

Supplementary table 1: Search strategy**Embase.com = 1'818 results**

Combination of concepts: ((1) AND (2) AND (3)) NOT 4)

1) Pregnancy, pregnant women, fetus, embryo
('pregnancy'/de OR 'adolescent pregnancy'/de OR 'first trimester pregnancy'/de OR 'pregnancy diabetes mellitus'/exp OR 'pregnant woman'/de OR 'prenatal exposure'/de OR 'prenatal drug exposure'/de OR 'maternal exposure'/de OR 'in utero exposure'/de OR 'prenatal development'/exp OR 'embryo'/de OR 'fetus'/de OR 'progeny'/de OR (pregnan* OR 'child bearing' OR childbearing OR gestation* OR 'in utero' OR 'intra uterin*' OR intrauterin* OR endouterin* OR fetal OR foetal OR fetus* OR foetus* OR prenatal OR pre-natal OR embryo* OR offspring* OR progeny OR (first NEXT/2 trimester*)):ab,ti,kw)
2) Metformin
:tn = Drug Tradenames; :rn = CAS Registry Numbers
'metformin'/de OR (metformin* OR methformin* OR dimethyldiguanide OR dimethylbiguanide OR dimethylbiguanide OR Dimethyl-biguanidine OR Dimethylbiguanidine OR dimethyl-guanyl-guanidine OR dimethyl-guanylguanidine OR dimethylguanylguanidine OR glucophage OR glukophage OR glucofag* OR dabex OR denkaform OR diabetase OR diabetformin OR diabetmin OR diabetosan OR diafat OR diaformin OR diaformina OR diametin OR dianben OR diformin OR dimefor OR dybis OR eraphage OR "espa-formin" OR "euform retard" OR fluamine OR flumamine OR fornidd OR fortamet OR glafornil OR glibudon OR glifage OR gliguanid OR glucaminol OR glucoform OR glucoformin OR glucohexal OR glucoless OR glucomet OR glucomin OR glucomine OR gluconil OR glucostop OR glucotika OR gludepatic OR glufor OR gluformin OR glumeformin OR glumet OR glustress OR glycipbage OR glycomet OR glycoran OR glyformin OR haurymellin OR hipoglucin OR islotin OR juformin OR "la 6023" OR la6023 OR maformin OR meglucon OR meguan OR melbin OR melformin OR mellittin OR merckformin OR mescorit OR metaformin OR metfogamma OR metforal OR metformax OR metiguanide OR metomin OR metphormin OR miformin OR "reglus 500" OR riomet OR risidon OR siamformet OR siofor OR thiabet OR vimetrol OR walaphage):ab,ti,kw,tn OR ("Actoplus Met" OR Avandamet OR Biocos OR Competact OR Diabesin OR Diabetex OR Diabiformin OR Efficib OR "Espa formin" OR Eucreas OR Glucobon OR Gliformin OR Glucovance OR Glumetza OR Icandra OR Invokamet OR Janumet OR Jentaduetto OR Kazano OR Kombiglyze OR Komboglyze OR Mediabeta OR Metaglip OR Metfin OR "MetfoLiquid GeriaSan" OR Prandimet OR Qternmet OR Segluromet OR Synjardy OR Trijardy OR Velmetia OR Xigduo OR Zomarist OR apophage OR aron OR benofomin OR deson OR dextin OR diabex OR diamin OR dmgg OR glucophage OR glucofago OR glupa OR glycon OR glymet OR i-max OR jesacrin OR lyomet OR neoform OR nndg):ab,ti,kw,tn OR ('657-24-9' OR '1115-70-4'):rn
3) Congenital malformations/abnormalities (including: cardiovascular malformations), pregnancy complications, stillbirths
('congenital disorder'/exp OR 'congenital heart disease'/exp OR 'congenital malformation'/exp OR 'fetus malformation'/de OR 'developmental disorder'/exp OR 'parameters concerning the fetus, newborn and pregnancy'/de OR 'teratology'/exp OR 'teratogenic agent'/de OR 'teratogenesis'/exp OR 'teratogenicity'/de OR 'embryotoxicity'/de OR 'postnatal development'/de OR 'prenatal development'/exp OR 'embryo mortality'/de OR 'fetus mortality'/de OR 'infant mortality'/de OR 'perinatal mortality'/exp OR 'prenatal mortality'/de OR 'embryo death'/de OR 'fetus death'/de OR 'perinatal death'/de OR 'newborn death'/de OR 'spontaneous abortion'/de OR 'first trimester pregnancy'/de OR 'fetus outcome'/de OR 'adverse neonatal outcome'/de OR 'fetus heart'/de OR 'fetus disease'/exp OR 'pregnancy outcome'/de OR 'stillbirth'/de OR 'pregnancy loss'/de OR 'pregnancy termination'/exp OR 'gestation period'/de OR 'fetus wastage'/de OR (malform* OR defect* OR anomal* OR deform* OR abnormal* OR dysmorph* OR ((congenital) NEAR/3 (lesion* OR disorder* OR syndrome* OR condition* OR difference* OR disease* OR illness* OR fusion*)) OR (development* NEAR/3 delay*) OR ((dead OR death* OR risk* OR injur* OR harm* OR complication* OR died OR loss OR mortalit*) NEAR/3 (embryo* OR fetus* OR fetal OR foetus* OR foetal OR intrauterin* OR endouterin* OR 'in utero' OR prenatal OR antepartum OR neonatal)) OR stillbirth* OR stillborn* OR

