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Prevalence, Trends, and Patterns of Use of Antidiabetic Medications Among Pregnant Women, 2001–2007

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Abstract

Objective—To describe the prevalence, trends, and patterns in use of antidiabetic medications to treat hyperglycemia and insulin resistance prior to and during pregnancy in a large U.S. cohort of insured pregnant women.

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Preliminary results of this study were presented at the Diabetes in Pregnancy Study Group – West (DPSG-W) meeting in Pasadena, California on May 18, 2012.

Methods—Pregnancies resulting in livebirths were identified (N=437,950) from 2001–2007 among 372,543 women 12–50 years of age at delivery from 10 health maintenance organizations participating in the Medication Exposure in Pregnancy Risk Evaluation Program. Information for these descriptive analyses, including all antidiabetic medications dispensed during this period, was extracted from electronic health records and infant birth certificates.

Results—Just over one percent (1.21%) of deliveries were to women dispensed antidiabetic medication(s) in the 120 days before pregnancy. Use of antidiabetic medications before pregnancy increased from 0.66% of deliveries in 2001 to 1.66% of deliveries in 2007 ($p<0.001$) due to a rise in metformin use. Most women using metformin before pregnancy had a diagnosis code for polycystic ovaries or female infertility (67.2%) while only 13.6% had a diagnosis code for diabetes. The use of antidiabetic medications during the second or third trimester of pregnancy increased from 2.8% of deliveries in 2001 to 3.6% in 2007 ($p <0.001$). Approximately two-thirds (68%) of women using metformin before pregnancy did not use any antidiabetic medications during pregnancy.

Conclusions—Antidiabetic medication use prior to and during pregnancy rose from 2001–2007, possibly due to increasing prevalence of gestational diabetes mellitus, type 1 and type 2 diabetes, and other conditions associated with insulin resistance.

INTRODUCTION

Medications used during the preconception period and during pregnancy, which are critical periods for maternal health and fetal development, require further attention (1). While an estimated two-thirds of women use prescription medications during pregnancy (2), up-to-date information on the full extent of the types of drugs prescribed to pregnant women in recent years is limited. One common condition during pregnancy, diabetes, is associated with increased risk of congenital abnormalities and other adverse pregnancy outcomes (3; 4).

Medications that reduce hyperglycemia or increase insulin sensitivity are often grouped as “antidiabetic medications” and are used to treat type 1 or type 2 diabetes and other conditions associated with insulin resistance as well as to treat gestational diabetes mellitus (GDM). With the increasing prevalence of GDM (5–8) and the increase in the overall proportion of women who have diabetes and become pregnant (9–12), more women may use these medications during their pregnancies to control hyperglycemia. This descriptive epidemiologic study was conducted as part of the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP) (13) to describe the prevalence, trends, and patterns of use of antidiabetic medications in the preconception period and during pregnancy based on maternal demographic characteristics.

MATERIALS AND METHODS

The MEPREP study is a collaborative effort between the U.S. Food and Drug Administration (FDA) and researchers from eleven health-plan affiliated research institutions: Group Health Research Institute (Washington); Harvard Pilgrim Health Care Institute (Massachusetts); HealthPartners Research Foundation (Minnesota); Kaiser Permanente Colorado, Georgia, Northern California, Southern California and Northwest (Oregon, Washington); LCF Research (New Mexico); Meyers Primary Care Institute (Massachusetts); and Tennessee State Medicaid (through the auspices of Vanderbilt University School of Medicine). Administrative health plan data are linked with clinical data systems to facilitate studies of medication use and pregnancy outcomes (13). These research institutions extracted information on maternal and infant enrollment, demographic characteristics, outpatient pharmacy dispensing, and diagnosis codes from outpatient and

inpatient health care encounters from their clinical and administrative data systems and linked them to infant birth certificates to obtain information on maternal race/ethnicity, parity, and infant's gestational age at birth (14). All data were de-identified and standardized across centers and summary data tables but not individual-level data were shared across the centers to conduct this study. The Institutional Review Board(s) of each organization and the state departments of public health (when applicable) approved the study.

