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Statins during pregnancy: A cohort study using the General Practice Research Database to investigate pregnancy loss

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Article summary

- The study is the first to report and analyse data on pregnancy loss following prescribing of statins during early pregnancy, work which was possible because the GPRD includes medical records for women for the period before as well as during pregnancy thus enabling early exposures and losses to be identified.
- The study found an increased proportion of pregnancies ending in a spontaneous loss compared to pregnancies where statins have not been prescribed.
- The study replicated the results found in other work that has shown that there is no difference in the proportion of offspring diagnosed with a major congenital

malformation compared with offspring of mothers who have not been exposed to statins during pregnancy.

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Abstract

Purpose: To determine if there are any differences between the types of pregnancy loss experienced by women who have been prescribed a statin just before or early in pregnancy compared to those who have not.

Methods: A retrospective cohort study using the General Practice Research Database was carried out. Women aged between 10-49 years at pregnancy start who received a prescription for a statin in the three months before and/or during the first trimester of pregnancy were matched to up to ten pregnancies on age at start date, diabetes and hypertension status before pregnancy. Pregnancies occurring 1/1/1992-31/3/2009 were included. Pregnancy losses were identified and categorised as spontaneous (including miscarriage), induced for medical, other or unknown reasons. Freetext was used to determine the type of loss where this was not clear from the medical records.

Results: 281 pregnancies potentially exposed to statins were identified and matched to 2643 unexposed pregnancies. 54.45% of pregnancies potentially exposed to a statin resulted in a delivery compared to 62.81% of those not exposed. 25.27% of all pregnancies potentially exposed to a statin resulted in a spontaneous loss compared to 20.81% in those not exposed. Using a time to event analysis with exposure as a time dependent covariate gave an adjusted hazards ratio of 1.67 (95% CI 1.25 to 2.23) of pregnancy loss in the statin exposed group.

Conclusions: This study is the first to report the differences in types of pregnancy loss following the potential exposure to a statin just before or early in pregnancy.

Introduction

There is growing potential for inadvertent use of statins during pregnancy. The increasing incidence of type 2 diabetes at a younger age, increasing levels of obesity and increasing numbers of women having children later in life lead to greater numbers who may already be prescribed statins before conception. A number of studies have investigated major congenital malformations and possible associations with statin use during the first trimester. Most of the papers published to date have not shown any statistically significant increased risk of major malformations following potential exposure to statins during the first trimester[1-4] although some of these studies were restricted by small sample sizes. However, while congenital malformations are very important to consider, pregnancy loss and other maternal and child outcomes should also be investigated.

To date very few studies have investigated pregnancy loss however when evaluating drug safety in pregnancy it is vital to consider both deliveries and losses.[5, 6] In this paper we will address this by evaluating if pregnancy loss due to miscarriage and induced termination are different between women who have received prescriptions for statins and those who have not.

Methods

The General Practice Research Database (GPRD) was used for this study (now known as the Clinical Practice Research Datalink). This database contains anonymised primary care medical records for approximately 7% of the UK population including prescriptions issued, medical diagnoses, test results and maternity information. Pregnancies have been identified and matched to offspring using an algorithm where codes relating to pregnancy are identified. From these the start and end dates of the pregnancy and outcome are determined (for example date of last menstrual period, delivery date). If information is missing then a pregnancy that results in a delivery is assumed to last for 40 weeks and a pregnancy that results in a termination is assumed to last for ten weeks. More information about this algorithm and testing undertaken to verify this is described in earlier work.[7]

A cohort of women with pregnancies ending between 1/1/1992 and 31/3/2009 where at least one prescription for a statin was recorded in the three months before the start of pregnancy or during pregnancy were identified. These pregnancies were matched to up to ten pregnancies where a statin was not prescribed. Pregnancies were matched on the mother's age at the start of the pregnancy (+/- 2 years) and whether or not the mother had diagnosis codes or treatment for diabetes and/or hypertension before the start of pregnancy. For all pregnancies included in the study, females needed to be aged between 10 and 49 years at the start of pregnancy and have data that is of a standard that is suitable for research (UTS) for at least nine months before the start of pregnancy and throughout the pregnancy. We do not expect to identify pregnancies where statins are prescribed in those aged 10 years but needed to specify a lower age limit for the study to ensure all those eligible are included.

