OPTIMIZING POSTPARTUM MATERNAL HEALTH TO PREVENT CHRONIC DISEASES

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Disclosures

• Research:
  • None

• Financial: none applicable to this presentation
  • PRIUM
  • QEessentials Market Research
  • M3 Global Research
  • Medscape
  • Guidepoint
Objectives

Following this presentation, participants will be able to:

1. Recognize the negative impact of gestational diabetes mellitus (GDM) and pregnancy induced hypertension (PIH) on future maternal health.

2. Teach patients and other clinicians the need for aggressive risk modification after GDM and PIH to avoid future chronic disease(s).

3. Initiate the most evidenced based initial management for patients with postpartum hyperglycemia and hypertension.
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3. Initiate the most evidenced based initial management for patients with postpartum hyperglycemia and hypertension.
Your next clinic patient…

- 42y G2P2002 who presents for her annual evaluation.

- Today her BP is 120/70 and her current weight is 185lbs (BMI of 28.6 kg/m²).

- Her prior obstetric history: gestational diabetes in both pregnancies, gestational hypertension in the second pregnancy only.

- She is asymptomatic.
Based on her obstetric history of GDM and PIH, she is high risk for which diseases?

<table>
<thead>
<tr>
<th>Gestational Diabetes</th>
<th>Hypertension in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypertension</td>
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</tr>
<tr>
<td>2. Diabetes Mellitus</td>
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</tr>
<tr>
<td>3. Heart Failure</td>
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</tr>
<tr>
<td>5. Stroke</td>
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</tr>
<tr>
<td>6. Coronary Artery Disease</td>
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</tr>
<tr>
<td>7. All of the above</td>
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</tbody>
</table>
Based on her obstetric history of GDM and PIH she is high risk for which diseases?

**Gestational Diabetes**

1. Hypertension
2. Diabetes Mellitus
3. Heart Failure
4. Kidney Failure
5. Stroke
6. Coronary Artery Disease
7. All of the above

**Hypertension in Pregnancy**

1. Hypertension
2. Diabetes Mellitus
3. Heart Failure
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5. Stroke
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7. All of the above
Based on her obstetric history of GDM and PIH she is high risk for which diseases?

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</tr>
<tr>
<td>7. All of the above</td>
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</tr>
</tbody>
</table>
Future Disease Predicted by Pregnancy

- **Hypertension**
  - Prevalence 77.9 million adults
  - Predicted by PIH disorders
    - Gestational hypertension
    - Preeclampsia
    - Eclampsia
    - HELLP Synd.

- **Diabetes Mellitus**
  - Prevalence 26 million adults
  - Predicted by Gestational Diabetes and PIH disorders

- **Overweight/Obesity**
  - Prevalence 78.6 million adults
  - Predicted by excess weight gain in pregnancy

- **Heart Failure**
  - Prevalence 5.8 million adults

- **Stroke**
  - Prevalence 6.3 million adults

- **Chronic Kidney Disease**
  - Prevalence 20 million adults
  - Predicted by GDM and PIH

- **Cardiovascular Disease** (CHD, CVD, PAD, CHF, VTE)
  - Prevalence 85.6 million adults
  - 44 million women
  - Predicted by GDM and PIH

CDC, 2011-2016
Associations of Pregnancy Complications With Calculated Cardiovascular Disease Risk and Cardiovascular Risk Factors in Middle Age

Background
• The nature and contribution of different pregnancy-related complications to future cardiovascular disease (CVD) and its risk factors and the mechanisms underlying these associations remain unclear.

Methods
• Prospective cohort of 3,416 women.

• Studied associations of 1) gestational diabetes, 2) hypertensive disorders of pregnancy, 3) preterm delivery, and 4) size for gestational age with calculated 10-year CVD risk (based on the Framingham score)

• A wide range of cardiovascular risk factors were measured 18 years after pregnancy (mean age at outcome assessment, 48 years)
Associations of Pregnancy Complications With Calculated Cardiovascular Disease Risk and Cardiovascular Risk Factors in Middle Age

Results

• Gestational diabetes mellitus was positively associated with fasting glucose and insulin, even after adjustment for potential confounders.

• Hypertensive disorders of pregnancy were associated with body mass index, waist circumference, blood pressure, lipids, and insulin.