The source population for this study included 684,635 deliveries to women aged 12 to 50 years with one or more live births between January 1, 2001 and December 31, 2007 while enrolled in any of the ten health maintenance organization that provided data for these analyses. Tennessee State Medicaid did not participate in this study. To be eligible for inclusion, women had to be continuously insured with pharmacy benefits from 180 days before pregnancy through their delivery date. The final sample was 437,950 deliveries (64% of the source population); the pharmacy benefit and continuous insurance requirements resulted in the exclusion of 4.5% and 31.5% of the deliveries, respectively.

All antidiabetic medications approved for use by the FDA during the study period were included in these analyses (Appendix 1, available online at http://links.lww.com/xxx). These medications were identified from the outpatient pharmacy dispensing data. Periods of drug exposure in relation to pregnancy and trimester were calculated from dispense dates and days supplied. For women with multiple refills of the same prescription, a 14-day grace period after the expected exhaustion of the days supplied was incorporated for each dispensing. A 120-day period before the estimated date of conception was used to identify dispensing before pregnancy as some health plans allow for up to 100-day supply per dispensing.

Women with a health care encounter occurring in the 180 days before pregnancy were identified as potentially having diabetes mellitus, polycystic ovaries, female infertility, or being overweight or obese using International Classification, 9th Revision, Clinical Modification (ICD-9-CM) codes for these conditions (Appendix 2, available online at http://links.lww.com/xxx) during the 180 days before pregnancy. Additionally, diagnosis codes indicative of diabetes and/or GDM occurring during the second or third trimester of pregnancy were identified. Maternal age, calendar year of delivery, and number of deliveries per woman during the study were derived from health plans' data systems; maternal race/ethnicity and education were from infant birth certificate data.

Gestational periods were defined using the last menstrual period (LMP) or gestational age information recorded in the infant birth certificates, when available (95% of deliveries). When an LMP date was available in the birth certificate, it was used as the first day of the pregnancy. If the LMP was missing or invalid, day zero was defined as the date of delivery minus the gestational age based on clinical or obstetric estimates. This definition was consistent with the approach used by the National Center for Health Statistics (15). When gestational age information was missing from the birth certificates, trimesters were estimated using the delivery date and ICD-9-CM codes (Appendix 2) (16; 17). Trimesters were categorized as first (days 0–90), second (days 91–180) and third (days 181 through delivery).

Descriptive statistics are presented to estimate the number and proportion of deliveries to women who were dispensed antidiabetic medications in the preconception period (120 days before pregnancy), and for the second and third trimesters combined. Medications were considered individually and presented in reference to maternal age categories and then combined into broader categories that included both monotherapy (insulin only, biguanide only [only metformin was available], other oral agents [other than metformin] only),

combinations of medications from these classes, and a summary category of any antidiabetic medication use. The unadjusted associations between antidiabetic medication use and maternal sociodemographic characteristics was assessed using chi-square tests. The unadjusted trends in the use of medications were assessed using the Cochran-Armitage trend test. Since one of the objectives of this study was to assess trends in prevalence of antidiabetic medication use and medication use can change within and between pregnancies, all women with one or more deliveries were retained in the final cohort instead of using the first, last, or randomly-selected delivery.

Analysis of medication initiation during pregnancy and switching of medications after conception was conducted by cross-tabulating antidiabetic medications used in the prepregnancy period (when applicable) with those used in the second or third trimester of pregnancy. We chose the second and third trimesters of pregnancy since treatment for GDM is most commonly initiated in the late second trimester and the early third trimester. The underlying reason for antidiabetic medication use was explored using the ICD-9-CM codes.

RESULTS

The final analytic sample for this descriptive study was composed of 437,950 deliveries to 372,543 women who had one or more live births during the study period. Of these deliveries; 42.4% were to non-Hispanic White women, 28.3% to Hispanic women, 12.3% to Asian women, 8.2% to Black women, and 8.5% were to women of other or unknown race/ethnicity. Most deliveries (63.4%) were to women with more than a high school education. The majority (85.1%) of the deliveries were at term (37–41 completed weeks of gestation) while 9.4% were preterm (<37 weeks of gestation) and 5.5% were post-term (≥ 42 weeks).

