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Stillbirth and associated perinatal outcomes in obstetric cholestasis: a systematic review and meta-analysis of observational studies

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ABSTRACT

Background: Obstetric cholestasis is a condition occurring in pregnancy with suspected adverse perinatal outcomes. Stillbirth is a significant adverse event associated with obstetric cholestasis and considered for intervention in pregnancy.
Objectives: There are multiple studies with epidemiological data with regards to the outcomes of obstetric cholestasis. Our hypothesis is to the test the association of stillbirth and related outcomes in obstetric cholestasis.
Search Strategy & Selection criteria: Two independent reviewers did independent searches and selection with a standardized design as outlined in the PRISMA statement.
Analysis: The retrieved relevant literature was subjected to a rigorous quality assessment and followed by standardized interpretable results.
Results: The pooled estimate in this study showed that there was no significant difference in the stillbirth rates in the obstetric (OC) population when compared to the non-obstetric cholestasis (reference) population. However, there was an increased risk of preterm birth in the OC population compared to the reference population; however, the cesarean section and induction of labor results were directly related.
Discussion: This study provides an epidemiological data related to the perinatal outcomes associated with obstetric cholestasis, specifically stillbirth. This result is likely to produce a benchmark for current evidence-based practice and to assist future research in understanding the implication of associated stillbirth risk and related outcomes with OC.

Contents

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Background

Obstetric cholestasis (OC), otherwise known as intrahepatic cholestasis of pregnancy is a condition specific to pregnancy The prevalence of OC is influenced by genetic and environmental factors and varies between 0.7 and 5% in different populations around the world [1]. Evidence also suggests a risk of recurrence of OC in up to two-third of subsequent pregnancies [2]. OC has been associated with an increased risk of perinatal morbidity and mortality [3–5], particularly with regards to stillbirths [6,7]. OC is commonly investigated as one potential cause in unexplained stillbirth [1].

Stillbirth is defined as 'a baby delivered at or after 24 + 0 weeks gestational age showing no signs of life, irrespective of when the death occurred' [8]. Stillbirth is common in pregnancy with about 1 in 200 babies born dead according to the Confidential Enquiry into Maternal and Child Health (CEMACH) report in 2009 [9] which is similar to the latest Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries in the UK (MBRRACE-UK) report of 4.16 stillbirths per 1000 total births in 2016 [8]. In a large prospective cohort study by United Kingdom Obstetric Surveillance System (UKOSS) looking at severe cases of OC, stillbirth rates in severe OC were reported to be increased (adjusted OR 2.58,95% CI 1.03–6.49) compared to controls [10]. A number of observational studies showing varied rates of stillbirth and associated perinatal outcomes with OC have been published. However, the available evidence has not been systematically reviewed and is widely debated.

The hypothesis is the question "Is OC associated with stillbirth" led to the aim of this study to provide an overview of stillbirth and other outcomes in OC to inform clinical and health policy decisions. The objective was to systematically review the available evidence as outlined in the PRISMA statement [11] and critically appraisal it to produce a summary outcome of results to give an insight into the epidemiological outcomes of OC available globally.

Methods

Protocol and registration

The study had a priori protocol designed and registered. (PROSPERO CRD42016052682).

Search strategy and selection criteria

The following electronic databases and registries were searched from inception up to 03 Nov 2018.

Databases (for published data): PubMed, Embase (OVID), CENTRAL (Cochrane central Register of Controlled Trials), Cumulative Index to Nursing and Allied Health (CINAHL) and Literatura Latino Americana em Ciências da Saúde (LILACS) and Cochrane Library's Database of Abstracts of Reviews of Effects (DARE).

Registries (for published and unpublished data): Clinicaltrials.gov, International Standard Randomized Controlled Trial Number registry and World Health Organization International Trials Registry Platform. (Appendix S1 in Supplementary material: Search sample for PubMed and Embase)

In addition to the above, grey literature was also searched for in Open Grey (www.opengrey.eu). Hand searches methodology was done where relevant literature was considered to be available for inclusion into the studies and when not possible to be obtained from the above defined search strategy. No language restriction was used and articles identified in Chinese were excluded as per eligibility criteria.

A search strategy was defined, agreed and independently carried by authors MM and AA. The searches were undertaken using index terms and key words relating to obstetric cholestasis (or) intrahepatic cholestasis of pregnancy, stillbirth (or) stillborn, neonatal (or) perinatal mortality (or) morbidity, premature (or) preterm birth, postpartum hemorrhage, meconium, cesarean section and induce (or) induced (or) induction of labo*.

