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

Alexander E. Hoffman

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

Abstract

Background

Statins are the most common and effective drug used to treat hyperlipidemia. Based on animal studies showing potential teratogenic effects at high doses, statins are contraindicated in pregnancy due to concern that they would disrupt cholesterol biosynthesis for the fetus. This review evaluates the current evidence of harm caused by statins when taken within the first trimester of pregnancy.

Methods

An exhaustive literature search was conducted in June 2015 using MEDLINE-Ovid, CINAHL, Evidence-Based Medicine Reviews Multifile, and Web of Sciences databases. Keywords searched included statin, 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. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group Guidelines was used to evaluate the quality of the remaining eligible articles.

Results

Three articles met the inclusion criteria for this systematic review. One retrospective study looked at 886,996 completed pregnancies, 1,152 of which took a statin during their first trimester, and found no significant teratogenic effects from first trimester statin therapy. The second retrospective cohort study with 288 pregnant women found no significant teratogenic effects from first trimester statin therapy. The prospective observational study included 498 women found no significant teratogenic effects from first trimester statin therapy. All studies were rated as having low quality of evidence based on GRADE guidelines.

Conclusion

Statins may not be as harmful during pregnancy as the FDA’s class X designation advises, but there is not enough statistical strength to change the current recommendation of the discontinuation of statins during pregnancy. Additional research to evaluate the long-term effects of in utero exposure to statins is needed.

Keywords

Statin, pregnancy, congenital malformation

Degree Type

Capstone Project

Degree Name

Master of Science in Physician Assistant Studies

First Advisor

Brent Norris, PA-C, MS

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/583
Second Advisor
Annjanette Sommers, PA-C, MS

Keywords
statin, pregnancy, and congenital malformation

Subject Categories
Medicine and Health Sciences

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Risk of Congenital Malformations With Statin Therapy

During the First Trimester of Pregnancy

Alexander Hoffman

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 13th, 2016

Faculty Advisor: Brent Norris, PA-C, MS

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Alexander Hoffman, a native of Oakland, California, graduated with honors from San Diego State University with a Bachelor of Arts in Psychology. He got his Emergency Medical Technician certification and began working on an ambulance and volunteering at his local hospital, food bank and the Folsom Street Fairs. After graduating with a Masters of Science in Physician Assistant Studies, he wishes to return to Oakland so that he can utilize his wide scope of medical knowledge to continue to serve his community.
Abstract

Background
Statins are the most common and effective drug used to treat hyperlipidemia. Based on animal studies showing potential teratogenic effects at high doses, statins are contraindicated in pregnancy due to concern that they would disrupt cholesterol biosynthesis for the fetus. This review evaluates the current evidence of harm caused by statins when taken within the first trimester of pregnancy.

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Statins may not be as harmful during pregnancy as the FDA’s class X designation advises, but there is not enough statistical strength to change the current recommendation of the discontinuation of statins during pregnancy. Additional research to evaluate the long-term effects of in utero exposure to statins is needed.

Keywords
Statin, pregnancy, congenital malformation
Acknowledgements

To Sylvia He, my fiancée, thank you for deciding to move up here to be with me and support me both emotionally and financially. You make me happier than I have ever been. I love you and I could have never done this without you.

To my parents: I would have never known what a physician assistant was without the two of you. You guys gave me the both the idea and the push to become something great. Your confidence in me never once wavered. Thank you.
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Table I: Characteristics of Reviewed Studies
Table II: Summary of Finding

List of Abbreviations

DMII..............................................................Diabetes Mellitus Type 2
FDA..............................................................Federal Drug Administration
GRADE.........Grading of Recommendations Assessment, Development and Evaluation
HMG CoA......................Hydroxymethylglutaryl Coenzyme A
ICD..............................................................International Classification of Disease
RAMQ.................................Régie de l’Assurance Maladie du Québec
TIS..............................................................Teratology Information Service
Risk of Congenital Malformations With Statin Therapy During the First Trimester of Pregnancy

