Top 5 Papers in Obstetric Medicine

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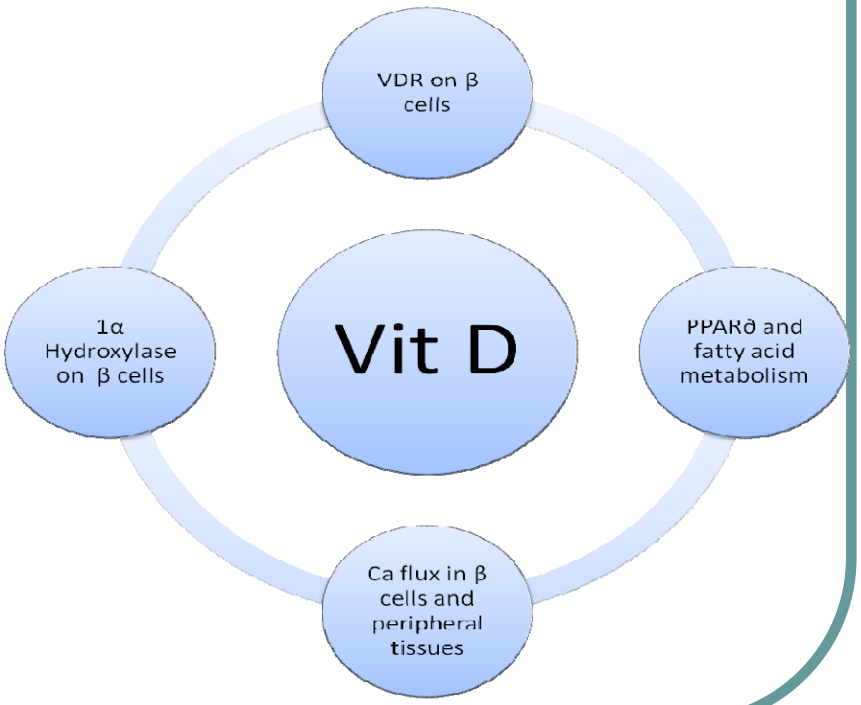
Top 5 Topics

1. Vitamin D: and GDM
2. OBESITY: Smoking and high BMI confers congenital heart anomalies in offspring
3. Nutrition: ROLO study
4. Vaccination: Flu vaccine in pregnancy
5. Drugs: ACE Inhibitors

Vitamin D and Glucose Homeostasis

- Growing evidence associating Vitamin D deficiency and type 2 diabetes mellitus*
- Unclear whether vitamin D affects GDM – conflicting results



*Pittas et al. Role of vit D/Ca in type 2 diabetes: systematic review and meta-analysis. J Clin Endocrinol Metab 2007; 92:2017-29.

AJOG 2012;207:182:e1-8.

Vitamin D deficiency in pregnancy and gestational diabetes mellitus

Heather H. Burris, MD, MPH; Sheryl L. Rifas-Shiman, MPH; Ken Kleinman, ScD; Augusto A. Litonjua, MD, MPH; Susanna Y. Huh, MD, MPH; Janet W. Rich-Edwards, ScD; Carlos A. Camargo Jr, MD, DrPH; Matthew W. Gillman, MD, SM

- To study the relationship between vitamin D status during pregnancy and gestational diabetes

Are the results of the study valid?

Was there a representative and well-defined sample of patients at a similar point in the course of the disease?

- Project Viva, MA (prospective prenatal cohort study of gestational factors and offspring health)
- Out of 2128 participants, 1314 mothers had second trimester 25(OH)D levels and GDM status information
- Enrolled <22 wk, singleton
- Gestational age of blood draw = 28 wks (SE 0.04)

Was there a representative and well-defined sample of patients at a similar point in the course of the disease?

Differences between participants and nonparticipants

	Participants (n=1314)	Nonparticipants (n=814)
Graduated from college	68%	59%
Age	32 years old	31 years old
GDM	5.2%	6.4%

Are the results of the study valid?

Was follow-up sufficiently long and complete?

- Covariates and confounding variables were collected through interviews, study questionnaires, and medical record reviews

Are the results of the study valid?

- Vitamin D measurement:
  - Used frozen non-fasting blood draw from 26-28 wks
  - Used chemiluminescence immunoassay first and then manual radioimmunoassay
  - Used US National Institute of Standards and Technology level 1
  - Average 2 values (r=0.81)

Were objective and unbiased outcome criteria used?

- Vitamin D status:

Severe deficiency	<25 nmol/L
Deficiency	25 to <50 nmol/L
Insufficiency	50 to <75 nmol.L
Sufficiency	>= 75 nmol/L

Were objective and unbiased outcome criteria used?

GDM diagnosis:

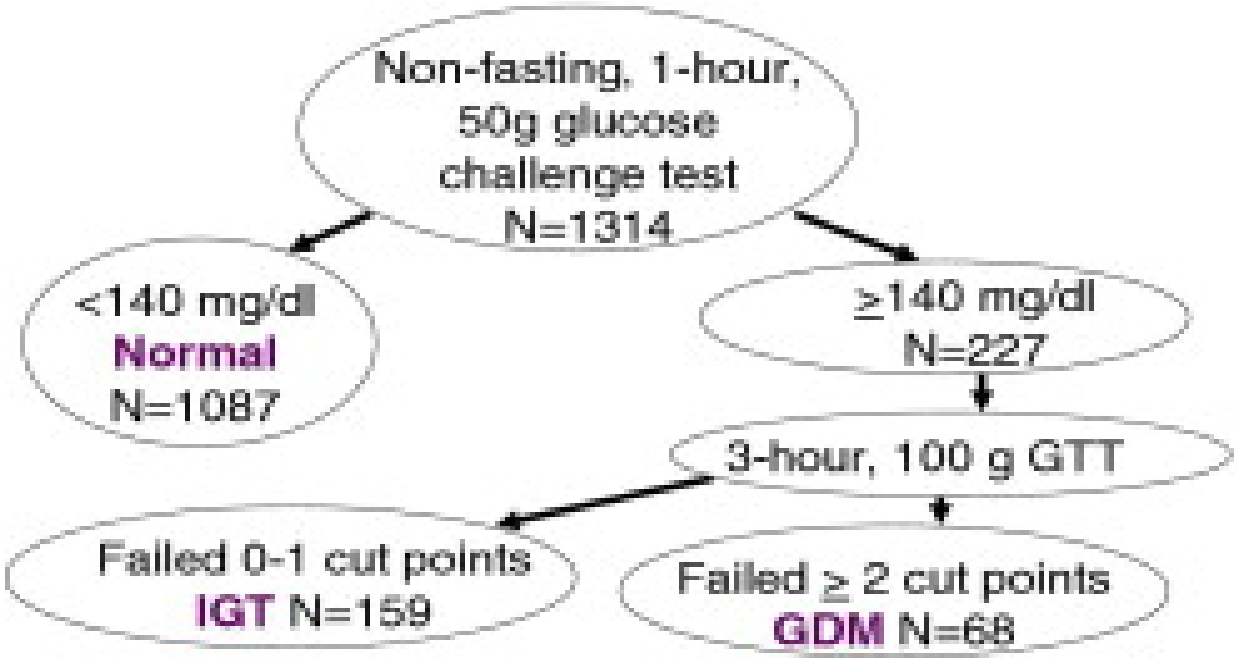


FIGURE 1 Project Viva Categorization of glucose tolerance based on 50-g, 1-hour, nonfasting glucose challenge test and subsequent fasting 100-g, 3-hour glucose tolerance test. <ce:italic> GDM</ce:italic> , gestational diabetes mellitus; <ce:ita...