Search results obtained was imported to Mendeley reference manager and duplicates were removed. Following this, authors MM and AA independently identified articles by screening titles. The authors then evaluated all full text abstracts of potentially relevant articles for their eligibility using criteria listed in Table 1. Any discrepancies in study selection were resolved through discussions at a consensus meeting. We had obtained all data electronically from databases and therefore no effort was made to contact authors of any included studies.

Data extraction and assessment of risk of bias

Details on study design, participants and clinical outcomes (stillbirths, cesarean section, induction of labor, preterm birth, meconium events, postpartum hemorrhage and admission to neonatal unit) were extracted.

Table 1
Study eligibility criteria.

A study was considered eligible if it:
- was a case-control or cohort study AND
- published either as an original full length article or letter in a peer reviewed journal AND
- included pregnant women with either singleton or multiple pregnancies with a diagnosis of OC (or) intrahepatic cholestasis of pregnancy (ICP) as per:
  - RCOG green top guidelines1 OR
  - WHO International classification of disease (ICD) codes AND
- reported stillbirth (as a primary outcomes) AND
- compared the outcomes in women diagnosed with OC or ICP with a control group (women without a diagnosed with OC or ICP).

The Newcastle - Ottawa Scale (NOS), a tool designed to assess the quality of non-randomized studies included in a systematic review and/or meta-analyses, was used to appraise studies [12]. The NOS star rating system was used to evaluate eight items grouped into three 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. As per the tool, a study could be given a maximum of one star for each numbered item within the selection and outcome categories and a maximum of two stars within the comparability category – Table 2. Studies with 0–3 stars (red color), 4–6 stars (yellow color) and 7–9 stars (green color) are classified as studies with high, moderate or low risk of bias respectively.

Data extraction and assessment of risk of bias was carried out by authors MM and AA independently. Any discrepancies in data extraction and risk assessment were resolved through discussions.

Data synthesis

Characteristics of included studies and the results of risk of bias assessment were tabulated. Where suitable data was available, meta-analyses of odds ratios (for binary outcomes) and were carried out in Review Manager 5.3 using a random effects model. In addition to the PRISMA-P checklist (Appendix S2 in Supplementary material), studies were cross checked using the meta-analysis of observational studies in epidemiology (MOOSE) (Appendix S3 in Supplementary material) approach to assess their suitability for meta-analysis. [12]

Statistical heterogeneity between studies was evaluated by visual inspection of forest plots and the I^2 statistic. A funnel plot was developed to undertake assessment of potential publication bias.

Subgroup analysis was performed for the stillbirth outcome and also for the secondary outcomes including cesarean section and induction of labor.

A subgroup analysis of cohort and case-control study was performed and results provided below.

Multiple sensitivity analysis on the primary outcome with expected heterogeneity of included observational studies and described below.

Ethics approval

This review did not require any ethics committee approval or informed patient consent as it entirely relies on published data.

Results

A total of 13 studies [13–25] met the inclusion criteria Fig. 1. A list of excluded studies [26–60] with reasons for exclusion can be found in supplementary file (Appendix S4 in Supplementary material).

Characteristics of included studies

Five case-control [13,14,18,19,25] and eight cohort studies [15–17,20–24]. The included studies were published between 1994 to 2016 and originated from different parts of the world including; Australia, China, Finland, India, Mexico, Saudi Arabia, Sweden, Switzerland, United Kingdom and The United States of America. Table3 shows the summary characteristics of the included studies.

Assessment of risk of bias

The risk of bias of studies as per the NOS tool assessment was considered to be low for 8 studies and moderate for 5 studies – Table 4. Publication bias was considered because of the stillbirth reporting variance in different countries across the world. However a funnel plot to assess of potential publication bias was symmetrical suggesting a possible absence of publication bias Fig. 2.

Outcomes

Outcomes from the observational studies were reported in different formats and were of various completeness. Narrative and tabulated summaries including diagnostic criteria of included studies are provided (Table 3 and supplementary file - Appendix S5 in Supplementary material). Meta-analyses were performed for four outcomes - stillbirth, cesarean section, induction of labor and preterm labor.

Table 2
Newcastle - Ottawa Scale categories and items.

