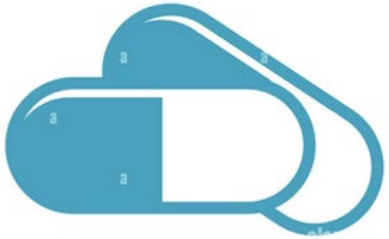
Terapia del diabete gestazionale: Insulina, Metformina o entrambe?



8 giugno 2024

Dr.ssa Eloisa Mariani (Monza)
Dr.ssa Veronica Resi (Milano)

Le dott.se Veronica Resi e Eloisa Mariani dichiara di NON aver ricevuto negli ultimi anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

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.).

Il parere della diabetologa

Il parere della ginecologa

International Journal of
Environmental Research and Public Health

2023

Article

Antidiabetic Therapy during Pregnancy: The Prescription Pattern in Italy

Anna Locatelli [1], Sara Ornaghi [1,*], Alessandra Terzaghi [1], Valeria Belleudi [2], Filomena Fortinguerra [3], Francesca Romana Poggi [2], Serena Perna [3], Francesco Trotta [3] and MoM-Net Group [†]

Coorte di **450.000 donne** tra i **15 e i 49 anni** che hanno partorito tra il **2016 e il 2018**, residenti in 8 Regioni italiane,
rappresentanti il **59%** delle donne italiane in gravidanza.

- **In Italia 40.000 diagnosi di GDM ogni anno** (ISS Diabete gestazionale, 2020)
- **Trattare l'iperglicemia riduce il rischio di complicanze materne e perinatali** (Crowther, C.A. PLoS Med. 2022; Ye,W; Luo, C; BMJ 2022)
- **La prima linea di trattamento è rappresentata dalla dieta e dall'attività fisica** (ADA 2020)

International Journal of *Environmental Research and Public Health*

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Antidiabetic Therapy during Pregnancy: The Prescription Pattern in Italy

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- **L'uso degli antidiabetici aumenta con il progredire della gravidanza raggiungendo il picco nel terzo trimestre (2,13%) a favore di insuline e analoghi**, trend riconducibile all'insorgenza del GDM;
- **Il profilo prescrittivo delle varie classi di antidiabetici è risultato in linea con le linee guida italiane che attualmente NON raccomandano l'uso di antidiabetici orali** come prima linea per il trattamento del GDM;
- **Una quota piccola ma NON trascurabile di "new users" ha utilizzato antidiabetici orali (3,8%)**.
- **Più del 97% di "new users" ha sospeso la terapia dopo il parto**

Table 3. Pattern of use of the different classes of antidiabetics in the trimesters before, during and after pregnancy.

	Trimester BEFORE Pregnancy						Trimester DURING Pregnancy						Trimester AFTER Pregnancy					
	−III		−II		−I		I		II		III		+I		+II		+III	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Main users N = 3103																		
Other (antidiabetic)	55	1.8	63	2	65	2.1	35	1.1	6	0.2	5	0.2	9	0.3	11	0.4	23	0.7
New antidiabetics	34	1.1	38	1.2	48	1.5	29	0.9	2	0.1	2	0.1	9	0.3	22	0.7	39	1.3
Oral antidiabetics	1117	36	1205	38.8	1303	42	902	29.1	349	11.2	263	8.5	239	7.7	338	10.9	376	12.1
Insulins and analogues	805	25.9	786	25.3	785	25.3	946	30.5	1294	41.7	1257	40.5	807	26	815	26.3	804	25.9
Not users	1092	35.2	1011	32.6	902	29.1	1191	38.4	1452	46.8	1576	50.8	2039	65.7	1917	61.8	1861	60
New users in pregnancy N = 9621																		
Other (antidiabetic)	0	0	0	0	0	0	14	0.1	15	0.2	4	0	3	0	5	0.1	7	0.1
New antidiabetics	0	0	0	0	0	0	7	0.1	3	0	5	0.1	0	0	4	0	9	0.1
Oral antidiabetics	0	0	0	0	0	0	283	2.9	235	2.4	361	3.8	75	0.8	96	1	117	1.2
Insulins and analogues	0	0	0	0	0	0	323	3.4	2778	28.9	7643	79.4	118	1.2	57	0.6	78	0.8
Not users	9621	100	9621	100	9621	100	8994	93.5	6590	68.5	1608	16.7	9425	98	9459	98.3	9410	97.8

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Anna Locatelli [1], Sara Ornaghi [1,*], Alessandra Terzaghi [1], Valeria Belleudi [2], Filomena Fortinguerra [3], Francesca Romana Poggi [2], Serena Perna [3], Francesco Trotta [3] and MoM-Net Group [†]

- **Nel II e III trimestre l'uso di terapia nelle donne straniere è il doppio rispetto alle italiane** (II trimestre: 1,8% vs 0,9%, III trimestre: 3,6% vs 1,8%);
- **Il consumo torna per tutte le popolazioni ai livelli pre-gravidanza nel post-partum**

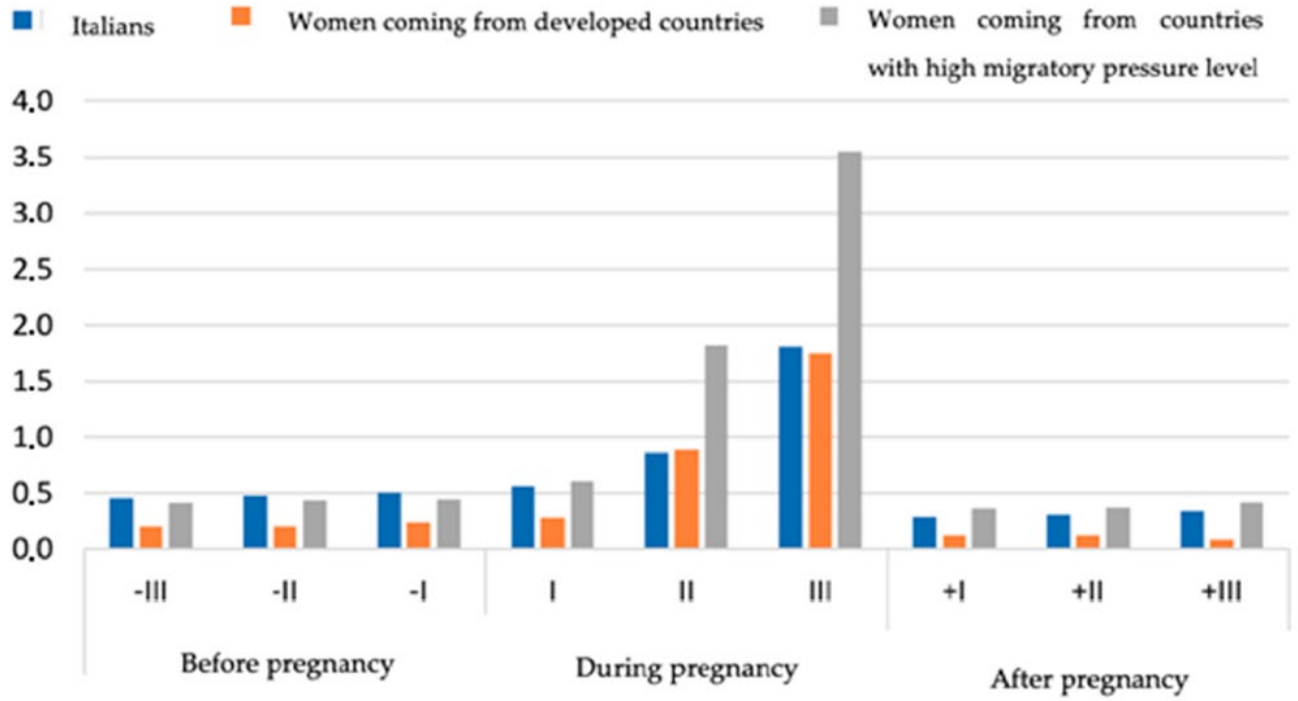


Figure 2. Prevalence of antidiabetic use before, during and after pregnancy.

Cosa dicono le Linee Guida?

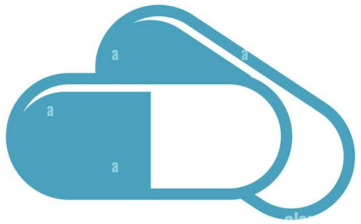
ACOG 2018
L'insulina è il trattamento da preferire, tuttavia in alcuni casi la metformina rappresenta una ragionevole alternativa.

ADA 2024
L'insulina come prima linea di trattamento, possibile uso della metformina come seconda linea.

