The 2023 Digital Learning Journey on Diabetes and Thyroid Disorders

Clinical considerations of endocrine disorders in pregnancy: from planning through birth

Novelties in the management of gestational diabetes

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SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

Disclosure

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The Metformin in Gestational Diabetes (MiG) trial

- Prospective randomized
- Open-label
- Metformin vs Insulin
- Multinational
- Multicentre
- N. 751
- At 20 to 33 weeks of gestation

Metformin Group (N = 363) Age 33.5±5.4

Insulin Group (N = 370) Age 33.0±5.1
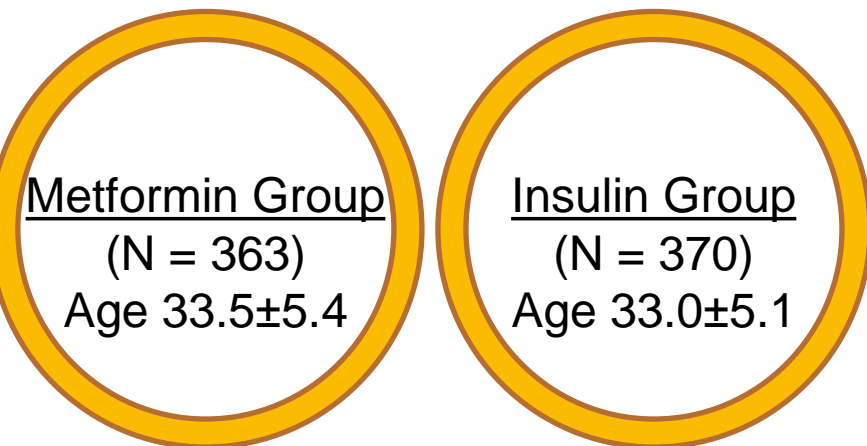
Primary Outcome: a composite of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar score less than 7, or prematurity.

Outcome	Metformin Group (N=363)	Insulin Group (N=370)	Relative Risk (95% CI)	P Value
	no. (%)			
Primary composite outcome	116 (32.0)	119 (32.2)	0.99 (0.80–1.23)	0.95
Recurrent blood glucose level <46.8 mg/dl†	55 (15.2)	69 (18.6)	0.81 (0.59–1.12)	0.21
Any blood glucose level <28.8 mg/dl	12 (3.3)	30 (8.1)	0.41 (0.21–0.78)	0.008
Respiratory distress‡	12 (3.3)	16 (4.3)	0.76 (0.37–1.59)	0.47
Transient tachypnea	7 (1.9)	8 (2.2)		
Respiratory distress syndrome	4 (1.1)	5 (1.4)		
Sepsis	1 (0.3)	5 (1.4)		
Pulmonary hypertension	0	2 (0.5)		
Phototherapy	29 (8.0)	31 (8.4)	0.95 (0.59–1.55)	0.85
Birth trauma§	16 (4.4)	17 (4.6)	0.96 (0.49–1.87)	0.90
Mild	16 (4.4)	15 (4.1)		
Moderate or severe	0	2 (0.5)		
5-Min Apgar score <7¶	3 (0.8)	1 (0.3)	3.06 (0.32–29.26)	0.37
Preterm birth (<37 wk of gestation)	44 (12.1)	28 (7.6)	1.60 (1.02–2.52)	0.04
Iatrogenic (indicated)	18 (5.0)	13 (3.5)	1.41 (0.70–2.84)	0.33
Spontaneous	26 (7.2)	15 (4.1)	1.77 (0.95–3.28)	0.07
Additional neonatal complications				
Admission to level 2 or 3 neonatal intensive care unit	68 (18.7)	78 (21.1)	0.89 (0.66–1.19)	0.43
>24-Hr stay in neonatal intensive care unit	46 (12.7)	45 (12.2)	1.04 (0.71–1.53)	0.83
	mean ±SD			
pH of umbilical-cord or scalp blood‖	7.27±0.07	7.26±0.07		0.32

Rowan JA et al,   N Engl J Med. 2008

The Metformin in Gestational Diabetes (MiG) trial

Maternal Outcomes

Variable	Metformin Group (N=363)	Insulin Group (N=370)	P Value
Glycemic control from randomization until delivery			
Capillary glucose level after an overnight fast — mg/dl	93.6±10.8	91.8±12.6	0.24
2-Hr postprandial capillary glucose level — mg/dl	111.6±10.8	115.2±16.2	0.003
Glycemic control at 1 week after randomization			
Capillary glucose level after an overnight fast — mg/dl	100.8±16.2	99.0±18.0	0.31
Postprandial capillary glucose level — mg/dl	117.0±16.2	120.6±18.0	0.006
Glycemic control during the last 2 wk before delivery			
Capillary glucose level after an overnight fast — mg/dl	90.0±10.8	88.2±12.6	0.16
2-Hr postprandial capillary glucose — mg/dl	109.8±12.6	111.6±18.0	0.19
Glycated hemoglobin at wk 36–37 — %§§	5.6±0.5	5.7±0.6	0.25
Plasma glucose level at wk 36–37 after an overnight fast — mg/dl¶¶	81.0±10.8	79.2±12.6	0.10
Capillary glucose level 12 hr before delivery — mg/dl‖‖	97.2±10.8	95.4±16.2	0.35
Hypertensive complications — no. (%)***			
Gestational hypertension	14 (3.9)	23 (6.2)	0.14
Preeclampsia	20 (5.5)	26 (7.0)	0.40
Weight change — kg			
Loss from enrollment to postpartum visit ¶¶¶	8.1±5.1	6.9±5.3	0.006
Gain from early pregnancy to enrollment‖‖‖	7.0±5.4	6.4±5.5	0.20
Gain from enrollment to 36 or 37 wk of gestation****	0.4±2.9	2.0±3.3	<0.001