Just over one percent (1.21%) of the deliveries were to women dispensed one or more antidiabetic medication(s) in the 120 days prior to conception (Table 1). Medications used most commonly during this period were metformin (0.84%) and insulin (0.33%). Antidiabetic medication use before pregnancy was significantly associated with increasing maternal age and education and race/ethnicity (Table 2, all p values <0.001). Native American women were most likely to be using antidiabetic medications (1.76%) and African American women were least likely to be using them (1.05%). Of the 5,299 deliveries to women using antidiabetic medications before pregnancy, 20.4% were preterm deliveries (<37 weeks) compared with 9.2% of the 432,651 deliveries to women who were not using these medications (p<0.001).

Antidiabetic medication use before pregnancy increased from 0.66% of deliveries in 2001 to 1.66% of deliveries in 2007 (p<0.001), representing a 2.5-fold increase (Table 2). The use of metformin in the prepregnancy period rose annually, from 0.24% of deliveries in 2001 to 1.16% of deliveries in 2007, representing a 3.8-fold increase over this 7-year period (p<0.001). In contrast, the use of insulin alone and other oral agents alone remained relatively stable. The majority of the women who used insulin alone (n=1,233) or in combination with oral agents (n=212) or metformin in combination with any other oral antidiabetic drug (n=299) had a diagnosis code for type 1 or type 2 diabetes (83.5%, 94.3%, and 78.6%, respectively) prior to pregnancy. Of the women who used metformin alone (n=3,208), only 13.6% had a diagnosis code for diabetes alone or in combination with other condition(s) of interest, while 67.2% had a code for polycystic ovaries or infertility. Specifically, 7.4% had codes for polycystic ovaries alone; 23.6% for polycystic ovaries and infertility; 1.8% for polycystic ovaries and overweight; 10.2% for polycystic ovaries, infertility and overweight; 20.6% for infertility only; 3.6% for infertility and overweight; 2.2% for overweight only; and 16.4% did not have any of these codes.

One or more antidiabetic medications were dispensed to women in the first trimester for 1.35% of deliveries and in the second or third trimester (combined) for 3.24% of deliveries. The most commonly used antidiabetic medications in the second or third trimester were insulin (2.45%) and sulfonylureas (0.83%) while the use of metformin (0.14%) during pregnancy was limited (Table 1). The use of antidiabetic medication was associated with increasing maternal age, decreasing maternal education, and maternal race/ethnicity. Native American women were most likely to be using antidiabetic medications during pregnancy (4.67%), while non-Hispanic White women were least likely to be using these medications (2.40%). Increasing duration of gestation was negatively associated with antidiabetic medication use: 5.6% of the preterm deliveries (<37 weeks) were to women who used antidiabetic medications compared with 3.0% of term deliveries (≥ 37 weeks).

The use of any antidiabetic medication during the second or third trimester of pregnancy increased significantly from 2.77% of all deliveries in 2001 to 3.62% of all deliveries in 2007 (p for trend <0.001) representing a 29% increase during this period (Table 3). The proportion of deliveries to women using insulin during their pregnancies decreased, from 2.41% in 2001 to 2.09% in 2007, while the use of other agents, most commonly sulfonylureas, increased from 0.29% to 1.09% and metformin use increased from 0.01% to 0.19%. Among the 14,185 deliveries to women who used one or more antidiabetic medications during pregnancy, 9.2% had ICD-9-CM codes for type 1 or type 2 diabetes only, 47.6% for GDM only, 41.3% for both GDM and diabetes, and 2.0% did not have a code for either condition. Among deliveries to women who used insulin only, 11.9% had codes for type 1 or type 2 diabetes only, 39.7% for GDM only, 48.2% for diabetes and GDM, and 0.2% did not have a code for either condition. In contrast, for deliveries to women who used oral agents, 76.9% had codes for GDM only, 0.8% for diabetes only, 21.9% had codes for diabetes and GDM, and 0.4% had no diabetes-related codes.