SID-AMD 2018
L'insulina è trattamento di scelta
Metformina stand-by

Insulina

Metformina

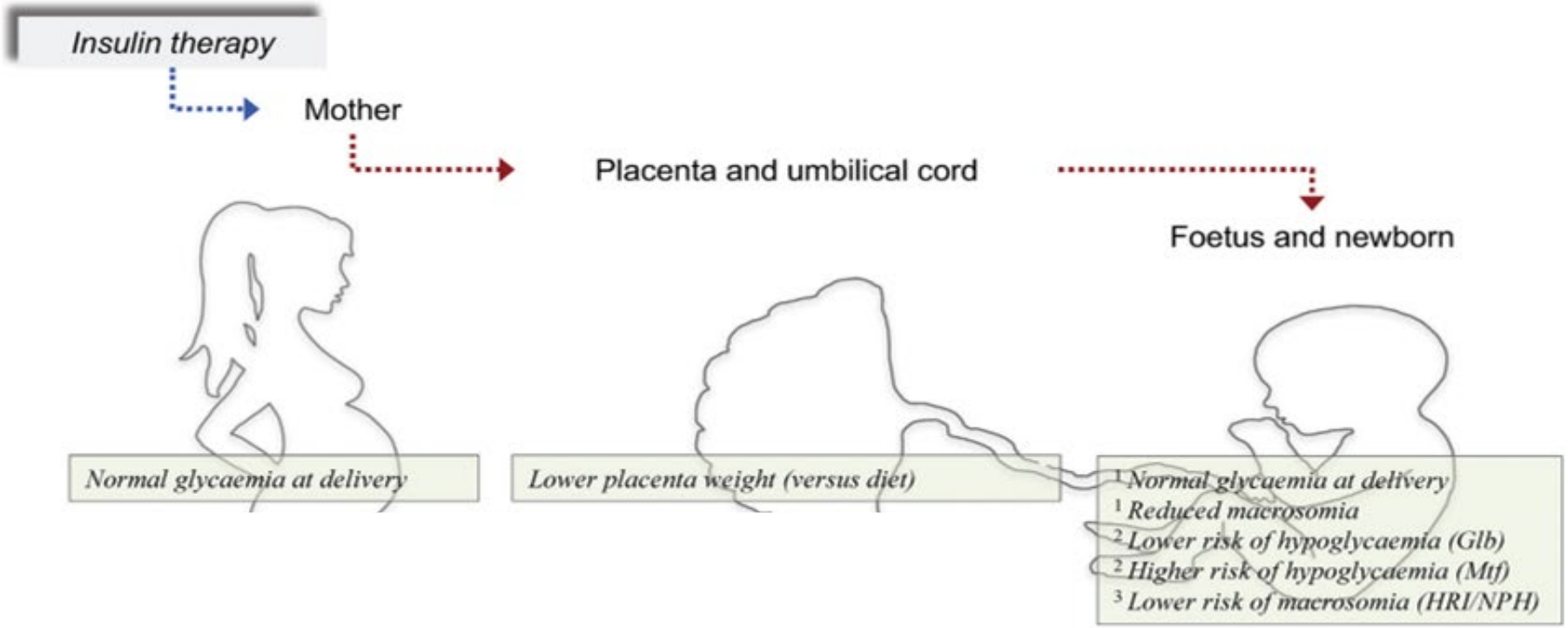


NICE 2015
metformina come prima linea di trattamento, possibile aggiunta di insulina

SMFM 2018
L'uso della metformina è ragionevole e sicuro.

AIFA 2022 e POSITION PAPER 2023 sottoscritto da SIMP e SIGO.

Insulin management of GDM



★ Insulin is the first-line antihyperglycemic medication recommended for treatment of GDM. None of the currently available insulin preparations has been demonstrated to cross the placenta.

★ Insulin remains the gold standard treatment for GDM women that do not reach glycemic targets with lifestyle intervention, as recommended by several guidelines. Insulin use reduces fetal and maternal morbidity

BBA - Molecular Basis of Disease 1864 (2018) 2949–295

Pregnancy physiology and insulin requirements

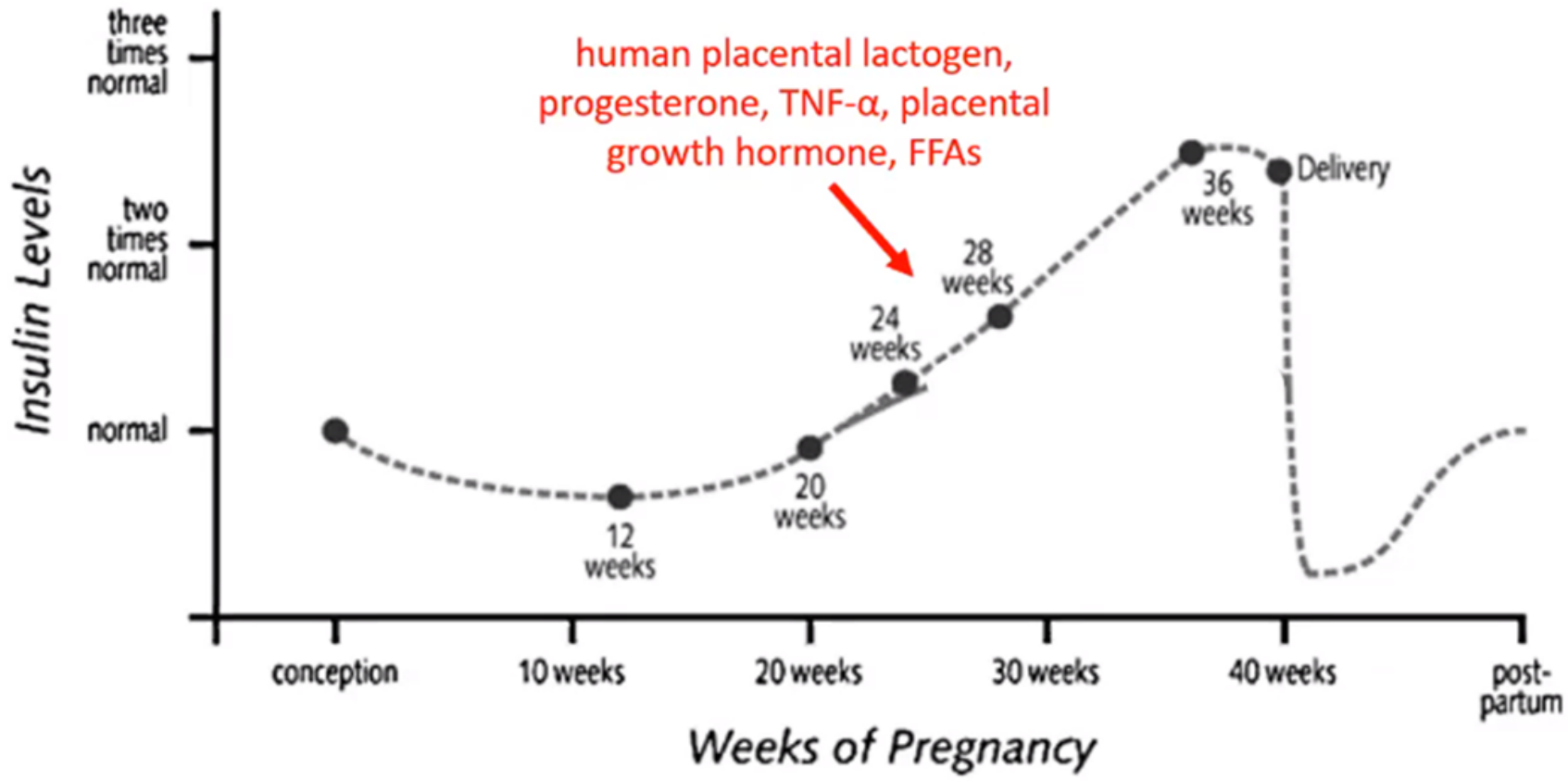


Figure Adapted from: Marcinkevage JA and Venkat Narayan KM. *Primary Care Diabetes* 2011; 5(2): 81-88.
Keely E, Barbour LA. Management of diabetes in pregnancy. *Endotext*. 2000-. 2014 Feb 14.
Ringholm L, et al. Nat Rev Endocrinol. 2012;8(11):659–667. Feldman AZ, et al. *Curr Diab Rep*. 2016.

Glycemic targets in pregnancy

	ADA 2018	SID-AMD 2018	FIGO 2015	CDA 2018
Fasting	≤ 95 mg/dL	**≤ 90 mg/dL**	≤ 95 mg/dL	≤ 95 mg/dL
One-hour postprandial	≤ 140 mg/dL	**≤ 130 mg/dL**	≤ 140 mg/dL	≤ 140 mg/dL
Two-hour postprandial	≤ 120 mg/dL	**≤ 120 mg/dL**	≤ 120 mg/dL	≤ 120 mg/dL

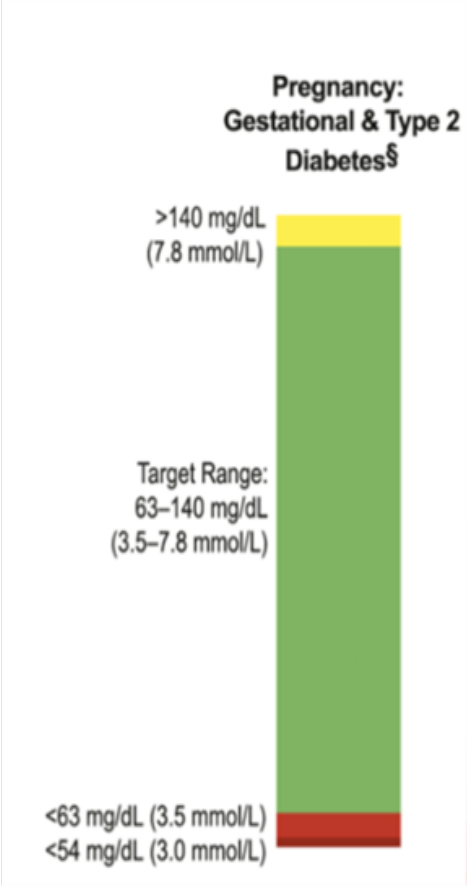
HbA1c the target is <6–6.5% (42–48 mmol/mol);
lower HbA1c—6% (42 mmol/mol) is optimal if it can be achieved without significant hypoglycemia

