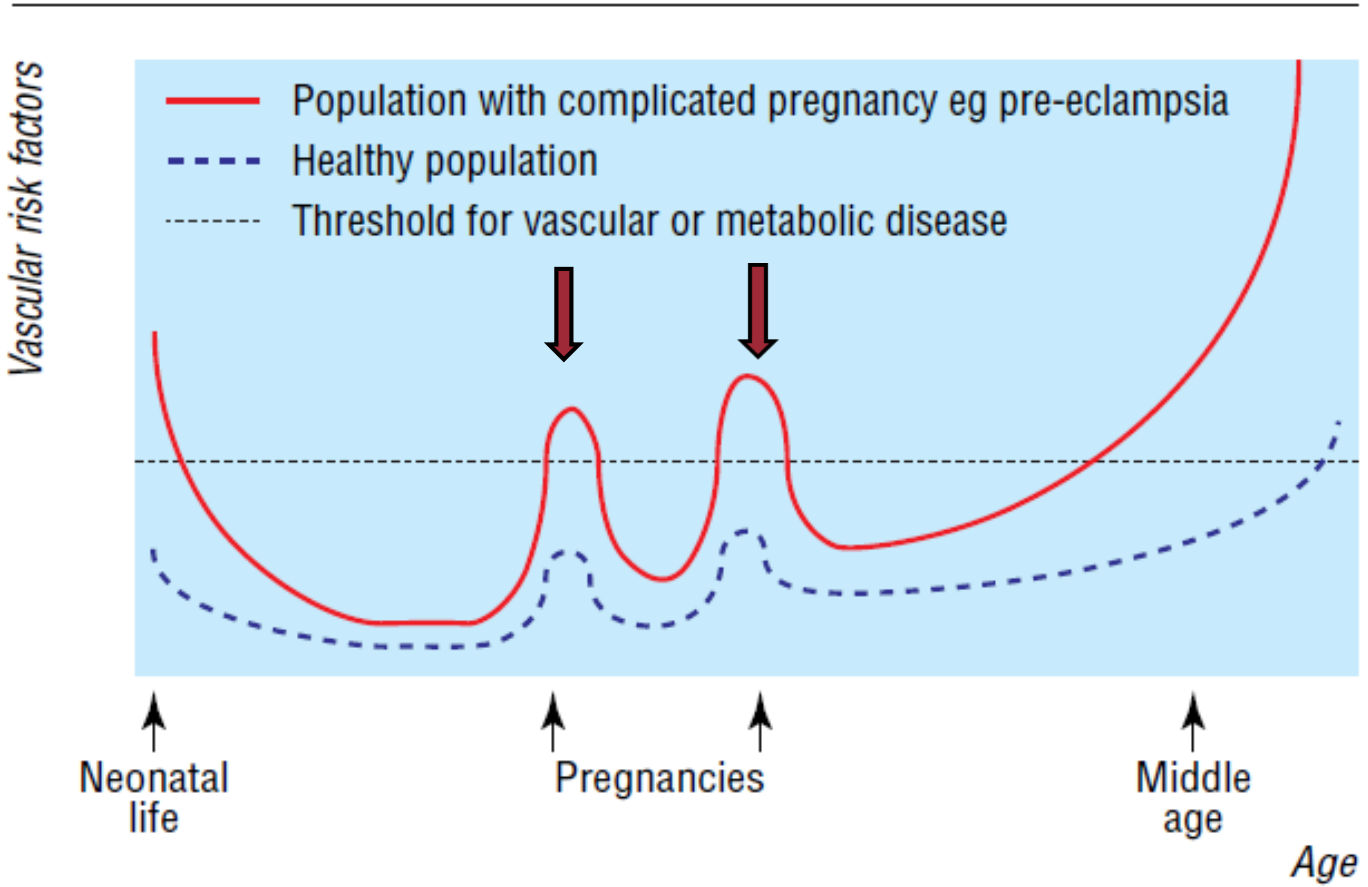
Preeclampsia, Gestational Diabetes, Preterm labor & Long-Term Maternal Atherosclerotic Morbidity