Results of Questionnaire on Acceptability of Treatment

Question	Metformin Group (N=334) no. (%)	Insulin Group (N=331) no. (%)	P Value
How often did you forget to take your medication?†			<0.001
Never or rarely	231 (69.4)	267 (80.7)	
1–3 times/wk	81 (24.3)	52 (15.7)	
4–6 times/wk	12 (3.6)	2 (0.6)	
>6 times/wk	9 (2.7)	10 (3.0)	
Which medication would you choose in another pregnancy?			<0.001
Metformin tablets	256 (76.6)	127 (38.4)	
Insulin injections	42 (12.6)	90 (27.2)	
Not sure	36 (10.8)	114 (34.4)	
In another pregnancy, if you were told you were likely to need insulin injections to control the sugar levels but could try metformin first, what would you prefer?			<0.001
Start with metformin and add insulin if needed	270 (80.8)	179 (54.1)	
Go straight to insulin injections	36 (10.8)	94 (28.4)	
Not sure	28 (8.4)	58 (17.5)	
Which part of your diabetes treatment was the easiest?			<0.001
Doing finger-prick tests	74 (22.2)	119 (36.0)	
Being careful with diet	63 (18.9)	95 (28.7)	
Taking medication	197 (59.0)	117 (35.3)	
Which part of your diabetes treatment was the hardest?			0.001
Doing finger-prick tests	123 (36.8)	91 (27.5)	
Being careful with diet	176 (52.7)	150 (45.3)	
Taking medication	35 (10.5)	90 (27.2)	

Rowan JA et al, : N Engl J Med. 2008

Metformin in gestational diabetes: the offspring follow-up (MiG TOFU)

- Longitudinal follow-up study of the offspring of women with GDM
- Metformin vs Insulin
- Multicentre
- N. 502

Adelaide Group (N = 109) Mean age 7

Auckland Group (N = 99) Mean age 9

Metformin Group (N = 58)

Insulin Group (N = 51)

Metformin Group (N = 45)

Insulin Group (N = 54)
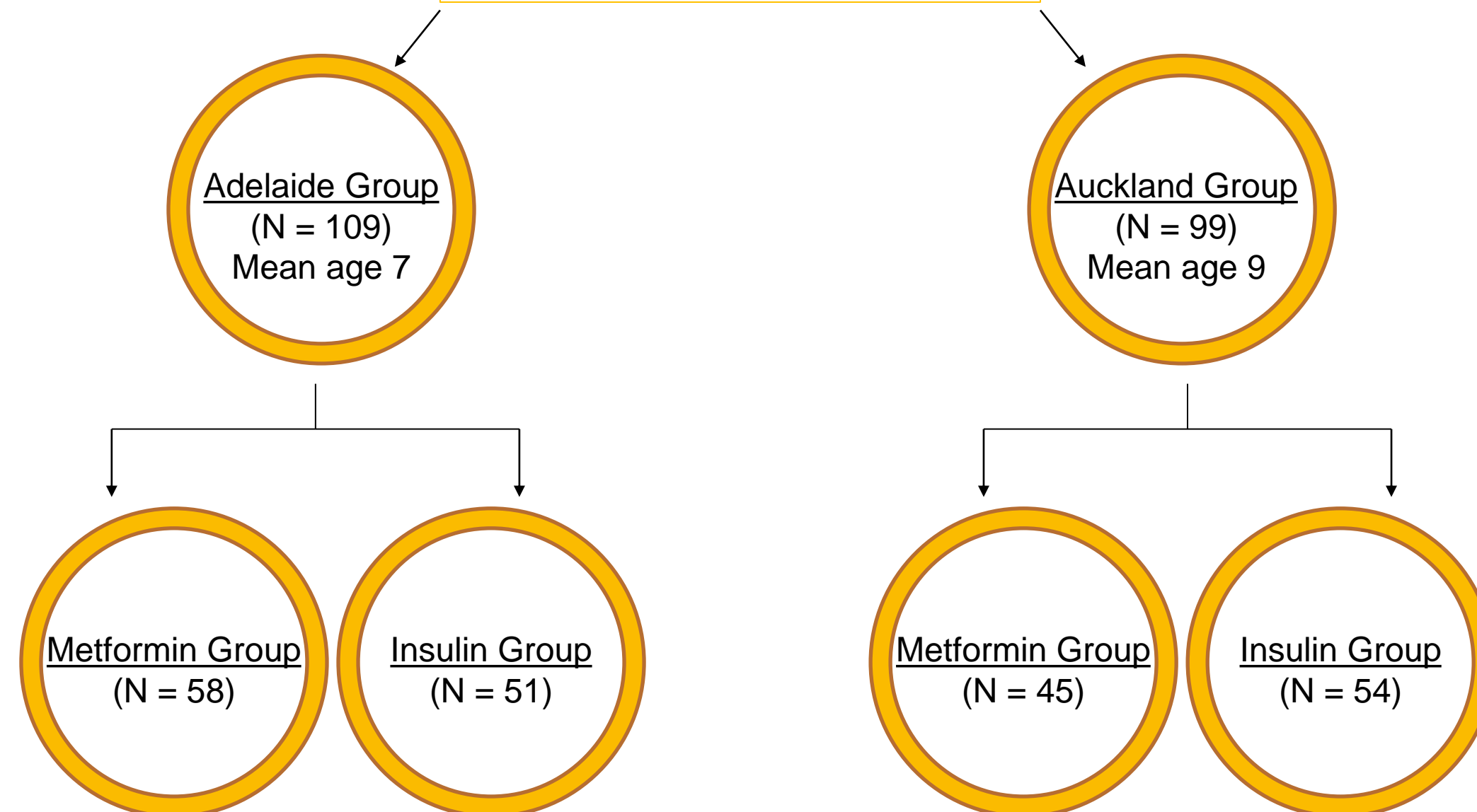
Objective: to compare body composition and metabolic outcomes at 7–9 years in offspring of women with GDM randomized to metformin (±insulin) or insulin treatment during pregnancy.

Children were assessed by anthropometry, BIA, DEXA, MRI and fasting blood

Rowan JA et al. BMJ Open Diabetes Res Care. 2018.

Metformin in gestational diabetes: the offspring follow-up (MiG TOFU)

