Hormonal Contraception and Risk of Thromboembolism in Women With Diabetes

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OBJECTIVE

To investigate safety of hormonal contraception with regard to thromboembolic events in women with type 1 or 2 diabetes.

RESEARCH DESIGN AND METHODS

We used data from 2002–2011 in Clinformatics Data Mart to identify women in the U.S., 14–44 years of age, with an ICD-9-CM code for diabetes and a prescription for a diabetic medication or device. We examined contraceptive claims and compared time to thromboembolism (venous thrombosis, stroke, or myocardial infarction) among women with diabetes dispensed hormonal contraception using a modification of Cox regression to control for age, smoking, obesity, hypertension, hyperlipidemia, diabetic complications, and history of cancer; we excluded data for 3 months after women gave birth.

RESULTS

We identified 146,080 women with diabetes who experienced 3,012 thromboembolic events. Only 28% of reproductive-aged women with diabetes had any claims for hormonal contraception, with the majority receiving estrogen-containing oral contraceptives. Rates of thromboembolism were highest among women who used the contraceptive patch (16 per 1,000 woman-years) and lowest among women who used intrauterine (3.4 per 1,000 woman-years) and subdermal (0 per 163 woman-years) contraceptives. Compared with use of intrauterine contraception, progestin-only injectable contraception was associated with increased risk of thromboembolism (12.5 per 1,000 woman-years; adjusted hazard ratio 4.69 [95% CI 2.51–8.77]).

CONCLUSIONS

The absolute risk of thromboembolism among women with type 1 or 2 diabetes using hormonal contraception is low. Highly effective, intrauterine and subdermal contraceptives are excellent options for women with diabetes who hope to avoid the teratogenic effects of hyperglycemia by carefully planning their pregnancies.

It is estimated that 2% of women in the U.S. between the ages of 20 and 39 years have diabetes (1). Because birth defects affect 5–8% of pregnancies conceived by women with diabetes, over twice the rate of the general population, preconception counseling is particularly important. Planning pregnancies allows for tight glycemic control before and during pregnancy, thus decreasing congenital malformations and fetal macrosomia (2). However, nearly two-thirds of pregnancies in women with diabetes are unplanned (3,4), and women with diabetes are less likely to receive contraceptive counseling or use contraception than women without diabetes (5–9).

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One concern with prescribing hormonal contraception to women with diabetes is the risk of thromboembolic complications, in particular cardiovascular disease and stroke. Prior epidemiologic studies suggest that combined hormonal contraception influences the risk of thromboembolism to the same extent in women with and without diabetes, but the absolute risk of thromboembolism is higher in those with diabetes because of the increased spontaneous incidence of thromboembolism in these patients (10,11). In a 15-year Danish historical cohort study, the relative risk of stroke and myocardial infarction (MI) among women who filled prescriptions for medications to treat diabetes, as compared with women without such prescriptions, was 2.73 for stroke (95% CI 2.32–3.22) and 4.66 for MI (95% CI 3.88–5.61) (12).

For women with medical conditions that increase their baseline risk of thromboembolism, such as women with advanced diabetes, or women with diabetes and other cardiovascular risk factors, progestin-only contraceptives are recommended by the World Health Organization (13). However, the majority of published studies regarding progestin-only contraception and thromboembolism have included only healthy women (14). This gap in evidence may be contributing to lower rates of contraceptive counseling, prescriptions, or services for women with diabetes as compared with women without a chronic medical condition (15).

In a recent systematic review, most progestin-only contraceptives were not associated with increased odds of venous or arterial thrombotic events (14). However, even in the few studies in which women with diabetes were included, sample sizes were small, and women with diabetes were not analyzed separately. Our study, therefore, used a large administrative health care claims dataset to investigate dispensing of prescription contraception to women with type 1 and type 2 diabetes and subsequent thromboembolic outcomes.

