Pre-Conception Care for Women with Chronic Medical Conditions

“Doctor, can I get pregnant?”

Natalie Dayan MD MSc FRCPC
General Internal Medicine & Obstetrical Medicine
McGill University Health Centre
Canadian Society of Internal Medicine
Annual Meeting 2016

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Definition: A Conflict of Interest may occur in situations where the personal and professional interests of individuals may have actual, potential or apparent influence over their judgment and actions.

I have nothing to declare
Canadian Society of Internal Medicine
Annual Meeting 2016

Some of the drugs, devices, or treatment modalities mentioned in this presentation are:

- Labetalol
- Nifedipine
- Methyldopa
- Hydralazine
Outline

• Review rationale for preconception care in women with chronic diseases and role of the general internist

• Case – based approach
  – Maternal factors affect pregnancy health
  – Rational medication management
Objectives

• Provide counseling to women with common chronic medical conditions before pregnancy regarding disease-specific perinatal risks to both mother and foetus

• Discuss potential effects that pregnancy may have on progression of several chronic conditions

• Recommend and select non-pharmacological and pharmacological therapies for optimal pre-pregnancy health that are safe to continue in pregnancy
Rationale for preconception care in women with chronic disease

- Most *determinants* of pregnancy health are present before pregnancy
- *Severe maternal morbidity* is increasing in Canada
- Prenatal care is often *too late* to have an impact on determinants & outcomes
- *Health optimization* prior to pregnancy improves maternal and fetal outcomes
The Modern Maternal Profile

DETERMINANTS OF HEALTH

• ↑ age at conception
• ↑ maternal BMI
• ↑ cardiovascular comorbidities
• ↑ complex medical conditions
The Modern Maternal Profile

DETERMINANTS OF HEALTH

- ↑ age at conception
- ↑ maternal BMI
- ↑ cardiovascular comorbidities
- ↑ complex medical conditions

CONSEQUENCES FOR MOM & BABY

- ↑ Infertility & IVF use
- ↑ prematurity/low birth weight/
- c-section/congenital anomalies
- ↑ preeclampsia, GDM
- Long-term cardiovascular sequelae...

The Placenta
Severe Maternal Morbidity in Canada

**FIGURE 1:** Temporal trends (95% CI) in severe maternal morbidity, Canada (excluding Quebec), 2003/04-2010/11

- **SMM:**
  - Sepsis
  - PPH
  - Transfusion
  - DIC
  - ARDS
  - Eclampsia
  - End-organ failure

Source: Canadian Institute for Health Information, Discharge Abstract Database (DAD).
Notes: CI - Confidence Interval. The DAD does not include data from Quebec. Manitoba data, which were incomplete for earlier years, were included from 2004/05.

Severe Maternal Morbidity in Canada

Pre-conception determinants of health

FIGURE 1: Temporal trends (95% CI) in severe maternal morbidity, Canada (excluding Quebec), 2003/04-2010/11

SMM: Sepsis, PPH, transfusion, DIC, ARDS, Eclampsia, End-organ failure

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Impact of maternal health on fetal development
Impact of maternal health on fetal development
Impact of maternal health on fetal development

**Mean Entry into Prenatal Care**

<table>
<thead>
<tr>
<th>CRITICAL PERIODS OF DEVELOPMENT</th>
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Preconception care is effective

- **Folic acid** supplementation reduces neural tube defects
  NEJM 1992; 327:1832-1835

- **Treatment of HIV** reduces vertical transmission

- **Glycemic control** improves birth outcomes
  Obstet Gyneco 2005; 105: 675-685

- Achieving **healthy BMI** improves fertility and birth outcomes
  Hum Reprod 1998; 13(6): 1502-1505
Preconception care ≠ pre-conception visit

The Importance of Preconception Care in the Continuum of Women’s Health Care

ABSTRACT: The goal of preconception care is to reduce the risk of adverse health effects for the woman, fetus, or neonate by optimizing the woman’s health and knowledge before planning and conceiving a pregnancy. Because reproductive capacity spans almost four decades for most women, optimizing women’s health before and between pregnancies is an ongoing process that requires access to and the full participation of all segments of the health care system.