Diabetes Canada Clinical Practice Guidelines Expert Committee. 2018;**42**(Suppl 1):S1-S325
American Diabetes Association. Management of diabetes in pregnancy: Standards of medical care in diabetes.
Diabetes Care. 2024;**41**(Suppl.1):S137-S143. DOI: 10.2337/dc18-S013

Continuous glucose monitoring-derived glycemic metrics and adverse pregnancy outcome among women with GDM: a prospective cohort study

Prospective cohort study of 1302 pregnant women with GDM at 26.0 weeks and followed them until delivery

Participants underwent a 14-day CGM (Freestyle Libre Pro) measurement upon recruitment



	Total	Any adverse pregnancy outcome	
		No	Yes
No. of participants	1302 (100%)	790 (60.7%)	512 (39.3%)
Age, years	31.2 (3.7)	31.3 (3.7)	31.0 (3.6)
Gestational age at baseline, weeks	22.1 (3.5)	21.9 (3.6)	22.3 (3.5)
Pre-pregnancy BMI, kg/m^2	26.0 (1.9)	26.0 (1.9)	26.0 (1.8)
CGM-derived metrics			
TIR, %	92.8 (85.4, 96.7)	92.8 (85.2, 96.7)	92.8 (85.7, 96.7)
TAR, %	1.1 (0.3, 2.6)	1.0 (0.3, 2.5)	1.2 (0.3, 3.0)
TBR, %	4.0 (0.9, 12.3)	4.5 (1.0, 12.8)	3.4 (0.8, 11.3)
AUC, mmol/L·h	112.8 (105.0, 120.6)	111.9 (104.6, 119.6)	114.2 (106.2, 122.7)
Nighttime MBG, mmol/L	4.1 (3.7, 4.4)	4.0 (3.7, 4.4)	4.1 (3.8, 4.5)
Daytime MBG, mmol/L	4.9 (4.6, 5.3)	4.9 (4.6, 5.2)	5.0 (4.6, 5.4)
Daily MBG, mmol/L	4.7 (4.4, 5.1)	4.7 (4.4, 5.0)	4.8 (4.5, 5.2)
MAGE, mmol/L	2.3 (1.9, 2.7)	2.3 (1.9, 2.6)	2.3 (1.9, 2.7)
CV, %	20.1 (17.4, 23.0)	20.2 (17.5, 22.8)	20.0 (17.4, 23.3)

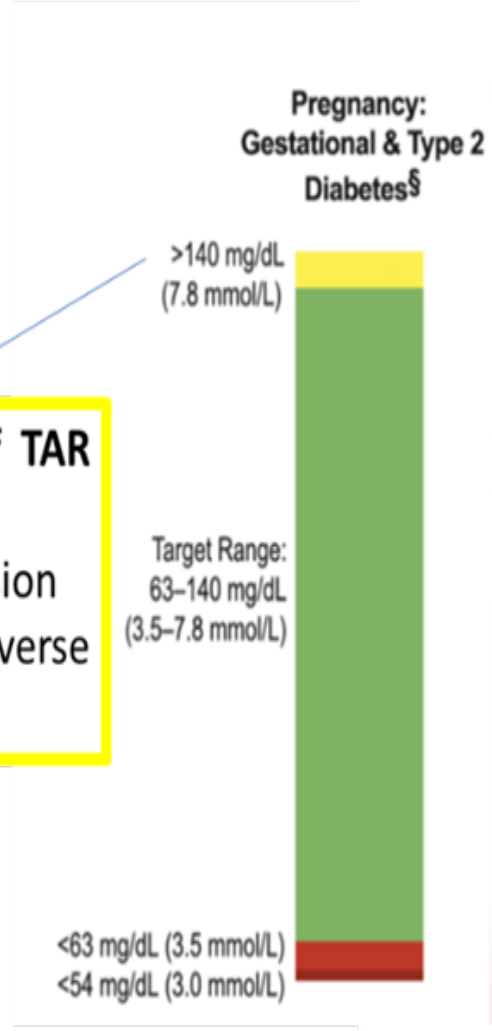
Diabetes Care 2017;40:1631–1640 | https://doi.org/10.2337/dc17-1600

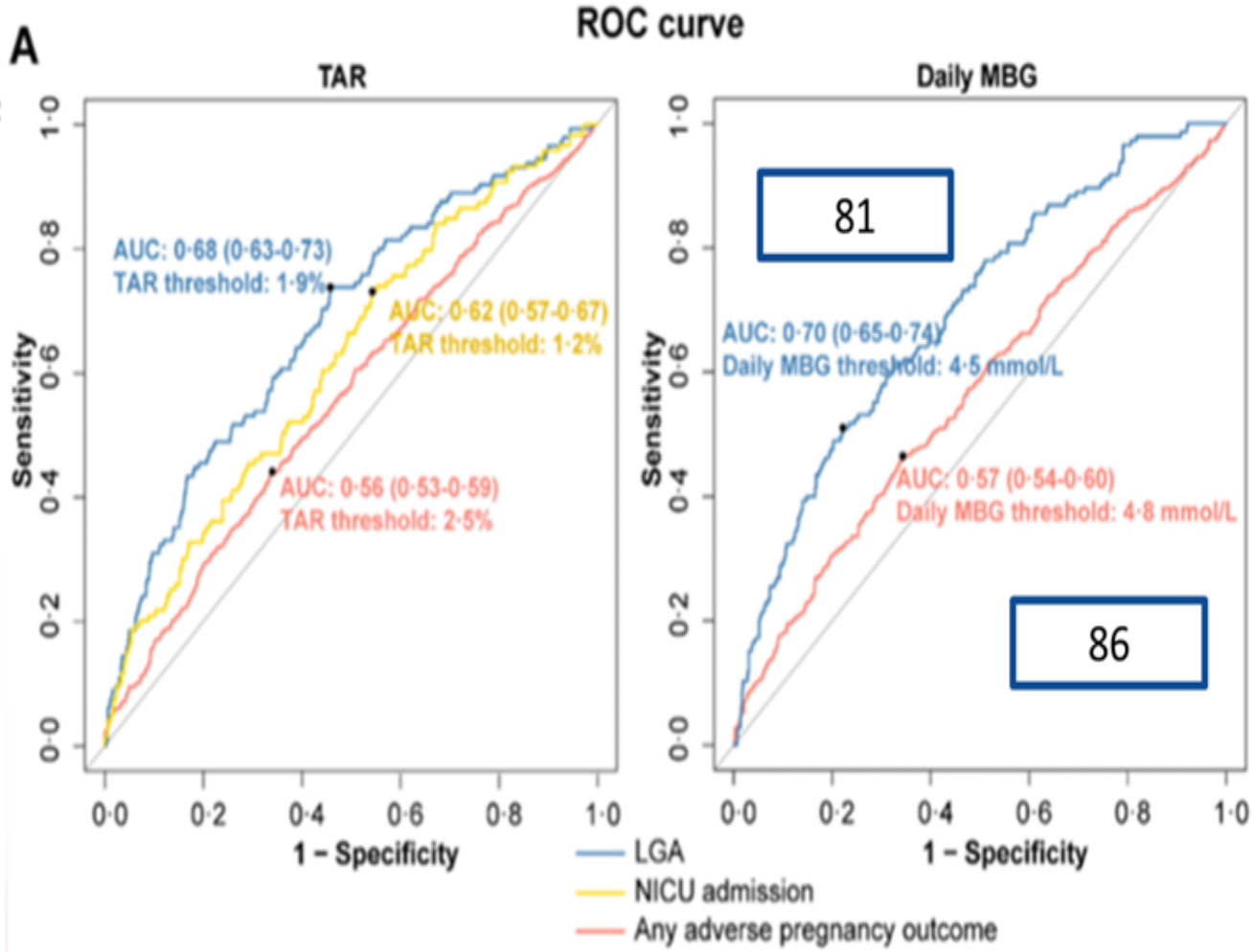
Liang, The Lancet Regional Health- Western Pacific 2023;39: 100823

Prospective cohort study of 1302 pregnant women with GDM at 26.0 weeks and followed them until delivery

Participants underwent a 14-day CGM (Free Pro) measurement upon recruitment

The cut-off value of TAR
1.9% for LGA
1.2% for NICU admission
2.5% for any adverse pregnancy outcome





