Ospedale di Bergamo

Sistema Socio Sanitario

Regione Lombardia

ASST Papa Giovanni XXIII

COMPLICANZE MATERNO-FETALI DEL DIABETE PRE-GESTAZIONALE

DR.SSA CHIARA BOSISIO - MMF ASST-PG23

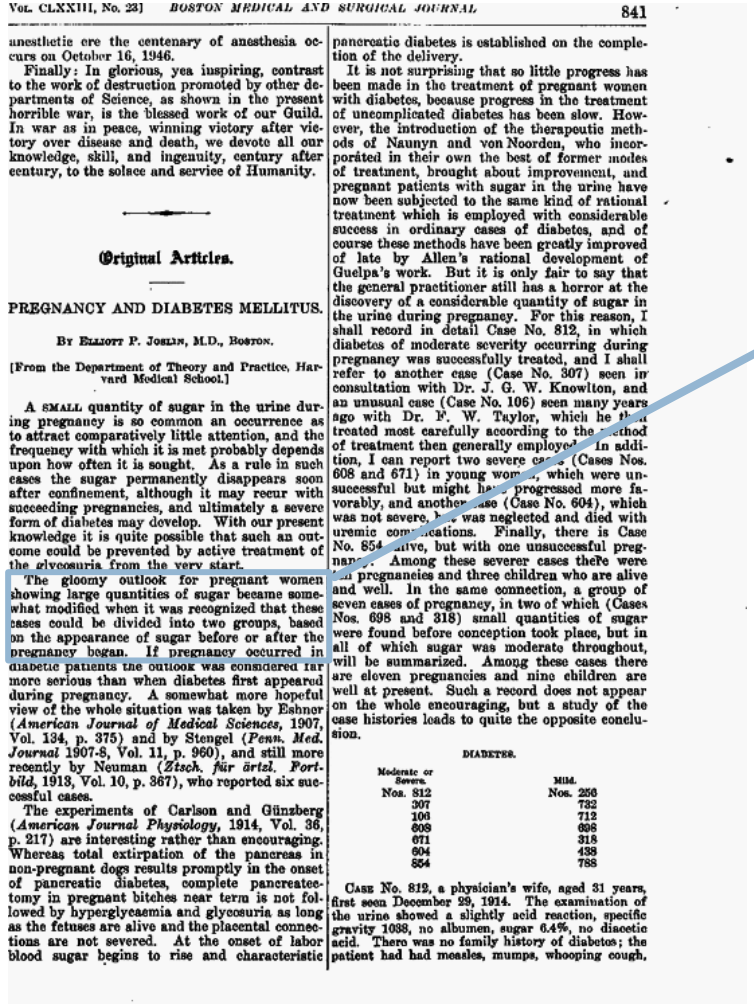
DISCLOSURE

La dr.ssa Chiara Bosisio dichiara di NON aver ricevuto negli ultimi due 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.).

DIABETES IN PREGNANCY: THE BEGINNING



Vol. CLXXIII, No. 23] BOSTON MEDICAL AND SURGICAL JOURNAL 841

anesthetic ere the centenary of anesthesia occurs on October 16, 1946.

Finally: In glorious, yea inspiring, contrast to the work of destruction promoted by other departments of Science, as shown in the present horrible war, is the blessed work of our Guild. In war as in peace, winning victory after victory over disease and death, we devote all our knowledge, skill, and ingenuity, century after century, to the solace and service of Humanity.

Original Articles.

PREGNANCY AND DIABETES MELLITUS.

By Elliott P. Joslin, M.D., Boston.

[From the Department of Theory and Practice, Harvard Medical School.]

A small quantity of sugar in the urine during pregnancy is so common an occurrence as to attract comparatively little attention, and the frequency with which it is met probably depends upon how often it is sought. As a rule in such cases the sugar permanently disappears soon after confinement, although it may recur with succeeding pregnancies, and ultimately a severe form of diabetes may develop. With our present knowledge it is quite possible that such an outcome could be prevented by active treatment of the glycosuria from the very start.

The gloomy outlook for pregnant women showing large quantities of sugar became somewhat modified when it was recognized that these cases could be divided into two groups, based on the appearance of sugar before or after the pregnancy began. If pregnancy occurred in diabetic patients the outlook was considered far more serious than when diabetes first appeared during pregnancy. A somewhat more hopeful view of the whole situation was taken by Eshner (*American Journal of Medical Sciences*, 1907, Vol. 134, p. 375) and by Stengel (*Penn. Med. Journal* 1907-8, Vol. 11, p. 960), and still more recently by Neuman (*Ztsch. für ärtzl. Fortbild*, 1913, Vol. 10, p. 367), who reported six successful cases.

The experiments of Carlson and Günzberg (*American Journal Physiology*, 1914, Vol. 36, p. 217) are interesting rather than encouraging. Whereas total extirpation of the pancreas in non-pregnant dogs results promptly in the onset of pancreatic diabetes, complete pancreatectomy in pregnant bitches near term is not followed by hyperglycaemia and glycosuria as long as the fetuses are alive and the placental connections are not severed. At the onset of labor blood sugar begins to rise and characteristic pancreatic diabetes is established on the completion of the delivery.

It is not surprising that so little progress has been made in the treatment of pregnant women with diabetes, because progress in the treatment of uncomplicated diabetes has been slow. However, the introduction of the therapeutic methods of Naunyn and von Noorden, who incorporated in their own the best of former modes of treatment, brought about improvement, and pregnant patients with sugar in the urine have now been subjected to the same kind of rational treatment which is employed with considerable success in ordinary cases of diabetes, and of course these methods have been greatly improved of late by Allen's rational development of Guelpa's work. But it is only fair to say that the general practitioner still has a horror at the discovery of a considerable quantity of sugar in the urine during pregnancy. For this reason, I shall record in detail Case No. 812, in which diabetes of moderate severity occurring during pregnancy was successfully treated, and I shall refer to another case (Case No. 307) seen in consultation with Dr. J. G. W. Knowlton, and an unusual case (Case No. 106) seen many years ago with Dr. F. W. Taylor, which he then treated most carefully according to the method of treatment then generally employed. In addition, I can report two severe cases (Cases Nos. 608 and 671) in young women, which were unsuccessful but might have progressed more favorably, and another case (Case No. 604), which was not severe, but was neglected and died with uremic complications. Finally, there is Case No. 854 alive, but with one unsuccessful pregnancy. Among these severer cases there were [illegible] pregnancies and three children who are alive and well. In the same connection, a group of seven cases of pregnancy, in two of which (Cases Nos. 698 and 318) small quantities of sugar were found before conception took place, but in all of which sugar was moderate throughout, will be summarized. Among these cases there are eleven pregnancies and nine children are well at present. Such a record does not appear on the whole encouraging, but a study of the case histories leads to quite the opposite conclusion.

DIABETES.

Moderate or Severe.	Mild.
Nos. 812	Nos. 256
307	732
106	712
608	698
671	318
604	439
854	788

Case No. 812, a physician's wife, aged 31 years, first seen December 29, 1914. The examination of the urine showed a slightly acid reaction, specific gravity 1038, no albumen, sugar 6.4%, no diacetic acid. There was no family history of diabetes; the patient had had measles, mumps, whooping cough,

The gloomy outlook for pregnant woman showing large quantities of sugar (in the urine) become somewhat modified when it was recognized that these case could be divided into tow groups, based on the **appearance of sugar before or after the pregnancy began.**

Bianchi, 2023

DEFINITIONS

Gestational diabetes (GDM) :

- Diabetes detected for the first time during pregnancy.
- Some cases may be type 2 diabetes not known before pregnancy.

Pre-gestational Diabetes (DM1 or DM2):

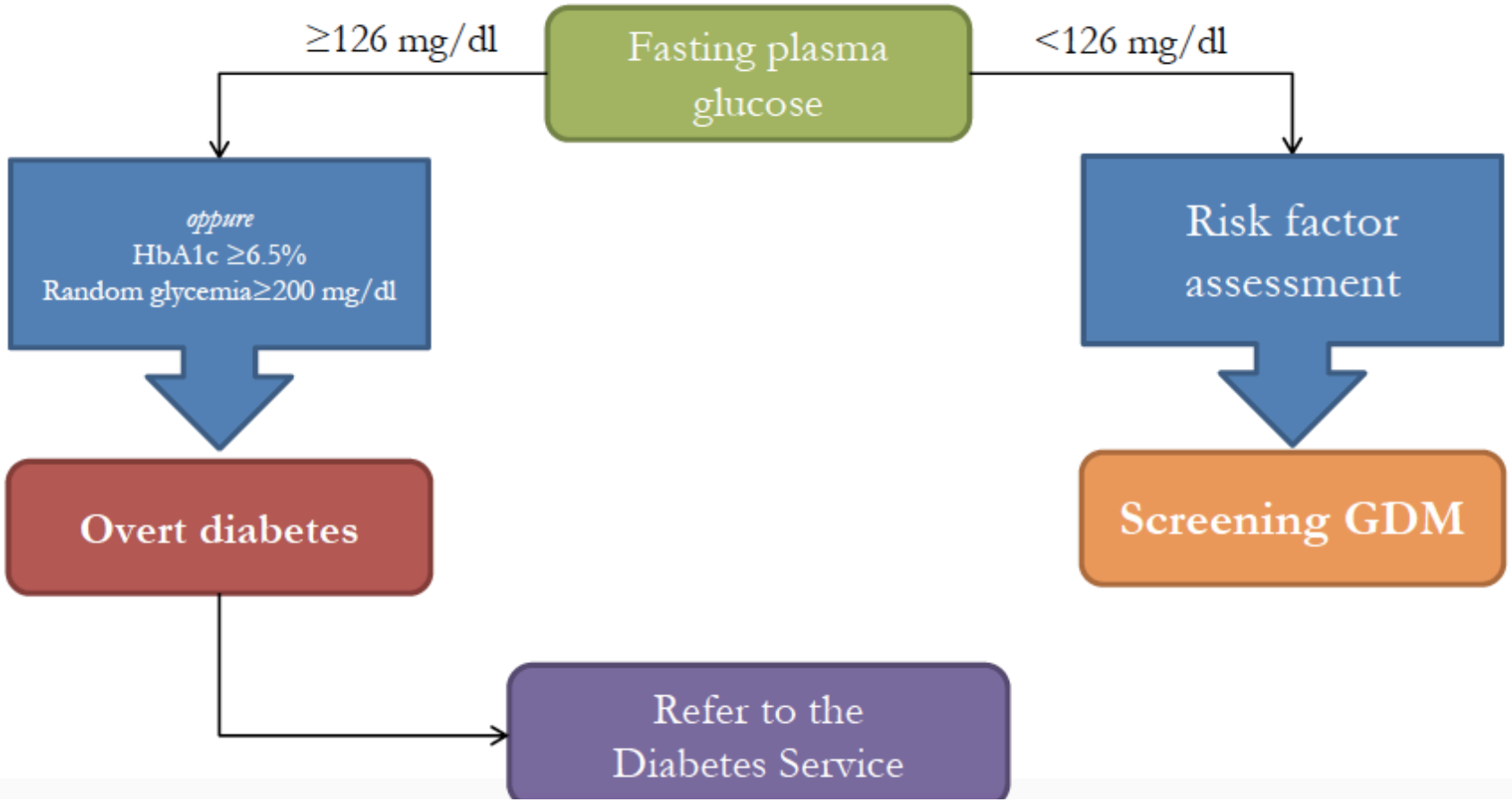
- Diabetes diagnosed before conception

All women with should, ideally, be screened for undiagnosed hyperglycemia before conception, or at least, in early pregnancy.

Bianchi, 2023

SCREENING FOR DIABETES IN PREGNANCY

All women should be screened for undiagnosed hyperglycemia before conception, or at least, in early pregnancy



Linee guida Ministero della Salute 2011 -Standard di cura del diabete SID-AMD 2018

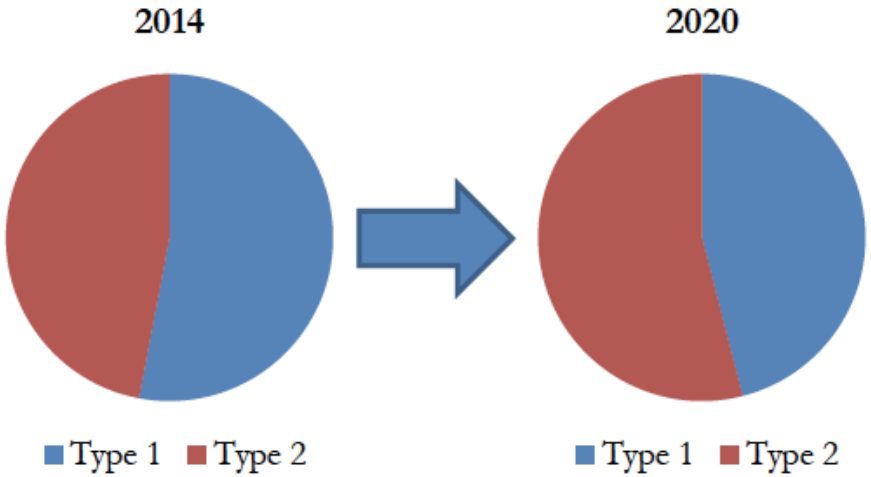
UNDIAGNOSED TYPE 2 DIABETES DURING PREGNANCY AND PERINATAL OUTCOMES

	GDM alone		Undiagnosed type 2 diabetes		Undiagnosed type 2 diabetes vs. GDM alone			
	No.	No. per 100	No.	No. per 100	age-adjusted odds ratio (95% CI)	*P*- value	fully-adjusted odds ratio (95% CI)*	*P*- value**
Maternal								
Gestational hypertension/ pre-eclampsia	6146	9.3	239	13.5	1.53 (1.33, 1.75)	<0.0001	1.56 (1.35, 1.79)	<0.0001
Caesarean section	24 606	37.1	774	43.7	1.31 (1.19, 1.44)	<0.0001	1.33 (1.21, 1.46)	<0.0001
Shoulder dystocia	1811	2.7	66	3.7	1.39 (1.09, 1.79)	0.0092	1.36 (1.06, 1.74)	0.0174
Neonatal								
Perinatal mortality	307	0.5	28	1.6	3.44 (2.33, 5.08)	<0.0001	3.37 (2.28, 4.98)	<0.0001
Preterm <37 weeks gestation	6224	9.4	264	14.9	1.69 (1.48, 1.93)	<0.0001	1.68 (1.47, 1.92)	<0.0001
Preterm <34 weeks gestation	1359	2	62	3.5	1.72 (1.33, 2.23)	<0.0001	1.70 (1.31, 2.21)	<0.0001
NICU admission	9671	14.6	431	24.3	1.89 (1.69, 2.11)	<0.0001	1.86 (1.66, 2.08)	<0.0001
Respiratory distress syndrome	738	1.1	36	2	1.84 (1.31, 2.58)	0.0004	1.82 (1.30, 2.56)	0.0005
Small for gestational age	7546	11.4	169	9.5	0.83 (0.71, 0.97)	0.0231	0.84 (0.71, 0.98)	0.0304
Large for gestational age	8345	12.6	392	22.1	2.01 (1.80, 2.26)	<0.0001	1.98 (1.76, 2.23)	<0.0001
Congenital anomalies	2158	3.3	99	5.6	1.76 (1.43, 2.17)	<0.0001	1.77 (1.44, 2.17)	<0.0001
Hyperbilirubinemia	4920	7.5	184	10.4	1.45 (1.24, 1.69)	<0.0001	1.47 (1.26, 1.72)	<0.0001
Neonatal hypoglycaemia	10 477	15.8	469	26.4	1.92 (1.73, 2.14)	<0.0001	1.90 (1.71, 2.12)	<0.0001

GDM, gestations diabetes; NICU, neonatal intensive care unit.
*Adjusted for age group, income quintile, visited primary care physician, parity, ethnicity and recent immigration.
**P-value threshold should be 0.003 to allow for multiple testing.

