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Supplementary table 1. Search strategy

MEDLINE (PubMed)

#1 "Glyburide"[MeSH] 5415
#2 "Metformin"[MeSH] 6142
#3 oral diabetes agent*[tiab] 12
#4 oral antidiabetic agent*[tiab] 658
#5 oral hypoglycemic agent*[tiab] 1406
#6 metformin[tiab] 8079
#7 glyburide[tiab] 1212
#8 glibenclamide[tiab] 6634
#9 glimepiride[tiab] 744
#10 glipizide[tiab] 830
#11 sulfonylurea[tiab] 4029
#12 sulphonylurea[tiab] 1331
#13 ((((((((((#1) OR #2) OR #3) OR #4) OR #5) OR #6) OR #7) OR #8) OR #9) OR #10) OR #11) OR #12 22521
#14 "Pregnancy"[MeSH] 682623
#15 "Diabetes, Gestational"[MeSH] 6200
#16 pregnan*[tiab] 353829
#17 gestation*[tiab] 138524
#18 GDM[tiab] 2545
#19 (((#14) OR #15) OR #16) OR #17) OR #18 797198
#20 (#13) AND #19 909
#21 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT (humans[mh] AND animals[mh])) 2713046
#22 (#20) AND #21 567

Cochrane Central Register of Controlled Trials (The Cochrane Library: Issue 4 of 12)

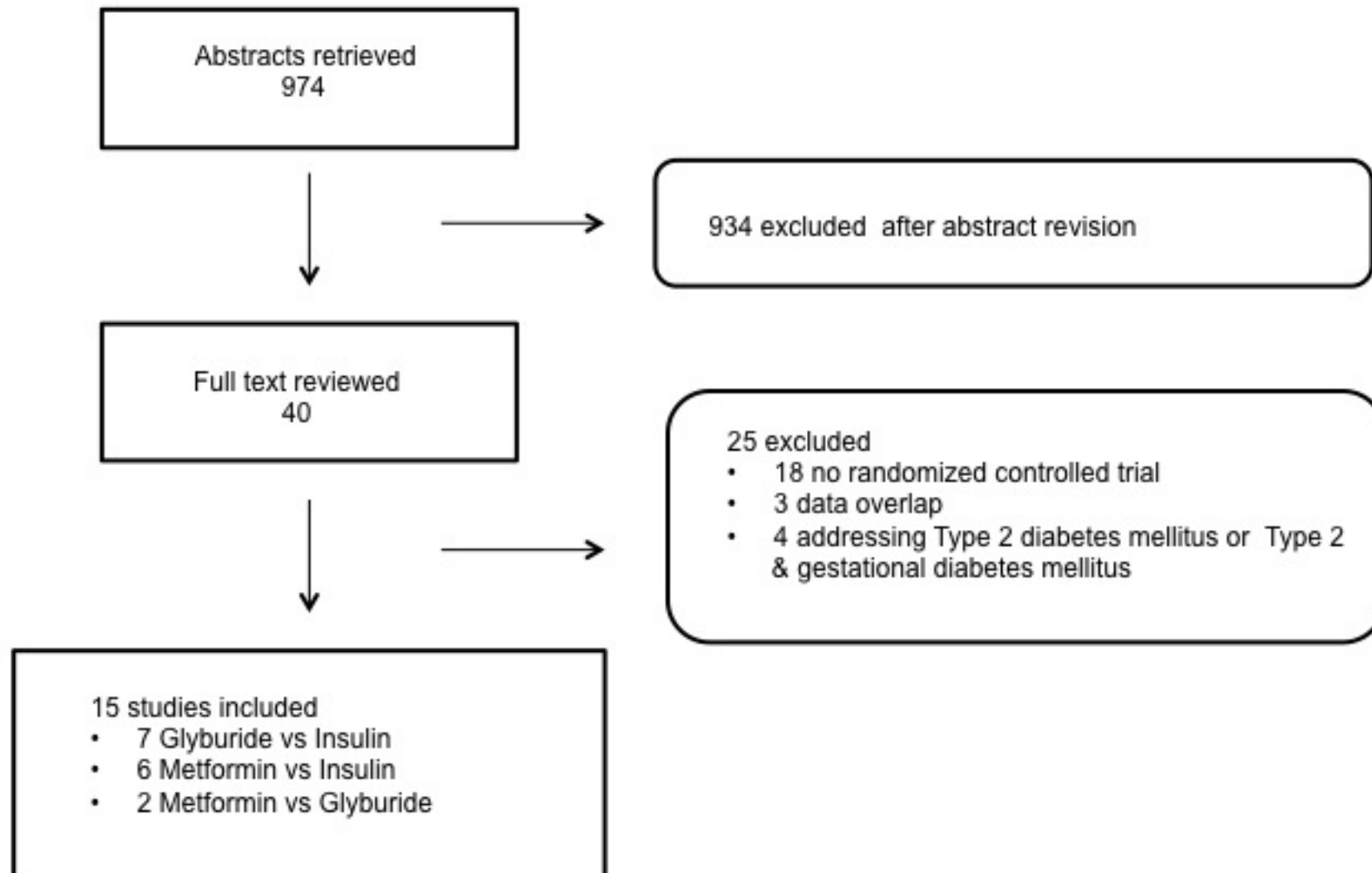
#1 MeSH descriptor: [Glyburide] explode all trees 473
#2 MeSH descriptor: [Metformin] explode all trees 1334
#3 oral diabetes agent*.ti,ab 872
#4 oral antidiabetic agent*.ti,ab 159
#5 oral hypoglycemic agent*.ti,ab 552
#6 metformin:ti,ab 1728
#7 glyburide:ti,ab 194
#8 glibenclamide:ti,ab 474
#9 glimepiride:ti,ab 215
#10 glipizide:ti,ab 179
#11 sulfonylurea:ti,ab 475
#12 sulphonylurea:ti,ab 258
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 3450
#14 MeSH descriptor: [Pregnancy] explode all trees 5310
#15 MeSH descriptor: [Diabetes, Gestational] explode all trees 276
#16 pregnan*.ti,ab 13670
#17 gestation*.ti,ab 6261
#18 GDM:ti,ab 118
#19 #14 or #15 or #16 or #17 or #18 19383
#20 #13 and #19 207 (164 in Clinical Trials)