• Large for gestational age was associated with greater waist circumference and glucose concentrations.

• Small for gestational age and preterm delivery were associated with higher blood pressure.

• Compared to the women without preeclampsia and/or gestational diabetes, the future CVD risk with that of patients with history of 1) preeclampsia was an OR of 1.31 (95 confidence interval, 1.11–1.53) and for 2) gestational diabetes was an OR of 1.26 (95 confidence interval, 0.95–1.68).
Conclusions

• Hypertensive disorders of pregnancy and pregnancy diabetes mellitus are independently associated with an increased calculated 10-year Framingham CVD risk.

• Preeclampsia may be the better predictor of future CVD because it was associated with a wider range of cardiovascular risk factors.
Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy

Objective
• The purpose of this study was to determine cardiovascular risk factors in women with a history of hypertensive pregnancy disorders at term (HTP) 2.5 years after pregnancy.

Study Design
• Multicenter cohort study in The Netherlands from June 2008 through November 2010

• Cardiovascular risk factors were compared 2.5 years after pregnancy between women with a history of HTP (N = 306) and women with a history of normotensive pregnancies at term (N = 99).

• Assessed risks included: blood pressure, anthropometrics, glucose, glycosylated hemoglobin, insulin, homeostatic model assessment score, total cholesterol, high-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein, and microalbumin and metabolic syndrome.
Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy

Results

• Hypertension and metabolic syndrome were more prevalent in HTP women compared with NTP women.

• HTP women had significantly higher systolic and diastolic blood pressure, higher body mass index, and higher waist circumference.

• Glucose, glycosylated hemoglobin, insulin, homeostatic model assessment score, total cholesterol, triglycerides, and high-sensitivity C-reactive protein levels were significantly higher and high-density lipoprotein (HDL) cholesterol was significantly lower in HTP women.

Conclusion

• In women with a history of HTP, hypertension and metabolic syndrome are more common, and they have higher levels of biochemical cardiovascular risk factors 2.5 years after pregnancy.
Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NTP (n = 99)</th>
<th>HTP (n = 306)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at follow-up, y</td>
<td>34 (4.7)</td>
<td>34 (5.2)</td>
<td>.67</td>
</tr>
<tr>
<td>Family history of early CVD, %</td>
<td>11 (11%)</td>
<td>48 (16%)</td>
<td>.15</td>
</tr>
<tr>
<td>Antihypertensive medication use</td>
<td>0 (0%)</td>
<td>29 (9%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Systolic blood pressure at follow-up, mm Hg</td>
<td>110 (9.3)</td>
<td>124 (13)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diastolic blood pressure at follow-up, mm Hg</td>
<td>72 (8.8)</td>
<td>82 (9.6)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Body mass index at follow-up, kg/m²</td>
<td>24 (4.6)</td>
<td>28 (5.5)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>81 (12)</td>
<td>90 (13)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>104 (11)</td>
<td>109 (12)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HDL cholesterol,&lt;40 mg/dL</td>
<td>10 (11%)</td>
<td>37 (12%)</td>
<td>.53</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>5 (5%)</td>
<td>73 (25%)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Smoking</td>
<td>19 (19%)</td>
<td>60 (20%)</td>
<td>.89</td>
</tr>
</tbody>
</table>

American Journal of Obstetrics and Gynecology, June 2012
Metabolic Syndrome – ATPIII Criteria

- **Abdominal obesity**, defined as a waist circumference in non-Asian women ≥88 cm (35 in) and in Asian women ≥80 cm (31.5 in)

- **Serum triglycerides** ≥150 mg/dL (1.7 mmol/L) *or drug treatment* for elevated triglycerides

- **Serum HDL cholesterol** <50 mg/dL (1.3 mmol/L) in women *or drug treatment* for low HDL cholesterol

- **Blood pressure** ≥130/85 mmHg *or drug treatment* for elevated blood pressure

- **Fasting plasma glucose** ≥100 mg/dL (5.6 mmol/L) *or drug treatment* for elevated blood glucose (prediabetes or diabetes mellitus)
Elevated blood pressure in pregnancy and subsequent chronic disease risk.