miscarriage* OR 'spontaneous abortion'* OR ((embryo OR fetus* OR foetus* OR pregnanc*) NEAR/3 (loss*)) OR (adverse NEAR/3 (fetal or foetal or neonatal OR pregnancy OR birth OR obstetric) NEAR/3 (effect* OR outcome*)) OR 'fetal heart' OR 'foetal heart' OR (first NEXT/2 trimester*) OR (early NEAR/3 pregnanc*) OR teratolog* OR teratogen* OR embryotox*):ab,ti,kw)
4) Limits: - excluding animal studies, conference abstracts, letters, notes, editorials
NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim)

Medline (Ovid) = 645 results

Combination of concepts: ((1) AND (2) AND (3)) NOT 4)

1) Pregnancy, pregnant women, fetus, embryo (exp Pregnancy/ OR Pregnancy in Adolescence/ OR Pregnancy Trimester, First/ OR exp Pregnancy in Diabetics/ or exp Diabetes, Gestational/ OR Pregnant Woman/ OR Prenatal Exposure Delayed Effects/ OR Maternal Exposure/ OR Embryo, Mammalian/ OR Fetus/ OR (pregnan* OR child bearing OR childbearing OR gestation* OR in utero OR intra uterin* OR intrauterin* OR endouterin* OR fetal OR foetal OR fetus* OR foetus* OR prenatal OR pre-natal OR embryo* OR offspring* OR progeny OR (first ADJ2 trimester*)).ab,ti,kf.)
2) Metformin .nm =name of substance word; .rn = Registry Number/Name of Substance exp Metformin/ OR (metformin* OR methformin* OR dimethyldiguanide OR dimethylbiguanide OR dimethylbiguanide OR Dimethyl-biguanidine OR Dimethylbiguanidine OR dimethyl-guanyl-guanidine OR dimethyl-guanylguanidine OR dimethylguanylguanidine OR glucophage OR glukophage OR glucofag* OR dabex OR denkaform OR diabetase OR diabetformin OR diabetmin OR diabetosan OR diafat OR diaformin OR diaformina OR diametin OR dianben OR diformin OR dimefor OR dybis OR eraphage OR "espa-formin" OR "euform retard" OR fluamine OR flumamine OR fornidd OR fortamet OR glafornil OR glibudon OR glifage OR gliguanid OR glucaminol OR glucoform OR glucoformin OR glucohexal OR glucoless OR glucomet OR glucomin OR glucomine OR gluconil OR glucostop OR glucotika OR gludepatic OR glufor OR gluformin OR glumeformin OR glumet OR glustress OR glyciphage OR glycomet OR glycoran OR glyformin OR haurymellin OR hipoglucin OR islotin OR juformin OR "la 6023" OR la6023 OR maformin OR meglucon OR meguan OR melbin OR melformin OR mellittin OR merckformin OR mescorit OR metaformin OR metfogamma OR metforal OR metformax OR metiguanide OR