Il /la dr./sa Angela Napoli dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Merck

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.).

Ipertensione in Gravidanza: Fattore di rischio Cardiovascolare

Angela Napoli

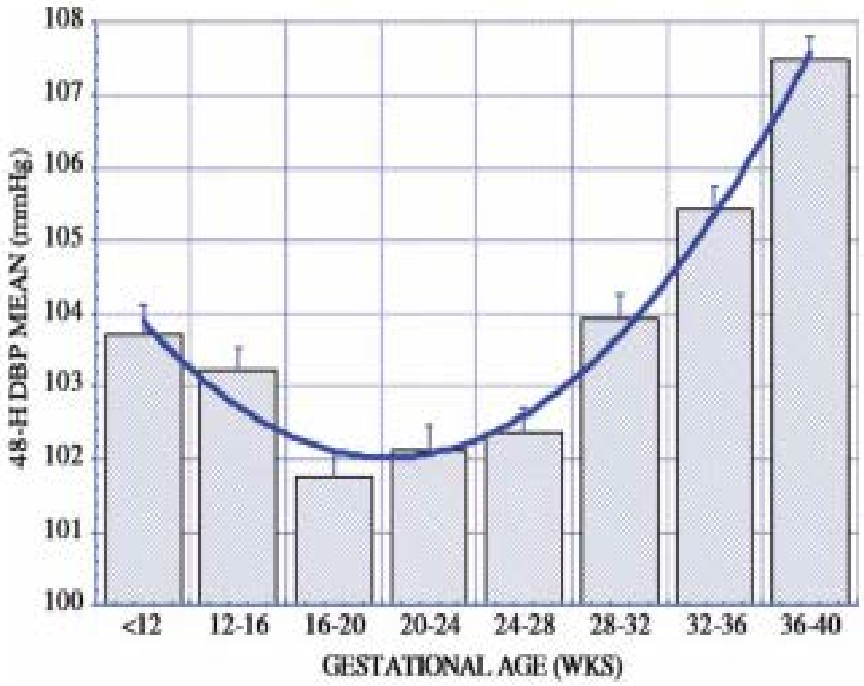
Chieti 19-20 aprile 2018

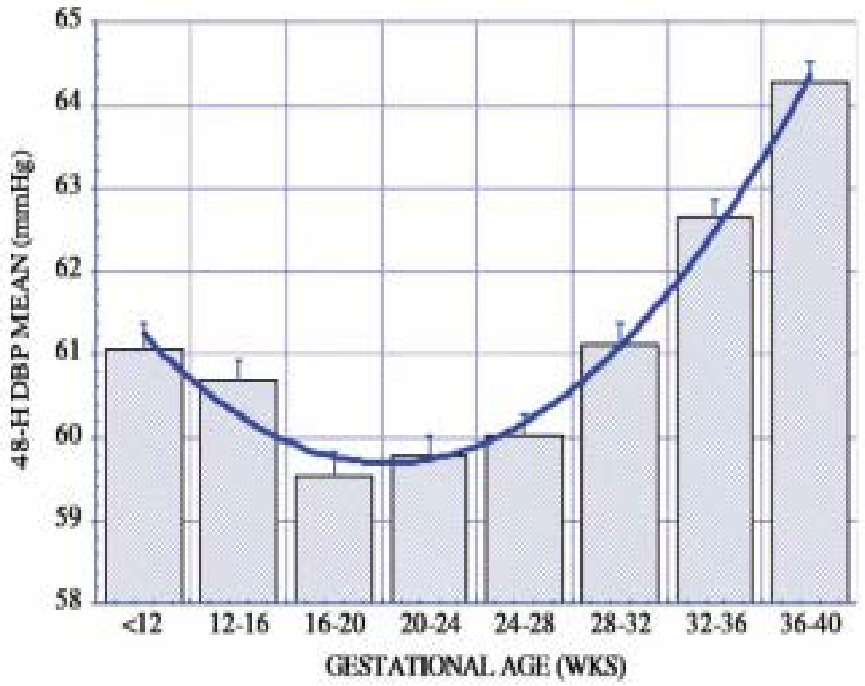
SAPIENZA
UNIVERSITÀ DI ROMA

Hypertension in Pregnancy: Diagnosis

Systolic BP≥ 140 and/or **Diastolic BP≥ 90 mmHg**

on 2 occasions more than 4-6 hours apart





Hypertension In Pregnancy

GESTATIONAL:

> the 20th Gestational week, It should resolve by 12 weeks postpartum.

CHRONIC:

antedating Pregnancy or <the 20th wk or persisting longer than 12 weeks postpartum

PRE-ECLAMPSIA 'PE' (MILD OR SEVERE):

EARLY <34 WEEKS, LATE >34 WEEKS
if also Proteinuria *Early onset rare*
≥ 0.3 g /24h, or U. Proteins/Creatinine ≥ 30 mg/mmol
>20a G.W. in Normotensive, Non Proteinuric Women
combined with Proteinuria on dipstick +1, after 21 g.w.

ECLAMPSIA:

Seizures + PE (in the absence of other neurologic conditions that could account for the seizure)