EMBASE (OVID Embase Classic+Embase)

1 exp glibenclamide/ (19156)
2 exp metformin/ (29677)
3 oral diabetes agent*.ti,ab. (19)
4 oral antidiabetic agent*.ti,ab. (1112)
5 oral hypoglycemic agent*.ti,ab. (2069)
6 metformin.ti,ab. (12825)
7 glyburide.ti,ab. (1573)
8 glibenclamide.ti,ab. (8721)
9 glimepiride.ti,ab. (1186)
10 glipizide.ti,ab. (1252)
11 sulfonylurea.ti,ab. (5443)
12 sulphonylurea.ti,ab. (2032)

13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (52632)
14 exp pregnancy/ (652287)
15 exp pregnancy diabetes mellitus/ (19212)
16 pregnan*.ti,ab. (480705)
17 gestation*.ti,ab. (179763)
18 GDM.ti,ab. (3864)
19 14 or 15 or 16 or 17 or 18 (856454)
20 13 and 19 (2280)
21 random:.tw. or placebo:.mp. or double-blind:.mp. (1050393)
22 20 and 21 (540)

Supplementary figure 1. Flow chart of articles through the selection process



Supplementary table 2. Characteristics and baseline data of the individual studies included in the meta-analyses

Glyburide vs Insulin	Author/ Country	GDM criteria	Blood glucose criteria for drug treatment (mmol/l)	Drug	Number of patients	Age (years)	Prepregnancy BMI (Kg/m ²)	OGTT fasting/ 2h blood glucose (mmol/l)	GA at entry (weeks)	HbA _{1c} at entry (%)
Glyburide vs Insulin	Langer 2000 ² USA	C & C	≥5.3 fasting ≥6.7 2h postprandial	Insulin Glyburide	203 201	30.0 29.0		5.49/ 9.74 5.43/ 9.74	27.0 28.0	5.6 5.7
	Silva 2007 ²⁰ Brazil	Local	≥5.0 fasting ≥5.6 2h postprandial	Insulin Glyburide	36 32	29.9 31.6	27.9 27.5		25.6 26.6	
	Anjalakshi 2007 ²¹ India	WHO	≥6.7 2h postprandial	Insulin Glyburide	13 10	27.5 24.9	25.3 22.8		22.6 22.5	5.75 5.48
	Ogunyemi 2007 ²² USA	Not given	Not given	Insulin Glyburide	49 48	Ns	30.8 32.0	6.43/ 11.0 5.76*/ 9.94*	24.6 28.1*	7.5 5.8*
	Lain 2009 ³ USA	C & C	>5.3 fasting >6.7 2h postprandial	Insulin Glyburide	41 41	31.2 32.2	30.9 33.4	5.64/ 9.62 5.61/ 9.83	30.6 30.8	5.0 5.0
