

A meta-analysis of the prevalence of gestational diabetes in patients diagnosed with obstetrical cholestasis



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BACKGROUND: Gestational diabetes and obstetrical cholestasis are common clinical conditions seen in clinical practice. There is evidence suggesting a coexisting relationship that could have a potential clinical implication related to stillbirth outcomes.

OBJECTIVE: This study aimed to determine the prevalence of gestational diabetes in women with obstetrical cholestasis.

STUDY DESIGN: A predefined protocol with a literature search was used to obtain all possible articles. A systematic review and meta-analysis of observational studies with quantifiable data published since 2010 were performed. Articles were evaluated and included in the study with specified criteria for the risk of bias using the Newcastle-Ottawa Scale. A meta-analysis was performed using Meta-analysis of Observational Studies in Epidemiology specifications to determine the prevalence of gestational diabetes in women with obstetrical cholestasis.

RESULTS: A total of 16,748 patients with obstetrical cholestasis from 21 studies were included. The prevalence of gestational diabetes in women with obstetrical cholestasis was 13.9% (20 studies analyzed). Gestational diabetes was more common in women with obstetrical cholestasis than in women without obstetrical cholestasis (odds ratio, 2.129; 95% confidence interval, 1.697–2.670; 10 studies). Gestational diabetes is twice more common in women with severe cholestasis than in women with mild cholestasis (odds ratio, 2.168; 95% confidence interval, 1.429–3.289; 4 studies).

CONCLUSION: There is an increase in the prevalence of gestational diabetes among women diagnosed with obstetrical cholestasis. Compared with women with mild cholestasis, the increased risk of gestational diabetes in women with severe cholestasis is more than doubled. This suggests that the 2 conditions may have some biological similarities that affect clinical outcomes.

Key words: gestational diabetes, meta-analysis, obstetrical cholestasis

Introduction

Obstetrical cholestasis (OC) is a common complication of pregnancy with a

wide range of prevalence (0.7%–5%) along with regional variations worldwide.¹ The prevalence of gestational diabetes (GD) is high worldwide² and varies in different populations but represents a significant disease.³

In the current obstetrical practice, women with GD are recommended to give birth at 39 weeks' gestation.⁴ In fact, most women are delivered at 36 to 42 weeks' gestation⁵ to reduce stillbirth (SB) rates associated with GD.

OC is commonly diagnosed earlier than 39 weeks' gestation, and generally, clinical practice follows an international recommendation to manage OC because of related complications, including SB.^{6,7} In both the United States and the United Kingdom, the current practice guidelines recommend that women diagnosed with OC should give birth at 37 0/7 weeks' gestation or earlier, depending on the severity of the OC.^{1,8,9}

There is increasing evidence supporting the role of primary bile acid receptors influencing lipid and glucose

homeostases,^{10–14} providing the biological assumption of the relationship between GD and OC. In addition, the association between glucose intolerance and dyslipidemia has been reported with evidence suggesting that the incidence of GD increases following the onset of OC.^{10,15–17}

Both OC and GD are associated with SB. However, the risk of SB associated with OC is a topic of debate, and individual patient data have shown evidence suggesting that the increased risk of SB is related to severe OC only.^{18,19} Given that there is an overlap of women with OC coexisting with GD, the relationship of OC to SB may be related to an increased prevalence of GD in severe OC cases. Therefore, it is necessary to explore the relation of GD in women diagnosed with varying severity of OC. We assumed that a higher prevalence of GD exists in women diagnosed with OC, with potential clinical implications, especially the risk of SB and its implication with the management of women with severe OC. Therefore, this study

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This study is registered on the International Prospective Register of Systematic Reviews database (number CRD42021223886).

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Why was this study conducted?

This study was conducted to understand the prevalence of gestational diabetes (GD) in women diagnosed with obstetrical cholestasis (OC) and its potential clinical implications.

Key findings

The key findings included the increased prevalence of GD in women diagnosed with OC.

What does this add to what is known?

We know that both conditions, OC and GD, contribute to stillbirths (SBs). This study has added that the 2 conditions are mutually inclusive as the new understanding may have an implication in SB reduction.

