ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2022 March 6; 10(7): 2053-2361

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 10 Number 7 March 6, 2022

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 7 March 6, 2022

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 7 March 6, 2022

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 7 March 6, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Feng Yin, MD, PhD, Assistant Professor, Department of Pathology and Anatomic Sciences, University of Missouri, Columbia, MO 65212, United States. fengyin@health.missouri.edu

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Lin-YuTong Wang*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

PUBLICATION DATE
March 6, 2022

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2022 March 6; 10(7): 2147-2158

DOI: 10.12998/wjcc.v10.i7.2147

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Association of types of diabetes and insulin dependency on birth outcomes

Pamela K Xaverius, Steven W Howard, Deborah Kiel, Jerry E Thurman, Ethan Wankum, Catherine Carter, Clairy Fang, Romi Carriere

Specialty type: Public, environmental and occupational health

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kamal H, Liu Z

Received: July 14, 2021
Peer-review started: July 14, 2021
First decision: August 8, 2021
Revised: September 21, 2021
Accepted: January 25, 2022
Article in press: January 25, 2022
Published online: March 6, 2022

Pamela K Xaverius, Deborah Kiel, Ethan Wankum, Department of Epidemiology and Biostatistics, Saint Louis University, St. Louis, MO 63104, United States

Steven W Howard, Department of Health Management and Policy, Saint Louis University, St. Louis, MO 63104, United States

Jerry E Thurman, Department of Endocrinology, Diabetes and Metabolism, SSM Health, St. Charles, MO 63303, United States

Catherine Carter, Division of Epidemiology, Institute for Health and Equity, Medical College of Wisconsin, Milwaukee, WI 53226, United States

Clairy Fang, Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, CA 90095, United States

Romi Carriere, Population Health Sciences Institute, Centre for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, England NE4 5PL, United Kingdom

Corresponding author: Pamela K Xaverius, MA, PhD, Professor, Department of Epidemiology and Biostatistics, Saint Louis University, 3545 Lafayette Avenue, St. Louis, MO 63104, United States. pam.xaverius@slu.edu

Abstract

BACKGROUND

Diabetes rates among pregnant women in the United States have been increasing and are associated with adverse pregnancy outcomes.

AIM

To investigate differences in birth outcomes (preterm birth, macrosomia, and neonatal death) by diabetes status.

METHODS

Cross-sectional design, using linked Missouri birth and death certificates (singleton births only), 2010 to 2012 (n = 204057). Exposure was diabetes (non-diabetic, pre-pregnancy diabetes-insulin dependent (PD-I), pre-pregnancy diabetes-non-insulin dependent (PD-NI), gestational diabetes- insulin dependent (GD-I), and gestational diabetes-non-insulin dependent (GD-NI)]. Outcomes

included preterm birth, macrosomia, and infant mortality. Confounders included demographic characteristics, adequacy of prenatal care, body mass index, smoking, hypertension, and previous preterm birth. Bivariate and multivariate logistic regression assessed differences in outcomes by diabetes status.

RESULTS

Women with PD-I, PD-NI, and GD-I remained at a significantly increased odds for preterm birth (aOR 2.87, aOR 1.77, and aOR 1.73, respectively) and having a very large baby [macrosomia] (aOR 3.01, aOR 2.12, and aOR 1.96, respectively); in reference to non-diabetic women. Women with GD-NI were at a significantly increased risk for macrosomia (aOR1.53), decreased risk for their baby to die before their first birthday (aOR 0.41) and no difference in risk for preterm birth in reference to non-diabetic women.

CONCLUSION

Diabetes is associated with the poor birth outcomes. Clinical management of diabetes during pregnancy and healthy lifestyle behaviors before pregnancy can reduce the risk for diabetes and poor birth outcomes.