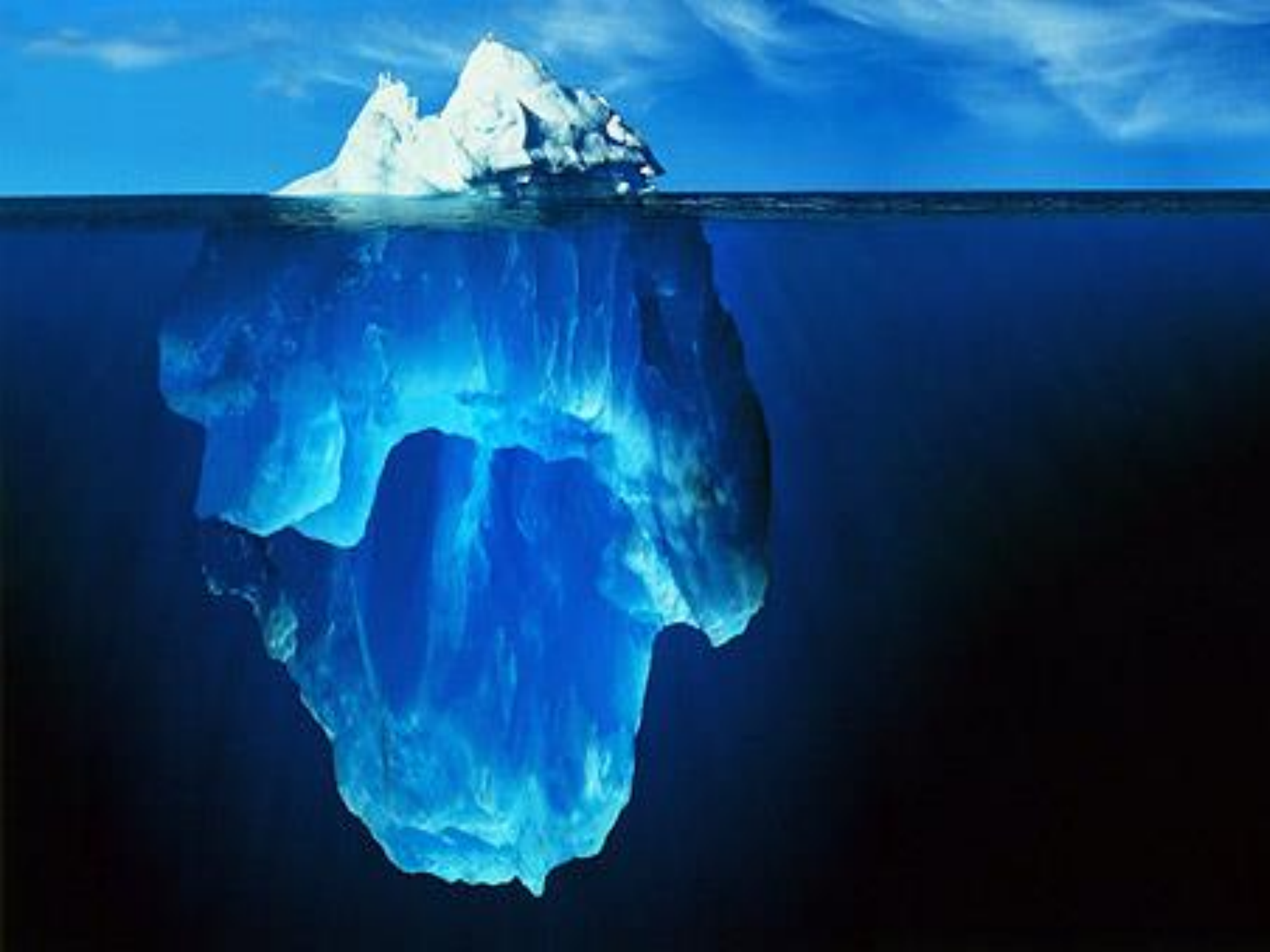
Eyal SHEINER MD PhD

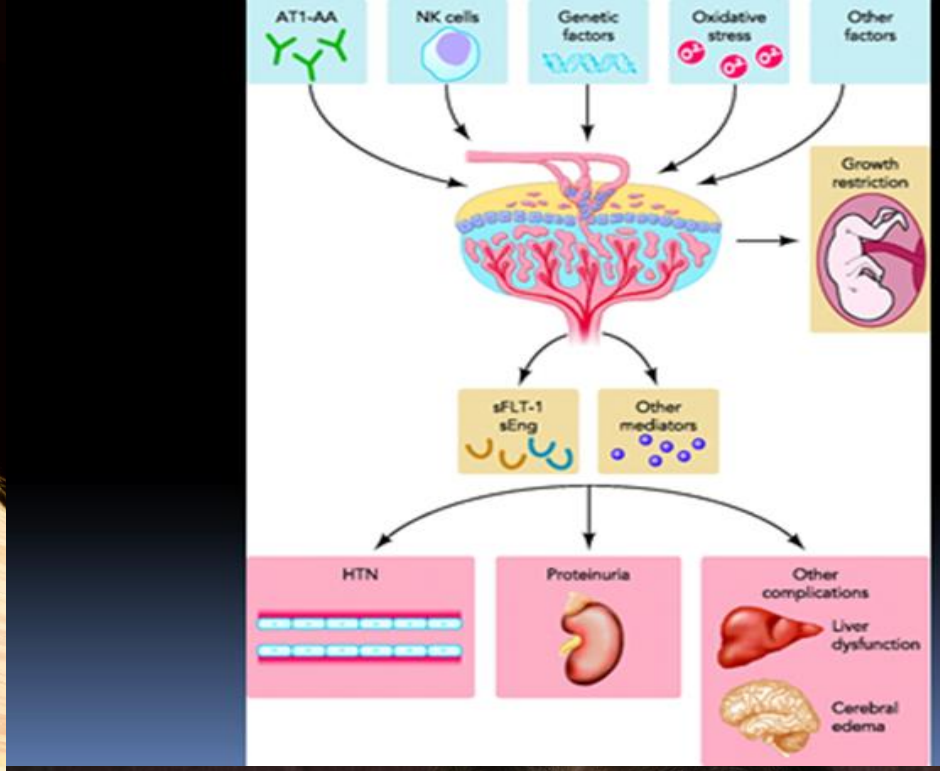
Professor and Chairman, Department of Obstetrics and Gynecology B, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

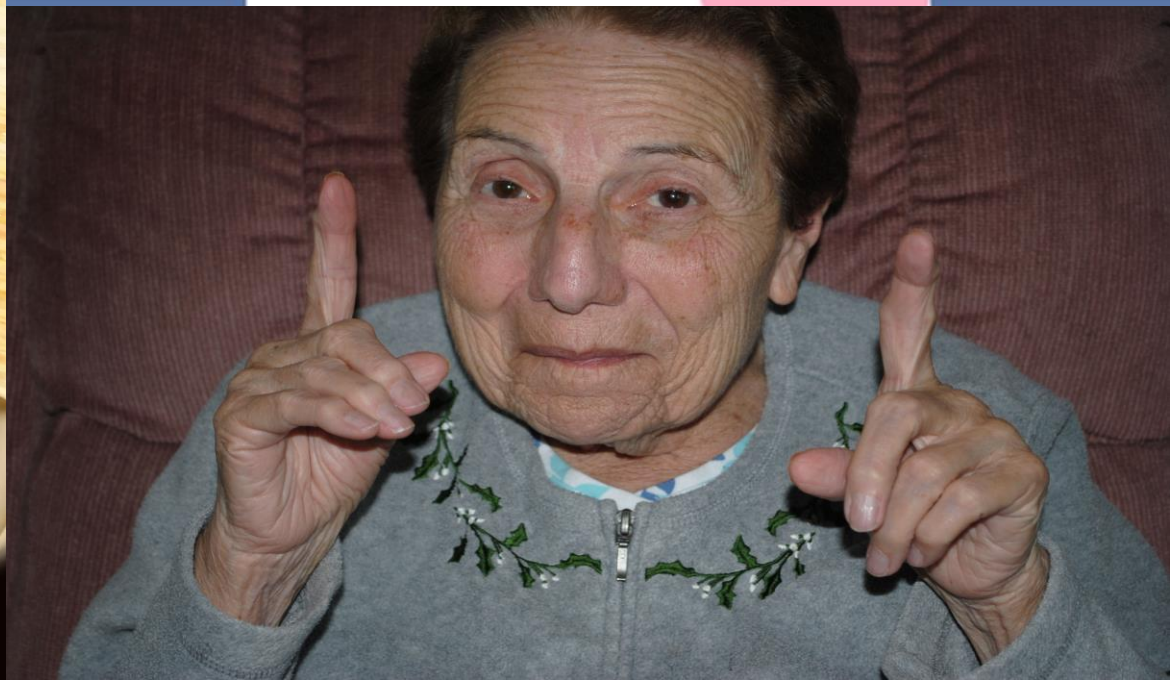
Pregnancy as a "stress test"



- *Sattar N et-al. BMJ 2002*




AT1-AA
NK cells
Genetic factors
Oxidative stress
Other factors
Growth restriction
sFLT-1
sEng
Other mediators
HTN
Proteinuria
Other complications
Liver dysfunction
Cerebral edema



Contents

- Preeclampsia
- GDM
- Other Pregnancy Complications
- Summary & Implications

CAN WE STUDY THIS?


DON"T BE A
STATISTIC!
thecandiesfoundation.org


Jan
10

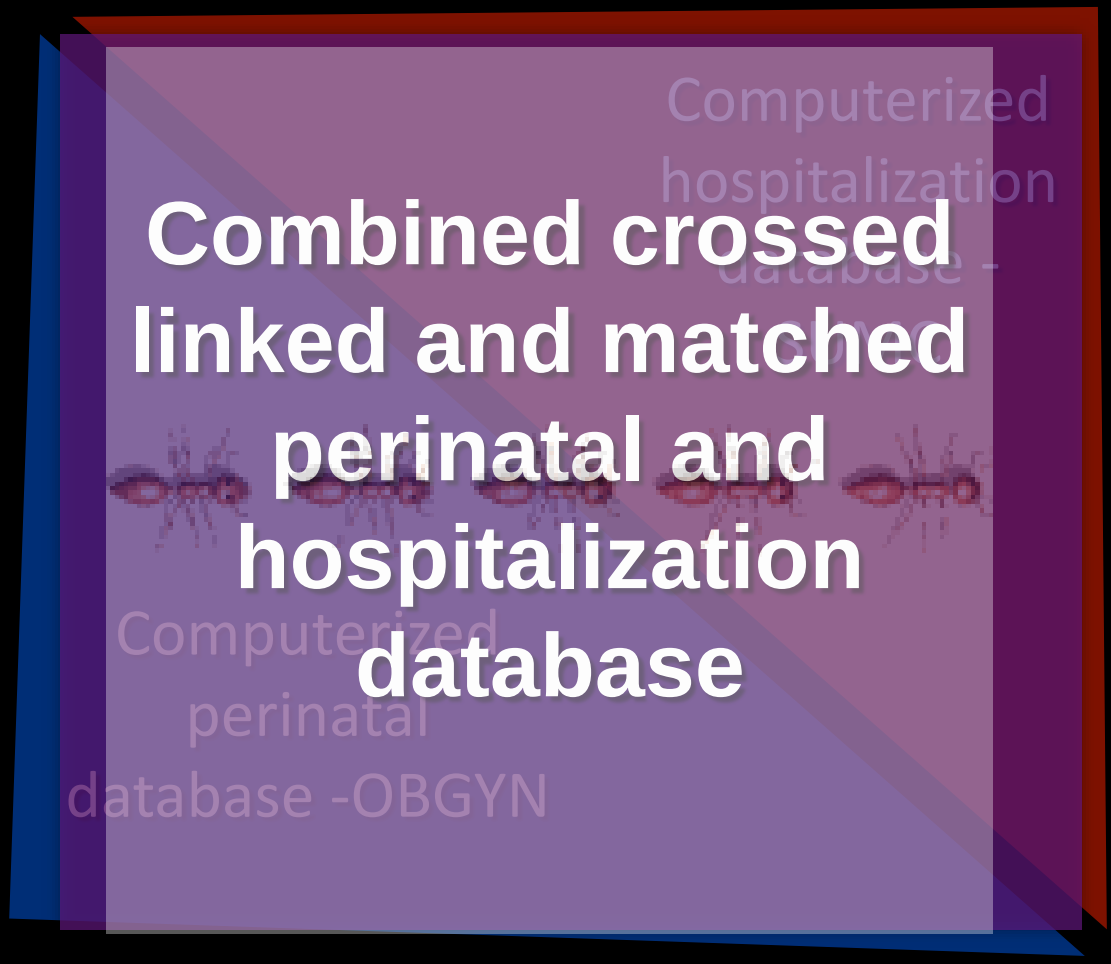
250,000

lucky us


aifa
Aviv
Jerusalem
NEGEV
המרכז הרפואי האוניברסיטאי סורוקה


SABAN BIRTH & MATERNITY CENTER
מרכז סבן למיילדות
EXPOSURE
Pregnancy and delivery data
OUTCOME
Hospitalizations at SUMC later in life