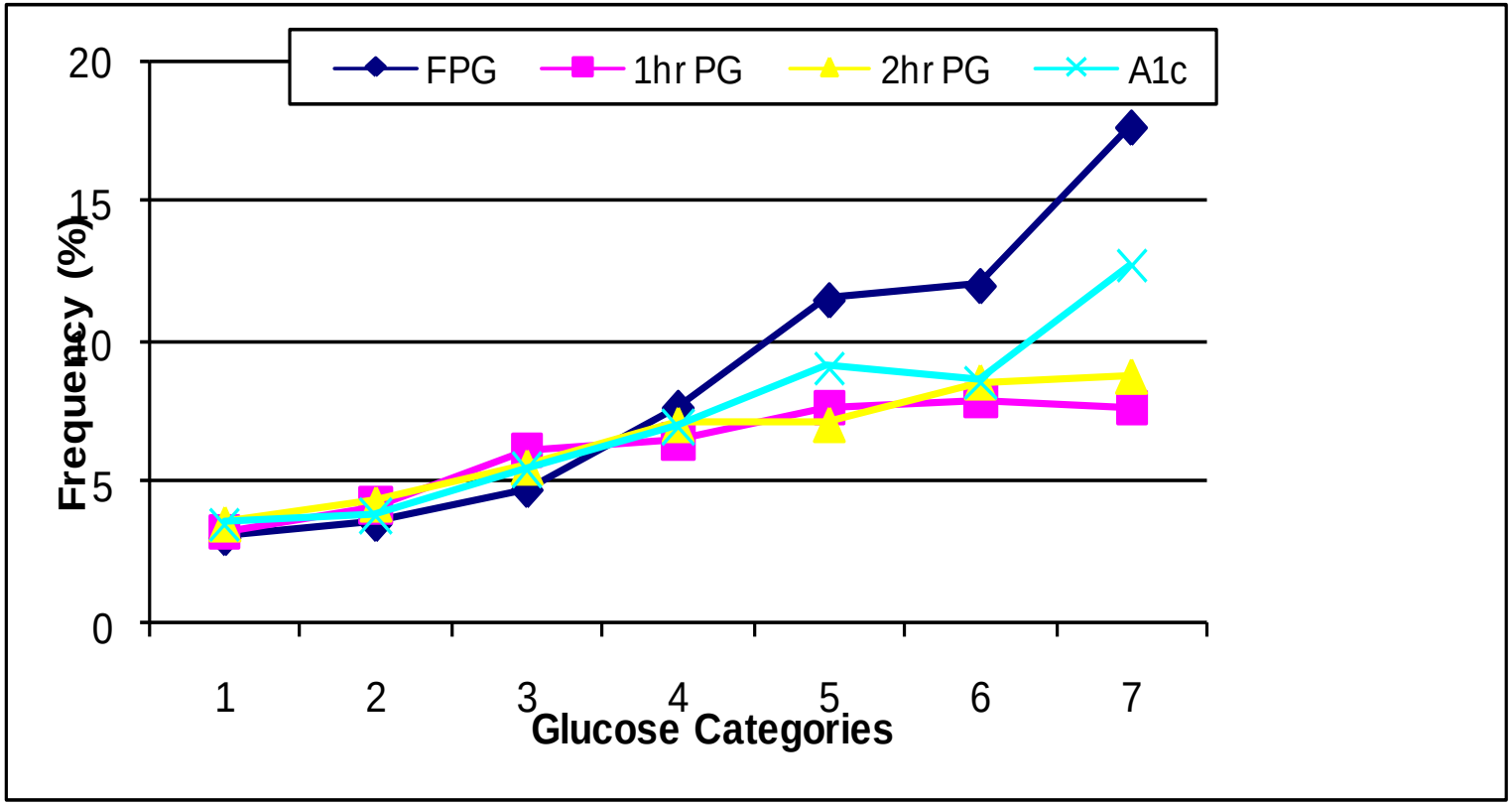
PE UPON CHRONIC/GESTATIONAL HYPERTENSION

‘HAPO’ Population: 23,316 Blinded Participants

Preeclampsia: 5,2%

Chronic Hypertension: 2,5%

Gestational Hypertension 5,87%



Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: preeclampsia

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group



For each Predictor:

3 Logistic Models: I, II , III

Model I

adjustment only for **Field Center**

Model II

adjustment for **Multiple Potential Prespecified Confounders**:
Maternal Age, Height, Smoking, Alcohol use, Family History of DM or of High BP, Gestational Age at the OGTT, Baby's Sex, Parity (0, 1, 2), any Maternal Urinary Tract Infection

For **Fasting C-Peptide** & measures of **Glycemia**, also included adjustment for *BMI*

For **BMI** as the predictor of interest also included adjustment for *FPG*

Model III

For analyses of **Fasting C - peptide** adjustment for *Fasting Glucose*
For **BMI** and measures of **Glycemia**, adjustment for *Fasting C-Peptide*

Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: preeclampsia

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group

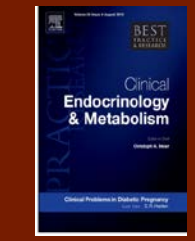


Strong, Independent Associations
of
Fasting C-peptide & BMI with Preeclampsia

Maternal Glucose Levels (below Diabetes Mellitus)
had Weaker Associations with Preeclampsia,
particularly after adjustment for fasting C-peptide & BMI

All types of hypertensive disorders in pregnancy are more frequent in diabetic women

Different distribution according to diabetes type.



Chronic Hypertension:

Type1: **2 – 11%**
Type2: 12 – 18%
GDM: 1 – 3 %

Pre-Eclampsia:

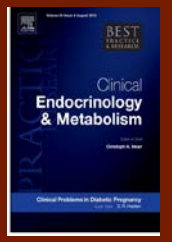
Type1: **3 – 50 %** (when nephropathy is pre-existing)
Type 2: 3 – 15 %
GDM: 2.8 – 6.7%

Gestational Hypertension:

Type1: **1.6 – 25.3%**
Type 2: 9 – 19.4 %
GDM: 6.9 – 28 %

Best Practice & Research Clinical Endocrinology & Metabolism 2010. Colatrella A, Napoli A

Type 1 Diabetes



Gestational Hypertension Risk

2–3 fold higher in women with **no nephropathy** than in controls. [28,30,34]

Unlike Pre-eclampsia, **Gestational Hypertension** per se, **No** association with **Retinopathy, D. Duration** or **Glycaemic Control.**

Nulliparity remains a **risk factor**

PE Risk

5–6 fold higher than general population [28,30–32,34]

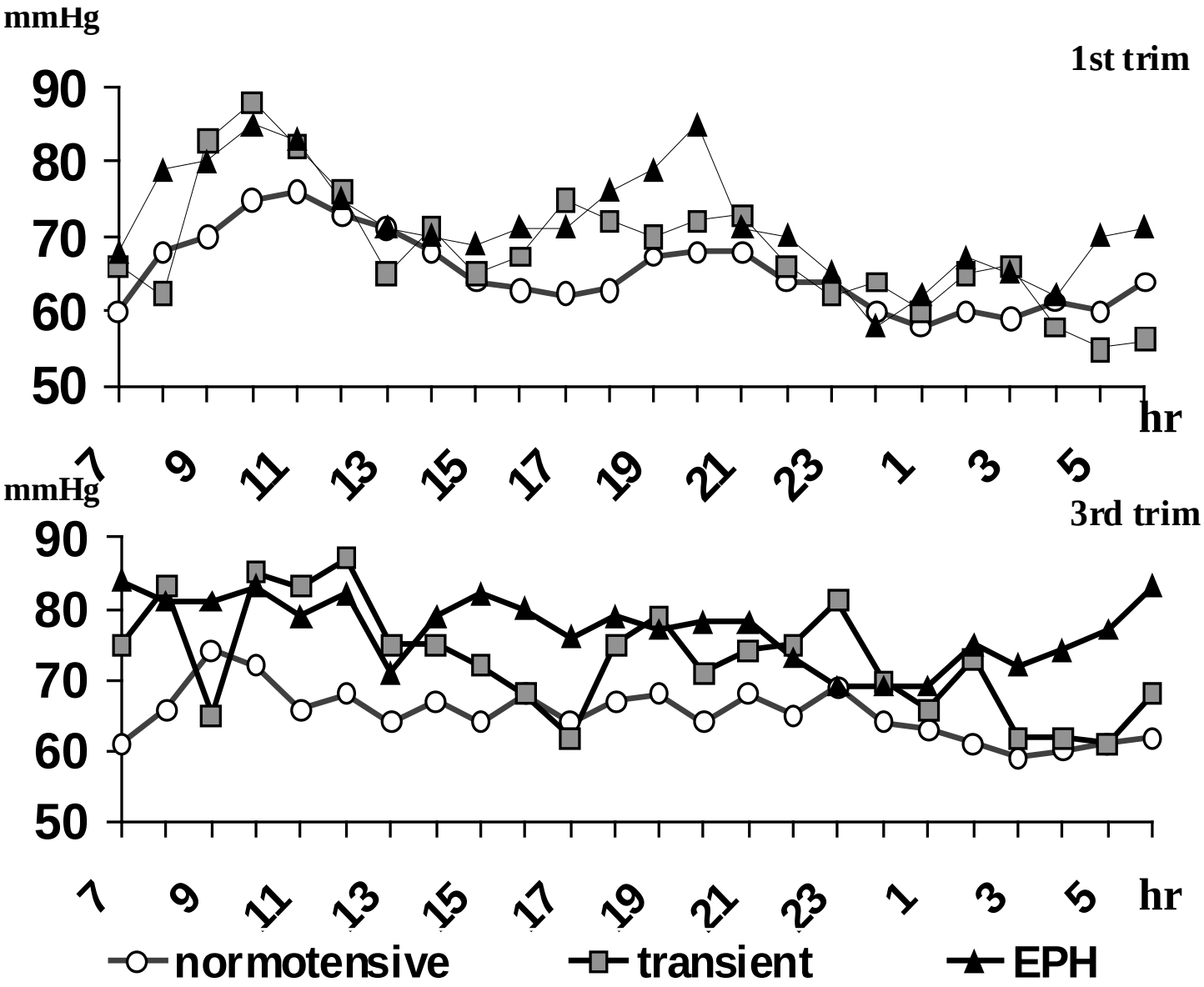
↑ with **Nulliparity,**[28–30,35] **Diabetes Duration,**[28,30] **Microvascular Complications** [25,28,32] & **Pre-existing hypertension** .[33]