Pregnancies were matched to babies using month and year of birth corresponding to pregnancy end date, general practice number and family number. Babies needed to be

registered within 62 days of the pregnancy end date in order to be considered as a match for the pregnancy. Major congenital malformations, as defined by EUROCAT [8], were identified through medical codes listed in the baby's medical record and any supporting information to confirm the diagnosis, was checked for. Major congenital malformations were compared between potentially exposed and unexposed groups. Medical codes relating to pregnancy losses were used to determine if the loss was spontaneous, induced for medical reasons, induced for non-medical reasons, induced for unknown reasons or where the cause could not be identified. From previous work[9] we have found that anonymised freetext entered by general practitioners to accompany medical codes can aid in determining the type of pregnancy loss and in checking details of stillbirths. Freetext was reviewed for all pregnancy losses where the type of loss was uncertain and for all stillbirths. Any disparities in pregnancy outcomes and dates of pregnancies were updated in the dataset used for the analysis.

Information about the type of statin prescribed and the date of prescription were identified. Prescribing was initially categorised according to whether the prescription was issued in the three months before pregnancy, trimester 1 (1-90 days from the start of pregnancy), trimester 2 (91-180 days from the start of pregnancy) or trimester 3 (from day 181 until the end of pregnancy). Information on BMI, smoking and alcohol was identified at or close to pregnancy start date and prescribing of other medication for cardiovascular disease, diabetes, epilepsy and folic acid during pregnancy were also identified in the year before and during pregnancy. Records for pre-eclampsia, gestational diabetes and gestational hypertension occurring during pregnancy were also identified. Where data was not recorded on smoking status, alcohol use or BMI, this was classified as missing data.

Statistical analyses were conducted using STATA 13.0. Pregnancy losses were described and analysed using the Cox proportional hazards model with left truncation at 8 weeks to account for the unknown number of pregnancies where a loss occurs before the pregnancy is recognised. This follows previous work [10] and enables us to overcome selection bias that would arise from not being able to fully account for all losses in early pregnancy. Failure is defined as those pregnancies ending in any type of termination. Potential exposure to a statin was defined as a time dependent covariate which used date and length of the prescription as the exposure period: only prescriptions overlapping pregnancy weeks 8 to 20 were included in this analysis. For pregnancy losses, where an exact pregnancy start date (such as the date of the last menstrual period) was not recorded, a default pregnancy length of ten weeks is used. Given that pregnancy losses are being analysed, this could affect the results therefore, where used, default pregnancy lengths of eight weeks and twelve weeks were also included to check for any differences in results that may be due to this defaulting. Proportionality of hazards was verified and the best model was chosen by evaluating fit with each covariate in a univariate model.

Results

In this study, 281 pregnancies were identified where a prescription for a statin had been issued in the three months before pregnancy start date (231 pregnancies) and/or during the first trimester of pregnancy (124 pregnancies). These pregnancies were matched to 2643 pregnancies where a statin had not been prescribed during pregnancy or in the three months before the pregnancy start date. 262 of the 281 potentially exposed pregnancies were matched to at least eight unexposed pregnancies. Of those where matches were more difficult to find, twelve of the potentially exposed pregnancies were in women aged 40-49 years. Characteristics of the study cohort are given in table 1. Those who received a statin before or during pregnancy had a higher BMI, were more likely to be a smoker and a greater proportion received other prescribed medications, especially those for cardiovascular disease. Even though the patients were matched for evidence of a diagnosis of diabetes before pregnancy they were not matched on type of diabetes or treatment, hence there was a higher number of pregnancies affected by type 2 diabetes that was treated with diet in those who did not receive a statin prescription compared to those who did receive a statin prescription.

Table 2 shows the numbers of pregnancies where statins were prescribed in the three months before the date of the last menstrual period (LMP) and each trimester. Simvastatin and atorvastatin were the statins that were most prescribed during the study period. While most women ceased to be prescribed statins after the first trimester, a small number did continue to receive prescriptions (8.9%).

Table 3 summarises the overall pregnancy outcomes identified for this cohort. The proportions of deliveries for the cohort is lower than would be expected which is likely to be related to the age of the women included in this study and because nearly half had pre-existing diabetes which increases the risk of miscarriage.[9] Where a statin prescription had been recorded in the three months before and/or during pregnancy, the proportion of pregnancies ending in a delivery was 54.45% compared with 62.81% of pregnancies in those where a statin had not been prescribed. For those who had statins prescribed during or in the three months before pregnancy, a quarter of all pregnancies ended in a spontaneous loss (i.e. miscarriage) and an eighth of all pregnancies ended in a termination induced for non-medical reasons (i.e. personal circumstances). To investigate whether these differences are due to the numbers of women with diabetes included in the study, separate analyses were conducted: 23.29% of pregnancies in women with diabetes and a statin prescription experienced a spontaneous loss compared with 20.52% in those who had diabetes but did not receive a statin prescription.

Table 4 shows the results of the univariate analyses comparing delivery with termination for all covariates individually. While all three models with differing default time periods for pregnancy loss were run, the results of the univariate analysis were very similar especially for the default of ten and twelve weeks therefore only one set of results is shown.