Outcome measure

The following are primary outcomes:

- 1 The prevalence of GD in women with OC in the published studies
- 2 The odds of GD between women with and without OC

The following are secondary outcomes:

- 1 The risk of SB in patients diagnosed with OC and GD
- 2 The odds of GD between women with mild or moderate OC and those with severe OC

aimed to calculate the prevalence and associated relationship of GD among pregnant women diagnosed with OC.

Methods
Search strategy

A systematic search on PubMed, Ovid Embase, the Cochrane Library, the Cumulative Index to Nursing and Allied Health Literature, Clinical-Trials.gov, and Web of Science with no language restriction was undertaken. Articles published in the last 10 years, that is, from January 1, 2010, to November 27, 2020, were included as changes in GD diagnosis are more relevant in the previous decade. Therefore, we only focused on publications in the last 10 years. In addition, international guidelines of OC were hand-searched to review citations to pick up all published articles.

The searches were done by 2 independent reviewers (M.M. and A.K.P.) who completed the screening process with all included studies meeting the inclusion criteria as mentioned below. We used the following search terms: “intrahepatic cholestasis,” “intrahepatic cholestasis of pregnancy,” “obstetric cholestasis,” “gestational diabetes mellitus,” and “gestational diabetes.” All retrieved articles of the search were available in English, and therefore, we did not need any official translation assistance. The search strategy is provided in the Appendix.

Inclusion criteria

Here, the studies included were those that described epidemiologic data of the pregnant population with OC and GD. Pregnant women diagnosed with OC or intrahepatic cholestasis of pregnancy represent the same diagnosis and population group. Diagnoses defined by the exclusion criteria using the International Classification of Diseases codes²⁰ and studies that used similar criteria using the Royal College of Obstetricians and Gynaecologists Green-top Guidelines were used.¹ GD cases with diagnostic criteria using either a 50-g or 75-g oral glucose tolerance test or as described by the National Institute for Health & Care Excellence were included.³ When clear diagnostic criteria were not identified, we specified them as “not given” and used them in this study along with a sensitivity analysis. Studies with both singleton and multiple pregnancies were included.

Observational studies with epidemiologic data, cross-sectional or prevalence studies, case-control studies, and cohort studies (prospective and retrospective designs) were included. Research letters and conference proceedings with published data were included. Case reports, case series, and reviews without quantifiable data were not included. Qualitative studies, editorials, commentaries, and animal studies were excluded. Studies reporting other causes of itching in pregnancy and other liver diseases in pregnancies were excluded.

Quality assessment and risk of bias

Here, 2 independent reviewers (M.M. and S.S.P.) completed the quality assessment separately and then combined their results. A uniform decision was made with all authors agreeing to finalize and include the studies after the quality assessment.

The Newcastle-Ottawa Scale (NOS) is a quality assessment tool used to determine the eligibility of observational epidemiology studies.²¹ The studies selected were all observational studies that met the inclusion criteria.

Using the NOS tool, each study is based on 8 items with 3 categories: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Per the tool, a study could be given a maximum of 1 star for each numbered item within the selection and outcome categories and a maximum of 2 stars within the comparability category as shown in [Table 1](#). Studies with 0 to 3 stars (red color), 4 to 6 stars (yellow color), and 7 to 9 stars (green color) are classified as studies with high, moderate, or low risk of bias, respectively. The risk of bias for each study was independently reviewed by 2 reviewers (M.M. and S.S.P.), and discrepant scores were resolved by consensus from all authors.

