TERAPIA DEL DIABETE IN GRAVIDANZA, OMBRE E LUCI SULLA METFORMINA, IPOGLICEMIZZANTI ORALI, TERAPIA INSULINICA

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COI

Il dr. Andrea Mario Bolla dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche: nessuno

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico chirurgici, ecc.)

AGENDA

Terapia del diabete in gravidanza, ombre e luci sulla metformina, ipoglicemizzanti orali, terapia insulinica

Terapia del diabete in gravidanza:

- Diabete gestazionale
- Diabete pre-gestazionale
  - Diabete di tipo 1
  - Diabete di tipo 2

Ipoglicemizzanti orali

Metformina

Terapia insulinica

AGENDA

Terapia del diabete in gravidanza, ombre e luci sulla metformina, ipoglicemizzanti orali, terapia insulinica

Ipoglicemizzanti orali

Metformina

Terapia insulinica

Utilizzabilità

- DPP4-i
- GLP1-ra
- SGLT2-i
- Pioglitazone
- Sulfaniluree

→ Controindicati

- Metformina

In Italia:
- Utilizzabile (da poco)
- Non raccomandata (per ora)

Punti critici:
- efficacia sul controllo glicemico materno
- passaggio trans-placentare
- possibili conseguenze perinatali, immediate e in particolare a distanza nel lungo termine

Ipoglicemizzanti orali

Case reports

Acta Diabetologica (2023) 60:137–138
https://doi.org/10.1007/s00592-022-01954-4

CASE REPORT

A case report on use of dulaglutide during the first weeks of pregnancy in woman affected by type 2 diabetes mellitus

Silvia Burlina[1] · Maria Grazia Dalfrà[1] · Rosaria Caprino[1] · Annunziata Lapolla[1]

In our case, dulaglutide did not affect embryo development; no minor or major malformations were observed and there were no complications, either maternal or fetal.

DIABETICMedicine
DOI: 10.1111/dme.12726

Case Report

Normal pregnancy outcome after first-trimester exposure to liraglutide in a woman with Type 2 diabetes

D. Greco
Unit of Diabetology, 'Paolo Borsellino' Hospital, Marsala, Italy

What's new?

- A normal pregnancy outcome was observed after first-trimester exposure to liraglutide in a woman with Type 2 diabetes.
- This report contributes to the limited knowledge regarding human exposure to liraglutide during pregnancy in women with diabetes.

frontiers in Pharmacology
ORIGINAL RESEARCH
published: 23 March 2022
doi: 10.3389/fphar.2022.826762

Empagliflozin Ameliorates Preeclampsia and Reduces Postpartum Susceptibility to Adriamycin in a Mouse Model Induced by Angiotensin Receptor Agonistic Autoantibodies

*Ruonan Zhai[1], Yuan Liu[1], Jiahao Tong[1], Ying Yu[1], Lin Yang[1], Yong Gu[1,2] and Jianying Niu[1]**

[1]Department of Nephrology, Shanghai Fifth People's Hospital, Fudan University, Shanghai, China, [2]Department of Nephrology, Huashan Hospital, Fudan University, Shanghai, China

Acta Diabetologica (2018) 55:759–761
https://doi.org/10.1007/s00592-018-1134-y

CASE REPORT

Empagliflozin, metformin and insulin degludec, during pregnancy: a case report

G. Formoso[1] · F. Ginestra[1] · G. Di Dalmazi[1] · A. Consoli[1]

In the case described, both empagliflozin and degludec were assumed by the patient during the embryogenic phase. Still, no major or minor malformations were observed in the newborn.

Received: 7 March 2022 | Revised: 14 April 2022 | Accepted: 5 May 2022
DOI: 10.1002/jmd2.12295

CASE REPORT

JIMD REPORTS SSIEM WILEY

Two successful pregnancies and first use of empagliflozin during pregnancy in glycogen storage disease type Ib

Sarah Catharina Grünert[1] | Stefanie Rosenbaum-Fabian[1] | Anke Schumann[1] | Anne-Christine Selbitz[2] | Waltraut Merz[3] | Andrea Gieselmann[4] | Ute Spiekerkoetter[1]

Glibenclamide

Original Investigation

Association of Adverse Pregnancy Outcomes With Glyburide vs Insulin in Women With Gestational Diabetes

Wendy Camelo Castillo, PhD; Kim Boggess, MD; Til Stürmer, PhD; M. Alan Brookhart, PhD; Daniel K. Benjamin Jr, PhD; Michele Jonsson Funk, PhD

JAMA Pediatr. 2015;169(5):452-458. doi:10.1001/jamapediatrics.2015.74
Published online March 30, 2015.

Table 2. Adverse Maternal and Neonatal Outcomes

	Events, No. (%)		IPTW Adjusted[a]	
Outcome	Glyburide	Insulin	RR (95% CI)	RD, % (95% CI)
Obstetric trauma	111 (2.2)	102 (2.4)	0.92 (0.71 to 1.20)	−0.19 (−0.81 to 0.43)
Cesarean delivery	2522 (50.6)	2201 (52.5)	0.97 (0.93 to 1.00)	−1.79 (−3.84 to 0.26)
NICU admission	509 (10.2)	302 (7.2)	1.41 (1.23 to 1.62)	2.97 (1.82 to 4.12)
Respiratory distress	144 (2.9)	73 (1.7)	1.63 (1.23 to 2.15)	1.11 (0.50 to 1.72)
Hypoglycemia	95 (1.9)	55 (1.3)	1.40 (1.00 to 1.95)	0.55 (0.03 to 1.06)
Jaundice	17 (0.3)	15 (0.4)	0.96 (0.48 to 1.91)	−0.02 (−0.26 to 0.22)
Birth injury	110 (2.2)	69 (1.6)	1.35 (1.00 to 1.82)	0.57 (0.01 to 1.14)
Preterm	472 (9.5)	371 (8.9)	1.06 (0.93 to 1.21)	0.57 (−0.62 to 1.75)
Large for gestational age	234 (4.7)	134 (3.2)	1.43 (1.16 to 1.76)	1.41 (0.61 to 2.20)

Nonostante questo molto utilizzata in USA

Glibenclamide, metformina, insulina

Comparative Efficacy and Safety of OADs in Management of GDM: Network Meta-analysis of Randomized Controlled Trials

Yun-Fa Jiang,* Xue-Yan Chen,* Tao Ding, Xiao-Feng Wang, Zhong-Ning Zhu, and Su-Wen Su