RESEARCH DESIGN AND METHODS

Data Source

The Clinformatics Data Mart is an administrative health claims database encompassing 15 million individuals annually from all 50 states. Over a 10-year period, 47 million unique individuals contributed information to the database. Clinformatics is composed primarily of commercial health plan data and contains medical claims, outpatient pharmacy claims, laboratory results, hospitalizations, standard pricing, coverage dates for members, and demographic information. Inpatient and outpatient services are coded with Current Procedural Terminology codes or Healthcare Common Procedure Coding System codes. Diagnoses are coded with ICD-9-CM diagnoses codes. All claims include the dates of service. Outpatient pharmacy data include National Drug Codes, drug brand names, generic classifications, quantity, days supplied, and date dispensed. Inpatient drugs are not included.

Study Population

We examined claims from 2002 to 2011 for females of reproductive age (14–44 years) who had at least one ICD-9 code for diabetes (250.xx) and a prescription for a diabetic medication or device. A list of diabetic medications and devices was developed by a board-certified internist based on medications/devices/supplies contained in the Clinformatics data set. Advanced diabetes, a covariate of interest, was defined as at least one ICD-9 code indicating nephropathy (250.4x), retinopathy (250.5x), neuropathy (250.6x), or macrovascular disease (250.7x). We calculated a Charlson Comorbidity Index for each participant using modified code from the Manitoba Center for Health Policy (16). The majority of the diagnoses listed in the Clinformatics database extended to the fourth or fifth digit, allowing the comorbidity index to produce reliable results.

Age at entry was based on a woman's first ICD-9 code for diabetes or prescription for a diabetic medication. However, if an individual was $<$14 years of age at the time of first ICD-9 code for diabetes, she was not included in the cohort until she turned 14 years of age. Likewise, women were excluded from the cohort once they turned 45 years of age. Observation time was calculated using eligibility dates. When women had multiple enrollment periods (because of changes or lapses in health insurance coverage), the period of longest enrollment was selected for inclusion.

Outcomes of Interest

The primary objective of this study was to compare time to thromboembolism among women dispensed progestin-only, combination, or no hormonal contraception. As our goal was to examine the safety of available contraceptives for women with type 1 and type 2 diabetes, we restricted this analysis to women with new thromboembolic events. New diagnoses of MI (ICD-9-CM 410.xx and 412) or stroke (ICD-9-CM 433.xx–436.xx, 437.6, 438.xx, and 671.5) had to be associated with a hospital admission. In addition, participants identified as having suffered a venous thromboembolism, whether that was a deep vein thrombosis or pulmonary embolism, were required to have been dispensed an anticoagulant within 30 days of the service date indicated by the relevant ICD-9 code for the thromboembolism. Other health conditions considered to be potential confounders included hyperlipidemia (272.0–272.4), hypertension (401.x–405.x), cancer (140.x–172.x, 174.x–195.8x, and 200.x–208.x), smoking (305.1 and 649.0–649.04), and obesity (278.00–278.01). Women with ICD-9 codes indicating pregnancy or a postpartum state were removed from analysis from the time of first pregnancy code until 3 months after any diagnostic or procedure code consistent with infant delivery.

Hormonal Contraception

Hormonal contraception was stratified by type (combined oral contraceptives, transdermal patch, vaginal ring, progestin-only pills, injection, subcutaneous implant, or intrauterine device [IUD]), type of progestin (categorized as desogestrel/gestodene, drospirenone, or levonorgestrel/other), and estrogen dose ($\geq$30 or $<$30 μg). Duration of contraception use was calculated in woman-years. This allowed fluidity among the groups so that a woman using more than one type of hormonal birth control over the time of her participation in the cohort could be included in multiple contraceptive groups.

Length of time on each hormonal contraceptive was determined by using the Medication History Estimator (MHE) program (17). The MHE uses eligibility data in parallel with the pharmacy claims data to construct a consecutive timeline of specified medications for each individual in the cohort. Based on prescription fill dates and days supply dispensed, the MHE searches pharmacy records for recurring fills of specified medications and calculates the total length of time an individual used

each medication. A participant was considered to have discontinued contraceptive use if 120 days (4 months) elapsed without a refill for oral contraceptives, the transdermal patch, or the vaginal ring. The end of use of depot medroxyprogesterone acetate (DMPA) was defined as 196 days (16 weeks) without a repeat injection code. For contraceptive methods that are primarily coded as procedures (i.e., IUDs and subdermal implants), we calculated length of use using placement, surveillance, and/or removal codes.