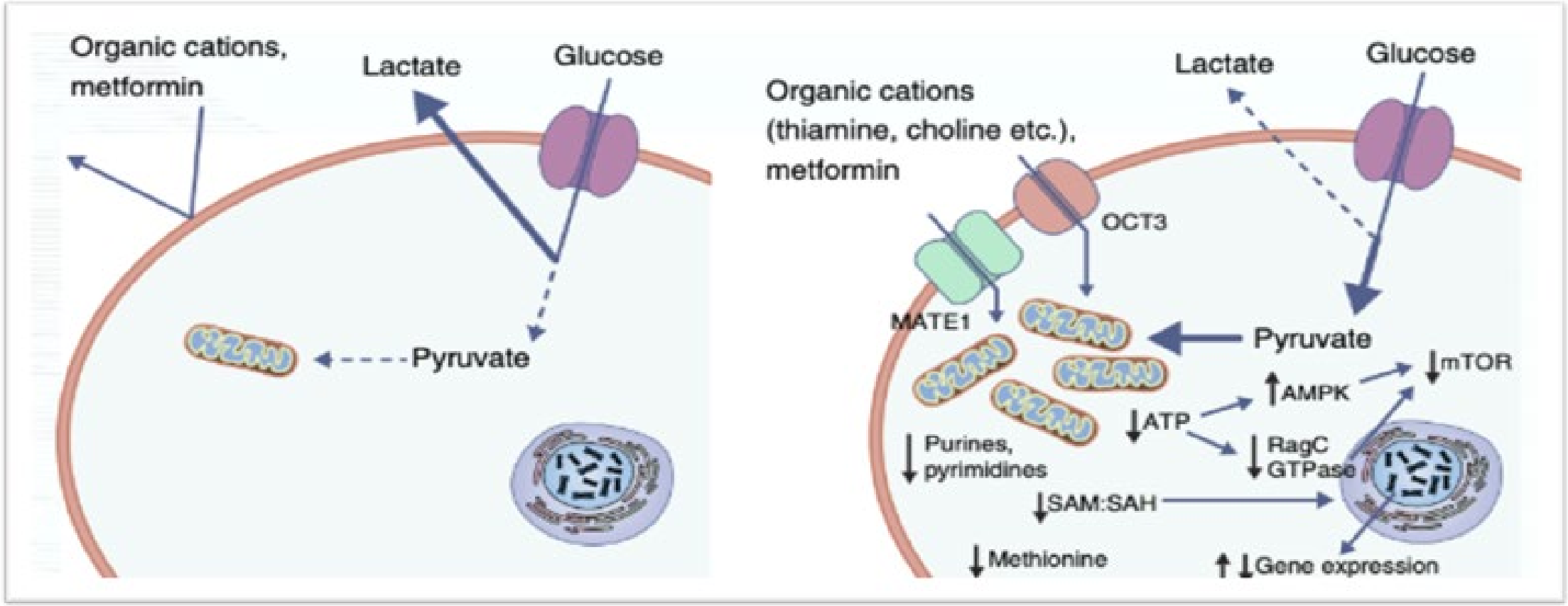
Metformina

2022: AIFA ha modificato l'indicazione terapeutica del farmaco Metformina cloridrato compresse a rilascio immediato e a rilascio prolungato relativamente all'uso in gravidanza e nel periodo peri-concezionale specificando che "se clinicamente appropriato, l'uso di metformina può essere considerato durante la gravidanza e nel periodo peri-concezionale in aggiunta o in alternativa alla terapia insulinica".

A proposed model for organic cation transport at the human placenta barrier

I TRIMESTER

II TRIMESTER



Lee HY 2014 Diabetes Metab Res 30:23-30 Feng L 2015 Gynecol Endocrinol 31:833-839

2023 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.

Table 8 Maternal outcomes in GDM women treated with metformin during pregnancy

	GDM women
Glycemic control	Comparable to insulin
Total insulin dose	Reduced as compared to insulin alone
Total GWG	Reduced
Gestational hypertension/Preeclampsia rate	No significant difference
Caesarian section	No significant difference
Preterm delivery (<37 weeks)	No significant difference

GWG, Gestational weight gain

Table 9 Neonatal and infant outcomes in GDM women treated with metformin during pregnancy

	GDM women
Newborns	
Birth weight	Lower
LGA/Macrosomia	Decreased
SGA	No significant difference
Hypoglycemia	Decreased
Neonatal intensive care unit admission	No significant difference
Infants	
BMI	Increased
Waist circumference	Increased

	MATERNAL OUTCOMES	INFANT OUTCOMES
Gestational Diabetes	Lower gestational weight gain (GWG) in obese women. Reduction in insulin dose in severe obese women.	Lower neonates birth weights. 7-9 years old infant are heavier and with higher waist circumferences, higher waist:height ratio, higher BMI and higher fat mass volume.

MIG trial 2008

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Metformin versus Insulin for the Treatment of Gestational Diabetes

Janet A. Rowan, M.B., Ch.B., William M. Hague, M.D., Wanzhen Gao, Ph.D., Malcolm R. Battin, M.B., Ch.B., and M. Peter Moore, M.B., Ch.B., for the MiG Trial Investigators*

Studio randomizzato.

733 donne con GDM tra 20-33sg con criteri per iniziare terapia: 363 pz insulina vs 370 pz Metformina (46% insulina supplementare).

BMI medio 35.

Outcome primario composito: ipoglicemia neonatale, distress respiratorio, necessità di fototerapia, traumi al parto, Apgar 5' < 7, prematurità.
Outcomes secondari: misure antropometriche neonatali, controllo glicemico materno, complicanze materne ipertensive, tolleranza glucidica post-partum, compliance al trattamento.

MIG trial

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

Non differenze significative nell'outcome primario composito (32.0% vs 32.2%, p 0.95).

Nel gruppo Metformina significativa riduzione di ipoglicemia neonatale severa.

Aumento di prematurità (↑ incidenza PP spontanei, non iatrogeni).

MIG trial: conclusioni

Nel gruppo metformina:

- Significativa **riduzione di GWG**;
- **Riduzione** della **quantità di insulina**;
- Significativa **riduzione di ipoglicemia neonatale severa**;
- **Non differenze significative tra gli outcomes secondari** (misure antropometriche neonatali);
- **Miglior compliance** al trattamento.

➡ **La Metformina** (da sola o con supplementazione di insulina) **è un'opzione di trattamento efficace e sicura per il GDM** che presenta i criteri per l'inizio della terapia farmacologica.

Diagnosi

1997

2011

Minicurva, OGTT 100 gr

OGTT 75 g

Dieta per 2 settimane,

se glicemie non controllate: **insulina**

Dieta per 2 sett, **metformina**,

+ insulina se non compenso

2008

Terapia

Current Research in Diabetes & Obesity Journal
ISSN: 2476-1435

Juniper Publishers

2018

Research Article
Volume 6 Issue 2 – March 2018
DOI: 10.19080/CRDOJ.2018.06.555684

Curre Res Diabetes & Obes J

Is Metformin a Safe and Effective Treatment of Gestational Diabetes Mellitus?

Clelia Callegari[1]*, Paola Algeri[1], Isabella Crippa[1], Eloisa Mariani[1], Serena Mussi[2], Irene Cameroni[1], Cristina Plevani[3], Nadia Roncaglia[1] and Patrizia Vergani[1]

Studio retrospettivo

763 pazienti con GDM: 78% in dieta; 22% in Metformina (5% con aggiunta di Insulina).

Table 1: Demographic characteristics of the study population.

	Diet (N=593)	Metformin (N=170)	p Value
Maternal Age	33.3±5.3	33.7±5.4	0.364
Nulliparity	331(55.8%)	81(47.7%)	0.067
Average pre-gestational BMI	25.6±5.3	29.1±6.2	<0.001
Pre-gestational BMI >30	86 (14.5%)	60(35.3%)	<0.001
GA at diagnosis (weeks)	28.2±5.0	25.3±6.0	<0.001
Caucasian ethnicity	455(76.7%)	93(54.7%)	<0.001
Asian ethnicity	63(10.6%)	30(17.7%)	0.017
Arab ethnicity	46(7.8%)	35(20.6%)	<0.001
Chronic Hypertension	15(2.5%)	13(7.7%)	0.004

Note: BMI: Body Mass Index; GA: Gestational Age

Table 2: Characteristics of pregnancy and delivery.

	Diet (N=593)	Metformin (N=170)	p Value
Cholestasis	18(3.0 %)	4(2.4%)	0.798
Preeclampsia	11(1.9%)	11(6.5%)	0.003
Hypotiroidism	63(10.6%)	35(20.6%)	<0.001
Intrauterine Fetal Demise	1(0.2%)	0	1.000
GA at delivery	39.0±2.0	38.0±1.2	<0.001
Preterm delivery <34 ws	9(1.5%)	2(1.2%)	1.000
Preterm delivery <37 ws	40(6.8%)	16(9.4%)	0.245
Induction of labor	239(44.7%)	116(79.5%)	<0.001
Vaginal delivery	482(81.3 %)	134(78.8%)	0.508
CS	111(18.7%)	36(21.2%)	0.508
Elective CS	58(52.3%)	34(66.7%)	0.176
CS in labour	53(47.7%)	12(33.3%)	0.176

Note: GA: Gestational Age; CS: Cesarean Section

Table 3: Neonatal outcomes.