BACKGROUND

Hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors, also known as statins, are the most common drugs to treat hyperlipidemia. Because its mechanism of action is primarily to inhibit cholesterol biosynthesis, statins have always been contraindicated in pregnancy due to how crucial cholesterol becomes in fetal development. All case reports of statin-exposed pregnancies have been associated with lipophilic statins (e.g., lovastatin, simvastatin, atorvastatin, and cerivastatin), particularly lovastatin, which tend to cross the placenta more readily than hydrophilic statins (e.g., pravastatin, rosuvastatin, and fluvastatin). The theory is the high affinity for lipid environments will cause these particular statins to cross into extrahepatic tissues, including the embryo during pregnancy, thereby disrupting cholesterol biosynthesis. A study in 2005 with no control group based on spontaneous reporting to the United States Food and Drug Administration described 22 incidences of major birth (mostly neuromuscular deformities) defects after first-trimester lipophilic statin exposure. The authors hypothesized that lipophilic statins having higher incidences of teratogenicity is due to their role in the dysregulation of the cholesterol synthesis with the Sonic-Hedgehog gene expression. Hedgehog is a name given to a family of morphogens that require the covalent bonding of cholesterol for their functioning. The Hedgehog pathway, particularly the Sonic-Hedgehog signaling molecule, is thought to have a critical role in the development of the central nervous system, face, skeleton, musculature, and viscera. Other studies however continue to find no evidence of increased risk for fetal defects as well as any detectable pattern of birth defects among live births (n = 64).
Obesity rates continue to rise in all age groups. Cardiovascular risk factors, such as hyperlipidemia, diabetes, and hypertension have followed suit, increasing the amount of younger individuals to be started on a statin. Half of pregnancies in the United States are unintended and advanced maternal age continues to increase, leading to a larger overlap between pregnancy and statin therapy, which means a higher rate of accidental exposure to statins during pregnancy. A preclinical study suggests statins may be able to help prevent preeclampsia, a complication that can potentially lead to premature delivery of the fetus. With more women on statins becoming inadvertently pregnant and indications of statins possibly preventing preeclampsia, there is a need to explore the risks and benefits statins have in pregnancy.

METHODS

An exhaustive literature search was conducted in June 2015 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.
RESULTS

Preliminary results generated 31 articles. Three articles were selected after further screening of abstracts and titles to meet inclusion criteria. Retrospective cohort studies\textsuperscript{10,20} were used in two of the articles each using a large database to find women in their first trimester that had been exposed to statins. The third study\textsuperscript{21} was a prospective study of women who contacted, or whose physician contacted one of any of the 11 Teratology Information Services to seek advice about statin exposure in the first trimester of pregnancy. See Table I.

Bateman et al

This observational retrospective cohort study\textsuperscript{20} evaluated the risks of major congenital malformations as well as specific organ malformations in infants of mothers exposed to statins within the first trimester of pregnancy. Cohorts were constructed by drawing from Medicaid Analytic eXtract, a database that contains information on Medicaid beneficiaries, from 2000-2007. The primary outcome measured congenital malformations in the infant. Congenital malformations were defined as central nervous system malformations; organ specific malformations; eye, ear, neck, and face, malformations; cardiac malformations; respiratory malformations; cleft palate or lip malformations; genitourinary malformations; musculoskeletal malformations; or other malformations. A congenital malformation was used if there was one identified with ICD-9 diagnostic codes on two or more separate days within the first three months of life. Covariates such as maternal demographics (eg, age at delivery, race/ethnicity, geographic region, year of delivery), obstetric characteristics (ie, multiparity and multiple gestations), chronic comorbid medical conditions (defined as diabetes mellitus II, dyslipidemia, pre-
existing hypertension, chronic renal disease, obesity, alcohol use, tobacco use, or illicit drug use) were accounted for. A list of other prescription drugs were examined and those taking drugs known to cause teratogenesis were excluded. The primary cohort began with 886,996 pregnancies, then narrowed down to 1152 women who filled at least two statin prescriptions during their first trimester. There were 73 of the 1152 (6.34%) that had congenital malformations, compared to the control group having 31,416 of 885,844 (3.55%). Adjusting for pre-existing diabetes, the relative risk dropped from 1.79 (1.43 to 2.23) to 1.34 (1.07 to 1.68). Further adjustment for all potential confounders decreased the relative risk further to 1.04 (0.79 to 1.37) and for a propensity score stratified analysis to 1.07 (0.85 to 1.37). There was no significant association between statin use and congenital malformations.

