Conclusions—Women with FH do not appear to have a higher risk of preterm delivery or of having infants with low birth weight or congenital malformations compared to women in general.

Methods and Results—We linked information from the Medical Genetics Laboratory with that of the Medical Birth Registry of Norway. We included 1869 FH women (≥14 years) from the Medical Genetics Laboratory and about 2 million (general population) from the Medical Birth Registry of Norway during the period 1967 to 2006. The registry match resulted in analysis of 2319 births of 1093 women with heterozygous FH. The mean (SD) prepregnancy total cholesterol concentration was 9.59 (2.06) mmol/L (370 [80 mg/dL]), whereas the concentration of total cholesterol was not available during pregnancy. The frequencies of prematurity, low birth weight, and congenital malformations for the 40-year period in the FH population were 6.8%, 5.0%, and 3.3%, respectively. The corresponding values for the general population were 6.2%, 5.2%, and 3.2%. The corresponding odds ratios were 1.11 (95% confidence interval 0.94–1.31; \( P=0.23 \)), 0.96 (0.79–1.15; \( P=0.64 \)), and 1.09 (0.87–1.37; \( P=0.45 \)).

Key Words: myocardial infarction ■ atherosclerosis ■ hypercholesterolemia, familial ■ pregnancy ■ registries

Epidemiology and Prevention

Pregnancy Outcomes in Familial Hypercholesterolemia
A Registry-Based Study

Ieva Toleikyte, MSc; Kjetil Retterstøl, MD; Trond Paul Leren, MD; Per Ole Iversen, MD

Background—Women with familial hypercholesterolemia (FH) are prone to early cardiovascular disease and death. It is unknown whether FH adversely affects pregnant women and birth outcomes. We determined whether heterozygous FH women are at higher risk of premature birth (<37 gestational weeks), delivering children with low birth weight (<2500 g) and/or with congenital malformations compared to women in general.

Methods and Results—We linked information from the Medical Genetics Laboratory with that of the Medical Birth Registry of Norway. We included 1869 FH women (≥14 years) from the Medical Genetics Laboratory and about 2 million (general population) from the Medical Birth Registry of Norway during the period 1967 to 2006. The registry match resulted in analysis of 2319 births of 1093 women with heterozygous FH. The mean (SD) prepregnancy total cholesterol concentration was 9.59 (2.06) mmol/L (370 [80 mg/dL]), whereas the concentration of total cholesterol was not available during pregnancy. The frequencies of prematurity, low birth weight, and congenital malformations for the 40-year period in the FH population were 6.8%, 5.0%, and 3.3%, respectively. The corresponding values for the general population were 6.2%, 5.2%, and 3.2%. The corresponding odds ratios were 1.11 (95% confidence interval 0.94–1.31; \( P=0.23 \)), 0.96 (0.79–1.15; \( P=0.64 \)), and 1.09 (0.87–1.37; \( P=0.45 \)).

Conclusions—Women with FH do not appear to have a higher risk of preterm delivery or of having infants with low birth weight or congenital malformations compared to women in general, but, although this is unlikely, some undetected bias may obscure the real differences. (Circulation. 2011;124:1606-1614.)

Key Words: myocardial infarction ■ atherosclerosis ■ hypercholesterolemia, familial ■ pregnancy ■ registries

Familial hypercholesterolemia (FH) is an autosomal dominantly inherited disorder of lipid metabolism caused by mutations in the low-density lipoprotein (LDL) receptor gene.\(^1\) This results in an accumulation of plasma LDL cholesterol leading to atherosclerosis and an increased risk of premature cardiovascular disease (CVD).\(^2\) Worldwide, >10 million people have FH, of which \( \approx 200 \text{,}000 \) die of CVD each year.\(^3\) Familial hypercholesterolemia is underdiagnosed, and only \( \approx 20\% \) of cases are identified.\(^4\) In Norway, the prevalence of heterozygous FH is \( \approx 1/300 \) in the general population. However the prevalence among reproductive women is unknown.\(^5\)