	Diet (N=593)	Metformin (N=170)	p Value
Birth Weight (g)	3255±513	3166±523	0.049
Macrosomia (>4000g)	34(5.7%)	4(2.4%)	0.107
LGA	33(5.6%)	14(8.2%)	0.208
SGA	23(3.9%)	7(4.1 %)	0.825
Apgar 5 min <7	9(1.5%)	3(1.8%)	0.735
pH <7.10	14(2.4%)	1(0.6%)	0.211
NICU admission	41(7.0%)	9(5.3%)	0.598
Jaundice	83(14.1%)	42(24.7%)	0.001
Hypoglycemia	13(2.2%)	3(1.8%)	1.000
Shoulder Dystocia	2(0.3%)	-	1.000
Neonatal fractures	1(0.2%)	1(0.6%)	0.397
RDS	14(2.4%)	3(1.8%)	0.776

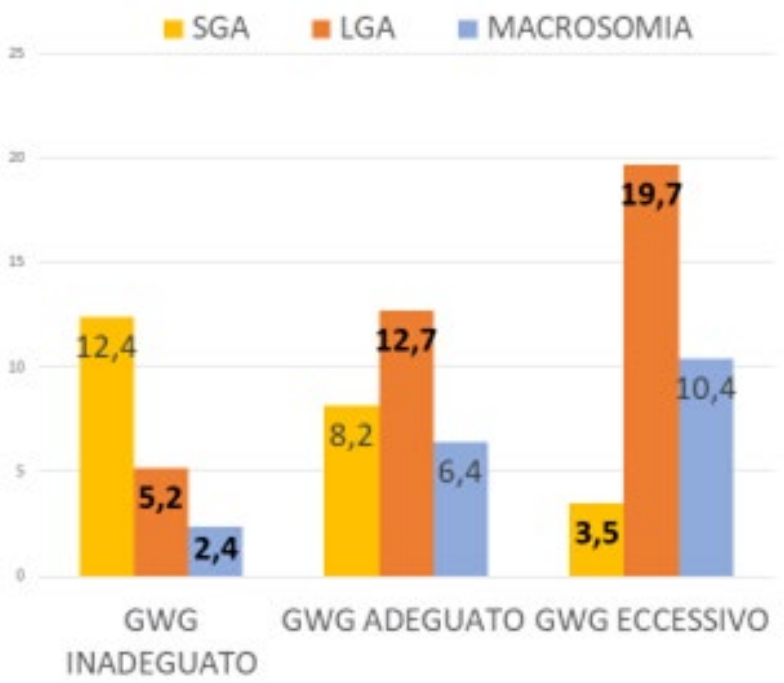
Note: LGA: Large for Gestational Age; SGA: Small for Gestational Age; NICU: Neonatal Intensive Care Unit; RDS: Respiratory Distress Syndrome

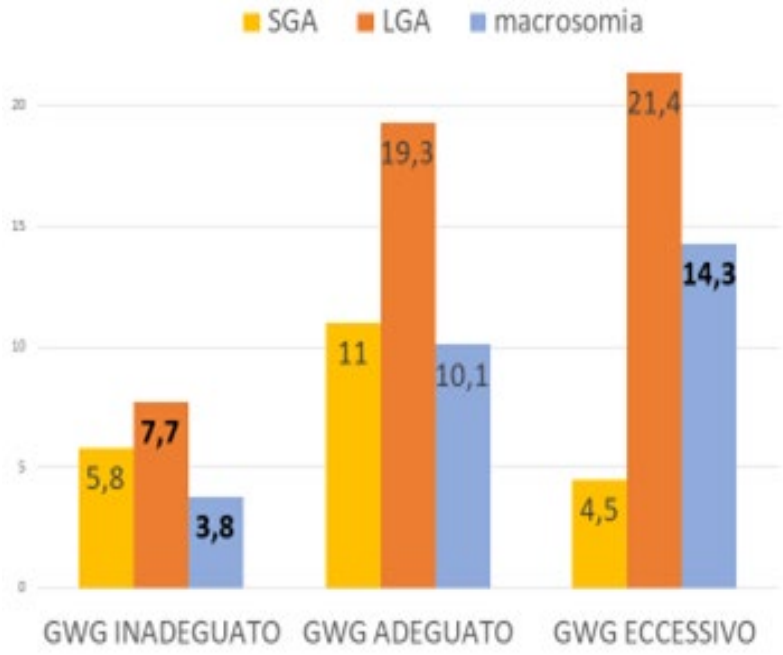
Conclusione:

Sebbene **la Metformina** sia utilizzata nelle pazienti con una forma più grave di GDM, essa **consente di** ottenere **esiti materni e perinatali simili a quelli delle pazienti con GDM meno severo** trattabile solo la dieta.

Eccessivo GWG e peso alla nascita

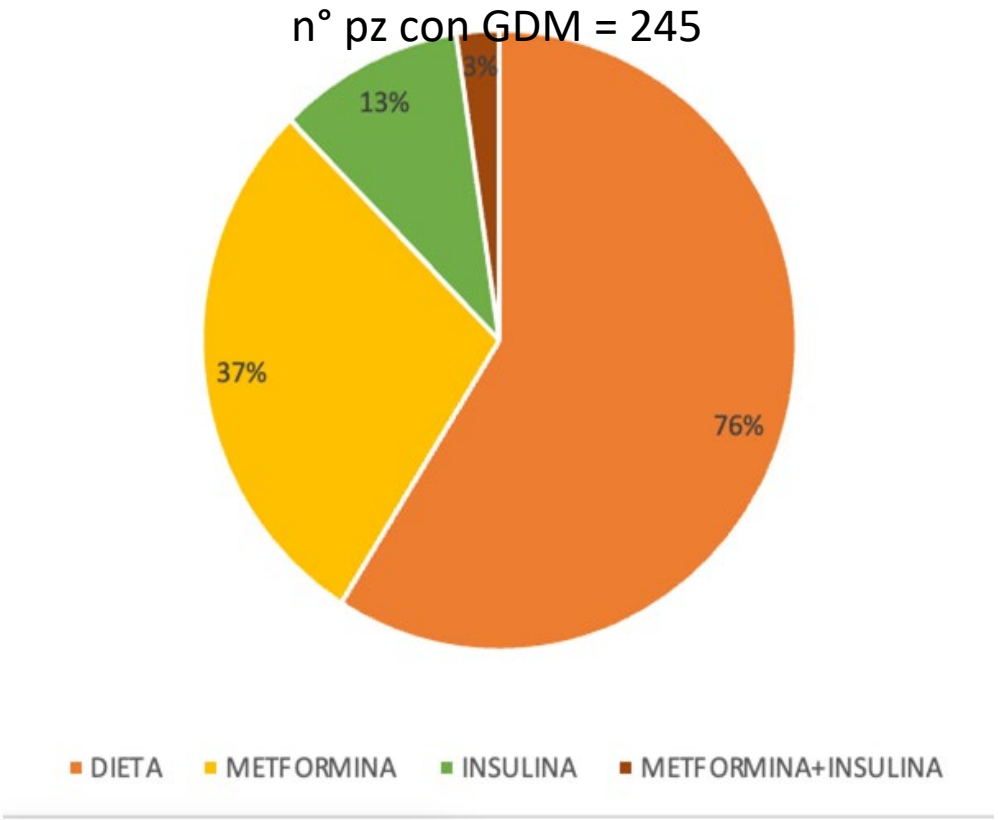
Da 01/2011 a 12/2017
Parti totali: 19 258
Diagnosi di GDM 1655 (8,5%)
BMI >30: 22%





Obesità (BMI >30): peso neonatale in relazione al GWG

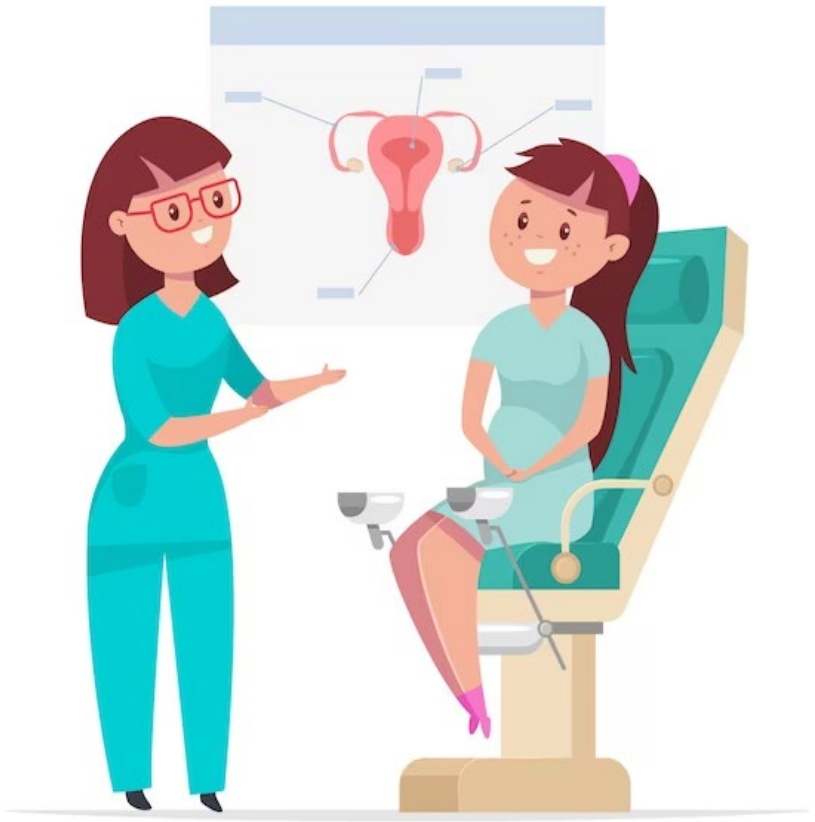
2023



	Dieta	Metformina	p Value
BMI pregravidico ≥ 30	21,3	51,3	<.001
Etnia caucasica	80	59	.011
Etnia araba	6,3	28,2	<.001
Incremento ponderale materno (Kg)	15	8,7	.014