The results indicated that smoking status, prescribing of folic acid and ACE inhibitors should be included in the final model. BMI will also be included in the final model as this is an

important covariate to consider in this study. While there may be a difference between lipophilic and hydrophilic statins, numbers prescribed hydrophilic statins in this study were small; it is not possible to include variables for prescription and type of statin in the final model due to collinearity problems.

Table 5 shows the results from the multivariate survival analysis with prescribing of statins included as a time dependent covariate. In using this time dependent covariate with left truncation at eight weeks, the number of potentially exposed pregnancies that were included in this model was 140. Three adjusted models are presented to account for the defaulting that is used for pregnancy losses where the pregnancy start date is not known. The time periods used were 8, 10 and 12 weeks; the results are very similar therefore the default of 10 weeks will be used as the overall result from the study.

In the unexposed group, 41 major malformations were identified in 40 liveborn infants and 8 malformations were identified in pregnancies that ended in a termination (2.9% of liveborn deliveries and terminations). In the group where a statin was received in the three months before or during the first trimester, seven malformations were identified in five liveborn infants with no malformations recorded in pregnancies that resulted in a termination (3.3% of liveborn deliveries and terminations).

Discussion

This study is one of the first to evaluate differences in pregnancy losses between women who are prescribed statins during pregnancy and those who are not. We have reported differences in the proportions of deliveries and pregnancy losses between these groups. This led to an adjusted hazard ratio of 1.67 (1.25 to 2.23) being found. The main difference was in the higher proportion of spontaneous losses: 25.27% of all potentially exposed pregnancies compared with 20.81% in those not exposed overall leading to losses occurring in 45.55% of all pregnancies in those prescribed a statin compared to 37.20% in those not prescribed a statin. Further investigation of the potential association between statin prescriptions and a reduced frequency of pregnancies resulting in a delivery indicated that smoking and type of diabetes were confounders however effect modification appears to still exist. Smoking is a well-known risk factor linked to increased rates of miscarriage and in a previous study that we conducted we found higher rates of pregnancy loss in those with both type 1 and type 2 diabetes.[9] We therefore matched on evidence of diabetes before pregnancy to try to overcome some of this difficulty however in the group not prescribed statins there were more people who had type 2 diabetes that was managed by diet therefore some residual confounding existed. However, separate analysis of those without diabetes indicated that proportions of pregnancies ending in a delivery was lower in those prescribed statins (54.11%) than those not prescribed statins (63.21%). We also reported on congenital malformations identified in the offspring: these results corresponded with those reported by others[1-4] with no differences in proportions found between mothers who had been prescribed statins and those who had not.

There are a number of strengths associated with this study. The GPRD is a powerful tool in assessing drug safety in pregnancy and has been used to study treatment of many chronic diseases during pregnancy.[9, 11, 12] Within the GPRD it is possible to include records for women from before the start of pregnancy through to the end of pregnancy, to determine whether the pregnancy resulted in a delivery or loss and if there were any malformations diagnosed, which is not possible with all data sources. The freetext was very valuable in determining the type of pregnancy loss where this was not apparent from the medical codes recorded. This allowed us to categorise 94% of the pregnancy losses into either spontaneous or induced. Other details identified within the freetext included a record noting patient concerns about potential exposures and reference was made to the Teratology Information Service. The freetext also gave more information about the pregnancy dates than can be obtained from just recorded codes. This enhances the accuracy of the study especially with regard to determining the classification of exposure. To reduce the potential impact of misclassification of statin exposure, a time dependent covariate was defined in order that only those prescriptions whose duration included weeks 8 to 20 of pregnancy were used in the analysis rather than the initial definition of any prescription in the three months before or during the first trimester of pregnancy. Changing the default length of the pregnancy loss also gave reassurance that the results are robust even if there has been a small amount of misclassification in the dates of the pregnancy. In studies using prescribing records there is the possibility of misclassification of exposures whereby a prescription is issued by the general practitioner but may not be dispensed or taken. Similarly there may be some

misclassification of smoking and alcohol consumption status whereby women make changes during pregnancy.