Of the 5,299 deliveries to women who were dispensed an antidiabetic drug during the preconception period, 2,995 (56.5%) used an antidiabetic drug during the second or third trimester of pregnancy. Of the 1,233 deliveries to women who used only insulin in the preconception period, 95.3% continued to use only insulin, 0.8% had an oral agent added, 0.4% switched from insulin to an oral agent, and 3.5% had no evidence of any antidiabetic medication dispensing during pregnancy. Of the 3,208 deliveries to women who used metformin alone in the preconception period, 8.8% continued to use metformin while 16.8% switched to insulin, 3.0% switched to another oral agent, 3.2% switched to other drug combinations, and 68.0% did not use any antidiabetic medication during pregnancy. Of the 341 women who used an oral agent other than metformin, most commonly a sulfonylurea, before pregnancy, 5.3% continued to use an oral agent only, 71.3% switched to insulin only, and 16.7% did not use any antidiabetic medication. Of the 432,651 deliveries to women with no antidiabetic medication use before pregnancy, 1.8% initiated insulin only, 0.1% insulin in combination with another antidiabetic drugs, 0.7% an oral agent other than metformin, <0.1% metformin only and the remaining 97.4% did not use any antidiabetic medications during the second or third trimester.

DISCUSSION

The use of antidiabetic medications in the preconception period rose significantly from 2001 to 2007, resulting in a 2.5-fold increase. The increase in the use of antidiabetic medications during the second or third trimester of pregnancy was more gradual, increasing by about 31% over the seven-year period. The increase in the use of antidiabetic medications before pregnancy is almost entirely due to increase in metformin use. Of the women who used metformin, less than 15% had a diagnosis code for diabetes prior to pregnancy while two-thirds had a code for polycystic ovaries or infertility, suggesting that most women using

metformin are being treated for polycystic ovaries or infertility associated with polycystic ovaries (18). Metformin increases the rate of ovulation among women with polycystic ovaries (19) but given that the majority (79%) of women with polycystic ovaries were also coded as having infertility suggests that most were trying to conceive, while a minority of the women may have experienced an unplanned pregnancy resulting from the side effect of the increased fertility.

During the second and third trimesters of pregnancy, we observed a small decrease in the use of insulin, with a concomitant increase in the use of sulfonylureas and to a lesser extent, metformin. Of the women who used metformin in the preconception period and continued to use an antidiabetic drug during pregnancy, about two-thirds (64.1%) switched to insulin or other oral agents by the second trimester, while the remainder continued to use metformin. Sulfonylureas are the most commonly used oral agents to treat GDM in the United States, whereas metformin is rarely used due to concerns that it crosses the placenta (20). Two meta-analyses of observational studies did not show an increase in congenital malformations or neonatal deaths associated with metformin use in pregnancy (21; 22). The Metformin in Gestational Diabetes (MiG) Trial, published in 2008 after the deliveries in the present study, reported that metformin (alone or in combination with insulin) was not associated with increased perinatal complications and women reported preferring metformin to insulin treatment (23). Based on previous studies, about one quarter of women diagnosed with GDM in the Kaiser Permanente Southern and Northern California regions, which combined comprise 74% of the current study sample, were treated with insulin or oral agents during their pregnancies during this period (24;25).

The MEPREP study cohort is comprised of deliveries resulting in live births to women who were insured with pharmacy benefits for at least six months before conception through delivery. The pre-pregnancy insurance criteria deemed necessary in order to report pre-pregnancy medication use and switching excluded the majority of women on Medicaid and other women who become insured after conception. Only 3.2% of the deliveries in this study were to women insured through Medicaid. While this report is based on prescription drug dispensing data, we were unable to assess whether women adhered to the regimen as prescribed by their physicians. Results of oral glucose challenge tests and oral glucose tolerance tests during pregnancy, which are not included in the MEPREP dataset, would have allowed us to better differentiate between women with diabetes and GDM (9; 26). Additionally, we did not have information on maternal height and weight across the 7-year study period in the MEPREP dataset to calculate body mass index. Strengths of the study include its' large racially/ethnically and geographically- diverse population of insured women with over 400,000 live births over a 7-year period, that deliveries occurred in 10 health plans across 8 different states with varying models of health care, and that medications were based on actual dispensing and not self-report.