Databases



Combined crossed linked and matched perinatal and hospitalization database

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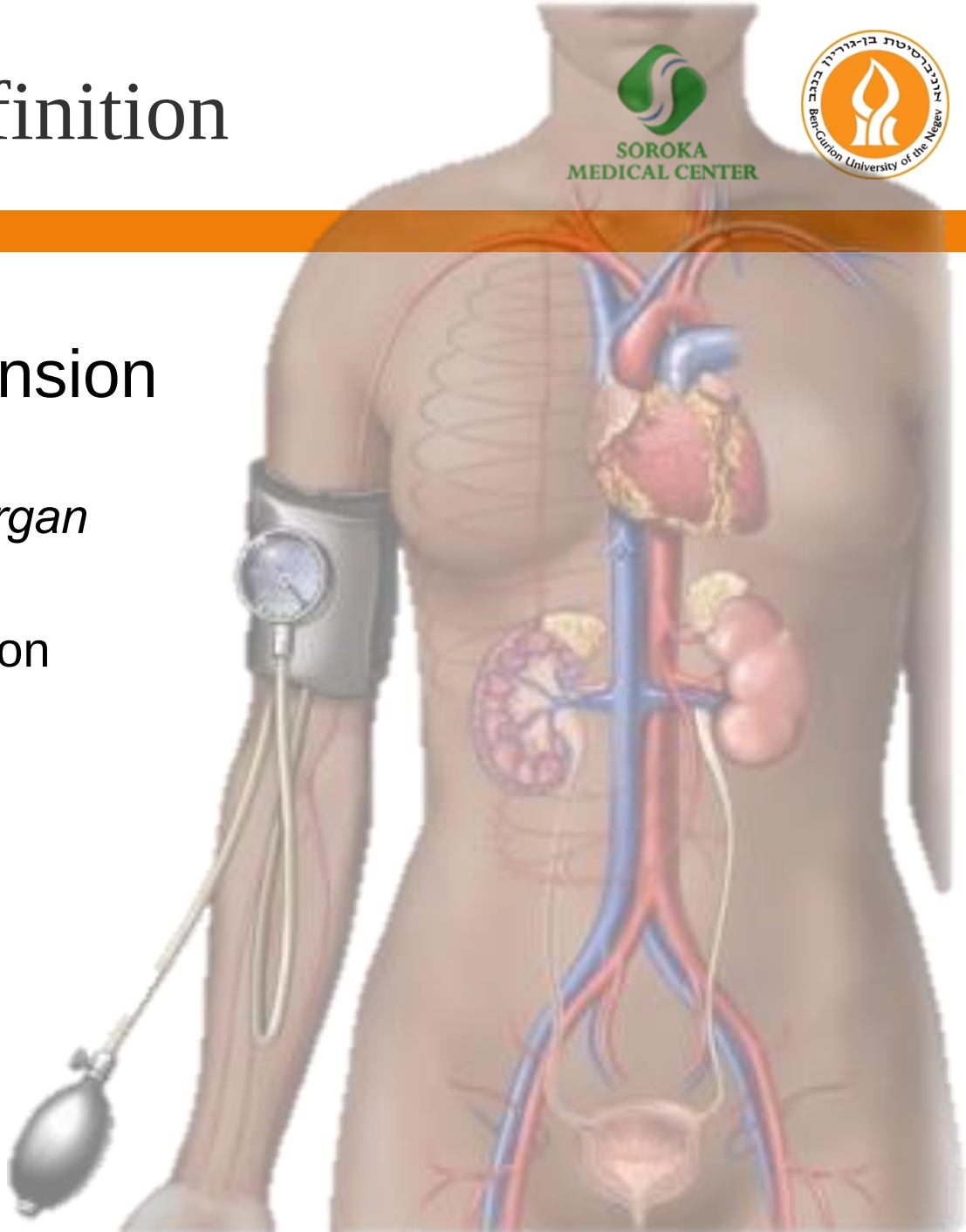
Preeclampsia, definition

New onset of hypertension
and

either proteinuria *or end-organ dysfunction*

after 20 weeks of gestation



These clinical manifestations result from microangiopathy of target organs, including:

brain,

liver,

kidney,

placenta

Potential maternal sequelae:
Pulmonary edema
Cerebral hemorrhage
Hepatic failure
Renal failure
Death

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It's the placenta

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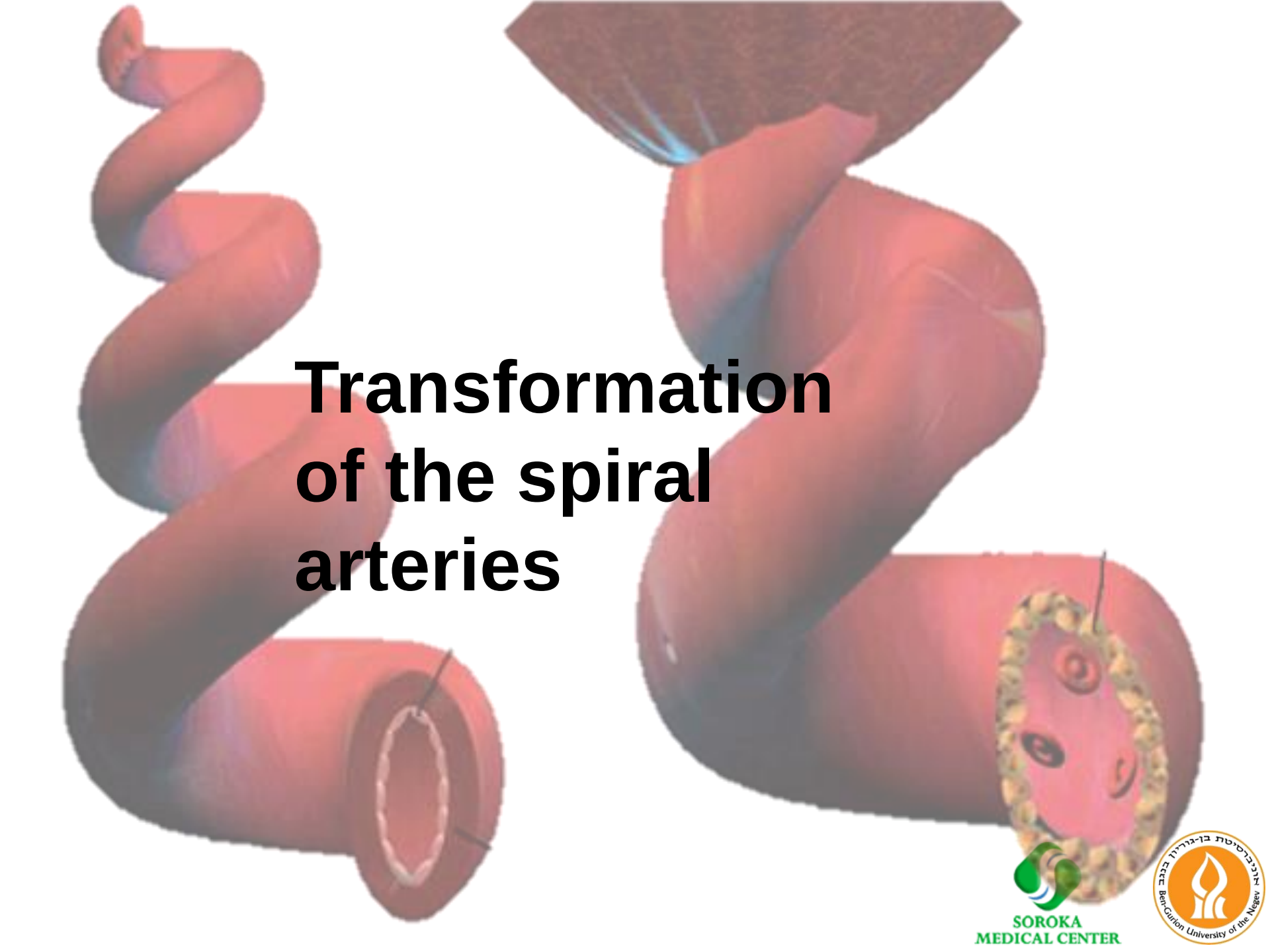
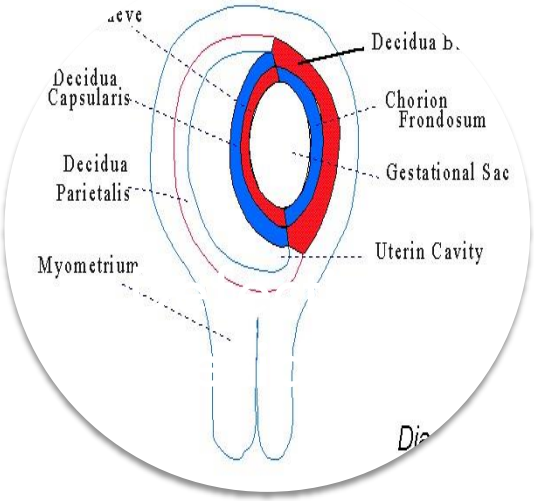

Transformation
of the spiral
arteries



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To cite: Kessous R, Shoham-Vardi I, Pariente G, *et al*. *Heart* 2015;**101**: 442–446.