Category	Items
Selection *Defined as a robust approach in selecting obstetric patients (max. 4 stars)*	1 Representativeness of the exposed cohort 2 Selection of the non-exposed cohort 3 Ascertainment of exposure 4 Demonstration that outcome of interest was not present at start of study
Comparability *Defined as a study design that utilized associate controls and/or additional controls to compare with the obstetric cholestasis cohort (max. 2 stars)*	1 Comparability of cohorts on the basis of the design or analysis controlled for confounders
Outcome *Defined as identification and quantification of data on stillbirth max. (3 stars)*	3 Assessment of outcome 4 Was follow-up long enough for outcomes to occur 5 Adequacy of follow-up of cohorts

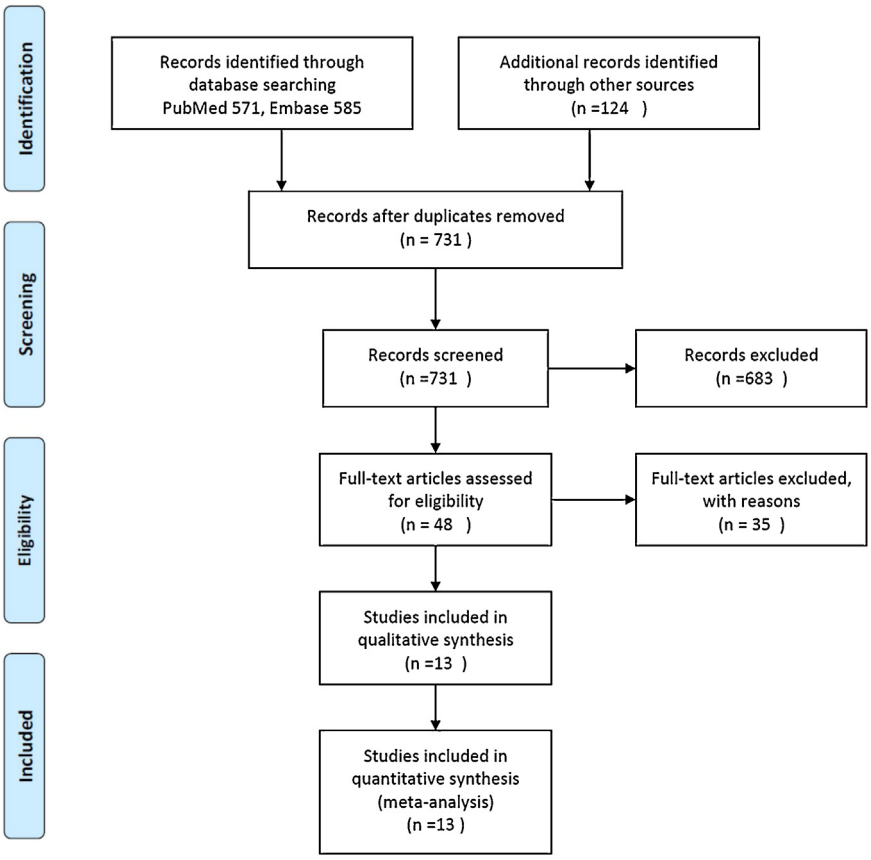

Fig. 1. PRISMA 2009 Flow Diagram.

Table 3
Summary characteristics of included studies.

Study author and year	Type of study	Enrolment period	Country of study	Women with OC	Women without OC	Reported outcomes: Primary	Reported outcome: Secondary
Rioseco 1994	Case-control	1988-1990	United States of America	320	320	Stillbirth	None
Heinonen 1999	Cohort	1990-1996	Finland	91	16818	Stillbirth	Preterm birth; Cesarean section; Meconium; Neonatal admission
Yoong 2008	Cohort	2002-2005	United Kingdom	144	144	Stillbirth	Cesarean section; Induction of labor; Meconium; Postpartum hemorrhage
Sosa 2009	Cohort	1999-2007	Mexico	50	51	Stillbirth	Meconium
Padmaja 2010	Case control	2003-2006	India	45	90	Stillbirth	Preterm birth; Cesarean section; Meconium; Postpartum haemorrhage; Neonatal admission
Turunen 2010	Cohort	1969-1988	Finland	687	1374	Stillbirth	Cesarean section; Induction of labor;
Al Shobaili 2010	Cohort	2008-2010	Saudi Arabia	76	200	Stillbirth	Preterm birth; Cesarean section; Meconium; Postpartum hemorrhage; Neonatal admission
Shemer 2013	Cohort	1997-2009	Sweden	5477	1208191	Stillbirth	Preterm birth; Cesarean section; Induction of labor;
Geenes 2014	Case control	2010-2011	United Kingdom	713	2205	Stillbirth	Preterm birth; Cesarean section; Neonatal admission
Martineau 2014	Case-Control	2005-2011	United States of America	143	57581	Stillbirth	Preterm birth; Cesarean section; Induction of labor;
Bannister-T 2014	Cohort	2001-2011	Australia	1868	972898	Stillbirth	Preterm birth; Cesarean section; Induction of labor; Postpartum hemorrhage
Liu 2016	Cohort	2006-2014	China	1319	92876	Stillbirth	Preterm birth; Meconium
Furrer 2016	Case control	2004-2014	Switzerland	345	1725	Stillbirth	Cesarean section; Induction of labor; Meconium; Neonatal admission

