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METHYLERGONOVINE MALEATE AND THE RISK OF MYOCARDIAL ISCHEMIA AND INFARCTION

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Abstract

Objectives—To examine the risk of acute coronary syndrome (ACS) and acute myocardial infarction (AMI) associated with Methylergonovine maleate (Methergine) use in a large database of inpatient delivery admissions in the United States.

Study design—We conducted a retrospective cohort study using data from the Premier Perspective Database, and identified 2,233,630 women hospitalized for delivery between 2007 and 2011 (approximately one-seventh of all U.S. deliveries during this period). Exposure was defined

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Disclosures:

SHD has consulted for Novartis, GSK-Biologics and AstraZenaca for unrelated projects.

by a charge code for methylergonovine during the delivery hospitalization. Study outcomes included acute coronary syndrome (ACS) and acute myocardial infarction (AMI). Propensity score matching was used to address potential confounding.

Results—Methylergonovine was administered to 139,617 (6.3%) patients. Overall, 6 patients exposed to methylergonovine (0.004%) and 52 patients unexposed to methylergonovine (0.002%) had an ACS. Four patients exposed to methylergonovine (0.003%) and 44 patients in the unexposed group (0.002%) had an AMI. After propensity score matching, the relative risk for ACS associated with methylergonovine exposure was 1.67 (95% CI 0.40 – 6.97) and the risk difference was 1.44 per 100,000 patients (95% CI -2.56, 5.45); the relative risk for AMI associated with methylergonovine exposure was 1.00 (95% CI 0.20 – 4.95) and the risk difference was 0.00 per 100,000 patients (95% CI -3.47, 3.47).

Conclusions—Despite studying a very large proportion of U.S. deliveries, we did not find a significant increase in the risk of ACS or AMI in women receiving methylergonovine compared with those who did not; estimates were increased only modestly or not at all. The upper limit of the 95% confidence interval of our analysis suggests that treatment with methylergonovine would result in no more than 5 additional cases of ACS and 3 additional cases of AMI per 100,000 exposed patients.

Keywords

Postpartum hemorrhage; Uterine atony; Methylergonovine; Myocardial Infarction

Introduction

Methylergonovine maleate (Methergine) is a semi-synthetic ergot alkaloid that acts directly on the smooth muscle of the uterus to cause rapid and sustained contraction.¹ It has a long track record of use to treat postpartum uterine atony,^{1, 2} the leading cause of postpartum hemorrhage.^{3, 4} Because of their effect on smooth muscle, ergot alkaloids, including methylergonovine, can induce vasoconstriction. They can cause clinically significant coronary vasospasm and there are several case reports of myocardial ischemia and infarction in association with obstetric exposure to ergot alkaloids,⁵⁻¹³ including one fatality.¹²

The U.S. Food and Drug Administration (FDA), in the January – March 2012 quarterly report from its Adverse Events Reporting System (FAERS), identified a “potential signal of serious risk/new safety information” regarding myocardial ischemia and infarction associated with methylergonovine-induced vasospasm.¹⁴ Following this, in June, 2012, the label for methylergonovine was changed to state that patients with “coronary artery disease or risk factors for coronary artery disease (e.g., smoking, obesity, diabetes, high cholesterol) may be more susceptible to developing myocardial ischemia and infarction associated with methylergonovine-induced vasospasm.”¹⁵

The FDA Adverse Events Reporting System relies on spontaneous reports of adverse events that clinicians attribute to medication exposures. While, like case reports, the system is useful in generating signals of potential harms associated with medications, it lacks both robust capture of events and information about the source population from which those

events are drawn. It cannot be utilized to determine the magnitude of the risks associated with a medication, nor can it account for potential confounders of any observed association. Signals of adverse drug effects in FAERS must be followed up with pharmacoepidemiologic studies to properly define if a causal effect is likely to be present and to quantify the magnitude of any observed increase in risk.

In order to determine the frequency of the postulated risk in routine practice, we sought to measure the occurrence of acute coronary syndrome (ACS) and acute myocardial infarction (AMI) following methylergonovine use in routine care, using a very large database of inpatient delivery admissions in the United States. This information can be useful in guiding clinicians' interpretation of the recent FDA report and label change and their choice of whether to use methylergonovine in the treatment of uterine atony.