There are very few other studies that report and evaluate pregnancy loss following exposure to statins during early pregnancy. Ofori *et al.*[3] found that 52 of 153 (34%) pregnancies where a statin prescription had been filled in the year before or during trimester 1 ended in miscarriage, stillbirth or unspecified abortion compared with 27% in those not receiving a statin.[13] These proportions are lower than those found in our study (stillbirth and pregnancy loss 46.3% in statin exposed and 38.2% in the unexposed group). Winterfeld *et al.* in their study using data from the European Network of Teratology Information Services reported that 14.5% of pregnancies where a woman had taken a statin during the first trimester of pregnancy ended in miscarriage compared with 7.6% of their unexposed comparator group.[2] These lower proportions potentially reflect lower rates of reporting to the Teratology Information Services than data recorded in primary care. A similar study from the Canadian Teratology Information Service reported 21.9% of statin exposed pregnancies ended in a miscarriage compared with 17.2% in non-exposed pregnancies.[4] A study of the Merck pharmacovigilance database reported 18 (8%) spontaneous and 49 (21.8%) elective abortions of 225 pregnancies with known outcomes although it is likely that these figures are underreported.[14]

Apart from statins being linked to the differences in pregnancy loss between the groups, a potential explanation could be that those who are prescribed statins just before or in the early stages of pregnancy have not planned their pregnancy since statins are contraindicated in pregnancy. It is generally recognised[15] that a break in treatment during pregnancy will not have a detrimental effect on a mother's health. There are very few records in the database indicating pre-conception care although these numbers are likely to underestimate the true picture. However prescribing of folic acid appears to have a protective effect on pregnancy loss which, while underestimated by the database because folic acid is available over the counter (400mcg dose) does indicate some pregnancy planning in women included in both groups. Other possible medical reasons were also investigated for the differences in pregnancy loss including diagnosis of antiphospholipid syndrome, systemic lupus erythematosus and polycystic ovary syndrome. Differences in proportions between those potentially exposed and those not exposed to statins was very small.

Work in animal models has also the use of statins to treat pre-eclampsia which would require statins to be used later on in pregnancy. In our study we found that very few women receive statin prescriptions beyond the first trimester of pregnancy: only 34 pregnancies where statins were prescribed in the second and/or third trimesters, five of which did not receive a prescription during the second trimester and therefore could have been preparing for restarting statins following delivery. Just two pregnancies received a prescription for pravastatin after the start of the second trimester therefore it is not possible to comment on the potential for the treatment of preeclampsia with this medication, from existing observational studies.

We have shown that there are important differences in the proportions of pregnancies that result in a pregnancy loss in those who have been prescribed a statin just before or during the first trimester of pregnancy compared with those who have not been prescribed a statin. These differences result from a higher proportion of spontaneous losses in those potentially exposed to a statin. This is the first study to fully evaluate pregnancy loss with statin exposure and emphasises the need to do further research in this area in order to further explain or refute this potential association. This is particularly important given the number of women of child bearing age who are being prescribed statins but who may also want to conceive.

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Approval: Approval to use this data was obtained from the General Practice Research Database Independent Scientific Advisory Committee, protocol 08_053. Ethics approval is granted as part of an MREC agreement for all GPRD studies.

Author contribution: AMcG designed the study, carried out all of the coding work, collated and cleaned the data, double-coded the freetext pregnancy losses, analysed the data and wrote the paper. JS wrote the alogrithms to identify the pregnancies and type of loss, extracted the data from the GPRD and contributed to the writing of the paper. RC reviewed the malformations, discussed the results and contributed to the writing of the paper.

1. Bateman BT, Hernandez-Diaz S, Fischer MA, et al. Statins and congenital malformations: cohort study. *BMJ* 2015; 350:h1035
2. Winterfeld U, Allignol A, Panchaud A, et al. Pregnancy outcome following maternal exposure to statins: a multicentre prospective study. *BJOG* 2013; 120:463-71
3. Ofori B, Rey E, Berard A. Risk of congenital anomalies in pregnant users of statin drugs. *Br J Clin Pharmacol* 2007; 64:496-509
4. Taguchi N, Rubin ET, Hosokawa A, et al. Prenatal exposure to HMG-CoA reductase inhibitors: effects on fetal and neonatal outcomes. *Reprod Toxicol* 2008; 26:175-7
5. Hook EB, Regal RR. Conceptus viability, malformation, and suspect mutagens or teratogens in humans. The Yule-Simpson paradox and implications for inferences of causality in studies of mutagenicity or teratogenicity limited to human livebirths. *Teratology* 1991; 43:53-9
6. Andrews E, Tennis P. Promise and pitfalls of administrative data in evaluating pregnancy outcomes. *Pharmacoepidemiol Drug Saf* 2007; 16:1181-3
7. Snowball J, de Vries C. Determination of pregnancy on the General Practice Research Database. *Pharmacoepidemiol Drug Saf* 2007; 16:S118
8. Dolk H. EUROCAT: 25 years of European surveillance of congenital anomalies. *Archives of Disease in Childhood Fetal and Neonatal Edition* 2005; 90:F355-F8
9. McGrogan A, Snowball J, de Vries CS. Pregnancy losses in women with Type 1 or Type 2 diabetes in the UK: an investigation using primary care records. *Diabet Med* 2014; 31:357-65
10. Sammon CJ, Snowball J, McGrogan A, de Vries CS. Evaluating the hazard of foetal death following H1N1 influenza vaccination; a population based cohort study in the UK GPRD. *PLoS One* 2012; 7:e51734
11. Charlton RA, Hutchison A, Davis KJ, de Vries CS. Asthma management in pregnancy. *PLoS One* 2013; 8:e60247
12. Charlton RA, Weil JG, Cunnington MC, de Vries CS. Identifying major congenital malformations in the UK General Practice Research Database (GPRD): a study reporting on the sensitivity and added value of photocopied medical records and free text in the GPRD. *Drug Saf* 2010; 33:741-50
13. Thorogood M, Seed M, De Mott K. Management of fertility in women with familial hypercholesterolaemia: summary of NICE guidance. *BJOG* 2009; 116:478-9
14. Pollack PS, Shields KE, Burnett DM, et al. Pregnancy outcomes after maternal exposure to simvastatin and lovastatin. *Birth Defects Res A Clin Mol Teratol* 2005; 73:888-96
15. Lipid modification: cardivoascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease: NICE2015 Contract No.: CG181.

