BMJ Open Diabetes Research & Care

Major malformations risk following early pregnancy exposure to metformin: a systematic review and meta-analysis

Nazanin Abolhassani ,[1,2] Ursula Winterfeld,[3] Yusuf C Kaplan,[4] Cécile Jaques,[5] Beatrice Minder Wyssmann ,[6] Cinzia Del Giovane,[7] Alice Panchaud[8,9]

To cite: Abolhassani N, Winterfeld U, Kaplan YC, *et al*. Major malformations risk following early pregnancy exposure to metformin: a systematic review and meta-analysis. *BMJ Open Diab Res Care* 2023;**11**:e002919. doi:10.1136/bmjdrc-2022-002919

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2022-002919).

Received 21 April 2022
Accepted 20 January 2023

For numbered affiliations see end of article.

Correspondence to
Dr Nazanin Abolhassani; nazanin.abolhassani@biham.unibe.ch

ABSTRACT

Metformin is considered as first-line treatment for type 2 diabetes and an effective treatment for polycystic ovary syndrome (PCOS). However, evidence regarding its safety in pregnancy is limited. We conducted a systematic review and meta-analysis of major congenital malformations (MCMs) risk after first-trimester exposure to metformin in women with PCOS and pregestational diabetes mellitus (PGDM). Randomized controlled trials (RCTs) and observational cohort studies with a control group investigating risk of MCM after first-trimester pregnancy exposure to metformin were searched until December 2021. ORs and 95% CIs were calculated separately according to indications and study type using Mantel-Haenszel method; outcome data were combined using random-effects model. Eleven studies (two RCTs; nine observational cohorts) met the inclusion criteria: four included pregnant women with PCOS, four included those with PGDM and three evaluated both indications separately and were considered in both indication groups. In PCOS group, there were two RCTs (57 exposed, 52 control infants) and five observational studies (472 exposed, 1892 control infants); point estimates for MCM rates in RCTs and observational studies were OR 0.93 (95% CI 0.09 to 9.21) (I^2=0%; Q test=0.31; p value=0.58) and OR 1.35 (95% CI 0.37 to 4.90) (I^2=65%; Q test=9.43; p value=0.05), respectively. In PGDM group, all seven studies were observational (1122 exposed, 1851 control infants); the point estimate for MCM rates was OR 1.05 (95% CI 0.50 to 2.18) (I^2=59%; Q test=16.34; p value=0.01). Metformin use in first-trimester pregnancy in women with PCOS or PGDM do not meaningfully increase the MCM risk overall. However, further studies are needed to characterize residual safety concerns.

INTRODUCTION

Metformin belongs to the biguanide class of glucose-lowering medications, and the mechanism of its antihyperglycemic effect is mainly by suppressing hepatic glucose production[1–4]; it is generally weight neutral with chronic use and does not increase the hypoglycemia risk.[5] Metformin features as the most widely used and current first-line pharmacological treatment for type 2 diabetes mellitus (T2DM) in the general population worldwide.[3 6] Furthermore, metformin is considered as an alternative to insulin therapy for gestational diabetes mellitus (GDM).[7–11] It is increasingly being used in the GDM indication as it has been shown to be a safe and effective alternative to insulin with respect to pregnancy outcomes[12 13]; it controls glycemia and prevents adverse maternal and neonatal outcomes associated with hyperglycemia; and notably, insulin resistance can be dealt more effectively with metformin.[10 14–16] Metformin is also commonly used for polycystic ovary syndrome (PCOS) associated infertility, a condition affecting 4%–20% of women of reproductive age worldwide.[17] However, evidence on safety and effectiveness to achieve glycemic targets in the treatment of pregestational diabetes mellitus (PGDM) in early pregnancy is still limited.[18 19]

Metformin freely crosses the placental barrier[12 20]; this has caused concerns regarding metformin exposure during the first trimester of pregnancy and its effect on embryological and fetal development.[12 21] There is no signal of any major teratogenic effect of metformin neither in animal studies[22 23] nor in few available studies in humans[24–26] as available data show no association with congenital malformations after exposure in the first trimester.[27 28] A meta-analysis performed in 2014 did not detect an increase in risk of major malformations after metformin use in pregnant women with PCOS.[25] The authors also aimed to analyze the risk of major congenital malformations (MCMs) after maternal metformin intake for T2DM; however, due to the insufficient number of studies, it was not feasible. Of interest, several studies investigating the pregnancy outcomes after metformin use during early pregnancy were published after this meta-analysis, which may allow for a meta-analytic synthesis.[29–35]

To better characterize the safety of metformin after its use in the first trimester of pregnancy, this study aims to systematically

assess whether first-trimester exposure to metformin is associated with an increased risk of MCM using a meta-analytic approach.

METHODS

Search strategy

Searches were conducted by two qualified librarians (CJ and BMW) from the Universities of Lausanne and Bern and the study authors in Medline (Ovid), Embase.com, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, WHO ICTRP, Web of Science Core Collection and Google Scholar from inception to 10 December 2021. The full search strategies for all databases are available in online supplemental table 1. A manual search including backward and forward citation tracking was held through the reference list of the included studies to identify other potentially eligible studies. The reporting of this systematic review was prepared in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[36] Findings were reported in adherence with the Meta-Analysis of Observational Studies in Epidemiology guidelines.[37] There were no date limitations.