Materials and Methods

COHORT

Study data were derived from the Premier Perspective Database, a hospital-based healthcare utilization database that has information on about one-seventh of all inpatient hospitalizations in the United States, for four year (4th quarter 2007 to 3rd quarter 2011). Premier provides these data to hospitals for benchmarking purposes. The database contains information on charges for medications, procedures, blood products, and diagnostic tests during each hospitalization, as well as patient demographic information and hospital characteristics. Discharge diagnoses are recorded using codes from the International Classification of Diseases, 9th revision- Clinical Modification (ICD 9-CM). This dataset has been used in multiple prior studies to evaluate the safety and effectiveness of various inpatient medications.¹⁶⁻¹⁹ These data are also used by the FDA for drug safety surveillance and by the Centers for Medicare and Medicaid Services for quality initiatives. The use of this dataset for research was approved by the institutional review board of the Brigham and Women's Hospital, Boston, MA and a Data Use Agreement was in place.

We identified all inpatient admissions of women age 12 to 55 for delivery using a validated algorithm as described by Kuklina et al.,²⁰ accounting for temporal changes in diagnostic coding (Appendix 1). This algorithm identifies delivery admissions by the presence of a diagnosis code for delivery or procedure codes indicating delivery (e.g. cesarean delivery, instrumented vaginal delivery). Hospitalizations with diagnoses indicating ectopic pregnancy, hydatiform mole, or other abnormal products of conception, or procedure codes indicating abortion were excluded. While methylergonovine is sometimes used to treat excessive bleeding following miscarriage or abortion, the majority of these patients are not hospitalized. Therefore, we would not have robust capture of the population exposed to methylergonovine in these clinical situations and would be unable to reliably calculate the frequency of the complication of ACS/AMI.

STUDY EXPOSURE AND OUTCOMES

Methylergonovine exposure was defined by the presence of a charge code for injectable or oral methylergonovine any time during the delivery hospitalization. The referent group consisted of patients without such a charge.

The primary study outcome was the development of acute coronary syndrome (ACS; composite of acute myocardial infarction and unstable angina) defined by ICD 9 CM codes 410.xx (excluding 410.x2) and 411.xx during the delivery hospitalization. As a secondary outcome, we identified the development of acute myocardial infarction (AMI) defined by the presence of ICD 9 CM codes 410.xx (excluding 410.x2). The ICD 9 CM codes for these conditions have been validated and shown to have very high positive predictive values.^{21, 22} As the posited mechanism for methylergonovine induced ACS/AMI is vasospasm, these events, if related to exposure, should occur during the index hospitalization.

COVARIATES

We identified as covariates conditions that might confound the association between methylergonovine exposure and ACS/AMI. These included patient demographics, obstetrical/medical conditions, markers of the presence, etiology, and severity of obstetric hemorrhage, and characteristics of the hospital at which delivery occurred. Demographic factors assessed included age (classified into 7 categories), race/ethnicity (classified as white, black, Hispanic, or other/unknown), and calendar year of delivery. Medical/obstetrical conditions were identified using ICD 9 CM codes (see Appendix 2) and chosen for inclusion as covariates based on their prior association with AMI in pregnancy^{23, 24} or biological plausibility as risk factors for ACS/AMI; these included hypertensive disorders (including pre-existing, gestational, or preeclampsia), diabetes (pre-existing or gestational), chronic ischemic heart disease, chronic renal disease, obesity, dyslipidemia, drug or alcohol abuse, tobacco use, asthma, hypercoagulable conditions, migraines, chronic anemia, delivery by cesarean, prior cesarean delivery, stillbirth/intrauterine fetal demise, multiple gestations, chorioamnionitis, and major puerperal infection.

Because postpartum hemorrhage is an indication for the administration of methylergonovine and has itself been identified as a risk factor for ACS/AMI,^{23, 25} we included multiple variables to identify the presence, etiology, and severity of postpartum hemorrhage. The presence and etiologies of postpartum hemorrhage were identified using ICD 9 CM codes (see Appendix 2) and included hemorrhage from uterine atony, abnormal placentation, uterine rupture, placental abruption, obstetric trauma, hemorrhage due to coagulopathy, amniotic fluid embolism, and delayed postpartum hemorrhage. Severity was measured by charge codes for the number of units of packed red blood cells transfused (categorized as 0, 1-5, 6-9, 10), number of units of fresh frozen plasma transfused (categorized as 0, 1-5, 6-9, 10), and whether the patient received platelets or cryoprecipitate or had a peripartum hysterectomy.