- Undiagnosed, untreated, or poorly controlled medical conditions
- Immunization history
- Medication and radiation exposure in early pregnancy
- Nutritional issues
- Family history and genetic risk
- Tobacco and substance use and other high-risk behaviors
- Occupational and environmental exposures
- Social issues
- Mental health issues
Preconception care ≠ pre-conception visit

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- Occupational and environmental exposures
- Social issues
- Mental health issues

**3 GOALS:**
- MANAGE CONDITION
- PROVIDE PROTECTION
- AVOID TERATOGEN

www.acog.org
Who should be providing pre-conception care?

• **Role of general practitioner:**
  – Address reproductive issues throughout a woman’s life

• **Role of general internist/medical specialist:**
  – Intervene at critical periods
Who should be providing pre-conception care?

- **Role of general practitioner:**
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[Diagram showing the timeline of reproductive stages: Menarche, Contraception and family planning, Fertility issues, Pregnancy complication, Post-pregnancy care, Peri-menopause]
The role of the general internist is increasing as the maternal medical profile is becoming more complex.
Pre-conception cases
Case 1: Chronic hypertension & advanced maternal age

- 45F GoPo Haitian origin with “primary infertility”
- Sent for medical optimization prior to in vitro fertilization
- Htn diagnosed 5 years ago – was on “combination pill” but stopped as wanted to conceive
- Gets influenza vaccine annually through CLSC
- Currently: takes folic acid 1 mg, no NSAIDs or other OTCs
- Good exercise tolerance, asymptomatic
Case 1

- O/E 180/100 (= both arms, confirmed on repeat)
- BMI 27 kg/m²
- Exam unremarkable
- Labs:
  - TSH normal, Testosterone normal
  - Fasting glucose 5.5, HbA1c 6.1%, 75-g OGTT normal, LDL 3.0, TG ok
  - Creat 80, normal K, serum calcium normal
  - UA bland, no microalbuminuria
  - EKG – borderline LVH
1. Manage/optimize chronic conditions

2. Provide protection (immunization/folic acid/ASA/contraception)

3. Avoid harmful exposures (smoking, teratogens)
Evidence-based preconception management of hypertension

Women of reproductive age with chronic hypertension should be counseled about the risks associated with hypertension during pregnancy for both the woman and her offspring and the possible need to change the antihypertensive regimen when she is planning a pregnancy.

Strength of evidence: A
Quality of evidence: II-2
ACOG 2008 & 2013

Preconception counseling for women with pre-existing hypertension is recommended.

Strength of recommendation: C
Quality of evidence: III
SOGC 2014
Chronic hypertension & pregnancy outcomes

Affects 2-5% of pregnancies and is rising

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No of studies</th>
<th>Estimated incidence (%) (95% CI)</th>
<th>Prediction intervals (95%)</th>
<th>Heterogeneity $\tau^2$</th>
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<tbody>
<tr>
<td>Superimposed pre-eclampsia</td>
<td>38</td>
<td>25.9 (21.0 to 31.5)</td>
<td>5.5 to 67.2</td>
<td>0.766</td>
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<tr>
<td>Caesarean section</td>
<td>27</td>
<td>41.4 (35.5 to 47.7)</td>
<td>15.5 to 73.2</td>
<td>0.413</td>
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<tr>
<td>Pre-term delivery (&lt;37 weeks)</td>
<td>30</td>
<td>28.1 (22.6 to 34.4)</td>
<td>6.8 to 67.6</td>
<td>0.286</td>
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<tr>
<td>Birth weight &lt;2500 g</td>
<td>14</td>
<td>16.9 (13.1 to 21.5)</td>
<td>5.7 to 40.6</td>
<td>0.286</td>
</tr>
<tr>
<td>Neonatal intensive care</td>
<td>16</td>
<td>20.5 (15.7 to 26.4)</td>
<td>5.9 to 51.3</td>
<td>0.403</td>
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<tr>
<td>Perinatal death</td>
<td>27</td>
<td>4.0 (2.9 to 5.4)</td>
<td>0.9 to 16.4</td>
<td>0.544</td>
</tr>
</tbody>
</table>

95% prediction intervals show uncertainty of range of possible incidence percentages for new study population, whereas 95% confidence intervals show uncertainty about estimate of average percentage incidence across study populations.
Chronic hypertension & pregnancy outcomes

We don’t know if BP control PRIOR to pregnancy improves these outcomes. BP control DURING pregnancy does not seem to affect these outcomes other than incident MATERNAL HYPERTENSION.