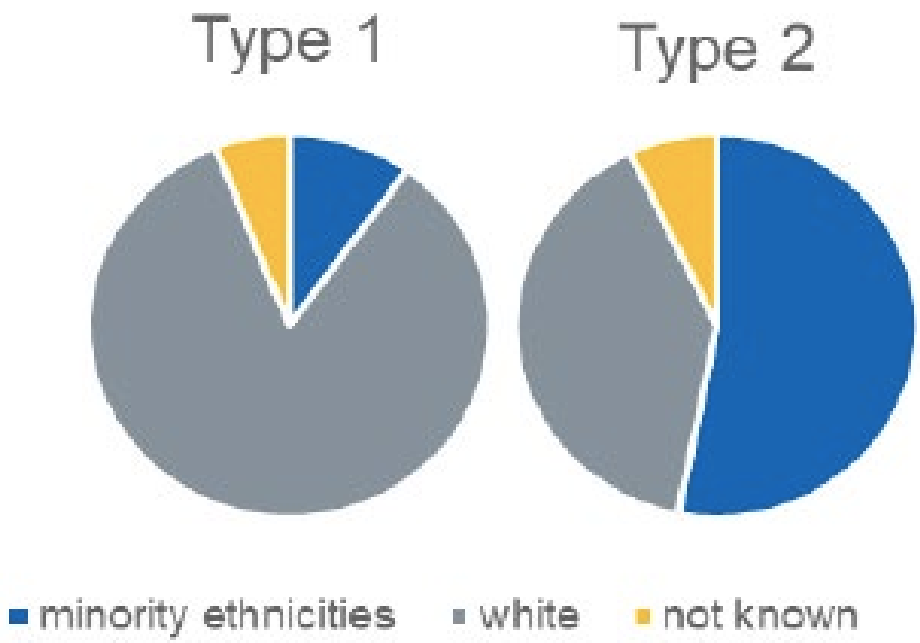
Lee D. Diabet Med 2020;37(10):1696-1704

PRE-GESTATIONAL DIABETES AND PREGNANCY NATIONAL PREGNANCY IN DIABETES (NPID)



	Type 1 diabetes (median & 10th-90th centile)	Type 2 diabetes (median & 10th-90th centile)
Numbers of women	4020	4920
Age at end of pregnancy (years)	30 (22 – 37)	34 (27 – 41)
Diabetes duration (years)	14 (3 – 25)	3 (0 – 10)
BMI (Kg/m2)	26.0 (21.2 – 34.0)	32.7 (24.8 – 42.7)

Women with type 2 diabetes now make up 54% of pregnancies,compared to 47% in 2014

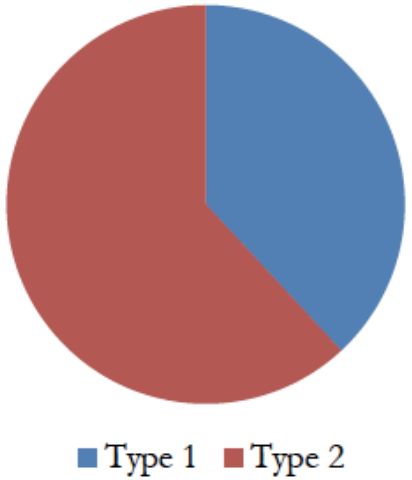


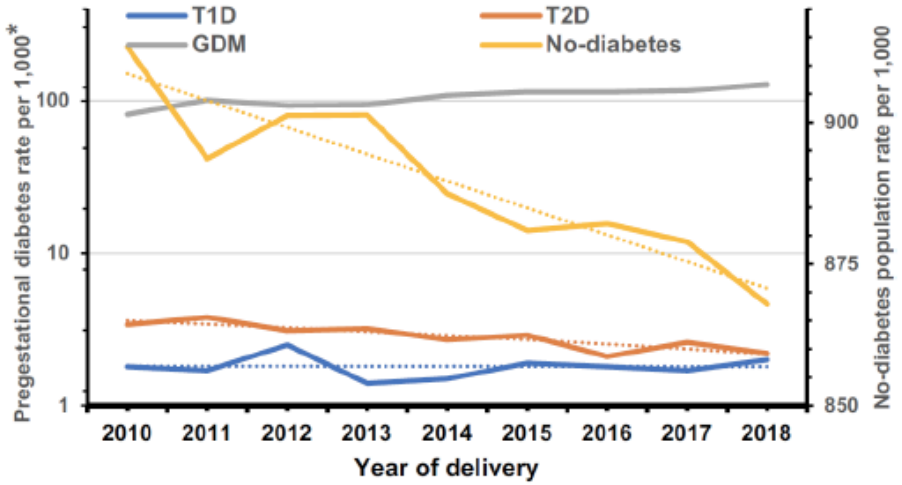
NHS Digital -National Pregnancy in Diabetes (NPID) Audit Report 2020, 2021

PRE-GESTATIONAL DIABETES AND PREGNANCY

206,917 singleton live births Italy from 2010 to 2018

- GDM in 21,613 pregnancies (10.46%)
- Type 2 diabetes in 606 (0.29%)
- Type 1 diabetes in 373 (0.18%)

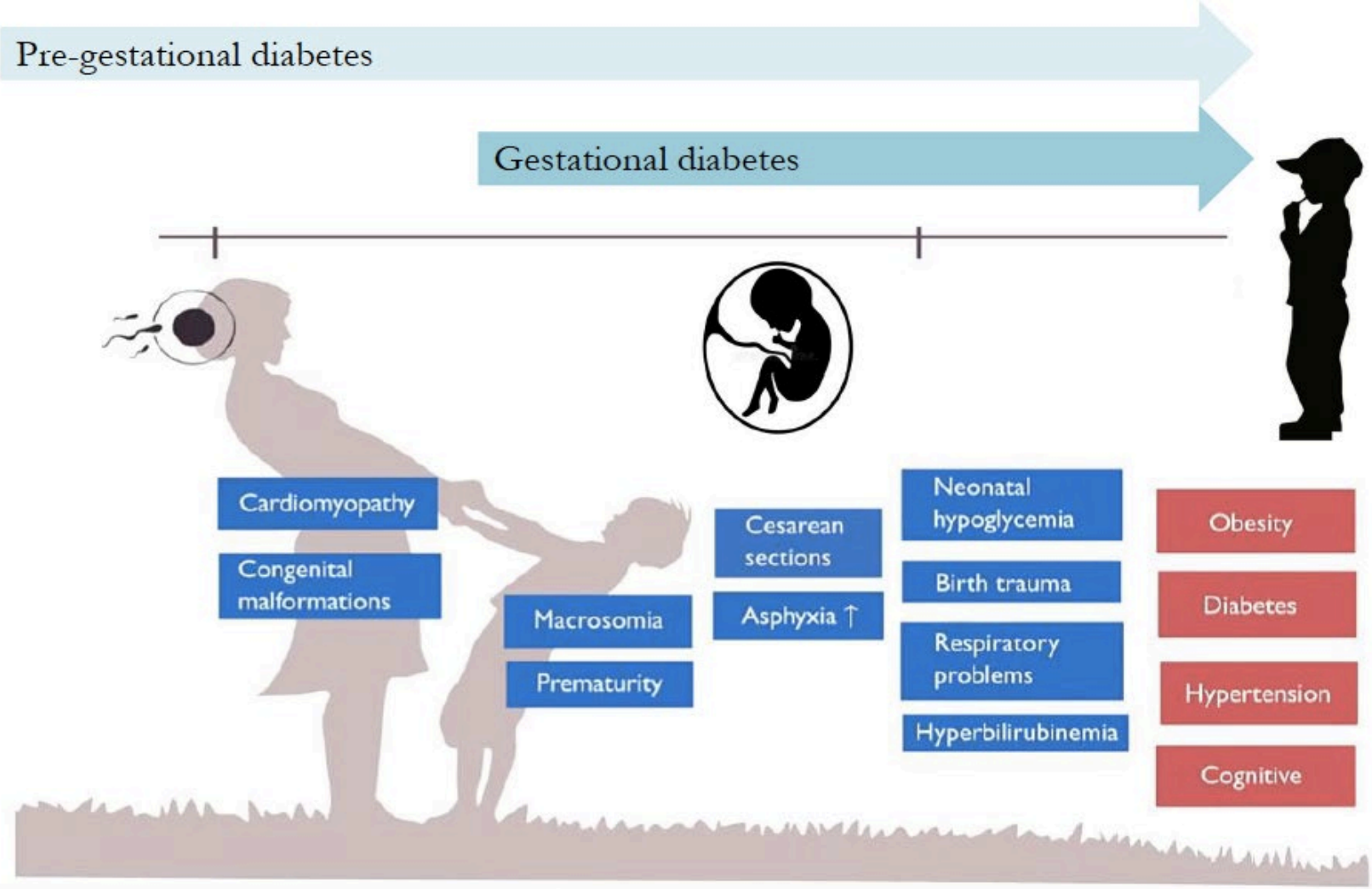




Pre-gestational Type 2 Diabetes is more prevalent than Type 1 Diabetes

Gualdani E. Acta Diabetol 2021;58(9):1169-1176

DIABETES IN PREGNANCY: NEONATAL AND INFANT OUTCOMES



C. Bianchi 2023

PRE-GESTATIONAL DIABETES AND PREGNANCY OUTCOMES

206,917 singleton live births, Italy from 2010 to 2018:

- GDM in 21,613 pregnancies (10.46%);
- Type 2 diabetes in 606 (0.29%);
- Type 1 diabetes in 373 (0.18%)

	Type 1 diabetes OR (95% CI)	Type 2 diabetes	GDM
a) Mothers' characteristics or deliveries' outcomes			
Pregestational overweight/obesity (BMI ≥ 30 kg/m^2)	1.49 (1.02–2.17)*	9.35 (7.84–11.14)*	2.72 (2.59–2.84)*
Migrant status	0.76 (0.56–1.03)	1.51 (1.22–1.87)*	1.53 (1.48–1.59)*
Previous spontaneous abortions (≥ 2)	1.12 (0.68–1.82)	4.19 (3.30–5.33)*	1.19 (1.12–1.27)*
Delivery at referral University Hospitals	2.79 (2.25–3.47)*	1.88 (1.58–2.24)*	1.18 (1.14–1.22)*
Preterm childbirth (< 37 wks.)	8.86 (7.18–10.94)*	2.60 (2.15–3.14)*	1.26 (1.21–1.32)*
Overall cesarean sections	3.75 (2.98–4.71)*	1.93 (1.62–2.28)*	1.22 (1.18–1.26)*
Emergency cesarean sections	1.69 (1.31–2.19)*	1.39 (1.13–1.72)*	1.16 (1.12–1.21)*
b) Neonates outcomes			
Macrosomia (birthweight > 4,000 g)	5.33 (3.70–7.67)*	1.92 (1.39–2.64)*	1.06 (0.99–1.13)
LGA**	4.75 (3.48–6.49) *	2.07 (1.60–2.66) *	1.08 (1.03–1.14)*
5-min Apgar score ≤ 7	2.31 (1.44–3.71)*	1.03 (0.56–1.89)	0.96 (0.84–1.09)
Fetal malformations	3.13 (1.29–7.59)*	1.69 (0.80–3.57)	0.83 (0.65–1.06)

ORs were adjusted for migrant status, age, parity, education degree, employment, calendar year of delivery, pregestational obesity, gestational week, modality of delivery (cesarean section yes/no) and regional hospital of delivery. Reference group: women without diabetes

*$p < 0.001$

** > 90th centile of z-score birthweight, adjusted for sex and gestational week

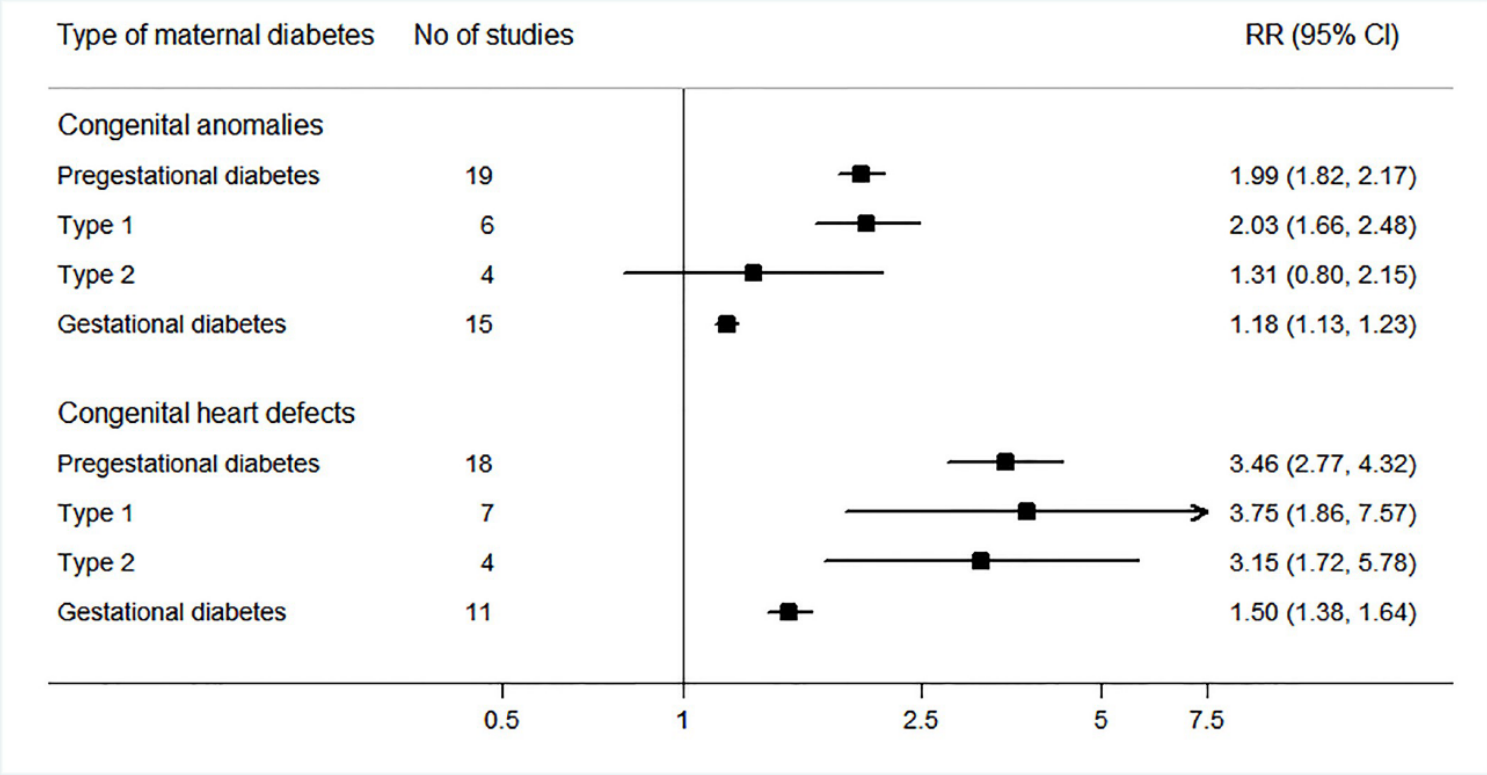
Neonatal complications are mostly associated with pre-gestational diabetes (T1DM>T2DM)

Gualdani E. Acta Diabetol 2021;58(9):1169-1176

RISKS OF CONGENITAL ANOMALIES ACCORDING TO DIFFERENT TYPES OF MATERNAL DIABETES

- Meta-analisysof 59 population-based studies with 80,437,056 participants
- 2,407,862 (3.0%) had pre-gestational diabetes (PGDM) and 2,353,205 (2.9%) women had GDM

Congenital anomalies and heart defects are mostly associated with pre-gestational diabetes