Characteristics of the hospital where the delivery occurred were also defined, as these may affect the decision to administer uterotonics and/or the accurate diagnosis of ACS/AMI. Hospitals accredited by the Association of American Medical Colleges were classified as

teaching hospitals. Annual delivery volume was determined for each hospital by dividing the total number of deliveries for each hospital during the study time period by the number of months that the hospital performed one or more deliveries and then multiplying this figure by 12. Hospitals were then divided into 3 roughly equally sized groups (in numbers of hospitals) and designated as small, medium or large delivery centers corresponding to an annual delivery volume of 805, 806 to 1891, and 1892, respectively.

STATISTICAL ANALYSIS

To adjust for potential differences between patients exposed to methylergonovine and those unexposed, we employed propensity score matching. A propensity score predicting methylergonovine exposure was estimated using a logistic regression model that included all the covariates described above (patient demographics, obstetrical/medical conditions, markers of the presence, etiology, and severity of obstetric hemorrhage, and characteristics of the hospital at which delivery occurred) without further selection. Patients exposed to methylergonovine were matched to those unexposed to methylergonovine based on propensity score in a 1:1 fixed ratio using a nearest neighbor algorithm with a caliper of 0.05.²⁶ This resulted in 138,412 matched pairs, such that 99.1% of the methylergonovine exposed patients were matched to an unexposed control. Relative risks and risk differences of ACS and AMI associated with methylergonovine exposure were then estimated directly.

SENSITIVITY AND SUBGROUP ANALYSES

As a sensitivity analysis, we estimated the risk of AMI and ACS associated with exposure to methylergonovine after adjusting for propensity score decile (as opposed to matching).²⁷ This approach preserves more of the cohort (in particular the unexposed) in the analysis and thus potentially increases the efficiency of the analysis. Patients in the unexposed group that had a propensity score lower than the lowest value observed in the exposed group and patients in the exposed group with a propensity score higher than the highest observed in the non-exposed group were excluded (n=59); trimming of the tails of the propensity score in this manner may further reduce residual confounding.²⁸

We also performed a sensitivity analysis using PS matching but excluding deliveries that occurred in hospitals where there were no documented administrations of methylergonovine during the study period (n=55,836). This was done to ensure that our results were not biased by the potential inclusion of deliveries occurring in hospitals where methylergonovine administration is not reliably coded.

Finally, we studied the subset of the cohort with known coronary artery disease or coronary disease risk factors, in keeping with the FDA's drug label revisions. For this analysis, we identified all admissions for patients with ICD 9 CM diagnostic codes indicating pre-existing hypertension, pre-existing diabetes, tobacco use, obesity, chronic renal disease, dyslipidemia, or chronic ischemic heart disease (Appendix 2).

Results

COHORT CHARACTERISTICS

The cohort consisted of 2,233,630 women hospitalized for delivery, or about one-seventh of all deliveries in the U.S. for the years studied. The mean age of patients in the cohort was 27.7; 51.4% were white. Cesarean delivery occurred in 34.0% of patients. Methylergonovine was administered during the delivery hospitalization to 139,617 (6.3%) patients.

There were several important baseline differences between patients who received methylergonovine and those who did not (Table 1). Methylergonovine exposed patients were somewhat younger than non-exposed patients, more likely to be of Hispanic ethnicity, and less likely to be white or black. They had a higher incidence of all of the etiologies of obstetric hemorrhage that were assessed and were more likely to be transfused packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate. They were more likely to undergo peripartum hysterectomy. They had a lower incidence of hypertensive disorders, obesity, drug abuse, asthma, prior cesarean delivery, and a higher incidence of chronic anemia, cesarean delivery, stillbirth, multiple gestation, chorioamnionitis, and major puerperal infection. They were less likely to deliver at a teaching hospital or a medium volume delivery center. After propensity score matching, these differences were no longer present and the absolute difference in the frequency of all measured covariates between the exposed and unexposed patients was less than 0.5% (Table 2).