Eligibility criteria

Studies were selected when they met the following criteria: randomized controlled studies (RCTs) and observational cohort studies with a control group (no teratogenic treatment or no treatment or insulin) investigating MCM after maternal use of metformin in early pregnancy (ie, from 2 to 10 weeks after the last menstrual period). Only studies with first trimester exposure were considered. Case–control studies, case reports and series, animal studies, editorials and reviews were excluded. Only published studies in English were included.

Outcome measures

The main outcome of interest for this meta-analysis were MCM overall. If the malformations reported by the studies were not classified, study authors classified them using the Malformation Coding Guides of European Surveillance of Congenital Anomalies (EUROCAT)[38 39] as major and minor for exclusion. JRC-EUROCAT Central Registry was consulted in cases of any disagreement among the authors regarding the classification. The secondary outcome of interest was the subgroup of cardiovascular malformations (eg, transposition of the great arteries and truncus arteriosus).

Study selection, data extraction and assessment of the risk of bias

Two reviewers (NA and UW) independently reviewed the studies using the Rayyan software (https://www.rayyan.ai) in a two-step process. First, the extracted articles were reviewed and selected by title and abstract. The first step selected papers were reviewed and selected by full paper read. We extracted the data using a standardized data extraction form in Excel as follows: main study author(s) and publication year, country, period and design of study, patients, metformin exposure and control group, number and demographics of participants (age and body mass index), total number of live births and MCM in metformin-exposed and control group. Any disagreement was discussed and resolved by consultation with another author (AP and YCK). For observational studies, we aimed to extract adjusted ORs; however, an adjusted result was reported for one study only.

For randomized studies, the risk of bias of each included study was assessed using the criteria of the Cochrane Collaboration.[40] These include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting. The risk of bias was judged on each criterion as 'low', 'high' or 'unclear'. Incomplete outcome data were judged as having low risk of bias when numbers and reasons of dropouts were balanced (ie, in the absence of a significant difference) between arms. Two reviewers assessed the risk of bias of each study independently and resolved disagreements by discussion to reach consensus. For prospective observational studies, the Newcastle-Ottawa scale for quality assessment of the study methodologies was used.[41] The reviewers were not blinded to the author names, institutions, results or journals of the publications.

Statistical analysis

The included studies were analyzed separately based on the indications, that is, PCOS and PGDM; in addition, within the PCOS indication group, the analysis were done separately per design of studies (RCTs and observational studies). ORs and 95% CIs were calculated using Mantel-Haenszel method, and outcome data were combined using a random-effects model. For observational studies, we aimed to combine adjusted ORs. However, we found only one study that reported the adjusted OR, and this was similar to the no-adjusted one. All the other studies reported the absolute number of participants with the event in each group. Therefore, we decided to combine the latter data. Heterogeneity was assessed using the Q and I^2 statistic and by visual inspection of the forest plots. An I^2 value between 25% and 50% was considered as low heterogeneity, between 50% and 75% moderate and >75% high heterogeneity.[42] Statistical analyses were conducted in STATA (StataCorp). The confidence of evidence generated by studies was assessed via the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (www.gradeworkinggroup.org). For PCOS we assessed GRADE in only RCTs.

Consent and ethics committee

Consent and ethics committee approval was not needed since this study is a systematic review and meta-analysis of the available data.

RESULTS

The selection process of studies fulfilling the inclusion criteria for the meta-analysis is shown in online

supplemental figure 1. Out of 3783 records initially identified by database and trial register searching, a total of 11 studies were eventually included in the review and meta-analysis: two RCTs[43 44] and nine observational studies.[29 31 35 45–50] The details of included studies and characteristics of the studies participants are presented in tables 1 and 2. Quality assessments of the included studies conducted separately based on the study design are presented in online supplemental figure 2 and table 2. Observational studies obtained a quality score from 5 to 8 out of 9, and the overall risk of bias of the included RCTs was low. Out of the 11 included studies, four included only pregnant women with PCOS, four others only pregnant women with PGDM and three evaluated both indications separately, and we used these three studies in both indication groups accordingly. Regarding the certainty of evidence, the results of GRADE assessment, done separately per studies on PCOS and PGDM indications, showed overall low and very low certainty, respectively (online supplemental table 3). Due to the low number of reported malformations, the analysis of the secondary outcome of interest (ie, subgroups of cardiovascular malformations) was not feasible. Also, as the number of included studies was less than 10 in each set of analysis, we could not use funnel plot to assess publication bias and small study effect.[51]

Studies on pregnant women with PCOS

Meta-analysis of overall MCM rates in metformin-exposed women with PCOS is presented in figure 1. Out of the seven studies with PCOS indication, there were two RCTs (with a total of 57 exposed and 52 control infants) and five observational studies (with a total of 472 exposed and 1892 control infants). The point estimate for the rates of MCM in RCTs and observational studies were OR 0.93 (95% CI 0.09 to 9.21) with I^2 of 0% (Q test=0.31; p value=0.58) and OR 1.35 (95% CI 0.37 to 4.90), with I^2 of 65% (Q test=9.43; p value=0.05), respectively.