Zhang NT. PLoS Med 2022;19(2):e1003900

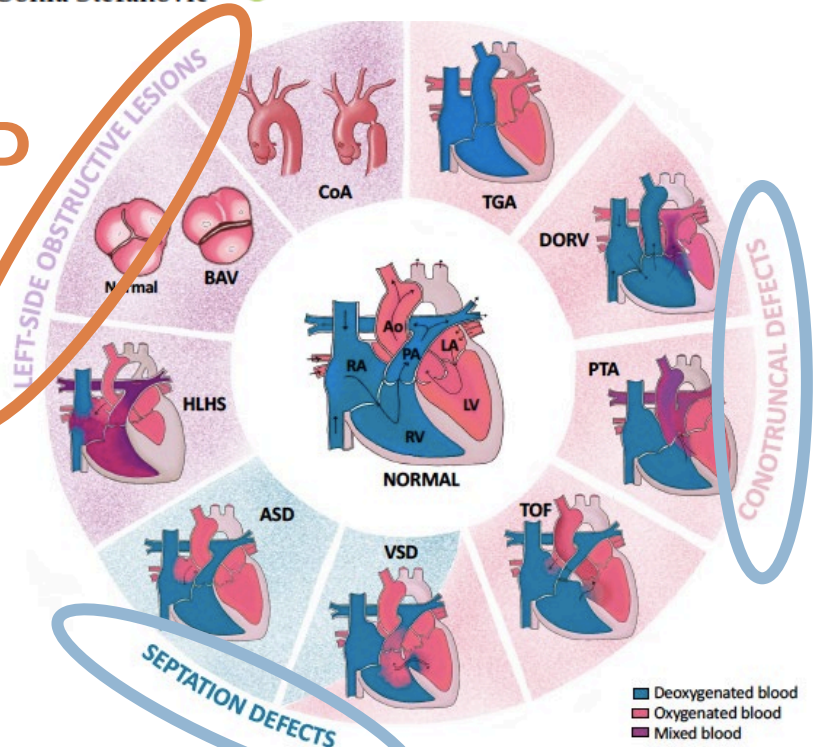
CONGENITAL CARDIOPATHIES AND PREGESTATIONAL DIABETES

Review

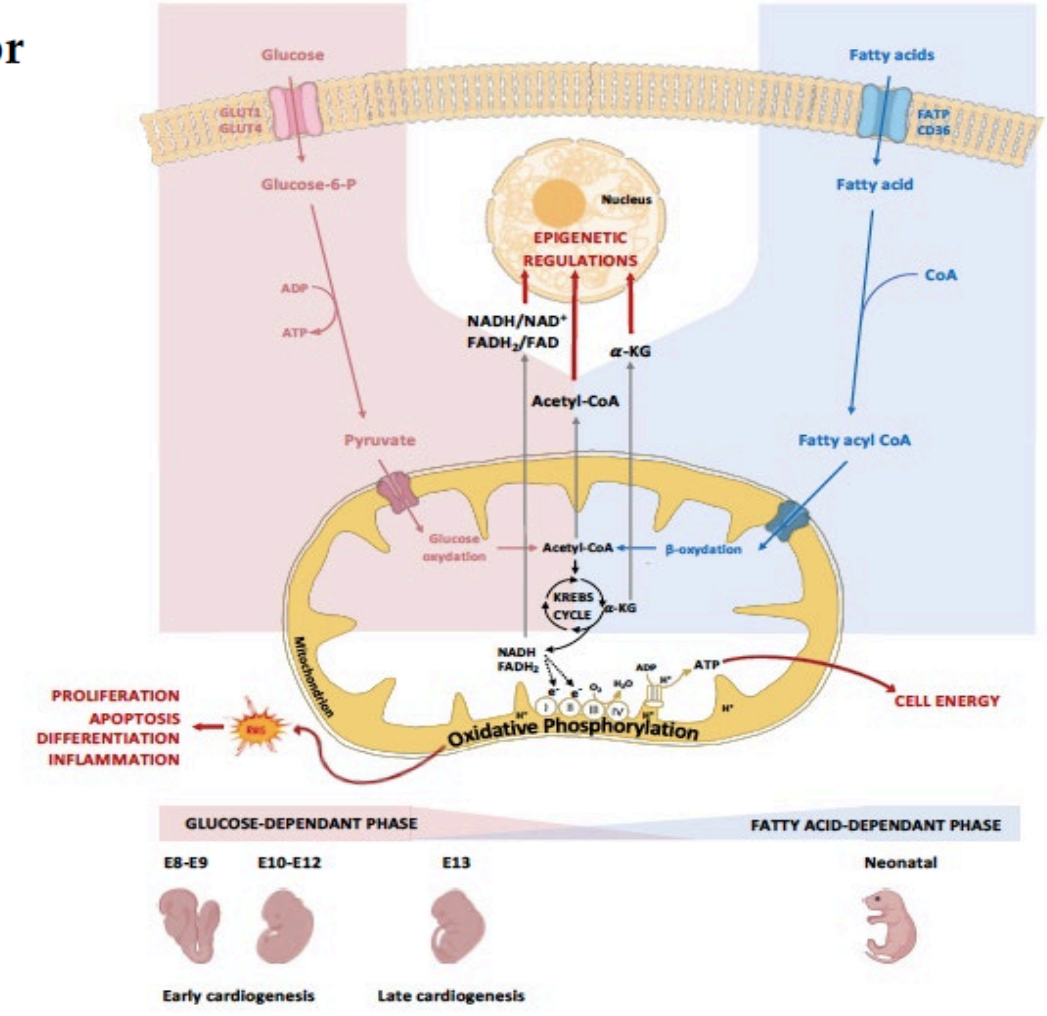
Maternal Pre-Existing Diabetes: A Non-Inherited Risk Factor for Congenital Cardiopathies

Stéphanie Ibrahim [1], Bénédicte Gaborit [2], Marien Lenoir [3], Gwenaelle Collod-Beroud [4] and Sonia Stefanovic [1,*]

T2D

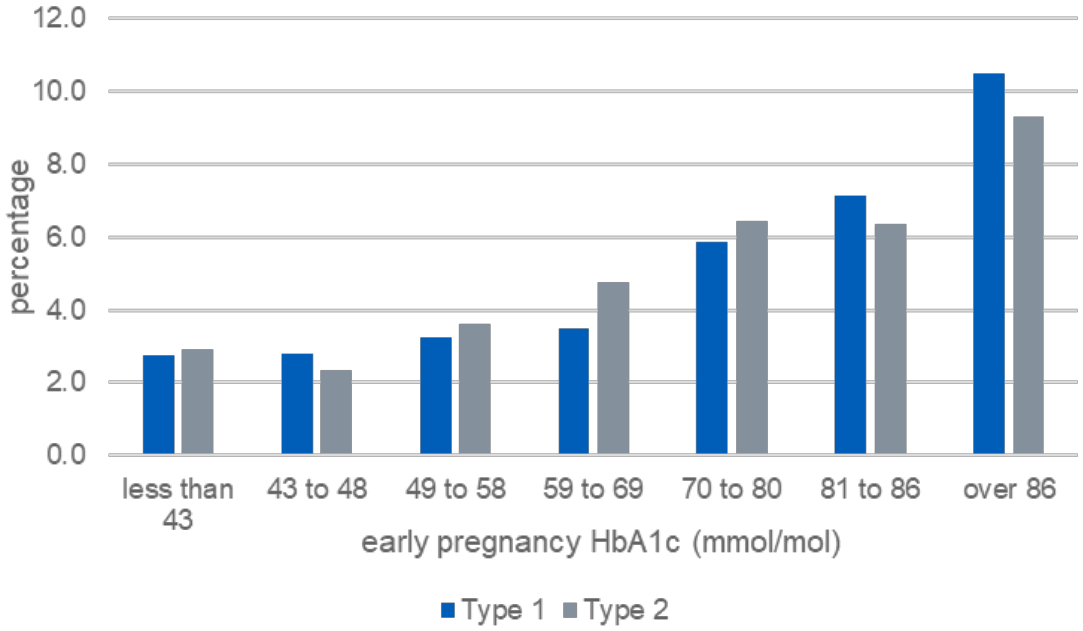


T1D



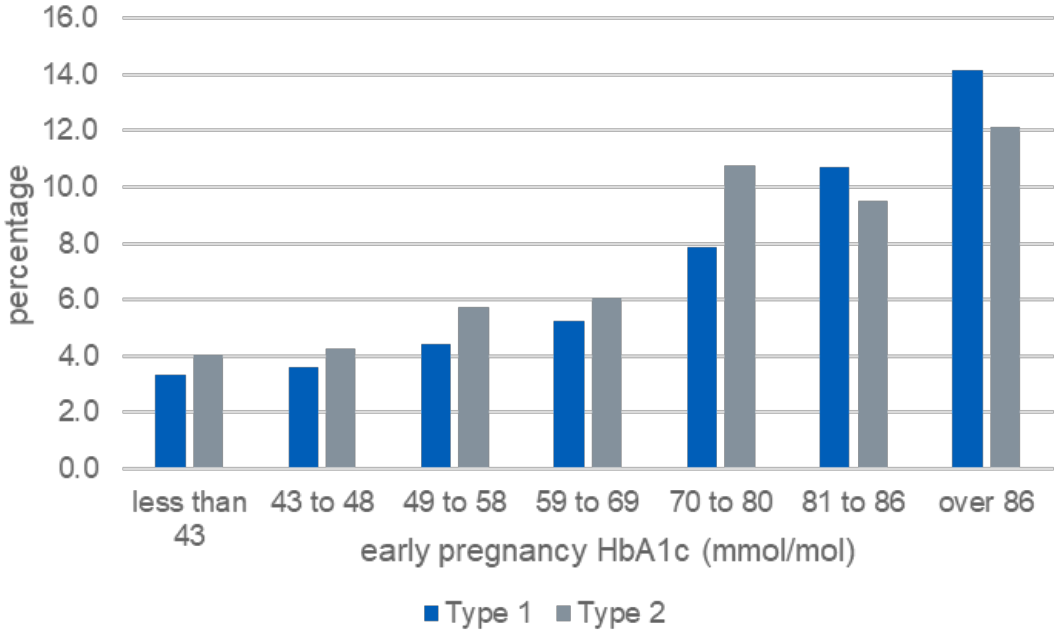
EARLY PREGNANCY HBA1C AND SERIOUS ADVERSE OUTCOMES (CONGENITAL ANOMALY & PERINATAL DEATH)

Congenital anomaly
By diabetes type and early pregnancy HbA1c



Rates of major congenital anomaly and serious adverse outcomes were lowest in women with early pregnancy HbA1c≤ 48mmol/mol (6.5%) and highest with HbA1c>86mmol/mol (10%)

Serious adverse outcome
by diabetes type and early pregnancy HbA1c



*Includes all pregnancies during 2014-2020 with singleton live births and terminations at any gestation, stillbirths and miscarriages after 20weeks

NHS Digital -National Pregnancy in Diabetes (NPID) Audit Report 2020, 2021

PRE-GESTATIONAL DIABETES IN PREGNANCY: COMORBIDITIES

Dyslipidemia

Overweight obesity

Hypertension

Diabetes chronic complications

CARE FOR WOMEN WITH PRE-GESTATIONAL DIABETES

	All patients n = 679	Type 1 DM n = 415	Type 2 DM n = 244	Other n = 20	p value T1DM vs T2DM
Age (years)	32.8 + 5.8	31.8 + 5.8	34.3 + 5.7	35.9 + 4.1	<0.05
Ethnicity					
Caucasian	524 (77.2%)	356 (85.7%)	149 (61.1%)	19 (95.0%)	<0.05
BMI (kg/m^2)	28.8 + 6.3	26.8 + 4.9	32.5 + 6.9	25.8 + 5.2	<0.05
BMI > 25	386 (56.8%)	209 (50.4%)	170 (69.7%)	7 (35.0%)	<0.05
BMI > 30	199 (29.3%)	71 (17.1%)	126 (51.6%)	2 (10.0%)	<0.05
Duration of DM (years)	11.8 + 10.8	14.6 + 8.6	6.8 + 6.3	14.3 + 9.1	<0.05
Gravidity	3	2	3	3	<0.05
Parity	1	1	1	1	NS
Retinopathy	112 (16.5%)	101 (24.3%)	5 (2%)	6 (30%)	<0.05
Hypertension	79 (11.6%)	37 (8.9%)	40 (16.4%)	2 (10%)	<0.05
Microalbuminuria	115 (16.2%)	76 (18.3%)	32 (13.1%)	7 (35%)	NS
PPC attendance	219 (32.3%)	143 (34.5%)	72 (29.5%)	4 (20%)	NS
Folic acid usage	349 (51.4%)	219 (52.8%)	121 (49.6%)	9 (45%)	NS
5 mg	277 (40.8%)	181 (43.6%)	88 (36.1%)	8 (40%)	NS
0.4 mg	53 (7.8%)	10 (1.4%)	29 (11.9%)	0	<0.05
Dose not stated	19 (4.3%)	28 (4.1%)	4 (1.6%)	1 (5%)	NS
No folic acid use	330 (48.6%)	196 (47.2%)	123 (50.4%)	11 (55%)	NS
Teratogenic meds	55 (8.1%)	18 (4.3%)	32 (13.1%)	5 (25%)	<0.05
Pre-pregnancy HbA1c	59.3 + 18.9	61.6 + 19.1	54.8 + 17.6	50.2 + 13.6	<0.05
Well prepared 3 criteria	108 (15.9%)	69 (16.6%)	25 (14.3%)	14 (70%)	NS
1st trimester HbA1c	54.9 + 15.8	57.8 + 15.8	49.5 + 14.3	53.2 + 17.4	<0.05
1st trimester HbA1c < 6.5% (48 mmol/mol)	190 (27.9%)	93 (22.4%)	92 (37.7%)	5 (25%)	<0.05
1st trimester HbA1c > 10% (86 mmol/mol)	29 (4.2%)	21 (5.1%)	6 (2.5%)	2 (10%)	NS
Booking < 8 weeks	280 (41.2%)	186 (44.8%)	87 (35.7%)	7 (35%)	<0.05
Weight gain (kg)	10.7 + 10.2	12.38 + 10.9	7.5 + 6.5	8.29 + 4.67	<0.05

PPC – pre-pregnancy clinic.

Newman C. Diabetes Res Clin Pract 2021;173:108685

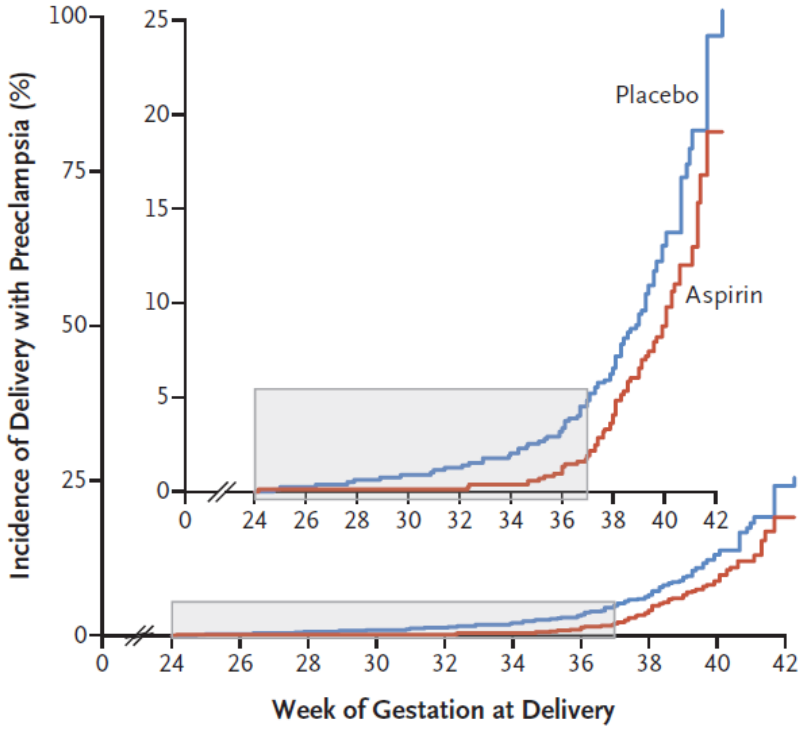
PREGNANCY COMPLICATIONS AND MODE OF DELIVERY IN WOMAN WITH TYPE 1 DIABETES

	Proportions (%)		OR (95% CI) for group differences	
Outcome variable	Type 1 diabetes	Nondiabetes	Crude	Adjusted
PIH	1.6	0.87	1.93 (1.50–2.49)	1.53 (1.18–1.99)
Preeclampsia, mild	9.7	2.0	5.37 (4.81–6.00)	4.30 (3.83–4.83)
Preeclampsia, severe	4.3	0.8	5.58 (4.75–6.57)	4.47 (3.77–5.31)
Cesarean section	46	12	5.85 (5.49–6.25)	5.31 (4.97–5.69)
Vacuum extraction/forceps	9.6	6.6	1.48 (1.33–1.66)	1.41 (1.25–1.58)

Data are proportions or OR (95% CI). n = 5,089 for diabetic pregnancies; n = 1,260,207 for control pregnancies. Adjusted OR, OR adjusted for group differences in maternal age, BMI, parity, chronic hypertensive disorder, smoking habits, and ethnicity.