ASSOCIATION OF METHYLERGONOVINE EXPOSURE WITH ACUTE CORONARY SYNDROME AND ACUTE MYOCARDIAL INFARCTION

In the overall cohort, 6 patients exposed to methylergonovine (0.004%) and 52 patients unexposed to methylergonovine (0.002%) had an ACS. None of the patients with ACS in the methylergonovine group died in-hospital and 3 (5.7%) of the patients with ACS in the unexposed group died. The unadjusted relative risk of ACS associated with methylergonovine exposure was 1.73 (95% confidence interval (CI) 0.74, 4.03). The unadjusted risk difference for ACS associated with methylergonovine exposure was 1.81 events per 100,000 patients (95% CI -1.69, 5.32). After adjustment for potentially confounding variables using propensity score matching, the relative risk was 1.67 (95% CI 0.40, 6.97) and the risk difference was 1.44 per 100,000 patients (95% CI -2.56, 5.45).

Among patients with any ACS, 4 in the methylergonovine exposed (0.003%) and 44 patients in the unexposed group had an AMI (0.002%); the unadjusted relative risk for AMI was 1.36 (95% CI 0.49, 3.79) and the risk difference was 0.76 per 100,000 patients (95% CI -2.11, 3.64). We again used propensity score matching to adjust for confounding and this resulted in a relative risk for AMI associated with methylergonovine exposure of 1.00 (95% CI 0.20, 4.95) and a risk difference per 100,000 patients of 0.00 (95% CI -3.47, 3.47).

SENSITIVITY ANALYSES

In analyses adjusted for PS decile, the relative risk for ACS associated with methylergonovine exposure was 1.22 (95% CI 0.51, 2.92) and for AMI was 0.99 (0.35, 2.84). These estimates are similar to those of the matched analysis, and the precision was

increased. We also performed a matched analysis excluding hospitals with no documented administrations of methylergonovine. In this analysis, there were 137,690 matched pairs. There was the loss of a single ACS/AMI event in the unexposed group and the number of events in the exposed group remained the same. Thus, we estimated a relative risk of 2.50 (95% CI 0.49,12.89) and a risk difference per 100,000 patients of 2.18 (-1.59, 5.94) for ACS and a relative risk of 1.50 (95% CI 0.25,8.98) and risk difference per 100,000 patients of 0.73 (95% CI -2.46, 3.91) for AMI. Note, the upper limit of the risk difference remained similar to that observed in the main analysis.

SUBGROUP ANALYSIS OF PATIENTS WITH CORONARY ARTERY DISEASE RISK FACTORS

The subset of the cohort with known coronary artery disease or coronary artery disease risk factors, including pre-existing hypertension, pre-existing diabetes, tobacco use, obesity, chronic renal disease, or dyslipidemia, included 269,817 patients (12.1% of the entire cohort) of whom 14,489 (5.4%) were exposed to methylergonovine. There was a single case of ACS (an AMI) among those exposed to methylergonovine in this sub-cohort. There were 28 cases of ACS and 24 cases of AMI in the 255,328 unexposed patients in the sub-cohort.

Discussion

Using this large, hospital-based sample of over 2.2 million delivery admissions in the U.S., we observed just 6 cases of ACS and 4 cases of AMI among the 139,617 patients exposed to methylergonovine. Despite studying a very large proportion of U.S. deliveries, we did not find a significant increase in the risk of ACS or AMI in women receiving methylergonovine compared with those who did not; estimates were increased only modestly or not at all. The upper limit of the 95% confidence interval of our analysis suggests that if there were any risk at all, treatment with methylergonovine would at most result in no more than 5 additional cases of ACS and 3 additional cases of AMI per 100,000 exposed patients. These estimates provide context regarding the magnitude of the potential risk recently highlighted by the FDA Adverse Events Reporting System and label changes concerning the risk of acute myocardial ischemia and infarction associated with methylergonovine exposure.

Clinicians must balance this very small potential increase in absolute risk of ACS and AMI associated with methylergonovine exposure with its proven benefit in treating uterine atony. Delay in the administration of uterotonic medications has been implicated as an important risk factor in the development of severe PPH.²⁹ Avoiding administering methylergonovine to patients with poor uterine tone because of concern about precipitating myocardial ischemia may have the unintended consequence of increasing maternal morbidity if it increased the occurrence of severe PPH. While pharmacologic alternatives to methylergonovine for the treatment of uterine atony exist, including carboprost and misoprostol, each of these medications also has important side-effects.³⁰ Further, it is not uncommon for patients to require treatment with more than one uterotonic to achieve adequate uterine tone.