Codes specifying the type of IUD (levonorgestrel or copper-bearing) were not frequently used by providers. Therefore, we were unable to distinguish between the two types of IUDs in our analyses, and we conservatively assumed that all IUDs were hormonal. If no removal codes were detected following IUD or implant placement, then we assumed that the contraceptive was used as specified in the package insert (3 years for implants and 5 years for the IUD) while the patient remained in the study cohort.

Statistical Analysis

In this longitudinal database, a woman's contraceptive exposure could change over time. Thus, sequential time for each exposure was calculated. Descriptive statistics were calculated by exposure, with individual women contributing variable amounts of observation time to each exposure. To calculate hazard ratios (HRs) of thromboembolism by exposure to a contraceptive, we used a modification of Cox regression that allowed for time-dependent covariates (i.e., changes in contraceptive use). Interactions between birth control exposure and age, advanced diabetes (i.e., diabetes with nephropathy, retinopathy, neuropathy, or macrovascular disease), hyperlipidemia, hypertension, cancer, obesity, and smoking were evaluated in each model. An α of 0.010 and biological rationale determined if models stratified by the covariate were calculated. All HRs were then adjusted for the following covariates of interest: age, advanced diabetes, hyperlipidemia, hypertension, cancer, obesity, and smoking. In models analyzing the association between specific types of birth control and thromboembolism, women who were not using the methods of interest were dropped from the model. If a woman used different types of hormonal contraception, only her time receiving that specific type of contraception was included in the model. All analyses were performed using SAS version 9.4. We considered an α of 0.05 to indicate statistical significance unless otherwise noted.

RESULTS

We identified 146,080 unique women with type 1 and type 2 diabetes between 14 and 44 years of age, of whom 25,590 (17.5%) had advanced diabetes. A substantial proportion of women treated for diabetes had ICD-9 codes indicating concurrent diagnoses of hypertension, hyperlipidemia, and/or obesity (Table 1). However, the median Charlson Comorbidity Index of our study population was only 2.0. In total, 478,650 woman-years of observation were available for women of reproductive age with diabetes.

Over the time period of study, the majority of women with diabetes (104,732; 72%) had no claims for hormonal contraception devices or prescriptions. Approximately one-fourth (n = 35,361) of women treated for diabetes were dispensed estrogen-containing contraception, and 2,263 were dispensed both estrogen-containing and progestin-only contraception during the time period of study. Among those who were dispensed estrogen-containing contraception, most (83%; n = 29,319) had gaps in their use of prescription contraception, leaving only 6,042

Table 1—Characteristics of women with diabetes included in the study cohort by type of contraceptive used

Characteristic	All women (n = 146,080)	Type of contraceptive* None (n = 139,358)	Progestin† (n = 8,250)	Estrogen-containing (n = 35,361)
Age first treated for diabetes, years				
14–19	7,813 (5.4)	7,605 (5.5)	257 (3.1)	3,117 (8.8)
20–24	8,834 (6.1)	8,239 (5.9)	839 (10.2)	4,387 (12.4)
25–29	18,118 (12.4)	16,999 (12.2)	1,804 (21.9)	7,524 (21.3)
30–34	28,727 (19.7)	27,217 (19.5)	2,287 (27.7)	8,639 (24.4)
35–39	39,512 (27.1)	37,834 (27.2)	2,016 (24.4)	7,163 (20.3)
40–44	43,076 (29.5)	41,464 (29.8)	1,047 (12.7)	4,531 (12.8)
Medical history				
Advanced diabetes	25,590 (17.5)	24,442 (17.5)	1,522 (18.5)	5,878 (16.6)
Hyperlipidemia (ICD-9 272.0–272.4)	38,068 (26.1)	36,112 (25.9)	1,846 (22.4)	9,082 (25.7)
Hypertension (ICD-9 401–405)	50,798 (34.8)	48,498 (34.8)	2,579 (31.3)	9,977 (28.2)
Cancer (ICD-9 140–208)	3,133 (2.1)	2,985 (2.1)	152 (1.8)	692 (2.0)
Smoking	9,950 (6.8)	9,622 (6.9)	613 (7.4)	1,746 (4.9)
Obesity	49,954 (34.2)	47,941 (34.4)	3,259 (39.5)	12,607 (35.7)
Charlson Comorbidity Index, median (range)	2.0 (1.0–23.0)	2.0 (1.0–23.0)	2.0 (1.0–17.0)	2.0 (1.0–18.0)
Years in category describing contraceptive use, median (range)	2.7 (<0.1 to 10.2)	2.4 (<0.1 to 10.1)	0.8 (<0.1 to 10.0)	0.8 (<0.1 to 10.1)
Number with TE	3,012	2,431	95	486
Woman-time in years	478,650	421,470	11,393	45,787
Crude rates of TE per 1,000 woman-years	6.3	5.8	8.3	10.6