PerssonM. Diabetes Care 2009;32(11):2005-9

ASPIRIN TO PREVENT PRE-ECLAMPSIA IN WOMAN AT HIGH RISK



No. at Risk										
Placebo	807	802	793	783	775	764	734	619	285	10
Aspirin	785	781	778	776	772	760	740	627	295	12

Rolnik DL. N Engl J Med2017;377(7):613-622

Recommendation

15.20 Pregnant individuals with type 1 or type 2 diabetes should be prescribed low-dose aspirin 100–150 mg/day starting at 12 to 16 weeks of gestation to lower the risk of preeclampsia.

Si raccomanda che alle gravide con fattori di rischio maggiori per preeclampsia (precedente preeclampsia pretermine, ipertensione cronica, diabete pregravidico, BMI > 30 kg/m², sindrome da anticorpi antifosfolipidi e procreazione medicalmente assistita per infertilità materna o inspiegata) vada iniziata una profilassi con 100-150 mg/die di Aspirina, idealmente prima delle 16 settimane e sicuramente entro le 20 settimane, come dimostrato da trial clinici controllati.

Antiplatelet agents

1.1.2 Advise pregnant women at high risk of pre-eclampsia to take 75–150 mg of aspirin[IV] daily from 12 weeks until the birth of the baby. Women at high risk are those with any of the following:

- hypertensive disease during a previous pregnancy
- chronic kidney disease
- autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension. **[2010, amended 2019]**

ADA. Diabetescare 2023; 46 (Suppl1):S254–S266
NICE guideline2015
Linee guida AIPE

PREGESTATIONAL DIABETES AND HPA

International Journal of
Molecular Sciences

MDPI

Article

Pregestational Prediabetes Induces Maternal Hypothalamic–Pituitary–Adrenal (HPA) Axis Dysregulation and Results in Adverse Foetal Outcomes

Mathuli Ngema, Nombuso D. Xulu, Phikelelani S. Ngubane and Andile Khathi *

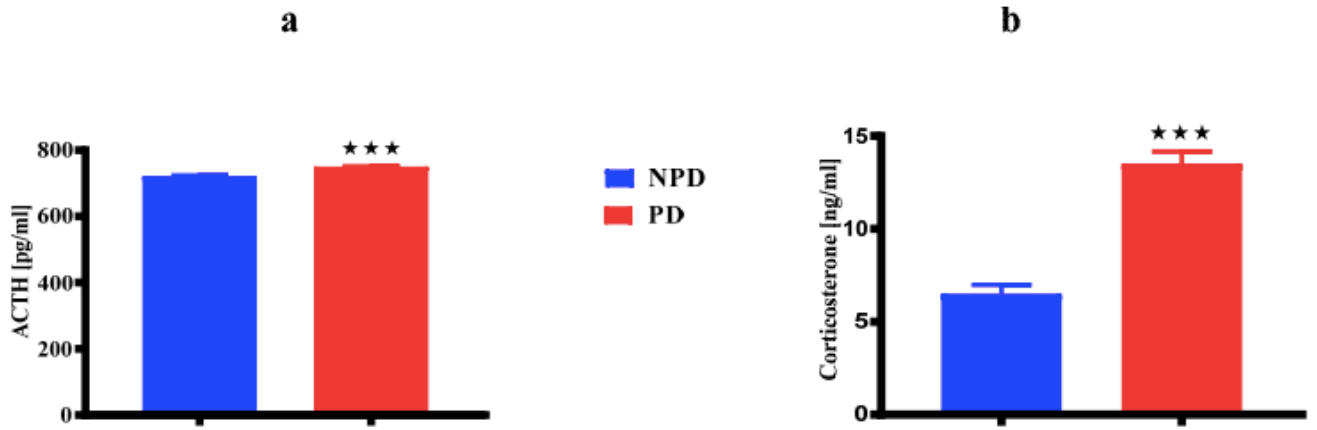


Figure 2. The dams' ACTH (**a**) and corticosterone (**b**) concentrations in the NPD and PD groups (n = 6 per group) at 21 days postpartum. Values are expressed as mean ± SEM. ★★★ $p < 0.001$ denotes comparison with NPD. The blue bar represents the NDP group and the red bar represents the PD group.

2024

PREGESTATIONAL DIABETES: DIFFERENCES IN OUTCOME

Table 2 Obstetric and perinatal outcomes according to the type of DM

	Type 1 DM	Type 2 DM	*p* value
Obstetrics outcomes			
Gestational week at delivery (weeks)	37.78 ± 1.02	37.31 ± 3.13	0.124
Induction of labour n (%)	100 (84.2)	88 (83)	0.838
Vaginal delivery n (%)	60 (50.4)	55 (50)	0.733
Gestational hypertension n (%)	1 (0.7)	5 (4)	0.070
Preeclampsia n (%)	6 (4.3)	6 (4.8)	0.820
Prematurity rate (%)	9.1	10.2	0.750
. Prematurity (weeks)	35.61 ± 0.50	31.50 ± 4.9	0.006
. Late prematurity n (%)	13 (100)	5 (35.7)	< 0.001
. Precocious prematurity n (%)	0 (0)	9 (64.3)	< 0.001
Obstetrical Complications n (%)	16 (13.9)	14 (13.6)	0.945
Obstetrical trauma n (%)	1 (0.9)	2 (2)	0.497
Miscarriage n (%)	17 (12.1)	9 (7.3)	0.190
Stillbirth (weeks)	37	27.66 ± 7.37	0.387
Stillbirth n (%)	1 (0.8)	3 (2.6)	0.354
Perinatal outcomes			
Female Sex n (%)	58 (48.7)	46 (44.2)	0.293
Birth weight (g)	3408 ± 505	3137 ± 817	0.003
Birth height (cm)	49.29 ± 2.28	48.61 ± 2.68	0.049
Adiposity Index	28.42 ± 4.76	28.04 ± 2.91	0.578
Macrosomia (≥ 4000g)	18 (15.3)	11 (10.4)	0.278
LGA (%)	45.3	36.1	0.173
SGA (%)	3.4	6.2	0.340
Apgar 1′	8.70 ± 1.11	8.51 ± 1.79	0.092
pH arterial	7.22 ± 0.12	7.23 ± 0.09	0.543
pH venous	7.25 ± 0.08	7.30 ± 0.09	0.002
Neonatal Complications n (%)	46 (39.7)	31 (31)	0.185
Hypoglycaemia n (%)	28 (24.6)	9 (8.9)	0.002
Respiratory distress Syndrome (RDS) n (%)	8 (7.1)	7 (7.1)	0.998
Hospital admission n (%)	25 (21.5)	19 (19.4)	0.148
Congenital Malformation n (%)	4 (3.5)	11 (10.8)	0.034

RESEARCH Open Access

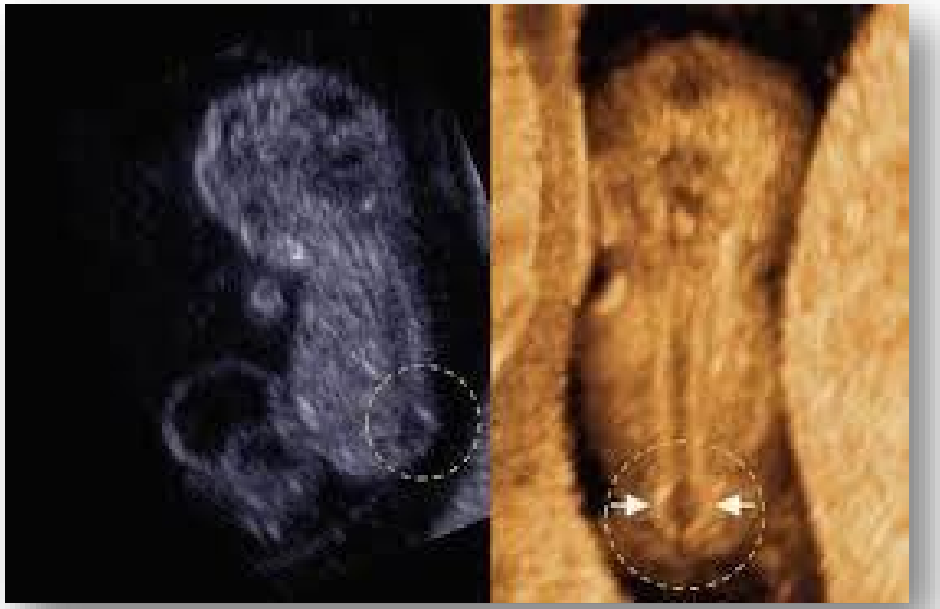
Prematurity and congenital malformations differ according to the type of pregestational diabetes

Monica Ballesteros[1,2,3*†], A Guarque[1,2,3], M Ingles[2,3], N Vilanova[5], M Lopez[1,3], L Martin[1,3], M Jane[1,3], L Puerto[3], M Martinez[3], M De la Flor[1,3], J Vendrell[1,2,4] and A Megia[1,2,4†]

2024

CARE FOR WOMEN WITH PRE-GESTATIONAL DIABETES

PREGESTATIONAL DIABETES AND SPINABIFIDA: POPULATION-BASED CASE-CONTROL STUDY

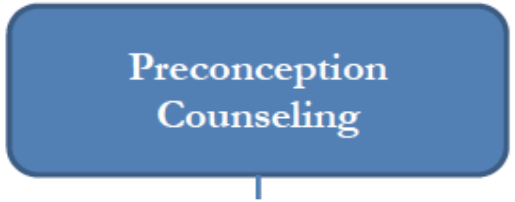


Maternal characteristics	All spina bifida Adjusted odds ratio[a,b] (95% confidence interval)	Isolated spina bifida Adjusted odds ratio[a,b] (95% confidence interval)
Pregestational diabetes		
No	Referent	Referent
Yes	4.35 (1.37, 13.82)	4.41 (1.07, 18.24)
Age at delivery (years)		
<20	0.98 (0.24, 4.06)	0.74 (0.10, 5.50)
20–34	Referent	Referent
≥35	0.97 (0.55, 1.71)	1.09 (0.54, 2.21)
Body mass index (kg/m^2)		
<18.5	0.70 (0.17, 2.90)	1.26 (0.30, 5.30)
18.5–24.9	Referent	Referent
25–29.9	1.20 (0.72, 2.00)	1.34 (0.69, 2.60)
≥30	2.02 (1.19, 3.41)	2.69 (1.42, 5.09)

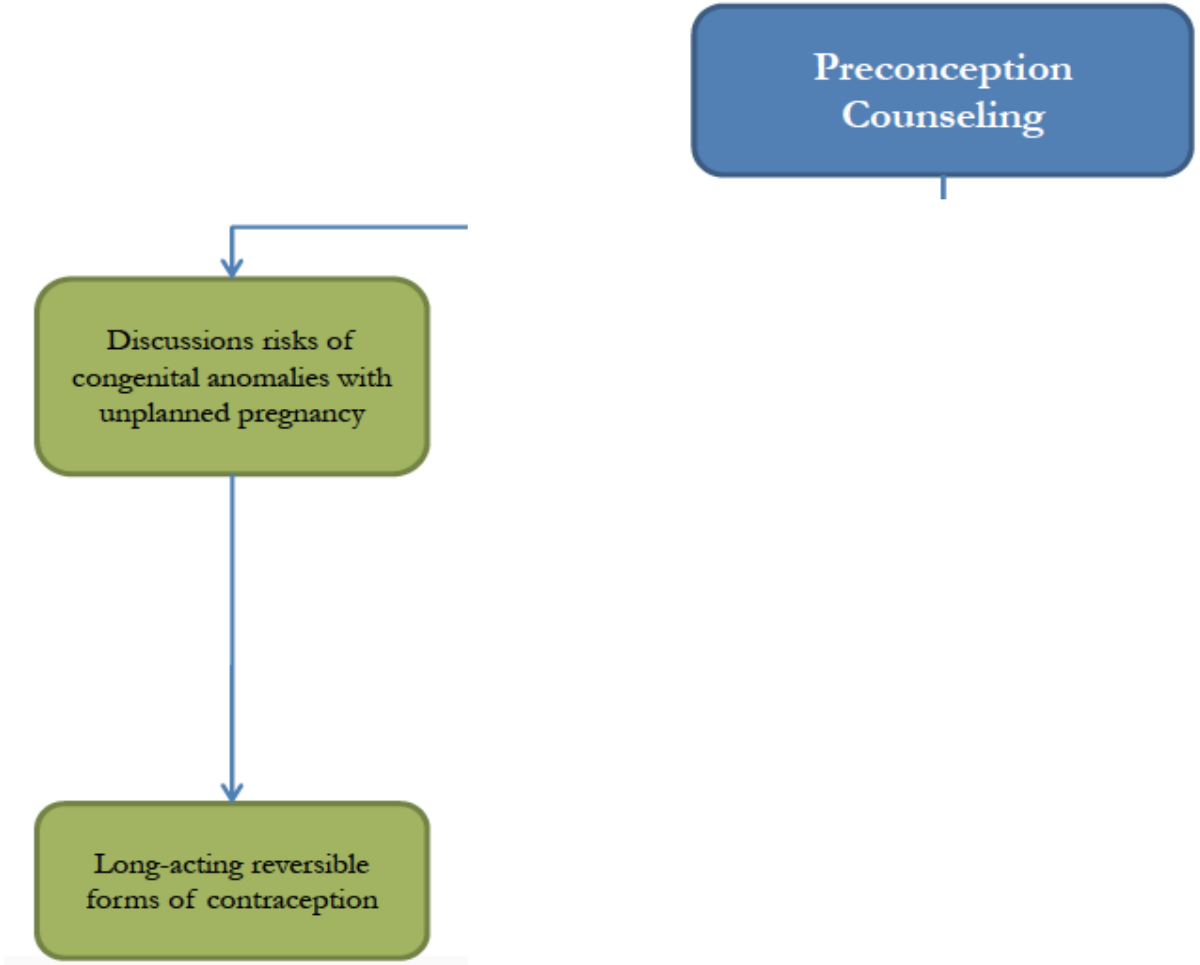
[a]Due to small number of cases, adjusted odds ratios and 95% confidence intervals are generated from exact logistic regression analysis.
[b]Each variable was adjusted for all other variables in the models presented for all spina bifida, and isolated spina bifida groups.