Table 1: Characteristics of the study cohort for those who received and did not receive a statin prescription including medical conditions diagnosed before pregnancy, medical conditions and medications prescribed during pregnancy.

		Statin prescription		No statin prescription	
		Number	**%**	**Number**	**%**
Total pregnancies		281		2643	
Total females		266		2453	
Age	15-19	4		40	1.51
	20-24	20	7.12	198	7.49
	25-29	44	15.66	405	15.32
	30-34	64	22.78	616	23.31
	35-39	73	25.98	767	29.02
	40-44	63	22.42	529	20.02
	45-49	13	4.63	88	3.33
BMI	<20	11	3.91	211	7.98
	20-24	74	26.33	851	32.2
	25-29	83	29.54	647	24.48
	30-34	56	19.93	329	12.45
	35-39	29	10.32	193	7.3
	40+	14	4.98	97	3.67
	Unknown	14	4.98	315	11.92
Smoking status	Smoker	87	30.96	685	25.92
	Non-smoker	143	50.89	1478	55.92
	Ex-smoker	50	17.79	451	17.06
	Unknown	1		29	1.1
Alcohol status	Drinker	173	61.57	1591	60.2
	Teetotal	62	22.06	444	16.8
	Ex-drinker	14	4.98	162	6.13
	Heavy drinker	6	2.14	31	1.17
	Unknown	26	9.25	415	15.7
Year of pregnancy start	1992-2000	22	7.83	248	9.38
	2000-04	78	27.76	1130	42.75
	2004-09	181	64.41	1265	47.86
Conditions diagnosed before pregnancy					
Diabetes		135	48.04	1186	44.87
	Type 1	48	17.08	364	13.77
	Type 2 managed by medication	72	25.62	289	10.93
	Type 2 not managed by medication	15	5.34	533	20.17
Hypertension		47	16.73	366	13.85
Cardiovascular disease		47	16.73	167	6.32
Renal disease		13	4.63	29	1.1
Antiphospholipid syndrome		0		4	

Systemic lupus erythematosus	2		4	
Polycystic ovary syndrome	19	6.76	110	4.16
Conditions diagnosed during pregnancy				
Pre-eclampsia	1	0.36	14	0.53
Gestational diabetes	7	2.49	15	0.57
Gestational hypertension	3		13	0.49
Medications prescribed during pregnancy				
5mg folic acid	50	17.79	283	10.71
400mcg folic acid*	76	27.05	454	17.18
Insulin	107	38.08	650	24.59
Oral antidiabetic treatment	65	23.13	226	8.55
Treatment for ketoacidosis	34	12.1	295	11.16
Hypertension medication	25	8.9	109	4.12
Beta blockers	53	18.86	165	6.24
Diuretics	38	13.52	139	5.26
Angina medication	19	6.76	14	0.53
Arrhythmia medication	3		4	
Non-statin lipid regulating medication	7	2.49	6	0.23
ACE inhibitors	73	25.98	135	5.11
Angiotensin II RA	17	6.05	43	1.63
Calcium channel blockers	32	11.39	106	4.01
Epilepsy medication	12	4.27	44	1.66

* Also available over the counter

Table 2: Statins prescribed in the three months before pregnancy and during each trimester

	3 months before LMP	**Trimester 1**	**Trimester 2**	**Trimester 3**	**Total pregnancies**
Lipophilic					
Simvastatin	124	98	17	12	**152**
Atorvastatin	86	63	9	6	**103**
Cerivastatin	2	1	0	0	**2**
Hydrophilic					
Rosuvastatin	5	4	0	0	**6**
Pravastatin	5	5	1	2	**8**
Fluvastatin	4	3	1	0	**4**
Combination	5	6	0	0	**6**
Total pregnancies	**231**	**180**	**28**	**20**	**281**