Children outcomes

	Subgroup seen at 7 years (Adelaide) n=109			Subgroup seen at 9 years (Auckland) n=99		
	Metformin n=58	Insulin n=51	P values	Metformin n=45	Insulin n=54	P values
Age (years)	7.0±1.0	7.4±1.1	0.02	8.9±0.5	8.9±0.4	0.23
Male/female (n)	35/23	23/28	0.16	28/17	28/26	0.32
Weight (kg)	26.9±5.2	26.3±4.9	0.59	37.0±12.6	32.7±7.7	0.049
Height (cm)	124.5±5.2	124.5±5.0	0.99	137.5±7.4	135.4±6.6	0.13
BMI (kg/m²)	17.2±2.5	16.9±2.5	0.48	19.3±4.6	17.7±3.0	0.051
Leg length (cm)	55.8±7.7	57.5±3.1	0.13	63.6±4.2	63.9±4.1	0.70
Head circumference (cm)	52.2±1.2	51.9±1.5	0.24	53.6±2.2	53.1±1.8	0.23
Chest circumference (cm)	63.5±6.0	63.1±5.0	0.66	70.4±10.2	67.7±8.0	0.16
Mid-upper arm circumference (cm)	19.7±2.4	19.5±2.3	0.54	23.0±4.3	21.2±2.9	0.02
Waist circumference (cm)	60.2±6.7	59.5±6.1	0.57	69.1±12.2	64.2±8.4	0.04
Hip circumference (cm)	67.6±6.4	67.7±5.7	0.90	77.6±11.1	74.7±7.1	0.16
Waist:height ratio	0.48±0.05	0.48±0.04	0.54	0.51±0.08	0.47±0.05	0.02
Triceps skinfold thickness (mm)	11.4±4.3	11.4±4.0	0.997	19.5±9.0	16.2±6.7	0.05
Subscapular skinfold thickness (mm)	8.0±5.6	7.5±5.3	0.65	13.1±9.6	10.5±6.8	0.14
Biceps skinfold thickness (mm)	6.9±3.8	6.7±2.8	0.72	13.9±7.5	11.8±5.9	0.14
DXA	n=32	n=29		n=45	n=53	
Fat-free mass (g)	19702±2564	19271±2532	0.51	24385±5894	22511±3689	0.07
Total fat (g)	7651±3906	7987±3339	0.72	12550±7214	10281±4550	0.07
Abdominal fat (g)	423±384	430±315	0.93	774±681	548±413	0.056
Thigh fat (g)	1252±618	1323±618	0.63	1983±1122	1655±710	0.10

	Subgroup seen at 7 years (Adelaide) n=109			Subgroup seen at 9 years (Auckland) n=99		
	Metformin n=58	Insulin n=51	P values	Metformin n=45	Insulin n=54	P values
Arm fat (g)	1079±492	1103±422	0.84	1568±801	1285±534	0.047
Abdominal fat:thigh fat ratio	0.30±0.11	0.30±0.10	0.99	0.34±0.13	0.30±0.09	0.15
Total fat %	26.8±7.6	28.5±6.8	0.37	32.0±8.5	30.3±6.6	0.28
Abdominal fat % of abdominal mass	21.3±11.8	22.4±10.5	0.71	29.7±14.4	26.6±10.5	0.24
Bioimpedance	n=56	n=51				
Fat-free mass (kg)	21.5±2.8	20.7±3.0	0.34	27.7±7.7	25.1±5.2	0.065
Total fat %	18.8±7.9	20.8±5.4	0.13	23.6±8.1	22.3±8.9	0.43
MRI – abdomen	n=7 Age:10.0±0.14 years	n=5 Age:10.0±0.08 years		n=42	n=50	
Abdominal fat volume (cm³)	2720±1786	1843±724	0.27	4172±2964	3120±1898	0.051
Abdominal fat % of abdominal volume	27.6±11.2	23.5±9.5	0.50	36.0±14.4	32.2±10.9	0.16
Abdominal subcutaneous fat volume (cm³)	1807±1468	1092±618	0.28	3231±2412	2398±1566	0.059
Abdominal subcutaneous fat %	17.5±9.6	14.1±8.6	0.54	27.6±12.3	24.4±9.7	0.18
Abdominal visceral fat volume (cm³)	913±610	752±221	0.54	941±629	722±365	0.051
Abdominal visceral fat %	10.1±4.8	9.3±1.2	0.69	8.5±3.1	7.7±1.9	0.19

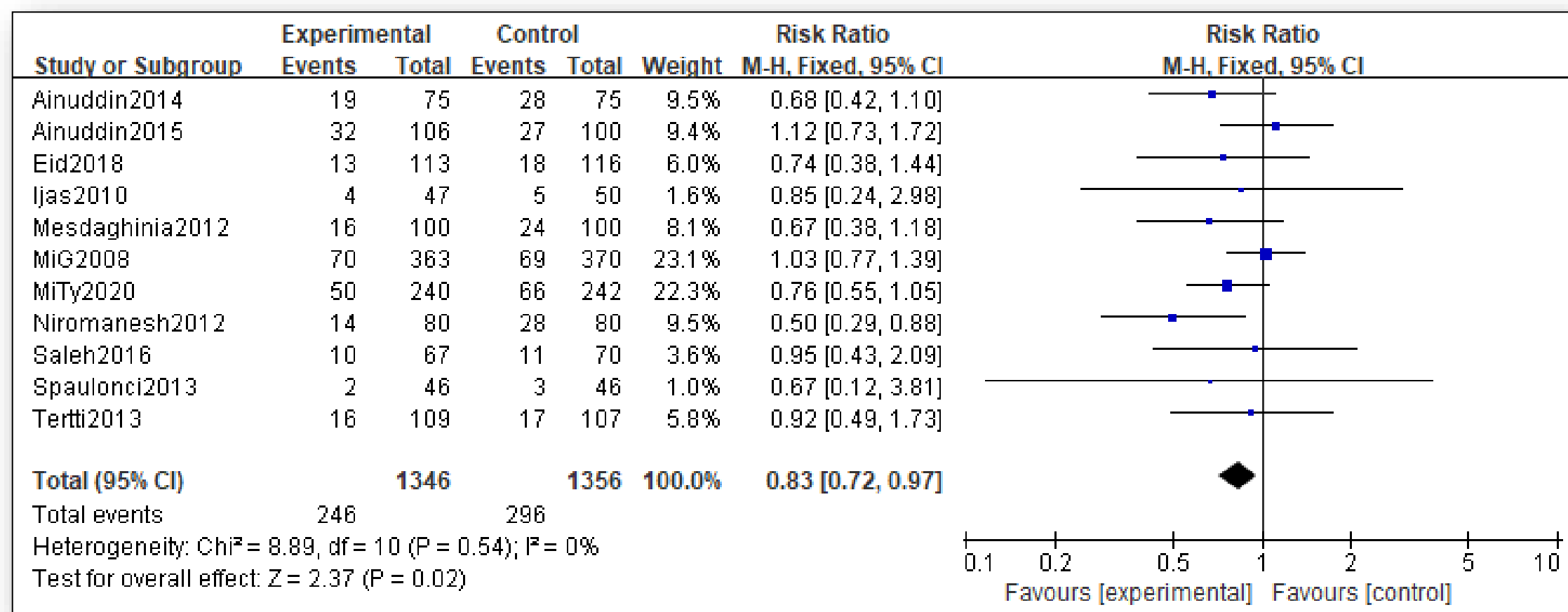Rowan JA et al. BMJ Open Diabetes Res Care. 2018.