Maternal hyperlipidemia is one of the most consistent metabolic changes during pregnancy. Plasma cholesterol and triglycerides may increase by 25% to 50% and 150% to 300%, respectively. During pregnancy, women with heterozygous FH show relative changes in plasma lipid levels that are similar to those in healthy women; however, the absolute increase is higher in FH.\(^6\)–\(^8\) Hyperlipidemia during pregnancy may induce atherosclerosis in the uteroplacental spiral arteries that, combined with hypercoagulation, may result in thrombosis and placental infarctions, leading to placental insufficiency and thereby fetal compromise.\(^9\) Maternal hyperlipidemia is associated with preterm delivery (birth < gestational week 37) and low birth weight (<2500 g).\(^10\) Whether FH women have increased risk of such adverse birth outcomes is not known. Although the results were not statistically significant, we found in a small prospective study that the frequency of premature deliveries among FH women was almost twice that of a healthy reference group (13.6% versus 7.4%).\(^8\) Importantly, while a woman is attempting to become pregnant—and during her pregnancy and lactation—most lipid-lowering drugs are not recommended. Thus, FH women are likely to be exposed to an accelerated atherosclerosis and may be at increased risk of premature CVD for many years. Nevertheless, little is known about the use of lipid-lowering therapy among pregnant FH women. Because women may not realize they are pregnant before some weeks after conception, they may have used statins, for example, early in the first trimester, a critical period for the developing fetus.
The primary aim of this study was to determine whether pregnant FH women have a higher risk of adverse birth outcomes (e.g., prematurity, low birth weight, and congenital malformations) compared with women in the general population. We also examined their use of lipid-lowering drugs. To do this, we linked data from the Medical Birth Registry of Norway (MBRN) with the registry of Norwegian FH patients.

Methods

The study was approved by the Regional Ethics Committee, the Health Directorate, the Norwegian Social Science Data Services, and the Data Inspectorate of Norway.

Registries

At the time of data collection, the registry of the Medical Genetics Laboratory, Oslo University Hospital, contained about 4,400 patients with a molecular genetic diagnosis of FH.

The MBRN is a population-based registry of all births in Norway since 1967. The registry is based on compulsory notification of every birth or abortion from 12 weeks of gestation onwards and includes information of the maternal health before and during pregnancy, complications during pregnancy and delivery, length of pregnancy, as well as information of the infant. A standard antenatal form is completed at visits to a general practitioner or a midwife during pregnancy, and is brought by the mother to the place of birth. Additional data are being added to the form until discharge from hospital after delivery. We used web-data from MBRN for the years 1967 to 2006, comprising more than 2.3 million births and including the FH population.

The FH Study Population

We identified 1872 FH women of fertile age (≥14 years old) from the Medical Genetics Laboratory registry. Of these, 65% were probands and 35% were family members. Moreover, 1102 FH women with a total of 2334 births had been recorded in the MBRN. Nine of them with a total of 15 births withdrew from the study. Thus, a total of 1093 FH women with 2319 births were included (the Figure, A). The results from this population were compared with those of the general Norwegian population for the period from 1967 to 2006.

Measurement of total serum cholesterol was performed before lipid-lowering drugs were started and obtained in the nonpregnant state. Some uncertainty exists relative to whether the total serum cholesterol levels were obtained in the fasting state. However, fasting has little impact on the levels of total serum cholesterol. In Norwegian hospitals, the reference ranges for serum total cholesterol concentrations among female women are 2.9 to 6.1 mmol/L (112 to 236 mg/dL; age 18 to 29 years) and 3.3 to 6.9 mmol/L (128 to 267 mg/dL; age 30 to 49 years).

In order to exclude misclassified FH births for prematurity analysis, we screened data for birth weight–gestational age consistency by estimating means and SDs and calculating z-scores, as suggested by Wilcox and Russell. This method identifies infants who are relatively small or large for their gestational age and compares them with infants of the same relative size at other gestational ages. Skjøven and colleagues have estimated means and SDs for Norwegian birth weight by gestational age, and these were used as references for calculation of z-scores. We chose to exclude 5 cases in gestational weeks 21 to 32 and 1 case in week 48 where a sex-specific weight for gestational age was larger than 3 SDs from the reference mean. In addition, 129 births were excluded because of missing data on gestational age, leaving 2184 births for analysis of prematurity (Figure, B). Three cases with missing birth weight, 1313 multipara births, 42 twin births, and 10 still births were excluded, leaving 951 first singleton live FH births for analysis of birth weight (the Figure, B).