Table 3: Pregnancy outcomes for those who receive a prescription for a statin compared with those who do not

Outcomes		**Statin prescription**			**No statin prescription**		
		N	% of all outcomes	% of losses	N	% of all outcomes	% of losses
Delivery		153	54.45		1660	62.81	
	Stillbirth	4	1.42		27	1.02	
	Livebirth	149	53.02		1633	61.79	
	Mother – baby matched	99			1347		
	Multiple births	3			33		
Termination		128			983		
	Trimester 1	113	40.21	88.28	866	32.77	88.10
	Trimester 2	15	5.34	11.72	117	4.43	11.90
	Spontaneous	71	25.27	55.47	550	20.81	55.95
	Hydatidiform mole	0	0.00	0.00	4	0.15	0.41
	Ectopic	3	1.07	2.34	30	1.14	3.05
	Induced (medical)	1	0.36	0.78	18	0.68	1.83
	Induced (non-medical)	35	12.46	27.34	269	10.18	27.37
	Induced (unknown reasons)	7	2.49	5.47	54	2.04	5.49
	Unknown	11	3.91	8.59	58	2.19	5.90

Table 4: Results for the univariate survival models comparing delivery and any type of termination with a default of 10 weeks for terminations where the start date of pregnancy could not accurately be determined.

	HR (95% CI)
Statin exposure	1.77 (1.35 to 2.33)
Statin type	
No statin	Reference
Lipophilic	1.55 (1.26 to 1.90)
Hydrophilic	1.19 (0.47 to 3.02)
Combination	1.23 (0.15 to 10.06)
Smoker	
Non-smoker	Reference
Yes	1.21 (1.03 to 1.43)
Ex-smoker	0.96 (0.79 to 1.18)
Unknown	1.07 (0.48 to 2.37)
BMI	
<20	1.23 (0.93 to 1.63)
20-24	Reference
25-29	1.00 (0.83 to 1.21)
30-34	1.15 (0.91 to 1.45)
35-39	1.21 (0.91 to 1.60)
≥40	1.02 (0.69 to 1.51)
Unknown	0.87 (0.67 to 1.13)
Alcohol use	
Non-drinker	Reference
Yes	0.85 (0.71 to 1.03)
Ex-drinker	0.86 (0.62 to 1.20)
Heavy drinker	1.23 (0.70 to 2.17)
Unknown	0.80 (0.62 to 1.04)
Beta blocker	1.15 (0.87 to 1.51)
Diuretics	1.09 (0.81 to 1.46)
Ace inhibitors	1.35 (1.02 to 1.77)
Angiotensin receptor blockers	1.18 (0.76 to 1.84)
Calcium channel blockers	0.92 (0.65 to 1.30)
Renal disease	1.71 (0.68 to 4.27)
Epilepsy	1.05 (0.66 to 1.68)
Folic acid (high or low dose)	0.64 (0.54 to 0.77)

Table 5: Multivariate survival analysis using Cox proportional regression with statin prescription as a time varying covariate

Default	8 weeks HR (95% CI)	10 weeks HR (95% CI)	12 weeks HR (95% CI)
Potential statin exposure	2.02 (1.26 to 3.22)	1.67 (1.25 to 2.23)	1.69 (1.23 to 2.31)
Smoking status			
Non-smoker	Reference	Reference	Reference
Yes	1.04 (0.80 to 1.35)	1.20 (1.02 to 1.41)	1.14 (0.96 to 1.35)
Ex-smoker	0.94 (0.69 to 1.29)	0.95 (0.77 to 1.16)	0.94 (0.76 to 1.16)
Unknown	0.81 (0.19 to 3.54)	1.15 (0.52 to 2.55)	1.11 (0.50 to 2.47)
BMI			
<20	1.14 (0.73 to 1.77)	1.17 (0.88 to 1.55)	1.18 (0.88 to 1.57)
20-24	Reference	Reference	Reference
25-29	1.03 (0.76 to 1.38)	1.00 (0.82 to 1.21)	0.99 (0.82 to 1.21)
30-34	1.22 (0.85 to 1.76)	1.20 (0.95 to 1.51)	1.19 (0.94 to 1.51)
35-39	1.28 (0.82 to 1.99)	1.24 (0.93 to 1.65)	1.19 (0.89 to 1.60)
≥40	1.11 (0.61 to 2.03)	1.03 (0.69 to 1.53)	1.01 (0.68 to 1.50)
Unknown	0.89 (0.59 to 1.35)	0.86 (0.66 to 1.12)	0.87 (0.66 to 1.14)
Folic acid prescribed (high or low dose)	0.62 (0.47 to 0.80)	0.62 (0.52 to 0.74)	0.60 (0.50 to 0.73)
Ace inhibitor prescribed	1.60 (1.05 to 2.45)	1.21 (0.91 to 1.61)	1.21 (0.90 to 1.63)