Data extraction

Here, 3 independent reviewers (M.M., S.S.P., and A.K.P.) collected the data

TABLE 1
NOS scoring

Number	Study, year	NOS selection	NOS comparability	NOS outcome	NOS total score
1	Bhagwat et al, ²² 2017	**		**	4
2	Baliutavičienė et al, ²³ 2011	**		**	4
3	Bayrak et al, ²⁴ 2015	*		*	2
4	Ensari et al, ²⁵ 2016	***	**	***	8
5	Gardiner et al, ²⁶ 2019	***	**	**	7
6	Kohari et al, ²⁷ 2017	**		***	5
7	Majewska et al, ²⁸ 2019	***		***	6
8	Marathe et al, ²⁹ 2017	***		***	6
9	Martineau et al, ¹⁶ 2014	***	**	***	8
10	Roy et al, ³⁰ 2021	***		**	5
11	Mei et al, ³¹ 2018	***		**	5
12	Wikström Shemer et al, ¹⁷ 2013	****	**	***	9
13	Bannister-Tyrrell et al, ³² 2014	***	*	**	6
14	Liu et al, ³³ 2016	****	**	***	9
15	Shan et al, ³⁴ 2016	***	**	***	8
16	Ozyuncu et al, ³⁵ 2019	**		*	3
17	Morton et al, ³⁶ 2019	**		**	4
18	Rimon et al, ³⁷ 2017	***	*	**	6
19	Puljic et al, ³⁸ 2015	****	**	**	8
20	Geenes et al, ³⁹ 2014	***	**	***	8
21	Garcia-Flores et al, ⁴⁰ 2015	***	**	***	8

NOS, Newcastle-Ottawa Scale.

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with a predefined Excel file to extract data independently. Accurate data collection was completed, and duplication of data from the published studies was excluded as some studies had more than 1 publication of the data, which has been represented in the excluded study. When GD data was not included and pooled together with all types of GD, we contacted the first author in one of the included studies, and accurate information was included with the response.²⁶ Data variables included the number of patients with OC and GD, the number of patients in the control population who had GD but without OC, the number of SBs in the combined obstetrical and GD populations. The severity of OC was divided into 2 categories: mild and moderate (mild OC

group) and severe (severe OC group; a bile acid of $>40 \mu\text{mol/L}$).

Meta-analysis

The Meta-analysis of Observational Studies in Epidemiology⁴¹ specification for reporting observational studies before proceeding with the meta-analysis was used.

The results of the studies included in the systematic review were analyzed and summarized. The analysis aimed to provide more precise estimates of the outcomes studied to provide a more robust epidemiologic estimate than individual studies.

All the extracted data from the included studies were subjected to meta-analysis using Comprehensive Meta-Analysis (version 3).⁴² We used a random-effects model for all meta-analysis. We

used individual studies with their event rate with lower and upper limits with 95% confidence intervals (CIs) when studying the relationship of GD in the obstetrical population, similarly in cases of SB. When there was a control group to study, the odds ratio with a 95% CI was used to compare the groups with lower and upper limits. The Forest plots provided the Q value, which is the sum of squared deviations of all estimates from the weighted pooled estimate (this is similar to the sum of squares in a primary study, except that these are computed on a standardized scale, in log units).

Heterogeneity

We addressed the weighted mean effect size, and we also considered how much the effects varied from study to study. The relevant statistics were given with a

Q value with the degrees of freedom and a *P* value. In addition, we considered the I^2 and Tau² statistics.⁴³ The I^2 statistics indicated the proportion of the observed variance reflecting differences in true effect size rather than sampling error and told us nothing about the absolute amount of variance. However, it provided context for understanding the variation in the Forest plot.

Prediction interval for prevalence

In addition to the weighted mean prevalence, we also provided the prediction interval, which is an estimate of an interval in which a future observation will fall, with a certain probability, given what has already been observed.⁴⁴

Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart is outlined in Figure 1, which shows 21 studies included in this study. The characteristics of the included studies are provided in Table 2, along with the risk of bias (NOS) in Table 1. Here, 9 of the included studies were of low risk of bias, 10 studies were of moderate risk of bias, and 2 studies had a high risk of bias.

There was a total of 16,748 patients with OC for this meta-analysis. Furthermore, 20 studies^{16,17,22–31,33–40} were included for understanding the prevalence of GD in the OC population.