Studies on pregnant women with PGDM

Meta-analysis of overall MCM rates in metformin-exposed women with PGDM is presented in figure 2. Seven observational studies with a total of 1122 exposed and 1851 control infants were pooled. The point estimate for the rates of MCM was OR 1.05 (95% CI 0.50 to 2.18) with I^2 of 59% (Q test=16.34; p value=0.01).

DISCUSSION

Based on the 11 included studies, metformin use during first trimester of pregnancy for PCOS and PGDM does not seem to significantly increase the risk of MCM. However, currently, more specific safety concerns including limited increased risks of specific congenital malformations such as cardiovascular birth defects cannot be ruled out because of a lack of data.

A previous systematic review and meta-analysis of nine controlled studies on women with PCOS showed that the rate of major birth defects in the metformin exposed group was not statistically increased compared with the disease-matched control group. This study involved 351 pregnancies in women exposed to metformin in utero and 178 pregnancies in women not exposed to metformin in utero and the OR of major birth defects was 0.86 (95% CI 0.18 to 4.08).[25] Due to small total sample size, this study failed to perform a meta-analysis on few studies reporting information on birth defect rate in PGDM women exposed to metformin during the first trimester of pregnancy. Another systematic review and meta-analysis of eight studies observed similar results with respect to major malformations. The OR for major malformations (including all studies with disease-matched controls) was 0.50 (95% CI 0.15 to 1.60).[24] This study also separated the analysis based on the PCOS and PGDM indications and reported the OR for PCOS as 0.33 (95% CI 0.07 to 1.56) and for PGDM as 0.85 (95% CI 0.14 to 5.11).

There is a paucity of information on metformin exposure in early pregnancy and the risk of MCM in the literature. Regarding the design of studies, the relevant information are mainly provided by observational studies as pregnant women have been historically excluded from RCTs.[52] For PGDM, there is limited number of studies as women are usually switched to insulin as a first choice treatment as soon as pregnancy is diagnosed because insulin does not cross the placenta.[53] For PCOS, metformin is likely to be discontinued as soon as a diagnosis of pregnancy is confirmed,[54] which is often done very early on in patients with this condition, and associated to a limited exposure to metformin in the first trimester, and thus patients with PCOS are most often not eligible for safety studies. This may explain the wide CI of OR for RCTs in our study, which is due to the very small number of events per arm over a small number of total sample size (ranging from 10 to 28 participants per arm). In addition, the studies on PCOS mainly focus on the ovulation and pregnancy rate and do not offer follow-up information until birth, which makes them ineligible to assess outcomes such as the risk of malformation. Thus, further larger studies are needed to address the safety of metformin first trimester exposure in pregnancy on longer term pregnancy outcomes such as MCM.

Poorly controlled pregestational diabetes is associated to an increased risk of major malformation ranging from 5% to 10% in live births (ie, baseline risk being 2%–4%).[55] The control of PGDM, in itself, is of paramount importance as proper metabolic control maintained throughout the first trimester of pregnancy can significantly reduce the malformation risk.[55 56] Such association makes it difficult to disentangle the effect of the underlying disease from the effect of metformin on any observed increased risk in most of the available safety studies without information on the level of control of the disease. This confounding by the underlying diabetes was illustrated in a previous observational study in which, after stratification, the risk of major malformation was 10% in PGDM pregnancies with at least one severity criterion for diabetes (ie, presence of any abnormal glucose