BACKGROUND:
- Preeclampsia, a new-onset hypertensive disorder of pregnancy, is associated with lifetime cardiovascular disease risk, but less is known about risk after other pregnancy-related hypertension.

METHODS:
- The Northern Finland Birth Cohort 1966 included all expected births from 1 year (N=12,055 women).
- Blood pressure measurements and other prospective data were determined from prenatal care records and questionnaires for 10,314 women.
- Subsequent diagnoses were ascertained (mean follow-up, 39.4 years).
- Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) estimated risks in hypertensive women compared with normotensive women.

Circulation, Feb 2013
Elevated blood pressure in pregnancy and subsequent chronic disease risk.

RESULTS:

- Gestational hypertension was associated with increased risk of:
  - Ischemic heart disease (HR, 1.44 [95% CI, 1.24-1.68])
  - Myocardial infarcts (HR, 1.75 [95% CI, 1.40-2.19])
  - Myocardial infarct death (HR, 3.00 [95% CI, 1.98-4.55])
  - Heart failure (HR, 1.78 [95% CI, 1.43-2.21])
  - Ischemic stroke (HR, 1.59 [95% CI, 1.24-2.04])
  - Kidney disease (HR, 1.91 [95% CI, 1.18-3.09])
  - Diabetes mellitus (HR, 1.52 [95% CI, 1.21-1.89]).

- Isolated **systolic** hypertension was associated with increased risk of myocardial infarct death (HR, 2.15 [95% CI, 1.35-3.41]), heart failure (HR, 1.43 [95% CI, 1.13-1.82]), and diabetes mellitus (HR, 1.42 [95% CI, 1.13-1.78]).

- Isolated **diastolic** hypertension was associated with increased risk of ischemic heart disease (HR, 1.26 [95% CI, 1.05-1.50]).

Circulation, Feb 2013
Elevated blood pressure in pregnancy and subsequent chronic disease risk.

CONCLUSIONS:

• Hypertension during pregnancy was associated with increased risk of subsequent cardiovascular disease and arterial hypertension.

• Women with chronic hypertension and superimposed preeclampsia/eclampsia had high risk for future diseases.

• Elevated blood pressure during pregnancy, regardless of type and even without known risk factors, signals high risk of 1) later cardiovascular disease, 2) chronic kidney disease, and 3) diabetes mellitus.

• Clinical monitoring, risk factor evaluation, and early intervention could benefit women with hypertension in pregnancy.
Stroke Prevention in Women

- Preeclampsia occurs in approximately 5% of pregnancies.

- A history of preeclampsia is associated with a 2-fold risk for stroke and a 4-fold risk for hypertension later in life.

- During pregnancy:
  - Consider treating women with a systolic blood pressure between 150 and 159 mm Hg or a diastolic blood pressure between 100 and 109 mm Hg of new onset during pregnancy (class IIa; level of evidence B).

  - Treatment of mild to moderately elevated blood pressure in pregnancy is associated with a 50% reduction in risk for severe hypertension (relative risk, 0.5 [CI, 0.41 to 0.61]).

- **After pregnancy:**
  - All women with a history of preeclampsia would probably benefit from lifestyle change and early assessment of cardiovascular risk and interventions.
Gestational diabetes mellitus and later cardiovascular disease

Objective: To identify if gestational diabetes mellitus (GDM) is a clinically useful marker of future cardiovascular disease (CVD) risk & if GDM combined with other risks (smoking, hypertension or body mass) identifies high-risk groups.

Design: Population-based case–control study of 2,639 women from the National Swedish register data from 1991-2008 with a cardiovascular event

Main outcome measures: Inpatient diagnoses or causes of death identifying 1) ischemic heart disease, 2) ischemic stroke, 3) atherosclerosis or 4) peripheral vascular disease.
Gestational diabetes mellitus and later cardiovascular disease

Methods

• Conditional logistic regression to examine associations with CVD before and after adjustment for conventional risk factors and confounders.

• Effect modification for the association of GDM with CVD by body mass index (BMI), smoking and chronic hypertension was assessed by stratification and interaction testing.

• Adjustment for diabetes post-pregnancy evaluated its mediating role.