Mowla S. Birth Defects Res 2020;112(2):186-195

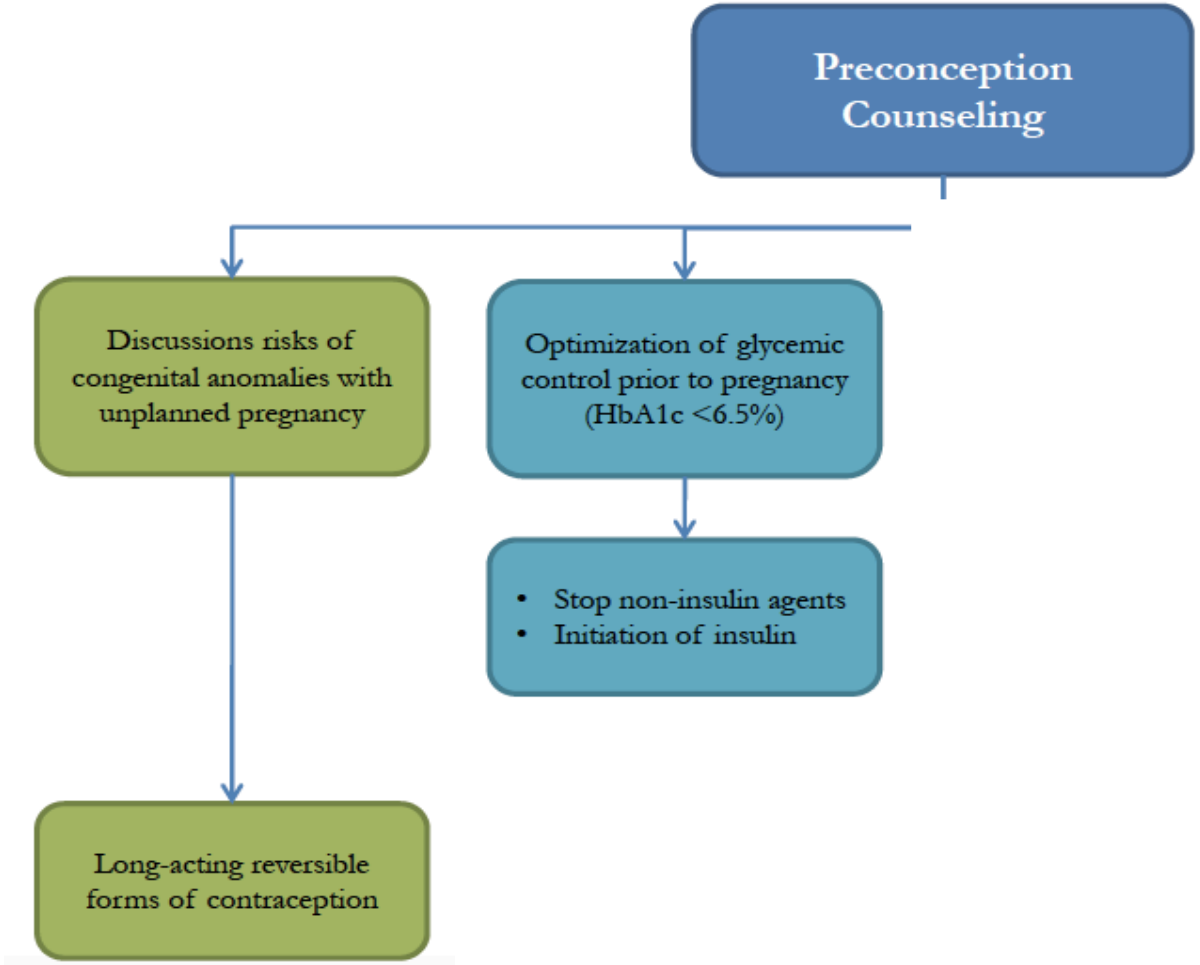
PRE-GESTATIONAL DIABETES AND PREGNANCY: PRECONCEPTION



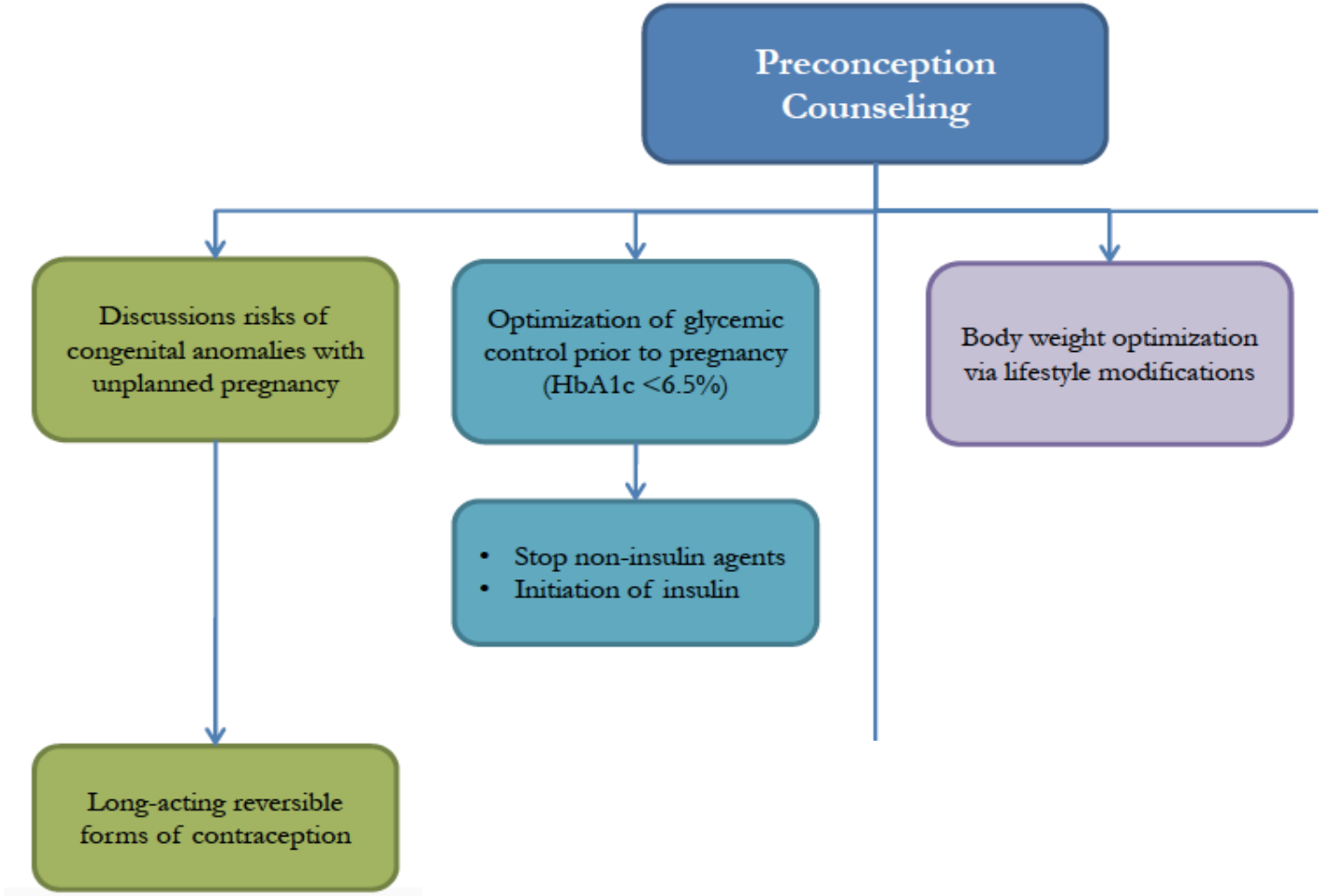
PRE-GESTATIONAL DIABETES AND PREGNANCY: PRECONCEPTION



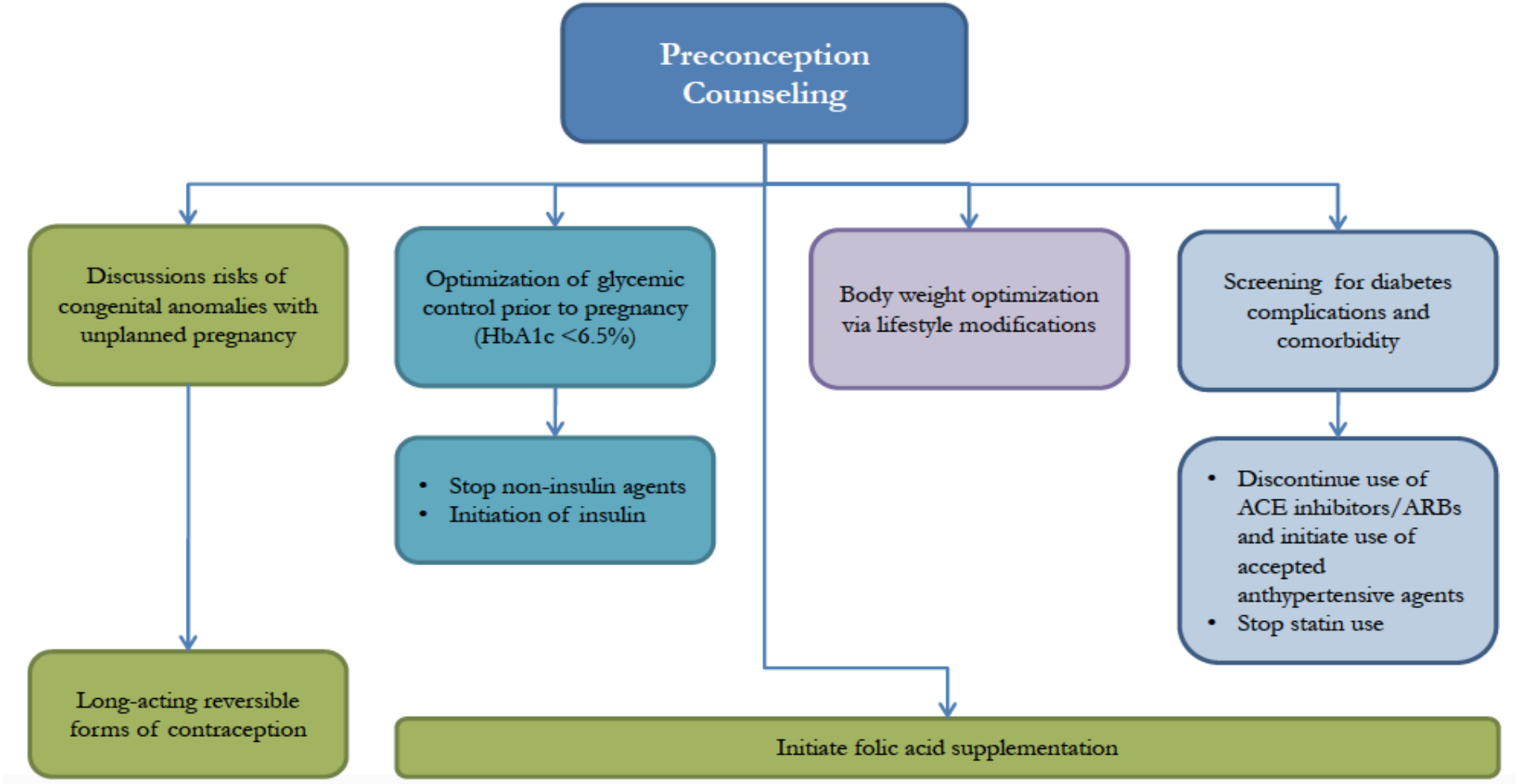
PRE-GESTATIONAL DIABETES AND PREGNANCY: PRECONCEPTION



PRE-GESTATIONAL DIABETES AND PREGNANCY: PRECONCEPTION

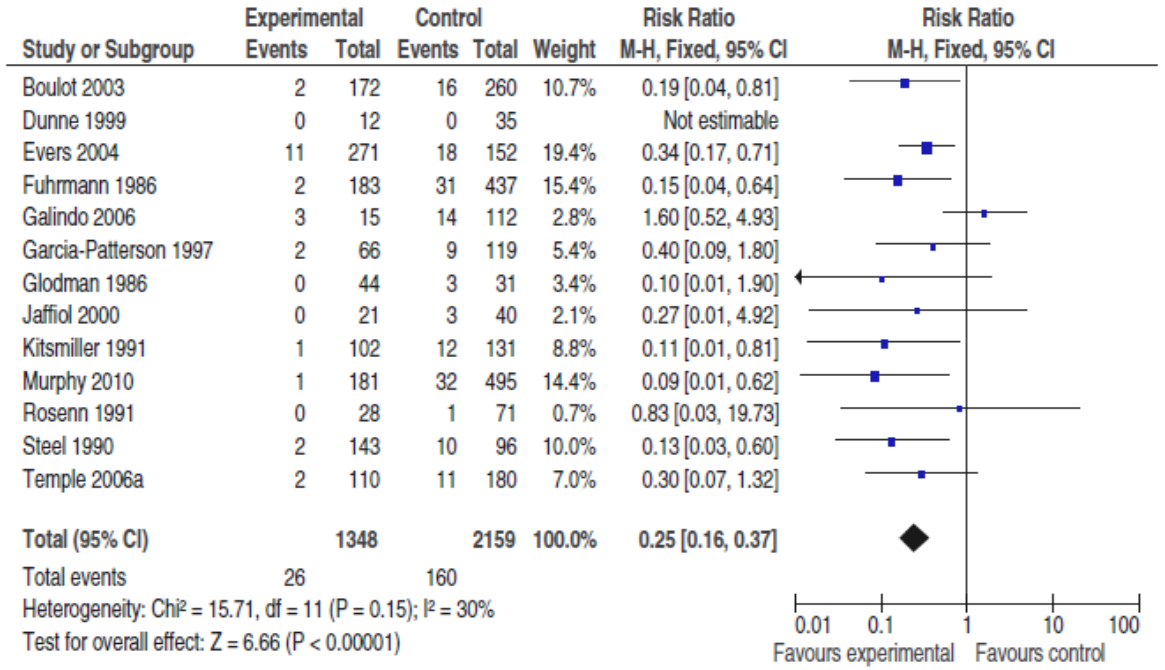


PRE-GESTATIONAL DIABETES AND PREGNANCY: PRECONCEPTION



PRE-PREGNANCY CARE

Risk for congenital malformation

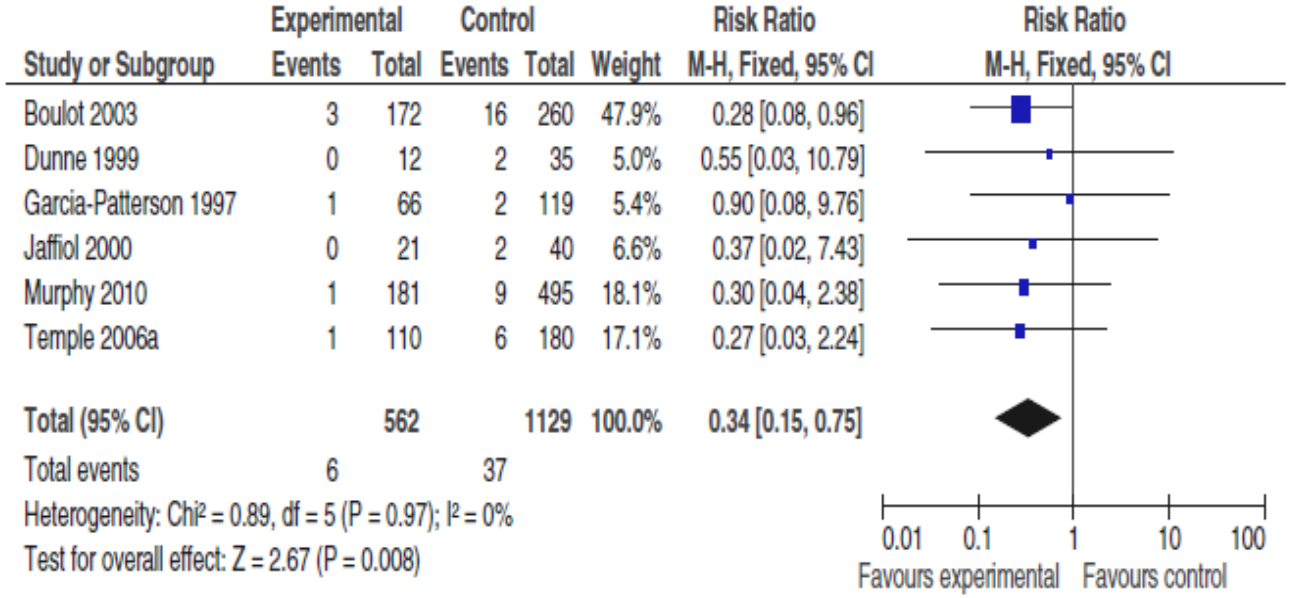


Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Boulot 2003	2	172	16	260	10.7%	0.19 [0.04, 0.81]
Dunne 1999	0	12	0	35		Not estimable
Evers 2004	11	271	18	152	19.4%	0.34 [0.17, 0.71]
Fuhrmann 1986	2	183	31	437	15.4%	0.15 [0.04, 0.64]
Galindo 2006	3	15	14	112	2.8%	1.60 [0.52, 4.93]
Garcia-Patterson 1997	2	66	9	119	5.4%	0.40 [0.09, 1.80]
Glodman 1986	0	44	3	31	3.4%	0.10 [0.01, 1.90]
Jaffiol 2000	0	21	3	40	2.1%	0.27 [0.01, 4.92]
Kitsmiller 1991	1	102	12	131	8.8%	0.11 [0.01, 0.81]
Murphy 2010	1	181	32	495	14.4%	0.09 [0.01, 0.62]
Rosenn 1991	0	28	1	71	0.7%	0.83 [0.03, 19.73]
Steel 1990	2	143	10	96	10.0%	0.13 [0.03, 0.60]
Temple 2006a	2	110	11	180	7.0%	0.30 [0.07, 1.32]
Total (95% CI)		**1348**		**2159**	**100.0%**	**0.25 [0.16, 0.37]**
Total events	26		160			

Heterogeneity: Chi² = 15.71, df = 11 (P = 0.15); I² = 30%

Test for overall effect: Z = 6.66 (P < 0.00001)