Association between PE & Poor Glycaemic Control,[32,35] **particularly in early pregnancy,**[26,28] has been reported, apart from one study.[29]

Hiilesmaa[28] :: **each 1% decrement of HbA_{1c} achieved by mid-pregnancy** (not during the latter half) **reduces the risk of PE by a factor of 0.6**

Diabetic Women who are **Parous, with neither** Nephropathy **nor R**etinopathy **& a D. Duration <15 years**, show a risk of **PE similar to Controls 2.8 vs 2.7%**

Best Practice & Research Clinical Endocrinology & Metabolism 2010. Colatrella A, Napoli A



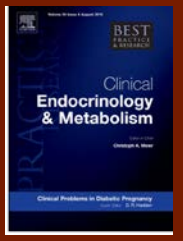
PE: 11.26%

GH: 25.3%

24-hr D. BP at the 1st & 3rd trim. of pregnacy in type1 diabetic women who remained Normotensive vs those who developed Hypertension

A. Napoli. Journal of Diabetes and its Complications, 2003

Type 1 Diabetes & Complications



Pre-pregnancy diabetic nephropathy,[24,25,27] **even incipient,**[29,35] represents the most important risk factor for **pre-eclampsia**

In these women, **the enhancement of albuminuria during pregnancy cannot be explained by a greater renal hyperfiltration.**[45]

Hypertension often associated with **clinical nephropathy worsens in pregnancy acquiring the characteristics of Preeclampsia**[46]**;**

Against a background of nephropathy, it may be difficult to diagnose pre-eclampsia confidently, as worsening diabetic nephropathy will produce a similar degree of hypertension and proteinuria.ù

A long-Term follow-up showed an accelerated progression of renal failure after delivery.[24<]

Type 2 diabetes

Emerging problem, often perceived as less serious than type 1D.[47]
Few studies on hypertensive disorders , [48–51] mostly retrospective or as comparison with type 1 and GDM .[36–44]

Hypertensive disorders are 2–4 times more common than in Non diabetic women,[48,51] as frequent as in women with type 1 diabetes.[39–41] Some authors observe
↑ **% Chronic Hypertension** than controls and type1D women[37,51]
↓ **PE** than type 1 diabetes.[51]
Hughes[50] reported ↑% PE (Australasian Society Classification)

Risk factors

Nulliparity, BMI, D. Duration, Metabolic Control, Vascular disease [36–38,51];
No association was found with ethnicity when available.[50]
Hypertension in T2D pregnancy is associated with an increased risk of premature delivery,[36,38,48] low birth weight[48]
If PE ↑ admission to NICUS[36] (> than Controls, <than T1D) .[37]

Hypertensive Disorders in Normal/Over-weight and Obese Type 2 Diabetic Pregnant Women

Authors: A. Colatrella[1], S. Braucci[1], C. Festa[1], P. Bianchi[2], F. Fallucca[1], L. Mattei[1], M. Trappolini[1], A. Napoli[1]

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All: 40.8%
Chronic: 18.4%
PIH: 17.1%
PE: 5.3%

Table 1 Clinical characteristics in type 2 diabetic and normal pregnant women.

	Type 2 diabetic women(n = 76)	Control women (n = 60)	*p*
Age (y)	32.7 ± 4.6	31.0 ± 5.3	ns
Smoking habit (%)	26.3	35.0	ns
Nulliparity (%)	22.0	61.9	0.0001
Previous abortion (n°)	0.5 ± 0.7	0.04 ± 0.2	0.001
Pregestational BMI (kg/m^2)	28.3 ± 6.3	22.4 ± 3.2	<0.0001
Classes of BMI:			0.0001
Normoweight (%)	30.0 (n = 23)	71.7 (n = 43)	
Overweight (%)	34.0 (n = 26)	25.0 (n = 15)	
Obese (%)	36.0 (n = 27)	3.3 (n = 2)	
Diabetes duration (y)	5.7 ± 4.5	–	
Age of onset (y)	26.8 ± 6.2	–	
Current pregnancy:			
Weight increase (kg)	7.8 ± 5.2	9.0 ± 1.4	ns
Spontaneous abortion (%)	7.9 (n = 6)	0	0.001
Pre-pregnancy HbA1c (%)	6.3 ± 2.1 (n = 22)	–	
HbA1c at conception (%)	6.2 ± 1.7 (n = 31)	–	
HbA1c at 3rd trimester (%)	5.3 ± 1.2 (n = 70)	–	
Cesarean section (%)	71.4 (n = 50)	36.6 (n = 22)	0.02
Delivery week	37.7 ± 2.7	39.7 ± 2.7	0.04
Preterm birth (<37th week) (%)	18.4 (n = 13)	1.6 (n = 1)	0.001
Birth weight (g)	3191.6 ± 711.7	3122.0 ± 448.0	ns
Malformations (%)	7.9 (n = 6)	0	0.001
Hypertension (%):	40.8 (n = 31)	10.0 (n = 6)	<0.0001
Chronic	18.4 (n = 14)	0	0.005
PIH	17.1 (n = 13)	8.3 (n = 5)	ns
Pre-eclampsia	5.3 (n = 4)	1.7 (n = 1)	ns

Hypertension (%) progressively **increased from N to OV to OB**
despite no difference of Age, D. Duration, HBA1C in Early & Late pregnancy, Smoking Habit
Compared with Normoweight T2D (BMI < 25) OR

OV: 2.9 **OB: 9.7**

Among the three groups no differences in week or type of delivery & / or n° of malformations.
Neonatal Weight (but not macrosomia) higher in **infants of obese diabetic women**,
related to **Pregestational Maternal BMI**

Table 3 Clinical characteristics in normoweight, overweight and obese type 2 diabetic pregnancies.