metomin OR metphormin OR miformin OR "reglus 500" OR riomet OR risidon OR siamformet OR siofor OR thiabet OR vimetrol OR walaphage).ab,ti,kf,nm OR ("Actoplus Met" OR Avandamet OR Biocos OR Competact OR Diabesin OR Diabetex OR Diabiformin OR Efficib OR "Espa formin" OR Eucreas OR Glucobon OR Gliformin OR Glucovance OR Glumetza OR Icandra OR Invokamet OR Janumet OR Jentaducto OR Kazano OR Kombiglyze OR Komboglyze OR Mediabet OR Metaglip OR Metfin OR "MetfoLiquid GeriaSan" OR Prandimet OR Qternmet OR Segluromet OR Synjardy OR Trijardy OR Velmetia OR Xigduo OR Zomarist OR apophage OR aron OR benofomin OR deson OR dextin OR diabex OR diamin OR dmgg OR glucophage OR glucofago OR glupa OR glycon OR glymet OR i-max OR jesacrin OR lyomet OR neoform OR nndg).ab,ti,kf,nm OR (9100L32L2N).rn
3) Congenital malformations/abnormalities (including: cardiovascular malformations), pregnancy complications, stillbirths (exp Congenital Abnormalities/ OR Heart Defects, Congenital/ OR Abnormalities, Drug-Induced/ OR Teratology/ OR Teratogens/ OR Teratogenesis/ OR Embryonic Development/ OR exp Fetal Development/de OR Embryo Loss/ OR Fetal Mortality/ OR exp Fetal Death/ OR Infant Mortality/ OR Perinatal Mortality/ OR

Perinatal Death/ OR exp Abortion, Spontaneous/ OR Pregnancy Trimester, First/ OR Fetal Heart/ OR Fetal Diseases/ OR exp Pregnancy Outcome/ OR (malform* OR defect* OR anomal* OR deform* OR abnormal* OR dysmorph* OR ((congenital) ADJ3 (lesion* OR disorder* OR syndrome* OR condition* OR difference* OR disease* OR illness* OR fusion*)) OR (development* ADJ3 delay*) OR ((dead OR death* OR risk* OR injur* OR harm* OR complicati* OR died OR loss OR mortalit*) ADJ3 (embryo* OR fetus* OR fetal OR foetus* OR foetal OR intrauterin* OR endouterin* OR in utero OR prenatal OR antepartum OR neonatal)) OR stillbirth* OR stillborn* OR miscarriage* OR spontaneous abortion* OR ((embryo OR fetus* OR foetus* OR pregnanc*) ADJ3 (loss*)) OR (adverse ADJ3 (fetal or foetal or neonatal OR pregnancy OR birth OR obstetric) ADJ3 (effect* OR outcome*)) OR fetal heart OR foetal heart OR (first ADJ2 trimester*) OR (early ADJ3 pregnanc*) OR teratolog* OR teratogen* OR embryotox*).ab,ti,kf.)
4) Limits: - excluding animal studies, conference abstracts, letters, notes, editorials
NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congress).pt.