Risk for perinatal mortality



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Boulot 2003	3	172	16	260	47.9%	0.28 [0.08, 0.96]
Dunne 1999	0	12	2	35	5.0%	0.55 [0.03, 10.79]
Garcia-Patterson 1997	1	66	2	119	5.4%	0.90 [0.08, 9.76]
Jaffiol 2000	0	21	2	40	6.6%	0.37 [0.02, 7.43]
Murphy 2010	1	181	9	495	18.1%	0.30 [0.04, 2.38]
Temple 2006a	1	110	6	180	17.1%	0.27 [0.03, 2.24]
Total (95% CI)		**562**		**1129**	**100.0%**	**0.34 [0.15, 0.75]**
Total events	6		37			

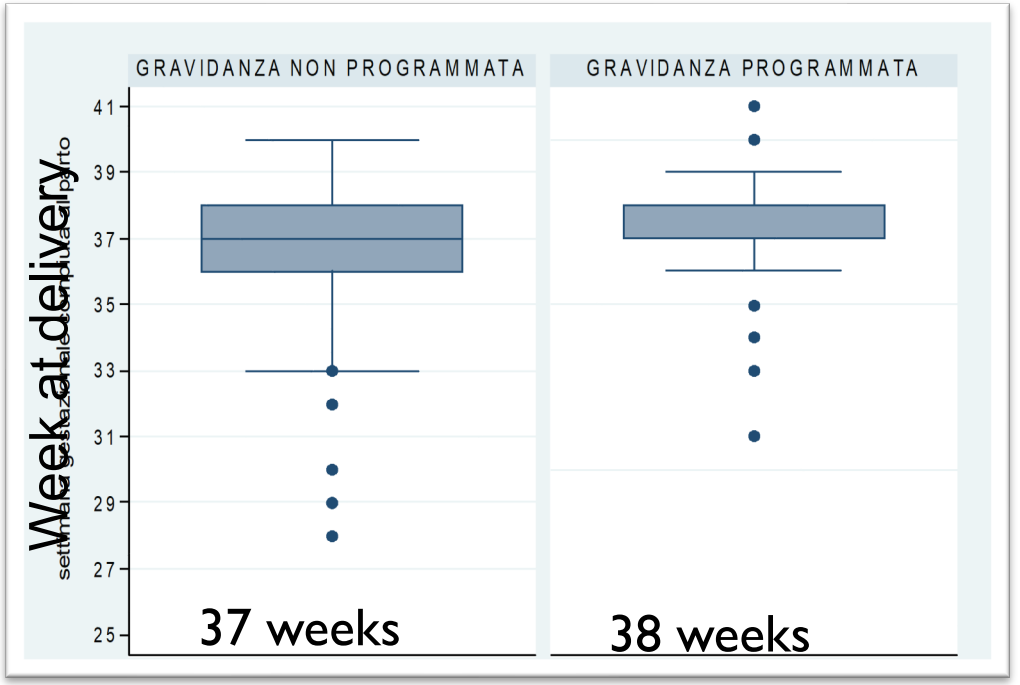
Heterogeneity: Chi² = 0.89, df = 5 (P = 0.97); I² = 0%

Test for overall effect: Z = 2.67 (P = 0.008)

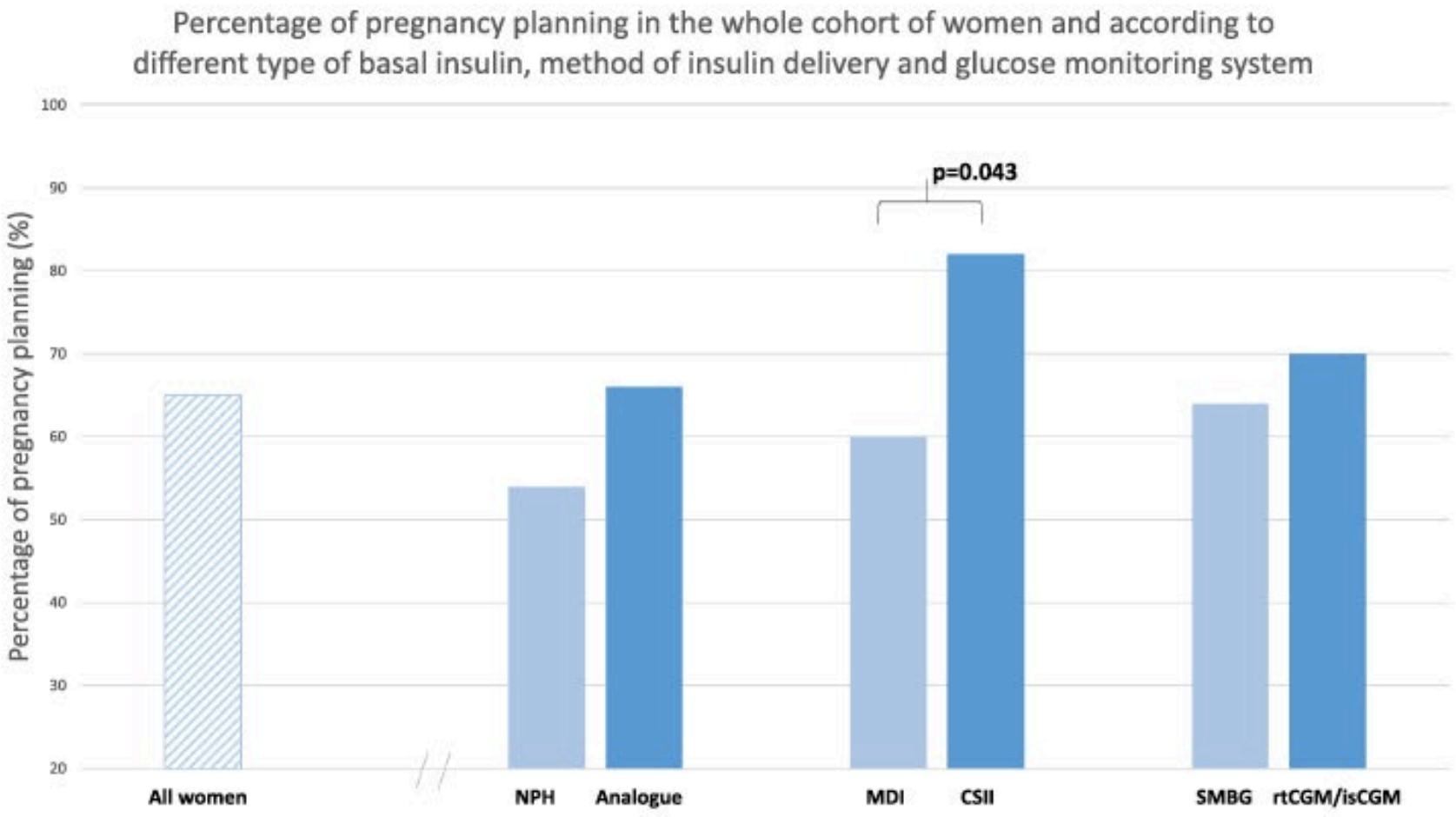
Pre-pregnancy care for women with pre-gestational type 1 or type 2 diabetes mellitus is effective in improving rates of congenital malformations, perinatal mortality

SWEET BABY

2012 - 2014

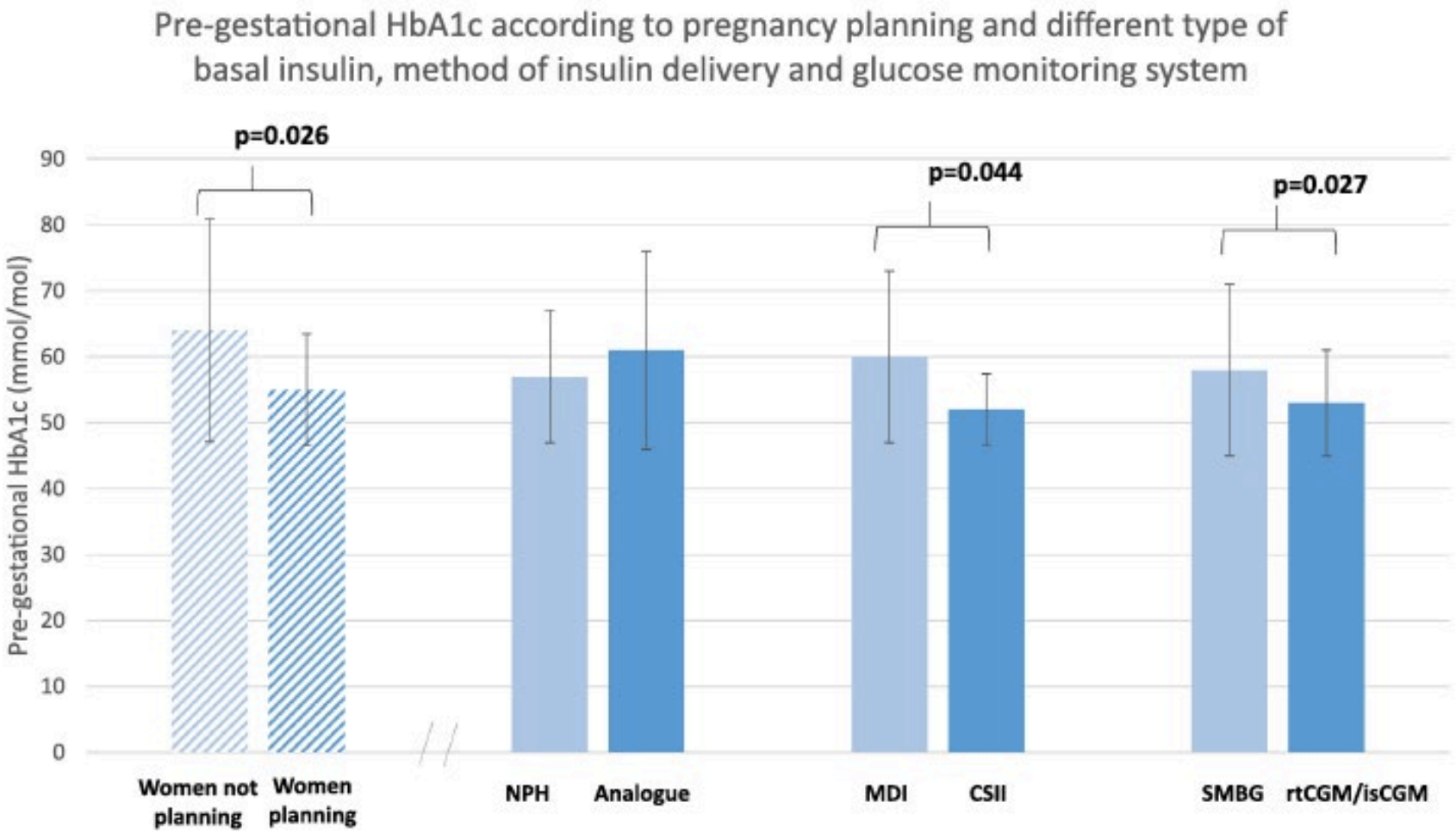


PREGNANCY PLANNING



CITRO ET AL 2023

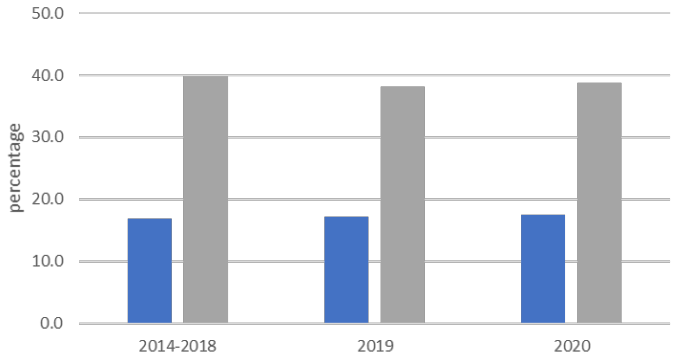
PREGNANCY PLANNING



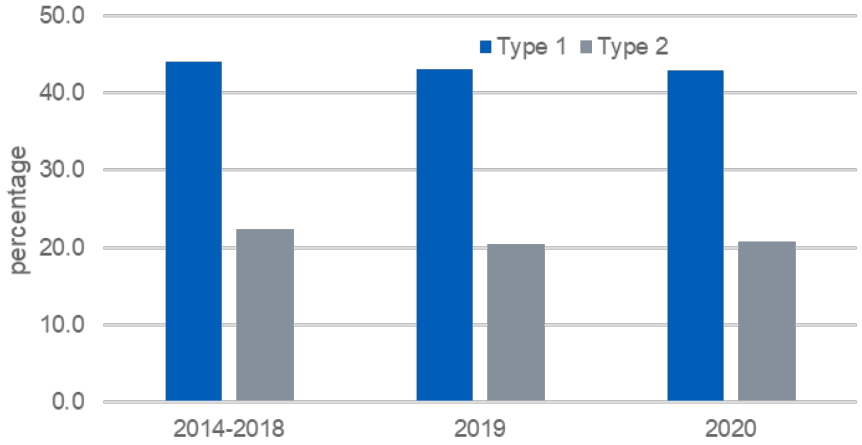
CITRO ET AL 2023

PRE-CONCEPTION CARE: GLUCOSE CONTROL,FOLIC ACID AND USE OF POTENTIALLY HARMFUL MEDICATIONS

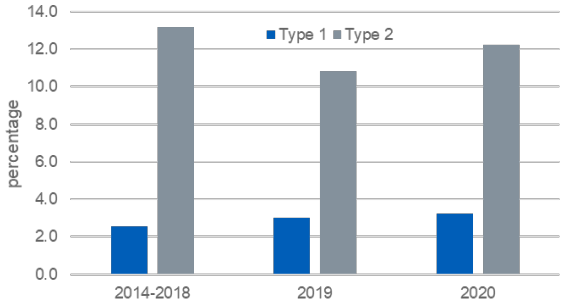
Pregnancies with Early HbA1c less than 48 mmol/mol



Pregnancies where 5 mg folic acid was taken prior to last mestrual period



Women who were taking statins or ACE inhibitors/ARBs, or who were on adverse diabetes medication at last mestrual period



Insufficient pre-conceptional care:
- HbA1 above target,
- low folic acid supplementation rates,
- up to 2% of women needing to take harmful drugs

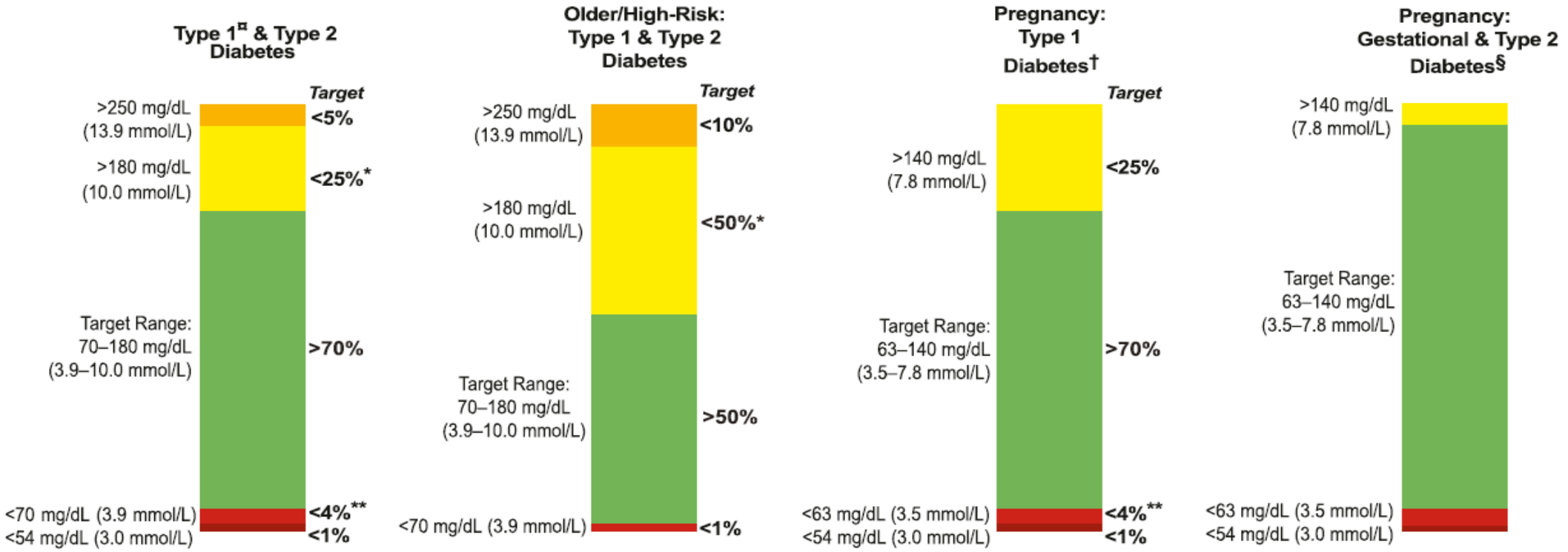
NHS Digital -National Pregnancy in Diabetes (NPID) Audit Report 2020, 2021

GLYCEMIC TARGET IN PREGNANCY

	Pre-conceptional HbA1c	2-3 trimester HbA1c	Gluose value in pregnancy
AMD-SID (2018)	≤6.5% (≤48 mmol/mol)	<6% (<42 mmol/mol)	• Fasting glucose ≤ 90 mg/dl • 1-hour postprandial glucose ≤130 mg/dl 1h • 2-hour postprandial glucose ≤120 mg/dl
ADA (2023)	≤6.5% (≤48 mmol/mol)	<6% (<42 mmol/mol)	• Fasting glucose 70-95 mg/dl • 1-hour postprandial glucose 110-140 mg/dl 1h • 2-hour postprandial glucose 100-120 mg/dl
NICE (2015)	≤6.5% (≤48 mmol/mol)	≤6.5% (≤48 mmol/mol)	• Fasting glucose <95 mg/dl • 1-hour postprandial glucose <140 mg/dl 1h • 2-hour postprandial glucose <115 mg/dl

SID-AMD 2018 –ADA. Diabetes care 2023; 46 (Suppl1):S254–S266 – NICE guideline 2015

CLINICAL TARGETS FOR CONTINUOUS GLUCOSE MONITORING



¤ For age <25 yr., if the A1C goal is 7.5%, then set TIR target to approximately 60%. (See *Clinical Applications of Time in Ranges* section in the text for additional information regarding target goal setting in pediatric management.)