The efficacy and safety of metformin in pregnancy of GDM or T2DM: a meta-analysis of 21 controlled trials
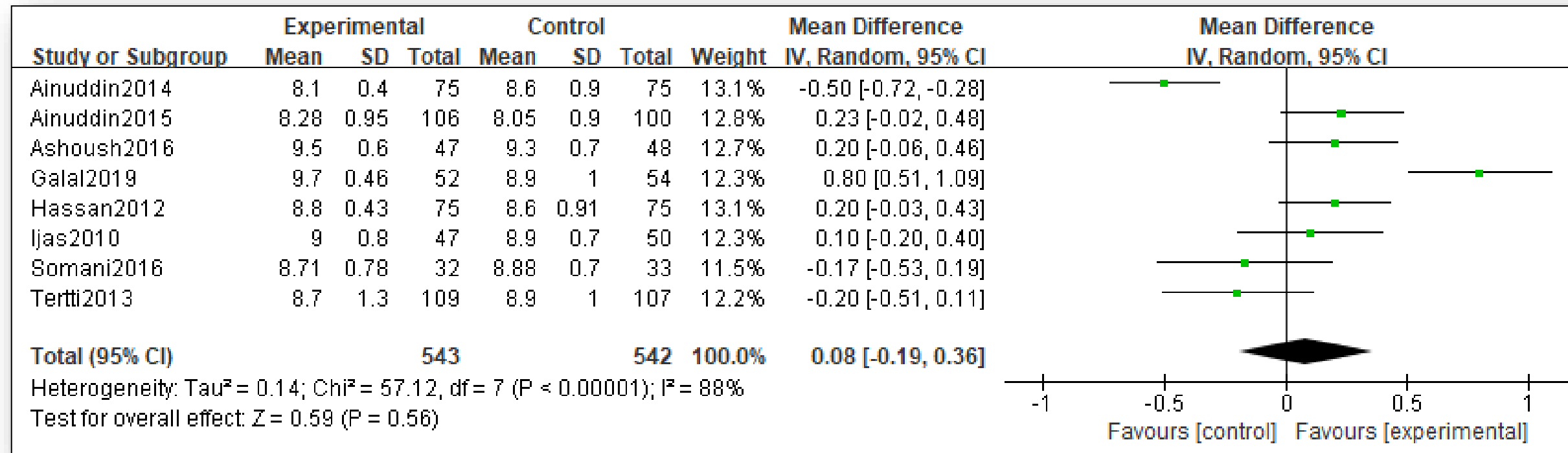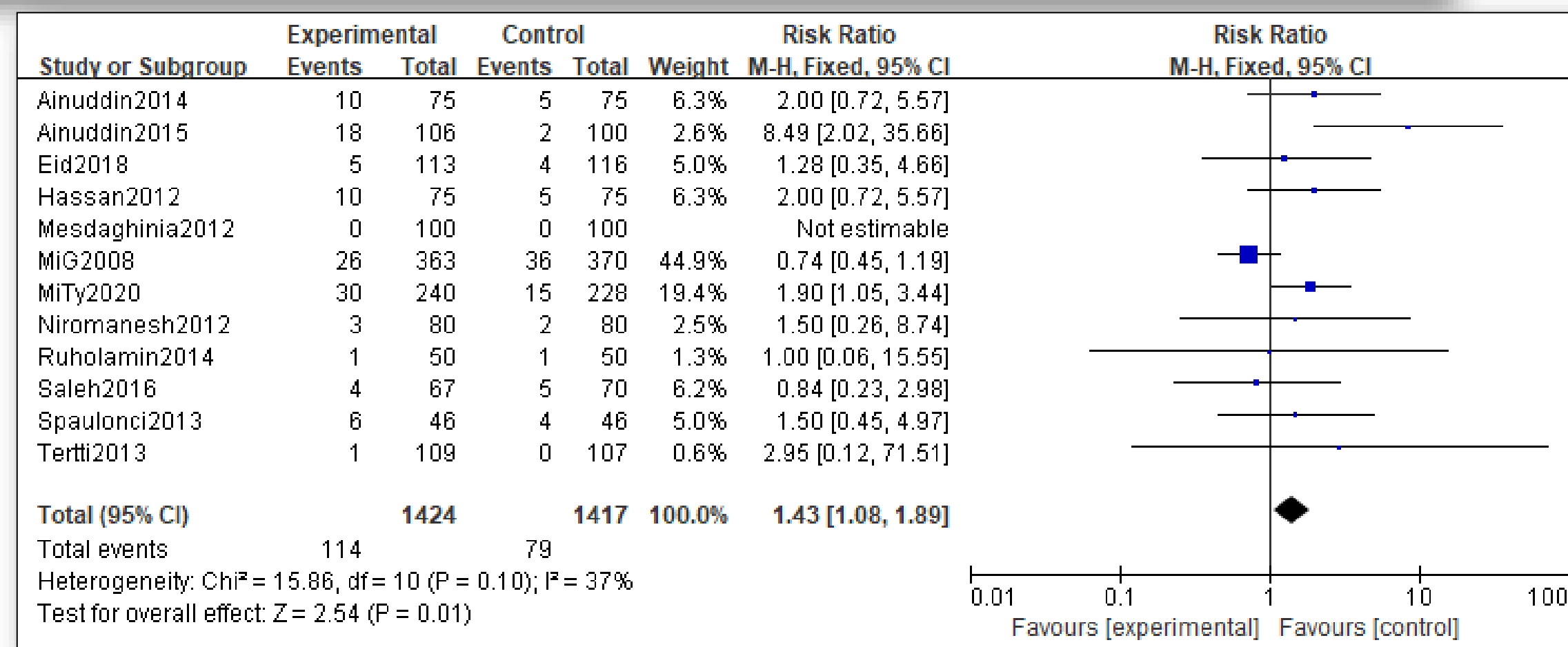