Results

• The adjusted odds ratios for the association of CVD are:
  • GDM is 1.51 (1.07–2.14)
  • Smoking is 2.23 (2.01–2.48)
  • Obesity is 1.98 (1.71–2.29)
  • Chronic HTN is 5.10 (3.18–8.18)
## Gestational diabetes mellitus and later cardiovascular disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n = 2,639)</th>
<th>Controls (n = 13,310)</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No GDM</td>
<td>2577 (97.6)</td>
<td>13162 (98.9)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>+ GDM</td>
<td>62 (2.4)</td>
<td>148 (1.1)</td>
<td><strong>1.51</strong> (1.07–2.14)</td>
<td><strong>0.019</strong></td>
</tr>
<tr>
<td>No Chronic HTN</td>
<td>2584 (97.9)</td>
<td>13265 (99.7)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>+ Chronic HTN</td>
<td>55 (2.1)</td>
<td>45 (0.3)</td>
<td><strong>5.10</strong> (3.18–8.18)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5–24</td>
<td>1470 (55.7)</td>
<td>8942 (67.2)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td><strong>Overweight</strong>: 25-29</td>
<td>686 (26.0)</td>
<td>2981 (22.4)</td>
<td><strong>1.34</strong> (1.21–1.50)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>Obese</strong>: &gt;30</td>
<td>421 (16.0)</td>
<td>1051 (7.9)</td>
<td><strong>2.01</strong> (1.74–2.33)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>No smoking</td>
<td>1708 (64.7)</td>
<td>10898 (81.9)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>+ Smoking</td>
<td>931 (35.3)</td>
<td>2412 (18.1)</td>
<td><strong>2.23</strong> (2.01–2.48)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
</tbody>
</table>

OR is adjusted for GDM, chronic HTN, smoking, BMI.

British Journal of Obstetrics & Gynecology, Nov 2014
Gestational diabetes mellitus and later cardiovascular disease

Results, cont.
• In stratified analysis the association of CVD with GDM was only seen among women with BMI ≥25 and <30, with an odds ratio of 2.39 (1.39–4.10)

• Adjustment for post-pregnancy diabetes attenuated the OR to 1.99 (1.13–3.52).

Conclusions
• In the absence of other recognized cardiovascular risk factors, such as smoking, obesity or chronic hypertension, GDM is a useful marker of raised CVD risk among women with BMI between 25 and 29 (overweight).
Gestational diabetes mellitus is a significant risk factor for long-term maternal renal disease

CONTEXT:
• GDM is an independent risk factor for recurrent long-term type 2 diabetes mellitus, cardiovascular morbidity, and vascular endothelial dysfunction.
• Data on the link between GDM and future long-term maternal renal disease are limited.

OBJECTIVE: investigate if GDM poses a risk for long-term maternal renal morbidity.

DESIGN/SETTING:
• Population-based non-interventional study at an academic medical center
• Compared the incidence of future renal morbidity in 97,968 women with prior singleton pregnancies with and without prior GDM
• Deliveries occurred during a 25-year period, with a mean follow-up of 11.2 years.

MAIN OUTCOME MEASURE: diagnosis of renal morbidities (hypertensive renal disease with or without renal failure, chronic renal failure, end-stage renal failure, or other renal morbidity)

J Clin Endocrinol Metab, April 2015
Gestational diabetes mellitus is a significant risk factor for long-term maternal renal disease

RESULTS:
- Of the study population, 9542 (9.7%) had at least 1 previous pregnancy with GDM.
- Women with GDM had higher rates of total renal morbidity (0.1% vs 0.2%, for no GDM and with GDM, respectively; odds ratio, 2.3, 95% confidence interval, 1.4-3.7; \( P < .001 \)).
- There is a significant dose-response association between the number of pregnancies with GDM and future risk for renal morbidity (0.1%, 0.2%, and 0.4% for no GDM, 1 episode of GDM, and 2 episodes of GDM, respectively; \( P < .001 \)).
- In a Cox proportional hazards model, adjusted for confounders, GDM was independently associated with future renal morbidity.

CONCLUSION:
- GDM is a significant risk factor for future maternal renal morbidity. The risk is more substantial for patients with recurrent episodes of GDM.
Based on her obstetric history of GDM and PIH, she is high risk for which diseases?