All 2319 births were analyzed for information about congenital malformations as provided in the MBRN and as based on the 10th International Classification of Diseases. Severe congenital malformations are classified according to the European Registration of Congenital Anomalies. For convenience, the 106 recorded mutations of the LDL-receptor gene were grouped into 9 categories. Mutation types that had <3% frequency among FH women were pooled into 1 category, denoted "other."

Statistical Analyses

We used the χ² test to compare frequency of prematurity (birth < gestational week 37), low birth weight (<2500 g), and congenital malformations between the FH and the general population. The corresponding P values were adjusted for multiple comparisons using the Bonferroni correction. The χ² test was also used to test if the individual mutation types were associated with increased frequency of prematurity. We estimated the frequencies of very low (<1500 g), extremely low (<1000 g), and high birth weight (>4500 g) infants.

To evaluate the contribution of potential risk factors for the frequency of prematurity, low birth weight, and congenital malformations, a multivariate analysis based on logistic regression was performed. We included clinically relevant factors in the multivariate analyses, namely lipid values, maternal age, parity, pregnancy-induced hypertension (including preclampsia), and smoking in the beginning and the end of pregnancy. The obtained values are reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). We limited these analyses for the years between 1999 and 2006 because the most comprehensive data set was available for singleton pregnancies during that time period (the Figure, C).

To analyze the frequency of prematurity and congenital malformations, as well as the changes in mean birth weight over time, 4 periods were compared: two 20-year periods: 1967 to 1986 and 1987 to 2006, and the period before and after statin introduction in the treatment of hypercholesterolemia: 1979 to 1991 and 1992 to 2006. The χ² test was used to analyze the change in frequencies of prematurity and congenital malformations whereas an independent sample t test was used to analyze the change in mean birth weight between different time periods and to compare mean birth weight between groups with and without statin therapy and to compare total cholesterol levels between FH women with and without the studied birth outcomes. One-sample t test was used to compare mean birth weight between the FH and the general population, and a 1-way analysis of variance to compare birth weight means among the most frequent mutation types. The analyses were performed using the Statistical Package of Social Sciences (SPSS Inc, Chicago, IL) version 16.0. The level of statistical significance was set at P<0.05 (2-sided tests).

Results

Characteristics of the FH Study Population

Among the 106 different mutations in the LDL-receptor gene that were detected, the 313+1, G>A and C210G mutations were most common and no homozygous patients were identified (Table 1).

The mean age for women giving birth for the first time was 28 years for both FH women and women in the general population. The fertility rate has also been similar between the 2 populations: From 1987 to 1996 and from 1997 to 2006, the fertility rate in FH population was 1.86 and 1.92, respectively, compared with 1.87 and 1.83, respectively, in the general population. Information about pregnancy and maternal health in the FH study population is presented in Table 2. None of the FH women was registered with type 2 diabetes mellitus before pregnancy, and gestational
diabetes was recorded in only 1 nulliparous pregnancy. Two FH women were recorded with an unclassified heart disease before pregnancy: 1 had a symptomatic heart disease, 1 had suffered a transient ischemic attack, and 1 had an undefined myocardial dysfunction before pregnancy. None of these 5 women gave birth prematurely or had infants with low birth weight or congenital malformations. No other cardiovascular events in the FH women during pregnancy were obtained from the registry data.

Only 1 case was reported with calcification and infarction of the placenta. The mother was 38 years old and gave birth to a healthy male neonate with birth weight of 4260 g in gestational week 42.

**Frequency of Prematurity**

Table 3 provides the estimated prematurity frequency in the FH and general populations. When these 2 study populations were compared, we could not find any apparent differences in
the frequency of prematurity regardless of whether we compared the entire study populations or subgroups according to parity.

Total cholesterol was (mean±SD) 9.30±2.38 mmol/L (359±92 mg/dL) among FH women giving birth prematurely, whereas it was 9.53±2.09 mmol/L (369±81 mg/dL) (P=0.25) among FH women delivering term infants. We could not detect any significant difference in prematurity frequency when FH women having total cholesterol in the highest quartile were compared with those having total cholesterol in the lowest quartile.