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95% prediction intervals show uncertainty of range of possible incidence percentages for new study population, whereas 95% confidence intervals show uncertainty about estimate of average percentage incidence across study populations.
Evidence-based preconception management of hypertension

- What should the BP target be?
  - Pre-pregnancy: CHEP guidelines (140/90 mmHg)
  - During pregnancy: SOGC guidelines (target BP range: 130-155/80-105)

www.hypertension.ca
Magee JOGC 2014
Multicentre open-label randomized clinical trial
987 women, ~75% with pre-existing hypertension

Less-tight control:
Target diastolic 100 mmHg

Tight control:
Target diastolic 85 mmHg

Primary outcome: composite of pregnancy loss or high-level neonatal care
Table 2. Primary and Other Perinatal Outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Less-Tight Control (N = 493)</th>
<th>Tight Control (N = 488)</th>
<th>Adjusted Odds Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome — no. (%)</td>
<td>155 (31.4)</td>
<td>150 (30.7)</td>
<td>1.02 (0.77–1.35)</td>
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<td>Pregnancy loss — no. (%)</td>
<td>15 (3.0)</td>
<td>13 (2.7)</td>
<td>1.14 (0.53–2.45)</td>
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<td>Miscarriage</td>
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<td>1 (0.2)</td>
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<tr>
<td>Ectopic pregnancy</td>
<td>0</td>
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<tr>
<td>Elective termination‡</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
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<tr>
<td>Perinatal death</td>
<td>14 (2.8)</td>
<td>11 (2.3)</td>
<td>1.25 (0.56–2.81)</td>
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<tr>
<td>Stillbirth</td>
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<td>7 (1.4)</td>
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<tr>
<td>Neonatal death</td>
<td>2 (0.4)</td>
<td>4 (0.8)</td>
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<tr>
<td>High-level neonatal care for &gt;48 hr — no./total no. (%)§</td>
<td>141/480 (29.4)</td>
<td>139/479 (29.0)</td>
<td>1.00 (0.75–1.33)</td>
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<tr>
<td>Gestational age at delivery — wk</td>
<td>36.8±3.4</td>
<td>37.2±3.1</td>
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<tr>
<td>Small-for-gestational-age newborns — no./total no. (%)¶</td>
<td>79/491 (16.1)</td>
<td>96/488 (19.7)</td>
<td>0.78 (0.56–1.08)</td>
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<tr>
<td>Birth weight &lt; 10th percentile</td>
<td>23/491 (4.7)</td>
<td>26/488 (5.3)</td>
<td>0.92 (0.51–1.63)</td>
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</table>

Table 3. Secondary and Other Maternal Outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Less-Tight Control (N = 493)</th>
<th>Tight Control (N = 488)</th>
<th>Adjusted Odds Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory complications — no./total no. (%)</td>
<td>82/480 (17.1)</td>
<td>67/479 (14.0)</td>
<td>1.19 (0.83–1.71)</td>
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<tr>
<td>Administration of oxygen beyond the first 10 min of life</td>
<td>34/479 (7.1)</td>
<td>25/477 (5.2)</td>
<td>1.24 (0.72–2.14)</td>
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<tr>
<td>Ventilatory support (with or without intubation) beyond the first 10 min of life</td>
<td>35/478 (7.3)</td>
<td>38/479 (7.9)</td>
<td>0.86 (0.53–1.40)</td>
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<tr>
<td>Use of surfactant</td>
<td>28/480 (5.8)</td>
<td>26/479 (5.4)</td>
<td>0.97 (0.55–1.69)</td>
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<tr>
<td>At least one serious neonatal complication — no./total no. (%)</td>
<td>40/480 (8.3)</td>
<td>40/479 (8.4)</td>
<td>0.96 (0.60–1.52)</td>
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<td>Serum creatinine level &gt; 2.3 mg/dl</td>
<td>0</td>
<td>1/488 (0.2)</td>
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<td>Severe hypertension — no. (%)</td>
<td>200 (40.6)</td>
<td>134 (27.5)</td>
<td>1.80 (1.34–2.38)</td>
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<tr>
<td>Preecclampsia — no./total no. (%)</td>
<td>241/493 (48.9)</td>
<td>225/488 (45.7)</td>
<td>1.14 (0.88–1.47)</td>
</tr>
<tr>
<td>Defined only by new proteinuria¶</td>
<td>148/493 (30.0)</td>
<td>132/488 (27.0)</td>
<td>1.08 (0.74–1.59)</td>
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<tr>
<td>At least one symptom of preecclampsia</td>
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<td>171/493 (34.7)</td>
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</table>