In the past decades, hyperglycemia during pregnancy was primarily a result of type 1 diabetes and GDM, but type 2 diabetes has emerged in adolescents and has become more prevalent in young adults over the last decade (27; 28) and the prevalence of GDM has increased (5). Additionally, the recently published criteria for the diagnosis of GDM (29), if adopted, will result in a significant increase in the prevalence of GDM (30; 31). The size and the scope of our study allows us to describe the exposure to antidiabetic medications in a contemporary cohort, but is only the first step in the process toward understanding the potential public health affect of using antidiabetic medications during pregnancy. Critical next steps for the MEPREP study involve assessing fetal harm, including low birth weight, and prediction of women at highest risk for adverse outcomes in relation to their antidiabetic medication use, taking into account the affect of their hyperglycemia.

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Appendix 2

International Classification of Diseases, 9th Revision, Clinical Modification Codes Used in This Study

Gestational Age at Delivery

765.20 - Unspecified weeks of gestation

765.21 - Less than 24 completed weeks of gestation

765.22 – 24 completed weeks of gestation

765.23 - 25–26 completed weeks of gestation

765.24 - 27–28 completed weeks of gestation

765.25 - 29–30 completed weeks of gestation

765.26 - 31–32 completed weeks of gestation

765.27 - 33–34 completed weeks of gestation

765.28 - 35–36 completed weeks of gestation

765.29 - 37 or more completed weeks of gestation

Type 1 or Type 2 Diabetes

250.xx, 249.0–249.9, 357.2, 362.01, 362.02, 362.03, 362.04, 362.07, 366.41, 648.0x

Gestational diabetes mellitus

648.8x

Polycystic ovaries syndrome

256.4

Female infertility

628

Overweight and obesity

278.0

Table 1

Use of Antidiabetic Medication(s) in the 4 months before Pregnancy and During the Second or Third Trimester of Pregnancy for 437,950 Pregnancies Resulting in a Live Birth, By Maternal Age Category and Drug Class, 2001–2007

	Maternal Age at Delivery (Years)						**Total**	
	12–24 Years		25–39 Years		40–50 Years		All Women 12–50 Years	
Deliveries	n=77,636	%	n=341,020	%	n=19,294	%	N=437,950	%
Any antidiabetic drug during the prepregnancy period *	375	**0.48**	4610	**1.35**	314	**1.63**	5299	**1.21**
By drug class								
Insulin	200	0.26	1153	0.34	98	0.51	1451	0.33
Thiazolidenediones	8	0.01	111	0.03	12	0.06	131	0.03
Biguanide (Metformin)	177	0.23	3319	0.97	183	0.95	3679	0.84
Sulfonylureas	30	0.04	524	0.15	73	0.38	627	0.14
Alpha glucosidase inhibitors	0	--	5	0.00	1	0.01	6	0.00
Meglitinide analogs	0	--	1	0.00	0	--	1	0.00
GLP-1 receptor agonists	0	--	1	0.00	0	--	1	0.00
Combination products †	0	--	4	0.00	0	--	4	0.00
Any antidiabetic drug during second or third trimester	869	**1.12**	11942	**3.50**	1376	**7.13**	14187	3.24
By drug class								
Insulin	704	0.91	8989	2.64	1027	5.32	10720	2.45
Thiazolidenediones	0	0.00	6	0.00	2	0.01	8	0.00
Biguanide (Metformin)	23	0.03	540	0.16	45	0.23	608	0.14
Sulfonylureas ‡	171	0.22	3085	0.90	388	2.01	3644	0.83
Alpha glucosidase inhibitors	0	--	2	0.00	0	--	2	0.00
Combination products †	1	0.00	2	0.00	0	--	3	0.00

GLP-1, glucagon-like peptide-1.

* Prepregnancy = 120 days prior to pregnancy.

[†]Medications in the combination drugs were disaggregated and included in the individual drug classes. For example, a woman on Glyburide-Metformin is counted in the metformin and sulfonylureas categories.

[‡]99% of women who were dispensed a sulfonylurea during pregnancy were dispensed glyburide

DPP-4 and Amyline Analogs were not used prepregnancy or during the second or third trimester of pregnancy.

GLP-1 receptor agonists and meglitinide analogs were not used during the second or third trimester of pregnancy.