Significant risk factors for prematurity among singleton FH pregnancies during the period 1999 to 2006 were pregnancy-induced hypertension (including preeclampsia) (OR 9.48, 95% CI 3.31–27.21, P=0.001) and maternal age (OR 0.86, 95% CI 0.78–0.95, P=0.02), when adjusted for parity, lipid values, and smoking in the beginning and the end of pregnancy. When comparing the first and the last 20-year periods, the frequency of prematurity increased in the FH and the general population from 4.8% to 8.0% (OR 1.12, 95% CI 1.07–1.17; P=0.01) and from 5.8% to 6.6% (OR 1.11, 95% CI 1.06–1.17; P=0.001), respectively.

There was a decrease in stillbirths among first singleton FH pregnancies from 2.4% in the first 20 years to 0.7% in the last 20 years (P=0.034). In the general population, the corresponding change was from 1.2% to 0.9% (P=0.001), a decrease not significantly different from that of the FH women.

The frequency of preterm delivery for the first singleton birth was lowest (5.3%) in FH women aged 20 to 24 years and largest (12.5%) for those older than 35 years. Furthermore, twin pregnancies accounted for 1.9% of all births and for 16.1% of premature births in the FH population.

### Prematurity, Drug Use, and Mutation Types

Drug use among FH women with first singleton births was recorded in 43 of 904 pregnancies (4.8%), of which 4 terminated prematurely. Nineteen women with pregnancies among the 2184 births used lipid-lowering drugs; 15 used statins, 3 used bile acid sequestrants, and 1 used a combination of them. None of these pregnancies terminated prematurely.

In order to examine whether the introduction of statins in the treatment of hypercholesterolemia influenced the frequency of prematurity, we compared the period before statin introduction (1979–1991) with the period after (1992–2006) in both study populations. Among the 904 FH women with first singleton births, the frequency of prematurity in the 2 periods was 7.2% and 8.0%, respectively (OR 1.12, 95% CI 1.06–2.02; P=0.70), whereas in the general population the frequency of prematurity increased from 5.6% to 6.3% (OR 1.12, 95% CI 1.11–1.14; P<0.001). The frequency of prematurity during the period from 1992 to 2006 (ie, after introduction of statins) was not different (P=0.20) between the 2 populations.

Birth Weight in the FH and General Populations, 1967 to 2006

The FH population had a higher percentage of deliveries in birth-weight group 3000 to 3499 g than the general population (OR 1.23, CI 1.07–1.40; P=0.003), and a lower percentage in birth-weight group 4000 to 4499 g (OR 0.70, CI 0.57–0.86; P=0.001). No data on these weight groups were available according to parity.

Table 3 provides the estimated frequency of low–birth weight infants in the FH and general populations. When these 2 study populations were compared, we could not find any apparent differences in the frequency of low birth weight regardless of whether we compared the entire study populations or subgroups according to parity. Moreover, there was no significant difference in the frequency of very low–, or extremely low–birth weight infants between the 2 study populations (data not shown). There was no significant difference in mean birth weight in the FH population when...

Total cholesterol was 9.46 ± 1.97 mmol/L (366 ± 76 mg/dL) among FH women delivering low–birth weight infants, whereas it was 9.52 ± 2.10 mmol/L (368 ± 81 mg/dL) (P = 0.75) among FH women delivering normal-weight infants. We could not detect any significant difference in the frequency of low birth weight when FH women having total cholesterol in the highest quartile were compared with those having total cholesterol in the lowest quartile.

The significant risk factor for low birth weight among singleton FH pregnancies during the period 1999 to 2006 was pregnancy-induced hypertension (including preeclampsia) (OR 18.76, 95% CI 6.24–56.40; P < 0.001) when adjusted for maternal age, parity, lipid values, and smoking in the beginning and the end of pregnancy.