**Table legenda:**
- †: Adjusted for maternal age, parity, smoking, and mode of delivery.
- ‡: Includes women with first-trimester versus second- or third-trimester onset.
- §: Includes women with no versus any preterm delivery.
- ¶: Includes women with no versus any PROM.

 Magee NEJM 2015
BOTTOM LINE: NO DIFFERENCE IN PRIMARY OUTCOME MORE SEVERE MATERNAL HTN IN LESS TIGHT GROUP EVIDENCE TO CONTINUE “TIGHT” BP CONTROL IN PREGNANCY
1. Manage/optimize chronic conditions

2. Provide protection (immunization/folic acid/ASA/contraception)

3. Avoid harmful exposures (smoking, teratogens)
Delay pregnancy/IVF until BP control

- Use contraceptive method that does not contain estrogen
ASA to prevent preeclampsia

Annals of Internal Medicine

LOW-DOSE ASPIRIN USE FOR THE PREVENTION OF MORBIDITY AND MORTALITY FROM PREECLAMPSIA
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

<table>
<thead>
<tr>
<th>Population</th>
<th>Asymptomatic pregnant women who are at high risk for preeclampsia</th>
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<tbody>
<tr>
<td>Recommendation</td>
<td>Prescribe low-dose (81 mg/d) aspirin after 12 weeks of gestation.</td>
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Table. Clinical Risk Assessment for Preeclampsia*

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Risk Factors</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>High†</td>
<td>History of preeclampsia, especially when accompanied by an adverse outcome</td>
<td>Recommend low-dose aspirin if the patient has ≥1 of these high-risk factors</td>
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<td>Multifetal gestation</td>
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<td>Chronic hypertension</td>
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<td>Type 1 or 2 diabetes</td>
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<td>Renal disease</td>
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<td></td>
<td>Autoimmune disease (i.e., systemic lupus erythematosus, the antiphospholipid syndrome)</td>
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<tr>
<td>Moderate‡</td>
<td>Nulliparity</td>
<td>Consider low-dose aspirin if the patient has several of these moderate-risk factors§</td>
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<td>Obesity (body mass index &gt;30 kg/m²)</td>
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<td>Family history of preeclampsia (mother or sister)</td>
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<td></td>
<td>Sociodemographic characteristics (African American race, low socioeconomic status)</td>
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<tr>
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<td>Age ≥35 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Personal history factors (e.g., low birthweight or small for gestational age, previous adverse pregnancy outcome, &gt;10-y pregnancy interval)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Previous uncomplicated full-term delivery</td>
<td>Do not recommend low-dose aspirin</td>
</tr>
</tbody>
</table>

Up to 25% risk reduction in PET in high-risk individuals
Acts to reduce microthrombi in decidual vessels and counteract ED?  

Ann Int Med 2014
Dietary/supplemental calcium

Society of Obstetricians and Gynecologists of Canada (SOGC):

47. Low-dose acetylsalicylic acid and calcium supplementation (of at least 1 g/d) for women with low calcium intake are recommended for prevention of preeclampsia in women at high risk. (I-A)
1. Provide protection (immunization/folic acid/ASA/contraception)

2. Manage chronic conditions

3. Avoid harmful exposures (smoking, teratogens)
Safe pharmacological treatment of hypertension in pregnancy

For women of reproductive age with chronic hypertension, the use of ACE inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists is not recommended unless there is a compelling reason, such as the presence of proteinuric renal disease.