ORIGINAL ARTICLE

Long-term maternal atherosclerotic morbidity in women with pre-eclampsia

Roy Kessous,[1] Ilana Shoham-Vardi,[2] Gali Pariente,[1] Ruslan Sergienko,[2] Eyal Sheiner[1]

Methods

Population-based retrospective cohort at the Soroka University Medical Center

BIRTHS
1988-2012

EXPOSURES

(1988-2012)

Preeclampsia

OUTCOMES

(1988-2012)

Hospitalization for cardiovascular and renal morbidity

Exclusion criteria

- **Multiple pregnancies**
- **Known cardiovascular disease**
- **Known renal disease**

Methods

- Perinatal and hospitalization databases
- Kaplan-Meier curves
- Cox proportional hazards models

Results

96370 women

Preeclampsia	No PET
7824 (8.1%)	88546 (91.9%)

CV Morbidity

4.6%	2.7%

Renal Morbidity

0.2%	0.1%

British Cardiovascular Society

To cite: Kessous R, Shoham-Vardi I, Pariente G, *et al*. *Heart* 2015;**101**: 442–446.

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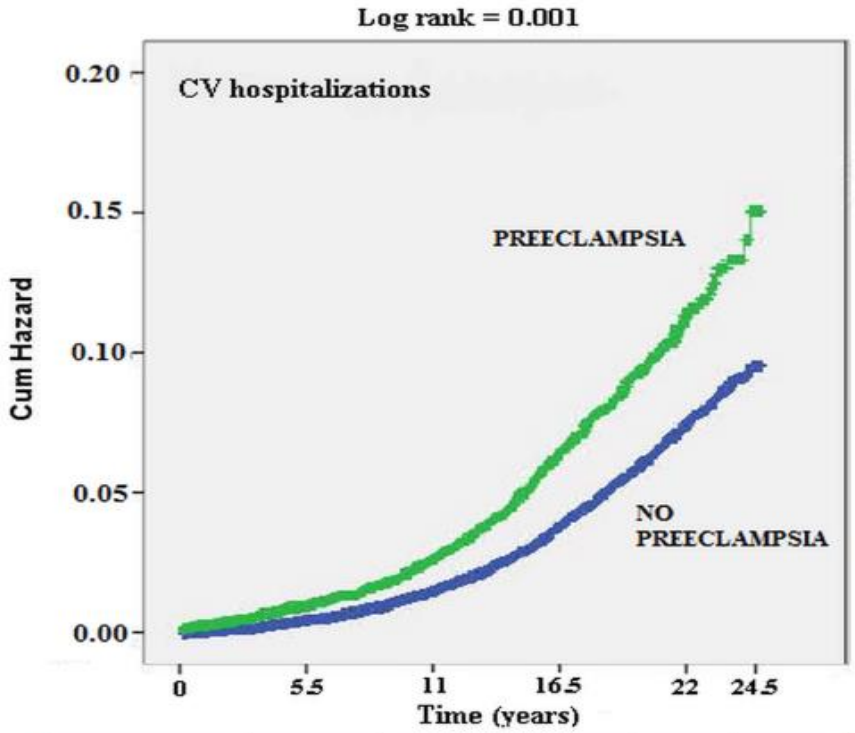
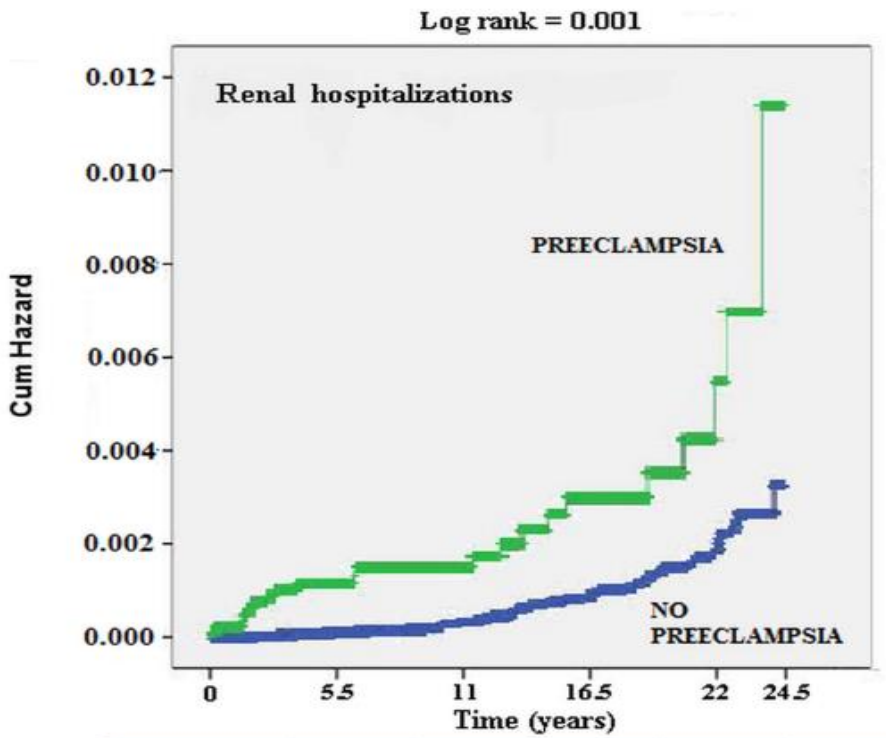


Time (years)	5.5	11	16.5	22	24.5
PET (n)	6085	4224	2335	825	113
No PET (n)	60820	42675	26368	9985	1637



Time (years)	5.5	11	16.5	22	24.5
PET (n)	6141	4329	2484	901	123
No PET (n)	61284	43479	27331	10756	1804

Long-term maternal atherosclerotic morbidity in women with pre-eclampsia

Roy Kessous,[1] Ilana Shoham-Vardi,[2] Gali Pariente,[1] Ruslan Sergienko,[2] Eyal Sheiner[1]

Table 4 Incidence of cardiovascular-related and renal-related hospitalisations and morbidity by pre-eclampsia severity

	No pre-eclampsia (n=88 546) (%)	Mild pre-eclampsia (n=6018) (%)	Severe pre-eclampsia (n=1719) (%)	Eclampsia (n=87) (%)	p Value*
Cardiac non-invasive diagnostic procedures	0.9	1.2	1.6	0.0	0.015
Cardiac invasive diagnostic procedures	0.3	0.6	0.5	0.0	0.008
Simple cardiovascular events	1.2	1.8	1.5	2.3	0.001
Complex cardiovascular events	1.3	2.8	3.4	4.6	0.001
Total cardiovascular hospitalisations	2.7	4.5	5.2	5.7	0.001
Renal-related hospitalisations	0.1	0.2	0.5	1.1	0.001

*Log-rank test.

Kessous R, *et al*. *Heart* 2015;**101**:442–446.

Long-term maternal atherosclerotic morbidity in women with pre-eclampsia

Roy Kessous,[1] Ilana Shoham-Vardi,[2] Gali Pariente,[1] Ruslan Sergienko,[2] Eyal Sheiner[1]

Table 5 Cox multivariable regression model for the risk of cardiovascular hospitalisation

	Adjusted HR	95% CI	p Value
Pre-eclampsia	1.7	1.6 to 1.9	0.001
Maternal age (years)	1.056	1.048 to 1.064	0.001
Parity at index pregnancy	1.123	1.107 to 1.139	0.001
Gestational diabetes mellitus	1.7	1.5 to 1.9	0.001
Obesity (pre-gestational BMI>30 kg/m^2)	1.9	1.5 to 2.5	0.001
Smoking	2.0	1.4 to 2.8	0.001

BMI, body mass index.