Table 5: update

	8 weeks	10 weeks	12 weeks
Statin prescription	1.91 (1.18, 3.11)	1.60 (1.19, 2.15)	1.62 (1.17, 2.24)
Non-smoker	Reference	Reference	Reference
Smoker	1.05 (0.80, 1.38)	1.21 (1.02, 1.43)	1.15 (0.97, 1.37)
Ex-smoker	0.97 (0.71, 1.34)	0.98 (0.79, 1.20)	0.98 (0.78, 1.20)
Unknown	0.80 (0.18, 3.53)	1.16 (0.52, 2.58)	1.13 (0.51, 2.53)
BMI			
<20	1.11 (0.71, 1.74)	1.15 (0.87, 1.53)	1.16 (0.87, 1.55)
21-24	Reference	Reference	Reference
25-29	1.01 (0.75, 1.36)	0.99 (0.82, 1.20)	0.99 (0.81, 1.21)
30-34	1.21 (0.84, 1.75)	1.20 (0.95, 1.52)	1.20 (0.94, 1.52)
35-39	1.23 (0.79, 1.93)	1.24 (0.93, 1.65)	1.19 (0.88, 1.59)
40+	1.11 (0.60, 2.03)	1.03 (0.69, 1.54)	1.01 (0.68, 1.50)
Unknown	0.85 (0.54, 1.35)	0.83 (0.62, 1.12)	0.85 (0.63, 1.14)
Teetotaller	Reference	Reference	Reference
Drinker of alcohol	0.80 (0.60, 1.07)	0.83 (0.69, 1.01)	0.81 (0.66 - 0.98)
Ex-drinker	1.04 (0.65, 1.67)	0.85 (0.61, 1.19)	0.85 (0.60 - 1.18)
Heavy drinker	1.12 (0.38, 3.27)	1.11 (0.61, 2.02)	1.18 (0.62 - 2.23)
Unknown	0.88 (0.57, 1.38)	0.89 (0.67, 1.19)	0.87 (0.65 - 1.15)
Folic acid prescribed (high or low dose)	0.59 (0.45, 0.78)	0.61 (0.51, 0.73)	0.60 (0.49, 0.72)
Ace inhibitor prescribed	1.56 (1.01, 2.42)	1.24 (0.92, 1.66)	1.23 (0.91, 1.67)
Beta-blocker	1.33 (0.86, 2.07)	1.02 (0.76, 1.37)	1.05 (0.78 - 1.41)
Diuretics	1.10 (0.70, 1.75)	0.94 (0.69, 1.29)	0.96 (0.70 - 1.32)
Angiotensin	1.14 (0.54, 2.42)	1.20 (0.76, 1.91)	1.19 (0.75 - 1.90)
Calcium channel blockers	0.65 (0.37, 1.15)	0.90 (0.63, 1.30)	0.87 (0.60 - 1.26)
Epilepsy	0.77 (0.34, 1.73)	0.99 (0.61, 1.60)	0.85 (0.50 - 1.42)
Renal	1.27 (0.32, 4.98)	1.18 (0.46, 3.03)	0.97 (0.35 - 2.66)