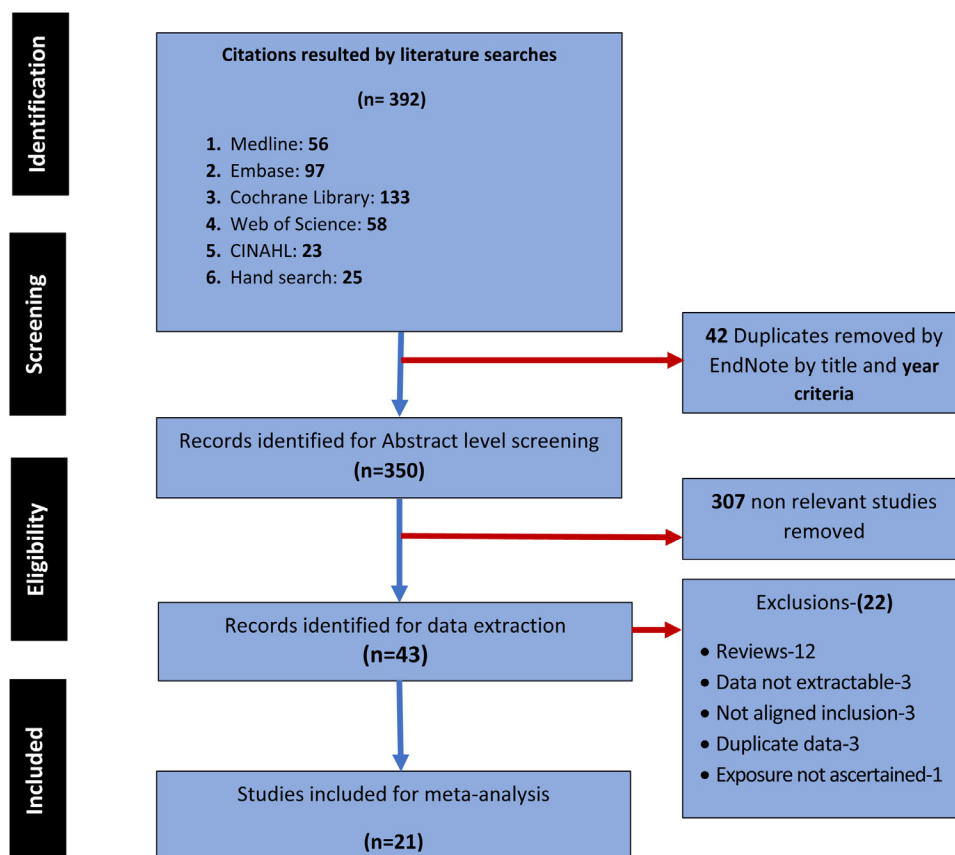
This meta-analysis showed a prevalence of GD of 13.9% within the population diagnosed with OC. The mean event rate (weighted) was 0.139 (95% CI, 0.099–0.193) (Figure 2).

The 95% prediction interval was between 2.5% and 49.7%. In 95% of the population, similar to those in the analysis, the true prevalence will fall somewhere in this range.

Sensitivity analysis

The event rate was similar when removing 2 studies^{25,35} with a high risk of bias (0.137; 95% CI, 0.095–0.193), when removing 2 studies with >5000 women with OC (0.164; 95% CI, 0.132–0.204),^{17,38} when including the studies

FIGURE 1
PRISMA flowchart



Adapted From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097

Adapted from Moher et al,⁴⁵ 2009.

CINAHL, Cumulative Index to Nursing and Allied Health Literature; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

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TABLE 2
Characteristics of the included studies

