Risk of Congenital Malformations With Statin Therapy During the First Trimester of Pregnancy

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Background

- Statins are the most common drugs to treat hyperlipidemia.
- Inhibits cholesterol biosynthesis
- Cholesterol is crucial in fetal development
- Statins have always been contraindicated in pregnancy\(^1\-^3\) (FDA Category X)
- Lipophilic statins higher risk with congenital malformation?\(^4\)

Background cont.

- Obesity/Cardiovascular risk factors are rising\(^5\)
- Half of pregnancies in United States are unintended\(^6\)
- Advanced Maternal Age increasing\(^7\)
- Some researchers believe that statins have a role in preventing preeclampsia\(^8\)
Methods

- An exhaustive literature search was conducted using MEDLINE-Ovid, CINAHL, Evidence-Based Medicine Reviews Multifile, and Web of Sciences databases. Keywords searched included statins, pregnancy, and congenital malformation. The search was further narrowed down to include only English-language articles and human studies published within the last ten years. Articles within a ten-year period that evaluated the possible congenital malformations of statin drugs in first trimester women were included. Meta-analyses, systematic review and case study articles were excluded. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group Guidelines was used to evaluate the quality of the remaining eligible articles.9


Methods

- Retrospective observational cohort study (Boston, MA, USA)
- Used Medicaid Analytic eXtract

Inclusion Demographics | Statins considered
--- | ---
- Age 12-55 | - Simvastatin
- Live born infants | - Lovastatin
- Filled statin at least twice during first trimester of pregnancy | - Fluvastatin
- | - Atorvastatin
- | - Cerivastatin
- | - Rosuvastatin

Primary outcome of malformation defined by:
- CNS malformations
- Eyes, ear, neck, face malformations
- Cardiac malformations
- Respiratory malformations
- Cleft palate/lip malformations
- Gastrointestinal malformations
- Genitourinary malformations
- Musculoskeletal malformations

Criteria of inclusion:
- Must have ICD-9 code on two or more separate days within first three months of life
Bateman et al\textsuperscript{10} cont.

**Covariates**

<table>
<thead>
<tr>
<th>Maternal demographics</th>
<th>Comorbid medical conditions</th>
<th>Obstetric characteristics</th>
<th>Drugs dispensed to mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at delivery</td>
<td>Pre-existing DM</td>
<td>Multiparity</td>
<td>Anti-HTN</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>Dyslipidemia</td>
<td>Multiple gestations</td>
<td>Oral DM</td>
</tr>
<tr>
<td>Geographic region</td>
<td>Pre-existing HTN</td>
<td></td>
<td>Other suspected teratogenic drugs</td>
</tr>
<tr>
<td>Year of delivery</td>
<td>Chronic renal dz</td>
<td></td>
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<tr>
<td></td>
<td>Obesity</td>
<td></td>
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<tr>
<td></td>
<td>ETOH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tobacco</td>
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<tr>
<td></td>
<td>Illicit drug use</td>
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<tr>
<td></td>
<td>Maternal age at delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maternal race/ethnicity</td>
<td></td>
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<tr>
<td></td>
<td>Maternal geographic region</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maternal year of delivery</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Results**

- Used Medicaid database which includes 886 996 pregnancies, 1 152 exposed to statins during first trimester
- 73 participants of 1 152 (6.34\%) had birth defects (statins)
- 31 416 of 885 844 (3.55\%) had birth defects (no statins)
- Adjusting for confounders such as Diabetes Mellitus II, a propensity stratified analysis score was calculated 1.07 (0.85 to 1.37)
- Found no significant differences between groups

Ofori et al (2007)\textsuperscript{11} methods

- Retrospective observational cohort study (Quebec, CAN)
- Used three population based registries called the Régie de l’Assurance Maladie du Québec (RAMQ) Med-Echo, and the fichier des événements démographiques du Québec between 01/1997 – 06/2003

<table>
<thead>
<tr>
<th>Inclusion Demographics</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 15-45</td>
<td>Filled category X drug</td>
</tr>
<tr>
<td>Live born infants</td>
<td></td>
</tr>
<tr>
<td>Filled a statin or</td>
<td></td>
</tr>
<tr>
<td>Fibrate/nicotinic acid at least once within the year before their pregnancy or within first trimester.</td>
<td></td>
</tr>
</tbody>
</table>
### Ofori et al 11 Methods cont.

<table>
<thead>
<tr>
<th>Statins included:</th>
<th>Fibrates/Nicotinic acid included:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Simvastatin</td>
<td>- Fenofibrate</td>
</tr>
<tr>
<td>- Lovastatin</td>
<td>- Bezafibrate</td>
</tr>
<tr>
<td>- Fluvastatin</td>
<td>- Gemfibrozil</td>
</tr>
<tr>
<td>- Rosuvastatin</td>
<td>- Nicotinic acid</td>
</tr>
<tr>
<td>- Pravastatin</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fill statins during first trimester</td>
<td>Fill fibrates/nicotinic acid during first trimester</td>
<td>Filled any of the three antilipaemic rx within 1 year to 1 month before pregnancy but not during pregnancy</td>
</tr>
</tbody>
</table>

### Ofori et al 11 cont. covariates

<table>
<thead>
<tr>
<th>Socio-demographic variables</th>
<th>Comorbid conditions within one year before or during pregnancy</th>
<th>Drugs dispensed to mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>Hyperthyroidism</td>
<td>Hyperthyroid Rx</td>
</tr>
<tr>
<td>Maternal status</td>
<td>Diabetes</td>
<td>Insulin</td>
</tr>
<tr>
<td>Years of education</td>
<td>Gestational diabetes</td>
<td>Oral hypoglycemic Rx</td>
</tr>
<tr>
<td>Insurance status</td>
<td>HTN</td>
<td></td>
</tr>
<tr>
<td>Number of hospitalizations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of ED visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of medical visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of OB/GYN visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of prenatal visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior pregnancies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Ofori et al 11 Results