Table 1 Characteristics of included studies

Author (year)	Country	Period of study	Study design	Patients	Metformin exposure (n=sample size)	Control (n=sample size)	Total number of LB in metformin-exposed group[1]; MCM	Total number of LB in control group[2]; MCM
Coetzee and Jackson (1984)[45]	South Africa	Not reported (duration: 5.5 years)	Retrospective	Pregnant women with established non-insulin-dependent diabetes	In the beginning, 1.5–3 g/day; later 1750–2550 mg/day during first trimester (n=20)	No treatment in first trimester (n=89)	20; 0	89; 5
Hellmuth *et al* (1994)[46]	Denmark	1966–1991	Retrospective	Pregnant women with T2DM	250–2000 mg/day at the time of conception and during first 8 weeks of pregnancy (n=7, out of them two continued metformin until delivery and five were changed to insulin)	Treated with sulphonylurea during the first trimester (one continued until delivery, 2 changed to metformin until delivery, 15 changed to insulin) (n=18)	7; 0	16; 0
Jakubowicz *et al* (2002)[47]	Venezuela	1996–2000	Retrospective	Non-diabetic pregnant women with PCOS	1000–2000 mg/day throughout pregnancy (n=65)	No treatment at the time of conception or during pregnancy (n=31)	61; 0	18; 0
Palomba *et al* (2005)[43]	Italy	2003 (6 months)	RCT	Non-obese primary infertile anovulatory women with PCOS	850 mg twice daily until confirmation of pregnancy (n=31)	Placebo (n=16)	28; 0	10; 0
Moll *et al* (2006)[44]	The Netherlands	2001–2004	RCT	Women with PCOS	Metformin 500–2000 mg/day until confirmation of pregnancy (n=111)	Clomifene citrate plus placebo (n=114)	29; 1 (atresia)	42; 1 (anencephaly)
Hameed *et al* (2011)[48]	Egypt	2008–2010	Observational	Infertile women with PCOS	Patients conceived while taking metformin (1000–2500 mg/day) with/without other ovulation inducing agents and continued metformin during pregnancy (n=31)	Patients who conceived without metformin and did not take it during pregnancy (n=26)	30; 0	19; 1 (atrial septal defect (A.SD))
Diav-Citrin *et al* (2018)[31]	Israel	2000–2013	Prospective observational cohort study	Pregnant women with PCOS or PGDM	Median daily dose: 1700 mg, at least in the first trimester of pregnancy, (21/170 (12.4%) continued throughout gestation; for PGDM or PCOS (n=170) (51 PCOS+119 PGDM)	Pregnant women with pregestational diabetes treated with insulin (n=93); non-teratogenic exposure (n=519)	135; 6 PCOS 45; 3 PGDM 90; 3	599; 14 519; 11 80; 3

Continued

Table 1 Continued

Author (year)	Country	Period of study	Study design	Patients	Metformin exposure (n=sample size)	Control (n=sample size)	Total number of LB in metformin-exposed group[1]; MCM	Total number of LB in control group[2]; MCM
Panchaud *et al* (2018)[35]	Multicenter (Europe)	1993–2015	Prospective observational cohort study	Pregnant women with a PGDM and other (obesity, ovary stimulation, insulin resistance, glucose intolerance, hyperglycemia)	Pregnant women on metformin during the first trimester of pregnancy for different indications relative to a matched unexposed reference group (n=458; of that 219 indication PGEM and 173 PCOS)	Randomly selected pregnant women who did not use metformin, insulin or other hypoglycemic agent at any time during pregnancy (n=479)	392; 20	431; 9
							PCOS	
							173; 3	431; 9
							PGDM	
							219; 17	431; 9
Scherneck *et al* (2018)[29]	Germany	2004–2014	Prospective observational cohort study	Pregnant patients affected by PCOS, T2DM and/or insulin resistance	Patients with metformin exposure (median dosage: 1500 mg/day (IQR 1000–2000)) at least between gestational week 2+0 to 12+6 days after first day of last menstrual period (n=336) (225 first, 71 first and second and 40 all three trimesters) (69 T2DM and 163 PCOS)	Matched controls were randomly selected from all eligible pregnant women (n=1011)	232; 11	913; 38
							PCOS	
							163; 8	913; 38
							PGDM	
							69; 3	913; 38
Kelty *et al* (2020)[49]	Australia	2003–2012	Retrospective cohort study	Pregnant women with gestational or T2DM)	Women treated with metformin (four 0.5 g tablets, two 1.0 g tablets or two 0.85 g tablets, daily) during pregnancy (n=108)	Women who were dispensed gliclazide during pregnancy (n=108)	108; 6	108; 8
Lin *et al* (2020)[50]	Taiwan	2003–2014	Retrospective cohort study	Women with pre-existing T2DM and singleton pregnancies	Metformin before and during pregnancy (n=626)	Insulin and no oral antidiabetic drugs before and during pregnancy (n=222)	2.72 stillbirth incidence; 609 live births; 33	3.60 stillbirth incidence; 214 live births; 21

1 and 2: these numbers were used for the meta-analysis.
LB, live births; MCM, major congenital malformations; PCOS, polycystic ovary syndrome; PGDM, pregestational diabetes mellitus; RCT, randomized controlled trials; T2DM, type 2 diabetes mellitus.

Table 2 Characteristics of the studies participants

Baseline characteristics of participants	Sample size		Age mean±SD (year)		BMI mean±SD	
	Metformin	Control	Metformin	Control	Metformin	Control
Coetzee and Jackson[45]	20	89	–	–	–	–
Hellmuth *et al*[46]	7	18	–	–	–	–
Jakubowicz *et al*[47]	65	31	29.5±3.7	30.0±3.2	27.1±1.7	26.9±0.4
Palomba *et al*[43]	31	16	26.4±2.9	25.9±2.7	27.0±2.9	26.7±2.8
Moll *et al*[44]	111	114	27.9±3.7	28.4±4.7	28.5±7.1	27.8±6.7
Hameed *et al*[48]	31	26	30.2±3.87	28.1±4.35	29.22±2.31	28.35±1.97
Panchaud *et al*[35]	392	431	35 (31–39)*	35 (31–38)	BMI† ≤30: 126 (28%) BMI >30: 106 (23%)	BMI† ≤30: 152 (32%) BMI >30: 17 (4%)
Diav-Citrin *et al*[31]	170‡	623‡	PGDM: 36.4±5.4	32.0±5.2	PGDM§: 31 (27-35)	23 (21–29)§
			PCOS: 30.9±4.9	31.0±4.8	PCOS§: 29 (24-37)	23 (21–29)§
Scherneck *et al*[29]	336¶	1011¶	23 (21–29)§	32 (28–35)§	29.4 (23.3–35.5)§	29.2 (23.8–35.4)§
Kelty *et al*[49]	108**	108**				
Lin *et al*[50] ††	626	222	33.51±4.31	34.48±4.02		