**Ofori et al**

This observational retrospective cohort study consisted of 288 pregnant women screened through three population based registries called the Régie de l’Assurance Maladie du Québec (RAMQ) Med-Echo, and the fichier des événements démographiques du Québec using the following eligibility requirements: must be between 15 and 45 years old at first day of gestation, be insured with RAMQ’s drug plan for at least 12 months following gestation, and have filled a prescription for either a statin, fibrate, or nicotinic acid in the year before or during pregnancy. Eligible participants were grouped into women prescribed statins in their first trimester (group A = 153), women prescribed a fibrate/nicotinic acid in the first trimester (group B = 29), and women prescribed statins between 1 year and 1 month before conception but not during pregnancy (group C = 106). The study measured the rate of congenital anomalies in infants diagnosed within the
first 12 months of life. Socio-demographic variables including maternal age, marital status (alone vs. cohabiting), number of years of education achieved, insurance status (welfare beneficiary vs. adherent), place of residence (urban vs. rural), were all included. Markers for health status included number of hospitalizations and emergency department visits, medical visits, prenatal visits, and women who had previous pregnancies were identified. Relevant chronic comorbidities that cause secondary hyperlipidemia included hypothyroidism, diabetes in the year before the pregnancy, gestational diabetes, hypertension in the year before the pregnancy. Ofori et al.\textsuperscript{10} searched for these comorbidities using ICD-9 codes in the RAMQ/Med-Echo databases and the American Hospital Formulary Service to detect if they had filled prescription medications. Those who were on greater than two prescription medications other than statins or fibrates/nicotinic acid during pregnancy were examined to see whether the prescriptions were filled before and/or any length of time during pregnancy. Birth weights and premature births were accounted for due to an increased risk of premature infants to have congenital anomalies. Of those in group A (n = 153), using statins before and during their first trimester, 69 women (45%) had live births, 32 women (21%) had induced abortions, and 52 women (34%) had miscarriage/stillborn/unspecified abortion. Of those in Group B (n = 29), using fibrates/nicotinic acid before and during their first trimester, 15 women (52%) had live births, 4 women (14%) had induced abortions, and 10 women (34%) had miscarriage/stillborn/unspecified abortion. Of those in group C (n = 106), using statins only between 1 year and 1 month before pregnancy, 67 women (63%) had live births, 10 women (10%) had induced abortions, and 29 women (27%) had miscarriage/stillborn/unspecified abortion. These pregnancy outcomes are summarized in
Figure I. Searching for the baby’s name, mother’s name, family name, and date of birth of the mother and baby, Ofori et al\textsuperscript{10} was able to link 64 of the 67 of the live births from group A, 14 of the 15 in group B, and 67 of the 67 in group C in to their medication and pregnancy database. The rate of congenital anomalies for group A was 3/64 (4.69%; 95% CI 1.00, 13.69). The rate for group B was 3/14 (21.43%; 95% CI 4.41, 62.57) and group C 7/67 (10.45%; 95% CI 4.19, 21.53). By comparison, the live-birth congenital anomaly rate in the rest of their registry was 6.97% (95% CI 6.77, 7.17). Adjusted OR for congenital anomalies for group A was 0.79 (95% CI 0.10, 6.02) and for group C 1.74 (95% CI 0.27, 11.27), when compared with group B. The adjusted OR for group A was 0.36 (95% CI 0.06, 2.18), when compared with group C. Ofori et al\textsuperscript{10} found no significant differences in the overall incidence of congenital anomalies in those that filled statin prescriptions during their first trimester of pregnancy compared to those who filled fibrates/nicotinic acid during their first semester of pregnancy or those who had filled a statin prescription within a year to a month of conception but discontinued statin therapy during their pregnancy.\textsuperscript{10}