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Table 2

Use of Antidiabetic Medication(s)* in the 4 Months Before Pregnancy Among 437,950 Pregnancies Resulting in a Live Birth, By Maternal Characteristics and Combinations of Drug Classes, 2001–2007

				Specific Antidiabetic Drug or Combinations of Drugs									
	Total Sample	Any Antidiabetic Medication Use		Insulin Only		Metformin Only		Other Oral Agent only		Insulin Plus Any Other Drug		Metformin Plus Any Drug Except Insulin	
	n	n	%†	n	%	n	%	n	%	n	%	n	%
All centers combined	437950	5299	1.21	1233	0.28	3208	0.73	341	0.08	218	0.05	299	0.07
Calendar year of delivery													
2001	46742	310	0.66	120	0.26	110	0.24	45	0.10	15	0.03	20	0.04
2002	62863	584	0.93	196	0.31	268	0.43	58	0.09	26	0.04	36	0.06
2003	65486	625	0.95	176	0.27	337	0.51	48	0.07	17	0.03	47	0.07
2004	65028	828	1.27	218	0.34	473	0.73	44	0.07	40	0.06	53	0.08
2005	64539	845	1.31	158	0.24	565	0.88	51	0.08	25	0.04	46	0.07
2006	66315	993	1.50	177	0.27	678	1.02	50	0.08	47	0.07	41	0.06
2007	66977	1114	1.66	188	0.28	777	1.16	45	0.07	48	0.07	56	0.08
Maternal age on date of delivery (years)													
Younger than 18	8617	12	0.14	11	0.13	1	0.01	0	--	0	0.00	0	--
18–24	69019	363	0.53	170	0.25	150	0.22	13	0.02	19	0.03	11	0.02
25–29	118076	1309	1.11	281	0.24	865	0.73	65	0.06	47	0.04	51	0.04
30–34	142349	2039	1.43	411	0.29	1337	0.94	121	0.09	79	0.06	91	0.06
35–39	80595	1262	1.57	274	0.34	714	0.89	100	0.12	61	0.08	113	0.14
40–44	18270	302	1.65	82	0.45	137	0.75	39	0.21	12	0.07	32	0.18
45–50	1024	12	1.17	4	0.39	4	0.39	3	0.29	0	0.00	1	0.10
Maternal race or ethnicity													
Non-Hispanic White	185614	2254	1.21	620	0.33	1452	0.78	67	0.04	56	0.03	59	0.03
Hispanic	124125	1452	1.17	301	0.24	773	0.62	158	0.13	86	0.07	134	0.11

				Specific Antidiabetic Drug or Combinations of Drugs									
	Total Sample	**Any Antidiabetic Medication Use**		**Insulin Only**		**Metformin Only**		**Other Oral Agent only**		**Insulin Plus Any Other Drug**		**Metformin Plus Any Drug Except Insulin**	
	n	**n**	**%†**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Asian American	53756	619	1.15	84	0.16	413	0.77	52	0.10	23	0.04	47	0.09
Black or African American	35767	377	1.05	114	0.32	146	0.41	46	0.13	27	0.08	44	0.12
Native American	1305	23	1.76	3	0.23	12	0.92	1	0.08	5	0.38	2	0.15
Other	21189	325	1.53	66	0.31	231	1.09	11	0.05	11	0.05	6	0.03
Unknown	16194	249	1.54	45	0.28	181	1.12	6	0.04	10	0.06	7	0.04
Maternal education (years)													
Fewer than 12	35095	309	0.88	76	0.22	130	0.37	54	0.15	12	0.03	37	0.11
12 (high school graduate)	99585	1056	1.06	271	0.27	541	0.54	98	0.10	65	0.07	81	0.08
More than 12	277643	3573	1.29	815	0.29	2292	0.83	173	0.06	129	0.05	164	0.06
Unknown	25627	361	1.41	71	0.28	245	0.96	16	0.06	12	0.05	17	0.07
Gestational age (completed weeks)													
Fewer than 28	2200	96	4.36	16	0.73	68	3.09	7	0.32	1	0.03	4	0.18
28 to 31	3885	123	3.17	24	0.62	73	1.88	12	0.31	9	0.04	5	0.13
32 to 36	34900	863	2.47	297	0.85	415	1.19	46	0.13	44	0.03	61	0.17
37 to 41	372719	3975	1.07	860	0.23	2476	0.66	259	0.07	160	0.06	220	0.06
42 or more	24246	242	1.00	36	0.15	176	0.73	17	0.07	4	0.04	9	0.04

*This analyses examined the following categories: insulin only, metformin only, other oral agents only (does not include metformin; includes sulfonylureas, thiazolidenediones, alpha glucosidase inhibitors, meglitinide analogs, glucagon-like peptide-1 receptor agonists, and combinations of these products), insulin in combination with metformin or other oral agent, and metformin plus other oral agent.