Data are n (%) unless otherwise indicated. TE, thromboembolism. *Women prescribed two different types of contraception during the study period appear twice in this table. †The progestin-only group includes all women using IUDs, although some IUDs may have contained copper instead of levonorgestrel.

(4%) who were dispensed enough contraception to allow continuous use over their entire period of observation. A minority of women (4%; *n* = 5,987) were dispensed purely progestin-only contraception, which included pills, DMPA, an implant, or an IUD. Among these women, 5,307 had gaps in use, leaving 680 (0.5%) who were dispensed enough progestin-only contraception to meet the definition of continuous use.

We identified 3,012 total thrombotic events in our study population over a total of 478,650 woman-years of observation, producing a rate of 6.3 thrombotic events per 1,000 woman-years of observation (95% CI 6.1–6.5 per 1,000 woman-years) (Table 1). Among women with diabetes, arterial thrombosis (2,015 out of 3,012; 67% of thrombotic events) was more common than venous thrombosis. Among women experiencing arterial thrombosis, strokes and transient ischemic attacks were more common (1,238 out of 3,012; 41% of thrombotic events overall) than MI (777 out of 3,012; 26% of events). We found that when compared with use of no hormonal contraception, estrogen-containing products were associated with an increased risk of thromboembolism (HR 3.38 [95% CI 2.94–3.88] in women <35 years of age and 1.79 [1.54–2.09] in women ≥35 years of age) (Table 2). When compared with no hormonal contraception, progestin-only products were associated with a modestly increased risk of thromboembolism in women <35 years of age (2.02 [1.51–2.70]) but were not associated with thromboembolism in older women. When directly compared with each other, the hazard of thromboembolism with progestin-only contraception was lower than for estrogen-containing contraception; this difference was statistically significant for women <35 years of age (0.60 [0.44–0.81]) but not for older women (0.74 [0.54–1.03]). The crude incidence rate of thromboembolism among women with diabetes using any type of hormonal contraception was 9.5 per 1,000 woman-years of use for women <35 years of age (95% CI 8.5–10.5) and 11.4 per 1,000 woman-years of use for women ≥35 years of age (10.0–13.0).

For women using combined hormonal contraceptive pills, we compared risk of thromboembolism by dose of estrogen and type of progestin (Table 3). We also compared progestin-only pills to combined oral contraception and did not find a difference in risk of thromboembolism in this analysis (Table 3). We did not find an increased risk of thromboembolism in women using pills with ≥30 μg estrogen as compared with those receiving "ultra–low-dose" pills. We also did not find an increased risk of thromboembolism with pills containing drospirenone or desogestrel/gestodene as compared with other types of progestin. Although the vast majority of estrogen-containing products were oral contraceptives, we also examined thromboembolic risk for the transdermal patch and vaginal ring as compared with combined oral contraceptives and found a modestly increased risk of thromboembolism for the transdermal patch (1.68 [1.14–2.49]), but not the vaginal ring (Table 3).

When compared with use of an IUD for contraception, progestin-only pills and DMPA were associated with an approximately four times increased risk of thrombosis (Table 4). Women using DMPA did tend to be older than IUD users and were more likely to be smokers (data not shown). However, these variables were controlled for in our analysis. Nonetheless, even among DMPA and progestin-only pill users, the absolute number of thrombotic events was low. The number of subdermal implantable progestin-only devices (Implanon and Nexplanon; Merck) prescribed was very small, and no thrombotic events were identified in this patient population, precluding detailed analysis.