*The mean of age (IQR) is for all metformin group including all indication (n=458).
†Number (percentage) is for all metformin group including all indication (n=458). 49% and 65% missing in metformin and control group, respectively.
‡For treatment group 119 PGDM and 51 PCOS. Control groups: 93 for PGDM; 530 for PCOS.
§Median (IQR).
¶All indication (PGDM and PCOS and other).
**Number of babies.
††Live birth: 609 and 214 in metformin and control group, respectively.
BMI, body mass index; PCOS, polycystic ovary syndrome; PGDM, pregestational diabetes mellitus.

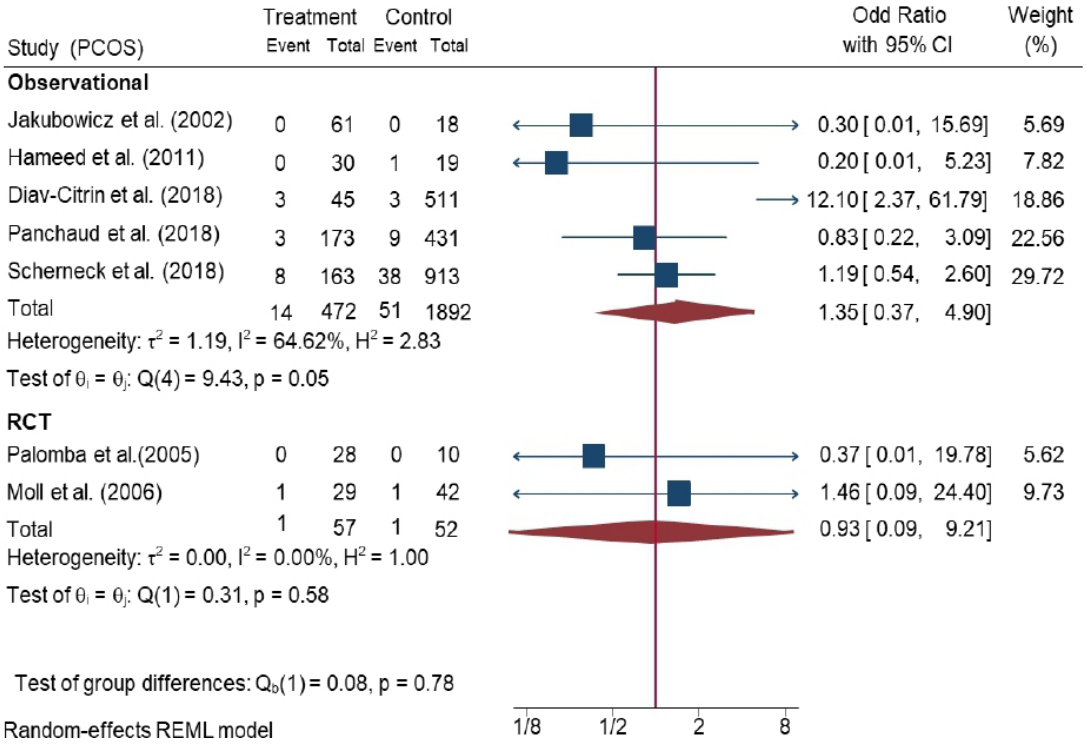

Figure 1 Meta-analysis of overall major congenital malformation (MCM) rates in metformin-exposed women with polycystic ovary syndrome (PCOS).