**Gestational Diabetes**
1. Hypertension
2. **Diabetes Mellitus**
3. Heart Failure
4. **Kidney Failure**
5. Stroke
6. **Coronary Artery Disease**
7. All of the above

**Hypertension in Pregnancy**
1. Hypertension
2. Diabetes Mellitus
3. Heart Failure
4. Kidney Failure
5. Stroke
6. Coronary Artery Disease
7. **All of the above**
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Following this presentation, participants will be able to:

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2. Teach patients and other clinicians the need for aggressive risk modification after GDM and PIH to avoid future chronic disease(s).

3. Initiate the most evidenced based initial management for patients with postpartum hyperglycemia and hypertension.
Cardiovascular disease risk is only elevated in hypertensive, formerly preeclamptic women

Objective:
• To analyze the predicted 10- and 30-year risk scores for cardiovascular disease (CVD) in patients who experienced preeclampsia (PE) 5–10 years previously vs healthy women.

Methods
• Observational study in a tertiary referral hospital in The Netherlands.

• There were 115 preeclampsia patients which were categorized into two groups, hypertensive \( (n = 21) \) and normotensive \( (n = 94) \), based on use of antihypertensive medication, and next categorized into subgroups based on the onset of preeclampsia: early-onset \( (n = 39) \), defined as preeclampsia before 34 weeks, versus late-onset PE \( (n = 76) \).

• The control group was 50 healthy parous controls who were between 25 and 45 years old, and had their first pregnancy 5–10 years earlier.

• All participants underwent cardiovascular risk screening 5–10 years after index pregnancy including BMI, BP, fasting glucose, insulin and lipid levels.

British Journal of Obstetrics and Gynecology, Aug 2014
Cardiovascular disease risk is only elevated in hypertensive, formerly preeclamptic women

Results

• Hypertensive versus normotensive women with history of preeclampsia had twice the CVD risk.

• Patients with history of early-onset preeclampsia clustered more often in the hypertensive group and showed significantly higher 10- and 30-year CVD risk estimates

<table>
<thead>
<tr>
<th></th>
<th>Controls (N=50)</th>
<th>Late Onset PE (N=39)</th>
<th>Early Onset PE (N=76)</th>
<th>P -Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 year Framingham risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>1.5%</td>
<td>3.1%</td>
<td></td>
<td>p &lt;0.01</td>
</tr>
<tr>
<td>Lipids</td>
<td>1.5%</td>
<td>1.3%</td>
<td>1.7%</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td>BMI</td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.7%</td>
<td>p 0.60</td>
</tr>
<tr>
<td>30 year Framingham risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>8.0%</td>
<td>19.0%</td>
<td></td>
<td>p &lt;0.01</td>
</tr>
<tr>
<td>Lipids</td>
<td>9.0%</td>
<td>7.0%</td>
<td>10.0%</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td>BMI</td>
<td>9.0%</td>
<td>8.0%</td>
<td>10.0%</td>
<td>p &lt;0.05</td>
</tr>
</tbody>
</table>

British Journal of Obstetrics and Gynecology, Aug 2014
Conclusions

• Women who are hypertensive after preeclampsia, have a twofold risk of developing CVD in the next 10–30 years.

• Women who are normotensive in the first 10 years after their preeclamptic pregnancy have a comparable future cardiovascular risk to healthy controls.

• Preventive strategies, early detection and corrective BP treatment towards healthy reference values reduces the risk of cardiovascular disease including heart failure, stroke, and renal disease.

• “We stress the importance of ongoing surveillance which at present we do not think is practiced consistently”
The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes

CONTEXT:
• In the Diabetes Prevention Program (DPP), intensive lifestyle (ILS) and metformin prevented or delayed diabetes in women with a history of GDM.

OBJECTIVE:
• Evaluate the impact of ILS and metformin intervention over 10 years in women with and without a history of GDM

DESIGN: This was a RCT conducted at 27 clinical centers with observational follow-up.

PARTICIPANTS:
• Three hundred fifty women with a history of GDM and 1,416 parous women with no history of GDM participated in the study.

• The participants had a BMI >24 kg/m² (for Asians, BMI >22 kg/m² qualified for entry) and impaired glucose tolerance with a FPG between 95-125 at study entry.
The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes

INTERVENTIONS: 1) placebo, 2) Intense lifestyle changes, or 3) metformin.