Key Words: Epidemiology; Pregnancy; Health care delivery; Birth outcomes; Gestational diabetes; Insulin

Core Tip: This study investigated the differences in birth outcomes by timing of diabetes (pre-gestational and gestational) status and insulin use. The odds for preterm birth (PTB) and macrosomia were the most increased (187% and 201%, respectively) among women with insulin-dependent pre-pregnancy diabetes, followed by non-insulin dependent prepregnancy diabetes (77% and 112%, respectively) in comparison with women without diabetes. Women with insulin dependent gestational diabetes were also at an increased risk for PTB and macrosomia (73% and 95%, respectively). Clinical management of diabetes during pregnancy and healthy lifestyle behaviors before pregnancy can reduce the risk for diabetes and poor birth outcomes.

Citation: Xaverius PK, Howard SW, Kiel D, Thurman JE, Wankum E, Carter C, Fang C, Carriere R. Association of types of diabetes and insulin dependency on birth outcomes. *World J Clin Cases* 2022; 10(7): 2147-2158
URL: https://www.wjgnet.com/2307-8960/full/v10/i7/2147.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i7.2147

INTRODUCTION

Diabetes mellitus (DM) rates in the United States have been increasing and women with diabetes in pregnancy have high rates of congenital anomalies, preeclampsia, preterm delivery, macrosomia, and perinatal mortality[1-7]. In the United States, approximately seven percent of pregnancies are affected by DM, a condition in which a woman's blood glucose levels are above normal. Traditionally, DM has been classified into one of three categories: Type 1 diabetes, type 2 diabetes, and gestational diabetes (GDM)[8]. All three forms result in the body's inability to produce enough insulin, the hormone responsible for cells taking in sugar from the bloodstream to be stored and later used as energy. Type 1 diabetes accounts for about 5% of all diabetes cases, mainly caused by the autoimmune system's attack on beta cells that create insulin-dependence, the etiology of which involves both genetic and environmental risk factors. Type 2 diabetes is not an autoimmune condition, but rather a metabolic condition often related to obesity, a sedentary lifestyle and poor diet, where the body loses its ability to respond to insulin, creating insulin-resistance[9,10]. GDM is diabetes that is diagnosed in a woman during pregnancy and accounts for about 85% of diabetes cases among pregnant women, also associated with genetic and environmental factors, with incidence rates also rising[11-13]. As the prevalence of DM is increasing among women, so too grows the public health threat this health condition poses to pregnancy and birth outcomes[14,15].

The effect of insulin resistance on birth outcomes has been well documented. For example, Klemetti *et al*[16] analyzed hospital data from 881 pregnant patients with type 1 diabetes, over a ten-year span (1998-2008), and found that poor glycemic control was associated with increases in emergency caesarean sections, macrosomia, and Neonatal Intensive Care Unit (NICU) admission rates. One large population study in Denmark found that among women with type 1 diabetes, those with the greatest glycemic control before pregnancy had the lowest risk for poor birth outcomes, including perinatal mortality and

serious adverse outcomes[17]. Others report that when evaluating type 2 diabetes, those with preconception care had lower rates of fetal malformations than those without preconception care[18]. A large meta-analysis supports the claim that there is evidence of increased pre-eclampsia, cesarean delivery, and macrosomia for women with type 1 diabetes that have poor glycemic control[19]. Conversely, strong glucose control among type 1 diabetes has been associated with decreased risk for perinatal mortality, decreased maternal hypoglycemia, and normal fetal weight[20-22].