**Winterfield et al**

This prospective, controlled, observational study\textsuperscript{21} looked at pregnant women who contacted, or whose physicians contacted a Teratology Information Service (TIS) regarding statin exposure during their first trimester of pregnancy. There were 249 women who met the criteria and were included in the study. Standardized methods\textsuperscript{22} were used by each center to collect data on maternal characteristics such as age, tobacco use, alcohol consumption, medical and obstetric histories were recorded and a corresponding control group of 249 additional women with similar demographics was formed. The time
during the pregnancy a statin was started, the duration the statin was taken and the dosage were recorded. After the expected delivery date, follow up was conducted via telephone interview or mailed questionnaire to either the woman or her physician. The follow-up data included pregnancy outcome, gestational age at delivery, birth weight, birth defects, and neonatal period. Statin therapy was started before conception in 89% of the exposed group. Close to half (48%) continued statin therapy beyond five weeks gestation and 21% beyond the seventh week. Of the exposed group, 6% continued therapy beyond the first trimester. The amount of live birth infants in the statin group was 194, and the control group was 224. Though there were 5 total major birth defects in the statin group, 8 were recorded when three were found to have congenital malformations in utero before being lost or electively terminated. The control group had 6 of 224 infants with congenital malformations. The rate of birth defects was not statistically significant (4.1% versus 2.7% odds ratio 1.5; 95% confidence interval 0.5-4.5, P = 0.43).²¹

**DISCUSSION**

The increasing rate of obesity in the United States leading to more cardiac risk factors paired with half of pregnancies being unplanned has led to an increased number of pregnant women being exposed to a statin, a medication that is contraindicated in pregnancy (FDA Class X). Some argue to avoid statins completely in young women who are not using effective contraception because the possible inadvertent use during pregnancy.¹²,²³ The focus of this systematic review was to evaluate the risk of birth defects in statin therapy during first trimester pregnancy.

The results of all three studies¹⁰,²⁰-²¹ did not detect any significant teratogenic effects of statins after exposure during the first trimester of pregnancy (Table II). These
negative findings support several published reports that there is no indication of increased risk for major birth defects with statin therapy during pregnancy.\textsuperscript{8-12} Ofori et al\textsuperscript{10} reported three congenital malformations with women who filled lovastatin, simvastatin and atorvastatin prescriptions. Their results support the prevailing theory that lipophilic statins tend to have high teratogenicity.\textsuperscript{24} Bateman et al\textsuperscript{20} found that 66 of the 73 statin-exposed birth defects came from lipophilic statins. The results from Winterfield et al\textsuperscript{21} had a contrary finding, showing that hydrophilic statins pravastatin and rosvastatin had a higher association with birth defects. Winterfield et al,\textsuperscript{21} however, had no one in their study exposed to lovastatin, the lipophilic statin most infamous in literature for its hypothesized teratogenicity.

**Strengths**

Bateman et al\textsuperscript{20} used Medicaid Analytic eXtract, one of the largest and comprehensive medical databases. They found 1152 out of 886 996 completed pregnancies that had filled statin prescriptions during their first semester, which gave the study more precision in terms of risk assessment. The comprehensive database allowed the study to sort through and exclude comorbid conditions based on their severity as well as other factors. Taking into account these covariates enables adjustments to the study to yield more accurate findings. The original claims in the study were collected in a prospective manner so the data used is not susceptible to recall bias.

Because Ofori et al\textsuperscript{10} used nicotinic or fibrates as their control group, they were able to match a control population that would resemble the statin group. Other studies tend to compare a statin group to a non-statin group. This meant that the non-statin group
would tend to have less comorbidities such as diabetes, hypertension, hypothyroid, renal impairment and would also tend to be younger.