**Birth Weight, Drug Use, and Mutation Types**

The birth weights for first singleton live births of mothers with (n = 42) or without (n = 909) any medication treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>FH Population</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at birth, mean (SD), y</td>
<td>2319</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Primipara, %</td>
<td>2319</td>
<td>42.2</td>
</tr>
<tr>
<td>Singleton, %</td>
<td>2319</td>
<td>98.2</td>
</tr>
<tr>
<td>Female babies, %</td>
<td>2319</td>
<td>47.4</td>
</tr>
<tr>
<td>In vitro fertilizing, %*</td>
<td>1373</td>
<td>1.2</td>
</tr>
<tr>
<td>Gestational diabetes mellitus, %</td>
<td>2319</td>
<td>0.3</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension, % †</td>
<td>2319</td>
<td>5.3</td>
</tr>
<tr>
<td>Eclampsia, %‡</td>
<td>2319</td>
<td>0.04</td>
</tr>
<tr>
<td>Preeclampsia, %§</td>
<td>2319</td>
<td>3.5</td>
</tr>
<tr>
<td>HELLP-syndrome, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication use, %</td>
<td>2319</td>
<td>5.0</td>
</tr>
<tr>
<td>Lipid-lowering drug use, %</td>
<td>2319</td>
<td>0.8</td>
</tr>
<tr>
<td>Gestational age at birth, mean (SD), wk</td>
<td>2167</td>
<td>40 (2)</td>
</tr>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>2294</td>
<td>3518 (581)</td>
</tr>
<tr>
<td>Mean birth length, cm</td>
<td>2228</td>
<td>50</td>
</tr>
<tr>
<td>Previous stillbirths, %</td>
<td>2319</td>
<td>1.6</td>
</tr>
<tr>
<td>Previous miscarriage/stillbirth before gestational week 12, %#</td>
<td>363</td>
<td>3.2</td>
</tr>
<tr>
<td>Previous miscarriage/stillbirth in gestational weeks 12–23, %</td>
<td>354</td>
<td>0.5</td>
</tr>
<tr>
<td>Folate supplementation before pregnancy, %##</td>
<td>430</td>
<td>14.9</td>
</tr>
<tr>
<td>Folate supplementation during pregnancy, %##</td>
<td>430</td>
<td>37.7</td>
</tr>
<tr>
<td>Multivitamin supplementation before pregnancy, %##</td>
<td>430</td>
<td>7.9</td>
</tr>
<tr>
<td>Multivitamin supplementation during pregnancy, %##</td>
<td>430</td>
<td>25.8</td>
</tr>
<tr>
<td>Smoked at the beginning of pregnancy, %##</td>
<td>374</td>
<td>19.0</td>
</tr>
<tr>
<td>Smoked at the end of pregnancy, %##</td>
<td>353</td>
<td>12.7</td>
</tr>
</tbody>
</table>

N indicates the No. of subjects with available data for the different variables; N/A, data not available from MBRN.
*Data available from MBRN since 1984.
†Pregnancy-induced hypertension refers to a condition with blood pressure at or above 140/90 mm Hg without proteinuria or other signs associated with preeclampsia.
‡Eclampsia refers to a condition with peripartum seizures among women with pregnancy-induced hypertension and where other causes of seizures have been excluded.
§Preeclampsia refers to a condition with blood pressure at or above 140/90 mm Hg and proteinuria (> 300 mg/24 h or +1 on urinary stix twice at least 6 h apart).
||HELP-syndrome consists of hemolysis (reduction in hemoglobin, rise in lactate dehydrogenase levels and reduced haptoglobin), elevated liver enzymes (above reference values), low platelet count (< 100 000/µL), and preeclampsia/eclampsia; data available from MBRN since 1998.
##Data available from MBRN since 1999.

We could not detect any significant difference in the values between the FH and the general populations relative to any of the variables.