The recent change in the label for methylergonovine suggested that there may be an increased risk of methylergonovine-induced myocardial ischemia and infarction in patients

with known CAD or CAD risk factors. We therefore also identified the sub-cohort of patients with chronic ischemic heart disease or risk factors including preexisting hypertension, pre-existing diabetes, tobacco use, obesity, chronic renal disease, and dyslipidemia. We found only 1 case of ACS/AMI in the 14,489 methylergonovine exposed patients with these risk factors. While observing only a single case precludes meaningful analysis of whether those with CAD risk factors are at heightened risk of methylergonovine induced myocardial ischemia and infarction, it does suggest that the absolute risk associated with methylergonovine exposure in these patients is also either zero or extremely low.

Our study should be interpreted in the context of the limitations inherent in its design. Because of the rarity of ACS and AMI in this population, the confidence intervals on our estimates of relative risk and risk differences are relatively wide. However, our study cohort was very large, containing information on over 2 million delivery admissions, which represents approximately one-seventh of all delivery hospitalizations in the United States over a 4 year period. A better powered study is unlikely to be performed given currently available data sources for performing pharmacoepidemiologic studies of inpatient medication exposures and adverse outcomes. Likewise, our study lacks power to explore the interactions between methylergonovine and other classes of medication which may potentiate its effects or to explore the risks associated with its use in particular subgroups of patients. An additional potential limitation is that outcomes are defined based on diagnostic codes since our study is based on healthcare utilization data collected primarily for billing purposes, and therefore lacks certain information, such as measured troponin levels and electrocardiogram findings, that would be helpful to validate the outcome based on clinical criteria. To overcome this, we used validated codes that have been shown to capture the occurrence of ACS and AMI with great accuracy.^{21, 22} We also rely on charge codes to ascertain exposure to methylergonovine. While in the Premier data there is an expectation that if a charge code is registered then the medication was administered, we cannot validate that this was the case in all instances; thus some misclassification of the exposure is possible. The Premier dataset only includes information on chronic conditions coded during the delivery hospitalization and some of these conditions, including obesity and tobacco use, are not well captured in healthcare utilization data. While we account for all measured confounders of the causal effect of methylergonovine on the risk of ACS and AMI using sophisticated analytic techniques, some bias in our estimates of effect due to residual confounding is therefore possible; yet given the infrequency of the outcomes of ACS and AMI, it is unlikely that this study question could be addressed without using such healthcare utilization data. Last, while we can only identify ACS and AMI events that occurred during the delivery hospitalization and not those that followed hospital discharge, the mechanism of methylergonovine induced ACS/AMI suggests that these events, if causally related to methylergonovine, would occur soon after exposure such that we should capture all relevant events in our analysis.

In conclusion, our study suggests that the increase in the risk of ACS or AMI following methylergonovine exposure, if present at all, is extremely small. The cumulative evidence available to date suggests methylergonovine should retain its role as an important drug in the armamentarium used to treat uterine atony and the postpartum hemorrhage for which it is an important risk.

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Condensation

We studied the risk of acute coronary syndrome and myocardial infarction associated with the administration of methylergonovine during the delivery hospitalization; estimates of risk were increased modestly or not at all.

Table 1

Baseline characteristics of patients in the overall cohort.

