Women who are pregnant, lactating, or of childbearing potential: overdue for inclusion in CV trials

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Relevant disclosures

• I serve on international committees that aim to increase representativeness in clinical trials

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Cardiovascular disease: a leading cause of death during pregnancy

• CVD is the leading cause of maternal mortality
  • Cardiomyopathy, HF, MI, and stroke account for > 33% of pregnancy-related deaths

• Burden of CVD during pregnancy is expected to increase
  • rising maternal age, earlier onset CVD, and increase in CV risk factors

• Pregnancy a period of hemodynamic changes, heightened CV risk

• ~32% of pregnant women with CVD use cardiovascular medications during their pregnancy

Collier, A Y & Molina, RL. Neoreviews. 2019; 20: e561–e574
CVD care during pregnancy and lactation is guided by low-quality evidence

- Most CV guideline recommendations in pregnancy and lactation informed by level C evidence
  - consensus of expert opinion, small studies, retrospective studies and/or registries

- 2018 ESC ‘Guidelines for the Management of Cardiovascular Disease During Pregnancy’ provides the most comprehensive recommendations
  - 90% of recommendations derived from level C Evidence

Sex-specific exclusion criteria are common in RCTs

- A systematic review of RCTs published in high-impact medical journals found that female biology was the basis of exclusion in 39% of trials, and that these sex-specific eligibility criteria were largely unjustified.

- In a review of 317 heart failure RCTs, 26% used sex-specific eligibility criteria and excluded women on the basis of existing pregnancy or childbearing potential - none provided a rationale for these exclusion criteria.
  - Independently associated (OR 2.1) with under-enrollment of women in the RCTs (PPR < 0.8)
  - Potential reasons
    - Time / testing for pregnancy
    - Conversations around intent / sexual activity / birth control / menopause

Sex-specific exclusion criteria were present in at least 81 of 317 (26%) HF RCTs 2000-2020

<table>
<thead>
<tr>
<th>Sex-related eligibility criteria reported in 81 RCTs</th>
<th>% of trials with exclusion criterion that under-enrolled females</th>
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<tbody>
<tr>
<td>Must not be pregnant (75% of trials)</td>
<td>83.6</td>
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<tr>
<td>Must be on a scientifically accepted method of contraception (43% trials)</td>
<td>83.0</td>
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<tr>
<td>Must not be lactating or nursing (32% trials)</td>
<td>69.2</td>
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<tr>
<td>Must be without childbearing potential based on surgical treatment (21% trials)</td>
<td>94.1</td>
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<tr>
<td>Must be confirmed post-menopausal (20% trials)</td>
<td>87.5</td>
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<tr>
<td>Must not have a desire to become pregnant during study period (10% trials)</td>
<td>75.0</td>
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<tr>
<td>Must not be of childbearing age (5% trials)</td>
<td>75.0</td>
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There are benefits of including pregnant and lactating women in cardiovascular RCTs

| Fetal Benefits | • Direct benefits of careful fetal monitoring  
|               | • Indirect benefits of careful maternal monitoring and care |

| Maternal Benefits | • Autonomy in providing informed consent to trial enrollment  
|                  | • Direct health benefits of careful monitoring and care |

| Societal Benefits | • Reliable estimates of treatment efficacy and safety  
|                  | • Improved understanding of pathologies and treatment for conditions that occur at greater frequencies in pregnancy  
|                  | • Improved fetal outcomes via evidence-based maternal care  
|                  | • Representative inclusion of women in cardiovascular trials  
|                  | • Reduction in disparities in cardiovascular care |

Unjustified exclusion from trial participation violates ethical principles

- Exclusion of women who are pregnant, lactating or of childbearing age from trials driven ‘protection by exclusion’ ideology
  - Aims to protect fetus >> mother from potential harm (lack of fetal consent)
  - Exclusion without justification violates
    - **Autonomy**
      - best preserved with informed discussion and consent
    - **Beneficence**
      - limited high-quality evidence regarding safety and efficacy, increasing susceptibility of harm
    - **Justice**
      - associated with under-enrollment of all women
      - pregnant and lactating women deprived of potentially beneficial therapies

Some exclusion criteria are justified

- Condition does not affect pregnant or lactating women
- Animal studies indicate biological likelihood of harm in humans
- Pre-clinical or clinical data demonstrate harm
- Intervention has known benefit or is clinically indicated
- Patient does not provide informed consent

Recommendations to increase representation of pregnant and lactating women in cardiovascular trials

Journals and funders
- Require justification for sex-specific exclusion criteria in grant applications and manuscript appendices
- Build capacity for and retain women trial leaders

Research institutes
- Include themes of health and research equity in research curricula
- Include maternal-fetal medicine specialists in trial committees
- Communicate information relevant to pregnant or lactating women
- Use justification schemes to guide selection of exclusion criteria
- Avoid combining pregnancy and lactation into a single exclusion criterion
- Avoid ‘childbearing years’ as an exclusion criterion

Research teams
Investigators