	Mukhopadhyay2012 ²³ India	WHO	≈5.0 fasting ≈6.7 2h postprandial	Insulin Glyburide	30 30	26.0 26.3	23.0 23.7		27.4 28.3	6.5 6.3
	Tempe 2013 ²⁴ India	C & C	≥ 5.0 fasting ≥ 6.7 2h postprandial	Insulin Glyburide	32 32	27.5 26.9			27.3 25.9	
	Moore 2007 ²⁵ USA	NDDG	≥ 5.8 fasting ≥ 6.7 2h postprandial	Insulin Metformin	31 32	27.7 27.1	35.3 39.7*		28.9 27.8	
Metformin vs Insulin	Rowan 2008 ⁴ Australia- New Zealand	ADIPS	>5.4 fasting >6.7 2h postprandial	Insulin Metformin	370 363	33.0 33.5	31.9 32.2	5.71/ 9.40 5.70/ 9.70	30.1 30.2	5.8 5.7
	Ijäs 2011 ²⁶ Finland	Local	>5.3 fasting >6.7 1.5h postprandial	Insulin Metformin	50 47	31.7 32.3	30.8 31.5	5.40/ 8.10 5.60/ 8.20	30.0 30.0	5.9 5.9
	Niromanesh 2012 ²⁷ Iran	C & C	>5.3 fasting >6.7 2h postprandial	Insulin Metformin	80 80	31.8 30.7	27.1 28.1	5.95/ 9.58 5.82/ 9.14	28.6 28.7	5.6 5.7
	Tertti 2013 ²⁸ Finland	Local	>5.5 fasting >7.8 1h postprandial	Insulin Metformin	107 110	32.1 31.9	28.9 29.4	5.60/ 7.90 5.50/ 8.30	30.4 30.3	5.50 5.48
	Spaulonci 2013 ²⁹ Brazil	C & C	>5.3 fasting >6.7 2h postprandial	Insulin Metformin	46 46	32.8 31.9	28.0 28.7		32.1 32.2	5.93 5.90
	Metformin vs Glyburide	Moore 2010 ³⁰ USA	C & C	≥ 5.8 fasting ≥ 6.7 2h postprandial	Glyburide Metformin	74 75	29.6 31.0	32.7 32.8		29.1 27.3
Silva 2012 ⁵ Brazil		WHO	≥ 5.0 fasting ≥ 6.7 1h postprandial	Glyburide Metformin	96 104	31.2 32.6	28.6 28.7	5.22/ 8.94 5.32/ 9.20	25.4 27.0	

GDM=Gestational Diabetes Mellitus; BMI=body mass index; OGTT=oral glucose tolerance test; HbA_{1c}=glycated haemoglobin; GA=gestational age; C & C=Carpenter and Coustan; WHO=World Health Organization; Ns=non-significant; NDDG=National Diabetes Data Group; ADIPS=Australasian Diabetes In Pregnancy Society.

* significant differences between groups

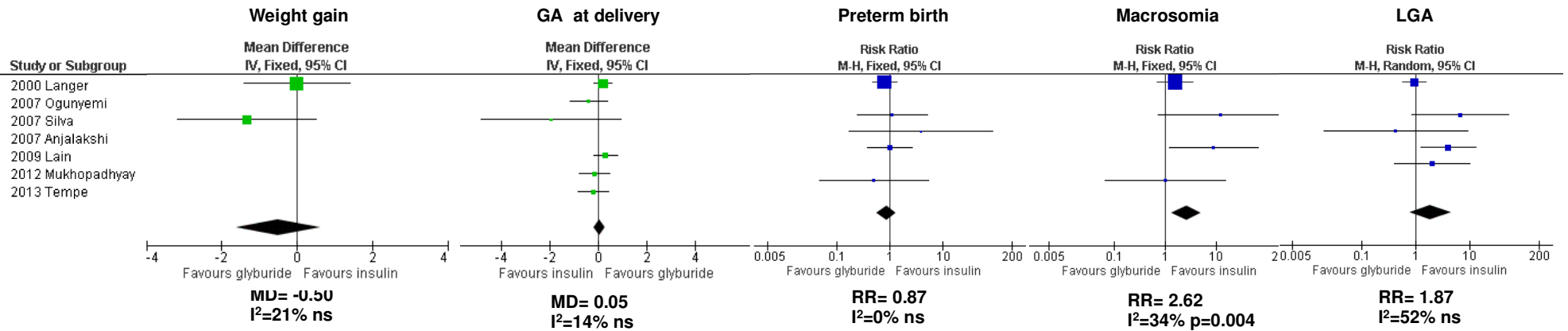
Supplementary table 3. Quality assessment of studies included in the meta-analyses