Cochrane CENTRAL = 306 trials

Cochrane Central Register of Controlled Trials - Combination of concepts: (1) AND (2) AND (3)

1) Pregnancy, pregnant women, fetus, embryo
((pregnan* OR child NEXT bearing OR childbearing OR gestation* OR "in utero" OR intra NEXT uterin* OR intrauterin* OR endouterin* OR fetal OR foetal OR fetus* OR foetus* OR prenatal OR pre-natal OR embryo* OR offspring* OR progeny OR (first NEAR/3 trimester*)):ab,ti,kw)
2) Metformin
(metformin* OR methformin* OR dimethyldiguanide OR dimethylbiguanide OR dimethylbiguanide OR Dimethyl-biguanidine OR Dimethylbiguanidine OR dimethyl-guanyl-guanidine OR dimethyl-guanylguanidine OR dimethylguanylguanidine OR glucophage OR glukophage OR glucofag* OR dabex OR denkaform OR diabetase OR diabetformin OR diabetmin OR diabetosan OR diafat OR diaformin OR diaformina OR diametin OR dianben OR diformin OR dimefor OR dybis OR eraphage OR "espa-formin" OR "euform retard" OR fluamine OR flumamine OR fornidd OR fortamet OR glaformil OR glibudon OR glifage OR gliguanid OR glucaminol OR glucoform OR glucoformin OR glucohexal OR glucoless OR glucomet OR glucomin OR glucomine OR gluconil OR glucostop OR glucotika OR gludepatic OR glufor OR gluformin OR glumeformin OR glumet OR glustress OR glyciphage OR glycomet OR glycoran OR glyformin OR haurymellin OR hipoglucin OR islotin OR juformin OR "la 6023" OR la6023 OR maformin OR meglucon OR meguan OR melbin OR melformin OR mellittin OR merckformin OR mescorit OR metaformin OR metfogamma OR metforal OR metformax OR metiguanide OR metomin OR metphormin OR miformin OR "reglus 500" OR riomet OR risidon OR siamformet OR siofor OR thiabet OR vimetrol OR walaphage OR "Actoplus Met" OR Avandamet OR Biocos OR Competact OR Diabesin OR Diabetex OR Diabiformin OR Efficib OR "Espa formin" OR Eucreas OR Glucobon OR Gliformin OR Glucovance OR Glumetza OR Icandra OR Invokamet OR Janumet OR Jentadueto OR Kazano OR Kombiglyze OR Komboglyze OR Mediabet OR Metaglip OR Metfin OR "MetfoLiquid GeriaSan" OR Prandimet OR Qternmet OR Segluromet OR Synjardy OR Trijardy OR Velmetia OR Xigduo OR Zomarist OR apophage OR aron OR benofomin OR deson OR dextin OR diabex OR diamin OR dmgg OR glucofage OR glucofago OR glupa OR glycon OR glymet OR i-max OR jesacrin OR lyomet OR neoform OR nndg):ab,ti,kw
3) Congenital malformations/abnormalities (including: cardiovascular malformations), pregnancy complications, stillbirths
((malform* OR defect* OR anomal* OR deform* OR abnormal* OR dysmorph* OR ((congenital) NEAR/3 (lesion* OR disorder* OR syndrome* OR condition* OR difference* OR disease* OR illness* OR fusion*)) OR

(development* NEAR/3 delay*) OR ((dead OR death* OR risk* OR injur* OR harm* OR complication* OR died OR loss OR mortalit*) NEAR/3 (embryo* OR fetus* OR fetal OR foetus* OR foetal OR intrauterin* OR endouterin* OR "in utero" OR prenatal OR antepartum OR neonatal)) OR stillbirth* OR stillborn* OR miscarriage* OR spontaneous NEXT abortion* OR ((embryo OR fetus* OR foetus* OR pregnanc*) NEAR/3 (loss*)) OR (adverse NEAR/3 (fetal or foetal or neonatal OR pregnancy OR birth OR obstetric) NEAR/3 (effect* OR outcome*)) OR "fetal heart" OR "foetal heart" OR (first NEAR/3 trimester*) OR (early NEAR/3 pregnanc*) OR teratolog* OR teratogen* OR embryotox*):ab,ti,kw)

Web of Science Core Collection = 730 results

Combination of concepts: (1) AND (2) AND (3)

