study. Years	Sample size	Age (years)	Follow-up	Exposure – Source of data
Soh et al. 2016	25,118	not	36.5 (IQR 33.2-39.5)	Birth notifications and/or maternity ward logbooks
Hvidtjørn et al. 2016	838,331	26.0 (SD 5.0)	15.0 (SD 8.0)	Birth registry
Peters et a. 2017	282,797	57.0	7.1 (IQR 6.2-8.1)	Self
Soh et al. 2015	3,977	Exposed: 29 (IQR 23 -31) Unexposed: 27 (IQR 23 - 30)	NR	Birth registry**

compared to women without gestational diabetes mellitus.

Preterm Birth and CVD-Related

Table 3 showed Characteristics of Studies selected for systematic review and meta-analysis. Four studies (cohort studies) have been included with sample sizes ranging from 14,062 to 902,008women. Women with a history of preterm birth were 60% (95% CI, 0.25 0.94) more likely to experience a cardiovascular event than women with no history of preterm birth. The odds ratio was (OR, 0.60 95% CI 0.25, 0.94. P= 0.00) (**Fig. 3**).

Miscarriage and CVD-Related

Table 4 showed Characteristics of Studies selected for systematic review and meta-analysis. Two studies (cohort studies) have been included. Because of variations in the exposure definition between studies, pooling was not performed. Across both cohort and case-control studies, there were large variations in effect estimates with several studies suggesting an increased risk of CVD and others suggesting no increased risk.

Stillbirth and CVD-Related

Table 5 showed Characteristics of Studies selected for systematic review and meta-analysis. Four studies

(cohort studies) have been included. No studies were included in the meta-analysis.

DISCUSSION

The results of the present study showed that women with a history of gestational hypertension, gestational diabetes, placental abruption, Preterm Birth and stillbirth are at risk for CVD. Six systematic studies examined the association between gestational diabetes, preeclampsia and preterm labor and its association with CVD (Robbins, et al. 2014. Brett, et al. 2006.Brown, et al. 2013. Heida, et al. 2016.Hopmans, et al. 2015.Grandi, et al. 2019). Although the results of present systematic review and meta-analysis were in similar to previous reviews, present study Examines studies from the last 5 years. According the recent recommendations from the American College of Obstetricians and Gynecologists and American Heart Association for enhanced screening for CVD and integrated care for women,(Grandi, et al. 2019) the results of the present study were in accordance with them. Previous studies have shown that physiological changes during pregnancy and stress can affect the mother's cardiovascular system(Brown, et al. 2018, Cheng, et al. 2017). In addition, obesity, high blood pressure, blood cholesterol, family history of CVD can be traditional risk factors for CVD. The results of the present study indicate that all pregnancy complications may affect CVD. Gestational hypertension, gestational diabetes, preterm labor, and stillbirth can increase the risk of maternal CVD. Given the limited number of studies to date that have examined the combined effects of multiple complications, we have not been able to assess the potential impact on the future risk of CVD. However, there is a need to investigate the potential mediating effects of cardiovascular risk factors on the association between pregnancy complications and CVD risk. This is needed to better understand the evidence of cardiovascular prevention in post-pregnancy women and the optimal follow-up time in these women. Further studies with the case group and control group and comparison of the two groups are also needed. Heterogeneity between studies may be due to definitions of exposure. Also, in the present study, there was no potential for diffusion bias, so it is not possible to conclude whether diffusion bias exists

CONCLUSION

Women with a history of gestational hypertension, gestational diabetes, preterm birth, and stillbirth are at higher risk for CVD than other women. There is insufficient evidence to draw significant conclusions about the risk of CVD associated with miscarriage.

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