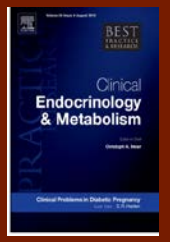
		N	OV	OB		p		
					χ^2	N vs OV	N vs OB	OV vs OB
	n°	23	26	27		ns	ns	ns
Prepregnancy BMI	kg/m²	21.3 ± 1.9	27.2 ± 1.4	35.0 ± 3.8		<0.0001	<0.0001	<0.0001
Age	y	32.4 ± 5.6	32.1 ± 3.9	33.0 ± 4.6		ns	ns	ns
Diabetes duration	y	6.8 ± 4.7	5.8 ± 5.5	6.6 ± 7.3		ns	ns	ns
Age of diagnosis	y	25.1 ± 8.6	26.1 ± 5.8	27.8 ± 5.0		ns	ns	ns
Early HbA1c	%	5.7 ± 1.4	6.4 ± 1.5	6.4 ± 2.3		ns	ns	ns
Late HbA1c	%	5.2 ± 1.0	5.8 ± 1.3	5.0 ± 1.4		ns	ns	ns
Smoking	%	26.1	15.4	33.3	ns			
Delivery's week		38.2 ± 2.1	37.0 ± 2.0	37.1 ± 3.7		ns	ns	ns
Type of delivery (CS)	%	56.5	84.6	70.4		ns	ns	ns
% of malformations	%	8.7	7.7	7.4		ns	ns	ns
Maternal weight gain	kg	10.1 ± 3.3	7.3 ± 6.6	7.1 ± 5.2		ns	ns	ns
Neonatal weight	g	2870 ± 480	2919 ± 801	3525 ± 455		ns	0.01	0.05
Macrosomia	%	0%	23.1%	29.6	ns			
% of hypertension	% (n°)	13.0 (3/23)	30.8 (8/26)	59.2 (16/27)	0.02			
chronic hypertension		4.3	19.2	25.9				
PIH		4.3	7.7	29.7				
PE		4.3	3.9	3.6				

BMI: OR 5,25
Smoking
HBA1C

Table 4 Multiple logistic regression analysis with hypertension and its subtypes as dependent variables in type 2 diabetic pregnant women.

Independent variables	Dependent variables *p* of the model and odds ratio (95 % IC)			
	Overall hypertension	Chronic hypertension	Gestational hypertension	Pre-eclampsia
pre-pregnancy BMI	0.008 OR 5.25 (1.3–21.6)	ns	ns	ns
weight increase	ns	ns	ns	ns
age	ns	ns	ns	ns
parity	ns	ns	ns	ns
smoking	ns	0.02 (inversely) OR 0.05 (0.006–0.5)	ns	ns
HbA1c 1st trim	ns	ns	ns	ns
HbA1c 2nd trim	ns	ns	0.05 OR 3.2 (0.33–31.1)	ns
HbA1c 3rd trim	ns	ns	ns	ns

Hypertension in Pregnancy



Women with either

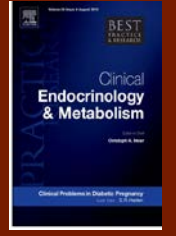
GH and PE: ↑ risk of GDM : OR 1.4 and 1.5.[59]

Gestational Hypertension

associated with a higher & obstetric intervention, planned deliveries through elective caesarean section or induction of labor, resulting in a earlier delivery of newborns with no difference in weight or other outcome measures.[63]

Pre-Eclampsia

associated to a Lower birth weight & a higher % SGA.[55]



Accurate Pregestational & Antenatal Assessment of

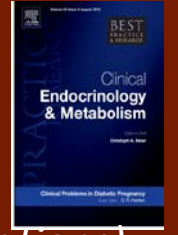
Hypertensive Disorders,

associated with Intensive Management

improves Diabetic Pregnancy Outcome,

even in microalbuminuric women with type 1 diabetes[64<<]

Long-term Outlook: type 1 diabetes



FinnDiane, a Nationwide prospective study
(standardised questionnaire on antihypertensive medication, (CHD) & diabetic complications)

PE & G.H. History ↑ risk of
Hypertension 11 yrs after

PE	GH	Normotensive in pregnancy
50%	41.9%	9.8%

↑risk

Diabetic Nephropathy	CHD
Pre-eclampsia	
41.9%	12.2%
Gestational Hypertension	
10.3%	3.2%
Normotensive women	
8.9 %	2.2% [70]

A **sight-threatening** deterioration of retinopathy was found in 50% of women whose pregnancy had been complicated by pre-eclampsia.[71]

Hypertensive Status During and After Pregnancy

Table 1 Demographic and clinical characteristics of the 103 women with gestational hyperglycemia at baseline and 3 years after delivery

	Baseline	3 years after delivery
Age (years)	33.3 ± 4.2	37.2 ± 4.6
Body mass index (kg/m^2)	23.6 (21.8–27.3)	24.7 (21.9–28.9)
Normal weight (%)	64 (62.1)	57 (55.3)
Overweight (%)	26 (25.2)	28 (27.2)
Obese (%)	13 (12.7)	18 (17.5)
Smoking habits (%)	0 (0)	27 (26.2)
Family history of diabetes mellitus in first-degree relatives *n* (%)	53 (51.4)	55 (53.4)
Family history of cardiovascular disease in first-degree relatives *n* (%)	64 (62.1)	68 (66.0)

During pregnancy

28.1% women had hypertension

24 GH; 4 Chronic H; 1 PE.

At follow-up

15.5% women were hypertensive

Table 3 Clinical characteristics of studied women sub-grouped according to the presence or absence of hypertensive disorders at follow-up

	Hypertensive patients ($n = 16$)	Normotensive patients ($n = 87$)	*p*
Body mass index (kg/m^2)			
Pre-gestational	27.9 (22.5–34.3)	23.5 (21.7–26)	0.02§
At follow-up	29.0 (23.3–38.2)	24.6 (21.8–28.1)	0.009§
Fasting glucose at follow-up (mmol/L)	5.5 ± 1.1	4.9 ± 0.7	0.01*
Abnormal oral glucose tolerance *n* (%)	10 (62.59)	23 (27.5)	0.06ℤ
Triglycerides at follow-up (mmol/L)	1.12 (0.97–1.38)	0.76 (0.61–1.20)	0.005§
Homeostasis model assessment insulin resistance at follow-up	4.2 (1.4–7.0)	1.0 (0.7–1.7)	0.0003§
Matsuda insulin sensitivity index at follow-up	4.0 (2.6–7.2)	7.3 (5.3–19.0)	0.01§
Insulinogenic index at follow-up	13.0 (6.8–22.7)	9.3 (6.5–17.2)	ns§
Oral disposition index at follow-up	1.4 (0.8–2.2)	2.2 (1.1–4.2)	ns§

Hypertensive disorders during pregnancy and 3 years after delivery in women with gestational hyperglycemia

C. Festa1 …· A. Napoli, JEI 2018

Table 2 Clinical and metabolic characteristics of women with gestational hyperglycemia sub-grouped according to the presence of hypertension in and after pregnancy