The significant risk factor for low birth weight among singleton FH pregnancies during the period 1999 to 2006 was pregnancy-induced hypertension (including preeclampsia) (OR 18.76, 95% CI 6.24–56.40; P < 0.001) when adjusted for maternal age, parity, lipid values, and smoking in the beginning and the end of pregnancy.
Table 3. Frequency of Prematurity, Low Birth Weight, and Congenital Malformations in the 2 Study Populations

<table>
<thead>
<tr>
<th></th>
<th>FH Population</th>
<th>General Population</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Prematurity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All births</td>
<td>6.8</td>
<td>2184</td>
<td>6.2</td>
<td>2 304 067</td>
</tr>
<tr>
<td>Singletons</td>
<td>5.8</td>
<td>2142</td>
<td>5.7</td>
<td>2 152 740</td>
</tr>
<tr>
<td>First singletons</td>
<td>6.4</td>
<td>904</td>
<td>6.5</td>
<td>890 790</td>
</tr>
<tr>
<td>Multipara singletons</td>
<td>5.4</td>
<td>1238</td>
<td>5.2</td>
<td>1 261 950</td>
</tr>
<tr>
<td>Low birth weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All births</td>
<td>5.0</td>
<td>2316</td>
<td>5.2</td>
<td>2 330 590</td>
</tr>
<tr>
<td>Singletons</td>
<td>4.2</td>
<td>2274</td>
<td>4.2</td>
<td>2 270 281</td>
</tr>
<tr>
<td>First singletons</td>
<td>5.4</td>
<td>961</td>
<td>5.1</td>
<td>937 572</td>
</tr>
<tr>
<td>Multipara singletons</td>
<td>3.3</td>
<td>1313</td>
<td>3.6</td>
<td>1 332 709</td>
</tr>
<tr>
<td>Congenital malformations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All births</td>
<td>3.3</td>
<td>2319</td>
<td>3.2</td>
<td>2 337 646</td>
</tr>
<tr>
<td>Singletons</td>
<td>3.4</td>
<td>2277</td>
<td>3.2</td>
<td>2 274 139</td>
</tr>
<tr>
<td>First singletons</td>
<td>4.1</td>
<td>962</td>
<td>3.6</td>
<td>939 109</td>
</tr>
<tr>
<td>Multipara singletons</td>
<td>3.0</td>
<td>1315</td>
<td>2.9</td>
<td>1 335 030</td>
</tr>
</tbody>
</table>

FH indicates familial hypercholesterolemia; OR, odds ratio; and CI, confidence interval.

during pregnancy were 3468±651 and 3447±560 g, respectively (P=0.84). The birth weights of infants of the 19 FH mothers using lipid-lowering drugs during pregnancy were 3453±637 g (ie, not significantly different from those not using any medication).

The birth weights were 3420±576 and 3500±586 g (P=0.11) before (years 1979–1991) and after (years 1992–2006) statin introduction, respectively, in the FH population (n=951). In the general population, mean birth weight increased moderately from 3484±234 to 3515±216 g (P<0.001).

The frequency of low birth weight according to mutational status is shown in Table 1. The frequency of low–birth weight infants was not significantly different between FH mutation types. For the 40-year observation period, the lowest birth weight was recorded for infants of FH women with mutations C210G (n=555 g) and S78X (n=555 g) and in the general population, mean birth weight was not significantly different between FH mutation types. No congenital malformations were recorded among the 19 FH women who took lipid-lowering drugs during pregnancy.

The frequency of all congenital malformations and the severe forms did not apparently change in the FH population. In the general population, the frequency of all congenital malformations did not change significantly from the period 1999 to 2006 was pregnancy-induced hypertension (including preeclampsia) (OR 7.64, 95% CI 2.35–24.89; P=0.001) when adjusted for maternal age, parity, lipid values, and smoking in the beginning and the end of pregnancy.

From the first to the last 20 year periods, the frequency of all and severe congenital malformations did not apparently change in the FH population. In the general population, the frequency of all and severe congenital malformations increased (P<0.001) from 2.5% to 3.9% and from 1.6% to 2.6%, respectively.

The frequency of all congenital malformations and the severe forms did not change significantly from the period before to the period after statin introduction among the FH women. In contrast, both all congenital malformations and the severe forms increased (P<0.001) in the general population from the period 1979 to 1991 to the period 1992 to 2006.

The frequency of congenital malformations according to mutational status is shown in Table 1. The frequency of congenital malformations was not significantly different between FH mutation types. No congenital malformations were recorded among the 19 FH women who took lipid-lowering drugs during pregnancy.