	Methylergonovine maleate exposed, N (%)	Non-exposed, N (%)	Difference (%)
Total	139617	2094013	
Demographics			
Age, years			
12-19	14538(10.41)	195250(9.32)	1.09
20-24	34561(24.75)	489503(23.38)	1.37
25-29	39650(28.40)	595818(28.45)	-0.05
30-34	31706(22.71)	506808(24.20)	-1.49
35-39	15395(11.03)	248285(11.86)	-0.83
40-44	3509(2.51)	54935(2.62)	-0.11
44-55	258(0.18)	3414(0.16)	0.02
Race/ethnicity			
White	68880(49.33)	1078758(51.52)	-2.19
Black	16378(11.73)	288592(13.78)	-2.05
Hispanic	19254(13.79)	226627(10.82)	2.97
Other/Unknown	35105(25.14)	500036(23.88)	1.26
Year of delivery			
2007	8858(6.34)	130629(6.24)	0.1
2008	35361(25.33)	521465(24.90)	0.43
2009	35089(25.13)	522008(24.93)	0.2
2010	34039(24.38)	516032(24.64)	-0.26
2011	26270(18.82)	403879(19.29)	-0.47
Etiology of obstetric hemorrhage and markers of its severity			
Abnormal placentation	4717(3.38)	22640(1.08)	2.3
PPH due to uterine atony	19410(13.90)	22915(1.09)	12.81
Amniotic fluid embolism	31(0.02)	74(0.00)	0.02
PPH due to coagulopathy	795(0.57)	3648(0.17)	0.4
Delayed PPH	2050(1.47)	3128(0.15)	1.32
Uterine rupture	144(0.10)	984(0.05)	0.05
Placental abruption	2016(1.44)	21504(1.03)	0.41
Antepartum hemorrhage from other sources	653(0.47)	6030(0.29)	0.18
Obstetric trauma	10808(7.74)	140088(6.69)	1.05
Packed red blood cells, units			
0	133312(95.48)	2078170(99.24)	-3.76
1-5	5580(4.00)	14893(0.71)	3.29
6-9	469(0.34)	670(0.03)	0.31
10	256(0.18)	280(0.01)	0.17

	Methylergonovine maleate exposed, N (%)	Non-exposed, N (%)	Difference (%)
Total	139617	2094013	
Demographics			
Fresh frozen plasma, units			
0	138386(99.12)	2092159(99.91)	-0.79
1-5	967(0.69)	1520(0.07)	0.62
6-9	157(0.11)	214(0.01)	0.1
10	107(0.08)	120(0.01)	0.07
Cryoprecipitate	422(0.30)	507(0.02)	0.28
Platelets	157(0.11)	405(0.02)	0.09
Peripartum hysterectomy	636(0.46)	1398(0.07)	0.39
Medical and obstetrical conditions			
Pre-existing hypertension	1491(1.07)	45246(2.16)	-1.09
Gestational hypertension	3294(2.36)	75697(3.61)	-1.25
Pre-existing hypertension with superimposed preeclampsia	278(0.20)	11946(0.57)	-0.37
Mild preeclampsia	1863(1.33)	50322(2.40)	-1.07
Severe preeclampsia/eclampsia	876(0.63)	31033(1.48)	-0.85
Pre-existing diabetes	1041(0.75)	19022(0.91)	-0.16
Gestational diabetes	7902(5.66)	116709(5.57)	0.09
Chronic ischemic heart disease	16(0.01)	312(0.01)	0
Chronic renal disease	368(0.26)	5313(0.25)	0.01
Obesity	4980(3.57)	80503(3.84)	-0.27
Dyslipidemia	82(0.06)	1519(0.07)	-0.01
Drug abuse	1574(1.13)	27339(1.31)	-0.18
Alcohol abuse	158(0.11)	2161(0.10)	0.01
Tobacco use	7954(5.70)	135032(6.45)	-0.75
Asthma	4333(3.10)	69247(3.31)	-0.21
Hypercoagulable state	409(0.29)	6378(0.30)	-0.01
Migraine headache	684(0.49)	9992(0.48)	0.01
Chronic anemia	17096(12.24)	168700(8.06)	4.18
Cesarean delivery	49033(35.12)	710555(33.93)	1.19
Previous cesarean delivery	18131(12.99)	345487(16.50)	-3.51
Stillbirth	1042(0.75)	12480(0.60)	0.15
Multiple gestation	4422(3.17)	38218(1.83)	1.34
Chorioamnionitis	4273(3.06)	31224(1.49)	1.57
Major puerperal infection	856(0.61)	6249(0.30)	0.31
Hospital characteristics			
Teaching hospital	43929(31.46)	763859(36.48)	-5.02
Delivery volume			
Low	13365(9.57)	173308(8.28)	1.29

	Methylergonovine maleate exposed, N (%)	Non-exposed, N (%)	Difference (%)
Total	139617	2094013	
Demographics			
Medium	32545(23.31)	535842(25.59)	-2.28
High	93707(67.12)	1384863(66.13)	0.99

Table 2

Baseline characteristics of patients in the propensity score matched cohort.