OUTCOMES MEASURE: diabetes mellitus.

RESULTS:
• Over 10 years, women with a history of GDM assigned to placebo had a 48% higher risk of developing diabetes compared with women without a history of GDM.

• In women with a history of GDM, ILS and metformin reduced progression to diabetes compared with placebo by 35% and 40%, respectively.

CONCLUSIONS:
• Women with a history of GDM are at an increased risk of developing diabetes.

• Both lifestyle and metformin were highly effective in reducing progression to diabetes during a 10-year follow-up period.
The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes

<table>
<thead>
<tr>
<th>Effect of DPP treatment on DM incidence</th>
<th>Hx GDM N = 350</th>
<th>Placebo N = 122</th>
<th>Metformin (850mg BID) N = 111</th>
<th>Intensive Lifestyle N = 117</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(number of cases per 100 person-years, age adjusted)</td>
<td>Yes (N = 122))</td>
<td>11.4</td>
<td></td>
<td></td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>No (N = 487)</td>
<td>6.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>(compared with placebo)</td>
<td>Yes (N = 111)</td>
<td><strong>6.8</strong></td>
<td>40.4</td>
<td>35.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No (N = 464)</td>
<td>6.7</td>
<td>3.3</td>
<td>29.7</td>
<td></td>
</tr>
<tr>
<td>Number Need to Treat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(to prevent one case in 10 yr compared with placebo)</td>
<td>Yes (N = 117)</td>
<td>7.6</td>
<td><strong>7.2</strong></td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No (N = 465)</td>
<td>4.7</td>
<td>48.8</td>
<td>9.9</td>
<td></td>
</tr>
</tbody>
</table>

Journal of Clinical Endocrinology & Metabolism, Apr 2015
Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus

BACKGROUND
- Obesity is associated with an increased risk of adverse pregnancy outcomes.
- **Lifestyle-intervention studies have not shown improved outcomes for obesity.**
- Metformin improves insulin sensitivity and in pregnant patients with GDM it leads to less weight gain than occurs in those who do not take metformin.

METHODS
- In this double-blind intention-to-treat RCT, we assigned pregnant women at 12 to 18 weeks gestation, without diabetes and who had a BMI >35 at study entrance to receive 3000mg daily metformin, or placebo (225 women in each group)

- The primary outcome was a reduction in the median neonatal birth-weight z score by 0.3 SD (equivalent to a 50% reduction, from 20% to 10%, in the incidence of LGA).

- **Secondary outcomes included maternal gestational weight gain and the incidence of GDM and preeclampsia,** as well as the incidence of adverse neonatal outcomes.

NEJM, Feb 2016
**RESULTS**

- A total of 50 women withdrew consent during the trial, which left 202 women in the metformin group and 198 in the placebo group.

- There was no significant between-group difference in the median neonatal birth-weight z score (0.05 in the metformin and 0.17 in the placebo group; P=0.66).

- The *median maternal gestational weight gain was lower in the metformin group* than in the placebo group (4.6 kg vs. 6.3 kg; P<0.001), *as was the incidence of preeclampsia* (3.0% vs. 11.3%; P=0.001).

- There were no significant between-group differences in the incidence of gestational diabetes, large-for-gestational-age neonates, or adverse neonatal outcomes.

**CONCLUSIONS**

- Among women without diabetes who had a BMI of more than 35, the *antenatal administration of metformin reduced maternal weight gain* but not neonatal birth weight.