Discussion

This registry study of 2319 births of 1093 women with heterozygous familial hypercholesterolemia demonstrates that the fre-
quency of preterm delivery (<37 weeks of gestation), low birth weight (<2500 g), and congenital malformations were apparently similar to those in the general population of women of childbearing age in Norway.

In addition to the hyperlipidemia, activation of coagulation and of vascular endothelium may confer increased risks of CVD among pregnant FH women. Case reports of unstable angina and acute myocardial infarction in pregnant women with heterozygous or homozygous FH have been described. In our study, CVD-related morbidity was low among the FH pregnant women, and importantly, no deaths were reported, but because of low numbers it was not possible to make a formal statistical evaluation of CVD risk and pregnancy in FH. A prospective trial with CVD morbidity and mortality as primary end points is therefore required to properly address whether an FH pregnancy is associated with increased risk of CVD.

Epidemiological data indicate that maternal hyperlipidemia is associated with preterm delivery. Because pregnant FH women have higher lipid levels and a more procoagulant profile than healthy women, they may be at a particular risk of compromised feto- and uteroplacental circulation, and therefore preterm births. Catov and colleagues showed that higher lipids in early pregnancy increased the risk of premature delivery in both overweight and normal weight women. Increased levels of cholesterol and triglycerides were associated with a 2.8-fold higher risk of prematurity before gestational week 34 and a 2-fold higher risk of delivery in gestational weeks 34 to 37. At variance with this, Edison and colleagues found an OR of 5.6 for preterm delivery among women with total cholesterol <4.1 mmol/L (159 mg/dL) compared with those with a cholesterol between 4.1 and 6.7 mmol/L (159 and 259 mg/dL). The corresponding OR for those with cholesterol >6.7 mmol/L (259 mg/dL) was 2.7. A randomized trial of 290 healthy pregnant women showed that a diet low in cholesterol (<150 mg/d) and in saturated fat (<8% of dietary energy) was associated with reduced maternal lipid concentrations and a prominent reduction in the frequency of preterm delivery (0.7% versus 7.4%). Possibly the decrease in the levels of LDL cholesterol improved placental blood flow and induced less local inflammation.

Preeclampsia increases the risk of preterm delivery. However, our data (Table 2) did not reveal any apparent differences in the frequencies of eclampsia, preeclampsia, or pregnancy-induced hypertension between the FH study group and the general population in Norway.

In the present study we did not detect any apparent increased risk of premature delivery in women with FH compared with women in the general population. The frequencies of conditions associated with prematurity were apparently similar between the pregnant FH women and the pregnant women in the general population. We could not detect any significant increased risk of prematurity when we compared pregnancies before and after introduction of statin therapy. Thus, severely elevated levels of LDL cholesterol were apparently not associated with increased risk of preterm delivery in the present study. The association between the level of LDL cholesterol and risk of preterm delivery observed in previous studies may in part depend on confounding factors, such as lifestyle and dietary habits. Alternatively, a more favorable diet and lifestyle pattern in FH women may reduce the high LDL cholesterol levels.

Interestingly, the FH women gave birth to more normal-weight infants and fewer high-weight infants compared with women in the general population. The explanation for this is unclear, but may indicate a better nutritional status of FH women, because low maternal weight gain is associated with an increased incidence of both low- and high–birth weight infants. Because we primarily focused on birth outcomes of nulliparous FH women and nulliparity reportedly reduces the probability of high birth weight, this may in part explain the lower number of infants in the high–birth weight group. Genetic factors may also modify birth weight. Importantly, the risk of delivering infants with either low, very low, or extremely low birth weight among the FH women was small and not significantly different from that of women in the general population.

If anything, these data suggest an adequate fetoplacental circulation among FH women. In the present study, only 1 case was noted of placental infarctions and calcifications among the FH women, but as this is not specifically recorded in the MBRN, placental insufficiency may be underestimated.

The introduction of statins had no apparent effect on birth weight in the FH population. Moreover, birth weight did not apparently differ among the different mutations of the LDL-receptor gene. Why those with the C210G mutation had a small but significantly lower birth weight compared with that in the general population is unexplained.