1) Pregnancy, pregnant women, fetus, embryo
TS=((pregnan* OR "child bearing*" OR childbearing OR gestation* OR "in utero" OR "intra uterin*" OR intrauterin* OR endouterin* OR fetal OR foetal OR fetus* OR foetus* OR prenatal OR pre-natal OR embryo* OR offspring* OR progeny OR (first NEAR/3 trimester*)))
2) Metformin
TS=(metformin* OR methformin* OR dimethyldiguanide OR dimethylbiguanide OR dimethylbiguanide OR Dimethyl-biguanidine OR Dimethylbiguanidine OR dimethyl-guanyl-guanidine OR dimethyl-guanylguanidine OR dimethylguanylguanidine OR glucophage OR glukophage OR glucofag* OR dabex OR denkaform OR diabetase OR diabetformin OR diabetmin OR diabetosan OR diafat OR diaformin OR diaformina OR diametin OR dianben OR diformin OR dimefor OR dybis OR eraphage OR "espa-formin" OR "euform retard" OR fluamine OR flumamine OR fornidd OR fortamet OR glaformil OR glibudon OR glifage OR gliguanid OR glucaminol OR glucoform OR glucoformin OR glucohexal OR glucoless OR glucomet OR glucomin OR glucomine OR gluconil OR glucostop OR glucotika OR gludepatic OR glufor OR gluformin OR glumeformin OR glumet OR glustress OR glyciphage OR glycomet OR glycoran OR glyformin OR haurymellin OR hipoglucin OR islotin OR juformin OR "la 6023" OR la6023 OR maformin OR meglucon OR meguan OR melbin OR melformin OR mellittin OR merckformin OR mescorit OR metaformin OR metfogamma OR metforal OR metformax OR metiguanide OR metomin OR metphormin OR miformin OR "reglus 500" OR riomet OR risidon OR siamformet OR siofor OR thiafet OR viametrol OR walaphage OR "Actoplus Met" OR Avandamet OR Biocos OR Competact OR Diabesin OR Diabetex OR Diabiformin OR Efficib OR "Espa formin" OR Eucreas OR Glucobon OR Gliformin OR Glucovance OR Glumetza OR Icandra OR Invokamet OR Janumet OR Jentadueto OR Kazano OR Kombiglyze OR Komboglyze OR Mediabet OR Metaglip OR Metfin OR "MetfoLiquid GeriaSan" OR Prandimet OR Qternmet OR Segluromet OR Synjardy OR Trijardy OR Velmetia OR Xigduo OR Zomarist OR apophage OR aron OR benofomin OR deson OR dextin OR diabex OR diamin OR dmgg OR glucofage OR glucofago OR glupa OR glycon OR glymet OR i-max OR jesacrin OR lyomet OR neoform OR nndg)
3) Congenital malformations/abnormalities (including: cardiovascular malformations), pregnancy complications, stillbirths
TS=((malform* OR defect* OR anomal* OR deform* OR abnormal* OR dysmorph* OR ((congenital) NEAR/3 (lesion* OR disorder* OR syndrome* OR condition* OR difference* OR disease* OR illness* OR fusion*)) OR (development* NEAR/3 delay*) OR ((dead OR death* OR risk* OR injur* OR harm* OR complication* OR died OR loss OR mortalit*) NEAR/3 (embryo* OR fetus* OR fetal OR foetus* OR foetal OR intrauterin* OR endouterin* OR "in utero" OR prenatal OR antepartum OR neonatal)) OR stillbirth* OR stillborn* OR miscarriage* OR "spontaneous abortion*" OR ((embryo OR fetus* OR foetus* OR pregnanc*) NEAR/3 (loss*)) OR (adverse NEAR/3 (fetal or foetal or neonatal OR pregnancy OR birth OR obstetric) NEAR/3 (effect* OR outcome*)) OR "fetal heart" OR "foetal heart" OR (first NEAR/3 trimester*) OR (early NEAR/3

pregnanc*) OR teratolog* OR teratogen* OR embryotox*))