Compared:
- statins (n = 64) (3 birth defects)  
  - (4.69%; 95% CI 1.00, 13.69); A:C OR = 0.36 (95% CI 0.06, 2.18)
- fibrates/nicotinic acid (n = 14) (3 birth defects)  
  - (21.43%; 95% CI 4.41, 62.07)
- antilipaemic therapy discontinued 1 year to 1 month prior to pregnancy (n = 67) (7 birth defects)  
  - (10.45%; 95% CI 4.19, 21.53); C:B OR = 1.74 (95% CI 0.27, 11.27)
- the live-birth congenital anomaly rate in the rest of their registry was 6.97% (95% CI 6.77, 7.17)
- No significant differences between groups
Winterfield et al (2012) methods

- Multicenter prospective observational study (Europe)
- Pregnant women (or their providers) who contacted one of 11 European Network of Teratology Information Services seeking advice about exposure to statins during pregnancy from 1990 – 2009.

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<th>Inclusion Demographics</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age 15-45</td>
<td>Filled a statin or fibrate within first trimester.</td>
</tr>
<tr>
<td>Filled category X drug</td>
<td></td>
</tr>
</tbody>
</table>

Inclusion Demographics
- Maternal age
- Tobacco use
- Alcohol consumption
- Medical history
- Obstetric history
- Medication exposure (timing in pregnancy, duration, dose, concomitant medication)

Exclusion criteria
- Pregnancy outcome
- Gestational age at delivery
- Birth weight
- Birth defects
- Neonatal complications

Winterfield et al methods cont.

Maternal Characteristics (collected during initial contact)
- Maternal age
- Tobacco use
- Alcohol consumption
- Medical history
- Obstetric history
- Medication exposure (timing in pregnancy, duration, dose, concomitant medication)

Birth Characteristics
- Pregnancy outcome
- Gestational age at delivery
- Birth weight
- Birth defects
- Neonatal complications

Winterfield et al Results

- Compared:
  - Statin group (n = 194) 8 with birth defects (3 in utero)
  - No Statin (n = 224) 6 with birth defects
  - (4.1% versus 2.7% odds ratio 1.5; 95% confidence interval 0.5-4.5, P = 0.43)

- Found no significant difference in the rate of major birth defects between statin-exposed pregnancies and the control group.
### Discussion

- **Strengths**
  - Bateman et al.\(^\text{10}\)
    - Large sample size
    - Very precise (compromises sensitivity by requiring two diagnoses for congenital anomalies and two prescription fillings for statins)
    - No recall bias
  - Ofori et al.\(^\text{11}\)
    - Used fibrates/nicotinic acid and women that had been previously exposed to statins but not during pregnancy (each group has similar age and comorbidities)
    - No recall bias
    - Accounted for more possible confounders
  - Winterfield et al.\(^\text{12}\)
    - Prospective study allowed for live follow-up for more accurate compliance, discontinuation and teratogenic diagnoses
    - Prospective study also allowed them to track and include non-live birth fetal malformations

### Discussion Cont.

- **Limitations**
  - Bateman et al.\(^\text{10}\)
    - Only included live births
    - Dosing not described
  - Ofori et al.\(^\text{11}\)
    - Small sample size
    - Only included live births
    - Difficult to detect compliance and discontinuation of statin
  - Winterfield et al.\(^\text{12}\)
    - Small sample size
    - Relied on self-reported data (questionnaires, telephone interviews) so confounders may have been underreported
Discussion Cont.

- Women in statin groups tend to have a higher incidence of diabetes mellitus, obesity, and advanced maternal age, all of which are associated with either miscarriage, perinatal complications, and congenital anomalies.

- Because the only ethical way to study statin exposure is by observing accidental exposure, a study with a large sample size that takes into account all covariates including in-utero malformations is important for precision.

**Table 1. Characteristics of Reviewed Studies**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Occupation</th>
<th>Inconsistency</th>
<th>Instructions</th>
<th>Fragility</th>
<th>Publication Bias</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanby et al. (2010)</td>
<td>Observational retrospective</td>
<td>Very serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None likely</td>
<td>Very low</td>
</tr>
<tr>
<td>Crain et al. (2010)</td>
<td>Observational retrospective</td>
<td>Serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None likely</td>
<td>Very low</td>
</tr>
<tr>
<td>Waterfield et al. (2010)</td>
<td>Observational prospective</td>
<td>Serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None likely</td>
<td>Very low</td>
</tr>
</tbody>
</table>

**Table Notes:**
- Adherence and severity are measured using the Jadad scale.
- Number of patients included in the study.
- Continency with in-utero disease, complications were not fully documented.

Conclusion

- Although most research in statin exposure during first trimester pregnancy seems to show no association, due to the statistical fragility of each study, there is not enough evidence to challenge the current recommendations to discontinue statin therapy during pregnancy.

- The current evidence can be used to reassure pregnant women with accidental exposure that birth defects are unlikely, which can prevent unnecessary elective terminations of pregnancy.

- Clinicians are urged to educate their patients on statins with using effective contraception and to avoid taking their statin if pregnancy is a possibility.
References


10. Alexander Hoffman

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THANK YOU!