	Methylergonovine maleate exposed, N (%)	Non-exposed, N (%)	Difference (%)
Total	138412	138412	
Demographics			
Age, years			
12-19	14419(10.42)	14636(10.57)	-0.15
20-24	34263(24.75)	34468(24.90)	-0.15
25-29	39305(28.40)	39155(28.29)	0.11
30-34	31425(22.70)	31272(22.59)	0.11
35-39	15262(11.03)	15128(10.93)	0.1
40-44	3484(2.52)	3510(2.54)	-0.02
44-55	254(0.18)	243(0.18)	0
Race/ethnicity			
White	68314(49.36)	68350(49.38)	-0.02
Black	16276(11.76)	16121(11.65)	0.11
Hispanic	19010(13.73)	19196(13.87)	-0.14
Other/Unknown	34812(25.15)	34745(25.10)	0.05
Year of delivery			
2007	8781(6.34)	8613(6.22) ^	0.12
2008	35008(25.29)	35053(25.33)	-0.04
2009	34769(25.12)	34682(25.06)	0.06
2010	33770(24.40)	33990(24.56)	-0.16
2011	26084(18.85)	26074(18.84)	0.01
Etiology of obstetric hemorrhage and markers of its severity			
Abnormal placentation	4580(3.31)	4638(3.35)	-0.04
PPH due to uterine atony	18518(13.38)	18617(13.45)	-0.07
Amniotic fluid embolism	28(0.02)	15(0.01)	0.01
PPH due to coagulopathy	703(0.51)	582(0.42)	0.09
Delayed PPH	1958(1.41)	1965(1.42)	-0.01
Uterine rupture	137(0.10)	123(0.09)	0.01
Placental abruption	1986(1.43)	2026(1.46)	-0.03
Antepartum hemorrhage from other sources	643(0.46)	634(0.46)	0
Obstetric trauma	10667(7.71)	10755(7.77)	-0.06
Packed red blood cells, units			
0	132654(95.84)	133098(96.16)	-0.32
1-5	5137(3.71)	4866(3.52)	0.19
6-9	402(0.29)	305(0.22)	0.07
10	219(0.16)	143(0.10)	0.06

	Methylergonovine maleate exposed, N (%)	Non-exposed, N (%)	Difference (%)
Fresh frozen plasma, units			
0	137344(99.23)	137605(99.42)	-0.19
1-5	844(0.61)	662(0.48)	0.13
6-9	138(0.10)	86(0.06)	0.04
10	86(0.06)	59(0.04)	0.02
Cryoprecipitate	344(0.25)	238(0.17)	0.08
Platelets	129(0.09)	90(0.07)	0.02
Peripartum hysterectomy	566 (0.41)	469 (0.34)	0.07
Medical and obstetrical conditions			
Pre-existing hypertension	1486(1.07)	1627(1.18)	-0.11
Gestational hypertension	3281(2.37)	3592(2.60)	-0.23
Pre-existing hypertension with superimposed preeclampsia	278(0.20)	334(0.24)	-0.04
Mild preeclampsia	1856(1.34)	2098(1.52)	-0.18
Severe preeclampsia/eclampsia	872(0.63)	1038(0.75)	-0.12
Pre-existing diabetes	1036(0.75)	988(0.71)	0.04
Gestational diabetes	7822(5.65)	7836(5.66)	-0.01
Chronic ischemic heart disease	16(0.01)	7(0.01)	0
Chronic renal disease	357(0.26)	351(0.25)	0.01
Obesity	4933(3.56)	5049(3.65)	-0.09
Dyslipidemia	80(0.06)	67(0.05)	0.01
Drug abuse	1569(1.13)	1510(1.09)	0.04
Alcohol abuse	157(0.11)	131(0.09)	0.02
Tobacco use	7911(5.72)	7699(5.56)	0.16
Asthma	4310(3.11)	4131(2.98)	0.13
Hypercoagulable state	408(0.29)	372(0.27)	0.02
Migraine headache	679(0.49)	623(0.45)	0.04
Chronic anemia	16786(12.13)	17163(12.40)	-0.27
Cesarean delivery	48574(35.09)	49092(35.47)	-0.38
Previous cesarean delivery	18026(13.02)	17565(12.69)	0.33
Stillbirth	1029(0.74)	1012(0.73)	0.01
Multiple gestation	4330(3.13)	4556(3.29)	-0.16
Chorioamnionitis	4150(3.00)	4339(3.13)	-0.13
Major puerperal infection	823(0.59)	809(0.58)	0.01
Hospital characteristics			
Teaching hospital	43666(31.55)	43608(31.51)	0.04
Delivery volume			
Low	13250(9.57)	13464(9.73)	-0.16
Medium	32346(23.37)	32130(23.21)	0.16
High	92816(67.06)	92818(67.06)	0