Mean difference for 5-min Apgar score between the metformin and insulin arms
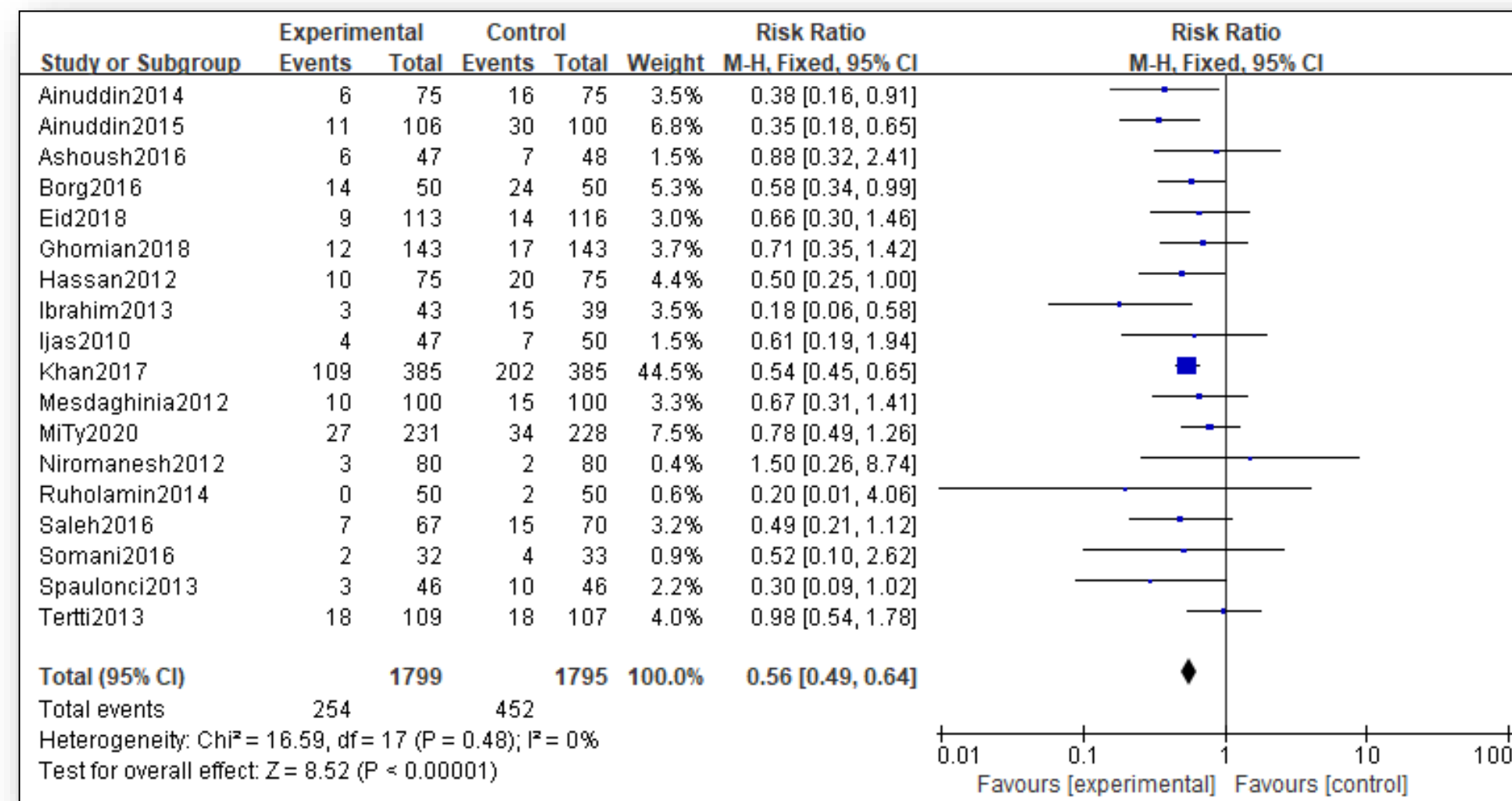
Risk ratio for neonatal hypoglycaemia between the metformin and insulin arms
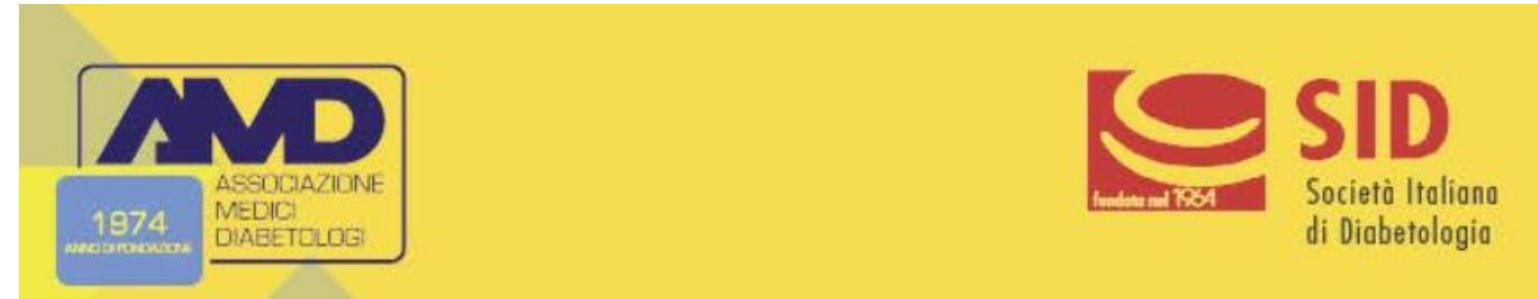
He K et al. J Clin Pharm Ther. 2022

Metformin

Risk ratio for large for gestational age (LGA>P90) between the metformin and insulin arms

Risk ratio for small for gestational age (SGA<P10) between the metformin and insulin arms

He K et al. J Clin Pharm Ther. 2022

Consensus positions

Pregnancy complicated by GDM	Metformin use could be a valid therapeutic option in obese GDM women to reduce GWG. In women with severe obesity metformin may reduce the insulin dose and the GWG.

American Diabetes Association® **Diabetes Care**

15.15 Insulin is the preferred medication for treating hyperglycemia in gestational diabetes mellitus. Metformin and glyburide should not be used as first-line agents, as both cross the placenta to the fetus. **A** Other oral and noninsulin injectable glucose-lowering medications lack long-term safety data.