Non differenze negli esiti materni e neonatali (ittero, ipoglicemia, ricovero in NICU, peso alla nascita)

OBIETTIVI DEL GINECOLOGO



- Controllare aumento del peso materno in gravidanza (soprattutto nelle pazienti obese);
- Controllare iperglicemie;
- Evitare ipoglicemie materne;
- Prevenire neonati SGA e LGA/macrosomia;
- Evitare ipoglicemie neonatali.

Esiti a breve termine

pharmaceuticals 2023

Review

Metformin in Gestational Diabetes Mellitus: To Use or Not to Use, That Is the Question

Vera Tocci [1,2,†], Maria Mirabelli [1,2,†], Alessandro Salatino [1], Luciana Sicilia [2], Stefania Giuliano [2], Francesco S. Brunetti [1], Eusebio Chiefari [1], Giovambattista De Sarro [1], Daniela P. Foti [3] and Antonio Brunetti [1,2,*]

Table 4. Summary of meta-analyses investigating the comparative effects of metformin administration during pregnancy in relation to alternative treatment options.

Meta-Analysis Outcomes	Summary of Results
Maternal outcomes §	• Lower gestational weight gain (mean difference 1.57 kg ± 0.60 kg) • Lower risk of any hypertensive disease of pregnancy (including pre-eclampsia) (odd ratio 0.76, 95% CI 0.60–0.95) • Higher risk of gastrointestinal side-effects (odds ratio 2.43, 95% CI 1.53–3.84) • No difference in risk of preterm birth (spontaneous or iatrogenic) (odds ratio 0.90, 95% CI OR 0.67–1.21) • No difference in risk of delivery by caesarean section (odds ratio 0.90, 95% CI 0.82–1.00) • Lower risk of maternal hypoglycemia (odds ratio 0.47, 95% CI 0.28–0.80)
Neonatal outcomes ‡	• Lower neonatal birthweight (mean difference −73.92 g, 95% CI −114.79–−33.06 g) • Lower risk of neonatal macrosomia (OR 0.60, 95% CI 0.45–0.79) • No difference in neonatal abdominal circumference (mean difference 0.00 cm, 95% CI −0.44–0.44 cm)

Esiti a breve termine

Acta Diabetologica (2023) 60:595–608
https://doi.org/10.1007/s00592-022-02016-5

2023

REVIEW ARTICLE

Short-term neonatal outcomes in women with gestational diabetes treated using metformin versus insulin: a systematic review and meta-analysis of randomized controlled trials

Bo Sheng[1,3] · Juan Ni[1,3] · Bin Lv[2,3] · Guoguo Jiang[4] · Xuemei Lin[1,3] · Hao Li[1,3]

24 studi - 4355 donne con GDM

RISULTATI:

neonati esposti in utero a Metformina vs Insulina:

- minor peso alla nascita (mean difference − 122 g; $p < 0.0001$)
- riduzione del 30% del rischio di macrosomia (RR 0.68; 95% CI 0.54, 0.86; $p = 0.001$)
- minor ricoveri in NICU (RR 0.73; 95% CI 0.61,0.88; $p = 0.0009$)
- riduzione del 44% di ipoglicemia neonatale (RR 0.65; 95% CI 0.52, 0.81; $p = 0.0001$)

NON CORRELAZIONE TRA ESITI E DOSE DI METFORMINA

Conclusions Our meta-analysis provides further evidence that metformin is a safe oral antihyperglycemic drug and has some benefits over insulin when used for the treatment of gestational diabetes, without an increased risk of short-term neonatal adverse outcomes. Metformin may be particularly useful in women with gestational diabetes at high risk for neonatal hypoglycemia, women who want to limit maternal and fetal weight gain, and women with an inability to afford or use insulin safely.

OBIETTIVI DEL DIABETOLOGO

- Mantenere uno stato di normoglicemia al fine di ridurre le complicanze materne e fetali, senza indurre episodi di ipoglicemia.
- Gestire la terapia medico-nutrizionale e valutare gli obiettivi di incremento ponderale
- Garantire alla paziente con GDM la terapia con maggior comprovata sicurezza e efficacia per lei e il bambino
- Intercettare e trattare le donne con GDM che presentano un rischio a lungo termine di sviluppare diabete di tipo 2

JAMA | Original Investigation

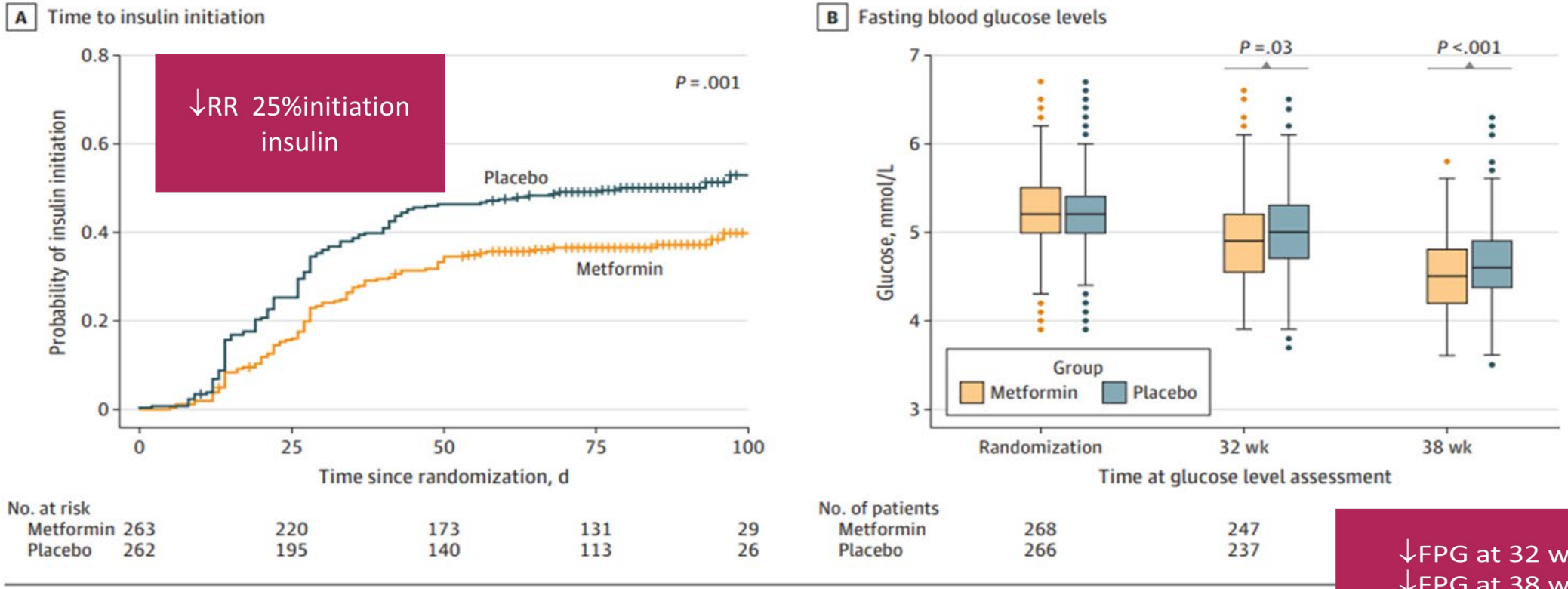
Early Metformin in Gestational Diabetes
A Randomized Clinical Trial

Double-blind placebo-controlled trial in 2 center in Ireland

510 women with GDM
At 27 weeks of gestation
BMI: 35 KG/Mq at enrollement

Metformin (2.5 g/day) vs. placebo

Figure 2. Time to Insulin Initiation and Fasting Blood Glucose Between Metformin and Placebo Groups