J Clin Endocrinol Metab, May 2015, 100(5):2071–2080

Table 2. Results of NMA and TMA From Maternal Outcomes

Study Group	n	TMA Effect Estimate (95% CI)	*P*	Egger's Test, *P*	NMA (95% CI)
Glycemic control					
HbA1c, %					
Metformin vs insulin	4	WMD, 0.05 (−0.11, 0.21)	.57	.248	0.02 (−0.16, 0.19)
Glyburide vs insulin	2	WMD, 0.01 (−0.26, 0.28)	.93		0.12 (−0.10, 0.27)
Metformin vs glyburide	2	WMD, −0.07 (−0.26, 0.11)	.44		−0.13 (−0.33, 0.12)
Fasting glycemic, mmol/L					
Metformin vs insulin	3	WMD, −0.00 (−2.56, 2.55)	1.00	.053	−0.26 (−4.16, 3.51)
Glyburide vs insulin	2	WMD, 1.65 (−0.98, 4.29)	.22		0.85 (−3.78, 5.31)
Metformin vs glyburide	3	WMD, −1.12 (−8.41, 6.17)	.76	.216	−1.11 (−5.27, 2.62)
Weight gain, kg					
Metformin vs insulin	4	WMD, −1.49 (−2.26, −0.31)	**.01**	.546	**−1.78 (−3.13, −0.29)**
Glyburide vs insulin	3	WMD, −1.13 (−2.47, 0.21)	.10	.327	−0.43 (−2.07, 1.24)
Metformin vs glyburide	2	WMD, −2.22 (−3.88, −0.56)	**.009**		−1.34 (−3.05, 0.38)
Cesarean delivery					
Metformin vs Insulin	7	OR, 0.93 (0.56, 1.47)	.76	.562	0.99 (0.58, 1.60)
Glyburide vs insulin	3	OR, 0.79 (0.55, 1.15)	.22	.207	0.75 (0.35, 1.29)
Glyburide vs metformin	3	OR, 0.72 (0.28, 1.90)	.51	.340	0.78 (0.35, 1.39)
Pre-eclampsia					
Metformin vs insulin	5	OR, 0.74 (0.48, 1.15)	.19	.660	0.78 (0.43, 1.40)
Glyburide vs insulin	2	OR, 1.15 (0.57, 2.32)	.70		1.35 (0.49, 3.05)
Glyburide vs metformin	1	OR, 1.54 (0.25, 9.51)	.64		1.86 (0.61, 4.74)

Abbreviation: n, number of included studies. The bold values mean significant associations.

Glyburide treatment is associated with increased risk of neonatal hypoglycemia, high maternal weight gain, high neonatal birth weight, and macrosomia.

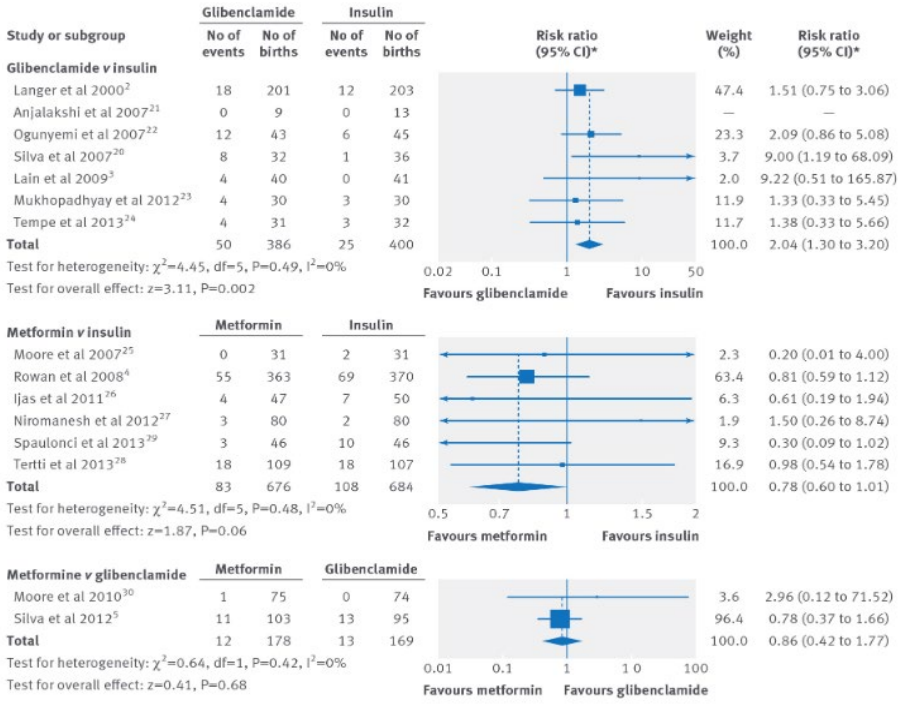
Table 3. Results of NMA and TMA From Neonatal Outcomes

Study Group	n	TMA Effect Estimate (95% CI)	*P*	Egger's Test, *P*	NMA (95% CI)
Birth weight, g					
Metformin vs insulin	8	WMD, −48.87 (−99.13, 1.39)	.06	.871	−45.1 (−108.3, 30.8)
Glyburide vs insulin	7	WMD, 130.68 (55.98, 205.38)	**.0006**	.093	**142.6 (66.2, 225.4)**
Metformin vs glyburide	3	WMD, −192.14 (−288.81, −95.47)	**<.0001**	.494	**−187.7 (−270.2, −106.5)**
Acarbose vs insulin	1	WMD, 91.4 (−145.32, 328.12)	.45		44.8 (−241.9, 314.1)
Glyburide vs acarbose	1	WMD, 153.00 (−123.52, 429.52)	.28		97.8 (−181.1, 364.5)
Hypoglycemia					
Metformin vs insulin	7	OR, 0.73 (0.55, 0.97)	**.03**	.480	0.91 (0.54, 1.58)
Glyburide vs insulin	6	OR, 2.64 (1.59, 4.38)	**.0002**	.042	**2.24 (1.18, 4.23)**
Glyburide vs metformin	3	OR, 1.09 (0.56, 2.15)	.79	.153	**2.59 (1.25, 5.01)**
Acarbose vs insulin	1	OR, 1.44 (0.08, 24.63)	.80		0.56 (0.01, 2.68)
Glyburide vs acarbose	1	OR, 9.00 (1.01, 80.03)	**.05**		0.25 (0.00, 1.21)
Acarbose vs metformin	0				0.71 (0.01, 3.32)
Gestational age, wk					
Metformin vs insulin	7	WMD, −0.16 (−0.30, −0.03)	**.02**	.939	−0.14 (−0.30, 0.02)
Glyburide vs insulin	5	WMD, 0.03 (−0.20, 0.27)	.79	0.271	0.01 (−0.20, 0.23)
Metformin vs glyburide	3	WMD, −0.09 (−0.37, 0.18)	.50	0.526	−0.13 (−0.35, 0.11)
Acarbose vs insulin	1	WMD, −0.30 (−1.00, 0.40)	.40		−0.11 (−0.82, 0.58)
Glyburide vs acarbose	1	WMD, −0.10 (−0.82, 0.62)	.79		−0.10 (−0.78, 0.53)
Premature birth					
Metformin vs insulin	4	OR, 1.63 (1.07, 2.48)	**.02**	0.337	1.65 (0.82, 2.60)
Glyburide vs insulin	3	OR, 0.86 (0.22, 3.34)	.82	0.729	1.23 (0.48, 2.57)
Glyburide vs metformin	2	OR, 0.84 (0.27, 2.57)	.76		0.79 (0.29, 1.73)
Macrosomia					
Metformin vs insulin	7	OR, 0.76 (0.50, 1.15)	.20	0.082	0.75 (0.33, 1.45)
Glyburide vs insulin	5	OR, 3.09 (1.59, 6.04)	**.0009**	0.185	**4.89 (1.69, 12.86)**
Glyburide vs metformin	2	OR, 3.17 (0.84, 12.00)	.09		**7.46 (2.20, 23.31)**
Glyburide vs acarbose	1	OR, 8.56 (0.43, 169.70)	.16		0.01 (0.00, 0.02)
NICU					
Metformin vs insulin	6	OR, 0.82 (0.63, 1.07)	.14	0.941	0.91 (0.62, 1.38)
Glyburide vs insulin	3	OR, 1.01 (0.53, 1.95)	.97	0.079	0.75 (0.38, 1.37)
Glyburide vs metformin	3	OR, 0.53 (0.24, 1.18)	.12	0.162	0.85 (0.43, 1.54)
Glyburide vs acarbose	1	OR, 2.49 (0.10, 64.62)	.58		0.44 (0.00, 1.56)