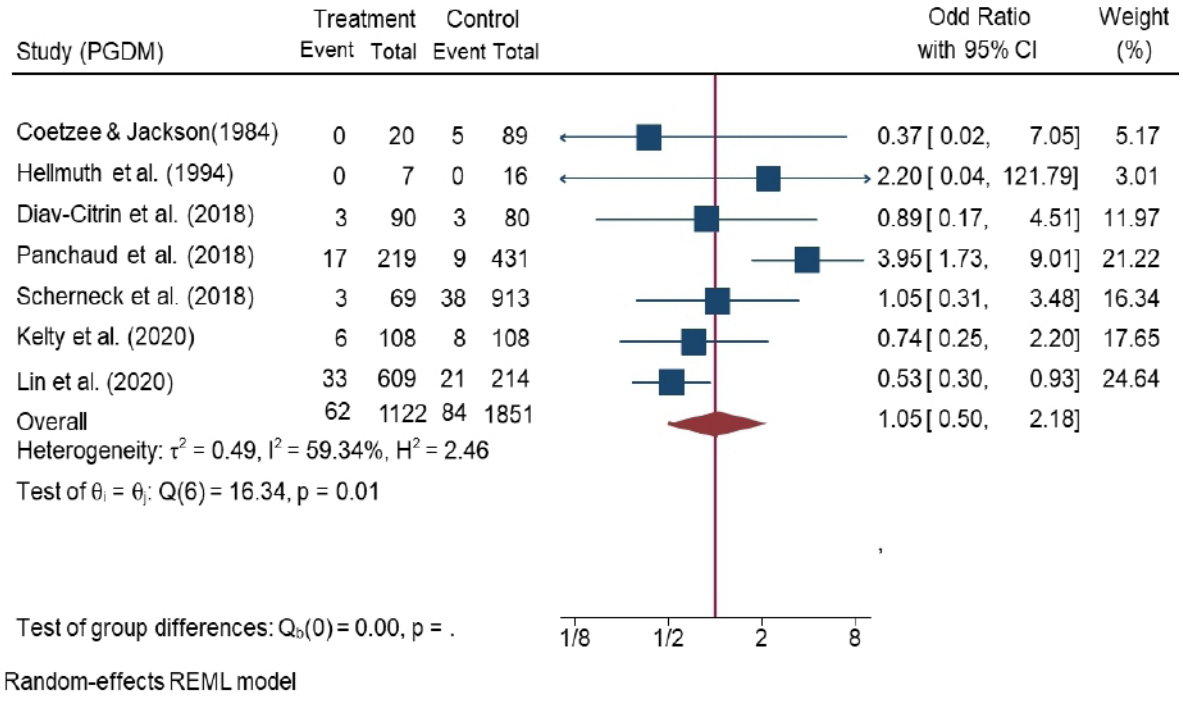

Figure 2 Meta-analysis of overall major congenital malformation (MCM) rates in metformin-exposed women with pregestational diabetes mellitus (PGDM).

test or concomitant use of other oral diabetic drugs or insulin), whereas it was similar in the reference group of patients not exposed to metformin (2.1%) and in those exposed to metformin for indications other than PGDM (1.7%).[35]

STRENGTHS AND LIMITATIONS

We adopted a rigorous search strategy, and this meta-analysis is the most comprehensive and updated quantitative synthesis of the safety of metformin in terms of MCM after early pregnancy exposure. Since previous most recent meta-analysis, five additional studies were extracted and included for current meta-analysis.[29 31 35 49 50] Out of these five studies, three had data on both PCOS and PGDM indications.[29 31 35] Furthermore, we provided results of the quality assessments of the included studies separately based on the study design as well as the confidence of evidence generated by RCTs using the GRADE approach, which was not the case in the previous studies. Nonetheless, this meta-analysis is limited by the quality and quantity of included studies coupled with the small sample size and number of events. In addition, due to indication bias, safety assessment of metformin in PCOS and PGDM is complex as the disease itself is associated with an increased congenital malformation risk that makes it difficult to disentangle the effect of the drug from the effect of the disease.[57–59]

In conclusion, evidence from this meta-analysis suggests that the use of metformin in first trimester of pregnancy in women with PCOS or PGDM do not meaningfully increase the risk of congenital malformations overall. However, further larger studies are needed to characterize more specifically residual safety concerns after metformin exposure in the first trimester.

Author affiliations
[1]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland
[2]Department of Epidemiology and Health Systems, Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Vaud, Switzerland
[3]Service de Pharmacologie Clinique, Centre Hospitalier Universitaire Vaudois, Lausanne University Hospital, Lausanne, Vaud, Switzerland
[4]Izmir University of Economics, School of Medicine, Izmir University of Economics, Izmir, Turkey
[5]Lausanne University Hospital and University of Lausanne, Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland
[6]Public Health & Primary Care Library, University Library of Bern, University of Bern, University of Bern, Bern, Switzerland
[7]Institute of Primary Health Care (BIHAM), University of Bern, University of Bern, Bern, Switzerland
[8]Primary Care Pharmacy, Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland, University of Bern, Bern, Switzerland
[9]Materno-fetal and Obstetrics Research Unit, Department "Femme-Mère-Enfant", University Hospital, Lausanne, Switzerland, University of Lausanne, Lausanne, Switzerland

Contributors AP, YCK and UW conceived the initial research project. CJ and BMW conducted the literature search. NA and UW independently reviewed the studies in a two steps process, extracted and selected articles. The disagreements were discussed and resolved by consulting with other coauthors (AP and YCK). NA performed the statistical analysis supervised by CDG. NA wrote the first draft of the manuscript. All authors critically revised the manuscript and approved the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iDs
Nazanin Abolhassani http://orcid.org/0000-0002-3616-3595
Beatrice Minder Wyssmann http://orcid.org/0000-0003-1345-2594