	Hypertensive in and after pregnancy (HH)	Normotensive in pregnancy and hypertensive after (NH)	Hypertensive in pregnancy and normotensive after (HN)	Normotensive in and after pregnancy (NN)	*p*
Number of subjects	11	5	18	69	
Body mass index before pregnancy (kg/m^2)	31.7 (28.4–34.8)	22.5 (21.0–26.1)	25.0 (22.8–29.9)	22.6 (21.4–25.8)	0.001^ 0.009†
Body mass index at follow-up (kg/m^2)	34.9 (27.1–39.2)	23.7 (22.3–26.1)	24.9 (22.8–28.8)	24 (21.7–27.7)	0.041* 0.03†
Weight gain at follow-up (kg)	4.78 ± 5.89	7.70 ± 7.61	1.09 ± 7.6	2.21 ± 4.96	ns
Fasting glucose (mmol/L)	5.4 ± 1.0	5.7 ± 1.4	5.2 ± 1.1	4.8 ± 0.5	0.008*
Total cholesterol at follow-up (mmol/L)	4.4 ± 0.8	5.9 ± 1.0	5.2 ± 0.8	4.9 ± 1.0	0.046^
High-density lipid cholesterol at follow-up (mmol/L)	1.1 ± 0.3	1.4 ± 0.3	1.4 ± 0.3	1.5 ± 0.4	0.028^ 0.028†
Low-density lipid cholesterol at follow-up (mmol/L)	2.8 ± 0.8	4.0 ± 0.9	3.4 ± 0.7	2.9 ± 1.0	0.025^
Homeostasis model assessment insulin resistance at follow-up	4.2 (1.3–7.9)	1.9 (1.5–5.7)	1.0 (0.8–2.4)	1.0 (0.7–1.6)	0.001^ 0.001† 0.004*
Metabolic syndrome at follow-up *n* (%)	7 (63.6)	1 (20)	3 (16.8)	6 (8.7)	0.0002ǂ
Abnormal glucose tolerance at follow-up *n* (%)	5 (45.4)	4 (80)	6 (33.3)	16 (23.2)	0.05ǂ
Diabetes mellitus (*n*)	2	2	2	4	
Impaired fasting glucose (*n*)	2	0	3	7	
Impaired glucose tolerance (*n*)	1	2	2	5	

Data are expressed as mean ± SD or as median and 25th–75th centile according to distribution

p significant: † HH vs NN; * HH vs HN

^Bonferroni post hoc, ǂ Chi-square test

Hypertension diagnosed in pregnancy present also after the delivery

HH 10.6%

Hypertensive in pregnancy and normotensive after

HN 17.5% ~ one in five women

Normotensive on pregnancy but hypertensive after

NH 4.8%

Normotensive before and after pregnancy

NN 66.9% the best clinical and metabolic profiles

Hypertensive disorders during pregnancy and 3 years after delivery in women with gestational hyperglycemia

C. Festa1 …· A. Napoli, JEI 2018

Table 4 Clinical and metabolic characteristics of the studied women according to glucose tolerance status at follow-up

	Impaired glucose tolerance ($n = 34$)	Normal glucose tolerance ($n = 69$)	p
Age (years)	38.1 ± 4.8	36.7 ± 4.4	0.46*
Follow-up length (months)	35.3 ± 23.4	30.7 ± 18.4	0.15*
Number of pregnancies	2 (1–3)	2 (1–3)	0.13*
Body mass index (kg/m^2)	27.7 (24–31.6)	23.9 (21.8–27.3)	0.01*
Systolic blood pressure (mmHg)	117.1 ± 14.4	108.8 ± 13.4	0.59*
Diastolic blood pressure (mmHg)	75.5 ± 10.6	69.6 ± 6.5	0.38*
Homeostasis model assessment insulin resistance at follow-up	1.53 (0.8–3.5)	1.15 (0.7–1.6)	0.07§
Matsuda insulin sensitivity index at follow-up	5.5 (3.8–9.1)	7.53 (5.4–10.9)	0.72§
Insulinogenic index at follow-up	7.6 (4.1–15.3)	10.8 (7.4–17.4)	0.60§
Triglycerides (mmol/L) at follow-up	0.97 (0.7–1.48)	0.75(0.6–1.2)	0.98§
Total cholesterol (mmol/L) at follow-up	5.12 ± 1.19	4.94 ± 0.85	0.10*
Low-density lipid cholesterol (mmol/L) at follow-up	3.23 ± 1.01	2.92 ± 0.88	0.40*
High-density lipid cholesterol (mmol/L) at follow-up	1.29 ± 0.3	1.47 ± 0.39	0.36*

Data are expressed as mean ± SD or as median and 25th–75th centile according to distribution

*t test, § Mann–Whitney

At last follow-up visit

Abnormal glucose tolerance in 31 (30.1%) women.

10 women developed diabetes, 11 women IFG, 9 IGT 1 IFG+IGT

Metabolic Syndrome **17 (16.5%)** women

in a larger percentage among hypertensive (**50%**) vs normotensive (9/87, **10.3%**) women at Follow up (p = 0.002).

When considering the **time when hypertension occurred** the **highest % MS** in Hypertensive group In & After pregnancy

HH 63,6 % vs **HN 10%** vs **NH 16.8%** vs **NN 8.7 %**

Hypertensive disorders during pregnancy and 3 years after delivery in women with gestational hyperglycemia
C. Festa1 …· A. Napoli, JEI 2018

NEW

NH

Hypertension manifested at F-up in five women who remained normotensive throughout gestation:

the Worst Glucose Tolerance Levels & LDL Cholesterol profiles at F-up

Hyperglycemia has an excitatory effect on the renin–angiotensin–aldosterone system Cholesterol ? [22].

Inverse & continuous relationship between cholesterol levels & endothelium-dependent vasodilatation,
….cholesterol levels **partly** explains variance in endothelium-dependent vasodilation [25].

Early treatment improves endothelial function [26].

…….Oxidative stress also oxidizes LDL cholesterol, which in turn activates the renin–angiotensin system and angiotensin II [27].

Some studies report increased ***Arterial Media-Intimal Thickness in women with previous gestational hyperglycemia*** *[28].*

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Hypertensive disorders during pregnancy and 3 years after delivery in women with gestational hyperglycemia
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None of the women who were found to have diabetes, IFG, IGT, hypertension or MS at follow-up was symptomatic or aware of their clinical condition.

Hypertensive disorders during pregnancy and 3 years after delivery in women with gestational hyperglycemia
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Subclinical Atherosclerosis in Women with p-GDM

Study	pGDM (n.)	Method of Assessment	Results
Hu (1988)	17	Echo tracking of aorta	Impaired
Anastasiou (1995)	33	Flow-mediated dilation	Impaired
Honnemann (2002)	17	Flow-mediated dilatation	Normal
Paradisi (2002)	25	Flow-mediated dilatation	Impaired
Heitritter (2005)	23	Echo tracking of aorta	Reduction of stroke volume Increased Total peripheral resistance
Bo (2006)	82	Intimal medial thickness	Higher

Mod from Banerjee M, Nat Clin Pr Cardiovasc Med, 2006

Association of Gestational Hypertension & **Chronic Hypertension** at the **inter-conception examination with type2D risk** among women with a **history of GDM**

A population-based study: **1261 Women** who had a **history of GDM at 1–5 years after delivery in Tianjin, China**.