There is an important gap in the published literature, however, regarding population level studies of diabetes during pregnancy. For example, several large cohort studies of birth certificate data have reported an association between diabetes and birth outcomes, although differences in birth outcomes between diabetes types have rarely been reported[5,15,23,24]. Further, when types of DM have been compared, the results have been inconsistent[6]. For example, one study comparing type 1 diabetes to type 2 diabetes reported pregnant women with type 1 diabetes had an increased risk for preterm birth, large for gestational age, and hypertension[25]. Others have reported no differences between pregnant women with type 1 diabetes and type 2 diabetes as it relates to rates of congenital malformations and perinatal mortality[26,27]. Still another study found that still births and congenital anomalies were highest in the type 1 diabetes group with the lowest glycemic levels, although women with GDM were not included in that study[28]. One population-based study in France reported that preterm birth and macrosomia rates were significantly higher for women with type 1 diabetes (ORs 5.8 and 7.7, respectively), type 2 diabetes (ORs 3.1 and 3.8, respectively), and GDM (ORs 1.2 and 1.8, respectively). Further, in that study, there was 95% confidence that the odds of perinatal mortality for women with type 1 diabetes were comparable with non-diabetic women (OR 1.8, 95%CI: 1.0, 3.1), yet significantly higher for women with type 2 diabetes (OR 3.6, 95%CI: 2.6, 5.0) and significantly lower yet for women with GDM (OR 0.70, 95%CI: 0.60, 0.80)[29]. A major limitation to that population based study in France was that they did not have any data on body mass index, an important variable related to diabetes and strong potential confounder. Given the inconsistent results of these previous studies, additional research is needed to clarify the differential impact of each type of DM on birth outcomes.

Understanding the differential impact of prepregnancy diabetes with and without insulin dependence and GDM can offer important clues to understanding the population impact of insulin dependence on birth outcomes in the United States. The newest United States standard birth certificate allows for the examination of DM as it is related to birth outcomes, based upon timing of DM (prepregnancy DM or GDM) and pre-pregnancy DM insulin dependence (insulin dependent DM: PD-I and non-insulin dependent DM: PD-NI) and GDM insulin-dependence (GD-I) and non-insulin-dependence (GD-NI). This study will explore how birth outcomes vary for women exposed to different categories of DM, marked PD-I, PD-NI, GD-I, and GD-NI and build upon previous studies by including potentially important confounders like body mass index (BMI) (a reliable measure for population-based surveillance)[30,31].

MATERIALS AND METHODS

Study design

We conducted a population-based cross-sectional study of live, singleton births in Missouri from 2010-2012 inked with death certificate data. We removed implausible BMI categories (< 12 and > 70 BMI), resident zip codes outside the state of Missouri, and gestational age less than 20 wk, bringing our sample to 207511[32]. Cases were also removed when birth weight, race/ethnicity, marital status, smoking status, maternal education, and maternal age were missing (1.7%), resulting in a final sample of 204057. Listwise deletion was used, as there was sufficient sample size to support removing data that was missing at random and the percent of cases that were removed was less than 5% of the overall sample[33,34].

Exposure

Diabetes categories were selected based upon diabetes status and insulin-dependence status identified on the birth certificate. Prepregnancy diabetes non-insulin dependent (PD-NI), or insulin dependent (PD-I), gestational diabetes-insulin dependent (GD-I) and non-insulin dependent (GD-NI) and nondiabetic. Birth certificate recorders gather DM information from prenatal records, and this data has been reported elsewhere as having moderate sensitivity[35].

Covariates

Demographic characteristics included: maternal age (< 19, 19-34, > 34), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and Other), education (less than high school, high school or GED, some college, college grad or more), adequacy of prenatal care (inadequate, intermediate, adequate, adequate plus, and unknown, based upon the Kotelchuck index), marital status, and Medicaid status. Maternal risk covariates included BMI category [< 18.5 (underweight), 18.5-24.9 (normal), 25-29.9 (overweight), ≥ 30 (obese)], smoking during pregnancy, prepregnancy hypertension, gestational hypertension, preeclampsia, and previous preterm birth. Covariates often found to correlate with

adverse birth outcomes were selected.

Outcomes

Preterm birth (gestational age < 37 wk), macrosomia (birth weight > 4000 g), and infant mortality (death < 365 d of age).