American Journal of Obstetrics and Gynecology Volume 207, Issue 3 2012 182.e1 - 182.e8

**140 mg/dl = 7.8 mmol/L*

Are the results of the study valid?

Were there adjustments for important prognostic factors?

- Multivariable-adjusted multinomial logistic regression model for severe vitamin D deficiency and odds of GDM/IGT
- Multivariate linear regression model for vitamin D and GDS
- For missing covariates, chained equations to multiply impute values for these covariates (10 imputed dataset on all subjects)

What are the results?

Table 2: Odds of gestational diabetes mellitus in subjects with **severe vitamin D deficiency (<25nmol/L**)

25-hydroxyvitamin D exposure	Odds ratio (95% CI)			
	Model 1 (unadjusted)	Model 2a	Model 3b	Model 4c
Gestational diabetes mellitus vs. normal glucose tolerance	3.6 (1.7, 7.8)	**3.1** (1.3, 7.4)	**2.3** (**0.9**, 5.7)	2.2 (0.8, 5.5)
Impaired glucose tolerance vs. normal glucose tolerance	1.4 (0.7, 3.0)	1.6 (0.7,3.5)	1.4 (0.6,3.2)	1.4 (0.6, 3.3)

a. adjusted for gestational age, season at blood draw, maternal age, race/ethnicity, education, marital status, smoking, and parity

b. adjusted for **prepregnancy BMI and pregnancy weight gain** to 20 wks

c. adjusted for **physical activity** during pregnancy and **dietary intake of fish and calcium**

What are the results?

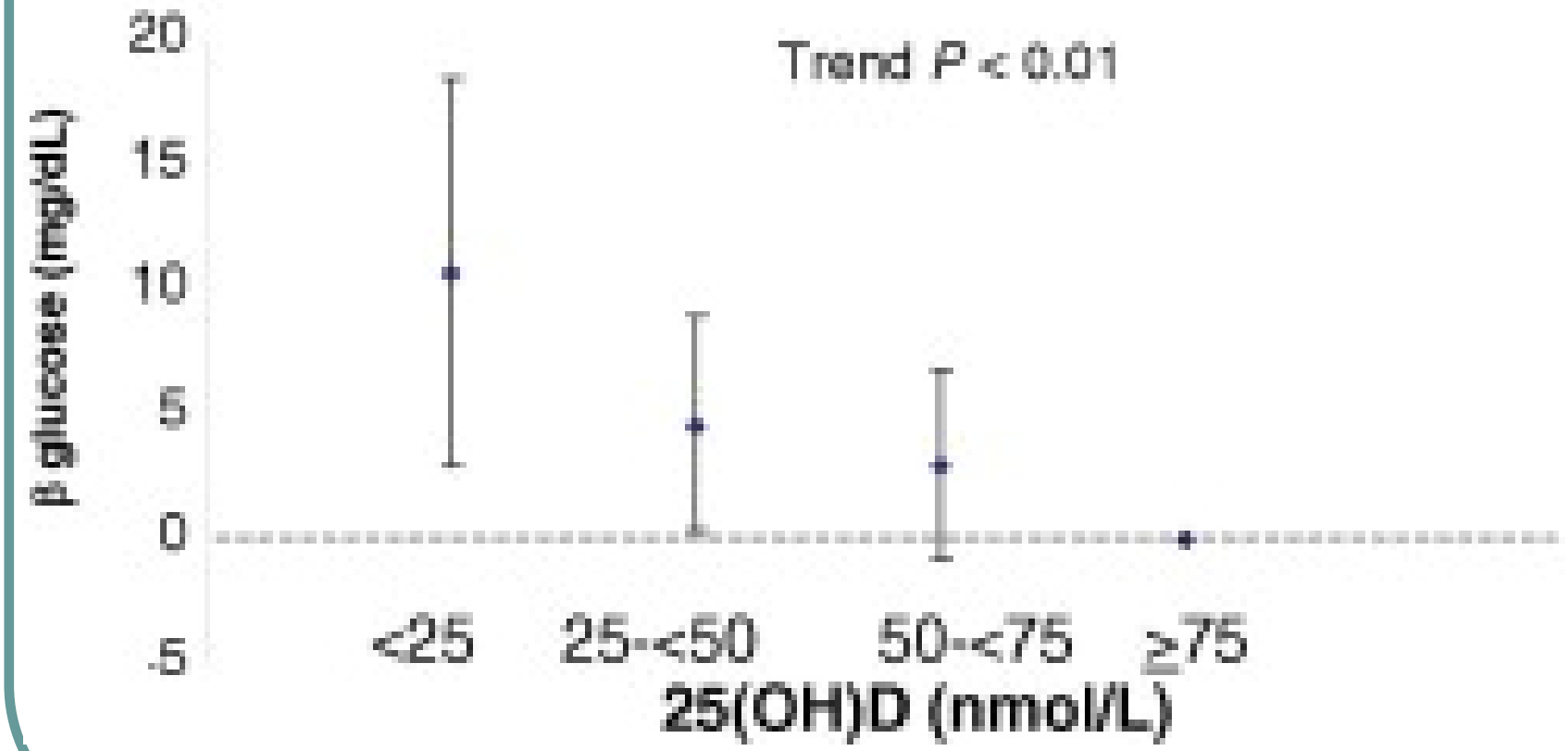


FIGURE 2 Glucose after glucose tolerance test by 25(OH)D category. Adjusted for all variables.

American Journal of Obstetrics and Gynecology Volume 207, Issue 3 2012 182.e1 - 182.e8

Will the results help me in caring for my patients?

Were the study patients similar to my own patients?

- Yes

Will the results help me in caring for my patients?

Will the results lead directly to selecting therapy?

- Negative study, also
  - Costs of testing
  - Time available for results
  - Even though….