Serial number	Study (first author)	Year	Place of study	Type of study	Diagnostic criteria	Obstetrical cholestasis (n)	Outcomes studied
1	Bhagwat et al ²²	2017	United Kingdom	Conference proceeding	Not given	36	GD prevalence in women with OC
2	Bayrak et al ²⁴	2015	Turkey	Retrospective cohort study	Not given	32	GD prevalence in women with OC; SB in women with OC with GD
3	Ensari et al ²⁵	2016	Turkey	Conference proceeding	Not given	49	GD prevalence in women with OC; risk of GD in women with OC compared with women without OC
4	Gardiner et al ²⁶	2019	Australia	Retrospective audit study	RANZCOG guidelines	319	GD prevalence in women with OC; risk of GD in women with OC compared with women without OC
5	Kohari et al ²⁷	2017	United States	Retrospective cohort study	ICD-9	849	GD prevalence in women with OC; SB in women with OC with GD
6	Majewska et al ²⁸	2019	Poland	Retrospective study	PTGiP guidelines	102	GD prevalence in women with OC
7	Marathe et al ²⁹	2017	Australia	Retrospective study	ICD-10	320	GD prevalence in women with OC; SB in women with OC with GD; OC severity in women with GD
8	Martineau et al ¹⁶	2014	United States	Case-control study	ICD-10	140	Risk of GD in women with OC compared with women without OC; SB in women with OC with GD
9	Roy et al ³⁰	2021	India	Prospective study	ACOG guideline	375	GD prevalence in women OC; OC severity in women with GD
10	Mei et al ³¹	2018	China	Retrospective observational study	Chinese guideline (ICD-10)	58	GD prevalence in women with OC; OC severity in women with GD
11	Wikström Shemer et al ¹⁷	2013	Sweden	Birth register study	ICD-10	5477	GD prevalence in women with OC; risk of GD in women with OC compared with women without OC; SB in women with OC with GD
12	Baliutavičienė et al ²³	2011	Lithuania	Retrospective study	Not given	99	GD prevalence in women OC; risk of GD in women with OC compared with women without OC
13	Bannister-Tyrrell et al ³²	2014	Australia	Cohort study	Not given	1870	Risk of GD in women with OC compared with women without OC; SB in women with OC with GD
14	Liu et al ³³	2016	United States	Cohort study	ICD-10	129	GD prevalence in women with OC; risk of GD in women with OC compared with

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(continued)

TABLE 2
Characteristics of the included studies (continued)

Serial number	Study (first author)	Year	Place of study	Type of study	Diagnostic criteria	Obstetrical cholestasis (n)	Outcomes studied
15	Shan et al ³⁴	2016	China	Retrospective cohort study	ICD-10	362	women without OC; SB in women with OC with GD; OC severity in women with GD
16	Ozyuncu et al ³⁵	2019	Turkey	Retrospective study	ICD-10	35	GD prevalence in women with OC
17	Morton et al ³⁶	2019	Australia	Retrospective audit study	ICD-10	193	GD prevalence in women with OC
18	Rimon et al ³⁷	2017	Israel	Cohort study	ICD-10	78	GD prevalence in women with OC
19	Puljic et al ³⁸ A	2015	United States	Retrospective cohort study	ICD-9	5545	GD prevalence in women with OC; risk of GD in women with OC compared with women without OC
20	Geenes et al ³⁹	2014	United Kingdom	Prospective cohort study	ICD-10	669	GD prevalence in women with OC; SB in women with OC with GD
21	Garcia-Flores et al ⁴⁰	2015	Spain	Prospective observational study	ICD-10	47	GD prevalence in women with OC; risk of GD in women with OC compared with women without OC

ACOG, American College of Obstetricians and Gynecologists; GD, gestational diabetes; ICD-10, International Classification of Diseases, Tenth Revision; OC, obstetrical cholestasis; P/GIP, Polish Society of Gynecologists and Obstetricians; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynecologists; SB, stillbirth.

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with low risk of bias (0.141; 95% CI, 0.102–0.192),^{23,26,27,30,33,24,38–40} and when removing studies without diagnostic criteria^{22–25} (marked as “not given”) (0.133; 95% CI, 0.091–0.192).

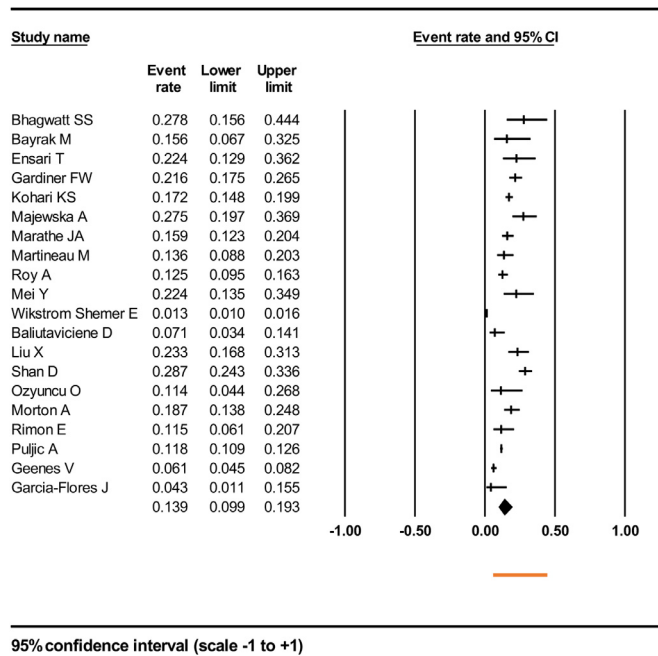
Overall, 10 studies^{16,17,23,25,26,32,33,34,38,40} with a control population were used in the analysis (Figure 3). Compared with women without OC, the mean odds of developing GD in women with OC are more than doubled (2.19; 95% CI, 1.67–2.67). With a mean odds ratio of 1.0, the null hypothesis test yielded a Z value of 6.539 with a corresponding P value of <.0001. We concluded that in women with OC, there is more likelihood of developing GD, confirming the initial hypothesis.