Abbreviation: n, number of included studies. The bold values mean significant associations.

Glibenclamide, metformina, insulina

Ipoglicemia neonatale



Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis

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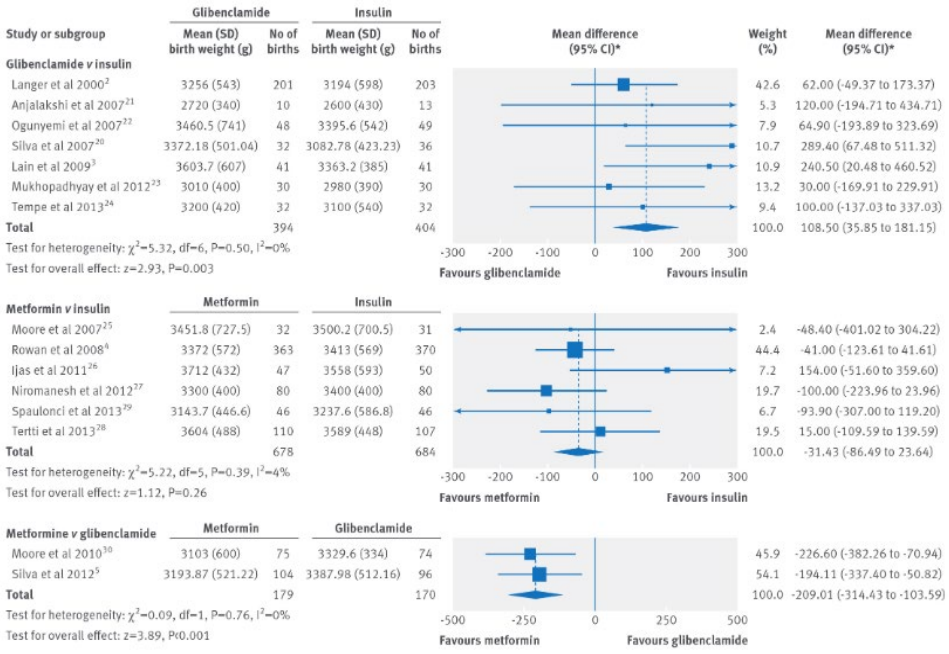
Peso alla nascita



At short term, in women with gestational diabetes requiring drug treatment, glibenclamide is clearly inferior to both insulin and metformin, while metformin (plus insulin when required) performs slightly better than insulin. According to these results, glibenclamide should not be used for the treatment of women with GDM if insulin or metformin is available.

Metformina – DMT2

Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo-controlled trial

Lancet Diabetes Endocrinol
2020; 8: 834–44

DMT2

Tutte in terapia insulinica

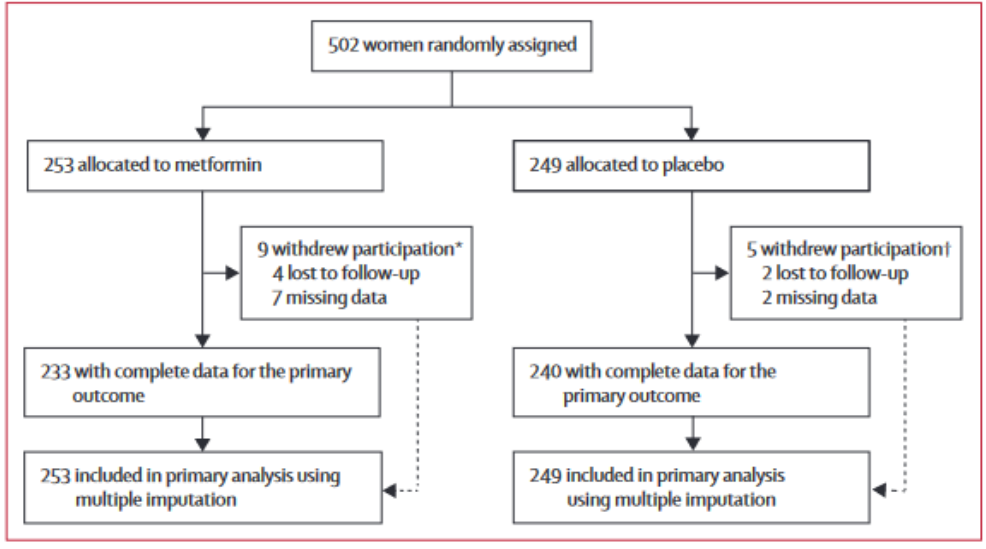


Figure 1: **Trial profile**

	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)