Nuha A. et al. *Diabetes Care* 1 January 2023; (Supplement_1): S254–S266.
Laura Sciacca et al. Position paper of the Italian Association of Clinical Diabetologists (AMD), Italian Society of Diabetology (SID), and the Italian Study Group of Diabetes in Pregnancy. Metformin use in pregnancy. (2023).
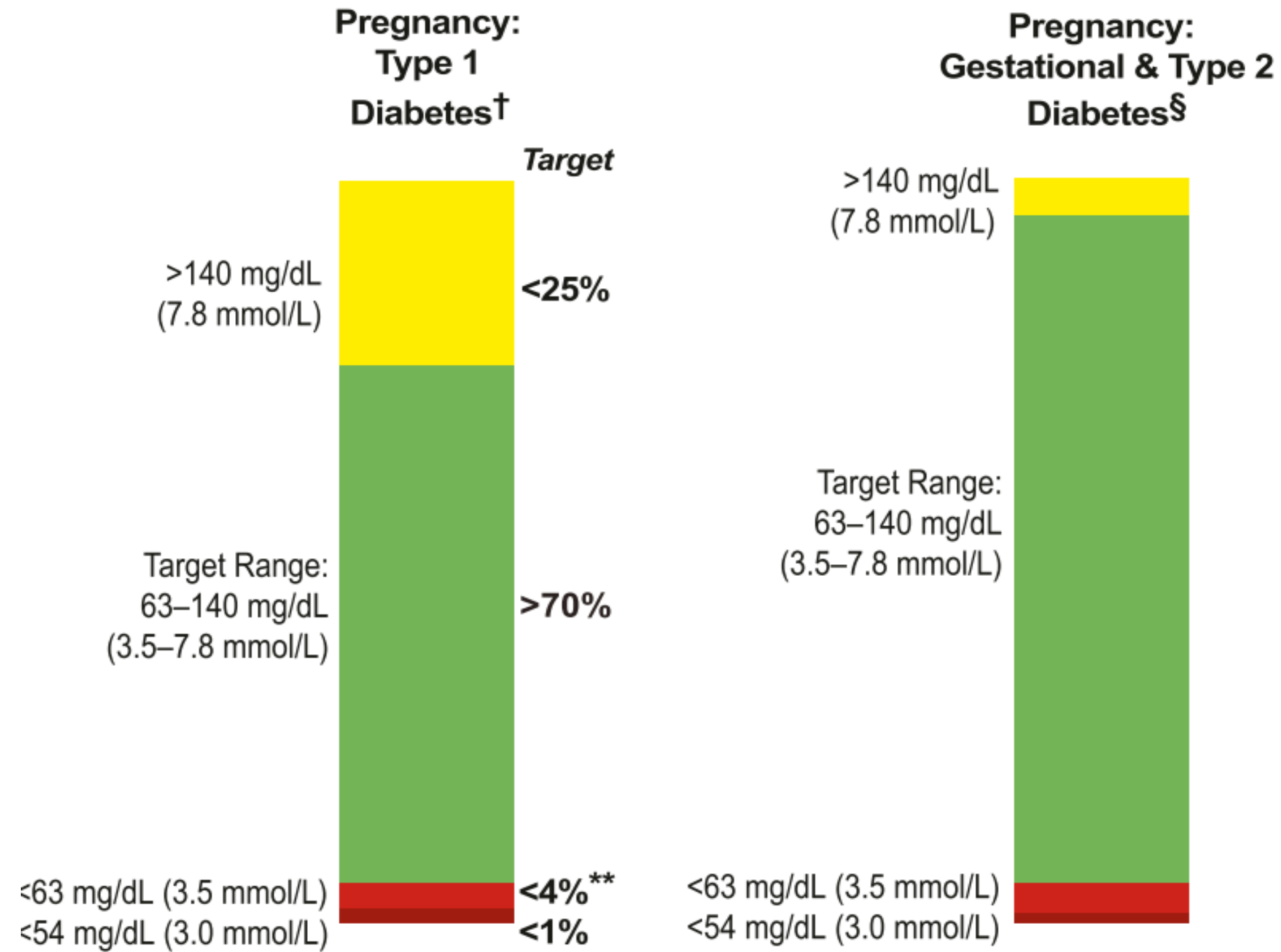
	CGM	Control	p value
Maternal outcomes			
Number assessed	100	102	..
Hypertensive disorders	18 (18%)	28 (27%)	0·13
Worsening chronic	2 (2%)	4 (4%)	0·68
Gestational	8 (8%)	9 (9%)	1·0
Pre-eclampsia	9 (9%)	18 (18%)	0·10
Caesarean section	63 (63%)	74 (73%)	0·18
Maternal weight gain (kg)*			
Entry to 34 weeks	13·1 (9·9–16·6)	13·7 (10·9–17·6)	0·22
From 16 to 34 weeks	8·9 (6·6–11·3)	9·7 (8·3–11·8)	0·09
Maternal length of stay (days)	3·5 (2·6–5·3)	4·2 (2·9–6·8)	0·10
Neonatal outcomes			
Number assessed	105	106	..
Pregnancy loss <20 weeks	5 (5%)	4 (4%)	1·0
Stillbirth	0	1	..
Termination	0	1	..
Congenital anomaly†	2	3	..
Preterm births			
Number assessed	100	102	..
Preterm <37 weeks	38 (38%)	43 (42%)	0·57
Early preterm <34 weeks	5 (5%)	11 (11%)	0·19
Gestational age at delivery‡	37·4 (36·7–38·1)	37·3 (36·0–38·0)	0·50
Birthweight			
Number assessed	100	100	..
Birthweight (g)	3545·4 (649·0)	3582·(777·0)	0·37
Median customised centile¶	92 (68–99)	96 (84–100)	0·0489
Small for gestational age (<tenth centile)	2 (2 %)	2 (2%)	1·0
Large for gestational age (>90th centile)	53 (53%)	69 (69%)	0·0210
Extremely large for gestational age (>97·7th centile)	36 (36%)	44 (44%)	0·31
Macrosomia (≥4000 g)	23 (23%)	27 (27%)	0·62
Neonatal complications			
Number assessed	100	100	..
Birth injury	1 (1%)	0	1·0
Shoulder dystocia	1 (1%)	0	1·0
Neonatal hypoglycaemia requiring intravenous dextrose	15 (15%)	28 (28%)	0·0250
Hyperbilirubinaemia	25 (25%)	31 (31%)	0·43
Respiratory distress	9 (9%)	9 (9%)	1·0
High-level neonatal care (NICU) >24 h	27 (27%)	43 (43%)	0·0157
Infant length of hospital stay	3·1 (2·1–5·7)	4·0 (2·4–7·0)	0·0091
Composite neonatal outcome¶	45 (42·9%)	56 (52·8%)	0·17

Multicentre, open-label, randomised controlled trial
N:325 women randomized 1:1 to CGM in addition to capillary glucose monitoring or capillary glucose monitoring alone.

Primary outcome: change in HbA1c%
Secondary outcome: Obstetric and neonatal parameters

Feig DS et al. Lancet Diabetes Endocrinol 2017

CGM-based targets for diabetes in pregnancy

Battelino T et al, Diabetes Care 2019

Conclusions

- The use of metformin could be a valid therapeutic option in women with GDM, particularly if affected by pre-gestational obesity.

- Women treated with metformin during pregnancy have better glycemic control, minor insulin requirements, and less gain pregnancy weight.

- Women prefer metformin therapy to insulin injection.