Vitamin D and Preeclampsia

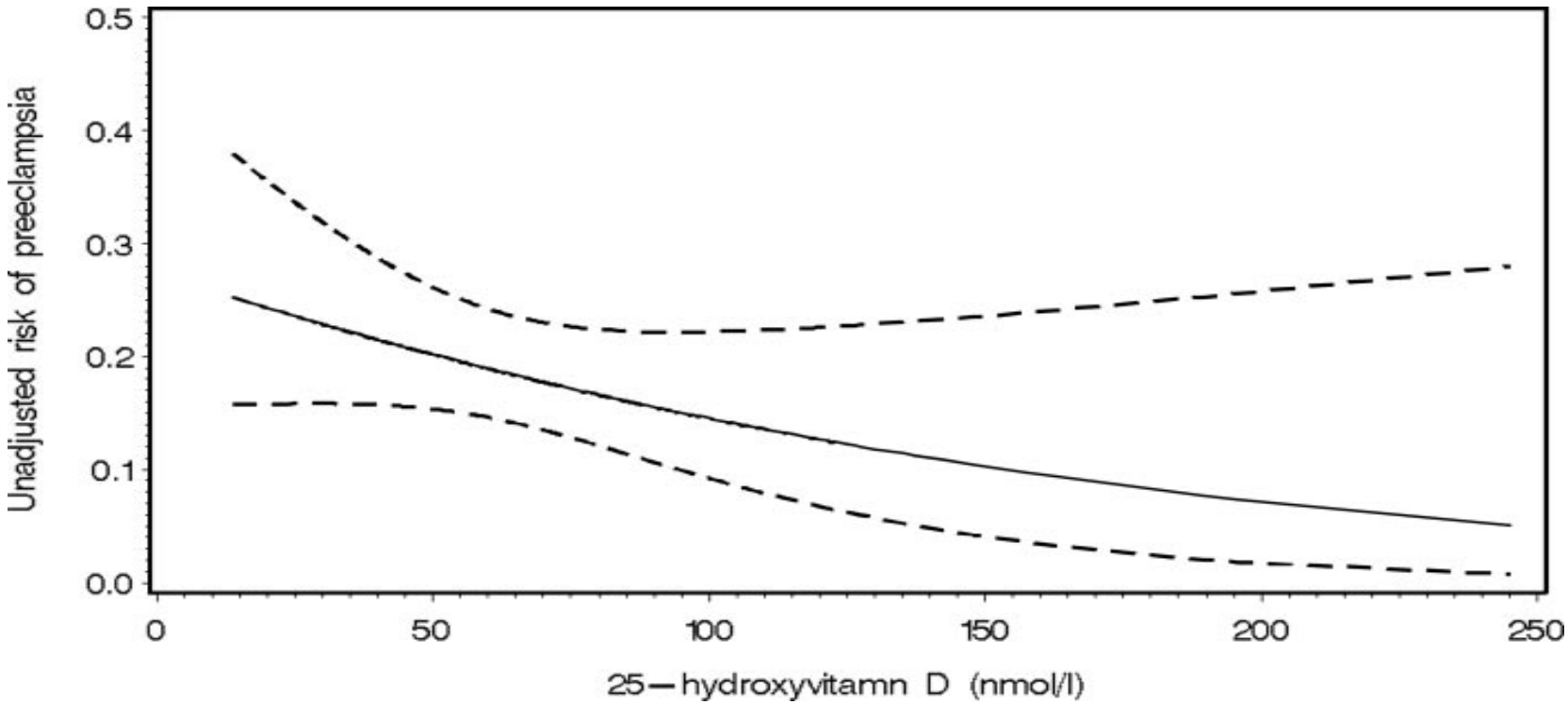


FIG. 1. Dose-response association between maternal serum 25-hydroxyvitamin D concentration at less than 22 wk gestation and the risk of preeclampsia derived from a logistic regression model (*P* 0.02). The *solid line* represents the point estimate, and the *dotted lines* represent the 95% confidence bands.

Ref: Bodnar et al. Maternal Vitamin D Deficiency Increases the Risk of Preeclampsia Risk J Clin Endocrinol Metab, September 2007, 92(9):3517–3522

Will the results help me in caring for my patients?

Are the results useful for counseling patients?

- For known severe vitamin D deficiency patient, counsel to have adequate vitamin D from diet or supplements
- Data for less severe vitamin D deficient patients less clear at this point

Not to every pregnant woman yet

Maternal Obesity and Risks in Offspring

- Maternal obesity is associated with an increased risk of structural anomalies, although the absolute increase is likely to be small.*

- Maternal smoking during pregnancy was associated with septal and right-sided obstructive defects.**

*JAMA. 2009 Feb 11;301(6):636-50.
Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. Stothard KJ et al

**Pediatrics. 2008 Apr;121(4):e810-6.
Maternal smoking and congenital heart defects.
Malik S et al. for National Birth Defects Prevention Study.

Heart 2012 (Jan 30); 98:474-479.

Combined adverse effects of maternal smoking and high body mass index on heart development in offspring: evidence for interaction?

Maria E Baardman,Wilhelmina S Kerstjens-Frederikse, Eva Corpeleijn, Hermien E K de Walle, Robert M W Hofstra, Rolf M F Berger, Marian K