	Author/ Country	Randomization	Allocation concealment	Blinding of patients and healthcare professionals	Published protocol / Selective outcomes reporting	Sample size calculation/ Attrition rates	Intention to treat	Comparability in baseline characteristics	Excluded in sensitivity analysis
Glyburide vs Insulin	Langer 2000 ² USA	Computer generated	Sealed envelopes	Open label	Not found All but SGA	Not described 0 vs 0%	Yes	Balanced	No
	Silva 2007 ²⁰ Brazil	Not described	Envelopes	Open label	Not found All but Apgar	Described 5.56% total	Yes	Balanced	No
	Anjalakshi 2007 ²¹ India	Not described	Not described	Open label	Not found Not predefined	Not described 23.1 vs 0%	Yes	Balanced	Yes
	Ogunyemi 2007 ²² USA	Computer generated	Sealed envelopes	Open label	Not found No	Not described 10.4 vs 8.2%	Yes	Unbalanced	No
	Lain 2009 ³ USA	Random permuted block	Sealed envelopes	Open label	Not found No	Described 16.3 vs 18.0%	Yes Stated	Balanced	No
	Mukhopadhyay2012 ²³ India	Table of random numbers	Not described	Open label	Not found No	Not described 0 vs 0%	Yes	Unbalanced	No
	Tempe 2013 ²⁴ India	Not described	Not described	Open label	Not found All but delivery type	Not described 11.1 vs 8.6%	Yes	Balanced	No
Metformin vs Insulin	Moore 2007 ²⁵ USA	Computer generated	Sealed envelopes	Open label	Not found No	Described 0 vs 0%	Yes	Unbalanced Height >1.60 Metformin Height <1.40 Insulin	Yes
	Rowan 2008 ⁴ Australia- New Zealand	Block size 4, stratified by site	Not described	Open label	Published No	Described 2.7 vs 2.11%	Yes Stated	Balanced	No
	Ijäs 2011 ²⁶ Finland	Generated manually	Sealed envelopes	Open label	Published No	Described 6 vs 0%	Yes	Balanced	No
	Niromanesh 2012 ²⁷ Iran	Computer generated	Sealed envelopes	Single blind (Obstetrician)	Published No	Described 7 vs 7%	Yes	Balanced	No
	Tertti 2013 ²⁸ Finland	Not described	Sealed envelopes	Open label	Published No	Described 0.9 vs 2.7%	Yes	Balanced	No
	Spaulonci 2013 ²⁹ Brazil	Computer generated	Not described	Open label	Published No	Described 2.1 vs 2.1 %	Yes Stated	Balanced	No
Metformin vs Glyburide	Moore 2010 ³⁰ USA	Computer generated	Sealed envelopes	Open label	Published No	Described 0 vs 0%	Yes	Balanced	No
	Silva 2012 ⁵ Brazil	Computer generated	Brown envelopes	Open label	Not published All but macrosomia	Not described 0 vs 0%	Yes	Balanced	No