- Metformin appears to reduce the risk of LGA, birth weight >4000 g, neonatal hypoglycemia and ICU admissions.

- Metformin may increase the risk of SGA.

- CGM should be suggested to all women with T1D in pregnancy

Back up slides

Risk of the primary long-term outcomes by exposure group

- Register-based cohort study
- Metformin vs Insulin vs Combination
- Multicentre
- N. 10.129

Metformin Group (N = 3.967)

Insulin Group (N = 5.273)

Combination Group (N = 889)

Primary outcome: long-term offspring obesity, hypoglycemia, hyperglycemia, diabetes, hypertension, polycystic ovary syndrome, and challenges in motor–social development

Outcome	Metformin (n=3967) Events* No.	%	OR (95% CI) Unadjusted	IPTW weighted‡	Combination treatment (n=889) Events* No.	%	OR (95% CI)† Unadjusted	IPTW weighted‡	Insulin (reference) (n=5273) Events* No.	%
LGA	159	4.0	0.63 (0.52 to 0.76)	0.82 (0.67 to 0.99)	104	11.7	2.00 (1.58 to 2.52)	1.58 (1.22 to 2.05)	328	6.2
SGA	92	2.3	1.93 (1.40 to 2.67)	1.65 (1.16 to 2.34)	15	1.7	1.40 (0.79 to 2.46)	1.21 (0.65 to 2.28)	64	1.2
Preterm birth	265	6.7	1.28 (1.07 to 1.52)	1.10 (0.91 to 1.31)	80	9.0	1.76 (1.36 to 2.28)	1.46 (1.10 to 1.95)	280	5.3
Neonatal mortality	5	0.1	2.22 (0.53 to 9.28)	1.30 (0.25 to 6.70)	3	0.3	5.95 (1.20 to 29.52)	1.31 (0.09 to 19.91)	3	0.1
Neonatal hypoglycemia	694	17.5	0.74 (0.67 to 0.82)	0.80 (0.72 to 0.89)	272	30.6	1.54 (1.32 to 1.80)	1.29 (1.09 to 1.53)	1173	22.3
Neonatal hyperglycemia	5	0.1	6.65 (0.78 to 56.97)	9.66 (0.72 to 130.37)	0	0.0	NA	NA	1	<0.1
Any major congenital anomaly	151	4.5	0.90 (0.73 to 1.11)	0.79 (0.63 to 0.99)	35	5.1	1.03 (0.71 to 1.48)	0.75 (0.50 to 1.14)	242	4.9

Brand KMG, BMJ Open Diabetes Res Care 2022

Risk of adverse outcomes at birth by exposure group

Outcome	Metformin (n=3967)				Combination treatment (n=889)				Insulin (reference) (n=5273)	
	Events*		OR (95% CI)		Events*		OR (95% CI)†		Events*	
	No.	%	Unadjusted	IPTW weighted‡	No.	%	Unadjusted	IPTW weighted‡	No.	%
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Metformin in women with type 2 diabetes in pregnancy (MiTy)

- Randomized
- Double masked
- Placebo controlled
- Multinational
- Multicentre
- N. 502 (age 18 – 45)
- 6 weeks of gestation

Metformin Group (N = 253)

Placebo Group (N = 249)

Primary outcome: pregnancy loss, preterm birth (<37 weeks' gestation), birth injury, moderate or severe respiratory distress syndrome, neonatal hypoglycemia, and NICU admission lasting >24 h; appendix p 34).

	Metformin (n=240)	Placebo (n=242)	p value	Effect size (95% CI)
Composite primary outcome*	94/233 (40%)	95/240 (40%)	0·86	RR 1·02 (0·83 to 1·26)
Pregnancy loss†	13/227 (6%)	14/236 (6%)	0·81	RR 0·96 (0·46 to 2·01)
Spontaneous abortion or miscarriage	4 (2%)	4 (2%)	0·97	RR 0·98 (0·25 to 3·79)
Stillbirth (≥20 weeks gestation)‡	2 (<1%)	7 (3%)	0·11	RR 0·28 (0·06 to 1·32)
Termination	2 (<1%)	2 (<1%)	0·84	RR 0·82 (0·12 to 5·5)
Neonatal death <28 days§	5/227 (2%)	1/236 (<1%)	0·14	RR 4·96 (0·61 to 40·63)
Livebirths	232	229	..	..
Preterm birth <37 weeks	60 (26%)	47 (21%)	0·16	RR 1·27 (0·91 to 1·77)
Birth injury¶	1/231 (<1%)	3/228 (1%)	0·37	RR 0·36 (0·04 to 3·36)
Respiratory distress syndrome¶	11/231 (5%)	8/228 (4%)	0·49	RR 1·36 (0·56 to 3·29)
Neonatal hypoglycaemia¶	27/231 (12%)	34/228 (15%)	0·41	RR 0·82 (0·52 to 1·30)
NICU admission >24 h¶	51/231 (22%)	46/228 (20%)	0·56	RR 1·10 (0·79 to 1·53)
Gestational age at birth, weeks	37·5 (2·2)	37·6 (2·0)	0·33	Difference −0·2 (−0·6 to 0·2)
Birthweight, g	3156 (742)	3375 (742)	0·0016	Difference −0·44 (−0·70 to −0·18)
Birthweight Z score	−0·01 (1·47)	0·45 (1·40)	0·0009	Difference −0·28 (−0·45 to −0·10)
Large for gestational age, >90th centile (adjudicated using Kramer[23])	50 (22%)	66 (29%)	0·067	RR 0·74 (0·54 to 1·02)
Extreme large for gestational age, >97th centile (using Kramer[23])	20 (9%)	34 (15%)	0·041	RR 0·58 (0·34 to 0·97)
Birthweight ≥4000 g	28 (12%)	44 (19%)	0·046	RR 0·65 (0·43 to 0·99)
Small for gestational age, <10th centile (using Kramer[23])‖	30 (13%)	15/228 (7%)	0·026	RR 1·96 (1·10 to 3·64)
Sum of skinfolds, mm**	16·0 (5·0)	17·4 (6·2)	0·024	Difference −1·4 (−2·6 to −0·2)
Neonatal body fat mass††[24]	13·2 (6·2)	14·6 (5·0)	0·017	Difference −1·5 (−2·7 to −0·3)
Cord blood C-peptide (pmol/L)‡‡	673 (435); 569 (360–901)	758 (595); 626 (433–878)	0·10	Ratio of means 0·88 (0·72 to 1·02)
Shoulder dystocia	4 (2%)	4 (2%)	1·0	RR 0·96 (0·25 to 3·69)
				(Table 2 continues on next page)