Winterfield et al\textsuperscript{21} as a prospective study was able to actively follow up to see if participants were compliant with their statin and recorded what day they had stopped using the drug. They also included non-live birth data on fetal malformations in both groups if they were found and before the fetus was miscarried or terminated.

**Limitations**

Bateman et al\textsuperscript{20} relied on coding to define the presence of a malformation. This indirect way of defining the outcome weakens the precision. They found, however, that when two or more codes are recorded on two different visits, the positive predictive value for correct diagnosis increases significantly.\textsuperscript{25} The same went for statin compliance. The nature of the study made it unable to verify whether patients took their statin. Since it is not safe to assume that a prescription that was filled was taken, considering only those who filled two prescriptions in their first trimester compromises sensitivity to strengthen specificity. Because only live births were included in this study, it does not take into account the fetal malformation rates prior to fetal termination.

Ofori et al\textsuperscript{10} had a very small sample size (n = 135). Like Bateman et al\textsuperscript{20} and most studies in this area of interest, Ofori et al\textsuperscript{10} also only looked at live births. Live births represent only a portion of the true population that has the potential to show congenital malformations. As a retrospective study, Ofori et al\textsuperscript{10} was unable to confirm whether or not participants complied with their statin therapy and the exact day they discontinued. However, they cite that absolute noncompliance with medications obtained
by pregnant women is known to be low at about 8%. There is no citation, however, for relative noncompliance.

Winterfield et al looked at the statin group as a homogenous group rather than inspecting each participant individually with the particular statin they were taking. Winterfield et al had a low sample size (n = 421). Research that looks at harm, particularly if the outcomes are rare, must have a large sample size to have more statistical authority. Another limitation is that since Winterfield et al relied on self-reported data via telephone interviews or mail-in questionnaires, many potential confounders were likely underreported and hence not documented. An example of this is metabolic syndrome is associated with hyperlipidemia, but obesity was likely underreported.

Due to the limitations and study design, these studies are not sufficient to change the current recommendations of statin use during pregnancy. Women in statin groups tend to have a higher incidence of diabetes mellitus, obesity, and advanced maternal age, all of which are associated with miscarriage, perinatal mortality, and congenital anomalies. Bateman et al had over 50% of its statin cohort between the ages of 30-39, while only 13% of their control was at the same age. Furthermore, 45.1% of the statin group had pre-existing diabetes compared to 3.1% in the control.

Research in this field remains promising. Hyperlipidemia, hypertension, cardiovascular disease, chronic kidney disease, and diabetes are often interrelated in individuals. Proving that statins may in fact benefit patients by keeping their lipid levels within normal limits and preventing the hypertension leading to preeclampsia can potentially be life-saving. Because the only ethical way to study statin exposure is by
observing accidental exposure, a large sample size is important for precision. At most, 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 statin patients on using effective contraception and to avoid taking their statin if pregnancy is possible.

CONCLUSION

Since they have been on the market, statins have always been considered contraindicated in pregnancy. Some researchers believe that statins have a role in preventing preeclampsia. 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. More research with larger sample sizes that look at the long-term effects is required to adequately assess the safety of statins during pregnancy. Though many questions still remain when looking at the risk of statins in pregnancy, the possibility of being able to control hyperlipidemia during pregnancy and prevent preeclampsia would greatly benefit the medical community.
REFERENCES


21. Winterfeld U; Allignol A; Panchaud A; Rothuizen LE; Merlob P; Cuppers-Maarschalkerweerd B; Vial T; Stephens S; Clementi M; De Santis M; Pistelli A; Berlin M; Elefteriou G; Mañáková E; Buclin T. Pregnancy outcome following maternal exposure to statins: a multicentre prospective study. BJOG: An International Journal of Obstetrics & Gynaecology. 2013;120(4):463-71