Statistical analysis

Crude and multivariate logistic regressions were calculated to assess differences between diabetes groups in outcomes, with 99.8% confidence intervals calculated to measure precision. Bonferroni correction was used for the twenty-four 95%CIs to give a nominal confidence level of 99.8%. Chi-square tests were used to assess differences in selected covariates. Cramer's V was used to assess the magnitude of the relationship between categorical variables where 0.1 indicates a weak relationship, 0.3 indicating a moderate relationship, and 0.5 indicating a strong relationship.

RESULTS

A larger proportion of non-diabetic women were under age 35, and white, non-Hispanic, when compared to diabetic women. In addition, non-diabetic women reported a higher proportion of women that received adequate prenatal care and lower proportion of women that received adequate-plus prenatal care, in comparison with diabetic women. In contrast, a significantly higher proportion of women with PD-I (51.4%), PD-NI (59.4%), GD-I (64.4%) and GD-NI (46.1%) reported 30+ BMI category (obese) and a lower proportion of normal weight gain during pregnancy (20.2%, 21.3%, 20.4%, and 25.8%, respectively) in comparison with non-diabetic women (22.5% and 28.2%, respectively) (Table 1).

Table 2 presents the crude and adjusted odds ratios for the relationship of diabetes status to each birth outcome. PD-I, PD-NI, GD-I, and GD-NI were significantly associated with an increased risk for preterm birth [cOR 4.15 (95%CI: 3.22, 5.34); cOR 2.45 (95%CI: 1.85, 3.24); cOR 2.54 (95%CI: 1.91, 3.39); and cOR 1.41 (95%CI: 1.27, 1.56); respectively]. PD-I, PD-NI, GD-I, and GD-NI were significantly associated with an increased risk for macrosomia [cOR 3.12 (95%CI: 2.19, 3.77); cOR 2.32 (95%CI: 1.74, 3.10); cOR 2.15 (95%CI: 1.58, 2.92); and cOR 1.57 (95%CI 1.42, 1.74), respectively]. The risk for infant mortality was significantly decreased for women in the GD-NI category [PD-I: cOR 1.87 (95%CI: 0.66, 5.28); PD-NI: cOR 1.90 (95%CI: 0.71, 5.10); GD-I: cOR 1.62 (95%CI: 0.54, 4.88); and GD_NI: cOR 0.51 (95%CI: 0.29, 0.89)], in reference to non-diabetic women. There were significantly different crude odds between both the PD-I and GD-NI categories for preterm birth and macrosomia, in comparison to all other preterm birth categories, while the PD-NI and GD-I categories were non-significantly different from each other. Only women within the GD-NI category had significantly different infant mortality rate in reference to non-diabetic women.

Table 2 also presents the adjusted odds ratios for the relationship of diabetes status to each birth outcome, adjusted for maternal age, race/ethnicity, maternal education, marital status, BMI. In the adjusted model, preterm birth remained significantly associated in three of the four categories: PD-I (2.87, 95%CI:2.19, 3.77), PD-NI (1.77, 95%CI: 1.31, 2.39), GD-I (1.73, 95%CI: 1.27, 2.35), while there was no significant difference in the GD-NI category (1.07, 95%CI: 0.96, 1.19). Macrosomia also remained significantly associated with all four categories: PD-I (3.01, 95%CI: 2.26, 4.01), PD-NI (2.12, 95%CI: 1.57, 2.86), GD-I (1.96, 95%CI: 1.42, 2.70), and GD-NI (1.53, 95%CI: 1.39, 1.70). Women with GD-NI were found to have a significantly lower risk for infant mortality [aOR 0.41 (0.23, 0.72)] in reference to non-diabetic women. There were significantly different adjusted odds between both the PD-I and GD-NI categories for preterm birth and macrosomia, in comparison to all other preterm birth categories, while the PD-NI and GD-I categories were non-significantly different from each other.