We found that the frequency of congenital malformations in general, and specifically the serious forms, was apparently not higher among the FH women than that of women in the general population. Somewhat surprisingly, the frequency of all and the severe forms of congenital malformations increased from the first to the last 20-year period in the general population. We have no explanation for this rise. In our multivariate analyses of the potential influence of relevant risk factors, pregnancy-induced hypertension was significantly associated with increased risk for all our 3 main end points (prematurity, low birth weight, and congenital malformations).

This is the largest study describing birth outcomes of FH pregnancies reported to date. Our study design using unique (Medical Genetics Laboratory) and mandatory (MBRN) registries probably ensured minimal loss of cases. Although we cannot rule out the possibility of bias in reporting to these registries, we believe that our data reflect the birth outcomes of a representative cohort of childbearing FH women. Notably, the FH diagnosis was confirmed with molecular gene testing.

Our study is limited to white women with the heterozygous form of FH, and we have no data on women with homozygous FH or on those of other ethnicities. Another weakness of the present study was the missing data on variables due to incomplete reporting to the MBRN, for example, information on previous miscarriages before gestational week 12 and in weeks 12 to 23. We did not have data on prepregnancy body
mass index or lifestyle (including nutritional habits) before and during pregnancy. The actual blood lipid levels during pregnancy were not recorded in either of the 2 registries. Moreover, we identified only 19 women who used lipid-lowering drugs during pregnancy, and information about the use of omega-3 supplements was not available. Because of low numbers in some subgroups (eg, those using lipid-lowering drugs), multivariate analyses could not be performed to give a detailed examination of all possible confounders affecting the risks of adverse birth outcomes in such subgroups. Because statins should not be used during pregnancy, statin use may be underreported, and this therefore may preclude reliable estimates of whether the use of such drugs increases the risk of the studied birth outcomes. Moreover, reporting FH cases in Norway to the Medical Genetics Laboratory registry is voluntary, but all FH cases that have been diagnosed with molecular gene testing are recorded. Another possible limitation is that we did not perform a population-based case-control study, because we wanted to compare the entire population of FH women in their childbearing age to the women in the general population. On the basis of our results, there is no particular reason to assume that the FH women differed from those of the general population apart from their lipid disorder. However, because data on socioeconomic status or education were not available, we cannot exclude that some selection bias was present. The study was restricted to Norway, and dietary habits, lifestyle, and reimbursement practices for lipid-lowering drugs vary between countries.

Among the 1093 FH women, there were 106 different mutations of the LDL-receptor gene, of which 313+1, G>A and C210G were most frequent. These, together with mutation S78X, account for ≈40% of the mutations among Norwegian FH patients although the C210G mutation is almost twice as frequent compared with earlier estimations.33,34

Many physicians are faced with the dilemma of giving advice to FH woman about pregnancy, because the risk for the woman and potential adverse birth outcome has not been known. The present study shows that severely increased levels of total and LDL cholesterol caused by a monogenetic disorder was apparently not associated with increased risk for mother or infant during pregnancy or delivery.

Disclosures
None.

References
CLINICAL PERSPECTIVE

Women with familial hypercholesterolemia (FH) are prone to early cardiovascular disease and death. Approximately 1:300 people are affected with FH in Norway. Lipid-lowering medication, with the exception of resins, is contraindicated during pregnancy. Stopping lipid-lowering medication may lead to a 40% to 50% increase in low-density lipoprotein (LDL) cholesterol. In addition, a 30% increase in LDL cholesterol and an approximate doubling in fasting triglycerides can also be expected. Because it is unknown whether FH adversely affects pregnant women and their birth outcomes in clinical terms, we analyzed 2319 births of 1093 women with FH. Firstly, this study shows that women with FH do not have an increased risk for prematurity (birth < gestational week 37), low birth weight (<2500 g), or frequency of congenital malformations. The results from the present study may thus be reassuring for FH women in childbearing age and their obstetricians. Secondly, some previous reports suggested that women with elevated cholesterol by itself, without FH, are at risk for adverse pregnancy outcomes. In this view, women with FH represent nature’s own experiment to test if elevated LDL cholesterol is responsible for adverse pregnancy outcomes. Data from this study show that a genetically determined elevated LDL cholesterol does not negatively affect pregnancy outcome, and therefore suggest that elevated LDL cholesterol per se may not influence pregnancy outcome.