Metformina – DMT2

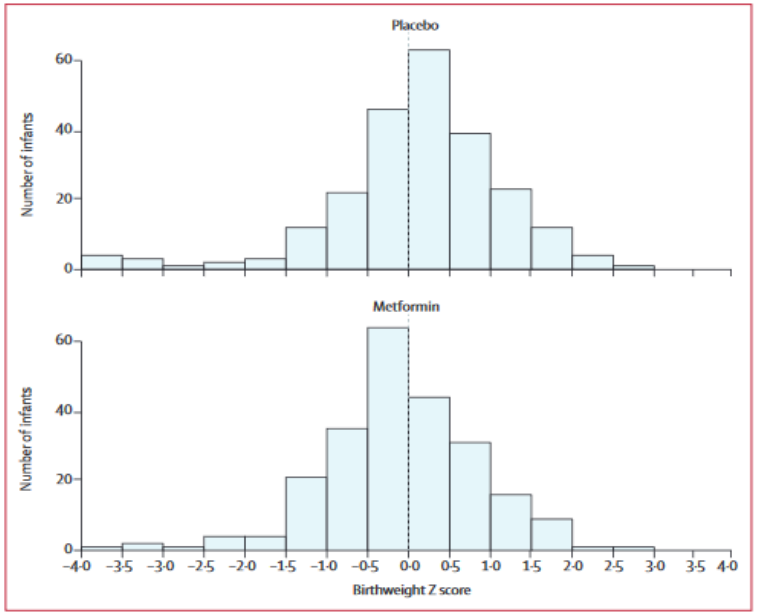


Figure 2: **Birthweight distributions in infants of women in the metformin and placebo groups**

We found several maternal glycaemic and neonatal adiposity benefits in the metformin group. Along with reduced maternal weight gain, insulin dosage, and rate of caesarean sections, and improved glyacaemic control, the lower adiposity and infant size measurements resulted in fewer large infants but a higher proportion of small-for-gestational-age infants.
Understanding the implications of these effects on infants will be important to properly advise patients who are contemplating the use of metformin during pregnancy.

	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 HbA_{1c} 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 HbA_{1c} 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)

Metformina – DMT2 – FU

Outcomes in children of women with type 2 diabetes exposed to metformin versus placebo during pregnancy (MiTy Kids): a 24-month follow-up of the MiTy randomised controlled trial

Lancet Diabetes Endocrinol 2023; 11: 191–202

- The metformin group reached a higher peak mean BMI at 6 months and continued to be higher from 6 months to 24 months, at which time they were similar to the placebo group
- At 24 months, metformin was not a predictor of adiposity, but several potentially modifiable risk factors were associated with child BMI Z score, including maternal pre-pregnancy BMI, low socioeconomic status, and reduced sleep time
- The children of women with type 2 diabetes were approximately 1 SD heavier than the WHO reference population

Data reassuring with regard to the use of metformin during pregnancy in women with type 2 diabetes and the long-term health of their children, with longer follow-up needed to assess if these findings persist.

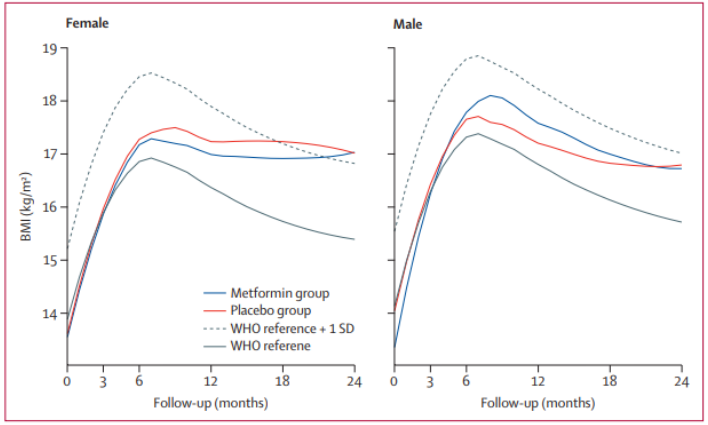


Figure 2: **BMI growth trajectories of infants up to 24 months**
The grey lines show the sex-specific WHO reference curves for the child at the mean BMI and at 1 SD above the mean BMI.

Metformina – DG

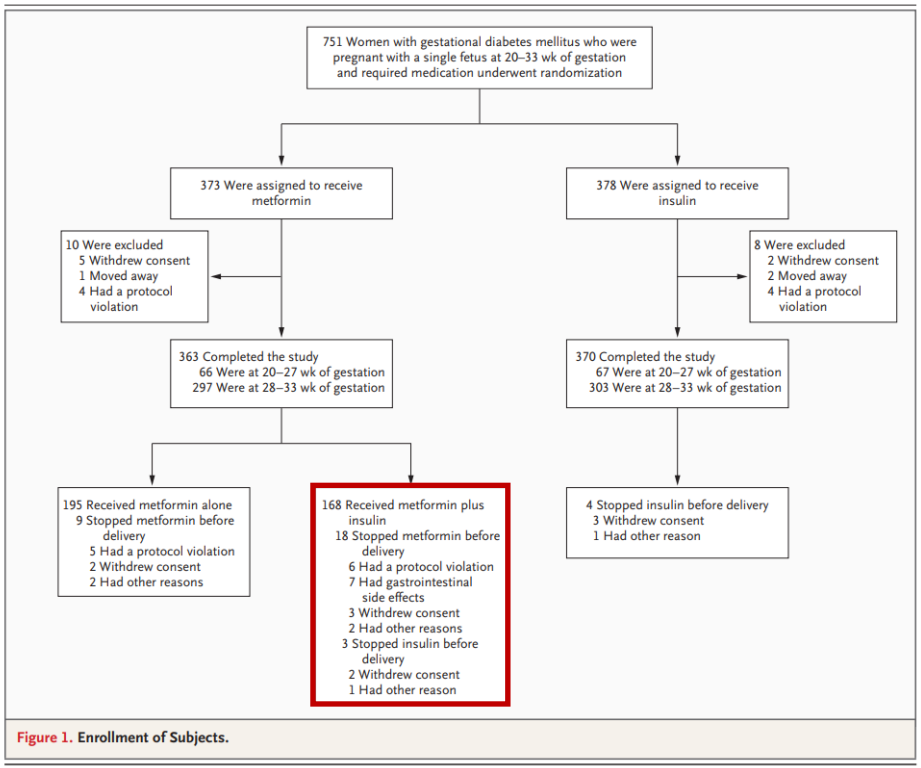


Figure 1. Enrollment of Subjects.