†All percentages shown are row percentages with all deliveries in the corresponding row as the denominator.

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Table 3

Use of Antidiabetic Medications* in the Second or Third Trimester of Pregnancy Among 437,950 Pregnancies Resulting in a Live Birth, By Maternal Characteristics and Combinations of Drug Classes, 2001–2007

	All Deliveries	Any Antidiabetic Drug Use		Insulin Use Only		Metformin Use Only		Other Agent Use Only		Insulin Plus Other Oral Agent		Metformin Plus Any Other Drug	
	n	n	%†	n	%	n	%	n	%	n	%	n	%
All centers combined	437950	14187	3.24	9993	2.28	410	0.09	3024	0.69	563	0.13	197	0.04
Year of delivery													
2001	46742	1296	2.77	1127	2.41	7	0.01	135	0.29	26	0.06	1	0.00
2002	62863	1876	2.98	1602	2.55	11	0.02	193	0.31	58	0.09	12	0.02
2003	65486	2028	3.10	1571	2.40	24	0.04	346	0.53	73	0.11	14	0.02
2004	65028	2137	3.29	1568	2.41	56	0.09	405	0.62	80	0.12	28	0.04
2005	64539	2131	3.30	1382	2.14	85	0.13	529	0.82	102	0.16	33	0.05
2006	66315	2293	3.46	1341	2.02	97	0.15	685	1.03	124	0.19	46	0.07
2007	66977	2426	3.62	1402	2.09	130	0.19	731	1.09	100	0.15	63	0.09
Maternal age at delivery (years)													
Younger than 18	8617	33	0.38	28	0.32	0	-	5	0.06	0	-	0	-
18–24	69019	836	1.21	650	0.94	16	0.02	143	0.21	21	0.03	6	-
25–29	118076	2850	2.41	2010	1.70	111	0.09	591	0.50	113	0.10	25	0.02
30–34	142349	4939	3.47	3506	2.46	161	0.11	1034	0.73	171	0.12	67	0.05
35–39	80595	4153	5.15	2853	3.54	99	0.12	926	1.15	198	0.25	77	0.10
40–44	18270	1291	7.07	896	4.90	21	0.11	299	1.64	55	0.30	20	0.11
45–50	1024	85	8.30	50	4.88	2	0.20	26	2.54	5	0.49	2	0.20
Maternal race or ethnicity													
Non-Hispanic White	185614	4460	2.40	3257	1.75	218	0.12	758	0.41	163	0.09	64	0.03
Hispanic	124125	5004	4.03	3696	2.98	100	0.08	963	0.78	173	0.14	72	0.06
Asian American	53756	2204	4.10	1362	2.53	33	0.06	675	1.26	108	0.20	26	0.05

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	All Deliveries	Any Antidiabetic Drug Use		Insulin Use Only		Metformin Use Only		Other Agent Use Only		Insulin Plus Other Oral Agent		Metformin Plus Any Other Drug	
	n	n	%†	n	%	n	%	n	%	n	%	n	%
Black or African American	35767	1328	3.71	1001	2.80	24	0.07	225	0.63	59	0.16	19	0.05
Native American	1305	61	4.67	46	3.52	4	0.31	6	0.46	4	0.31	1	0.08
Other	21189	661	3.12	300	1.42	13	0.06	304	1.43	34	0.16	10	0.05
Unknown	16194	469	2.90	331	2.04	18	0.11	93	0.57	22	0.14	5	0.03
Maternal education (completed years)													
Fewer than 12	35095	1261	3.59	938	2.67	13	0.04	241	0.69	43	0.12	26	0.07
12	99585	3451	3.47	2541	2.55	68	0.07	671	0.67	123	0.12	48	0.05
More than 12	277643	8535	3.07	5859	2.11	306	0.11	1911	0.69	345	0.12	114	0.04
Unknown	25627	940	3.67	655	2.56	23	0.09	201	0.78	52	0.20	9	0.04
Gestational age (completed weeks)													
Fewer than 28	2200	91	4.14	68	3.09	6	0.27	12	0.55	3	0.14	2	0.09
28 to 31	3885	217	5.59	157	4.04	12	0.31	33	0.85	8	0.21	7	0.18
32 to 36	34901	1968	5.64	1443	4.13	47	0.13	373	1.07	73	0.21	32	0.09
37 to 41	372718	11304	3.03	7919	2.12	322	0.09	2469	0.66	445	0.12	149	0.04
42 or more	24246	607	2.50	406	1.67	23	0.09	137	0.57	34	0.14	7	0.03