# Table I. Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bateman et al(^a)</td>
<td>Observational retrospective</td>
<td>Very Serious(^a)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None likely</td>
<td>Very Low</td>
</tr>
<tr>
<td>Ofori et al(^b)</td>
<td>Observational retrospective</td>
<td>Serious(^b)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious(^c)</td>
<td>None likely</td>
<td>Very Low</td>
</tr>
<tr>
<td>Winterfield et al(^d)</td>
<td>Observational prospective</td>
<td>Serious(^d)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious(^c)</td>
<td>None likely</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

\(^a\)Authors did not describe the dosing for statins  
\(^b\)Study only included live births  
\(^c\)Small sample size  
\(^d\)Confounders such as maternal disease, comorbidities were not fully documented

# Table II. Summary of Findings

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Group</th>
<th>Number of Patients</th>
<th>Number of congenital malformations (%)</th>
<th>Relative Risk (95% CI)</th>
<th>Adjusted OR for Congenital Anomalies group A: group C (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bateman et al(^a)</td>
<td>Retrospective</td>
<td>Statin</td>
<td>1152</td>
<td>73 (6.34)</td>
<td>1.79 (1.43 - 2.23)</td>
<td>1.34 (1.07 - 1.68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No statin</td>
<td>885 844</td>
<td>31 416 (3.55)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Ofori et al(^b)</td>
<td>Retrospective</td>
<td>Prescribed statins only before and during first trimester (Group A)</td>
<td>64</td>
<td>3 (4.69)</td>
<td>1.00 - 13.69</td>
<td>0.36 (0.06, 2.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrate/nicotinic acid (Group B)</td>
<td>14</td>
<td>3 (21.43)</td>
<td>4.41 - 62.57</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prescribed statins only between 1 year and 1 month before pregnancy (Group C)</td>
<td>67</td>
<td>7 (10.45)</td>
<td>4.19 - 21.53</td>
<td></td>
</tr>
<tr>
<td>Winterfield et al(^d)</td>
<td>Prospective</td>
<td>Statin</td>
<td>249</td>
<td>6/197 (4.1)</td>
<td>1.5 (0.5 to 4.5)</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No statin</td>
<td>249</td>
<td>6/224 (2.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIGURE 1

Pregnancy Registry
N = 110,313

- group A: User of statins only before & during 1st trimester n = 153
  - Live births N = 70 (32%)
    - Atorvastatin 35%
    - Fluvastatin 6%
    - Pravastatin 26%
    - Simvastatin 17%
  - Induced abortions N = 42 (21%)
    - Atorvastatin 63%
    - Fluvastatin 5%
    - Pravastatin 23%
    - Simvastatin 12%

- group B: Users of fibrate or niacin acid only before & during 1st trimester n = 20
  - Live births N = 13 (65%)
    - Fenofibrate 62%
    - Gemfibrozil 8%
    - Hydralazine 1%
    - Propranolol 1%
    - Phenytoin 1%
  - Induced abortions N = 7 (35%)
    - Fenofibrate 43%
    - Gemfibrozil 16%
    - Hydralazine 15%
    - Propranolol 15%
    - Phenytoin 11%

- group C: Users of statins only between 1st & 2nd trimester n = 16
  - Live births N = 17 (69%)
    - Atorvastatin 51%
    - Fluvastatin 8%
    - Pravastatin 21%
    - Simvastatin 13%
  - Induced abortions N = 5 (30%)
    - Atorvastatin 40%
    - Fluvastatin 13%
    - Pravastatin 4%
    - Simvastatin 22%

Figure 2
Pregnancy outcomes according to study group. Women aged 15-44 years on first day of gestation; covered by Régie de l'Assurance Maladie du Québec drug insurance for ≥12 months before pregnancy and during pregnancy. Women excluded: users of other known teratogens (category X drug, carbamazepine, phenytin, valproic acid, lithium, acetamin, antineoplastic agents, levonorgestrel and etonogestrel). Induced abortions identified by ICD-9 codes 633.0-633.3, 635.0-635.3, 798.