CONCLUSIONS

Our analysis of claims data from 146,080 commercially insured women with diabetes found that the absolute risk of thromboembolism among women with type 1 and type 2 diabetes using hormonal contraception is low, with <17 events per 1,000 woman-years of use independent of type of contraceptive used. We also found that arterial events were more common than venous thrombosis, accounting for two-thirds of thromboembolic events. All analyses were adjusted for patient age, advanced diabetes, hyperlipidemia, hypertension, cancer, and smoking. The contraceptives most likely to be associated with thromboembolism were the contraceptive patch and vaginal ring. The contraceptives least likely to be associated with thromboembolism when used by women with diabetes were the intrauterine and subdermal contraceptives, although the

Table 2—Crude incidence rates and adjusted HRs for thromboembolic events in women with diabetes by contraception use at the time of the TE stratified by age

	Number of TEs/woman-years			Thrombosis per 1,000 woman-years of use			Adjusted HR* (95% CI)		
	Estrogen	Progestin	None	Estrogen	Progestin	None	Estrogen vs. no hormonal	Progestin vs. no hormonal	Progestin vs. estrogen
<35 years	300/29,988	50/6,905	650/189,481	10.0	7.2	3.4	3.38 (2.94–3.88) ($P < 0.0001$)	2.02 (1.51–2.70) ($P < 0.0001$)	0.60 (0.44–0.81) ($P = 0.0009$)
≥35 years	186/15,798	45/4,488	1,781/231,988	11.8	10.0	7.7	1.79 (1.54–2.09) ($P < 0.0001$)	1.33 (0.99–1.79) ($P = 0.0593$)	0.74 (0.54–1.03) ($P = 0.0741$)

TE, thromboembolism. *Adjusted for age, advanced diabetes, hyperlipidemia, hypertension, cancer, obesity, and smoking.

Table 3—Crude incidence rates and adjusted HRs of TE in women with diabetes by COC formulation

Contraception	Women	Woman-years	*N* with TE	Thrombosis per 1,000 woman-years of use	Adjusted HR* (95% CI)	*P* value
Any COC	35,360	45,787	486	10.6		
Estrogen doses						
≥30 μg	33,992	43,856	460	10.5	0.71 (0.48–1.05)	0.09
<30 μg	2,109	1,930	26	13.5	Reference	
Different COC formulations						
COC with drospirenone	6,576	6,598	65	9.9	1.03 (0.78–1.36)	0.86
COC with desogestrel/gestodene	12,907	13,974	143	10.2	1.04 (0.84–1.28)	0.72
COC with other progestin type (norethindrone, ethyndiol, etc.)	17,602	21,717	226	10.4	Reference	
Progestin-only pills	3,306	1,901	26	13.7	1.22 (0.81–1.83)	0.34
Different estrogen-containing formulations						
Any COC	32,606	42,289	436	10.3	Reference	
Transdermal patch†	2,224	1,645	27	16.4	1.68 (1.14–2.49)	0.0091
Vaginal ring‡	2,026	1,853	25	13.5	1.45 (0.97–2.18)	0.0703

COC, combined oral contraceptive; TE, thromboembolism. *Adjusted for age, advanced diabetes, hyperlipidemia, hypertension, cancer, obesity, and smoking. †Transdermal contraceptive patch (EVRA; Johnson & Johnson). ‡Combined hormonal vaginal ring (NuvaRing; Merck Sharp & Dohme).

amount of woman-time with subdermal contraceptives was very small. As these highly effective reversible contraceptives are typically 20 times as effective as oral contraceptives (18), they are excellent options for women with diabetes who wish to avoid the teratogenic consequences of hyperglycemia by carefully planning their pregnancies. Unfortunately, the large majority (72%) of women with diabetes in this study received no prescription contraception and may face greater risk of undesired pregnancy than warranted. Further, among women prescribed short-acting methods, the vast majority had gaps in use.

