Supplemental Online Content

Boggess KA, Valint A, Refuerzo JS; et al. Metformin plus insulin for preexisting diabetes or gestational diabetes in early pregnancy: the MOMPOD randomized clinical trial. *JAMA*. doi:10.1001/jama.2023.22949

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. MOMPOD Study Sensitivity Analyses

	N	*BMI Imputed Model		Complete Case Model		Unadjusted for Baseline Covariates	
		Odds Ratio (95% CI) Metformin Vs. Placebo	P-value	Odds Ratio (95% CI) Metformin Vs. Placebo	P-value	Odds Ratio (95% CI) Metformin Vs. Placebo	P-value
Sensitivity Analysis 1 Adjusted: Modified intent-to-treat population setting missing primary outcome to event	794	0.86 (0.63, 1.19)	0.36	0.88 (0.63, 1.23)	0.46	--	--
Sensitivity Analysis 2, Unadjusted: Modified intent-to-treat population setting missing primary outcome to event.	794	--	--	--	--	0.861 (0.631, 1.174)	0.34
Sensitivity Analysis 3: Modified intent-to-treat population removing missing primary outcome	768	0.87 (0.63, 1.20)	0.57	0.89 (0.64, 1.24)	0.48	--	--
Sensitivity Analysis 4: Per protocol population setting missing primary outcome to event	560	0.77 (0.52, 1.13)	0.18	0.804 (0.54, 1.19)	0.28	--	--

BMI refers to the maternal baseline body mass index, which was missing in 32 participants. Adjusted models were created with participants missing BMI data excluded and with missing BMI data imputed. Adjusted models adjusted for study site, timing of diabetes diagnosis (preexisting versus during pregnancy), gestational age at randomization stratified at 18 weeks, and baseline maternal BMI as a continuous variable.

eTable 2. Prespecified Subgroup Analyses by Maternal Baseline Variables

	Composite Outcome Event n (%)		
	Metformin (N=397)	**Placebo (N=397)**	**Adjusted OR (95% CI)**
Maternal Baseline BMI[a]			
≥ 30 kg/m^2	219/307 (71.3)	202/274 (73.7)	0.88 (0.61-1.28)
< 30 kg/m^2	54/76 (71.1)	78/105 (74.3)	0.88 (0.45, 1.74)
Missing	7/14 (50.0)	12/18 (66.7)	
Timing of Diabetes Diagnosis[b]			
Preexisting	229/311 (73.6)	244/313 (78.0)	0.78 (0.54, 1.13)
During Pregnancy	51/86 (59.3)	48/84 (57.1)	1.12 (0.60, 2.06)
Gestational Age at Randomization[c]			
18 weeks - < 23 weeks	106/162 (65.4)	113/165 (68.5)	0.89 (0.56-1.43)
10 weeks - < 18 weeks	174/235 (74.0)	179/232 (77.2)	0.84 (0.55-1.29)

Prespecified subgroups include timing of diabetes diagnosis, maternal BMI at randomization, and gestational age at randomization. All odds ratios are shown for metformin versus placebo. The denominator for percent reported is the overall number of subjects within the subgroup assigned to the treatment. All interaction tests resulted in P > 0.10.

[a]Adjusted for timing of timing of diabetes diagnosis (pregestational versus diagnosed early in pregnancy) and gestational age at randomizations stratified at 18 weeks.
[b]Adjusted by gestational age at randomizations stratified at 18 weeks, and baseline maternal BMI as a continuous variable.
[c]Adjusted by timing of diabetes diagnosis (pregestational versus diagnosed early in pregnancy), and baseline maternal BMI as a continuous variable.