Quality of evidence: Low
Strength of recommendation: Qualified

112. The following antihypertensive drugs are all acceptable for use in the first trimester of pregnancy: methyldopa, labetalol, and nifedipine. (II-2B)

113. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be discontinued when planning pregnancy or as soon as pregnancy is diagnosed. (II-2D)

114. Atenolol should be discontinued when pregnancy is diagnosed. (I-D)

115. Planned changes in antihypertensive agent(s) for care in pregnancy should be made while the woman is planning pregnancy if the woman has uncomplicated pre-existing hypertension, or, if in the presence of comorbid conditions, she is likely to conceive easily (within 12 months). (III-L)
Safe pharmacological treatment of hypertension in pregnancy

For women of reproductive age with chronic hypertension, the use of ACE inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists is not recommended unless there is a compelling reason, such as the presence of proteinuric renal disease.

Quality of evidence: Low
Strength of recommendation: Qualified

CAVEAT: ACE inhibitors cause FETOPATHY not EMBRYOPATHY and can be safely continued in those who need them up until + pregnancy test

112. The following antihypertensive drugs are all acceptable for use in the first trimester of pregnancy: methyldopa, labetalol, and nifedipine. (II-2B)

113. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be discontinued when planning pregnancy or as soon as pregnancy is diagnosed. (II-2D)

114. Atenolol should be discontinued when pregnancy is diagnosed. (I-D)

115. Planned changes in antihypertensive agent(s) for care in pregnancy should be made while the woman is planning pregnancy if the woman has uncomplicated pre-existing hypertension, or, if in the presence of comorbid conditions, she is likely to conceive easily (within 12 months). (III-L)
Safe Rx preconception → pregnancy

- **Avoid**: atenolol, ACE inhibitors/ARB
- **Caution**: diuretics
- **Non-pharm**: no salt avoidance in pregnancy, exercise is ok, avoid excessive gestational weight gain

**Table 8. Doses of the most commonly used agents for treatment of blood pressures 149 to 159/90 to 105 mmHg**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metyldopa</td>
<td>250 to 500 mg po bid-qid (max 2 g/d)</td>
<td>There is no evidence to support a loading dose of metyldopa.</td>
</tr>
<tr>
<td>Labetalol</td>
<td>100 to 400 mg po bid-tid (max 1200 mg/d)</td>
<td>Some experts recommend a starting dose of 200 mg po bid.</td>
</tr>
<tr>
<td>Nifedipine*</td>
<td>XL preparation (20 to 60 mg po OD, max 120 mg/d)</td>
<td>Ensure that the correct form of nifedipine has been prescribed so that the XL preparation is not confused with the capsules.</td>
</tr>
</tbody>
</table>

*The prolonged action nifedipine tablet is no longer available in Canada.
Safe Rx preconception ➔ pregnancy

- Decreased dose needed in T₁
- Dosing frequency increased in T₂-T₃

Magriples Am J Perinatology 2013
What about her age?

What about the effect of IVF?
Obstetric outcomes at advanced maternal age

<table>
<thead>
<tr>
<th>Complication</th>
<th>40 - 44 years (n=31,662) OR (95%)</th>
<th>≥ 45 years (n=1,205) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational diabetes</td>
<td>3.43 (3.04 – 3.86)</td>
<td>4.71 (2.87 – 7.73)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>3.29 (3.01 – 3.59)</td>
<td>6.38 (4.67 – 8.72)</td>
</tr>
<tr>
<td>Severe preeclampsia</td>
<td>2.40 (1.26 – 1.56)</td>
<td>1.86 (1.17 – 2.97)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>2.66 (2.58 – 2.73)</td>
<td>3.77 (3.33 – 4.26)</td>
</tr>
</tbody>
</table>

Reference group – age 20 - 29

Jacobbsen, Obstet Gynecol 2004
Severe maternal morbidity in assisted reproduction pregnancies – US data

SMM:
- Sepsis
- PPH
- transfusion
- DIC
- ARDS
- Eclampsia
- End-organ failure

Martin Obstet Gynecol 2016
Management - pre-IVF stress test
Management - pre-IVF stress test

Third-party Reproduction
Sperm, egg, and embryo donation and surrogacy

The female partner should have an evaluation of her uterine cavity with a hysterosalpingogram (HSG), sonohysterogram (SHG), or hysteroscopy. If the female recipient is over the age of 45 years, a more thorough evaluation with assessment of cardiac function, risk for pregnancy-induced hypertension, and gestational diabetes should be considered. A
Case 1 recommendations