As combined hormonal contraceptives, which contain both estrogen and progestin, are known to increase risk of thromboembolism in the general population (19), we were not surprised to find this to also be true for women with type 1 and type 2 diabetes. Estrogen exerts a negative influence on the anticoagulant protein C pathway and is likely the primary mechanism for the prothrombotic effect of combined hormonal contraceptives (20), as well as postmenopausal hormones (21). Although one recent French study reported that women (<1% of whom had diabetes) using oral contraceptives with only 20 μg estrogen were less likely to experience pulmonary embolism, stroke, and MI than those using products containing 30–40 μg estrogen, our study, like most prior studies of the general population, did not show that ultra–low-dose estrogen products were associated with a decreased risk of thromboembolism for women with diabetes (22,23). We also did not find an increased risk of thromboembolism with agents containing the progestin types of desogestrel or drospirenone, a finding that has been reported in multiple other retrospective studies, although not substantiated in the prospective European Active Surveillance study (22–24).

With regard to progestin-only contraception, concern for a possible increased risk of thromboembolism stems from reports that higher-dose progestins used for noncontraception purposes are associated with venous thromboembolism (25,26). In addition, an international study reported a possible increase in stroke risk in women with hypertension who used injectable progestin-only contraceptives (27). Most recently, a study from the Netherlands reported that women using DMPA had a 3.6-fold (1.8–7.1) increased risk of venous thromboembolism compared with nonusers of hormonal contraceptives (28). Our work supports these findings, as we identified a fourfold increased risk of thromboembolism in women using progestin-only pills or DMPA when compared with women with IUDs. Our findings may underestimate the risk of progestin-only pills, as postpartum women, the most common users of these agents, were excluded from all analyses, leaving only 1,902 woman-years of use to analyze (29).

The primary strength of this work is the data source, which provides access to >100,000 women with diabetes, a patient population that is often excluded from other large studies of contraception use.

Limitations of this work include the typical limitations of administrative data analysis, which are dependent on proper documentation and coding by medical providers. Administrative data does not include family history of thrombosis,

Table 4—Crude incidence rates and adjusted HRs of thrombosis between users of different types of progestin-only contraception for women

Contraceptive	Women	Woman-years	*N* with TE	Thrombosis per 1,000 woman-years of use	Adjusted HR* (95% CI)	*P* value
Progestin-only pill	3,306	1,902	26	14.5	3.69 (2.10–6.48)	<0.0001
Injectable DMPA	2,266	4,293	52	12.5	4.69 (2.51–8.77)	<0.0001
Implant†	124	163	0	0		
IUD	2,730	5,036	17	3.4	Reference	

TE, thromboembolism. *Adjusted for age, advanced diabetes, hyperlipidemia, hypertension, cancer, obesity, and smoking. †Implanon and Nexplanon (Merck).

and risk factors such as smoking and obesity are typically undercoded by providers (30,31). Use of administrative data also does not allow us to know the exact timing of thromboembolism in relation to start of contraceptive use, and thromboembolism is known to be more common in new users. Our data source was also almost exclusively a commercially insured population, so our results may not be applicable to the Medicaid or uninsured populations. Contraceptives can also be obtained through Title X clinics such as Planned Parenthood, which would not be billed to insurance; therefore, some women coded as no hormonal contraceptive use may have been miscoded. Our analysis did not control for acute thrombotic risk factors such as recent trauma or major surgery. Finally, we had very small numbers of implant users, and larger studies are needed to definitively show low thromboembolic event rates in women with diabetes.

Currently, diabetes affects ~2 million U.S. women of reproductive age. Even among women with "uncomplicated" diabetes (<20 years of diabetes and no end-organ disease), it appears that clinicians may avoid combined hormonal contraceptives because of concerns of cardiovascular side effects (32), in large part because of the lack of published data directly relevant to women with diabetes. Our results demonstrate the safety of hormonal contraception use in women with type 1 and type 2 diabetes, with an overall low absolute risk of ~1 thromboembolic event per 100 woman-years of use. The contraceptives with the lowest absolute risk were the intrauterine and implantable subdermal contraceptives, and these highly effective reversible contraceptives are excellent options for women with diabetes.

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