NEJM, Feb 2016
# Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus

## Table 2. Pregnancy Outcomes, According to Study Group.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metformin (N=202)</th>
<th>Placebo (N=198)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median weight gain (IQR) — kg</td>
<td>4.6 (1.3 to 7.2)</td>
<td>6.3 (2.9 to 9.2)</td>
<td>—</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational diabetes mellitus — no./total no. (%)</td>
<td>25/202 (12.4)</td>
<td>22/195 (11.3)</td>
<td>1.11 (0.60 to 2.04)</td>
<td>0.74</td>
</tr>
<tr>
<td>Preeclampsia — no./total no. (%)</td>
<td>6/202 (3.0)</td>
<td>22/195 (11.3)</td>
<td>0.24 (0.10 to 0.61)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension — no./total no. (%)</td>
<td>13/202 (6.4)</td>
<td>13/195 (6.7)</td>
<td>0.96 (0.43 to 2.13)</td>
<td>0.93</td>
</tr>
<tr>
<td>Delivery by cesarean section — no./total no. (%)</td>
<td>80/202 (39.6)</td>
<td>82/195 (42.1)</td>
<td>0.93 (0.62 to 1.38)</td>
<td>0.79</td>
</tr>
<tr>
<td>Postpartum hemorrhage — no./total no. (%)</td>
<td>19/202 (9.4)</td>
<td>16/195 (8.2)</td>
<td>1.16 (0.58 to 2.33)</td>
<td>0.67</td>
</tr>
</tbody>
</table>
Objectives

Following this presentation, participants will be able to:

1. Recognize the negative impact of gestational diabetes mellitus (GDM) and pregnancy induced hypertension (PIH) on future maternal health.

2. Teach patients and other clinicians the need for aggressive risk modification after GDM and PIH to avoid future chronic disease(s).

3. Initiate the most evidenced based initial management for patients with postpartum hyperglycemia and hypertension.
POSTPARTUM HYPERTENSION
Medications

- Oral nifedipine improves renal blood flow with resultant diuresis, which makes it the drug of choice for postpartum volume overload.

- Diuretics may also be needed in women with volume overload, particularly women with pulmonary edema.

- An angiotensin-converting-enzyme (ACE) inhibitor (with contraception!) should be started for all diabetics.

- Spironolactone (with contraception!) pairs well with diuretics to avoid iatrogenic hypokalemia.

- **Beta blockers are the 4th or 5th line therapy for hypertension.**
Breastfeeding

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium channel antagonists:</strong></td>
<td></td>
</tr>
<tr>
<td>Nifedipine (Procardia)</td>
<td>10-20 mg twice daily</td>
</tr>
<tr>
<td>Nifedipine XL</td>
<td>30-60 mg once daily</td>
</tr>
<tr>
<td>Amlodipine (Norvasc)</td>
<td>5-10 mg once daily</td>
</tr>
<tr>
<td><strong>Angiotensin converting enzyme (ACE) inhibitors:</strong></td>
<td></td>
</tr>
<tr>
<td>Enalapril (Vasotec)</td>
<td>5-20 mg twice daily</td>
</tr>
<tr>
<td>Captopril</td>
<td>12.5 - 25mg three times daily</td>
</tr>
<tr>
<td><strong>α/β blockers:</strong></td>
<td></td>
</tr>
<tr>
<td>Labetalol (Trandate)</td>
<td>100-600 mg 2-3 times daily</td>
</tr>
<tr>
<td>Atenolol (Tenormin)</td>
<td>25-100 mg once daily</td>
</tr>
</tbody>
</table>

*Note:* agents with high protein binding and low lipid solubility are less likely to be transferred in breast milk.
Discharge Planning

• Goal blood pressure for a safe discharge is <150/90 in healthy women, <140/90 in women with chronic hypertension and <140/80 in women with and/or diabetes mellitus

• Instruct women to measure blood pressure at least once daily and report any symptoms until her next visit in 1 week.

• SAFETY: Teach women prior to discharge the appropriate ways to measure blood pressure to avoid 1) falsely elevated measurements and 2) continuation of unnecessary medications.
Outpatient follow-up

- Check renal function within one week for patients on diuretics and ACE inhibitors. Anticipate GFR increase up to 25% with an ACE.

- Antihypertensive medications are discontinued if the BP remains below the hypertensive levels for at least 48 hours.

- Blood pressure should be checked weekly for two weeks following medication cessation to confirm normal blood pressures.

- All women with any form of hypertension affecting pregnancy deserve a follow-up appointment to 1) confirm blood pressure normalization, 2) stop unnecessary medications, and 3) evaluate for etiologies of secondary hypertension in women <40 years.
Future Screening

• Women with history of hypertensive disorders in pregnancy, including preeclampsia, need annual monitoring of risk factors.

• Ideal timing varies but is not later than 1 year postpartum.

• Screening should include evaluation for risk factors including: BP, BMI, smoking, alcohol, sleep quality and activity level. Annual labs should include: glucose, creatinine, urinalysis, and lipids.