Primary outcome

Stillbirth

This outcome was reported in all 13 included studies. The included studies were of two designs i.e. case-control and cohort designs, we therefore subjected the meta-analysis as described below and presented in the

The pooled estimates for OC showed that the stillbirth rates did not have a significant difference in outcome compared to stillbirth rates when the population did not have obstetric cholestasis OR 1.22 (0.73–2.04), with a subgroup analysis of cohort study showed OR 0.91 (0.66–1.25) with an $I^2 = 7\%$. Therefore the cohort subgroup analysis showed that OC was associated with a stillbirth rate of 5.25 per 1000 births compared to the reference population without

Table 4
NOS SCORING.

Study author and year	NOS Selection	NOS Comparability	NOS Outcome	NOS Total score
Rioseco 1994	***	**	*	6
Heinonen 1999	***	**	***	8
Yoong 2008	**	**	**	6
Sosa 2009	**	*	**	5
Padmaja 2010	**	**	***	7
Turunen 2010	***	*	***	7
Al Shobaili 2010	***	**	***	8
Geenes 2014	***	*	***	7
Shemer 2013	***	**	***	8
Martineau 2014	****	**	**	8
Bannister-T 2014	***	**	*	6
Liu 2016	****	**	**	8
Furrer 2016	**	*	***	6

obstetric cholestasis (non-OC), with a stillbirth rate of 4.91 per 1000 births and this was not statistically significant.

A sensitivity analysis for stillbirth events was performed after the removal of the studies where there was no stillbirth [17,20,23] in either group (OR 1.13,0.65–1.95), alternatively studies with wider confidence intervals [14,17,20,22,23] were removed (OR1.45,0.82–2.55) and finally data from the studies published before year 2010 [13,17,20,23] were removed (OR 1.12,0.62–2.01). This suggests that as heterogeneity was assumed with the included observational studies, however, with various sensitivity analyses, the primary outcome showed similar results as described above and therefore the reliability of the primary outcome results is more robust. The Forest plot is provided in Fig. 3

Secondary outcomes

Cesarean section

This outcome was reported in 10 studies [14–19,22–25]. All of the 10 studies have presented the cesarean section as a similar outcome, with a variance in comparability of elective versus emergency cesarean section, however when both elective and emergency was combined together they were considered as a comparable group and therefore we analyzed as below.

The pooled estimates for cesarean section in the OC population when compared to the non-OC group showed an OR 1.28 (1.15–1.42). The subgroup analysis with cohort study showed a similar OR 1.34 (1.27–1.41). However the subgroup of case-control studies

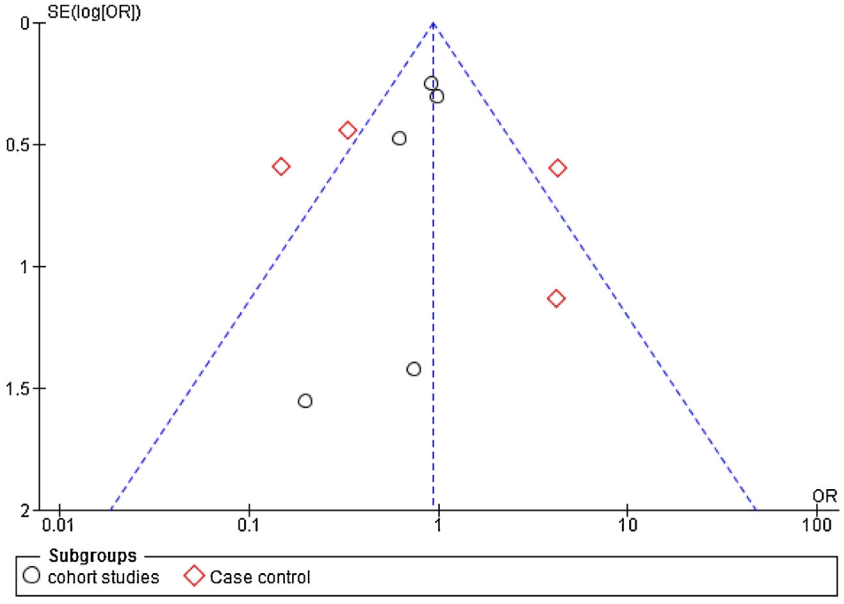

Fig. 2. Funnel plot of stillbirth in patients with OC compared with patients without OC.