A total of 8 studies^{16,17,24,27,29,32,33,39} reporting SB (Figure 4) suggest that the overall risk of SB was 9 per 1000 deliveries. In 95% of the population, similar to those in the analysis, the true prevalence will fall somewhere in the range of 9 to 87 per 1000 deliveries (prediction interval).

There were data from 4 studies^{29,30,31,33}, that investigated the severity of OC (Figure 5). We compared the number of patients with mild OC (serum bile acids <40 μmol/L) and severe OC (serum bile acids >40 μmol/L) who developed GD. Compared with the mild OC group, the prevalence of GD in the severe OC group was 2.168 (95% CI, 1.429–3.289), refuting the null hypothesis that the prevalence was the same in either group.

Discussion

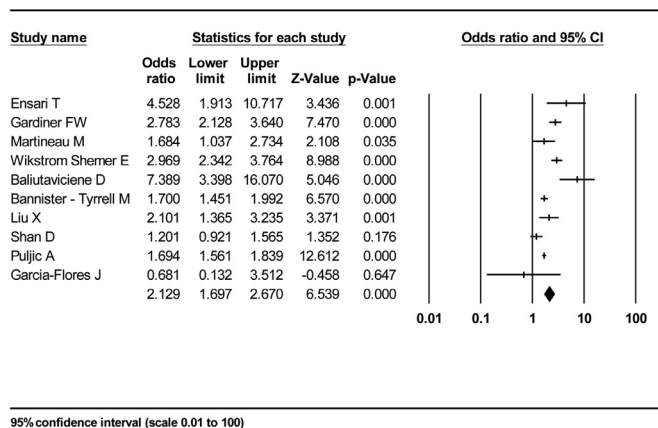
This meta-analysis of published literature showed that the overall prevalence of GD in the studied cohorts is 13.9%. A prediction interval ranging from 2.5% to 49.7% suggested that the risk of developing GD in women with OC is considerably higher and has regional variation. When OC cases were compared with a control population without OC, the odds of developing GD was >2. In addition, this analysis demonstrated a dynamic relationship between OC and GD as severe cases of OC have approximately double the prevalence of GD compared with mild cases of OC.

FIGURE 2
Forest plot

Forest plot of prevalence of gestational diabetes in patients with obstetrical cholestasis.

CI, confidence interval.

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FIGURE 3
Forest plot

Forest plot of the odds of GD between women with and without OC.

CI, confidence interval; GD, gestational diabetes; OC, obstetrical cholestasis.

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The relationship between SB and OC is related to the severity of OC, with severe cases demonstrating a high rate of SB.¹⁸ As the cause of SB associated with OC has not been defined, and as the cause of SB in pregnant patients

with GD has not been defined, it is tempting to think that there may be a similar pathology involved. The increased risk of SB in women with OC may be secondary to the development of GD. The increased vigilance for GD

development once OC has been diagnosed may potentially address the problem of SB in cases of severe OC.