	Prior GDM+GH vs GDM	Prior GDM+Hypert at F-up vs Prior GDM +normotensive
D2diab OR	3.98 risk CI =1.94-8.02	
D2 diab OR		3.38 CI =1.66-6.87
Pre-diab OR		2.97 CI =1.75-5.05

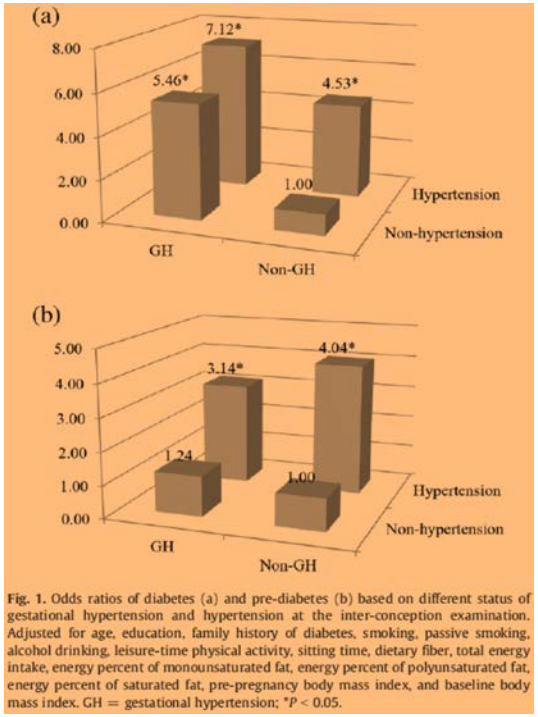


Fig. 1. Odds ratios of diabetes (a) and pre-diabetes (b) based on different status of gestational hypertension and hypertension at the inter-conception examination. Adjusted for age, education, family history of diabetes, smoking, passive smoking, alcohol drinking, leisure-time physical activity, sitting time, dietary fiber, total energy intake, energy percent of monounsaturated fat, energy percent of polyunsaturated fat, energy percent of saturated fat, pre-pregnancy body mass index, and baseline body mass index. GH = gestational hypertension; *$P < 0.05$.

Each 5 mmHg increase in diastolic blood pressure contributed to a **1.49-fold higher risk** (95% CI: 1.18–1.88) for **type 2D** and a **1.42-fold higher risk** (95% CI: 1.22–1.65) **for prediabetes**

History of GDM and **Long-term CVD Risk** in a Large Prospective Cohort of US Women. **The Nurses'Health Study II (NHSII)**

Observational cohort study of US female nurses with ongoing f-up

89479 women who reported at least1 pregnancy **free of CVD** & **cancer** at **baseline**, **1989**

Follow-up through May31, **2015**

complete for **> 90% of eligible participants**.

History of GDM

was self-reported at via biannual questionnaire updated

Behavioral Characteristics, Health Outcomes & Lifestyle Factors

History of GDM: 5292 women (5.9%)

Age 34.9(4.7) years

in at least1 pregnancy either at **baseline(58%**) or follow-up (**42%**).

JAMA Intern Med. 2017

History of GDM & Long-term CVD Risk

The Nurses'Health Study II (NHSII)

1161 Self-reported Non Fatal or Fatal Myocardial Infarction or Stroke

Adjusting for **Age**, **Prepregnancy BMI** & **Other Covariates**:

GDM vs no GDM was associated with subsequent CVD (HR: 1.43)

Additional adjustment for **Weight gain since pregnancy** and **updated Lifestyle Factors** (**HR,1.29**) attenuated association

Classifying GDM by progression to T2D in relation to CVD risk

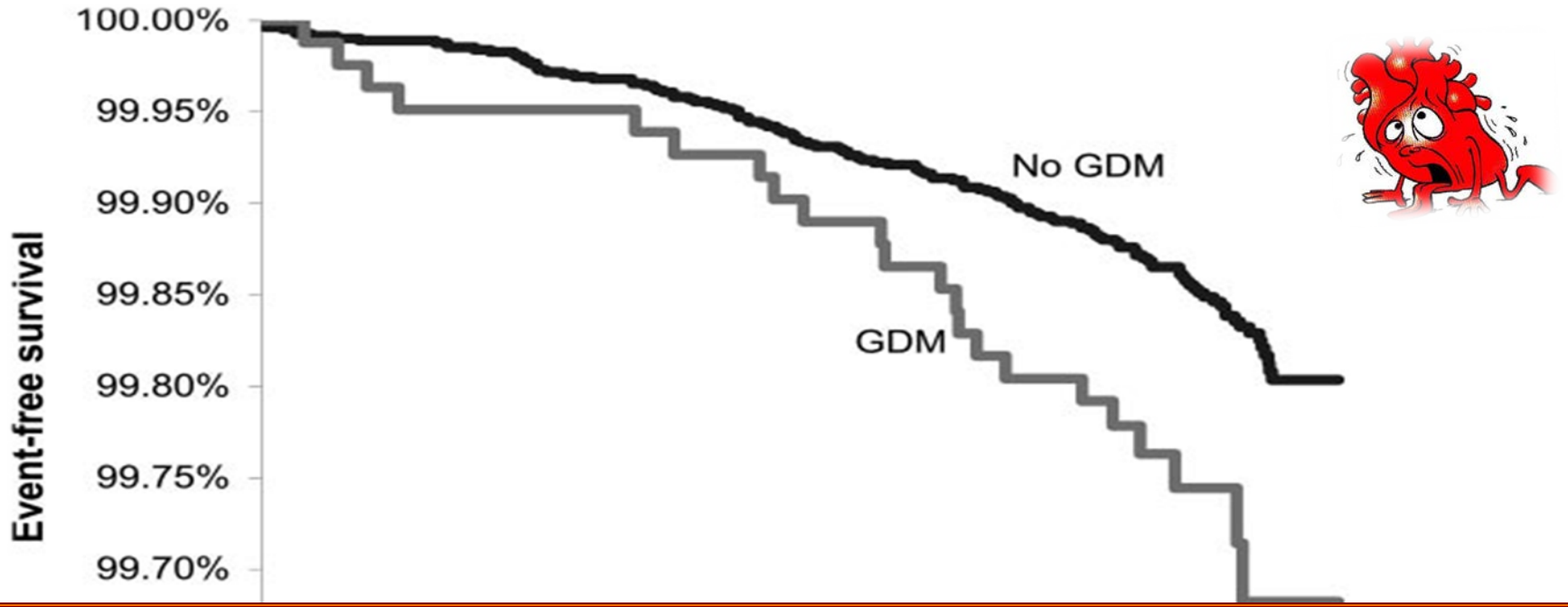
positive association for
GDM with progression toT2D vs no GD or T2D (**HR,4.02)**
attenuated relationship for
GDM only (**HR,1.30**)

JAMA Intern Med. 2017

GDM was positively associated with CVD later in life through a sustained unhealthy lifestyle after pregnancy

JAMA Intern Med. 2017

Kaplan-Meier survival curves for CVD & CAD events & hazard ratios derived from Cox proportional hazards regression.



Young women with GDM had increased risk for **CVD & CAD**
Much of this risk was attributable to subsequent development of type 2 diabetes.

Follow-up time (years)

No. at risk							
GDM	8,191	8,185	8,177	8,170	8,160	8,142	2,709
No GDM	81,262	81,201	81,142	81,056	80,951	80,827	26,986

Shah BR,
Increased risk of cardiovascular disease in young women following GDM.
Diabetes Care 31: 1668-1669; 2008

Prepregnancy Overweight and Gestational Diabetes as Determinants of Subsequent Diabetes and Hypertension after 20-Year Follow-Up





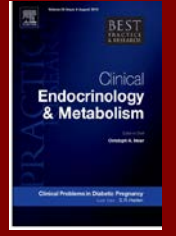
TABLE 2. Prevalence and estimates of risk for diabetes and hypertension 20 yr after delivery in the NFBC 1986 mothers

Determinants of risk	Diabetes			Hypertension		
	Prevalence (%)	HR (95% CI)	PAF (%)	Prevalence (%)	HR (95% CI)	PAF (%)
GDM						
Normal weight	7.1	10.61 (4.17, 27.00)[a]	5.2	10.0	1.52 (0.72, 3.21)	0.5
Overweight	25.9	47.24 (25.53, 87.40)[a]	15.8	44.4	9.16 (6.06, 13.85)[a]	4.4
OGTT normal						
Normal weight	1.3	1.87 (0.93, 3.76)	5.3	6.4	0.94 (0.70, 1.27)	−0.6
Overweight	8.4	12.63 (7.39, 21.57)[a]	22.2	18.0	2.86 (2.10, 3.90)[a]	6.0
Controls	0.7	1 (ref)		6.8	1 (ref)	





FIG. 2. Time-to-event curves of diabetes and hypertension 20 yr after delivery in the NFBC 1986.