Metformin versus Insulin for the Treatment of Gestational Diabetes

The NEW ENGLAND JOURNAL *of* MEDICINE

Table 2. Primary Outcome and Additional Neonatal Complications.*

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

Metformina – DG – FU

Table 3—*Two-year-old measurements*

	Metformin (n = 154)	Insulin (n = 164)	P value
Adjusted age (months)	28.7 ± 3.6	29.4 ± 3.8	0.08
Sex: male/female (n)	86/68	79/85	0.21
Weight (kg)	14.3 ± 2.1	14.0 ± 2.2	0.18
Height (cm)	90.7 ± 4.9	91 ± 4.8	0.68
Leg length (cm) (height minus crown to rump)	37.9 ± 3.1	38.1 ± 3.3	0.61
Head circumference (cm)	49.4 ± 1.8	49.3 ± 1.7	0.52
Chest circumference (cm)	52.1 ± 3.0	51.6 ± 3.0	0.12
Upper-arm circumference (cm)	17.2 ± 1.5	16.7 ± 1.5	0.002
Waist circumference (cm)	50.5 ± 3.5	50.1 ± 4	0.33
Hip circumference (cm)	52.1 ± 4.0	51.6 ± 4.0	0.28
Waist-to-hip ratio	0.97 ± 0.05	0.97 ± 0.05	0.95
Triceps skinfold thickness (mm)	10.1 ± 2.0	9.9 ± 2.4	0.50
Subscapular skinfold thickness (mm)	6.3 ± 1.9	6.0 ± 1.7	0.02
Biceps skinfold thickness (mm)	6.0 ± 1.9	5.6 ± 1.7	0.04
DEXA	N = 57	N = 57	
Total fat (g)	2,421 ± 1,002	2,274 ± 711	0.37
Abdominal fat (g)	132 ± 73	131 ± 60	0.92
Thigh fat (g)	266 ± 96	262 ± 86	0.83
Arm fat (g)	196 ± 104	181 ± 74	0.36
Abdominal-to-thigh fat ratio	0.48 ± 0.1	0.50 ± 0.1	0.33
Lean body mass (g)	10,756 ± 1,283	10,736 ± 1,401	0.94
Bone mineral content (g)	389 ± 69	390 ± 70	0.95
FFM	11,095 ± 1,293	11,126 ± 1,458	0.91
Total fat (%)	16.4 ± 4.9	16.9 ± 4	0.34
Abdominal fat (% of fat mass)	5.3 ± 1.3	5.6 ± 1.3	0.20
Thigh fat (% of fat mass)	11.3 ± 2.5	11.4 ± 2.5	0.73
Arm fat (% of fat mass)	7.82 ± 1.7	7.75 ± 1.6	0.81
Bioimpedance	N = 103	N = 118	
FFM (kg)	11.8 ± 1.89	11.4 ± 1.45	0.13
Total fat (%)	16.5 ± 9.07	17.1 ± 6.99	0.58

Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU)

Body composition at 2 years of age

Diabetes Care 34:2279–2284, 2011

CONCLUSIONS—Children exposed to metformin had larger measures of subcutaneous fat, but overall body fat was the same as in children whose mothers were treated with insulin alone. Further follow-up is required to examine whether these findings persist into later life and whether children exposed to metformin will develop less visceral fat and be more insulin sensitive. If so, this would have significant implications for the current pandemic of diabetes.

Metformina – DG – FU

Table 4 Subgroup of children seen at 7–9 years: measures at 7–9 years

	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
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

BMJ Open Diabetes Research & Care

Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7–9 years of age

Janet A Rowan,[1] Elaine C Rush,[2] Lindsay D Plank,[3] Jun Lu,[2] Victor Obolonkin,[2] Suzette Coat,[4] William M Hague[4,5]

In conclusion, this study reports similar total and abdominal body fat percent and metabolic measures in 7–9 years old offspring of women with GDM randomized to metformin or insulin treatment during pregnancy.

The 9-year-old offspring of women randomized to metformin were larger than those whose mothers had been randomized to insulin.

Future studies will determine the relevance of this finding. Our data, when considered in combination with animal data, also suggest possible interactions between metformin and the intrauterine environment and raise some interesting questions for further study.

Metformina – obesità

Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial

Lancet Diabetes Endocrinol 2015; 3: 778–86

- BMI > 30
- Metformin has no significant effect on birthweight percentile in obese pregnant women
- Further follow-up of babies born to mothers in the EMPOWaR study will identify longer-term outcomes of metformin in this population; in the meantime, metformin should not be used to improve pregnancy outcomes in obese women without diabetes.

Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus

N Engl J Med 2016;374:434-43.
DOI: 10.1056/NEJMoa1509819

- Among women without diabetes who had a BMI of more than 35, the antenatal administration of metformin reduced maternal weight gain but not neonatal birth weight

Metformina – conclusioni

Contents lists available at ScienceDirect
EBioMedicine
journal homepage: www.ebiomedicine.com
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Published by THE LANCET

Review

Metformin from mother to unborn child – Are there unwarranted effects?

Linh Nguyen [a,b], Shiao-Yng Chan [c,d], Adrian Kee Keong Teo [a,b,e,f,*]

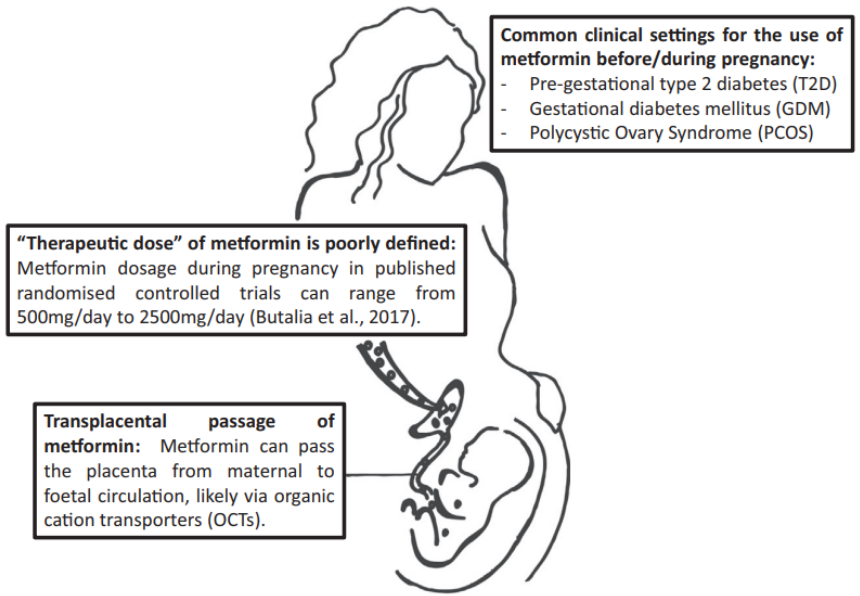


Fig. 1. The passage of metformin from mother to offspring. Metformin is becoming a popular agent to control insulin resistance before and during pregnancy. However, unlike insulin, metformin can pass through the placenta, likely *via* the organic cation transporters (OCTs). The foetus is exposed to at least half to the same concentration of metformin in maternal plasma, which can reach approximately 100 μM (Eyal et al., 2010). It is possible that there are mechanisms of counter-transport which might account for the difference in metformin concentrations between maternal and foetal circulation.