• Achieve better BP control prior to conception
• Labetalol prescribed 200 BID with follow-up 2 weeks → increased and nifedipine XL added
• Target BP 140/90 – dose adjustments in T1
• Counsel on effects of age, IVF, htn
• Other: baseline PET labs, self-monitoring of BP, MFM referral, close monitoring and follow-up
Case 2: Woman with epilepsy

- 26 year old woman sent by GP for preconception medical assessment
- Epilepsy diagnosed as a child
- Wants to become pregnant in the next year
- Meds: valproic acid 500 mg
- Non-smoker, EtOH 2-5 drinks per week
- No seizures x 6 years
- No family history of NTDs or major congenital malformation
- O/E 110/60. Normal physical exam
- Basic bloodwork normal
1. Provide protection (immunization/folic acid/ASA/contraception)

2. Manage/optimize chronic conditions

3. Avoid harmful exposures (smoking, teratogens)
Delay pregnancy since the patient is taking a teratogen

- Note: interactions between combined hormonal contraception and AEDs metabolized in liver:
  - Topiramate
  - Carbamazepine
  - Phenytoin

*Crawford, CNS Drugs 2002*
High dose folic acid

- Women with epilepsy have risk of congenital malformations (NTDs>others) 2-3X general population (2-5%)
- Folic acid should be started preconception


4. Botto LD, Khoury M, Mulinare J, Erickson JD. Periconceptional

5. Women in intermediate- to high-risk categories for NTDs (NTD-affected previous pregnancy, family history, insulin-dependent diabetes, epilepsy treatment with valproic acid or carbamazepine) should be advised that high-dose folic acid (4.0 mg–5.0 mg daily) supplementation is recommended. This should be taken as folic acid alone, not in a multivitamin format, due to risk of excessive intake of other vitamins such as vitamin A. (I-A)
High-dose folic acid

Table 2: Serum folate concentrations after increases in folic acid intake in younger women according to background serum folate and the predicted reduction in neural tube defect risk.
1. Provide protection (immunization/folic acid/ASA/contraception)

2. Manage/optimize chronic conditions

3. Avoid harmful exposures (smoking, teratogens)
Evidence-based preconception management of epilepsy

- Shared elements in general management and preconception management:
  - Ensure good seizure control with least amount of medication at the lowest dose
  - Monotherapy if possible
  - Avoid seizure triggers
  - Avoid abrupt discontinuation of medications

- The majority (90%) of women with epilepsy will have a normal pregnancy
- Being seizure free within the last year predicts a seizure-free pregnancy
- Postpartum may be a time of increased frequency of seizures

AJOG 2008
Effect of epilepsy on perinatal outcomes?

- Slight increased risk of miscarriage, antepartum/postpartum hemorrhage, C-section, HDP
- Risk most pronounced in AED vs no AED, and according to number of AEDs

Viale Lancet 2015
AED withdrawal?

- Should be attempted 6-12 months prior to conception since up to 30% have seizure recurrence after AED withdrawal within this period ¹

- Optimal candidate:
  - Normalized EEG
  - No cerebral dysfunction
  - Normal brain imaging
  - No seizure in 2-4 years on AED

¹ Chadwick, Recent Advances in Epilepsy 1985
“Safe” pharmacological options for epilepsy in pregnancy

- All AEDs are associated with NTDs
- AED registry [www.massgen.org/aed](http://www.massgen.org/aed)
- Valproic acid appears most harmful

Table 2. Overall frequencies (%) of major congenital malformations (malformed/exposed) for different monotherapies