ClinicalTrials.gov = 59 results

(Expert Search)

(metformin OR dimethylbiguanide OR Dimethylguanylguanidine OR Glucophage) AND (pregnancy OR pregnant OR childbearing OR gestation OR foetus OR fetus OR embryo) AND (malformation OR defect OR anomaly OR deformity OR abnormality OR dysmorphism OR abortion OR stillbirth OR miscarriage OR teratology OR teratogen OR teratogenicity OR embryotoxicity OR fetotoxicity) OR MITY

ICTRP Search Portal = 25 results

<https://trialsearch.who.int/>

(Standard search)

pregnan* AND malform* AND metformin OR
pregnan* AND birth defect* AND metformin OR
pregnan* AND anomal* AND metformin OR
pregnan* AND abnormal* AND metformin OR
pregnan* AND deform* AND metformin OR
teratolog* AND metformin OR
teratogen* AND metformin OR
fetus AND metformin OR
neonatal AND metformin OR
abortion* AND metformin OR
miscarriage* AND metformin OR
stillbirth* AND metformin OR
pregnancy outcomes AND metformin OR
MITY

Google scholar = first 200 results (out of 41'500)

metformin|dimethylbiguanidine|gliformin|glucophage|glumetza|riomet
pregnancy|pregnant|gestation|foetus|fetus|embryo|infant|"first trimester"
malformation|defect|anomalies|deformity|abnormalities|abortion|stillbirth|miscarriage|teratogenic|teratology

Supplementary table 2: Risk of bias for retrospective/ prospective/ cohort studies as assessed by the Newcastle-Ottawa scale (NOS)

Indication	Author (year)	Study design	Selection				Comparability	Outcome			Quality Score
			Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up (Loss of follow-up)*	
PCOS	Jakubowicz et al. (2002)	Retrospective study	*	*	*	NA	**	*	*	*	8/9
	Hameed et al. (2011)	Observational cohort	*	*	*	NA	*	*	*	*	7/9
PGDM	Coetzee & Jackson (1984)	Retrospective study	*	*	*	NA			*	*	5/9
	Hellmuth et al. (1994)	Retrospective study	*	*	*	NA		*	*	*	6/9
	Kelty et al. (2020)	Retrospective cohort	*	*	*	NA	*	*	*	*	7/9
	Lin et al. (2020)	Retrospective observational cohort	*	*	*	NA	*	*	*	*	7/9
Both	Diav-Citrin et al. (2018)	Prospective observational cohort	*	*	*	NA	*	*	*	*	7/9
	Panchaud et al. (2018)	Prospective observational cohort	*	*	*	NA	*	*	*	*	7/9
	Scherneck et al. (2018)	Prospective observational cohort	*	*	*	NA	*		*	*	6/9

Abbreviations: PCOS, polycystic ovary syndrome; PGDM, pre-gestational diabetes mellitus.

Supplementary table 3: GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) assessment of studies