*This analyses examined the following categories: insulin only, metformin only, other oral agents only (does not include metformin; includes sulfonylureas, thiazolidenediones, alpha glucosidase inhibitors, and combinations of these products), insulin with on oral agent (other than metformin), and metformin plus any other antidiabetic drug.

†All percentages shown are row percentages with all deliveries in the corresponding row as the denominator.

Appendix 1

List of Antidiabetic Medications* by Duration of Action (Where Applicable) and U.S. Food and Drug Administration Pregnancy Category and Approval Date

Medication Class and Name	Duration of Action	FDA Pregnancy Category	FDA* Approval Date
Insulin			
Insulin Zinc Extended	Long	B	
Insulin Glargine	Long	B	4/20/2000
Insulin Detemir	Long	B	6/16/2005
Insulin Aspart	Rapid	B	6/7/2000
Insulin Lispro	Rapid	B	
Insulin Glulisine	Rapid	B	4/16/2004
Insulin Isophane	Intermediate	B	
Insulin Zinc	Intermediate	B	
Insulin Regular	Short	B	
Insulin Regular Powder Inhale	Short	B	
Insulin Isophane and Reg	Varied	B	
Insulin Aspart Protamine and Aspart	Varied	B	11/1/2001
Insulin Lispro Protamine and Lispro	Varied	B	
Thiazolidinediones			
Pioglitazone		C	
Rosiglitazone		C	
Troglitazone†		B	
Biguanides			
Metformin		B	
Sulfonylureas			
Acetohexamide		C	
Glipizide		C	
Glyburide		C	
Tolazamide		C	
Glimepiride		C	
Chlorpropamide		C	
Tolbutamide		C	
Dipeptidyl Peptidase-4 Inhibitors			
Saxagliptin		B	7/31/2009
Sitagliptin		B	10/16/2006
Incretin Mimetic Agents			
Exenatide		C	4/28/2005
Alpha Glucosidase Inhibitors			

Medication Class and Name	Duration of Action	FDA Pregnancy Category	FDA* Approval Date
Miglitol		B	
Acarbose		B	
Meglitinide Analogs			
Repaglinide		C	
Nateglinide		C	12/22/2000
Amylin Analog			
Pramlintide		C	3/16/2005
Combination Products			
Sitagliptin-Biguanide		B/B	3/30/2007
Saxagliptin-Biguanide		B/B	11/5/2010
Repaglinide-Biguanide		C/B	6/23/2008
Pioglitazone-Biguanide		C/B	8/29/2005
Rosiglitazone-Biguanide		C/B	10/10/2002
Pioglitazone-Glimepiride		C/C	7/28/2006
Rosiglitazone-Glimepiride		C/C	11/23/2005
Glipizide-Biguanide		C/B	10/21/2002
Glyburide-Biguanide		C/B	7/31/2000

FDA, U.S. Food and Drug Administration.

*Approval dates are listed if the approval date was on or after January 1, 2000. Empty cells indicate that the drug was approved before January 1, 2000.

†Troglitzone was removed from the U.S. market on March 22, 2000. All other drugs remained on the market from their approval date through the end of the study.

FDA Pregnancy Category B: Either animal-reproduction studies have not demonstrated a fetal risk, but no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

FDA Pregnancy Category C: 1) Animal reproduction studies have shown an adverse event on the fetus (teratogenic or embryocidal or other) and there are no adequate and well-controlled studies in humans, no adequate and well controlled studies in pregnant women, or no animal reproduction studies and no adequate and well-controlled studies in humans. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.