DISCUSSION

This large population-based study found that women with pregestational DM had the highest increased risk for preterm birth and macrosomia, with the highest risk for women with insulin dependent pre-pregnancy diabetes, in reference to non-diabetic women. Statistically, there was no significant difference between the risks for preterm birth and macrosomia among women with PD-NI and GD-I. Interestingly, women with gestational diabetes that had no insulin-dependence were at a 59% reduced risk for infant mortality in comparison with women without diabetes. These findings are fairly comparable to the large population-based study in France, although our odds are slightly lower perhaps due to our ability to include BMI in our adjusted model[33]. With the growing prevalence of DM, the differential impact of type of diabetes on birth outcomes is important to identify so evidence-based plans can be implemented to reduce the deleterious impact of this growing public health crisis.

Interestingly, differences in risks between types of DM seem to reflect differences in timing of DM (pre-pregnancy *vs* gestational) and insulin use. For example, the odds for preterm birth and macrosomia

Table 1 Distribution of demographic factors and birth outcomes by diabetes status (*n* = 203222)

	Overall		Non-diabetic		PD-I		PD-NI		GD-I		GD-NI		Chi-Square	Cramer's V
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%		
	204057	100.00%	192329	94.40%	733	0.40%	798	0.40%	742	0.40%	9455	4.60%		
Age													< 0.0001	0.06
≤ 19	19374	9.50%	18915	9.80%	31	4.20%	25	3.10%	20	2.70%	383	4.10%		
20-34	163515	80.10%	154633	80.40%	553	75.40%	598	74.90%	563	75.90%	7168	75.80%		
≥ 35	21168	10.40%	18781	9.80%	149	20.30%	175	21.90%	159	21.40%	1904	20.10%		
Race													< 0.0001	0.02
White Non-Hispanic	157144	77.00%	148434	77.20%	532	72.60%	539	67.50%	492	66.30%	7147	75.60%		
Black Non-Hispanic	30053	14.70%	28420	14.80%	139	19.00%	182	22.80%	161	21.70%	1151	12.20%		
Hispanic	10638	5.20%	9813	5.10%	41	5.60%	50	6.30%	60	8.10%	674	7.10%		
Other Non-Hispanic	6222	3.00%	5662	2.90%	21	2.90%	27	3.40%	29	3.90%	483	5.10%		
Education													< 0.0001	0.02
Less than HS	32650	16.00%	30970	16.10%	134	18.30%	118	14.80%	106	14.30%	1322	14.00%		
HS or GED	49222	24.10%	46356	24.10%	188	25.60%	216	27.10%	203	27.40%	2259	23.90%		
Some college	64878	31.80%	60666	31.50%	282	38.50%	274	34.30%	298	40.20%	3358	35.50%		
College grad or more	57307	28.10%	54337	28.30%	129	17.60%	190	23.80%	135	18.20%	2516	26.60%		
Married/paternity													< 0.0001	0.02
Married paternity acknowledged	121764	59.70%	114191	59.40%	430	58.70%	490	61.40%	444	59.80%	6209	65.70%		
Not married paternity acknowledged	54920	26.90%	52032	27.10%	191	26.10%	202	25.30%	184	24.80%	2311	24.40%		
Paternity not acknowledged	27373	13.40%	26106	13.60%	112	15.30%	106	13.30%	114	15.40%	935	9.90%		
Adequacy of prenatal care													< 0.0001	0.05
Inadequate	26633	13.10%	75618	39.30%	122	16.60%	187	23.40%	134	18.10%	2769	29.30%		
Intermediate	14269	7.00%	25365	13.20%	57	7.80%	89	11.20%	89	12.00%	1033	10.90%		
Adequate	78830	38.60%	13762	7.20%	24	3.30%	35	4.40%	34	4.60%	414	4.40%		
Adequate plus	64277	31.50%	58787	30.60%	410	55.90%	390	48.90%	395	53.20%	4295	45.40%		
Unknown	20048	9.80%	18797	9.80%	120	16.40%	97	12.20%	90	12.10%	944	10.00%		