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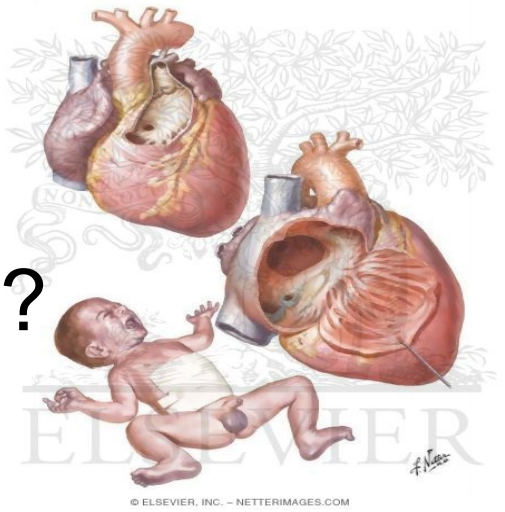
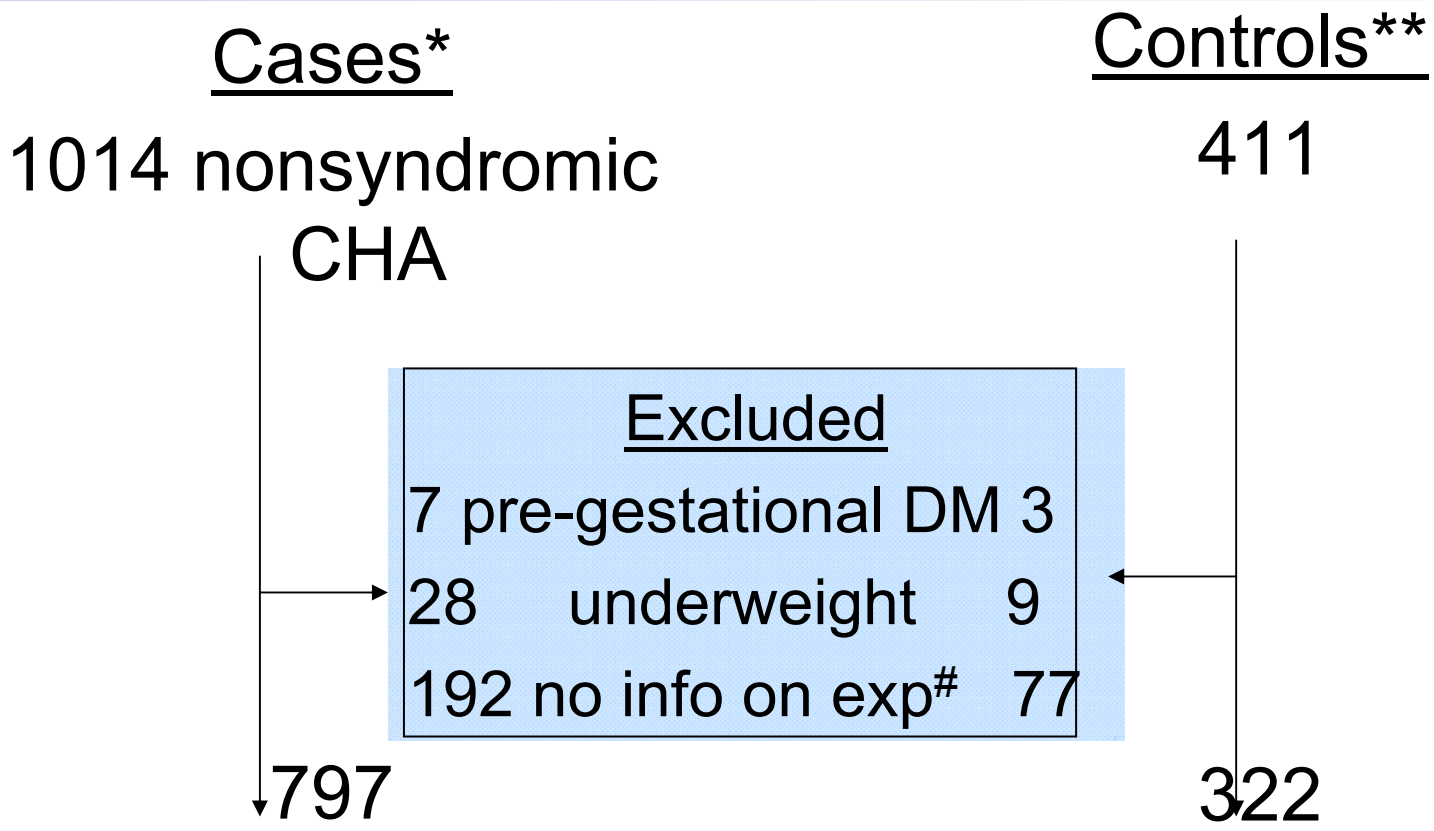


Are the results valid? Were there clearly identified comparison groups that were similar with respect to important determinants of outcomes, other than the one of interest?



*Eurocat Northern Netherlands, a population-based birth defects registry (annual births is 19,000) between 1997-2008

- *non-cardiac chromosomal anomaly from same geographical area and same birth-years

- **Exposures including:** BMI or smoking, pre-gestational diabetes

Are the results of the study valid?
Were the outcomes and exposures measured in the same way in the groups being compared?

Cases

- Outcomes:
  - seen by pediatrician or peds cardiologist.
  - Notification of children and fetuses with birth defects is voluntary
- Exposures:
  - Questionnaire on pre-pregnancy weight, chronic illnesses, lifestyle factors such as smoking* but cases may minimize reporting

Controls:

- Outcomes:
  - Echo proven CHA
- Exposures:
  - same way as cases

-Participation rate 80%

- *smoking defined as smoking before and during first trimester

Were the outcomes and exposures measured in the same way in the groups being compared?

- Interaction was assessed using the synergy factors (SF) by the method of Cortin-Borja*
- SF= $\frac{OR_{xy} \text{ for 2 dichotomous determinants}}{OR_x \times OR_y}$

* BMC Res Notes:2009; 2:105.

Are the results of the study valid?

Was follow-up sufficiently long and complete?

- Eurocat follows children up to 16 years old, but not controls.

Is the temporal relationship correct?

- Yes

What are the results?

- No difference between two groups on:
  - First pregnancy
  - Chronic illness
  - Education level
  - Folic acid use
  - Alcohol consumption
  - Gestational diabetes

- Difference between cases and controls:
  - Maternal age — 30 (27-34) vs. 33 (29-36)
  - High BMI — 35.3% vs. 29.2%
  - Peri-conceptional smoking — 25% vs. 18.9%

What are the results?

	Cases (n=797)		Controls (n=322)	
	Smoking		Smoking	
	No	Yes	No	Yes
Normal BMI	390 (49%)	126 (16%)	175 (54%)	53 (17%)
High BMI (overweight and obese)	208 (26%)	73 (9%)	86 (27%)	8 (2%)
-Overweight	146 (18%)	54 (7%)	69 (21%)	8 (2%)
-Obese	62 (8%)	19 (2%)	17 (5%)	0 (0%)

Normal body mass index (BMI) 18.5–24.9 kg/m2; high BMI ≥25.0 kg/m2; overweight 25.0–29.9 kg/m2; obese ≥30 kg/m2.

Table 3 : Crude and adjusted ORs (95% CI) for maternal smoking, high BMI and both factors combined for different cardiac subgroups

	Normal BMI	High BMI (≥25 kg/m^2)	Normal BMI	**High BMI** (≥25 kg/m^2)
	No smoking (n)	No smoking (n)	Smoking (n)	**Smoking** (n)
Chromosomal controls (n=322)	175	86	53	8
All CHA (n=797)				
N	390	208	126	73
OR (95% CI)	ref	1.09	1.07	**4.10 (1.93 to 8.68)**
OR_{adj} (95% CI)*	ref	1.05	0.96	**2.65 (1.20 to 5.87)**
Septal defects (n=349)				
N	177	86	59	27
OR (95% CI)	ref	0.99	1.10	**3.34 (1.48 to 7.55)**
OR_{adj} (95% CI)*	ref	0.95	1.00	**2.60 (1.05 to 6.47)**

Continued on next slide

*OR adjusted for maternal age, education level, folic acid use and peri-conceptional alcohol consumption.