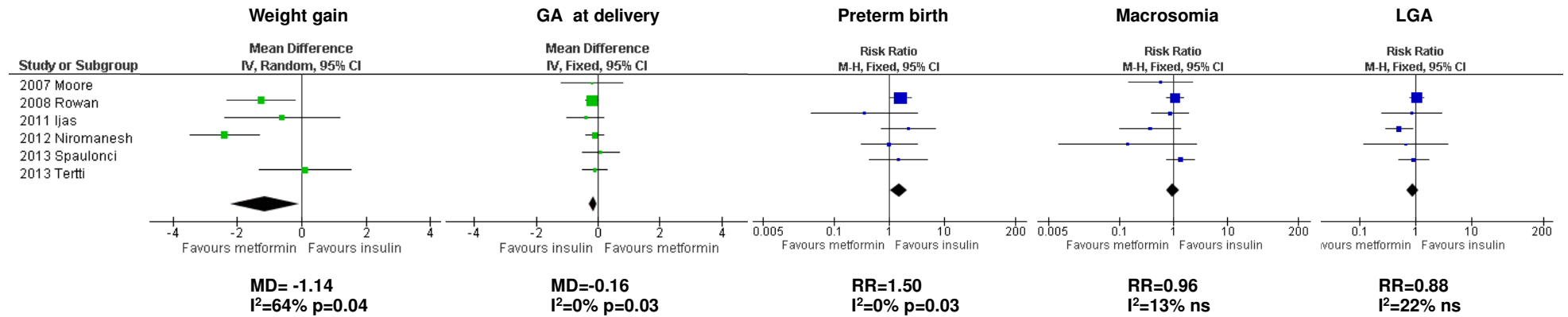
SGA= Small-for-gestational age newborns

Supplementary figure 2. Forest plot of primary outcome variables with significant differences* in women with gestational diabetes mellitus requiring drug treatment

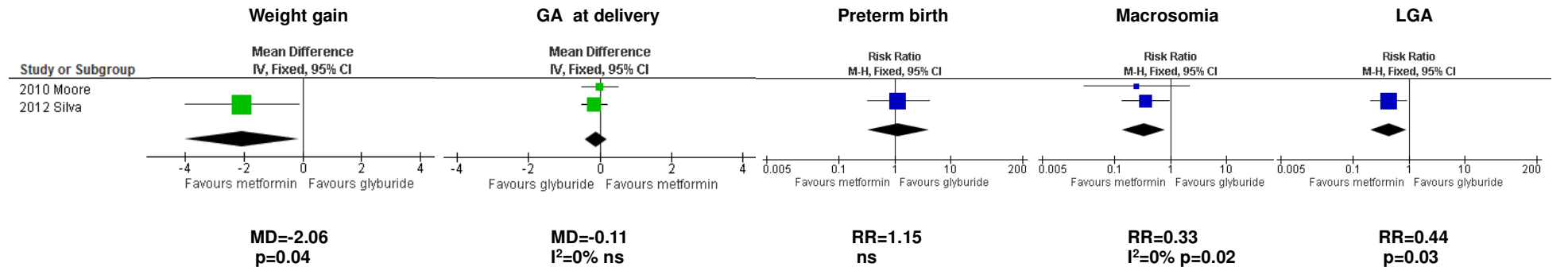
A) Glyburide vs Insulin



B) Metformin vs Insulin



C) Metformin vs Glyburide



*Forest plots for birthweight and any neonatal hypoglycemia are depicted in figures 1 and 2 of the main text

Supplementary table 4. Baseline patient characteristics in randomized controlled trials comparing glyburide or metformin vs insulin or vs each other in women with gestational diabetes mellitus

		Number of studies	Number of patients treated with glyburide	Number of patients treated with insulin	Mean difference	Relative risk	P	I ²
Glyburide vs Insulin	Maternal age (years)	6	346	355	-0.32 (-1.09 to 0.45)	-	0.46	24
	Prepregnancy BMI (Kg/m ²)	5	161	169	0.43 (-0.64 to 1.50)	-	0.43	6
	Gestational age at entry (weeks)	7	394	404	0.59 (-0.03 to 1.20)	-	0.06	22
	Fasting plasma glucose at OGTT (mmol/l)	3	290	293	-0.21* (-0.53 to 0.12)	-	0.21	71
	2h postprandial glucose at OGTT (mmol/l)	3	290	293	-0.21* (-0.83 to 0.41)	-	0.50	62
	HbA _{1c} at entry (%)	5	330	336	-0.38* (-0.88 to 0.11)	-	0.13	90
	Number of prior pregnancies (per patient)	1	32	36	-0.40 (-1.20 to 0.40)	-	0.33	-
	% of prior pregnancies	2	73	73	-	1.17* (0.38 to 3.63)	0.79	81
Metformin vs Insulin	Maternal age (years)	6	678	684	0.01 (-0.55 to 0.58)	-	0.97	0
	Prepregnancy BMI (Kg/m ²)	6	596	618	0.78 (0.15 to 1.41)	-	0.01	0
	Gestational age at entry (weeks)	6	678	684	0.01 (-0.31 to 0.32)	-	0.97	0
	Fasting plasma glucose at OGTT (mmol/l)	4	558	567	-0.0 (-0.15 to 0.02)	-	0.12	31
	2h postprandial glucose at OGTT (mmol/l)	4	557	556	0.11* (-0.26 to 0.49)	-	0.55	58
	HbA _{1c} at entry (%)	5	628	602	-0.04 (-0.10 to 0.02)	-	0.19	0
	Number of prior pregnancies (per patient)	2	79	81	-0.34 (-1.01 to 0.34)	-	0.33	38
	% of prior pregnancies	5	646	653	-	0.94 (0.83 to 1.07)	0.34	0
Metformin vs Glyburide	Maternal age (years)	2	179	170	1.36 (0.07 to 2.64)	-	0.04	0
	Prepregnancy BMI (Kg/m ²)	2	179	170	0.09 (-1.16 to 1.33)	-	0.89	0
	Gestational age at entry (weeks)	2	179	170	-0.63* (-2.91 to 1.64)	-	0.58	65
	Fasting plasma glucose at OGTT (mmol/l)	1	104	96	0.10 (-0.19 to 0.39)	-	0.49	-
	2h postprandial glucose at OGTT (mmol/l)	1	104	96	0.26 (-0.05 to 0.57)	-	0.10	-
	HbA _{1c} at entry (%)	0	-	-	-	-	-	-
	Number of prior pregnancies (per patient)	1	104	96	0.37 (0.20 to 0.72)	-	0.04	-
	% of prior pregnancies	0	-	-	-	-	-	-