↓FPG at 32 wk
↓FPG at 38 wk

Long Term Fetal Outcome: 7-9 YEARS OF AGE

MiG TOFU

Longitudinal Follow-up study of the offspring of MiG

7 years in Adelaide
9 years in Auckland

BIA, DEXA, MRI

Table 3 Subgroup of children seen at 7–9 years: measures at age 2 years

	7 years subgroup also seen at 2 years (Adelaide) n=79			9 years subgroup also seen at 2 years (Auckland) n=99		
	Metformin n=40	Insulin n=39	P values	Metformin n=45	Insulin n=54	P values
Age (years)	2.7±0.2	2.7±0.2	0.90	2.3±0.2	2.3±0.3	0.29
Male/female (n)	25/15	18/21	0.22	28/17	28/26	0.32
Weight (kg)	14.9±1.6	14.8±2.2	0.70	14.0±2.3	13.3±1.9	0.09
Height (cm)	93.3±3.8	93.8±4.2	0.58	89.4±4.7	89.9±4.6	0.55
Leg length (cm)	38.7±2.8	39.4±2.8	0.40	37.3±3.2	37.7±3.7	0.60
Head circumference (cm)	50.2±1.3	49.7±1.7	0.17	49.3±1.6	49.0±2.1	0.34
Chest circumference (cm)	52.8±2.5	52.2±3.0	0.40	52.2±3.0	50.7±2.7	0.01
Mid-upper arm circumference (cm)	16.8±1.2	16.5±1.4	0.25	17.5±1.6	16.3±1.3	0.0001
Waist circumference (cm)	51.0±3.0	50.2±3.2	0.30	50.5±3.6	48.8±3.7	0.02
Hip circumference (cm)	52.6±2.8	52.4±3.6	0.83	51.9±4.2	50.3±3.7	0.0496
Waist:height ratio	0.53±0.03	0.53±0.02	0.24	0.56±0.04	0.54±0.04	0.01
Triceps skinfold thickness (mm)	9.5±1.9	9.1±2.0	0.40	10.2±2.2	9.8±2.2	0.37
Subscapular skinfold thickness (mm)	6.2±1.3	5.9±1.4	0.31	7.2±2.1	6.3±1.9	0.02
Biceps skinfold thickness (mm)	5.4±1.4	5.0±1.2	0.25	6.7±1.9	5.9±1.9	0.046
DXA	n=11	n=11		n=28	n=37	
Fat-free mass (kg)	12.1±1.2	12.0±1.5	0.80	11.1±1.5	11.0±1.5	0.79
Total fat (g)	2310±643	2162±390	0.51	2406±1016	2145±714	0.25
Abdominal fat (g)	122±37	109±37	0.42	127±77	123±65	0.81
Thigh fat (g)	264±49	257±87	0.83	258±110	246±96	0.65
Arm fat (g)	185±61	191±67.0	0.82	205±114	163±79	0.10
Abdominal fat:thigh fat ratio	0.5±0.1	0.4±0.1	0.56	0.5±0.1	0.5±0.5	0.37
Total fat %	16.0±3.8	15.3±2.0	0.58	17.3±5.1	16.0±3.6	0.25
Abdominal fat: % of total fat mass	0.5±0.1	0.4±0.1	0.56	0.5±0.1	0.5±0.5	0.37
Bioimpedance	n=28	n=31		n=33	n=43	
Fat-free mass (kg)	12.9±1.4	12.7±1.8	0.56	11.2±1.6	11.0±1.5	0.67
Total fat %	12.8±5.5	13.6±4.5	0.57	17.2±5.0	17.5±4.8	0.80

AUCKLAND COHORT 9 YEARS

	Metformin	Insulin	p value
Weight (kg)	14.3±2.1	14.0±2.2	0.18
Waist (cms)	50.5±3.5	50.1±4.0	0.33
Upper arm circ (cms)	17.2±1.5	16.7±1.5	0.002
Triceps skinfold (cms)	10.1±2.0	9.9±2.4	0.5
Subscapular skinfold (cms)	6.3±1.9	6.0±1.7	0.02
Biceps skinfold (cms)	6.0±1.9	5.6±1.7	0.04
DEXA total fat (g)	2421±1002	2274±711	0.37
Abdominal fat (g)	132±73	131±60	0.92

BMJ Open Diab Res Care 2018;6:e000456

ADELAIDE COHORT 7 YEARS

- Baseline characteristics: similar metformin vs insulin
- Metformin group had higher glycemia
- Metformin offspring were LARGER at birth

AUCKLAND COHORT 9 YEARS

- Population heterogeneous: in metformin group women had higher BMI
- Maternal glycemia were similar
- Metformin group had less weight gain

Higher nutrient load in utero (higher maternal glucose) «protected» by metformin

«Undernutrition» for the fetus with a lower birth weight led to offspring with higher sc fat

Do not overrestric the intake of CHO and calories and stop metformin if there are signs of placental insufficiency

Metformin versus insulin therapy for gestational diabetes: Effects on offspring anthropometrics and metabolism at the age of 9 years: A follow-up study of two open-label, randomized controlled trials

TABLE 1 Anthropometric measures and blood pressure at the age of 9 years in the offspring of mothers with gestational diabetes mellitus treated with metformin or insulin

	All children			Boys			Girls		
	Metformin n = 82	Insulin n = 90	*P* value	Metformin n = 42	Insulin n = 44	*P* value	Metformin n = 40	Insulin n = 46	*P* value
Age, years	9.0 (9.0-9.1)	9.0 (9.0-9.1)	0.50†	9.0 (9.0-9.1)	9.0 (9.0-9.1)	0.27†	9.0 (9.0-9.1)	9.1 (9.0-9.1)	0.87†
Height, cm	136.7 ± 6.01	136.4 ± 6.66	0.74	137.5 ± 6.12	137.9 ± 7.43	0.80	135.9 ± 5.86	135.0 ± 5.56	0.46
Relative height, SD	0.11 ± 1.06	0.09 ± 1.12	0.90	0.14 ± 1.11	0.26 ± 1.31	0.66	0.09 ± 1.01	-0.06 ± 0.90	0.47
Weight, kg	32.6 (29.5-37.9)	32.8 (28.6-40.5)	0.92†	32.3 (29.0-39.1)	33.8 (28.5-40.6)	0.62†	33.5 (29.8-37.0)	32.0 (28.6-39.5)	0.49†
BMI, kg/m^2	17.5 (16.3-19.4)	17.7 (16.1-20.1)	0.78†	17.3 (16.0-18.8)	17.9 (16.3-20.8)	0.46†	17.8 (16.9-19.6)	17.6 (16.0-20.0)	0.79†
Normal weight§ (adjusted BMI < 25.0 kg/m^2)	60 (73.2)	60 (66.7)	0.35‡	32 (76.2)	31 (70.5)	0.55‡	28 (70.0)	29 (63.0)	0.50‡
Overweight or obese§ (adjusted BMI ≥ 25.0 kg/m^2)	22 (26.8)	30 (33.3)		10 (23.8)	13 (29.5)		12 (30.0)	17 (37.0)	
Waist circumference, cm	59.3 (56.2-64.5)	59.7 (55.9-66.9)	0.55†	59.3 (56.1-64.1)	61.7 (58.2-69.9)	0.17†	59.4 (56.2-64.8)	58.2 (54.8-65.5)	0.69†
Waist: height ratio	0.43 (0.4-0.5)	0.44 (0.4-0.5)	0.20†	0.43 (0.4-0.5)	0.45 (0.4-0.50)	0.06†	0.44 (0.4-0.5)	0.44 (0.4-0.5)	0.92†
Waist: height ratio < 0.5	69 (84.1)	76 (84.4)	0.96‡	36 (85.7)	36 (81.8)	0.63‡	33 (82.5)	40 (87.0)	0.57‡
Waist: height ratio > 0.5	13 (15.9)	14 (15.6)		6 (14.3)	8 (18.2)		7 (17.5)	6 (13.0)	
Systolic BP, mmHg	106.0 ± 9.38	104.8 ± 9.84	0.43	106.5 ± 9.22	107.2 ± 9.97	0.76	105.3 ± 9.62	102.5 ± 9.24	0.42†
Diastolic BP, mmHg	59.4 ± 7.35	60.2 ± 7.57	0.45	61.9 ± 7.62	60.1 ± 7.53	0.23†	58.7 ± 7.10	58.7 ± 7.36	1.00

Note: Data are expressed as mean ± standard deviation, median (interquartile range) or n (%). The *t*-test was used unless stated otherwise (†Mann-Whitney *U*-test, chi-squared or ‡Fisher's exact test). §Age- and sex-specific adjusted BMI cut-off points are used according to Cole et al.[25]

Abbreviations: BP, blood pressure; BMI, body mass index.

Elisa Paavilainen Diabetes Obes Metab. 2022;24:402–410

Metformin in pregnancy and childhood neurodevelopmental outcomes: a systematic review and meta-analysis

Hannah G. Gordon, MD; Jessica A. Atkinson, BBiomedSc (Hons); Stephen Tong, PhD; Parinaz Mehdipour, PhD; Catherine Cluver, PhD; Susan P. Walker, MD; Anthea C. Lindquist, DPhil; Roxanne M. Hastie, PhD

RESULTS:

7 studies - 14.042 children; follow up 14 years of age.

Metformin use during pregnancy was not associated with neurodevelopmental delay in infancy (RR, 1.09; 95% CI 0.54-2.17) or at ages 3 to 5 years (RR 0.90; 95% CI 0.56-1.45).

When compared with unexposed peers, metformin use during pregnancy was **not associated with altered motor scores** (mean difference, 0.30; 95% CI 1.15-1.74) **or cognitive scores** (mean difference, 0.45; 95% CI 1.45-0.55).