Table 6

Comparing outcomes of delivery and termination for non-medical reasons

	8 weeks	10 weeks	12 weeks
Statin prescription	1.49 (0.62, 3.55)	1.90 (0.97, 3.72)	1.68 (0.82, 3.41)
Smoker			
Yes	1.59 (0.99, 2.55)	1.69 (1.18, 2.44)	1.65 (1.14, 2.38)
No	Reference	Reference	Reference
Ex-smoker	0.96 (0.51, 1.81)	0.87 (0.53, 1.43)	0.90 (0.55, 1.49)
Unknown	-	1.26 (0.15, 10.73)	1.12 (0.13, 9.51)
BMI			
<20	0.55 (0.19, 1.53)	0.80 (0.40, 1.58)	0.76 (0.37, 1.54)
21-24	Reference	Reference	Reference
25-29	1.20 (0.69, 2.10)	1.28 (0.83, 1.97)	1.36 (0.87, 2.11)
30-34	0.92 (0.42, 2.05)	1.17 (0.65, 2.11)	1.14 (0.62, 2.092)
35-39	1.51 (0.67, 3.41)	1.41 (0.73, 2.71)	1.35 (0.70, 2.59)
40+	1.26 (0.41, 3.81)	1.48 (0.66, 3.28)	1.57 (0.70, 3.52)
Unknown	1.02 (0.48, 2.20)	0.87 (0.46, 1.64)	0.95 (0.50, 1.80)
Folic acid prescribed (high or low dose)	0.16 (0.08, 0.32)	0.16 (0.09, 0.28)	0.16 (0.09, 0.28)
Ace inhibitor prescribed	2.36 (1.00, 5.57)	1.85 (0.91, 3.75)	2.02 (0.99, 4.147)
Alcohol			
Yes	0.82 (0.47, 1.45)	0.77 (0.50, 1.20)	0.75 (0.48 - 1.17)
No	Reference	Reference	Reference
Ex-drinker	1.52 (0.59, 3.92)	1.34 (0.64, 2.81)	1.32 (0.63 - 2.718)
Heavy drinker	2.56 (0.40, 16.44)	1.07 (0.20, 5.70)	1.08 (0.20 - 5.71)
Unknown	0.87 (0.37, 2.04)	0.91 (0.47, 1.75)	0.83 (0.43 - 1.62)
Beta-blocker	1.37 (0.54, 3.44)	1.16 (0.53, 2.53)	1.21 (0.55 - 2.66)
Diuretics	1.37 (0.48, 3.91)	1.07 (0.43, 2.64)	1.06 (0.43 - 2.61)
Angiotensin	0.40 (0.04, 3.89)	0.41 (0.08, 2.16)	0.42 (0.08 - 2.18)
Calcium channel blockers	0.66 (0.20, 2.16)	0.71 (0.27, 1.88)	0.71 (0.27 - 1.88)
Epilepsy	-	0.52 (0.11, 2.39)	0.24 (0.03 - 1.91)
Renal	-	-	-

Spontaneous loss versus delivery

	8 weeks	10 weeks	12 weeks
Statin prescription	2.51 (1.27, 4.96)	1.73 (1.17, 2.56)	1.86 (1.21, 2.85)
Smoker			
Yes	0.73 (0.49, 1.07)	1.03 (0.83, 1.28)	1.00 (0.80, 1.26)
No	Reference	Reference	Reference
Ex-smoker	1.00 (0.67, 1.50)	0.93 (0.72, 1.20)	0.93 (0.72, 1.21)
Unknown	0.72 (0.08, 6.30)	1.15 (0.39, 3.35)	1.15 (0.39, 3.36)
BMI			
<20	1.31 (0.71, 2.42)	1.20 (0.82, 1.75)	1.24 (0.84, 1.81)
21-24	Reference	Reference	Reference
25-29	0.88 (0.58, 1.33)	0.89 (0.70, 1.14)	0.88 (0.68, 1.13)
30-34	1.36 (0.86, 2.16)	1.28 (0.96, 1.69)	1.30 (0.97, 1.73)
35-39	1.31 (0.72, 2.38)	1.29 (0.91, 1.83)	1.23 (0.85, 1.76)
40+	1.09 (0.50, 2.41)	0.94 (0.57, 1.56)	0.91 (0.55, 1.51)
Unknown	0.74 (0.38, 1.44)	0.81 (0.55, 1.20)	0.83 (0.56, 1.23)
Folic acid prescribed (high or low dose)	0.88 (0.63, 1.24)	0.84 (0.68, 1.04)	0.81 (0.65, 1.01)
Ace inhibitor prescribed	1.02 (0.57, 1.83)	0.98 (0.67, 1.43)	0.90 (0.61, 1.33)
Alcohol			
Yes	0.69 (0.47, 1.00)	0.81 (0.64, 1.03)	0.78 (0.61 - 0.99)
No	Reference	Reference	Reference
Ex-drinker	0.78 (0.42, 1.47)	0.66 (0.42, 1.02)	0.67 (0.43 - 1.05)
Heavy drinker	-	1.02 (0.41, 2.53)	1.14 (0.46 - 2.86)
Unknown	0.85 (0.47, 1.53)	0.82 (0.57, 1.19)	0.80 (0.55 - 1.15)
Beta-blocker	1.62 (0.90, 2.91)	1.10 (0.76, 1.57)	1.15 (0.80 - 1.66)
Diuretics	1.47 (0.80, 2.71)	1.17 (0.79, 1.71)	1.17 (0.79 - 1.72)
Angiotensin	0.91 (0.35, 2.37)	1.17 (0.67, 2.02)	1.23 (0.708 - 2.16)
Calcium channel blockers	0.64 (0.31, 1.32	0.94 (0.61, 1.45)	1.01 (0.567 - 1.82)
Epilepsy	1.15 (0.46, 2.86)	1.08 (0.61, 1.91)	1.62 (0.40 - 6.51)
Renal	2.05 (0.16, 26.03)	2.40 (0.66, 8.73)	-