† Percentages of time in ranges are based on limited evidence. More research is needed.

§ Percentages of time in ranges have not been included because there is very limited evidence in this area. More research is needed. Please see *Pregnancy* section in text for more considerations on targets for these groups.

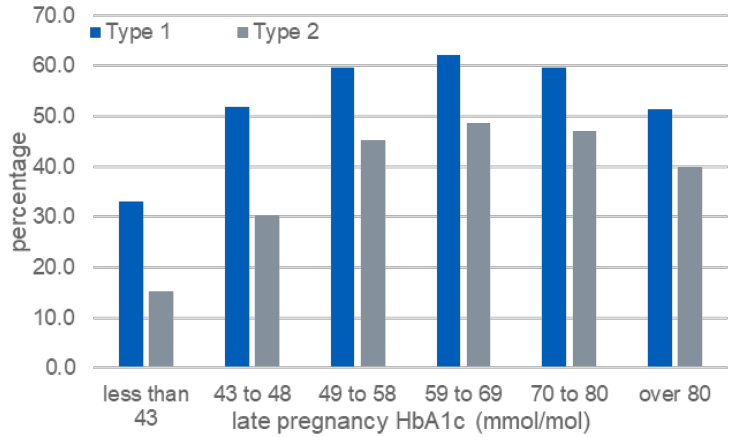
* Includes percentage of values >250 mg/dL (13.9 mmol/L).

** Includes percentage of values <54 mg/dL (3.0 mmol/L).

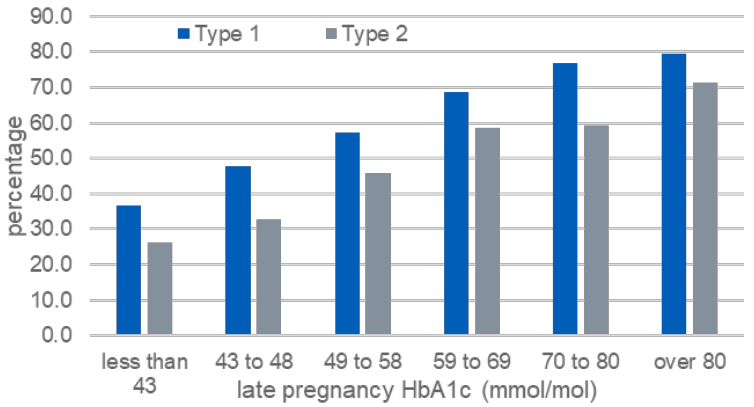
Battelino T. Diabetes Care 2019;42(8):1593-1603

LATE PREGNANCY HBA1C AND NEONATAL COMPLICATIONS

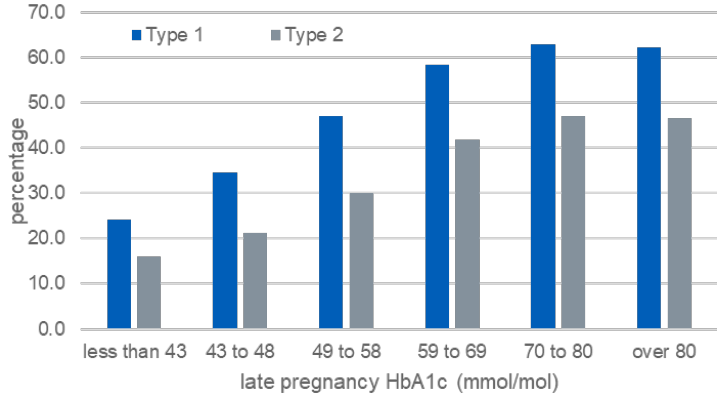
Large for gestational age



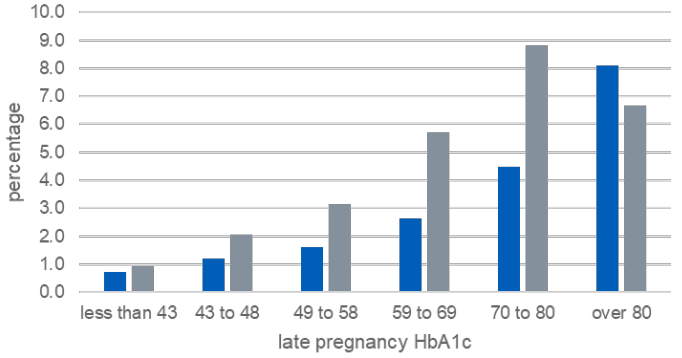
Babies admitted to neonatal care



Preterm live births before 37 weeks



Perinatal death



NHS Digital -National Diabetes Audit 2019–2020

INCIDENCE OF LGA IN WOMEN WITH DM1

Ospedale di Bergamo
Sistema Socio Sanitario
Regione Lombardia
ASST Papa Giovanni XXIII

- 34 women D1T who delivered in Bg (3/2016 - 9/2020)
- 18 (53%) neonates LGA
- Mean glycemia (CGM) during II and III trimester → higher risk of LGA
- Not significant relation with A1c
- ↓Time in range (63-140 mg/dl) ↑ time above range (> 140 mg/dl) during third trimester → higher risk LGA

Dodesini - SID 2022

INCIDENCE OF LGA IN WOMEN WITH DM1

Table 1 A1c, mean glycaemia and CGM metrics in two groups divided by trimester.

	I trimester		II trimester		III trimester	
	AGA (n = 16)	**LGA** (n = 18)	**AGA** (n = 16)	**LGA** (n = 18)	**AGA** (n = 16)	**LGA** (n = 18)
Body weight (kg)	61,7 ± 11,5	71,9 ± 10,3[a]	67,2 ± 12,3	79,3 ± 8,4[a]	72,5 ± 11,8	84,2 ± 11,7[a]
BMI (kg/m²)	23,8 ± 4,7	26,5 ± 3,4	26,1 ± 4,3	28,8 ± 3,2	26,9 ± 4,3	30,7 ± 4,2[a]
Daily insulin doses (U/kg)	0,7 ± 0,2	0,7 ± 0,3	0,8 ± 0,3	0,9 ± 0,3	1 ± 0,4	1,1 ± 0,3
A1c (mmol/mol)	50 ± 9	53 ± 8	44 ± 7	44 ± 8	48 ± 9	47 ± 8
CGM metrics	**AGA** (n = 13)	**LGA** (n = 15)	**AGA** (n = 15)	**LGA** (n = 18)	**AGA** (n = 16)	**LGA** (n = 18)
Mean glycaemia (mg/dl)	125,8 ± 20,3	137,2 ± 17,8[a]	120,6 ± 16,3	132,9 ± 14,7[a]	124,3 ± 18,8	139,4 ± 14,8[a]
TAR (%) > 140 mg/dl	33 ± 15,5	40,8 ± 14,7	29,1 ± 12,5	37,3 ± 12,7	31,1 ± 16,3	43,5 ± 13,6[a]
TIR (%) 63–140 mg/dl	59,6 ± 10,8	55,5 ± 14,5	63,5 ± 9,6	58,5 ± 12,3	64 ± 14,2	53,6 ± 12,7[a]
TBR (%) < 63 mg/dl	7,48 ± 7,33	3,63 ± 2,2	7,4 ± 6,48	4,21 ± 2,33	4,96 ± 3,7	2,85 ± 2,24[a]
TBR (%) < 54 mg/dl	3,98 ± 4,32	1,47 ± 1,1	3,62 ± 3,87	1,93 ± 1,37	2,13 ± 1,84	1,21 ± 1,29[a]

Data are mean ± SD.
[a] $p<0.05$ vs AGA.

Ospedale di Bergamo
Sistema Socio Sanitario
Regione Lombardia
ASST Papa Giovanni XXIII

Maternal glycaemic levels are associated with incidence of large for gestational age neonates in type 1 diabetic women in pregnancy – Dodesini et al

TREATMENT MODEL

KEY POINTS

- Screening before conception, or at least, in early pregnancy
- P-GD in pregnancy is complex + additional risk factors
- Appropriate planning + optimization of glycemic control
- Adopt lifestyle changes
- Multidisciplinary team

Ospedale di Bergamo

Sistema Socio Sanitario

Regione Lombardia

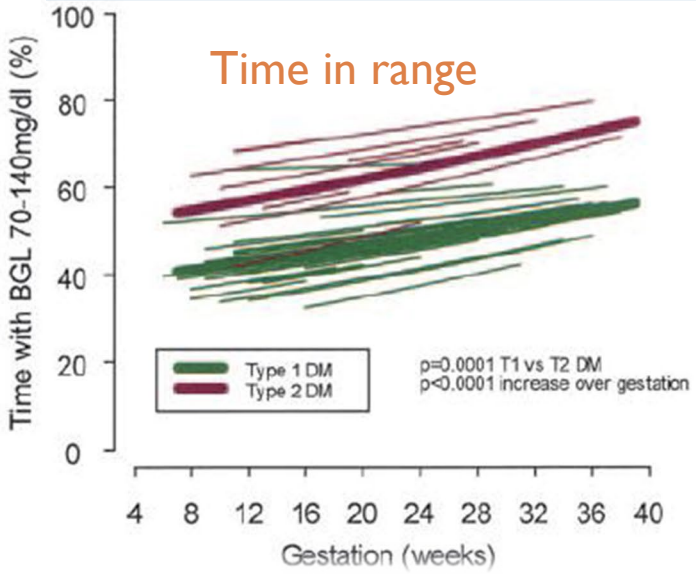
ASST Papa Giovanni XXIII

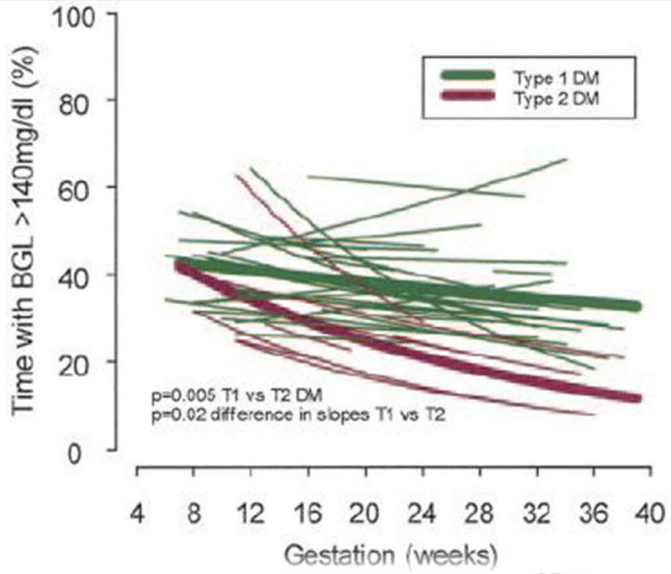
THANK YOU

Dr.ssa Chiara Bosisio
MMF ASST Papa Giovanni XXIII

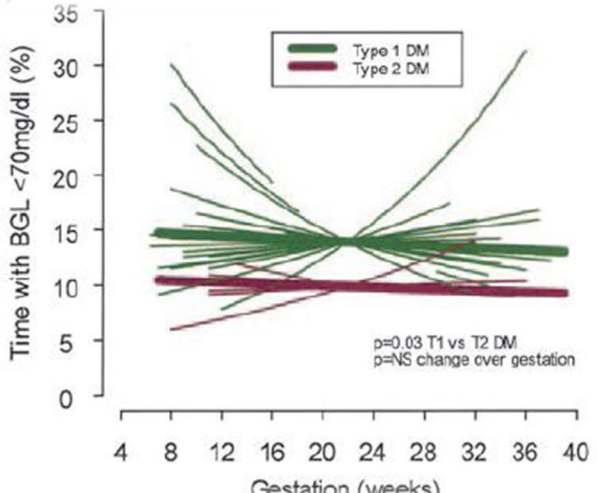
CHANGES IN THE GLYCEMIC PROFILES OF WOMEN WITH PRE-GESTATIONAL DIABETES DURING PREGNANCY

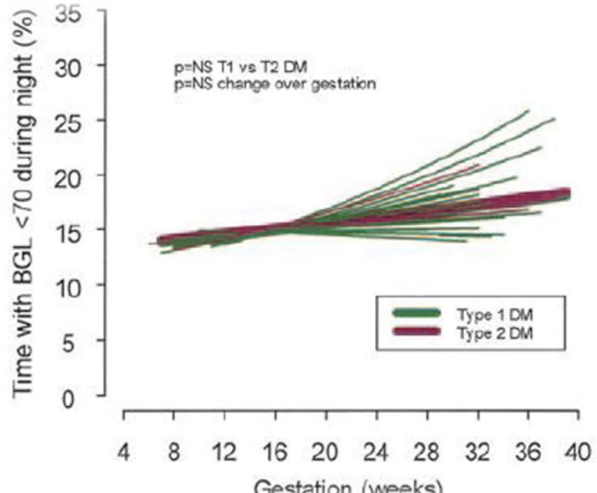
Time in range





Time below range

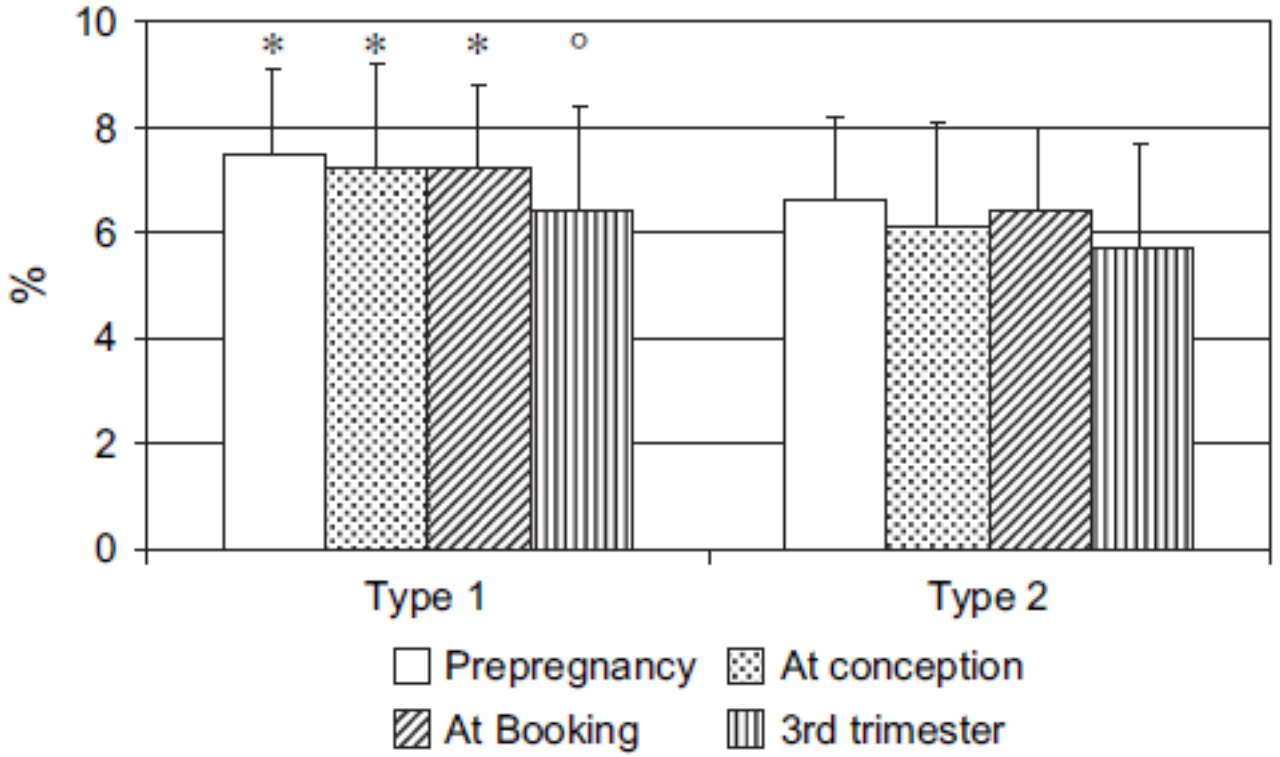




Murphy HR. Diabetes Care 2007; 30:2785–2791

METABOLIC CONTROL AT CONCEPTION AND DURING PREGNANCY

Prospective study in 33 centers in Italy
between 1999 and 2003
504 women with type 1 diabetes and 164 with type 2