Metformina – conclusioni

DMT2, terapia insulinica ± metformina, alla 6-23 SG (MiTy): con metformina

- minor incremento di peso, minor fabbisogno insulinico, meno TC
- miglior compenso glicemico, meno adiposità
- minor peso alla nascita, meno LGA
- più SGA

FU 2 anni (MiTy Kids): dati rassicuranti con necessità di follow-up più lungo

DG, metformina vs placebo (MiG): con metformina

- 46.3% necessità di aggiunta di insulina
- minor incremento ponderale e miglior compenso glicemico post-prandiale
- più parto pre-termine, meno ipoglicemie neonatali

FU 2 anni (MiG-TOFU): con metformina più tessuto adiposo sottocutaneo e uguale adiposità totale
FU 7-9 anni (MiG TOFU): simile adiposità e parametri metabolici, a 9 anni maggiore circonferenza addome con metformina

Non effetto sul peso alla nascita nelle donne con obesità preconcezionale
Non prevenzione DG se PCOS

Quale terapia insulinica

Terapia insulinica MDI con analoghi, secondo andamento glicemico individuale

Analoghi rapidi

Durante la gravidanza possono essere mantenuti o introdotti in terapia gli analoghi rapidi dell'insulina aspart (I A) e lispro (I A), potenzialmente più efficaci dell'insulina umana regolare nel controllare l'iperglicemia postprandiale, con minor rischio di ipoglicemia (VI B).

Anche faster aspart utilizzabile in gravidanza.

Non vi sono al momento dati sufficienti sull'uso in gravidanza dell'analogo rapido glulisina.

Quale terapia insulinica

Analoghi lenti

Il trattamento con gli analoghi ad azione ritardata può essere preso in considerazione per la terapia della donna in gravidanza sia per quanto riguarda detemir (II B), che glargine (IV B).
Anche glargine U-300 utilizzabile in gravidanza.

Insulin degludec versus insulin detemir, both in combination with insulin aspart, in the treatment of pregnant women with type 1 diabetes (EXPECT): an open-label, multinational, randomised, controlled, non-inferiority trial

Elisabeth R Mathiesen, Amra Ciric Alibegovic, Rosa Corcoy, Fidelma Dunne, Denice S Feig, Moshe Hod, Ting Jia, Balamurali Kalyanam, Soumitra Kar, Alexandra Kautzky-Willer, Cassio Marchesini, Rustam D Rea, Peter Damm, on behalf of the EXPECT study group

Lancet Diabetes Endocrinol
2023; 11: 86–95

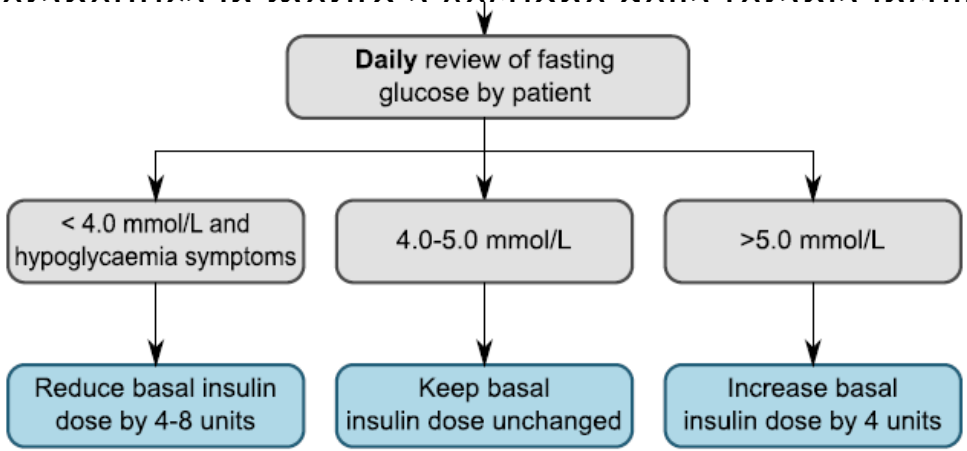
- In pregnant women with type 1 diabetes, degludec was found to be non-inferior to detemir
- Compared with detemir, no additional safety issues were observed with degludec

Il trattamento con degludec durante la gravidanza può essere preso in considerazione, se clinicamente necessario.

Terapia insulinica

IMPORTANZA DELL'EDUCAZIONE TERAPEUTICA

- Team multidisciplinare con personale infermieristico e dietista
- Importanza della mediatrice culturale
- Educazione terapeutica in merito a gestione della terapia insulinica
- Educazione [illegible] sale



McGovern AP et al., Diab Med, 2022

AGENDA

Terapia del diabete in gravidanza, ombre e luci sulla metformina, ipoglicemizzanti orali, terapia insulinica

- Ipoglicemizzanti orali
- Metformina
- Terapia insulinica

Terapia del diabete in gravidanza:

- Diabete gestazionale
- Diabete pre-gestazionale
  - ➢ Diabete di tipo 1
  - ➢ Diabete di tipo 2

Diabete gestazionale – terapia

Alterazione metabolica più comune in gravidanza
Necessità di raggiungere gli obiettivi glicemici per ridurre il rischio di complicanze materne e fetali

Gestione:
- Autocontrollo glicemico
- Prima linea terapeutica: terapia nutrizionale

Tabella VI.B2 Obiettivi glicemici in gravidanza (sangue capillare intero).

A digiuno	≤ 90 mg/dl
1 ora dopo il pasto	≤ 130 mg/dl
2 ore dopo il pasto	≤ 120 mg/dl

- Schema alimentare personalizzato secondo abitudini e BMI
- Adeguato apporto calorico e di nutrienti, garantendo compenso glicemico ottimale e evitando ketosi

Tabella VI.B3. Fabbisogno energetico e incremento ponderale raccomandato in base al BMI pregravidico. L'aumento ponderale raccomandato presuppone un incremento di 0,5-2 kg nel primo trimestre della gravidanza.