<table>
<thead>
<tr>
<th>Source</th>
<th>Valproate</th>
<th>Carbamazepine</th>
<th>Lamotrigine</th>
<th>Phenobarbital</th>
<th>Phenytoin</th>
<th>Levetiracetam</th>
<th>Oxcarbazepine</th>
<th>Topiramate</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURAP⁴</td>
<td>9.7% (98/1,010)</td>
<td>5.6% (79/1,402)</td>
<td>2.9% (37/1,280)</td>
<td>7.4% (16/217)</td>
<td>5.8% (6/103)</td>
<td>1.6% (2/126)</td>
<td>3.3% (6/184)</td>
<td>6.8% (5/73)</td>
</tr>
<tr>
<td>NAAPR⁷</td>
<td>9.3% (30/332)</td>
<td>3.6% (11/1,033)</td>
<td>1.9% (31/1,562)</td>
<td>5.5% (11/199)</td>
<td>2.9% (12/416)</td>
<td>2.4% (11/450)</td>
<td>2.2% (4/182)</td>
<td>4.2% (15/359)</td>
</tr>
<tr>
<td>UKIr4⁸,¹¹</td>
<td>6.7% (82/1,220)</td>
<td>2.6% (43/1,657)</td>
<td>2.3% (49/2,098)</td>
<td>3.7% (3/82)</td>
<td>0.7% (2/304)</td>
<td>4.3% (3/70)</td>
<td>4.3% (3/70)</td>
<td>4.3% (3/70)</td>
</tr>
<tr>
<td>NMBR⁹</td>
<td>6.3% (21/333)</td>
<td>2.9% (20/685)</td>
<td>3.4% (28/833)</td>
<td>7.4% (2/27)</td>
<td>8.6% (8/119)</td>
<td>1.7% (2/118)</td>
<td>1.8% (1/57)</td>
<td>4.2% (4/248)</td>
</tr>
<tr>
<td>SMBr²</td>
<td>4.7% (29/619)</td>
<td>2.9% (38/1,430)</td>
<td>2.9% (32/1,100)</td>
<td>6.7% (8/119)</td>
<td>(0/61)</td>
<td>3.7% (1/27)</td>
<td>7.7% (4/52)</td>
<td>7.7% (4/52)</td>
</tr>
</tbody>
</table>

Data from different prospective registers: EURAP, European and International Registry of Antiepileptic Drugs in Pregnancy; NAAPR, North American Antiepileptic Drug and Pregnancy Registry; UKIr4, UK and Irish Epilepsy and Pregnancy Registers; Medical Birth Registry of Norway; SMBr, Swedish Medical Birth Register.

¹⁰As reported in.¹⁰
Case 2 recommendations

- If acceptable to patient, delay conception 6-12 months
- Start high dose folic acid
- Use barrier contraception
- Review old imaging/EEGs in conjunction with neurology and trial off AED
- If seizure recurs, start other AED
Summary

Preconception care...

• Is a longitudinal process
• Can ensure a safer pregnancy
• Role for general internists/medical specialists is increasing
Summary

Management of common chronic conditions such as hypertension & epilepsy requires knowledge about:

• Disease-specific risks in pregnancy
• Effect of pregnancy on disease progression
• Safety of available Rx
• Use of preventive treatments
Preconception Health Care Tool

Preconception Health Care involves identifying potential physical, genetic, psychosocial, environmental, and behavioral risk factors for adverse pregnancy outcomes, and reducing those risks prior to conception through counseling, education, and intervention. Preconception Health Care focuses on health promotion and illness prevention for everyone of reproductive age. It is an important opportunity for primary care providers to improve maternal and infant outcomes, as the critical period for fetal development often occurs before prenatal care begins. Each of the preconception topics below should be addressed with every individual of reproductive age on an ongoing basis.

### Prevent & Promote

<table>
<thead>
<tr>
<th>Reproductive Life Plan: Ask all individuals of reproductive age, &quot;Would you like to have a child in the next year?&quot; Encourage all individuals to make a Reproductive Life Plan.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
</tr>
<tr>
<td>Not sure</td>
</tr>
<tr>
<td>Inform women of reproductive age that natural fertility and assisted reproductive technology success is significantly lower for women in their late 30s-40s.</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

### Screen

<table>
<thead>
<tr>
<th>Reproductive History: A detailed reproductive history should be obtained for all individuals.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravidity (G):</td>
</tr>
<tr>
<td>Full-term (T):</td>
</tr>
<tr>
<td>Details:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screen if High Risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia</td>
</tr>
<tr>
<td>Syphilis</td>
</tr>
<tr>
<td>Trichomonas</td>
</tr>
<tr>
<td>Gonorrhea</td>
</tr>
<tr>
<td>Genital Herpes (If lesions)</td>
</tr>
</tbody>
</table>

### Manage

<table>
<thead>
<tr>
<th>Manage (LMP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>If positive pregnancy test, discuss options for prenatal care and refer accordingly</td>
</tr>
</tbody>
</table>

| Provide appropriate referrals |
| Advise women with prior cesarean delivery to wait at least 18 months prior to conception |
| Recommended folate acid (mg) daily prior to conception and for 12 weeks after conception if positive history of neural tube defect |
| Recommend 18 and <59 month interpregnancy interval (IPI) |

### Sexual Health:

All individuals should be counselled about safer sexual practice.