I²=Heterogeneity; BMI=Body mass index; OGTT=Oral glucose tolerance test; HbA_{1c}=Glycated haemoglobin

* Estimated using a random effects model because I²>50%,

Supplementary table 5. Meta-analysis of randomized controlled trials comparing glyburide vs insulin in women with gestational diabetes mellitus· Sensitivity analysis

		Number of studies	Number of patients treated with glyburide	Number of patients treated with insulin	Mean difference	Relative risk	P	I ²
Primary outcomes	End 3rd trimester HbA _{1c} (%)	2	231	233	0.00* (-0.24 to 0.25)	-	0.99	63
	Severe maternal hypoglycaemia (%)	4	277	278	-	Not estimable (0 vs 0)	-	-
	Preeclampsia (%)	3	265	271	-	0.93 (0.51 to 1.68)	0.80	19
	Weight gain (kg)	2	233	239	-0.50 (-1.62 to 0.62)	-	0.38	21
	Caesarean section (%)	3	276	284	-	0.86 (0.68 to 1.10)	0.24	0
	Gestational age at delivery (weeks)	6	384	391	0.05 (-0.18 to 0.28)	-	0.69	14
	Preterm birth (%)	4	306	312	-	0.84 (0.55 to 1.29)	0.42	0
	Birth weight (g)	6	384	391	108 (33.2 to 183)	-	0.005	6
	Macrosomia (%)	5	336	342	-	2.62 (1.35 to 5.08)	0.004	34
	Large-for-gestational age (%)	4	304	310	-	2.15* (0.80 to 5.77)	0.13	62
	Small-for-gestational age (%)	3	274	280	-	0.97 (0.51 to 1.85)	0.92	37
	Any neonatal hypoglycaemia (%)	6	377	387	-	2.04 (1.30 to 3.20)	0.002	0
	Perinatal mortality (%)	3	277	287	-	1.45 (0.29 to 7.21)	0.65	0
Secondary outcomes	Fasting blood glucose (mmol/l)	3	274	280	0.06 (-0.06 to 0.19)	-	0.33	0
	Postprandial blood glucose (mmol/l)	3	274	280	0.07 (-0.11 to 0.25)	-	0.46	0
	Weight gain since entry (kg)	0	-	-	-	-	-	-
	Pregnancy-induced hypertension (%)	0	-	-	-	-	-	-
	Induction (%)	0	-	-	-	-	-	-
	Cord C-peptide (nmol/l)	1	31	28	0.07 (-0.14 to 0.27)	-	0.53	-
	Cord insulin (pmol/l)	2	232	231	-3.68 (-24.5 to 17.2)	-	0.73	0
	1 min Apgar <7 (%)	0	-	-	-	-	-	-
	5 min Apgar <7 (%)	0	-	-	-	-	-	-
	Obstetric trauma (%)	0	-	-	-	-	-	-
	Severe neonatal hypoglycaemia [†] (%)	2	72	77	-	5.31 (0.63 to 44.9)	0.13	0
	Neonatal jaundice (%)	3	262	265	-	1.72 (0.75 to 3.94)	0.20	0
	Neonatal respiratory distress syndrome (%)	2	231	233	-	0.61 (0.19 to 1.92)	0.39	0
	Stillbirth (%)	4	307	313	-	1.32 (0.33 to 5.22)	0.70	0
	Neonatal mortality (%)	2	244	251	-	1.01 (0.06 to 16.0)	0.99	-
NICU admission (%)	4	302	306	-	0.97 (0.56 to 1.69)	0.92	0	