Kessous R, *et al*. *Heart* 2015;**101**:442–446.

Long-term maternal atherosclerotic morbidity in women with pre-eclampsia

Roy Kessous,[1] Ilana Shoham-Vardi,[2] Gali Pariente,[1] Ruslan Sergienko,[2] Eyal Sheiner[1]

Table 6 Cox multivariable regression model for the risk of renal-related hospitalisation*

	Adjusted HR	95% CI	p Value
Pre-eclampsia	3.7	2.3 to 6.0	0.001
Maternal age (years)	1.053	1.009 to 1.098	0.018
Parity at index pregnancy	1.154	1.069 to 1.247	0.001
Gestational diabetes mellitus	1.9	1.1 to 3.2	0.030

*The model also controlled for obesity and smoking

Kessous R, *et al*. *Heart* 2015;**101**:442–446.

Long-term maternal atherosclerotic morbidity in women with pre-eclampsia

Roy Kessous,[1] Ilana Shoham-Vardi,[2] Gali Pariente,[1] Ruslan Sergienko,[2] Eyal Sheiner[1]

What might this study add?

This study further establishes this link and in addition shows that there is a 'dose–response' association between the severity of pre-eclampsia (no pre-eclampsia 2.7% vs mild pre-eclampsia 4.5% vs severe pre-eclampsia 5.2% and eclampsia 5.7%, respectively; p=0.001) and the number of episodes of pre-eclampsia (no pre-eclampsia 2.7% vs one event of pre-eclampsia 4.4% vs ≥2 events 6.0%, respectively; p=0.001) to this future risk. Furthermore, this study helps to establish a new link between pre-eclampsia and future risk for renal morbidity.

Kessous R, *et al*. *Heart* 2015;**101**:442–446.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ORIGINAL ARTICLE

An association between gestational diabetes mellitus and long-term maternal cardiovascular morbidity

Roy Kessous,[1] Ilana Shoham-Vardi,[2] Gali Pariente,[1] Michael Sherf,[3] Eyal Sheiner[1]

Kessous R, *et al*. *Heart* 2013;**99**:1118–1121. doi:10.1136/heartjnl-2013-303945

ORIGINAL ARTICLE

An association between gestational diabetes mellitus and long-term maternal cardiovascular morbidity

Roy Kessous,[1] Ilana Shoham-Vardi,[2] Gali Pariente,[1] Michael Sherf,[3] Eyal Sheiner[1]

Table 2 Incidence of cardiovascular morbidity and hospitalisation during the follow-up period in patients with and without a history of gestational diabetes mellitus (GDM) after adjustment for maternal age and ethnicity

	GDM (n=4928) (%)	No GDM (n=42 981) (%)	Adjusted OR*	95% CI	p Value
Non-invasive cardiac diagnostic procedures	2.1	1.0	1.8	1.4 to 2.2	0.001
Invasive cardiac diagnostic procedures	0.8	0.4	1.4	0.99 to 2.1	0.051
Simple cardiovascular events	7.4	2.1	2.7	3.1 to 2.4	0.001
Complex cardiovascular events	0.2	0.1	1.7	3.3 to 0.9	0.111
Cardiovascular hospitalisations	8.9	3.1	2.3	2.5 to 2.0	0.001
Death during hospitalisation	0.1	0.1	1.7	4.4 to 0.6	0.284

An association between gestational diabetes mellitus and long-term maternal cardiovascular morbidity

Roy Kessous,[1] Ilana Shoham-Vardi,[2] Gali Pariente,[1] Michael Sherf,[3] Eyal Sheiner[1]

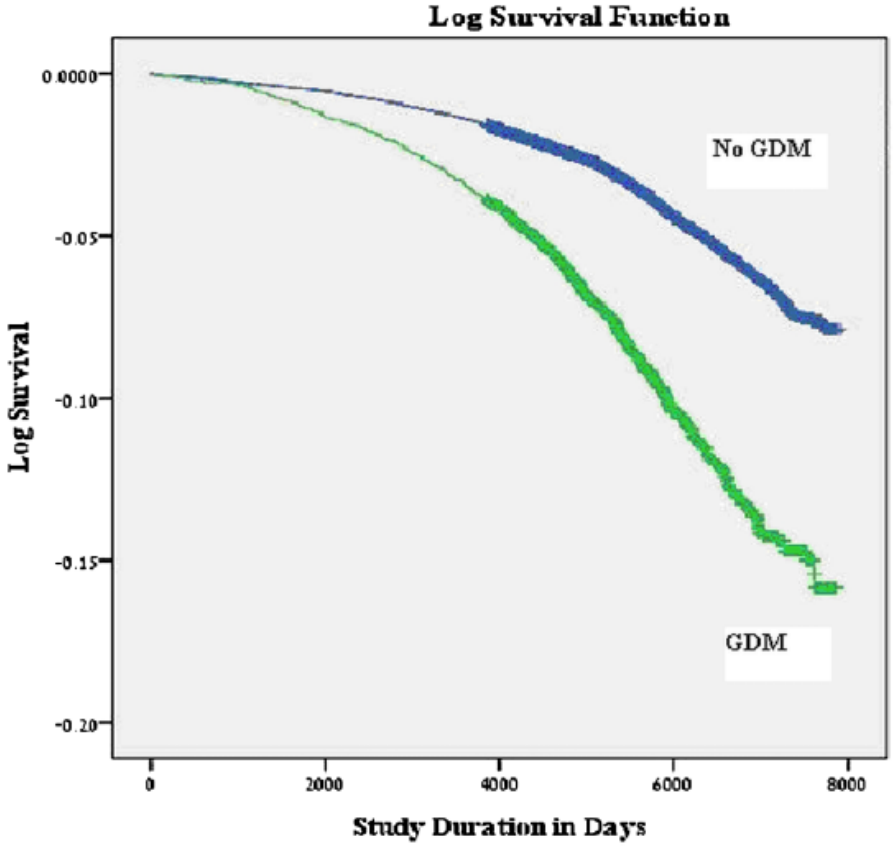

Figure 1 Kaplan–Meier survival analysis curve (presenting the log survival function) for cardiovascular-associated hospitalisation of patients with and without a history of gestational diabetes mellitus (GDM). p=0.001 (log rank test). This figure is only reproduced in colour in the online version.

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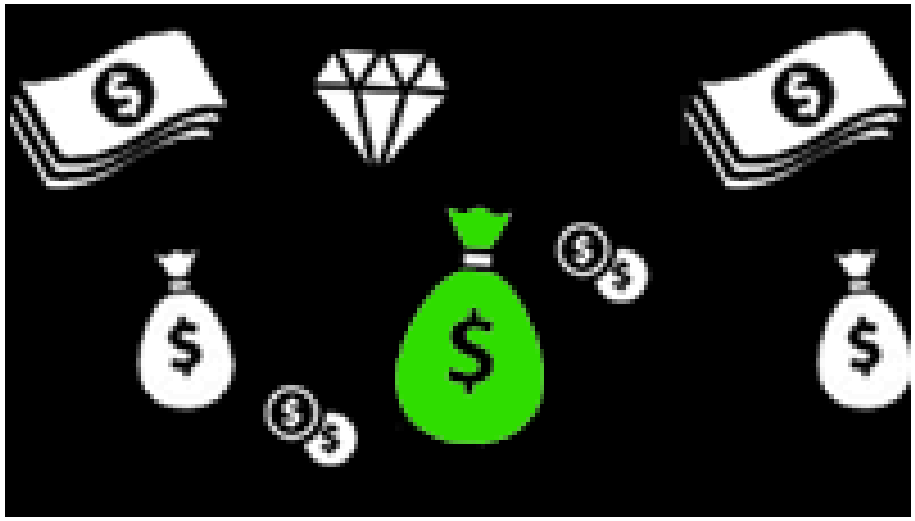
Preterm Birth

15 million births annually worldwide.

26 billion dollars in the US



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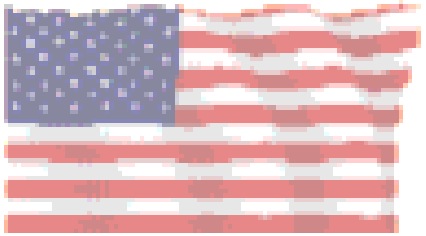
2. Villar J, Abalos E, Carroli G, Giordano D, Wojdyla D, Piaggio G, et al. Heterogeneity of perinatal outcomes in the preterm delivery syndrome. Obstet Gynecol 2004;104:78–87.