### Chronic Medical Conditions: Optimize management for the following diseases, as suboptimal control or treatments can increase risk for adverse maternal and/or infant outcomes.

- **McDonald** should be consulted for the safety of any medications taken by patients with chronic conditions.
- **Asthma**: Delay conception until good control is achieved.
- **Cancer**: All individuals with cancer should be counselled regarding the potential effects of treatment on fertility and informed of options to preserve fertility, if desired, and referred appropriately.
- **Diabetes**: Increased risk of birth defects can be mitigated with good preconception glycemic control. Encourage conception for those without good control. Folic acid (4mg): daily prior to conception and for 12 weeks after conception. ACE inhibitors and statins are contraindicated. Estrogen-containing contraception options should be avoided for those with DM >20 years or target organ damage.
- **HIV**: Transmission risk to fetus is 2% with antiretroviral therapy. Efavirenz is contraindicated. Antiretroviral drugs may interfere with hormonal contraceptive methods. Refer to specialist.
- **Hypertension**: Increased risk for adverse fetal and maternal outcomes. Assess for target organ damage in those with long-standing hypertension. Alternatives to ACE are recommended in women of reproductive age. Avoid estrogen-containing contraception options for women with severe hypertension.
- **Infertility**: Counseling regarding options to achieve conception is recommended.
- **Macrocystic Disease**: Counselling women to delay conception until disease is in remission. Conception during active episode increases risk of miscarriage, premature delivery, stillbirth, or low birth weight.
- **Phenylketonuria**: Encourage maintenance of low phenylalanine level during preconception and especially prior to conception.
- **Renal Disease**: Optimal control prior to conception, including normal BP. Use alternative ICP medications if unable to control with specialist.
- **Seizure Disorders**: Discuss potential pregnancy outcomes related to seizures and seizure medications. Take leucine and folic acid daily prior to conception and for 12 weeks after conception. Lowest dose of one medication recommended, when possible. Valproic acid, lithium, and topiramate are contraindicated. Many antiepileptic medications may interfere with hormonal contraceptive methods.
- **Systemic Lupus Erythematosus, Rheumatoid Arthritis, and other Autoimmune Diseases**: Delay conception until good control is achieved. Discuss natural history of disease during/after pregnancy. Cyclophosphamide, Methotrexate, and Leflunomide are contraindicated. Avoid estrogen-containing contraception options in women with SLA and positive/unknown antiphospholipid antibody. Discuss use of aspirin and heparin with rheumatologist for women with SLE and antiphospholipid antibody syndrome.
- **Thromboembolic Disease**: Counsel women that risk for VTE during pregnancy and postpartum is increased, and many will require anticoagulation treatment. Coumadin is contraindicated. Avoid estrogen-containing contraceptive options.
- **Thyroid Disease**: Achieve euthyroid state prior to conception. Women with hyperthyroidism should increase their dose of levothyroxine by 10% or more as pregnancy nears. Radioactive iodine is contraindicated. Screen all women for CBC and TSH prior to conception.

### For more information regarding preconception chronic disease management, visit the Before, Between, & Beyond Pregnancy Preconception Care Clinical Toolkit.

### Medications:

- **Human teratogenic risk is unknown for the majority of medications. Use caution when prescribing for women of reproductive age. Consult Material.**
- **Screen for teratogenic medication use:**
  - Prescribed Medications
  - Over-the-Counter Medications
  - Complementary and Alternative Therapy (herbal, natural, weight loss, athletic supplements, etc.)
- **Potentially teratogenic medications should be changed to safer options. Women should be counselled not to stop prescribed medications without consulting with their provider.**
- **Renal impairment**: Avoid and delay starting for at least 2 weeks before conception and for 12 weeks after conception for women taking folic acid antagonists (e.g., methotrexate, sulfasalazine, and anticonvulsants).
ASA to prevent preeclampsia

Imbalance between vasodilators (prostaglandin) and vasoconstrictors (thromboxane) contributes to ED

→ ASA level of action

Magee JOGC 2014