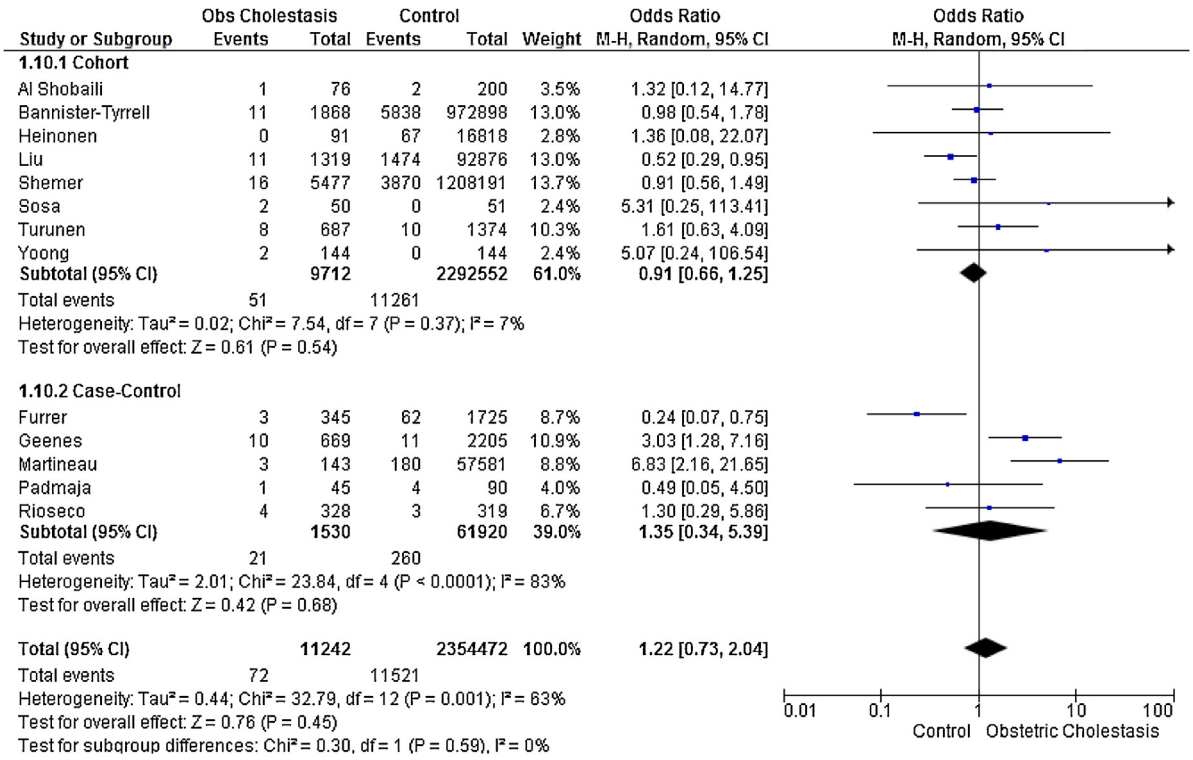

Fig. 3. Results of meta-analysis of stillbirth events in patients with OC compared with patients without OC.

showed a paradox of no difference in cesarean section with an OR 1.11(0.87–1.41). The Forest plot is provided in Fig. 4.

Induction of labor

Induction of labor was reported by 6 studies [15,16,18,23–25] and all studies that reported on induction of labor also reported cesarean section. Pooled estimates of induction of labor in women with OC compared to women without OC showed an OR of 3.03 (1.38–6.68) – Fig. 4. To understand the paradox of the cesarean section results, a subgroup analysis by study design were undertaken. The results showed cohort studies had an OR of 3.34 (1.38–8.07) while results for case-control studies showed an OR of 2.56 (0.41–15.87).

Induction of labor with obstetric cholestasis compared to the control had a pooled estimate of OR 3.03(1.38–6.68). All the studies reporting induction of labor had also reported cesarean section.