Born too soon…
Incidence

5% - 18%

11.4% in the United States

7.4% in Israel



1. Steer P. The epidemiology of preterm labour. BJOG 2005; 112(suppl 1):1–3.
2. Wen SW, Smith G, Yang Q, Walker M. Epidemiology of preterm birth and neonatal outcome. Semin Fetal Neonatal Med 2004;9:429–35.
3. Blondel B, Macfarlane A, Gissler M, Breart G, Zeitlin J, PERISTAT Study Group. Preterm birth and multiple pregnancy in European countries participating in the PERISTAT pr
4. Public Health Agency of Canada. Canadian perinatal health report, 2003. Available at: http://www.phac-aspc.gc.ca/publicat/ cphr-rspc03/index.html. Retrieved November 15
5. Laws PJ, Grayson N, Sullivan EA.Australia's mothers and babies 2004. Sydney: Australian Institute of Health and Welfare, National Perinatal Statistics Unit. 2006.
6. Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2005. Natl Vital Stat Rep 2006;55:1–18.

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Romero R, Mazor M, et al. Am J Obstet Gynecol. 1992 Jan;166(1 Pt 1):129-33.
.75-84:(9606)5;371 2008 . Lancet.Goldenberg RL, Romero R

An association between preterm delivery and long-term maternal cardiovascular morbidity

Roy Kessous, MD; Ilana Shoham-Vardi, PhD; Gali Pariente, MD; Gershon Holcberg, MD; Eyal Sheiner, MD, PhD

OBJECTIVE: The purpose of this study was to investigate whether a history of preterm delivery (PTD) poses a risk for subsequent maternal long-term cardiovascular morbidity.

STUDY DESIGN: A population-based study compared the incidence of cardiovascular morbidity in a cohort of women who delivered preterm (<37 weeks' gestation) and tho period. Deliveries occurred durir until 2010. Kaplan-Meier survi mulative incidence of cardiovascular hospitalizations. Cox proportional hazards models were used to estimate the adjusted hazard ratios for cardiovascular hospitalizations.

RESULTS: During the study period 47,908 women met the inclusion criteria; 12.5% of the patients (n = 5992) delivered preterm. During a follow-up period of >10 years, patients with PTD had higher rates of simple and complex cardiovascular events and higher rates of total cardiovascular-related hospitalizations. A linear association was found between the number of previous PTD and future risk for cardiovascular hospitalizations (5.5% for ≥2 PTDs; 5.0% for 1 PTD vs 3.5% in the comparison group; $P < .001$). The association remained significant for spontaneous vs induced PTD and for early (<34 weeks) 6 days' gestation) PTD. In a : adjusted for pregnancy con- tes mellitus, preeclampsia, and obesity, PTD was associated independently with cardiovascular hospitalizations (adjusted hazard ratio, 1.4; 95% confidence interval, 1.2–1.6).

CONCLUSION: PTD is an independent risk factor for long-term cardiovascular morbidity in a follow-up period of more than a decade.

Key words: cardiovascular morbidity, hospitalization, long term, pregnancy, preterm delivery

★ EDITORS' CHOICE ★

Cite this article as: Kessous R, Shoham-Vardi I, Pariente G, et al. An association between preterm delivery and long-term maternal cardiovascular morbidity. Am J Obstet Gynecol 2013;209:368.e1-8.

PTD

TABLE 4

OR of cardiovascular morbidity and hospitalization during the follow-up period in patients with spontaneous PTD and PTD after induction of labor

	Induction (n = 6239)			Spontaneous (n = 41,669)		
Variable	OR	95% CI	*P* value	OR	95% CI	*P* value
Cardiac noninvasive diagnostic procedures	1.3	0.5–2.1	.962	1.3	1.1–1.7	.044
Cardiac invasive diagnostic procedures	2.0	0.8–4.9	.110	0.9	0.6–1.6	.971
Simple cardiovascular events	1.9	1.4–2.7	.001	1.4	1.2–1.7	.001
Complex cardiovascular events	2.6	0.5–12.5	.215	3.8	2.2–6.6	.001
Total cardiovascular hospitalizations	1.7	1.3–2.4	.001	1.4	1.2–1.6	.001

CI, confidence interval; *OR*, odds ratio; *PTD*, preterm delivery.

Kessous. PTD and future risk for cardiovascular disease. Am J Obstet Gynecol 2013.

Am J Obstet Gynecol 2014;211:416.e1-12.

Is stillbirth associated with long-term atherosclerotic morbidity?

Gali Pariente, MD; Ilana Shoham-Vardi, PhD; Roy Kessous, MD; Ruslan Sergienko; Eyal Sheiner, MD, PhD

TABLE 2

Incidence of cardiovascular- and renal-related morbidity and hospitalizations[a]

Variable	Stillbirth (n = 1879), % (n)	No stillbirth (n = 97,401), % (n)	Odds ratio	95% confidence interval	*P* value
Cardiac noninvasive diagnostic procedures	1.1 (21)	1.0 (974)	1.06	0.6–1.6	.78
Cardiac invasive diagnostic procedures	0.6 (11)	0.4 (390)	1.4	0.8–2.7	.18
Simple cardiovascular events	2.2 (41)	1.3 (1266)	1.7	1.2–2.2	.001
Complex cardiovascular events	3.0 (56)	1.7 (1656)	1.8	1.3–2.3	< .001
Total cardiovascular hospitalizations	4.9 (92)	3.2 (3117)	1.5	1.2–1.8	< .001
Renal morbidity	0.4 (8)	0.1 (97)	3.1	1.4–6.6	.001

[a] During the follow-up period in patients with and without a history of at least 1 stillbirth

Pariente. Stillbirth and long-term atherosclerotic morbidity. Am J Obstet Gynecol 2014.

Paediatric and Perinatal Epidemiology
Affiliated to the Society for Pediatric and Perinatal Epidemiologic Research

32

doi: 10.1111/ppe.12089

Placental Abruption as a Significant Risk Factor for Long-term Cardiovascular Mortality in a Follow-up Period of More Than a Decade

Gali Pariente,[a] Ilana Shoham-Vardi,[b] Roy Kessous,[a] Michael Sherf,[c] Eyal Sheiner[a]

[a]*Department of Obstetrics and Gynecology, Soroka University Medical Center, Faculty of Health Sciences*

[b]*Department of Epidemiology and Health Services Evaluation*

[c]*Soroka University Medical Center, Clalit Health Services (Southern District), Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel*

Paediatric and Perinatal Epidemiology, 2014, **28**, 32–38

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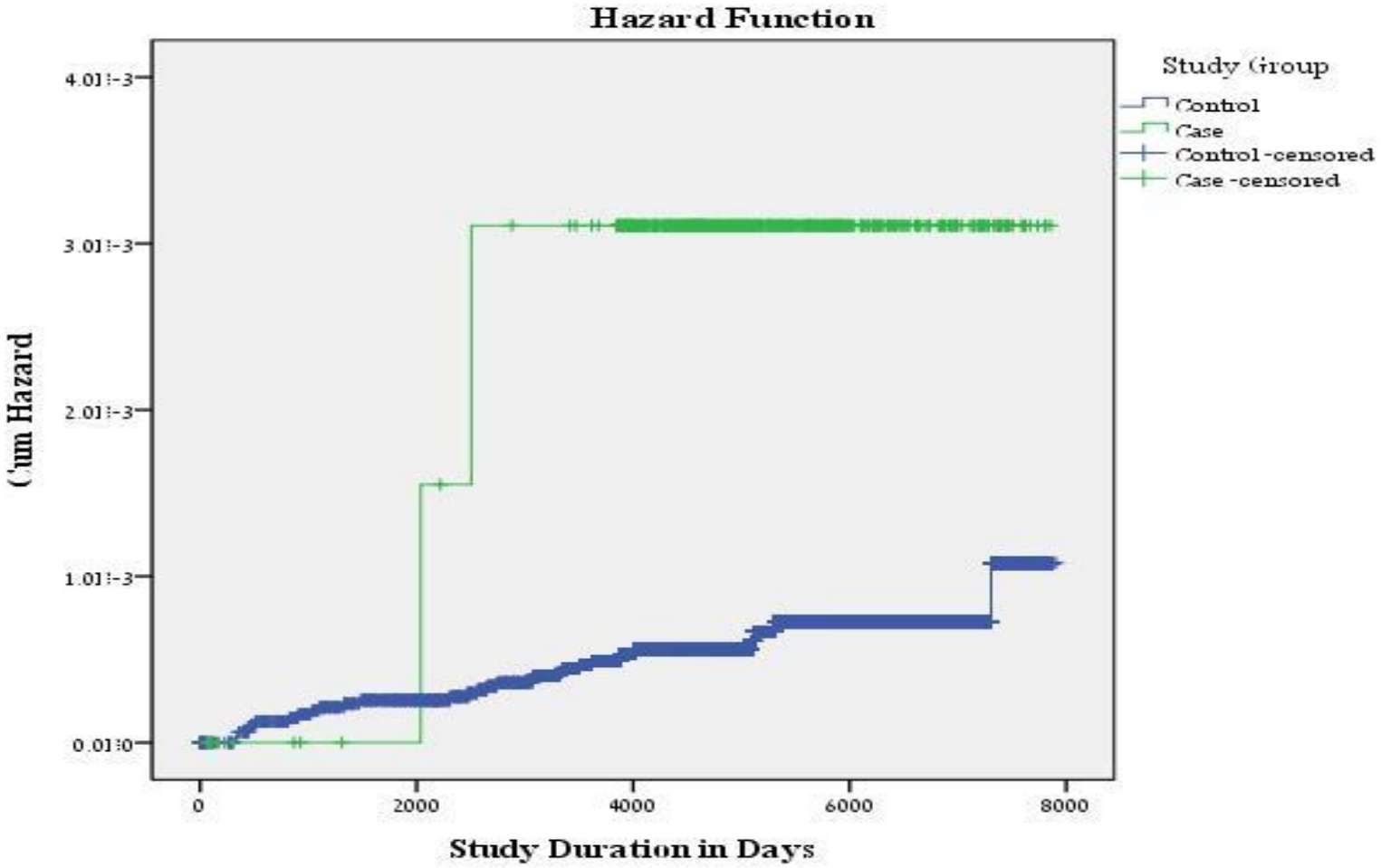
Placental abruption