Long-term Outlook of Hypertension in Pregnancy has shown an increased Risk of Hypertension and Cardiovascular Events, later in Life

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Hypertensive Disorders of Pregnancy and Offspring Cardiac Structure and Function in Adolescence

Simon Timpka, MD, PhD; Corrie Macdonald-Wallis, PhD; Alun D. Hughes, MBBS, PhD; Nishi Chaturvedi, MD; Paul W. Franks, PhD; Debbie A. Lawlor, PhD; Abigail Fraser, PhD

Fetal exposure to PE is associated with higher BP & later risk of Stroke

We investigate the associations of Maternal PE, GH, & Maternal BP change in pregnancy with Offspring Cardiac Structure and Function in Adolescence

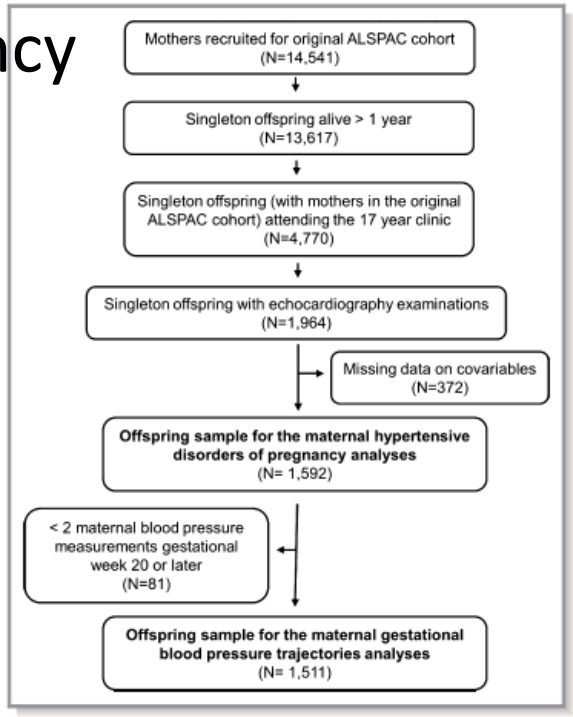


Figure 1. Study sample flow chart. ALSPAC indicates Avon Longitudinal Study of Parents and Children.

Adolescent offspring exposed to Maternal

PE & GH were associated with **Greater relative Wall Thickness**.

PE was also associated with a Smaller Left Ventricular End-diastolic Volume …..

early signs of **concentric remodeling** and affect future cardiac function as well as **risk of cardiovascular disease**

fspring Cardiac Structure *Timpka et al*

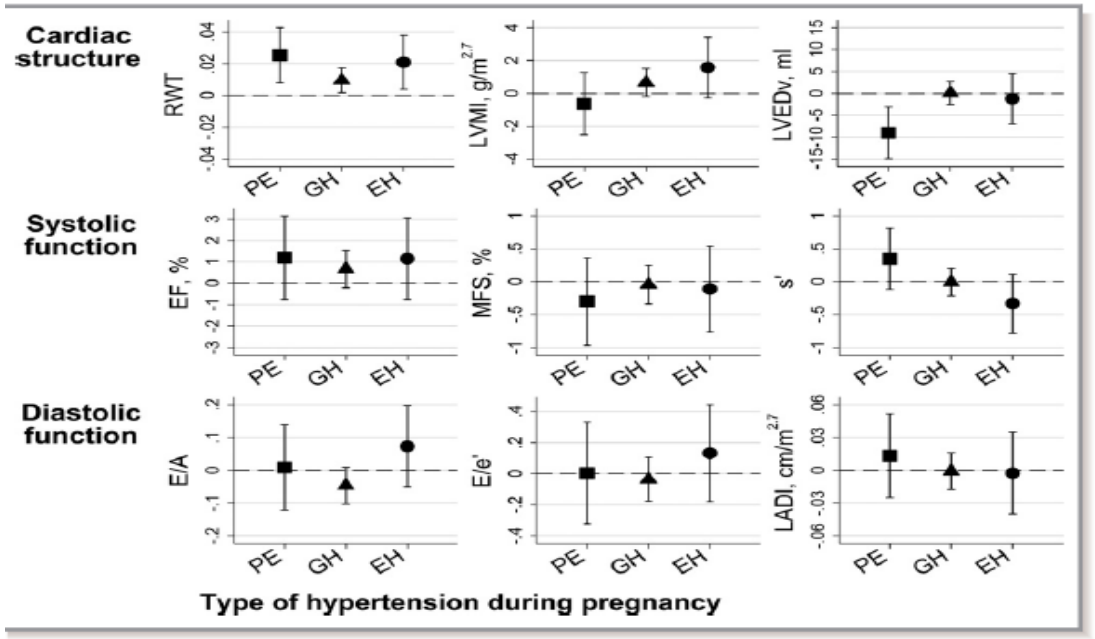


Figure 2. Mean difference (95% CI) in adolescent echocardiography measures between offspring exposed o preeclampsia, gestational hypertension, and essential hypertension in utero compared to offspring of normotensive women. Results obtained from the main model (model II). EF indicates ejection fraction; EH, essential hypertension; GH, gestational hypertension; LADI, left atrial diameter indexed to height in $m^{2.7}$; LVEDv, left ventricular end diastolic volume; LVMI, left ventricular mass indexed to height in $m^{2.7}$; MFS, left ventricular midwall fractional shortening; PE, preeclampsia; RWT, relative wall thickness.

Grazie

Angela Napoli

Chieti 19-20 aprile 2018

SAPIENZA
UNIVERSITÀ DI ROMA

Prospective studies on the association between GH & risk of T2D

Several studies in Australia, Denmark (Lykke et al., 2009), Canada (Feig et al., 2013), and Norway (Engeland et al.,2011) with long follow-up (3.7–21 yrs) showed that **GH has a 2–3.1 times high risk of T2D**.

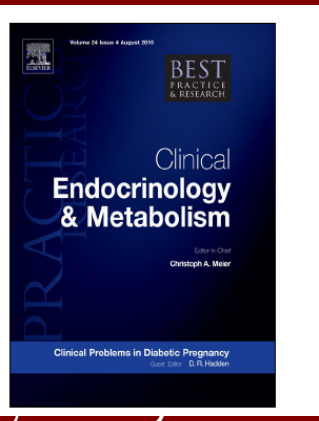
Other studies conducted in Japan (Kurabayashi et al., 2013) & New York City (Savitz et al., 2014) **No association between gestational hypertension & T2D risk**.
In the Japanese study the women were nurses, may be healthier than the general population, (selection bias)

The New York study **confirmed diabetes status only through hospital discharge diagnoses**, *missed many cases of diabetes treated outside hospital and all cases of asymptomatic diabetes*.