Clinical Science, Jan 2016
POSTPARTUM HYPERGLYCEMIA
NORMAL POSTPARUM GLUCOSE

- If **fasting glucose** postpartum is <100 (normal):
  - TEACH: the woman of her **elevated lifetime risk** for diabetes mellitus, heart disease and stroke
  - TEST in 6-12 weeks with postpartum screening
  - TREAT with increased physical activity and healthy nutrition.
Future Screening:

- Test women with history of GDM every 1-3 years if OGTT at 6-12w is normal
  - Frequency of screening is based on risk factors: family history, pre-pregnancy BMI, need for diabetic medications during pregnancy

- Ongoing screening may include A1c, FPG, OGTT using non-pregnancy values

- 1) Metformin and 2) intensive lifestyle changes prevent or delay progression to diabetes mellitus

American Diabetes Association, Jan 2016
**PREDIABETES**

- If **fasting glucose** postpartum is **100-125**, she has **prediabetes** – aka elevated fasting glucose or impaired glucose tolerance

  - TEACH the woman of her **elevated lifetime risk** for diabetes mellitus, heart disease and stroke

  - TEST in 12 weeks with postpartum screening including A1c

  - TREAT with intensive lifestyle changes and if A1c is 5.7%-6.4%, add metformin XL 750mg twice daily with meals

  - SCREEN annually thereafter for glucose abnormalities
DIABETES MELLITUS

• If fasting glucose postpartum is $>$126, repeat the test in 24 hours to confirm the diagnosis of diabetes mellitus

• TEACH the women of her elevated lifetime risk for heart disease, kidney disease and stroke

• TEST in 12 weeks with A1c only

• TREAT with intensive lifestyle changes including a diabetic diet, metformin XL 750mg twice daily with meals +/- other diabetic medications if A1c $>$8%

• SCREEN for nephropathy (microalbumin/creatinine ratio $>$30) and if present, start an ACEI (lisinopril 2.5mg qd if not breastfeeding)
Key Points

• GDM and PIH have a significant negative impact on future maternal health and are opportunities for intensified preventive medicine.

• All women with history of preeclampsia need annual evaluation within the first 6-12 months of delivery to optimize health

• Calcium channel blockers, diuretics and ACE inhibitors are first line therapy for hypertension and some are compatible with breastfeeding. Beta blockers are not first line therapy, even in breastfeeding.

• Women with a history of GDM should be treated metformin and/or intensive lifestyle changes to prevent development of diabetes

• Consider treatment with metformin in obese pregnant women to decrease weight gain and avoid preeclampsia.
Your next clinic patient…

- 42y G2P2002 who presents for her annual evaluation.

- Today her BP is 120/70 and her current weight is 185lbs (BMI of 28.6 kg/m²).

- Her prior obstetric history: gestational diabetes in both pregnancies, gestational hypertension in the second pregnancy only.

- She is asymptomatic.
Question 1

Based on her history of **gestational diabetes**, this patient is at increased risk of which of the following?

- Hyperlipidemia
- Stroke
- Hypertension
- Heart Failure
Question 1

Based on her history of gestational diabetes, this patient is at increased risk of which of the following?

- Hyperlipidemia
- Stroke
- Hypertension
- Heart Failure
Question 2

Based on her history of gestational hypertension, this patient is at increased risk of which of the following?

- Hyperlipidemia
- Obesity
- Prediabetes
- Heart Disease
Question 2

Based on her history of **gestational hypertension**, this patient is at increased risk of which of the following?

- Hyperlipidemia
- Obesity
- Prediabetes
- **Heart Disease**
Bibliography

- **American Diabetes Association Guidelines**, Jan 2016: Gestational Diabetes Mellitus Postpartum Follow-up


- **Circulation**, Feb 2012. Associations of Pregnancy Complications With Calculated Cardiovascular Disease Risk and Cardiovascular Risk Factors in Middle Age.


- **Journal of Clinical Endocrinology & Metabolism**, April 2015. Gestational diabetes mellitus is a significant risk factor for long-term maternal renal disease.


“Pregnancy …an opportunity to identify women at increased risk…allowing lifestyle changes and, if required, other interventions aimed at reducing that risk…earlier in the life course”