How strong is the association between exposure and outcome? How precise is the estimate of the risk?

Interaction (adjusted synergy factors and 95% CIs) for maternal smoking and high BMI combined for different cardiac subgroups relative to non-cardiac chromosomal controls

Cardiac subgroups	Interaction (SF) (95% CI)*	p Value
All CHA (n=797)	2.62 (1.12 to 6.17)	0.027
Septal defects (n=349)	2.75 (1.07 to 7.08)	0.036
Conotruncal defects (n=115)	4.28 (1.26 to 14.51)	0.020
Outflow tract anomalies (n=265)	2.94 (1.12 to 7.71)	0.028
Left ventricular outflow tract obstructive anomalies (n=139)	3.59 (1.19 to 10.87)	0.024
Right ventricular outflow tract obstructive anomalies (n=126)	2.87 (0.94 to 8.79)	0.065

* Adjusted for maternal age, education level, folic acid use and peri-conceptional alcohol consumption.

Will the results help me in caring for my patients?

Are the results applicable to my practice?

- Caution, as unknown association between lifestyle factors and other determinants between mothers of children with chromosomal disorder and mothers of non-malformed children.

What is the magnitude of the risk?

- Congenital heart anomalies occur at about 8 per 1000 births
- Smoking and overweight/obesity synergistically confer a 1.1 - 6.2 times the risk of congenital heart anomalies

Will the results help me in caring for my patients?

Should I attempt to stop the exposure?

- Despite limitations of missing data and small OR etc, other benefits to counsel to stop smoking and lower pre-pregnancy BMI
  - Yes, I would counsel patients to stop smoking and lower BMI, adding this information of potential increased congenital heart anomalies

Maternal Obesity/Weight Gain Increase Macrosomia

- Increased maternal BMI* increases birthweight**
- Increased gestational weight gain also increases birthweight**

* Seidman et al. The effect of maternal weight gain in pregnancy on birth weight. Obstet Gynecol 1989; 74:240-6.

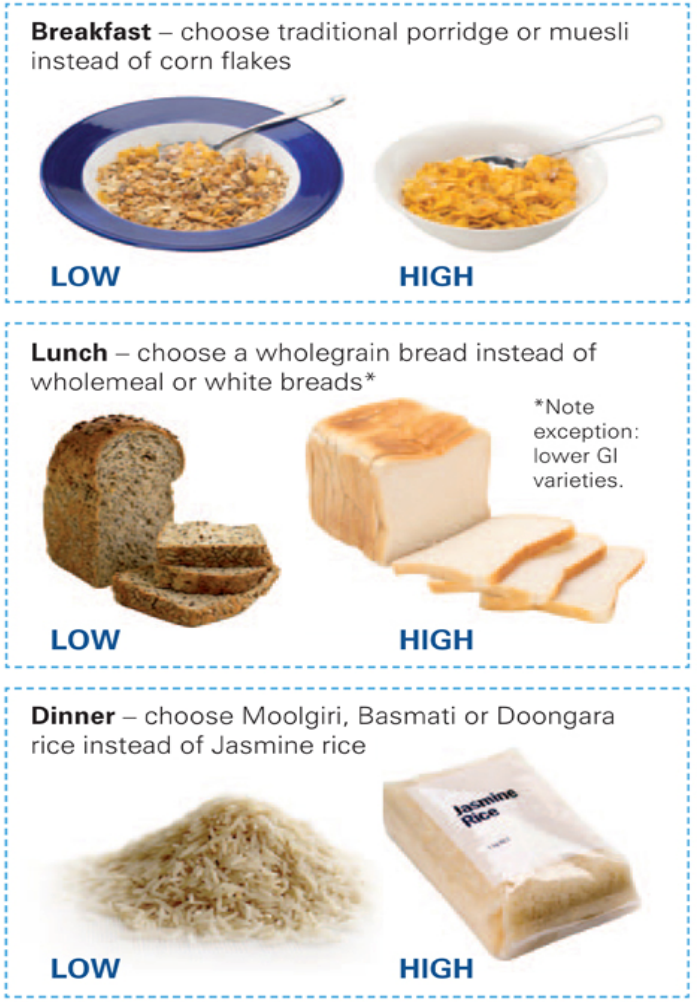
**Siega-Riz et al. A systematic review of outcomes of maternal weight gain according to IOM recommendations. Am J Obstet Gynecol 2009; 201:339 e1-14

BMJ 2012 Aug 30; 345:e5605.

Low glycemic index diet in pregnancy to prevent macrosomia (ROLO study): Randomised control trial.

Jennifer M Walsh, Ciara A McGowan, Rhona Mahony, Michael E Foley, Fionnuala M McAuliffe

UCD Obstetrics and Gynaecology, School of Medicine and Medical Science, University College Dublin, National Maternity Hospital, Dublin, Ireland.



Are the results valid?

Was the assignment of patients to treatments randomized?