Struttura	BMI (kg/m²)	Fabbisogno energetico kcal/kg/die	Aumento ponderale totale (kg)	Aumento ponderale kg/ sett. nel 2°-3° trimestre
Sottopeso	<18.5	40	12.5-18	0.51 (0.44-0.58)
Normopeso	18.5-24.9	30	11.5-16	0.42 (0.35-0.50)
Sovrappeso	25-29.9	24	7-11.5	0.28 (0.23-0.33)
Obese	≥30	12-24	5-7 (9)	0.22 (0.17-0.27)

Diabete gestazionale – terapia

Se con terapia nutrizionale target glicemico non raggiunto in 2 settimane

Per gli Standard è indicato iniziare una terapia insulinica MDI con analoghi, secondo andamento glicemico individuale

RCP aggiornata metformina (2022)
Gravidanza: «Esistono prove limitate e contrastanti sull'effetto della metformina sull'esito del peso a lungo termine dei bambini esposti in utero. La metformina non sembra influenzare lo sviluppo sociale e motorio dei bambini fino a 4 anni di età esposti durante la gravidanza, sebbene i dati sugli esiti a lungo termine siano limitati. Se clinicamente necessario, l'uso della metformina può essere preso in considerazione durante la gravidanza e nella fase periconcezionale in aggiunta o in alternativa all'insulina»
Allattamento: «Nei modelli animali, la metformina viene escreta nel latte durante l'allattamento. Ad oggi sono disponibili solo dati limitati e non esaustivi nell'uomo. Pertanto la metformina non deve essere assunta durante l'allattamento»

AMD ASSOCIAZIONE MEDICI DIABETOLOGI 1974 — Metformina in gravidanza — SID Società Italiana di Diabetologia

Con queste premesse, le società scientifiche AMD e SID pur valutando positivamente che tale trattamento possa essere preso in considerazione in specifici contesti, suggeriscono, così come riportato nella RCP, una attenta e precisa valutazione clinica dei singoli casi che auspicano rimanga affidata a specialisti esperti in gestione di gravide diabetiche.

Canadian guidelines

Contents lists available at ScienceDirect
Canadian Journal of Diabetes
journal homepage: www.canadianjournalofdiabetes.com
DIABETES CANADA
CJD

2018 Clinical Practice Guidelines

Diabetes and Pregnancy

Diabetes Canada Clinical Practice Guidelines Expert Committee

Denice S. Feig MD, FRCPC, Howard Berger MD, Lois Donovan MD, FRCPC, Ariane Godbout MD, FRCPC, Tina Kader MD, FRCPC, Erin Keely MD, FRCPC, Rema Sanghera MA, RD

Gestational Diabetes Mellitus
During Pregnancy

- Untreated gestational diabetes leads to increased maternal and perinatal morbidity. Treatment reduces these adverse pregnancy outcomes.
- In women at high risk of undiagnosed type 2 diabetes, early screening (<20 weeks) with an A1C should be done to identify women with potentially overt diabetes to guide fetal surveillance and early maternal treatment, including self-monitoring of blood glucose, interventions that promote healthy behaviours and healthy weight gain.
- The diagnostic criteria for gestational diabetes (GDM) remain controversial; however, these guidelines identify a "preferred" and an "alternate" screening approach. The preferred approach is an initial 50 g glucose challenge test, followed, if abnormal, with a 75 g oral glucose tolerance test. A diagnosis of GDM is made if one plasma glucose value is abnormal (i.e. fasting ≥5.3 mmol/L, 1 hour ≥10.6 mmol/L, 2 hours ≥9.0 mmol/L). The alternate approach is a 1-step approach of a 75 g oral glucose tolerance test. A diagnosis of GDM is made if one plasma glucose value is abnormal (i.e. fasting ≥5.1 mmol/L, 1 hour ≥10.0 mmol/L, 2 hours ≥8.5 mmol/L).
- First-line therapy consists of diet and physical activity. If glycemic targets are not met, insulin or metformin can then be used.

<u>GDM</u>

The use of insulin to achieve glycemic targets has been shown to reduce fetal and maternal morbidity.

While metformin appears to be a safe alternative to insulin therapy, it does cross the placenta. Long-term follow up from 18 months to 2 years indicate that metformin exposure in-utero does not seem to be harmful with regards to early motor, linguistic, social, metabolic and neurodevelopmental outcomes; longerterm follow up is not yet available.

The use of glyburide during pregnancy is not recommended as first- or second-line treatment, but may be used as third-line treatment if insulin is declined by the mother and metformin is either declined or insufficient to maintain good glycemic control.

<u>TYPE 2 DIABETES</u>

There is insufficient evidence to recommend the addition of metformin to insulin in pregnant women with type 2 diabetes.

ADA guidelines

15. Management of Diabetes in Pregnancy: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S254–S266 | https://doi.org/10.2337/dc23-S015

Recommendations

15.14 Lifestyle behavior change is an essential component of management of gestational diabetes mellitus and may suffice as treatment for many individuals. Insulin should be added if needed to achieve glycemic targets. A

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.

Metformina?

Difficile gestione

15. Management of Diabetes in Pregnancy: *Standards of Care in Diabetes—2023*

Diabetes Care 2023;46(Suppl. 1):S254–S266 | https://doi.org/10.2337/dc23-S015

- Alcune donne con GDM che richiedono una terapia medica, a causa di costi, barriere linguistiche, difficoltà nella comprensione o influenze culturali, potrebbero non essere in grado di utilizzare l'insulina in modo sicuro o efficace.
- In queste donne i farmaci orali possono rappresentare un'alternativa, dopo discussione sui rischi noti e sulla necessità di ulteriori dati di sicurezza a lungo termine nella prole.
- Tuttavia, a causa del potenziale di ridotta crescita fetale e acidosi nel contesto dell'insufficienza placentare, la metformina non deve essere utilizzata nelle donne con ipertensione o pre-eclampsia o che presentino un rischio di riduzione della crescita del feto.

Low resources

Metformin can facilitate treatment in diabetes in pregnancy in low-resourced settings *(Ashwal E et al., Best Pract & Res Clin Obst and Gyn, 2015)*

AGENDA

Terapia del diabete in gravidanza, ombre e luci sulla metformina, ipoglicemizzanti orali, terapia insulinica

- Ipoglicemizzanti orali
- Metformina
- Terapia insulinica

Terapia del diabete in gravidanza:

- Diabete gestazionale
- Diabete pre-gestazionale
  - ➢ Diabete di tipo 1
  - ➢ Diabete di tipo 2

Diabete pre-gestazionale

PROGRAMMAZIONE !!!

Programmazione

Table 2 Proportions of specialists and fellows who responded correctly to selected questions of the survey, related to counselling women with pregestational diabetes about pregnancy, % (95% CI).