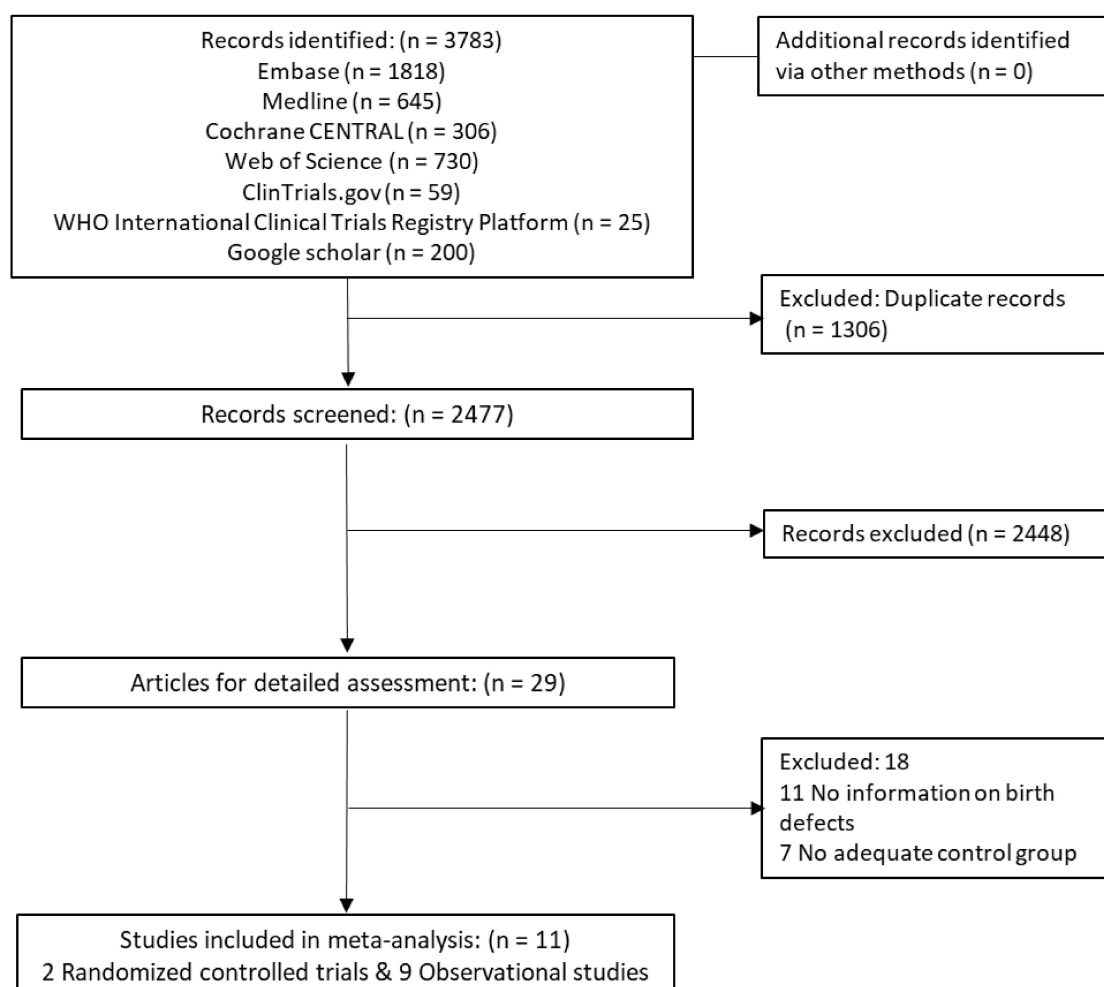
Indication	Number of studies	Study design	Risk of bias/ Study Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of participants		Effect		Certainty
								Exposed Group	Control Group	Relative (95% CI)	Absolute	
PCOS	N=2	Randomized controlled studies	Not serious	No ^a	No	Very Serious ^b	Undetected	1/57	1/52	0.93 (0.09-9.21)	2 more per 1000	⊕⊕○○ Low
								(1.8%)	(1.9%)		(from 18 fewer to 134 more)	
PGDM	N=7	Observational studies	Serious	Moderate ^c	No	Serious ^b	Undetected	62/1122	84/1851	1.05 (0.50-2.18)	3 more per 1000	⊕○○○ Very low
								(5.5%)	(4.5%)		(from 22 fewer to 49 more)	

^a I2=00.0%

^b Due to small sample size and number of events; Confidence interval (CI) includes both no effect and appreciable benefit or harm

^c I2 = 59.34

^d Included studies were all observational and extracted data were not-adjusted.

Supplementary figure 1: Flowchart of study selection process

Supplementary Figure 2: Risk of bias for Randomized controlled trial using Cochrane Collaboration Criteria

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	selective outcome reporting
Palomba et al. (2005)						
Moll et al. (2006)						

Risk of bias in individual randomised studies. +, low risk of bias; ?, unclear risk of bias; -, high risk of bias