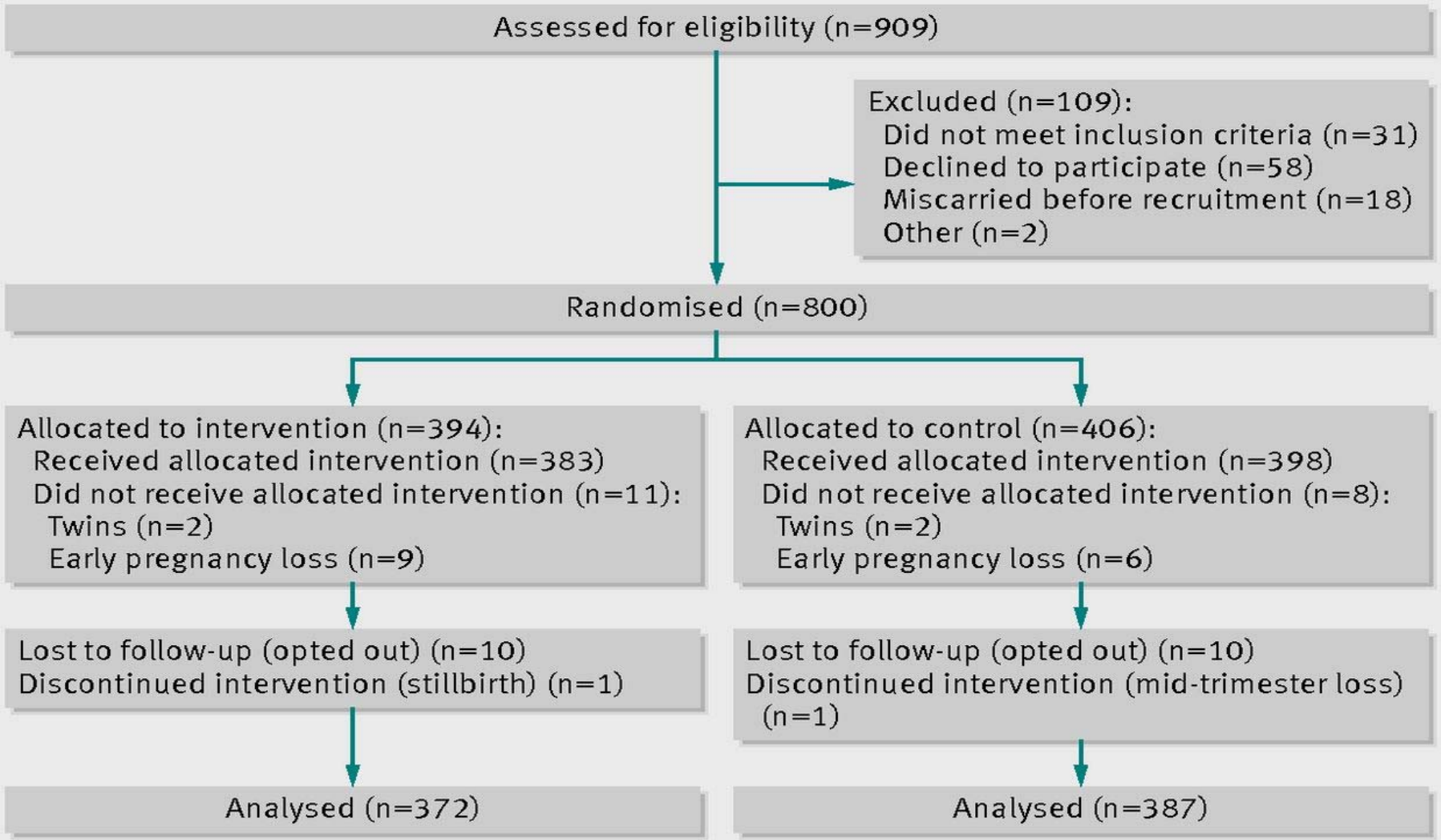
- Yes, RCT

- 2007-2011
- Inclusion: women in their *secondary* pregnancies who have previously delivered an infant >4000 g recruited in first prenatal visit
- Exclusion: <18 years old, >18 wks gestation, multiple pregnancy, underlying medical disorders including previous history of GDM, on drugs

Intervention: Low glycemic index (GI) diet

- Intervention – one dietary group education (2 hours) on general guidelines and focused education on GI (mean gestation age of attendance 15.7 wks). Then meet with dietitian at 28 and 34 weeks for reinforcement of low GI diet.
- Control – no advice on diet or gestational weight gain

Were all patients who entered trial properly accounted for and attributed to its conclusion? Were follow ups complete?



Were patients analyzed in the groups to which they were randomized?

- Not an intention to treat analysis
  - Women miscarried could not complete study
  - Women lost to follow up cannot provide data to questionnaire at 34 weeks

Were patients, health workers, and study personnel “blind” to treatment?

- No – not possible to blind the dietary intervention.
- Women in the control group may seek dietary modifications themselves.

Were the groups similar at the start of the trial?

- Yes

Baseline	**Intervention** n=383	**Control** n=398
Age (years)	32.0 (4.2)	32.0 (4.2)
Gestational age at recruitment (wks)	13.0 (2.3)	12.9 (2.2)
Weight (kg)	73.8 (14.8)	73.4 (13.7)
Height (cm)	166.3 (6.4)	168.9 (6.5)
BMI (kg/m2)	26.8 (5.1)	26.8 (4.8)
Mid upper arm circumference (cm)	29.5 (3.6)	29.5 (3.4)
Fasting glucose (mmol/L)	4.5 (0.36)	4.5 (0.38)
Previous birthweight (g)	4253 (261)	4242 (236)
No (%) smoker	17 (4)	12 (3)

Aside from the experimental intervention, were the groups treated equally?

- Yes
  - Both had measurements for height, weight, arm circumference, fasting blood glucose, demographic data
  - 28 wks GDS (50 g). If >=8.3 mmol/L, then GCT (3 h 100 g, using Carpenter and Coustan criteria)
  - Fetal biometry assessed by ultrasound at 34 wks
  - At delivery, record birthweight, length, ponderal weight (100 x mass in g/height in cm^2).
  - All had 3 food diaries of 3 days each, to estimate glycemic index and glycemic load
  - Except: Only intervention group had questionnaire on adherence to glycemic index diet at 34 wks

What were the results?

- Primary outcome of birthweight – no difference

Table 2

Comparison of infant, fetal, and maternal outcomes between intervention and control groups. Values are mean (SD) unless stated otherwise

Outcome	Intervention group (n=372)	Control group (n=387)	Mean difference (95% CI)	P value
Birthweight (g)	4034 (510)	4006 (497)	28.6 (−45.6 to 102.8)	0.449
Birthweight centile	70.5 (25.6)	72.8 (25.6)	−1.6 (−5.39 to 2.2)	0.409
No (%) birth weight >4000 g	189 (51)	199 (51)	—	0.88
Ponderal index at birth	2.76 (3.8)	2.75 (0.33)	0.011 (−0.36 to 0.39)	0.95
Birthweight difference* from first pregnancy (g)	−214.2 (541)	−250.8 (512)	−36.6 (−120.15 to 46.95)	0.507
Fasting glucose at 28 weeks (mmol/L)	4.45 (0.4)	4.51 (0.6)	−0.058 (−0.146 to 0.03)	0.198
Glucose challenge test at 28 weeks (mmol/L)	6.47 (1.4)	6.67 (1.7)	−0.205 (−0.44 to 0.031)	0.088
Cord blood glucose (mmol/L)	4.17 (1.1)	4.16 (1.2)	0.014 (−0.19 to 0.217)	0.896

How large was the treatment effect? How precise was the estimate of the treatment effect?