	Specialists n = 234		Fellows n = 108	
	Received training n = 139 (59%)	Received no training n = 97 (41%)	Received training n = 57 (52%)	Received no training n = 53 (48%)
In women with diabetes it is important to plan a pregnancy	100%	100%	98.2% (90.6–100.0)	100%
In women with diabetes there is an increased risk of macrosomia	100%	97.9% (92.7–99.7)	100%	98.1% (89.9–100.0)
Identification of the magnitude of the excess of congenital malformations in the offspring of women with diabetes	36.7% (28.7–45.3)	38.1% (28.5–48.6)	36.8% (24.4–50.6)	28.3% (16.8–42.3)
Identification of the level of HbA1c recommended at conception	91.4% (85.4–95.4)	83.5% (74.6–90.3)	87.7% (76.3–94.9)	83.0% (70.2–91.9)
Women with type 2 diabetes should be transferred to insulin prior to conception in the majority of cases	91.4% (85.4–95.4)	84.5% (75.8–91.1)	89.5% (78.5–96.0)	88.7% (77.0–95.7)
Women with diabetes should be prescribed a higher dose of folic acid than women without diabetes	18.0% (12.0–25.4)	16.5% (9.7–25.4)	19.3% (10.0–31.9)	26.4% (15.2–40.3)
Women with diabetes can use hormonal contraceptive:				
Yes	59.0% (50.3–67.2)	52.6% (42.2–62.7)	52.6% (39.0–66.0)	43.4% (29.8–57.7)
Yes, if glucose control is good	38.8% (30.7–47.5)	43.3% (33.3–53.7)	43.8% (30.7–57.6)	47.2% (33.3–61.4)
Some of the drugs commonly prescribed to patients with diabetes are not recommended in pregnancy	97.1% (92.8–99.2)	96.9% (91.2–99.4)	98.2% (90.6–100.0)	96.2% (87.0–99.5)
In women with diabetes there is an increased risk of negative fetal outcomes in case of poor glucose control at conception	43.2% (34.8–51.8)	35.0% (25.6–45.4)	45.6% (32.4–59.3)[a]	26.4% (15.3–40.3)
In women with diabetes there is an increased risk of negative maternal outcomes in case of poor glucose control at conception	54.7% (46.0–63.1)	49.5% (39.2–59.8)	56.1% (42.4–69.2)	39.6% (26.4–54.0)
There are increased risks for a pregnancy associated to overweight/obesity	38.1% (30.0–46.7)	30.9% (21.9–41.1)	26.3% (15.5–39.7)	20.8% (10.8–34.1)

Confidence intervals for proportions were calculated using the binomial exact method.
[a] p = 0.024 vs fellows who did not receive training.

Nutrition, Metabolism & Cardiovascular Diseases (2020) **30**, 1520–1524

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

SHORT COMMUNICATION

Awareness about diabetes and pregnancy among diabetes specialists and fellows: The YoSID diabetes and pregnancy project

Andrea M. Bolla [a], Nicoletta Dozio [b], Marina Scavini [a,*], Elena Succurro [c], Andrea Tummina [d], Elisabetta Torlone [e], Ferdinando C. Sasso [f], Ester Vitacolonna [g]on behalf of the Young professionals of SID (YoSID), and of the Joint Diabetes and Pregnancy Study Group[1]of the Italian Association of Clinical Diabetologists (AMD) and the Italian Diabetes Society (SID)

- Acido folico
- Modifica terapia (se necessario)
- Ottimizzazione compenso
- Screening complicanze

Programmazione – DMT1

- Inizio supplementazione con acido folico
- Sospensione eventuali farmaci controindicati (es. ACE-I, statine)
- Screening complicanze e funzione tiroidea
- Obiettivo HbA1c < 6.5 % preconcezionale

- Ottimizzare terapia insulinica
- Eventuale inizio utilizzo di tecnologie in preconcezionale

Programmazione – DMT2

- Inizio supplementazione con acido folico
- Sospensione eventuali farmaci controindicati (es. ACE-I, statine)
- Screening complicanze e funzione tiroidea
- Obiettivo HbA1c < 6.5 % preconcezionale

- Attenzione alla dieta e modifica della terapia con sospensione farmaci non autorizzati e eventuale passaggio a terapia insulinica secondo andamento glicemico

PCOS

Among PCOS patients *(Palomba et al., Human Reproduction Update, 2015)*:
3- to 4-fold increase in pregnancy-induced hypertension and preeclampsia; 3-fold increase in GDM; 2-fold higher chance for premature delivery

Possibile ruolo di metformina nel preconcezionale o in gravidanza, tuttavia dati non univoci:

Preconcezionale

- six-month metformin administration is significantly more effective than six-cycle clomiphene treatment in improving fertility in anovulatory nonobese PCOS women *(Palomba S et al., JCEM, 2005)*
- clomiphene is superior to metformin in achieving live birth in infertile women with PCOS, although multiple birth is a complication *(Legro RS et al., NEJM, 2007)*

Gravidanza

- minor incremento di peso gestazionale con metformina in caso di donna con PCOS *(Tarry-Adkins JL et al., Scientific Reports, 2021)*
- metformin treatment from first trimester to delivery did not reduce pregnancy complications in PCOS *(Vanky E et al., JCEM, 2010)*
- non differenza nello sviluppo di DG se insulino-resistenza preconcezionale trattata con metformina *(Valdes E et al., J Obstet Gynaecol Res, 2018)*
- follow-up of 4-year-old offspring demonstrated higher BMI and increased obesity in the offspring exposed to metformin when used in pregnancy for PCOS *(Hanem LGE et al., J Clin Endocrinol Metab, 2018)*

15.16 Metformin, when used to treat PCOS and induce ovulation, should be discontinued by the end of the first trimester. A *(ADA Recommendations 2023)*

Dati promettenti (in particolare in relazione a calo ponderale e riduzione dei livelli di testosterone libero) su possibile utilizzo GLP1-ra nella donna con PCOS *(Abdalla MA et al., Ther Adv Endocrinol Metab, 2021; Cena H et al., JCEM, 2020)*

- con attenzione se paziente poco affidabile su programmazione della gravidanza

CONCLUSIONI

- Importanza della programmazione

- Terapia insulinica sicura e efficace, attualmente gold standard come ipoglicemizzante in gravidanza

- Altri ipoglicemizzanti orali: controindicati
- Metformina:
  - ridotta efficacia rispetto a insulina se in monoterapia
  - possibile valore aggiunto quando associata all'insulina (meno incremento ponderale materno, miglior compenso glicemico, meno LGA) a fronte di aumento di SGA
  - attraversa la placenta, da approfondire dati sul lungo-termine in termini di adiposità

  - possibile ruolo nel preconcezionale (es. PCOS)?
  - possibile opzione, in DG e DMT2 in gravidanza, in aggiunta a insulina in certi casi come obesità severa?
  - possibile opzione terapeutica se terapia insulinica difficilmente praticabile / rifiutata?

  <u>Sempre dopo adeguata informazione della paziente</u>

RINGRAZIAMENTI

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Grazie per aver ascoltato papà!