Birthweight distributions in infants of women in the metformin and placebo groups

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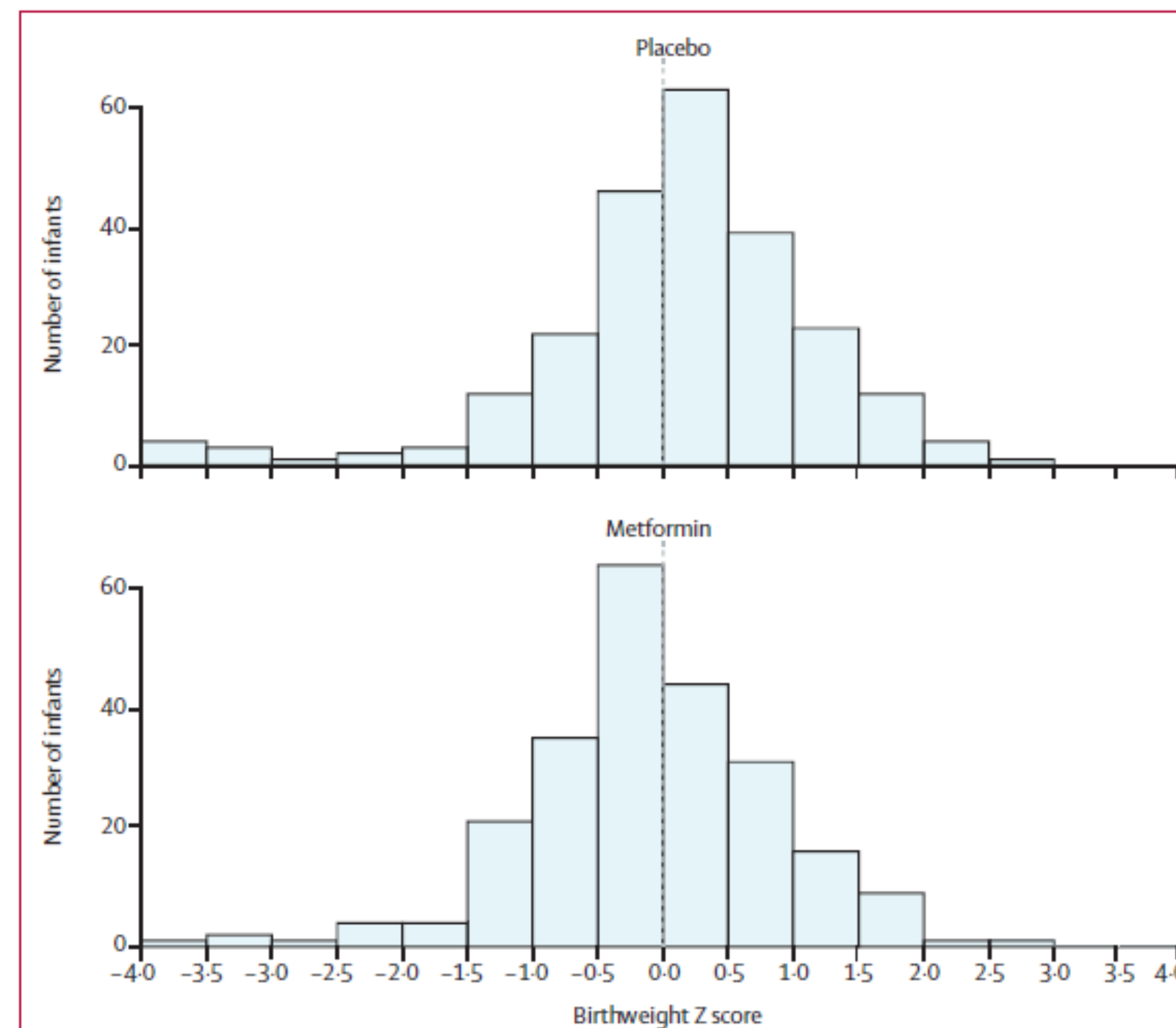
Metformin in women with type 2 diabetes in pregnancy (MiTy)

	Metformin (n=240)	Placebo (n=242)	p value	Effect size (95% CI)
Maternal weight gain, kg*				
Overall weight gain	7·2 (5·3)	9·0 (4·7)	<0·0001	Difference −1·8 (−2·7 to −0·9)
Weekly weight gain	0·4 (0·3)	0·5 (0·3)	<0·0001	Difference −0·10 (−0·15 to −0·05)
Last HbA₁c concentration in pregnancy, mmol/mol†‡	41·0 (8·5)	43·2 (−10)	0·015	Difference −0·18 (−0·33 to −0·03); difference −2·0 (−3·6 to −0·3)
Last HbA₁c concentration in pregnancy, %	5·90% (0·78)	6·10% (0·94)	0·015	Difference −0·18 (−0·33 to −0·03); difference −2·0 (−3·6 to −0·3)
Total insulin dose at 34 or 36 weeks, units per kg per day§	1·1 (1·0)	1·5 (1·1)	<0·0001	Difference −0·4 (−0·5 to −0·2)
Total insulin dose at 34 or 36 weeks, units per day¶	109·8 (105·1)	155·3 (134·0)	<0·0001	Difference −43·9 (−61·5 to −26·2)
Long-acting insulin at 34 or 36 weeks, units per day‖	42·8 (46·0)	55·7 (47·6)	0·004	Difference −12·7 (−21·4 to −4·0)
Short-acting insulin at 34 or 36 weeks, units per day**	66·9 (75·1)	99·1 (108·8)	<0·0001	Difference −32·0 (−49·7 to −14·4)
Caesarean section††	125/234 (53%)	148/236 (63%)	0·031	RR 0·85 (0·73 to 0·99)
Primary caesarean section	65/125 (52%)	68/148 (46%)	0·32	RR 1·13 (0·89 to 1·44)
Any hypertensive disorder‡‡	55 (23%)	56 (23%)	0·93	RR 0·99 (0·72 to 1·35)
Gestational hypertension	13 (5%)	15 (6%)	0·82	RR 0·92 (0·46 to 1·85)
Worsening chronic hypertension during pregnancy§§	20/237 (8%)	22 (9%)	0·68	RR 0·89 (0·51 to 1·56)
Pre-eclampsia	37 (15%)	30 (12%)	0·29	RR 1·27 (0·82 to 1·97)

Maternal outcomes

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Agenda

❑Past and present Management (Timelines)

❑**Novelties:**

Metformin

❑Conclusions

THANK YOU

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