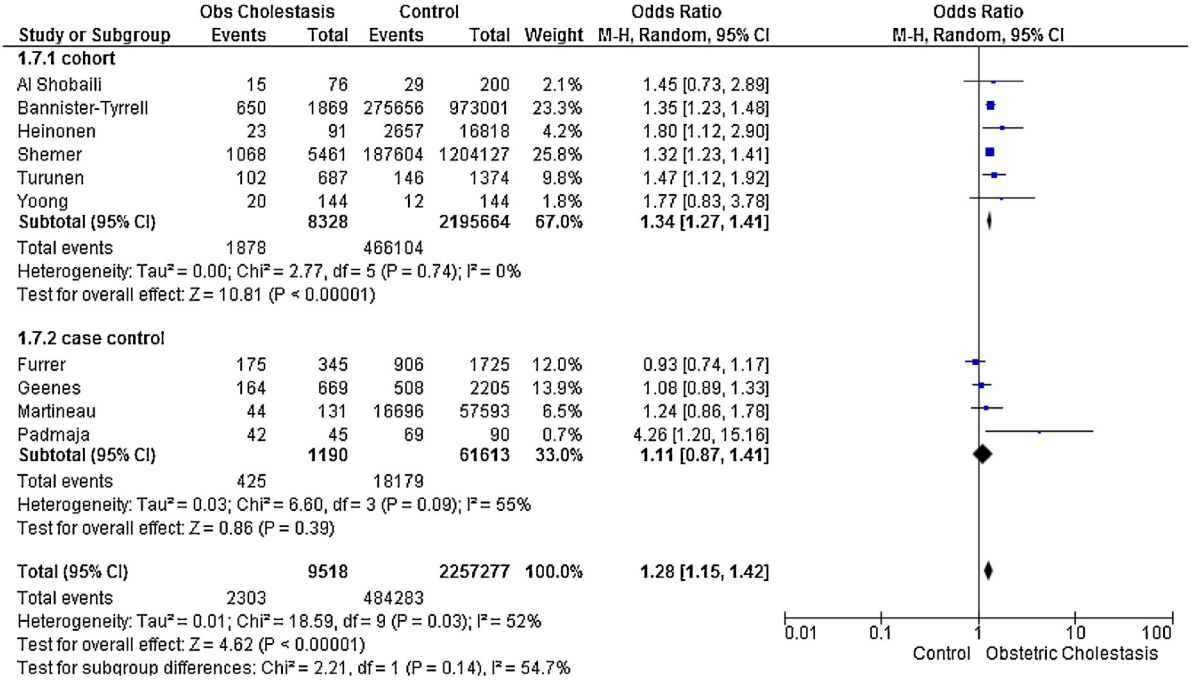

Fig. 4. Results of meta-analysis of Cesarean section in patients with OC compared with patients without OC.

When we split the cohort and case-control to understand the paradox of cesarean section this showed the cohort studies had an OR of 3.34 (1.38–8.07), while the case-control studies showed an OR of 2.56 (0.41–15.87). This might explain the cesarean paradox of no difference does exist even with the induction group. The Forest plot is provided in Fig. 5.

Preterm birth

This outcome was reported in 8 studies [14–19,21,22]. All of the 8 studies used a delivery gestational age below 37 weeks gestation and therefore it was considered to be a group useful for meta-analysis.

The pooled estimates for preterm birth rates in the OC population when compared to the regular (non-OC) group showed an OR 3.60 (2.61–4.96). The Forest plot is provided in Fig. 6.

Other outcomes

Meconium intrapartum events with obstetric cholestasis showed an OR 2.29 (1.35–3.88) when compared with the control (non-OC).

Postpartum hemorrhage in OC compared to the non-OC group showed an OR 2.33(0.75–7.16) and the need for neonatal admission in the OC compared to the regular population was OR1.74 (1.03–2.96).

Discussion

This is the first study that systematically reviews current evidence and undertakes a meta-analysis of outcomes associated OC. comprehensive literature search was performed, which identified 8 cohort and 5 case-control studies that met the inclusion criteria. Results suggest stillbirth rates in women with OC are not significantly different when compared to women without OC. However overall pooled estimates and a subgroup analysis of cohort studies showed as increase of cesarean section and induction of labour in women with OC compared with women without OC. However no significant difference was seen for the outcomes in case control studies. An increase in preterm births, meconium intrapartum events and need for neonatal admission in women with OC compared with women without OC was also noted but with no statistical difference in post-partum hemorrhage. The overall risk of bias in included studies was considered low to moderate according to the NOS scoring.

Comparison with previous studies

Incidence of stillbirth rates of approximately 2% were reported in women with OC [7,61]. In a previous study, a delayed diagnosis of OC has been associated with an increased risk of stillbirths [62] and early delivery to reduce the risk [62–64], However, findings from the meta-analysis suggest no increase in risk of stillbirths. Similar results of stillbirth are shown in the recent systematic review specifically looking at biomarkers used in OC [65]. However for symptomatic OC the treatments benefits exists without much of a difference in stillbirths [66] and perinatal outcomes unless they were classified as severe OC [67].

Previous studies have found an increased rate of cesarean section in women with OC of up to 36% [68], These results are in line with findings of this study. However, the assumed cesarean section rate showed a paradox of higher rates in the cohort studies and no difference in the case control studies. - This may be attributable due to multiple variables including, the increased preterm birth rates, possible higher intrapartum meconium events (approximately 3 fold) and also other variables not included in the study such as increased interventions including abnormal cardiotocographic / electronic fetal monitoring abnormalities.