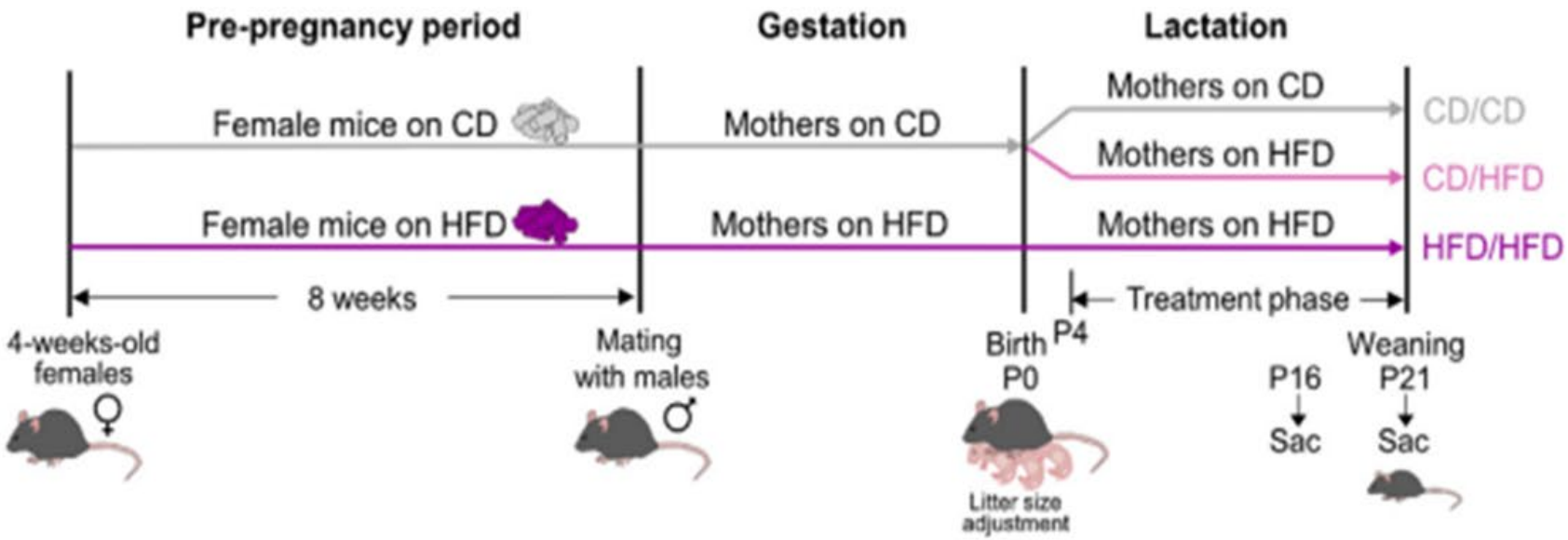
CONCLUSION:

in utero exposure to metformin does not seem to be associated with adverse neurodevelopmental outcomes in children up to the age of 14 years. These findings provide reassurance to clinicians and pregnant women considering metformin use during pregnancy.

Does metformin treatment lead to long-term negative physiological changes in the offspring, especially in connection with the development of neuronal circuits in the hypothalamus, a critical region in the regulation of energy homeostasis?

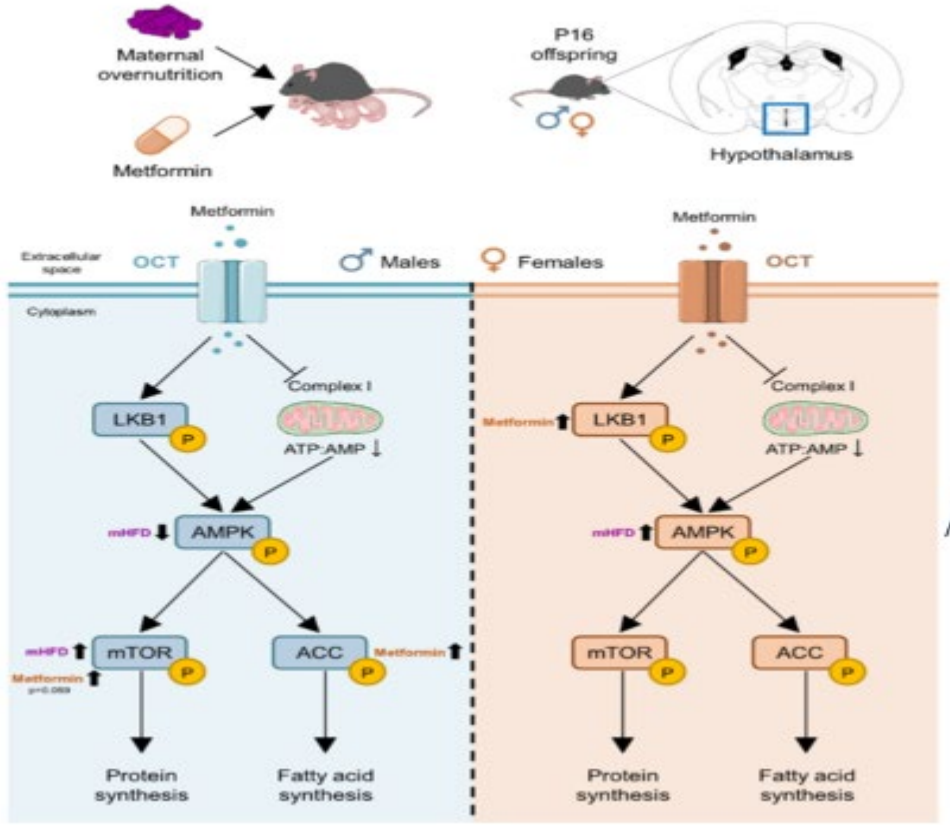
severe obesity before pregnancy

excessive weight gain during pregnancy



- These metabolic states were achieved by means of different feeding patterns, with the mice receiving either a high-fat or control diet.
- Treatment involved insulin, metformin, or a placebo, whereby the dosage was based on standard human treatments.

Cantacorps, Molecular Metabolism, Volume 79, 2024, ISSN 2212-8778, https://doi.org/10.1016/j.molmet.2023.101860.

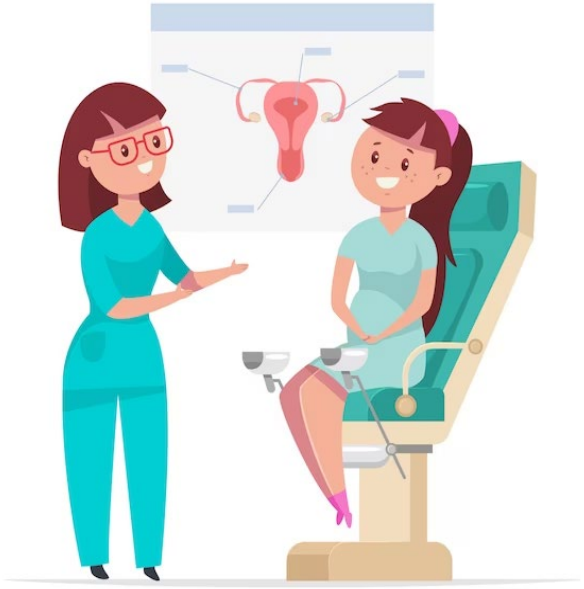


Sex-Specific Brain Signaling Changes

Early metformin exposure increased phosphorylation of the upstream kinase LKB1 in females, whereas downstream components of AMPK signaling were affected in males.

- ★ As a result of antidiabetic treatment **we were able to identify alterations in the weight gain and hormonal status of the offspring, which were critically dependent on the metabolic state of the mother**. Indicate that the maternal metabolic state must be taken into account before starting the treatment of gestational diabetes.
- ★ Our results therefore highlight the need for a deeper understanding of how maternal metabolic state (**excessive weight gain versus stable weight during GDM treatment**) affects the developing offspring.
- ★ **Sex-Specific Brain Signaling Changes:** The study identifies sex-specific alterations in hypothalamic AMPK signaling in offspring exposed to metformin, pointing to nuanced differences in treatment response

CONCLUSIONI DEL GINECOLOGO



- Controllare aumento del peso materno in gravidanza (soprattutto nelle pazienti obese);
- Controllare iperglicemie;
- Evitare ipoglicemie;
- Prevenire neonati SGA e LGA/macrosomia;
- Evitare ipoglicemie neonatali.

TERAPIA PERSONALIZZATA

- BMI MATERNO
- COMPLIANCE DELLA PAZIENTE
- RISCHIO SGA/COMORBILITA' MATERNE
- SESSO FETALE

Necessità di ulteriori studi su effetti a lungo temine

CONCLUSIONI DEL DIABETOLOGO

- ★ Terapia personalizzata più adeguata per ogni paziente
- ★ L'utilizzo della metformina deve essere valutato come una terapia di supporto in popolazioni selezionate.
- ★ Aggiornamento delle raccomandazioni con le nuove EBM
- ★ Studi long-term con fenotipizzazione genetica e cluster metabolici delle donne con GDM

Conclusioni