Recurrent pregnancy loss: a risk factor for long-term maternal atherosclerotic morbidity?

Roy Kessous, MD; Ilana Shoham-Vardi, PhD; Gali Pariente, MD; Ruslan Sergienko; Gershon Holcberg, MD; Eyal Sheiner, MD, PhD

Recurrent pregnancy loss is an independent risk factor for long-term CV morbidity

American Journal of Obstetrics & Gynecology OCTOBER 2014

International Journal of Gynecology and Obstetrics 123 (2013) 68–71

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International Journal of Gynecology and Obstetrics

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

CLINICAL ARTICLE

Association between delivery of a small-for-gestational-age neonate and long-term maternal cardiovascular morbidity ☆

Gali Pariente [a], Eyal Sheiner [a,*], Roy Kessous [a], Sherf Michael [b], Ilana Shoham-Vardi [c]

[a] Department of Obstetrics and Gynecology, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel
[b] Soroka University Medical Center, Clalit Health Services (Southern District), Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel
[c] Department of Epidemiology and Health Services Evaluation, Ben-Gurion University of the Negev, Beer-Sheva, Israel

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AHA guidelines

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

AHA Guideline

Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update

A Guideline From the American Heart Association

EXECUTIVE WRITING COMMITTEE

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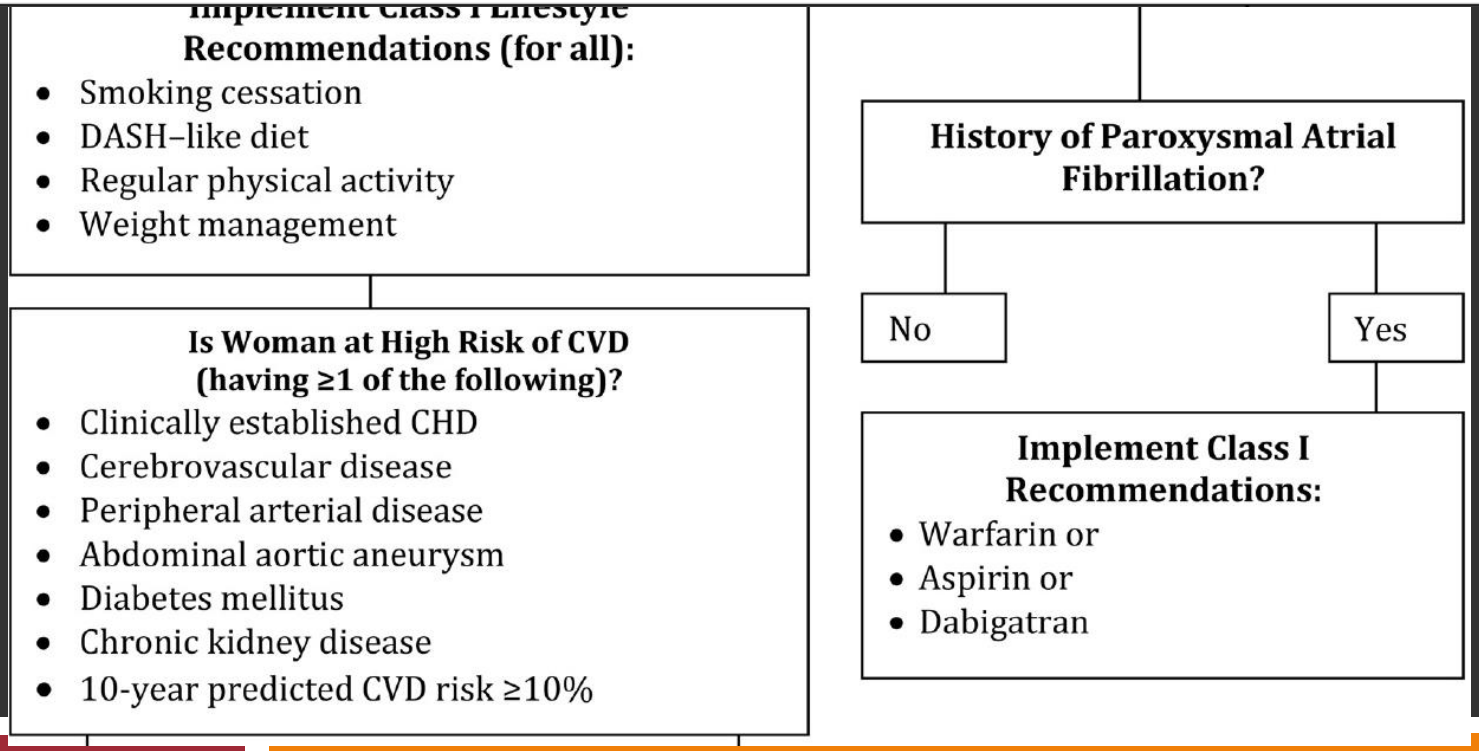
Circulation March 22, 2011

Evaluation of CVD Risk:

- Medical history/family history/pregnancy complication history
- Symptoms of CVD
- Depression screening in women with CVD
- Physical examination including blood pressure, body mass index, waist size
- Laboratory tests including fasting lipoproteins and glucose
- Framingham risk assessment if no CVD or diabetes