I²=Heterogeneity; HbA_{1c}= Glycated haemoglobin

* Estimated using a random effects model because I²>50%

† Defined by authors or requiring intravenous glucose and/or NICU admittance

Supplementary table 6. Meta-analysis of randomized controlled trials comparing metformin vs insulin in women with gestational diabetes. Sensitivity analysis

		Number of studies	Number of patients treated with metformin	Number of patients treated with insulin	Mean difference	Relative risk	P	I ²
Primary outcomes	End 3rd trimester HbA _{1c} (%)	4	508	533	-0.04 (-0.09 to 0.02)	-	0.21	24
	Severe maternal hypoglycaemia (%)	3	236	237	Not estimable (0 vs 0)	-	-	-
	Preeclampsia (%)	5	646	653	-	0.82 (0.56 to 1.20)	0.32	0
	Weight gain (kg)	4	468	505	-1.14* (-2.22 to -0.06)	-	0.04	64
	Caesarean section (%)	5	646	653	-	0.99 (0.86 to 1.14)	0.86	23
	Gestational age at delivery (weeks)	5	646	653	-0.16 (-0.30 to -0.02)	-	.03	0
	Preterm birth (%)	5	646	653	-	1.50 (1.04 to 2.16)	0.03	0
	Birth weight (g)	5	646	653	-31.0 (-86.8 to 24.8)	-	0.28	23
	Macrosomia (%)	5	646	653	-	0.99 (0.75 to 1.31)	0.93	22
	Large-for-gestational age (%)	5	646	653	-	0.88 (0.69 to 1.11)	0.28	22
	Small-for-gestational age (%)	5	646	653	-	0.88 (0.58 to 1.33)	0.53	0
	Any neonatal hypoglycaemia (%)	5	645	653	-	0.79 (0.61 to 1.03)	0.09	0
	Perinatal mortality (%)	4	600	607	-	1.00 (0.14 to 7.12)	0.99	0
	Secondary outcomes	Fasting blood glucose (mmol/l)	3	489	496	0.06 (-0.01 to 0.13)	-	0.12
Postprandial blood glucose (mmol/l)		3	489	496	-0.12* (-0.28 to 0.04)	-	00.14	59
Weight gain since entry (kg)		4	565	533	-1.23* (-1.72 to -0.73)	-	<0.001	61
Pregnancy-induced hypertension (%)		3	553	557	-	0.53 (0.31 to 0.90)	0.02	0
Induction (%)		3	520	527	-	0.91 (0.81 to 1.02)	0.11	46
Cord C-peptide (nmol/l)		0	-	-	-	-	-	-
Cord insulin (pmol/l)		1	220	234	7.64 (-92.7 to 108)	-	0.88	-
1 min Apgar <7 (%)		0	-	-	-	-	-	-
5 min Apgar <7 (%)		1	363	370	-	3.06 (0.32 to 29.3)	0.33	-
Obstetric trauma (%)		2	472	477	-	0.86 (0.45 to 1.63)	0.64	2
Severe neonatal hypoglycaemia [†] (%)		3	519	527	-	0.62 (0.42 to 0.94)	0.02	48
Neonatal jaundice (%)		5	645	653	-	0.93 (0.67 to 1.28)	0.66	0
Neonatal respiratory distress syndrome (%)		4	598	603	-	1.21 (0.62 to 2.37)	0.57	0
Stillbirth (%)		4	600	607	-	1.00 (0.14 to 7.12)	0.99	0
Neonatal mortality (%)		4	599	606	-	Not estimable (0 vs 0)	-	-
NICU admission (%)		4	599	607	-	0.89 (0.71 to 1.10)	0.28	0

I²=Heterogeneity; HbA_{1c}=Glycated haemoglobin

* Estimated using a random effects model because I²>50%

† Defined by authors or requiring intravenous glucose and/or NICU admittance