Induction of labour in gestational weeks 37–39 is commonly performed with the perspective to avoid the complication of stillbirth [68]. Therefore, the paradox of cesarean section may be a represented with the induction of labor outcome as it also showed the same paradox as the cesarean section. Therefore it appears the paradox may be true. As matter of fact, it may be the case that there is no significant difference in stillbirth rates. Therefore, it is likely the cesarean section and induction rates are possible non-significant or may represent the reason for keeping the stillbirth rates non-significant.

Preterm births in previous studies have shown to occur in 44% of women with OC [7,61]. The findings of the meta-analysis showed as increased preterm birth rate. These results are a direct representation of the comparison groups showing an increased rate with the OC population; this included both spontaneous preterm birth and iatrogenic preterm birth. The difference between the spontaneous and iatrogenic preterm birth were not studied, however, some of the included studies [16,19,21] showed significant rates of iatrogenic preterm birth as a likely contributor. This could possibly be due to the intervention associated with OC.

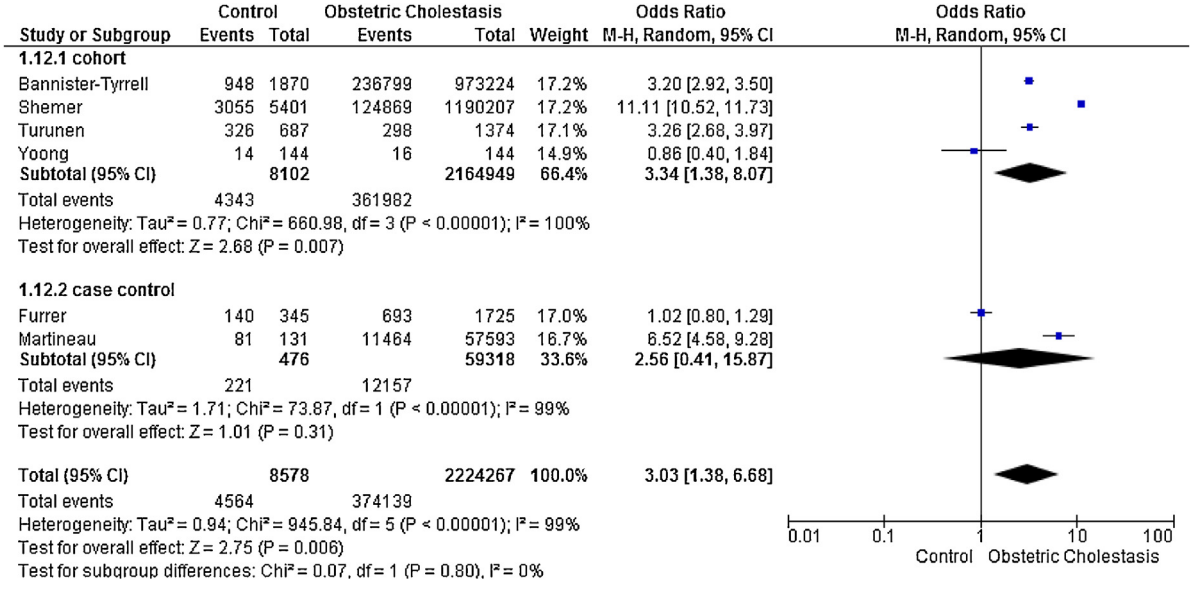

Fig. 5. Results of meta-analysis of induction of labor in patients with OC compared with patients without OC.