❑ *Mosca L et al. Circulation 2011*

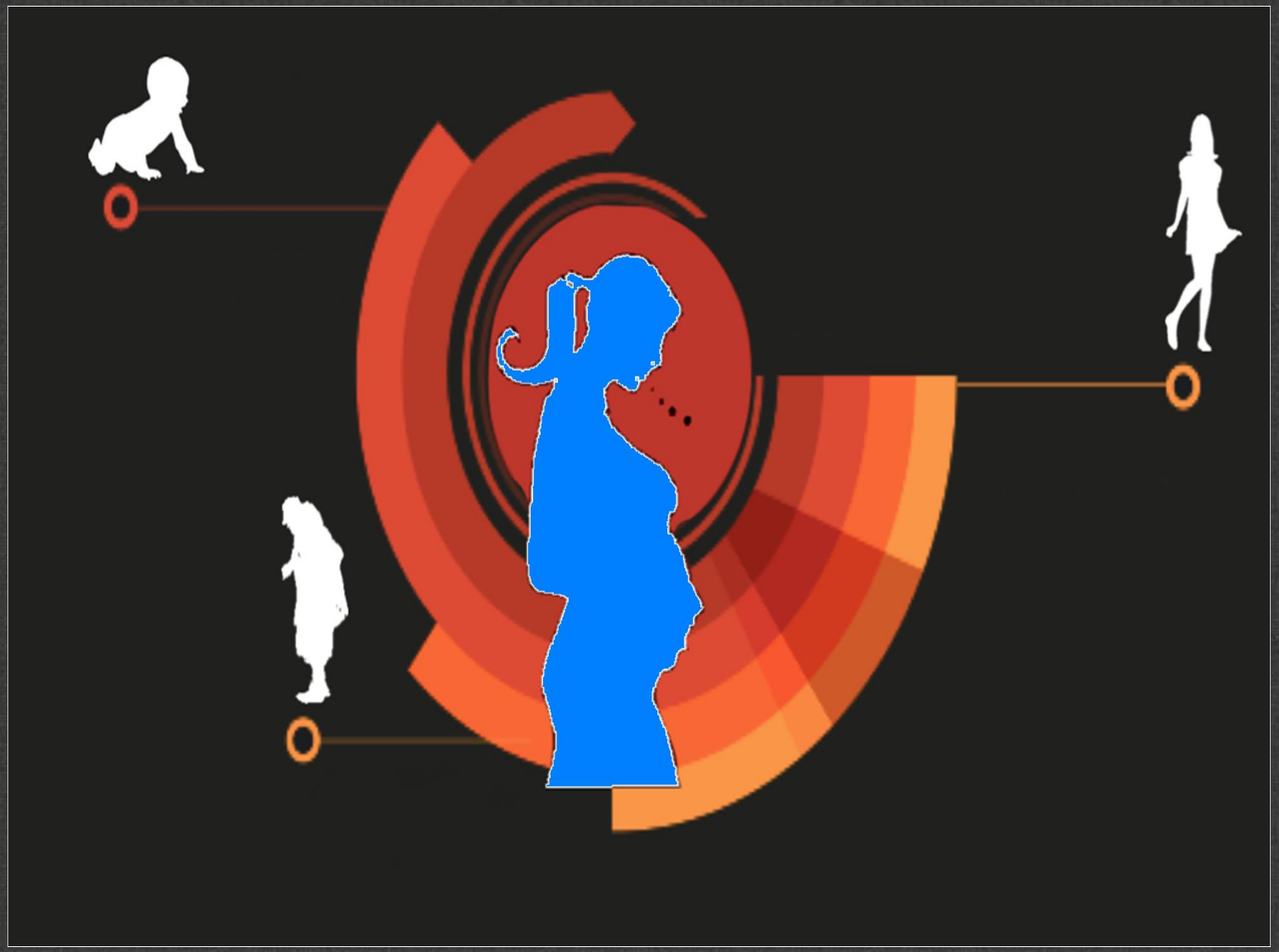
Table 2. Classification of CVD Risk in Women

Risk Status	Criteria
High risk (≥1 high-risk states)	Clinically manifest CHD
	Clinically manifest cerebrovascular disease
	Clinically manifest peripheral arterial disease
	Abdominal aortic aneurysm
	End-stage or chronic kidney disease
	Diabetes mellitus
	10-y Predicted CVD risk ≥10%
At risk (≥1 major risk factor[s])	Cigarette smoking
	SBP ≥120 mm Hg, DBP ≥80 mm Hg, or treated hypertension
	thickened IMT)
	Poor exercise capacity on treadmill test and/or abnormal heart rate recovery after stopping exercise
	Systemic autoimmune collagen-vascular disease

Other pregnancy complications?

History of preeclampsia, gestational diabetes, or pregnancy-induced hypertension

- *Mosca L et al. Circulation 2011*



The Long Term Impact of Medical Complications in Pregnancy

A Window into Maternal and Fetal Future Health

Pregnancy serves as a physiological stress test. Consequently, it can be considered as a window of opportunity for early detection of predispositions for future maternal and neonatal morbidities. Such data may warrant consideration of specific screening programs for patients with a history of adverse pregnancy outcome as well as for their offspring. Accumulating evidence now shows that vascular complications of pregnancy are related to increased risk for future cardiovascular morbidity. Moreover, a link exists between pregnancy complications such as preeclampsia, gestational diabetes mellitus, preterm delivery, placental abruption, and recurrent pregnancy loss to multiple long-term maternal and neonatal morbidities.

This sensible book draws on evidence-based data, provides updated evidence focusing on the impact of pregnancy complications on long-term morbidity of both mother and child and aims to give a clear and comprehensive set of tools for general practitioners counseling women in different stages of their lives. Chapters are contributed by a multidisciplinary team of obstetricians, oncologists, pediatricians, internal medicine specialists, and psychiatrists. The book may serve as a valuable resource for a broad spectrum of clinicians and healthcare professionals. Medical and nursing students as well as residents in family medicine, obstetrics, and pediatrics may derive great benefit from it in various stages of their training.

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SERIES IN MATERNAL-FETAL MEDICINE

The Long Term Impact of Medical Complications in Pregnancy

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Eyal Sheiner

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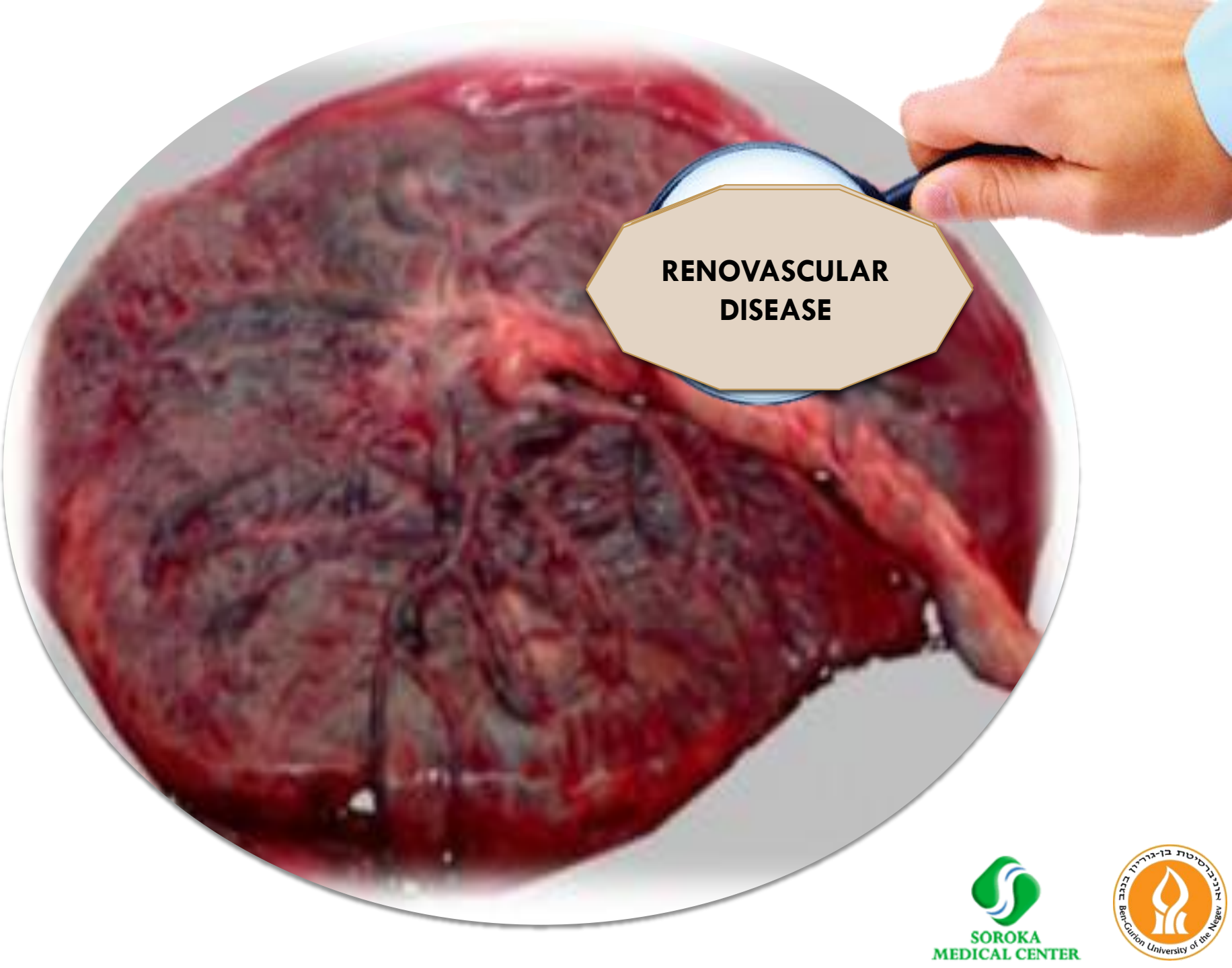

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IMPLICATION

Cardiovascular risk estimation is sub optimal

Obstetric history is easy to collect and could be of potential use for atherosclerotic risk stratification

Cardiovascular and metabolic stress associated with pregnancy provide a unique opportunity to estimate a woman's lifetime risk

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