REFERENCES

1 LaMoia TE, Shulman GI. Cellular and molecular mechanisms of metformin action. *Endocr Rev* 2021;42:77–96.
2 Natali A, Ferrannini E. Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: a systematic review. *Diabetologia* 2006;49:434–41.
3 Foretz M, Guigas B, Bertrand L, *et al*. Metformin: from mechanisms of action to therapies. *Cell Metab* 2014;20:953–66.
4 Sanchez-Rangel E, Inzucchi SE. Metformin: clinical use in type 2 diabetes. *Diabetologia* 2017;60:1586–93.
5 Inzucchi SE, Bergenstal RM, Buse JB, *et al*. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetes Care* 2012;35:1364–79.
6 Song R. Mechanism of metformin: a tale of two sites. *Diabetes Care* 2016;39:187–9.
7 Niromanesh S, Alavi A, Sharbaf FR, *et al*. Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial. *Diabetes Res Clin Pract* 2012;98:422–9.
8 NICE guidelines. National institute for health and care excellence: clinical guidelines. In: *Diabetes in Pregnancy: Management of Diabetes and Its Complications from Preconception to the Postnatal Period*. London: National Institute for Health and Care Excellence (UK), 2015.
9 Zhao LP, Sheng XY, Zhou S, *et al*. Metformin versus insulin for gestational diabetes mellitus: a meta-analysis. *Br J Clin Pharmacol* 2015;80:1224–34.
10 Rowan JA, Hague WM, Gao W, *et al*. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008;358:2003–15.
11 Nicholson W, Bolen S, Witkop CT, *et al*. Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. *Obstet Gynecol* 2009;113:193–205.
12 Wouldes TA, Battin M, Coat S, *et al*. Neurodevelopmental outcome at 2 years in offspring of women randomised to metformin or insulin treatment for gestational diabetes. *Arch Dis Child Fetal Neonatal Ed* 2016;101:F488–93.
13 Gui J, Liu Q, Feng L. Metformin vs insulin in the management of gestational diabetes: a meta-analysis. *PLoS One* 2013;8:e64585.
14 Li G, Zhao S, Cui S, *et al*. Effect comparison of metformin with insulin treatment for gestational diabetes: a meta-analysis based on RCTs. *Arch Gynecol Obstet* 2015;292:111–20.
15 Evans JL, Youngren JF, Goldfine ID. Effective treatments for insulin resistance: TRIM the fat and douse the fire. *Trends Endocrinol Metab* 2004;15:425–31.
16 Su DF, Wang XY. Metformin vs insulin in the management of gestational diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2014;104:353–7.
17 Deswal R, Narwal V, Dang A, *et al*. The prevalence of polycystic ovary syndrome: a brief systematic review. *J Hum Reprod Sci* 2020;13:261–71.
18 Beyuo T, Obed SA, Adjepong-Yamoah KK, *et al*. Metformin versus insulin in the management of pre-gestational diabetes mellitus in pregnancy and gestational diabetes mellitus at the Korle BU teaching hospital: a randomized clinical trial. *PLoS One* 2015;10:e0125712.
19 Ainuddin JA, Karim N, Zaheer S, *et al*. Metformin treatment in type 2 diabetes in pregnancy: an active controlled, parallel-group, randomized, open label study in patients with type 2 diabetes in pregnancy. *J Diabetes Res* 2015;2015:325851.
20 Tertti K, Laine K, Ekblad U, *et al*. The degree of fetal metformin exposure does not influence fetal outcome in gestational diabetes mellitus. *Acta Diabetol* 2014;51:731–8.
21 Gray SG, McGuire TM, Cohen N, *et al*. The emerging role of metformin in gestational diabetes mellitus. *Diabetes Obes Metab* 2017;19:765–72.
22 TUCHMANN-DUPLESSIS H, MERCIER-PAROT L. Repercussions of a hypoglycemic drug, N-N-dimethylbiguanide HCl, on gestation and fetal development in rats. *C R Hebd Seances Acad Sci* 1961;253:321–3.
23 Denno KM, Sadler TW. Effects of the biguanide class of oral hypoglycemic agents on mouse embryogenesis. *Teratology* 1994;49:260–6.
24 Gilbert C, Valois M, Koren G. Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. *Fertil Steril* 2006;86:658–63.
25 Cassina M, Donà M, Di Gianantonio E, *et al*. First-Trimester exposure to metformin and risk of birth defects: a systematic review and meta-analysis. *Hum Reprod Update* 2014;20:656–69.
26 Bao LX, Shi WT, Han YX. Metformin versus insulin for gestational diabetes: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2021;34:2741–53.
27 Feng Y, Yang H. Metformin-a potentially effective drug for gestational diabetes mellitus: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2017;30:1874–81.
28 Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. Lippincott Williams & Wilkins, 2012.
29 Scherneck S, Schlinke N, Beck E, *et al*. Pregnancy outcome after first-trimester exposure to metformin: A prospective cohort study. *Reprod Toxicol* 2018;81:79–83.
30 Given JE, Loane M, Garne E, *et al*. n.d. Metformin exposure in first trimester of pregnancy and risk of all or specific congenital anomalies: exploratory case-control study. *BMJ*:k2477.
31 Diav-Citrin O, Steinmetz-Shoob S, Shechtman S, *et al*. In-utero exposure to metformin for type 2 diabetes or polycystic ovary syndrome: A prospective comparative observational study. *Reprod Toxicol* 2018;80:85–91.
32 Dasgupta R, Ramachandran R, Mathews JE, *et al*. How safe is metformin when initiated in early pregnancy? A retrospective 5-year study of pregnant women with gestational diabetes mellitus from india. *Diabetes Res Clin Pract* 2018;137:47–55.
33 Elmaraezy A, Abushouk AI, Emara A, *et al*. Effect of metformin on maternal and neonatal outcomes in pregnant obese non-diabetic women: a meta-analysis. *Int J Reprod Biomed* 2017;15:461–70.
34 Feig DS, Murphy K, Asztalos E, *et al*. Metformin in women with type 2 diabetes in pregnancy (mity): a multi-center randomized controlled trial. *BMC Pregnancy Childbirth* 2016;16:173.
35 Panchaud A, Rousson V, Vial T, *et al*. Pregnancy outcomes in women on metformin for diabetes or other indications among those seeking teratology information services. *Br J Clin Pharmacol* 2018;84:568–78.
36 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
37 Stroup DF, Berlin JA, Morton SC, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12.
38 European surveillance of congenital anomalies. EUROCAT subgroups of congenital anomalies. 2021. Available: https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/JRC-EUROCAT-Section-3.3-23-9-2020.pdf
39 European Surveillance Of Congenital Anomalies. Minor anomalies for exclusion. 2021. Available: https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/JRC-EUROCAT-Section-3.2-23-9-2020.pdf
40 Higgins JPT, Thomas J, Chandler J, *et al*. Cochrane handbook for systematic reviews of interventions. 23 September 2019.
41 Wells GA, Shea B, O'Connell D, *et al*. *The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Oxford, 2000.
42 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses [BMJ (Clinical research ed)]. *BMJ* 2003;327:557–60.
43 Palomba S, Orio F, Falbo A, *et al*. Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing

clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2005;90:4068–74.
44 Moll E, Bossuyt PMM, Korevaar JC, *et al*. Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial [BMJ (Clinical research ed)]. *BMJ* 2006;332:1485.
45 Coetzee EJ, Jackson WP. Oral hypoglycaemics in the first trimester and fetal outcome. *S Afr Med J* 1984;65:635–7.
46 Hellmuth E, Damm P, Mølsted-Pedersen L. Congenital malformations in offspring of diabetic women treated with oral hypoglycaemic agents during embryogenesis. *Diabet Med* 1994;11:471–4.
47 Jakubowicz DJ, Iuorno MJ, Jakubowicz S, *et al*. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2002;87:524–9.
48 Abd El Hameed AA, Shreif HE, Mowafy HE. The role of continuing metformin therapy during pregnancy in the reduction of gestational diabetes and improving pregnancy outcomes in women with polycystic ovary syndrome. *Middle East Fertility Society Journal* 2011;16:204–8.
49 Kelty E, Tran DD, Atkinson A, *et al*. Maternal and neonatal health outcomes associated with the use of gliclazide and metformin for the treatment of diabetes in pregnancy: a record linkage study. *Diabetes Technol Ther* 2020;22:96–102.
50 Lin S-F, Chang S-H, Kuo C-F, *et al*. Association of pregnancy outcomes in women with type 2 diabetes treated with metformin versus insulin when becoming pregnant. *BMC Pregnancy Childbirth* 2020;20:512:512.:.
51 Lau J, Ioannidis JPA, Terrin N, *et al*. The case of the misleading funnel plot [BMJ (Clinical research ed)]. *BMJ* 2006;333:597–600.
52 Blehar MC, Spong C, Grady C, *et al*. Enrolling pregnant women: issues in clinical research. *Womens Health Issues* 2013;23:e39.
53 Jovanovic L, Pettitt DJ. Treatment with insulin and its analogs in pregnancies complicated by diabetes. *Diabetes Care* 2007;30 Suppl 2(Supplement_2):S220–4.
54 Gargaun S, Ryan E, Greenblatt E, *et al*. Pregnancy outcome in women with polycystic ovary syndrome exposed to metformin. *Can J Clin Pharmacol* 2003;10:e149.
55 Reece EA. Diabetes-Induced birth defects: what do we know? what can we do? *Curr Diab Rep* 2012;12:24–32.
56 Dunne F, Brydon P, Smith K, *et al*. Pregnancy in women with type 2 diabetes: 12 years outcome data 1990-2002. *Diabet Med* 2003;20:734–8.
57 Bell R, Glinianaia SV, Tennant PWG, *et al*. Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: a population-based cohort study. *Diabetologia* 2012;55.
58 Hansen M, Kurinczuk JJ, Milne E, *et al*. Assisted reproductive technology and birth defects: a systematic review and meta-analysis. *Hum Reprod Update* 2013;19:330–53.
59 Mathiesen ER, Ringholm L, Damm P. Pregnancy management of women with pregestational diabetes. *Endocrinol Metab Clin North Am* 2011;40:727–38.