Table 2

Comparison of infant, fetal, and maternal outcomes between intervention and control groups. Values are mean (SD) unless stated otherwise

Outcome	Intervention group (n=372)	Control group (n=387)	Mean difference (95% CI)	P value
Weight gain at 24 weeks (kg)	5.3 (2.7)	5.5 (2.7)	−0.244 (−0.786 to 0.299)	0.378
Weight gain at 28 weeks (kg)	7.1 (2.8)	7.7 (3.0)	−0.593 (−1.072 to −0.114)	0.015
Weight gain at 34 weeks (kg)	10.1 (3.7)	10.9 (3.9)	−0.83 (−1.48 to −0.182)	0.012
Weight gain at 40 weeks (kg)	12.2 (4.4)	13.7 (4.9)	−1.346 (−2.451 to −0.241)	0.017

Gained 0.24 to 2.5 kg (or 0.53 to 5.5 lbs) less than control group

	Intervention	Control	P value
Exceed recommended gestational weight gain*	38%	48%	0.01
- Normal BMI women	15%	26%	0.02
- Overweight women	53%	67%	0.02
- Obese women	60%	57%	0.8

*According to Institute of Medicine

Will the results help me in caring for my patients?

Can the results be applied to my patient care?

- Yes

Were all clinically important outcomes considered?

- Yes

Are the likely treatment benefits worth the potential harms and costs?

- No harm
- Costs of dietary counseling if not already in routine care
- 80% adhered to low GI diet

Breakfast – choose traditional porridge or muesli instead of corn flakes

LOW

HIGH

Lunch – choose a wholegrain bread instead of wholemeal or white breads*

LOW

*Note exception: lower GI varieties.

HIGH

Dinner – choose Moolgiri, Basmati or Doongara rice instead of Jasmine rice

LOW

HIGH

In general,

why not if have a dietitian in clinic?

Influenza Vaccination in Pregnancy

- Influenza in pregnancy associated with
  - increased risk of pregnancy complications, including preterm delivery and fetal distress
- Vaccination with the trivalent inactivated influenza vaccine reduces all febrile respiratory illness by approx one third in vaccinated mothers and newborns*
- Maternal antibodies from vaccination cross placenta and provide neonatal protection for first few months

*Zaman et al. Effectiveness of maternal influenza immunization on mothers and infants. NEJM 2008; 359:1555-64.

Vaccination Policy and Uptake

History

- 2004 CDC and Prevention recommended vaccination of all women regardless of gestational age
- Flu vaccine uptake:
  - 10-24% pregnant women
  - Went up to 49% after 2009 H1N1 influenza pandemic
- Concerns about safety of vaccine in pregnancy
- Few studies have data on vaccine in first trimester
- In fact, 2009 review concluded that there was insufficient evidence to recommend routine use of trivalent influenza vaccine during the first trimester of pregnancy*

**Skowronski DM and DeSerres G. Vaccine (2009) 27:35; 4754-70.*

Obstet Gynecol 2012 Sep; 120:532

Effect of influenza vaccination in the first trimester of pregnancy

Jeanne S. Sheffield, Laura G. Greer, Vanessa L. Rogers, Scott W. Roberts,Heather Lytle, Donald D. McIntire, and George D. Wendel, Jr

Objective: To compare neonatal outcomes in women with first trimester vaccine with those with second and third trimester vaccines or those unvaccinated

Are the results of the study valid? Were there clearly identified comparison groups that were similar with respect to important determinants of outcomes, other than the one of interest?

Retrospective cohort on women receiving prenatal care in Texas Southwestern Center clinics

<u>Vaccinated</u>

- October 2003 to March 2008 (starting Oct 2004 offered first trimester vaccination)

<u>Non-Vaccinated</u>

- Women receiving prenatal care during same duration delivered in the same institution

Are the results of the study valid?
Were the outcomes and exposures measured in the same way in the groups being compared?

- Vaccination record linked with obstetrics database
- Malformations of live births and stillbirths from newborn nursery records and discharge records obtained

What are the results?

Table 1. Characteristics of the Women Receiving an Influenza Vaccination During Pregnancy

	Vaccination (n=8,690)	No Vaccination (n=76,153)	P
Age (y)	26.8±5.9	26.0±5.9	<.001
15 or younger	43 (0)	848 (1)	<.001
35 or older	967 (11)	7,044 (9)	<.001
Race			<.001
Black	760 (9)	7,678 (10)	
White	276 (3)	2,782 (4)	
Hispanic	7,505 (86)	62,878 (83)	
Other	149 (2)	1,815 (2)	
Nulliparity	2,325 (27)	24,180 (32)	<.001
Obstetric complication	6,256 (72)	36,687 (48)	<.001
Clinic attendance			
Hypertension	745 (9)	6,754 (9)	.4
Diabetes (overt and GDM)	1,000 (12)	4,343 (6)	<.001
Multiple gestation	171 (2)	751 (1)	<.001
Body mass index (kg/m^2)	32.3±5.8	31.5±5.6	<.001

GDM, gestational diabetes mellitus.

Data are mean±standard deviation or n (%) unless otherwise specified.

What are the results?

Table 2. Delivery and Neonatal Outcomes for the Entire Cohort

	Vaccination (n=6,864)	No Vaccination (n=76,919)	P
Estimated gestational age (wk)	39.3±1.8	39.3±2.0	.9
36 or less	469 (6)	4,612 (6)	.004
31 or less	65 (0.7)	962 (1.3)	<.001
Birth weight (g)	3,329±577	3,324±581	.43
Less than 10th percentile	844 (11)	8,183 (11)	.9
Less than 3rd percentile	311 (4)	2,579 (3)	.5
Greater than 90th percentile	971 (11)	7,939 (11)	.1
Major malformations	136 (2)	1,163 (2)	.9
Stillbirth	30 (0.3)	436 (0.6)	.006
NICU admission	210 (2)	2,043 (3)	.1
Neonatal death	19 (0.2)	298 (0.4)	.01
Neonatal pneumonia	96 (1)	627 (1)	.01
Hyperbilirubinemia	305 (3)	2,684 (4)	.7

NICU, neonatal intensive care unit.

Data are mean±standard deviation or n (%) unless otherwise specified.

How strong is the association between exposure and outcome? How precise is the estimate of the risk?

Table 3. Odds Ratios and 95% Confidence Intervals for Selected Neonatal Outcomes by Trimester of Influenza Vaccination

n=447 n=8243

	First Trimester	Second-Trimester and Third-Trimester Vaccination	n
Major malformations	0.67 (0.36–1.26)	1.01 (0.84–1.22)	1.0 (referent)
Stillbirths	2.54 (0.36–18.10)	1.85 (1.13–2.40)	1.0 (referent)
Neonatal pneumonia	1.83 (0.46–7.35)	0.73 (0.58–0.91)	1.0 (referent)
NICU admission	0.42 (0.29–0.63) *	1.23 (1.05–1.43)	1.0 (referent)

NICU, neonatal intensive care unit.

The OR in this table is the number for non-vaccinated group compared to the vaccinated group by trimester (ie the higher the number, the less of the outcome by the vaccination group)

*did not result in an increase in neonatal death or prolonged length of stay

Limitations:

- Non-vaccinated group could have been vaccinated elsewhere

Will the results help me in caring for my patients?