eTable 3. Counts of Maternal Serious Adverse Events*

Maternal	Metformin/ Insulin (n=397)	Insulin Alone (n=397)	Unadjusted Rate Difference (%), 95% CI events per pregnancy, metformin – insulin alone
Death	2 (1)	1 (0)	0.25 (-0.60, 1.11)
Any serious maternal adverse event	92	88	1.01 (-4.82, 6.83)
[a]Cardiac/pulmonary/respiratory mediastinal disorders	5	4	0.25 (-1.22, 1.72)
[b]Gastrointestinal/genitourinary	3	6	- 0.76 (-2.23, 0.72)
Hyperglycemia/diabetic ketoacidosis	12	8	1.01 (-1.17, 3.19)
Hypertension	11	9	0.50 (-1.68, 2.68)
Hypoglycemia	1	2	-0.25 (-1.11, 0.60)
[c]Infections	9	17	-2.02 (-4.49, 0.46)
Pregnancy complications Fetal growth restriction [#]HELLP syndrome Oligohydramnios Placental previa with hemorrhage Postpartum hemorrhage Preeclampsia/gestational hypertension Preterm labor Preterm rupture of membranes	56 1 0 1 1 2 48 1 2	47 1 2 1 0 0 36 4 4	2.27 (-2.40, 6.94)
[d]Psychiatric disorders	2	1	0.25 (-0.60, 1.11)
Vaginal bleeding	0	2	-0.50 (-1.20, 0.19)
[e]Other	6	6	0.00 (-1.70, 1.70)

Data presented as number (%) of randomized participants who took at least one dose of study agent. Some participants had more than one serious adverse event and all events are included in counts.
*Serious adverse events include those that result in death, are life threatening, require or prolong inpatient hospitalization, result in persistent or significant disability or incapacity, or result in a congenital anomaly.
[a] Consists of stroke, cardiac arrest, heart failure/pulmonary edema, chest pain, dyspnea, asthma
[b] Consists of hyperemesis, abdominal pain, constipation, gastroenteritis, pancreatitis, ovarian cyst, shortened cervix, vaginal discharge
[c] Consists of COVID-19, influenza, pneumonia, endometritis, amnionitis, puerperal infection, osteomyelitis, cystitis, pyelonephritis, gastroenteritis, viral infection, postoperative wound infection, sepsis, abscess
[d] Consists of bipolar disorder, depression, psychosis
[e] Consists of anemia, motor vehicle accident, injury from fall, homelessness, adrenal insufficiency, gastroparesis, cerclage placement, headache, ovarian cyst

eTable 4. Fetal/Neonatal Severe Adverse Events*

Fetal/Neonatal	Metformin/Insulin	Insulin Alone	Unadjusted Rate Difference (%), 95% CI events per pregnancy, metformin – insulin alone
Miscarriage < 20 weeks	7/385 (2)	4/380 (1)	0.77 (-0.92, 2.45)
Stillbirth ≥ 20 weeks	3/379 (1)	7/377 (2)	-1.07 (-2.69, 1.56)
Neonatal death within 28 days of live birth	1/379 (1)	2/377	-0.27 (-1.16, 0.63)
Any serious neonatal adverse event[6]	63/379	82/377	-5.13 (-10.73, 0.47)
Congenital birth defect	13	8	
[1]Cardiac	9	6	0.78 (-1.20, 2.77)
[2]Gastrointestinal/genitourinary	2	1	0.26 (-0.63, 1.16)
[3]Other birth defect	2	1	0.53 (-0.51, 1.56)
[4]Genetic disorder	1	0	0.26 (-0.25, 0.78)
Metabolic derangement	10	24	
Hypoglycemia	8	13	-1.34 (-3.68, 1.00)
Hyperbilirubinemia/jaundice	2	10	-2.12 (-3.90, -0.35)
Hypocalcemia	0	1	-0.27 (-0.78, 0.25)
Prematurity	19	22	-0.82 (-4.05, 2.41)
Respiratory distress/failure/immaturity	7	12	-1.34 (-3.57, 0.89)
[5] Other complications	6	6	-0.01 (-1.79, 1.77)

Data presented as number (%) of randomized participants who took at least one dose of study agent and for whom fetal/neonatal data was available. Some participants had more than one serious adverse event and all events are included in counts.

*Serious adverse events include those that result in death, are life threatening, require or prolong inpatient hospitalization, result in persistent or significant disability or incapacity, or result in a congenital anomaly.

[1] Consists of atrial septal defect, ventricular septal defect, persistent fetal circulation, tetralogy of Fallot, truncus arteriosus

[2] Consists of anal atresia, ambiguous genitalia

[3] Consists of cleft lip, pulmonary malformation, laryngeomalacia

[4] Beckwith Wiedemann syndrome

[5] Consists of necrotizing enterocolitis, interventricular hemorrhage, seizures, testicular torsion, viral infection, hypertension, pulmonary hypertension, hydrops, small for gestational age, preeclampsia, hemolysis