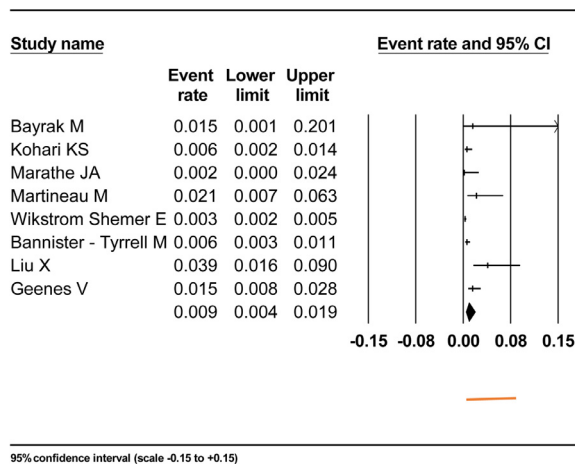
Because there are several cases of GD coexisting in women with OC, this may affect populations where universal screening of GD is not performed. In regions of universal screening, GD is usually diagnosed during pregnancy. However, if a patient is negative in the early screening for GD but develops OC, we recommend further monitoring these patients for GD.

The risk of SB is a known entity and more likely to occur in women with severe OC.^{19,39} This study has described that the prevalence of GD in women with severe OC is twice that of women with mild OC, which may correlate with the increased risk of SB.

Therefore, the potential clinical implication includes awareness that the coexistence of the 2 conditions (OC and GD) may be related to SBs, and clinicians need to be vigilant in screening patients for GD. Further work is required to study whether the risk of SB can be effectively addressed. Specifically, future studies need to describe the severity of GD when it is diagnosed in women with OC. GD is a condition with a wide range of severity, associated treatment modalities, and risk profile. GD may be managed with simple dietary modifications, be associated with minimal increased risk of SB, need to be treated with oral hypoglycemic agents or insulin, and be associated with substantially increased perinatal mortality even when managed in specialist centers. There is no data to describe the severity of GD occurring in women with OC. When the nature and severity of GD associated with OC is described, this understanding may inform clinical practice modifications to reduce the burden of SBs.

Strengths and limitations

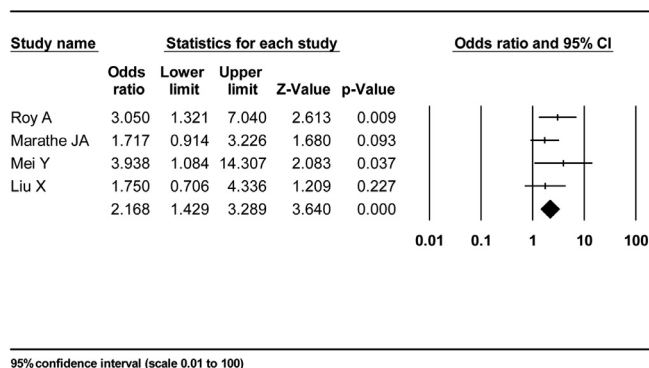
This meta-analysis and systemic review has 21 included studies, which is the largest number of included studies on this topic currently available. Furthermore, we had predefined criteria with all studies meeting the inclusion criteria. We have conducted a subjective risk

FIGURE 4
Forest plot

Forest plot of the risk of stillbirth in patients diagnosed with OC and GD.

CI, confidence interval; GD, gestational diabetes; OC, obstetrical cholestasis.

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FIGURE 5
Forest plot

Forest plot of the odds of GD between the mild OC group and severe OC groups.

CI, confidence interval; GD, gestational diabetes; OC, obstetrical cholestasis.

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assessment of the included studies and presented them in a table. We have included all the relevant meta-analysis for this prevalence study and presented the plots with all possible explanations. The limitations included that we only have data from observational studies. The study has clearly shown the variations across the studies, and we have investigated the heterogeneity and explained it as appropriate. We have provided the temporal relationship of SB with regard to the higher prevalence

of GD in women diagnosed with OC; however, we could not find any study that could explain the direct cause of SB related to OC and GD.

Finally, our study lacked evidence to describe the severity, treatment modalities, and prognosis of GD in women with OC.

Conclusion

This meta-analysis has provided insight into the need to explore the underlying causes of GD when a diagnosis of OC is

made. Moreover, the likelihood of women with OC developing GD is double the background rate and is higher in severe OC cases. This association may be a factor that increases the risk of SB.

Further studies relating to the topic should include GD as a variable to understanding the relationship and ensure that the associations obtained from this study hold true or valid and that interventions are assessed appropriately. ■

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.xagr.2021.100013](https://doi.org/10.1016/j.xagr.2021.100013).

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