- Continue to recommend flu vaccine to pregnant patients
- Counsel patients that T1 influenza vaccine:
  - Did not increase major malformations
  - (Increased NICU admissions but no increased neonatal death or prolonged LOS)
- Vaccination in any trimester:
  - Decreased overall stillbirth rate
  - Decreased neonatal death
  - Decreased preterm delivery <32 wks

Yes

ACE Inhibitors

- Cross human placenta
- Second trimester exposure associated with fetal renal failure, hence late fetal deaths
- First trimester exposure shown to be teratogen*, but paper later criticized to not adjust for obesity
- Certain renal patients with proteinuria may benefit from not stopping ACE Inhibitors too early preconception as it may take a long time for some to conceive and time off ACEI may accelerate their progression to ESRD

*Cooper et al. NEJM 2006; 354;2443-51

BMJ 2011;343:d5931 doi: 10.1136/bmj.d5931

Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study

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Are the results of the study valid?

Methods:

- Retrospective, population based cohort based on >465000 mother-infant pairs from 1995-2008 in the Kaiser Permanente Northern California system (automated clinical and pharmacy databases)
- From Pharmacy Information Management system capturing all prescription drugs info (date of dispensed and days of supplies)
- Calculate gestational age from clinical database

Were there clearly identified comparison groups that were similar with respect to important determinants of outcomes, other than the one of interest?

- Yes
- Classified into:
  - 1. ACEI users
  - 2. Users of other antihypertensives (other than ACEI)
  - 3. Hypertension controls (no BP meds)
  - 4. Normal controls
- Exclude ARBs
- Confounders such as diabetes, age, maternal weight were obtained in all groups
- Classified into different periods of exposure:
  - First trimester only
  - Any exposure in first trimester
  - Exposure in second or third trimesters only

Are the results of the study valid?
Were the outcomes and exposures measured in the same way in the groups being compared?

- Yes
- Exposure (ACEI, other antihypertensives) through pharmacy databases
- Outcomes (malformations) through Kaiser Permanent Northern California automated databases which has been validated through a random audit comparing with clinical data (n=237)
- California birth certificate data for additional variables/potential confounders

Are the results of the study valid?

Was follow-up sufficiently long and complete?

- Yes. Infants followed till end of study, but most malformations were identified before 1 year old.

Is the temporal relationship correct?

- Yes

Is there a dose-response gradient?

- Not stated.

What are the results?

- How strong is the association between exposure and outcome? How precise is the estimation of the risk?

Table 2
Risk of major birth defects in offspring of 465 754 women who delivered in the Kaiser Permanente Northern California region during 1995–2008 by maternal use of antihypertensive medications during pregnancy

	No (%) of mother-infant pairs	Odds ratio (95% CI)		
		Crude	Adjusted*	
Any birth defect				
Normal controls†	22 429/416 218 (5.4)	Reference	Reference	—
Hypertension controls‡	2247/31 274 (7.2)	1.36 (1.30 to 1.42)	1.25 (1.19 to 1.31)	Reference
Antihypertensive use:				
Only in 1st trimester:				
Other antihypertensives§	79/1141 (6.9)	1.31 (1.04 to 1.64)	1.22 (0.97 to 1.54)	1.00 (0.79 to 1.27)
ACE inhibitors¶	34/400 (8.5)	1.63 (1.15 to 2.32)	1.20 (0.84 to 1.72)	0.97 (0.67 to 1.41)
Only in 2nd or 3rd trimesters:				
Other antihypertensives§	1334/13 117 (10.2)	1.99 (1.88 to 2.11)	1.94 (1.83 to 2.05)	1.53 (1.43 to 1.65)
ACE inhibitors¶	7/51 (13.7)	2.80 (1.26 to 6.21)	2.34 (1.05 to 5.22)	1.88 (0.84 to 4.20)

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*Adjusted for pre-existing diabetes, maternal age, ethnicity, parity, and maternal weight, and with different reference categories (normal controls or hypertension controls).

Risk of major birth defects in offspring of 462 655 women without pre-existing diabetes who delivered in the Kaiser Permanente Northern California region during 1995–2008 by maternal use of antihypertensive medications during the first trimester of pregnancy and an underlying diagnosis of hypertension

	No (%) of mother-infant pairs	Odds ratio (95% CI)		
		Crude	Adjusted*	
Any birth defect				
Normal controls†	22 277/414 567 (5.4)	Reference	Reference	—
Hypertension controls‡	2162/30 585 (7.1)	1.34 (1.28 to 1.40)	1.25 (1.19 to 1.31)	Reference
Antihypertensive use:				
Other antihypertensives§:				
Without hypertension	53/733 (7.2)	1.37 (1.04 to 1.82)	1.32 (1.00 to 1.75)	1.08 (0.81 to 1.43)
With hypertension	21/378 (5.6)	1.04 (0.67 to 1.61)	0.96 (0.62 to 1.50)	0.81 (0.52 to 1.26)
ACE inhibitors¶:				
Without hypertension	0/22 (0)	NA	NA	NA
With hypertension	15/226 (6.6)	1.25 (0.74 to 2.11)	1.17 (0.69 to 1.98)	0.97 (0.57 to 1.65)

*Adjusted for pre-existing diabetes, maternal age, ethnicity, parity, and maternal weight, and with different reference categories (normal controls or hypertension controls).

Will the results help me in caring for my patients?

Are the results applicable to my practice?

- Yes

What is the magnitude of the risk?

- Underlying hypertension, and not ACE inhibitors or other antihypertensives in first trimester, has an odds of 1.19 – 1.31 of causing malformations

Should I attempt to stop the exposure?

- No need to panic if patient is still on ACE inhibitors in first trimester but do stop in early pregnancy
- ACE inhibitors do cause fetal toxicity if used in second and third trimesters

Top 5 Topics - Summary

1. **Severe Vitamin D deficiency and GDM** – OR weakened when adjusted for obesity. Not ready to give everyone vitamin D. Need RCT.
2. **Smoking and high BMI** - may increase congenital heart anomalies in offspring by 2.6 times. Take advantage of this result in counseling on smoking cessation and normalizing BMI.
3. **Low glycemic index counseling in women with previous macrosomic baby** - did not lower birthweight but women gained 1.3 kg (or 3 lbs) less in the pregnancy. No harm. If already have a dietitian in clinic, include this dietary counseling.

Top 5 Topics – Summary…cont'd

4. **Influenza Vaccination in first trimester** - appears to not cause malformations. Vaccination in any trimester in pregnancy improve some neonatal outcomes.
5. **ACE Inhibitors in first trimester** – not teratogenic, nor other antihypertensives. Underlying hypertension increases risk for malformations.

Thank you!