Type 1 vs. type 2: $^{*}p < 0.0001, ^{\circ}p = 0.04$

Lapolla A. NutrMetabCardiovascDis2008;18(4):291-7

FOLIC ACID INTAKE ON THE ASSOCIATION AMONG DIABETES MELLITUS, OBESITY, AND SPINABIFIDA

Preexisting Diabetes	<400 µg Folic Acid	Ca/Co	aOR[a] (95% CI)
No	No	242/3827	1.0 (ref)
No	Yes	803/4798	1.99 (1.69, 2.34)
Yes	No	1/15	1.31 (0.17, 10.30)
Yes	Yes	7/24	3.95 (1.56, 10.00)
RERI (95% CI): 1.65 (−2.87, 6.18)			

	Folic acid	
	400 µg/day	5 mg/day
AMD-SID 2018	√	
ADA 2023	√	
NICE 2015		√

Parker SE. Am J ObstetGynecol2013;209(3):239.e1-8

SAFETY AND RISK OF COMMON DIABETES MEDICATION BEFORE AND DURING PREGNANCY

Medication	Category in pregnancy	Advice
Metformin	A	Not associated with an increase in congenital malformation or early pregnancy loss When used to treat polycystic ovary syndrome and induce ovulation, should be discontinued by the end of the first trimester
Incretin-based therapies (DPP-4 inhibitors and GLP-1 RA)	C	Cease and institute insulin therapy
SGLT-2 inhibitors	D	
Glitazones	C	
Sulfonylureas	C	
Insulin		
Aspart, Lispro	A	Safe to use
Glulisine	B	Insufficient evidence about use.
Detemir, Glargine, Degludec	A	Safe to use

A: safetouse; **B**: Insufficientevidenceaboutuse; **C**: Caution: harmfuldamage; **D**: Dengerous: toxicor teratogenic; **X**: Avoidin pregnancy

PRE-GESTATIONAL DIABETES AND PREGNANCY OUTCOMES IN TUSCANY

206,917 singleton live birthsin Tuscany, Italy from 2010 to 2018:

- GDM in 21,613 pregnancies (10.46%);
- Type 2 diabetes in 606 (0.29%);
- Type 1 diabetes in 373 (0.18%)

	Type 1 diabetes OR (95% CI)	Type 2 diabetes	GDM
a) Mothers' characteristics or deliveries' outcomes			
Pregestational overweight/obesity (BMI ≥ 30 kg/m^2)	1.49 (1.02–2.17)*	9.35 (7.84–11.14)*	2.72 (2.59–2.84)*
Migrant status	0.76 (0.56–1.03)	1.51 (1.22–1.87)*	1.53 (1.48–1.59)*
Previous spontaneous abortions (≥ 2)	1.12 (0.68–1.82)	4.19 (3.30–5.33)*	1.19 (1.12–1.27)*
Delivery at referral University Hospitals	2.79 (2.25–3.47)*	1.88 (1.58–2.24)*	1.18 (1.14–1.22)*
Preterm childbirth (< 37 wks.)	8.86 (7.18–10.94)*	2.60 (2.15–3.14)*	1.26 (1.21–1.32)*
Overall cesarean sections	3.75 (2.98–4.71)*	1.93 (1.62–2.28)*	1.22 (1.18–1.26)*
Emergency cesarean sections	1.69 (1.31–2.19)*	1.39 (1.13–1.72)*	1.16 (1.12–1.21)*
b) Neonates outcomes			
Macrosomia (birthweight > 4,000 g)	5.33 (3.70–7.67)*	1.92 (1.39–2.64)*	1.06 (0.99–1.13)
LGA**	4.75 (3.48–6.49) *	2.07 (1.60–2.66) *	1.08 (1.03–1.14)*
5-min Apgar score ≤ 7	2.31 (1.44–3.71)*	1.03 (0.56–1.89)	0.96 (0.84–1.09)
Fetal malformations	3.13 (1.29–7.59)*	1.69 (0.80–3.57)	0.83 (0.65–1.06)

ORs were adjusted for migrant status, age, parity, education degree, employment, calendar year of delivery, pregestational obesity, gestational week, modality of delivery (cesarean section yes/no) and regional hospital of delivery. Reference group: women without diabetes

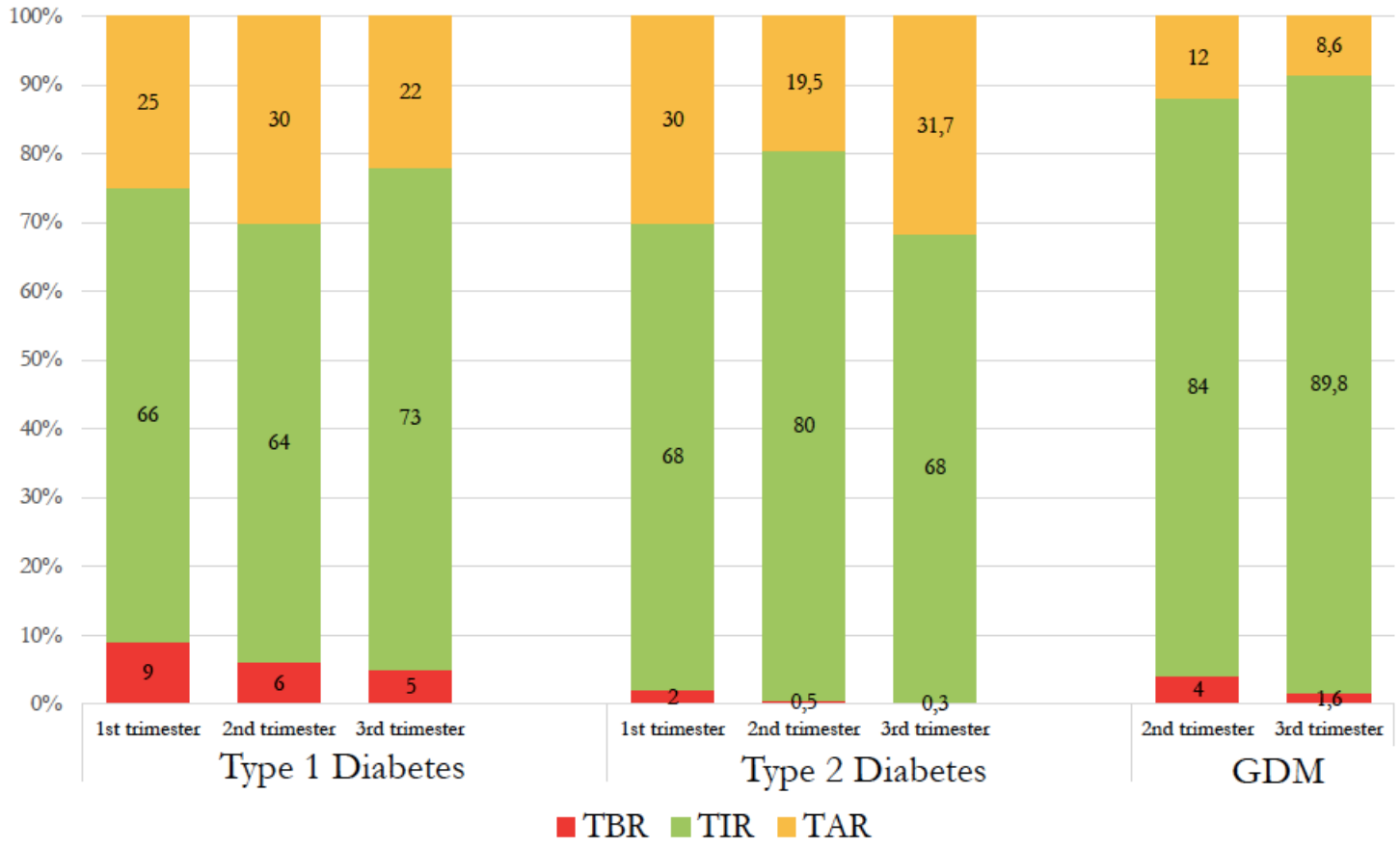
*$p < 0.001$

** > 90th centile of z-score birthweight, adjusted for sex and gestational week

Neonatal complications are mostly associated with pre-gestational diabetes (T1DM>T2DM)

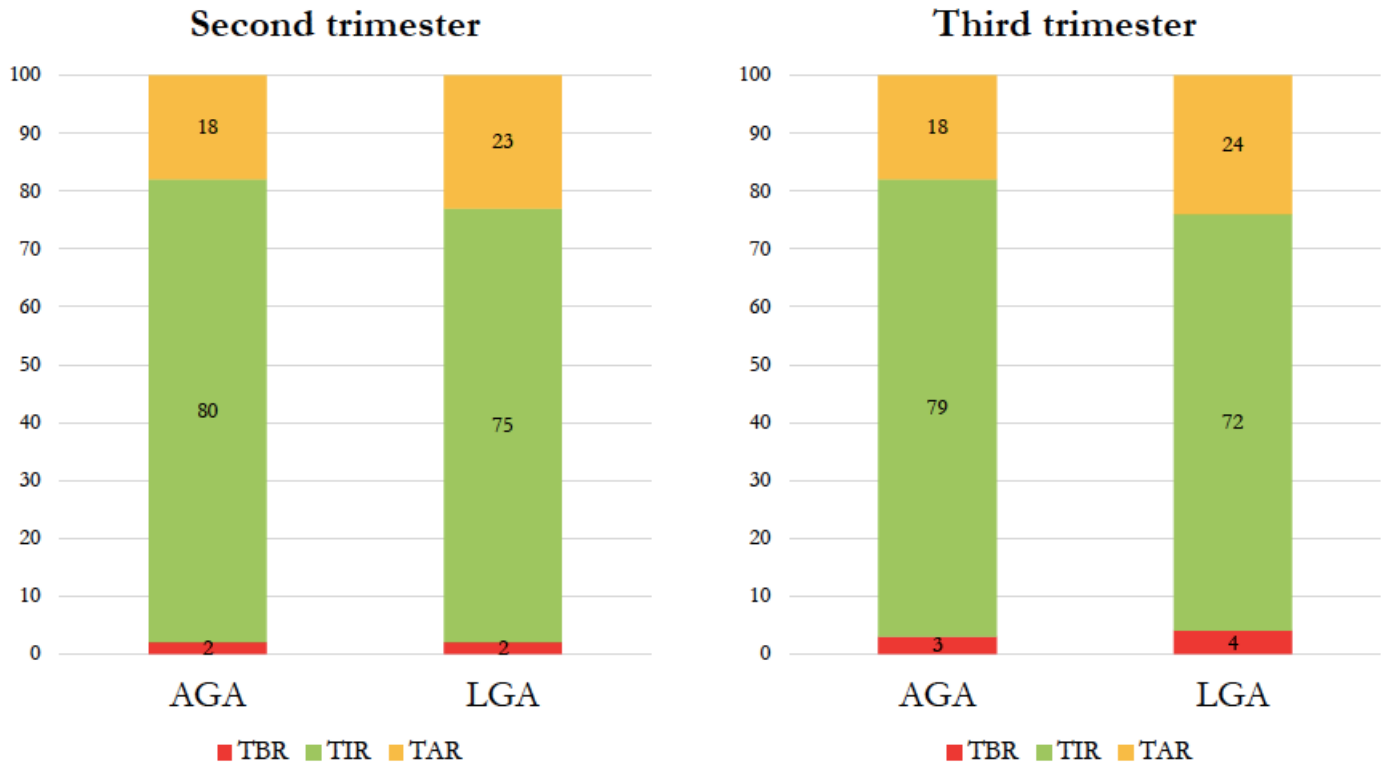
Gualdani E. Acta Diabetol 2021;58(9):1169-1176

CGM-DERIVED METRICS IN PREGNANCY



CitroF, BertolottoA, Aragona M, Bianchi C. *Unpublisheddata*. 2023

CGM-DERIVED METRICS IN PREGNANCY AND RISK OF LGA BABIES



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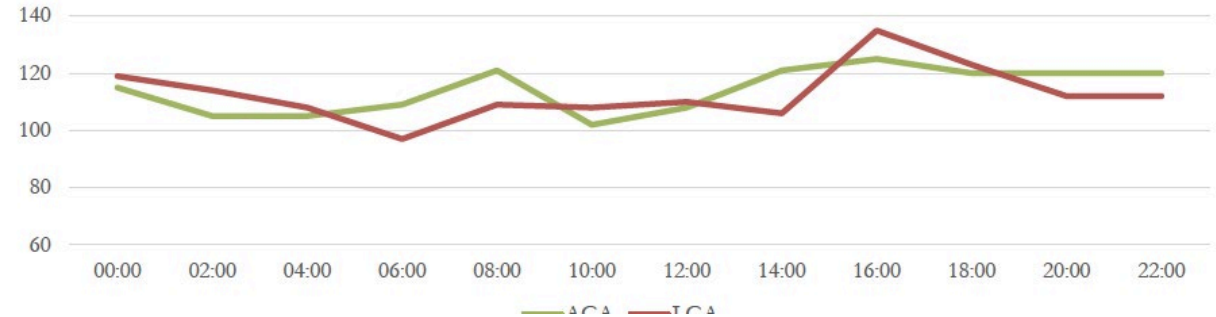
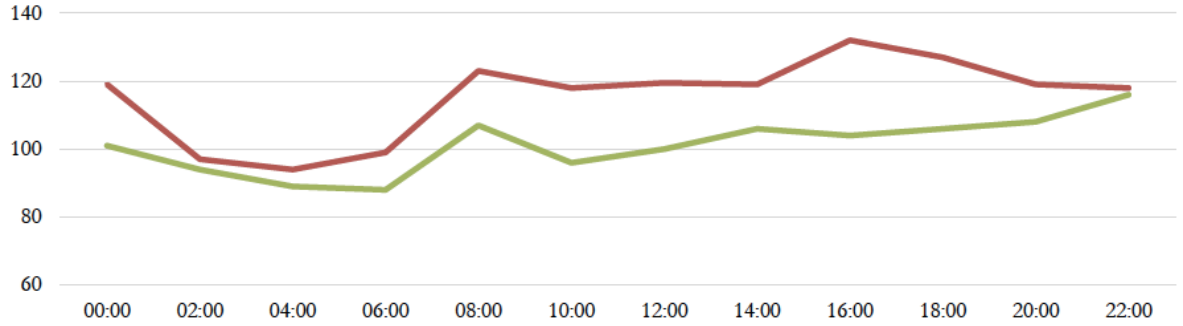
CGM-DERIVED METRICS IN PREGNANCY AND RISK OF LGA BABIES

Bi-hour mean glucose (mg/dl) at second trimester



Bi-hour mean glucose (mg/dl) at third trimester



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