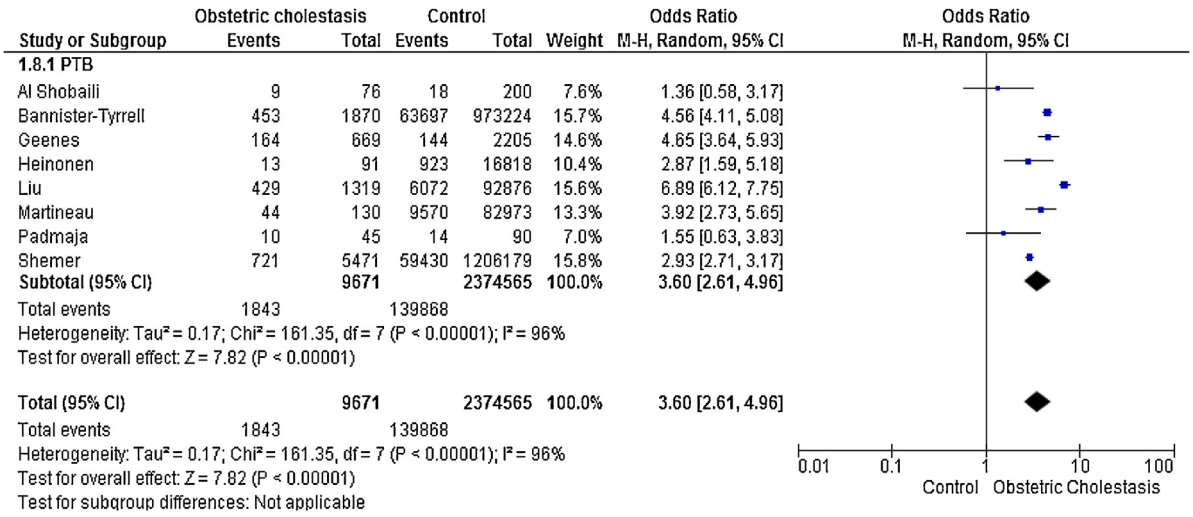

Fig. 6. Results of meta-analysis of preterm birth in patients with OC compared with patients without OC.

Differences in post-partum hemorrhage rates were not statistically significant; but the neonatal admission rates were 74% higher in the OC compared to the reference population. Possibly this was secondary to the larger prevalence of preterm birth however, if this was directly as a representation of the preterm group, was not possible to assess this outcome from our study design.

Strengths and limitations

This study has some limitations. Firstly, while a comprehensive search was undertaken to retrieve unpublished data, none was identifies and therefore the review findings are based upon published data only. Secondly, the findings of this study are based on observational studies, most of which had small sample sizes. Thirdly, the findings may have been influenced due to the different ways in which outcomes were selected and reported in individual studies.

Implications for clinical practice and policy

The study was not able to demonstrate that the actual stillbirth rates are reduced secondary to current practice as advised by international bodies such as the RCOG [1]. These guidelines may lead to intervention in pregnancies affected with OC such that the stillbirth rate is reduced. However, it may be that clinicians are intervening the obstetric population when there is not much evidence to show reduction in stillbirth rates as previously presumed, but instead contributing to an increase in relevant obstetric outcomes such as iatrogenic preterm births which are all likely due to increased intervention without statistically significant added benefits.

However as some of the included studies suggest a significant increased rates of stillbirth with the specific group of severe obstetric cholestasis [19,67], we recommend a definite need for intervention in this specific group as per the RCOG recommendation [1] "women should be informed that the case for intervention (after 37 weeks of gestation) maybe stronger in those with more severe biochemical abnormality (transaminase and bile acids)". However we still lack the evidence when there is no severe obstetric cholestasis diagnosed and possibly associated with unwanted increased risks.

We should therefore include these findings when we proceed for early intervention as we currently lack evidence for supporting our intervention for early delivery when there is no diagnosis of severe obstetric cholestasis.

Even though the paradox of cesarean section and induction of labor may suggest that we need a much more robust testing before we conclude that either of the outcomes is different in the OC population and we may not be able to include these information's when we use for patient counselling until higher evidence arises.

To avoid these stillbirths, there has been international acceptance of active management of OC-affected pregnancies with the goal of delivering the infant at <39 weeks. The general agreement suggests that delivery should not be delayed after 37–38 wks of gestation in patients with OC but not all obstetric professionals accept the association between OC and stillbirth or agree with the concept of active management in OC. Although American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine endorsed active management of OC-affected pregnancies, RCOG reported that active management of OC should be replaced by individual management decisions according to the evidence concerning the known perinatal risk of early term birth vs the small but unknown risk of OC-associated term still birth

Conclusions

This study provides an overview of risks associated with obstetric cholestasis based on currently available literature for the management of OC in pregnancy. The currently available evidence on risk factors of OC is still limited in quantity and remains inconclusive given the lack of robustly conducted studies. In light of this, there is a need for large prospective studies to determine the impact of OC on perinatal outcomes which are appropriately selected

Systematic review registration

PROSPERO CRD42016052682

Funding

No funding obtained for this study

Conflict of interest

The authors have no conflicts of interest to declare.

Ethics approval

No ethical consideration as published data used for the systematic review.

Disclosure

All authors disclose with no financial, personal, political, intellectual or religious interest in development of this systematic review.

Contribution to authorship

All authors contributed significantly to be included as authors of the study.

MM conceptualized the idea to perform the study and designed the initial protocol and registration process. MM along with AA participated as the two independent reviewers for searches, identifying study subjects and collecting data independently, when discrepancies arouse SL contributed with finalizing the included studies. MM did the statistical analysis with support from MA and AAk. JK contributed in overall assessment and revision at each stage of the study.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eurox.2019.100026.

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