Table 3

Relative Risk and Risk Difference per 100,000 patients of Acute Coronary Syndrome and Acute Myocardial Infarction in Patients Exposed to Methylergonovine maleate Compared to Unexposed Patients

	Number of outcomes / Number of patients		Risk ratio (95% CI)	Risk difference (95% CI) per 100,000 patients
	Methylergonovine maleate exposed	Non-exposed		
Acute coronary syndrome				
Unadjusted	6/139,617	52/2,094,013	1.73 (0.74-4.03)	1.81 (-1.69,5.32)
Propensity score matched	5/138,412	3/138,412	1.67 (0.40,6.97)	1.44 (-2.56,5.45)
Acute myocardial infarction				
Unadjusted	4/139,617	44/2,094,013	1.36 (0.49,3.79)	0.76 (-2.11,3.64)
Propensity score matched	3/138,412	3/138,412	1.00 (0.20,4.95)	0.00 (-3.47,3.47)

Appendix 1

Diagnostic and procedure codes used in the selection of the cohort.

	Codes
Inclusion criteria	
ICD-9 CM diagnosis codes	
Outcome of delivery	V27.x
Normal delivery	650.x
ICD-9 CM procedure codes	
Forceps, vacuum, and breech extraction	72.x
Internal and combined version and extraction	73.22
Other manually assisted deliveries	73.59
Episiotomy	73.6
Cesarean delivery	74.0-74.2, 74.4, 74.9
Exclusion criteria	
ICD-9 CM diagnosis codes	
Ectopic or molar pregnancy	630.x-633.x
Pregnancy with an abortive outcome	634.x-639.x
ICD-9 CM procedure codes	
Abortion	69.01, 69.51, 75.0

Appendix 2

Diagnostic and procedure codes used in the definition of medical and obstetrical conditions.

	ICD 9 diagnosis or procedure code
Sources of OB hemorrhage	
Abnormal placentation (including placenta previa)	666.0x, 667.0x, 667.1x, 641.0x, 641.1x
Uterine atony	666.1x
Amniotic fluid embolism	673.1x
PPH due to coagulopathy	666.3x
Delayed PPH	666.2x
Uterine rupture	665.0x, 665.1x
Placental abruption	641.2x
Antepartum hemorrhage from other sources	641.3x, 641.8x, 641.9x
Obstetric trauma	665.3x to 665.9x; 664.2x to 664.9x
Mode of delivery	
Cesarean delivery	74.0-74.2, 74.4, 74.9
Hypertensive disorders	
Pre-existing hypertension	401.x-405.x, 642.0x-642.2x, 642.7x
Gestational hypertension	642.3x
Pre-existing hypertension with superimposed preeclampsia	642.7x
Mild preeclampsia	642.4x
Severe preeclampsia	642.5x, 642.6x
Diabetes	
Pre-existing diabetes	250.x, 648.0x
Gestational diabetes	648.8x
Other chronic medical conditions	
Chronic ischemic heart disease	412.x, 414.x
Chronic renal disease	581.x-583.x, 585.x, 587.x, 588.x, 646.2x
Obesity	278.00, 278.01, 649.1x, V85.3, V85.4
Dyslipidemia	272.0x, 272.2x, 272.4x
Drug abuse	304.x, 305.2x-305.9x, 648.3x
Alcohol abuse	291.xx, 303.xx, 305.0x
Tobacco use	305.1.x, 649.0x, V15.82
Asthma	493.x
Hypercoagulable state	289.81, 289.82
Migraine headache	346.x
Chronic anemia	280.x-281.x, 285.2x-285.9x
Other obstetric conditions	
Previous cesarean delivery	654.2x
Stillbirth	V27.1, V27.3, V27.4, V27.6, V27.7, 656.4x
Peripartum hysterectomy	68.3x-68.9x
Multiple gestation	V27.2-V27.8, 651.x
Chorioamnionitis	658.4x

ICD 9 diagnosis or procedure code	
Major puerperal infection	670.x