Long-term outlook: type 2 diabetes

There are no data about the long-term impact of hypertensive disorders in pregnancy in type 2diabetic women.

Long-term outlook: gestational diabetes



Hypertension after GDM is generally described as one of the compor
the metabolic
syndrome (Table 7).[72–81] Two of these studies exploring the risk factors
hypertension later in life,
validate the role of insulin resistance[74] and of the fasting blood glucose
pregnancy.[73] A recent prospective, population-based study82 show tha
years after delivery, the greatest fraction of
risk for hypertension is attributable to pre-pregnancy overweight, especially when combined with
GDM with a cumulative incidence of 44.4% (hazard ratio HR 9.16). A longitudinal study observed that
28% of 103 women with GH developed hypertension in pregnancy, and three years later, 16 women
(15.5% of the same population) were found to be hypertensive: 11 of them had been hypertensive (four
chronic and seven gestational) in pregnancy, and five just at the follow-up. The hypertension correlated
with BMI either in pregnancy or at the follow-up.83

Hypertension & Materno-fetal Outcome in Diabetic & Normal Pregnant Women

No correlation with

Parity, D. Duration, Metabolic Control (HbA1c, capillary BG, episodes of ketonuria)

Creatinine, Microalbuminuria or Insulin Need

Hypertension neither influenced **Week of Delivery** nor **Type of delivery:**

Week Normo vs Hypertensive: **37.9 ± 2.2 vs 37.9 ± 1.7 wk, ns**

Spontaneous Delivery: Normo vs Hypertensive: **35.6 vs 19.4 %, ns**

as well as APGAR score at 1 st and 5 th min & other Neonatal Complications

Table 2 Women' characteristics in normo and hypertensive type 2 diabetic pregnancies.

Types of hyper-tension	Age (y)	Age of diagnosis (y)	DM Dura-tion (y)	Prepregn. BMI (kg/m^2)	HbA1c at conception (%)	Caesarean Section (%)	Week of delivery	Neonatal weight (g)	APGAR 1'
1) N	31.6 ± 4.8	25.2 ± 6.0	6.0 ± 4.5	26.6 ± 6.9	6.0 ± 1.5	64.4	37.9 ± 1.2	2985.5 ± 656.8	8.0 ± 1.8
2) CH	35.2 ± 2.8	28.0 ± 4.6	7.4 ± 4.8	33.6 ± 8.6	7.2 ± 2.8	85.7	37.6 ± 2.2	3178.7 ± 270.9	8.7 ± 0.6
3) PIH	32.2 ± 3.6	28.4 ± 4.7	3.4 ± 3.1	35.4 ± 5.1	6.0 ± 1.0	69.2	38.6 ± 1.2	3766.9 ± 551.3	7.9 ± 0.6
4) PE	40.5 ± 3.5	39.5 ± 3.5	1.0 ± 0.5	29.3 ± 4.8	7.0 ± 2.4	100	36.5 ± 2.2	3085.0 ± 364.7	6.0 ± 1.4
p	u-T test	u-T test	u-T test	u-T test	u-T test	χ^2	u-T test	u-T test	u-T test
1 vs 2	**0.02**	0.2	0.4	**0.02**	0.1	0.1	0.7	0.6	0.2
1 vs 3	0.7	0.2	0.1	**0.003**	0.9	0.7	0.4	**0.006**	0.8
1 vs 4	**0.01**	**0.002**	0.1	0.6	0.4	0.1	0.4	0.8	0.06
2 vs 3	**0.04**	0.9	0.06	0.6	0.4	0.3	0.3	0.7	0.09
2 vs 4	**0.03**	**0.008**	0.1	0.6	0.9	0.4	0.6	0.9	**0.02**
3 vs 4	**0.01**	**0.01**	0.3	**0.04**	0.5	0.2	0.08	0.03	**0.05**

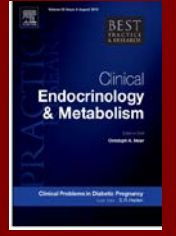
(N: normotensive; CH: chronic hypertension; PIH: pregnancy-induced hypertension; PE: pre-eclampsia)

Normotensive diabetic women showed higher BP levels than normotensive controls from the 1st trimester

systolic blood pressure 123.8 ± 18.9 vs 101.2 ± 14.9 mmHg, p = 0.03;

Diastolic blood pressure 77.0 ± 9.9 vs 63.7 ± 8.5 mmHg, p = 0.02)

despite a similar age and not significantly higher pregestational BMI.



Most of the studies explore hypertension just as one of diabetic pregnancy outcomes
Outcome of pregnancy in relation to hypertension per se is limited.
The majority is in relation to PE

Pre-Eclampsia

is associated with a marked increase in
Primary Caesarean Section, Preterm Birth, Admission to NICUs

Different Risk Factors and Pregnancy Outcomes would support the hypothesis that PE and GH might be largely separate entities.
However this position is not unanimously accepted

Chronic Hypertension

increases with **Age** and **Duration of Diabetes**
predicts higher rates of **Prematurity** and **Neonatal Morbidity** especially with **superimposed PE**

Association of Gestational Hypertension & **Chronic Hypertension** at the **inter-conception examination with type2D risk** among women with a **history of GDM**

A population-based study among **1261 Women** who had a **history of GDM at 1–5 years after delivery in Tianjin, China**.
Logistic regression or Cox regression was used to assess the associations of GH & CH at the Inter-conception Examination with Pre-diabetes & type 2D Risks

	Prior GDM+GH vs GDM	Prior GDM+Hypert at F-up vs Prior GDM +normotensive
D2diab OR	3.98 risk CI =1.94-8.02	
D2 diab OR		3.38 CI =1.66-6.87
Pre-diab OR		2.97 CI =1.75-5.05

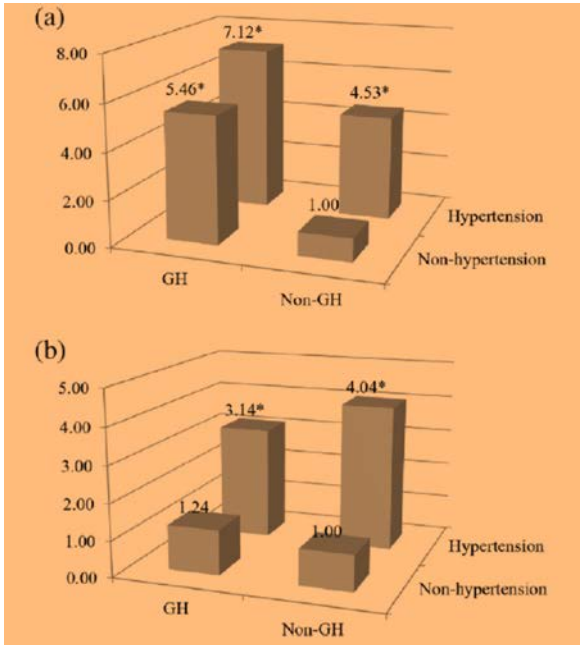


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CONCLUSIONS

Both GH at **the index pregnancy** & **CH at the inter-conception examination** were significantly & independently associated with **type 2 diabetes** among women with **prior GDM**.

CH at the inter-conception examination was independently associated with **pre-diabetes** among women with **prior GDM**