Medicaid													< 0.0001	0.01
Medicaid	96861	47.50%	91165	47.40%	300	40.90%	362	45.40%	319	43.00%	4715	49.90%		
Private	88330	43.30%	83149	43.20%	378	51.60%	375	47.00%	387	52.20%	4041	42.70%		
Other	9697	4.80%	9244	4.80%	23	3.10%	27	3.40%	20	2.70%	383	4.10%		
Missing	9169	4.50%	8771	4.60%	32	4.40%	34	4.30%	16	2.20%	316	3.30%		
Smoking during pregnancy													0.002	0.01
No	153347	75.10%	144659	75.20%	506	69.00%	585	73.30%	539	72.60%	7058	74.60%		
Yes	50710	24.90%	47670	24.80%	227	31.00%	213	26.70%	203	27.40%	2397	25.40%		
Hypertension (prepregnancy gestational eclampsia)													< 0.0001	0.06
Yes	10862	5.30%	182744	95.00%	639	87.20%	712	89.20%	628	84.60%	8472	89.60%		
No	193195	94.70%	9585	5.00%	94	12.80%	86	10.80%	114	15.40%	983	10.40%		
Sexually transmitted infection													0.004	0.01
Yes	2055	1.00%	1911	1.00%	5	0.70%	16	2.00%	13	1.80%	110	1.20%		
No	202002	99.00%	190418	99.00%	728	99.30%	782	98.00%	729	98.20%	9345	98.80%		
Previous preterm birth													< 0.0001	0.04
Yes	6321	3.10%	5697	3.00%	66	9.00%	59	7.40%	50	6.70%	449	4.70%		
No	197736	96.90%	186632	97.00%	667	91.00%	739	92.60%	692	93.30%	9006	95.30%		
BMI category													< 0.0001	0.08
Underweight	9037	4.40%	8812	4.60%	6	0.80%	5	0.60%	5	0.70%	209	2.20%		
Normal weight	97666	47.90%	94641	49.20%	177	24.10%	163	20.40%	100	13.50%	2585	27.30%		
Overweight	48393	23.70%	45603	23.70%	173	23.60%	156	19.50%	159	21.40%	2302	24.30%		
Obese	48961	24.00%	43273	22.50%	377	51.40%	474	59.40%	478	64.40%	4359	46.10%		
Weight gain													< 0.0001	0.03
Normal gain	57096	28.00%	54188	28.20%	148	20.20%	170	21.30%	151	20.40%	2439	25.80%		
Under gain	36867	18.10%	34032	17.70%	117	16.00%	172	21.60%	157	21.20%	2389	25.30%		
Over gain	103203	50.60%	97568	50.70%	444	60.60%	417	52.30%	413	55.70%	4361	46.10%		
Missing	6891	3.40%	6541	3.40%	24	3.30%	39	4.90%	21	2.80%	266	2.80%		
Preterm birth													< 0.0001	0.06

Full term	188239	92.20%	14341	7.50%	193	26.30%	141	17.70%	133	17.90%	1010	10.70%		
Preterm	15818	7.80%	177988	92.50%	540	73.70%	657	82.30%	609	82.10%	8445	89.30%		
Macrosomia													< 0.0001	0.05
No	187065	91.70%	176873	92.00%	576	78.60%	663	83.10%	626	84.40%	8327	88.10%		
Yes	16992	8.30%	15456	8.00%	157	21.40%	135	16.90%	116	15.60%	1128	11.90%		
Infant mortality													< 0.0001	0.01
No	203010	99.50%	191334	99.50%	725	98.90%	789	98.90%	734	98.90%	9428	99.70%		
Yes	1047	0.50%	995	0.50%	8	1.10%	9	1.10%	8	1.10%	27	0.30%		

PD-I: Pre-pregnancy diabetes-insulin dependent; PD-NI: Pre-pregnancy diabetes-non-insulin dependent; GD-I: Gestational diabetes- insulin dependent; GD-NI: Gestational diabetes-non-insulin dependent.

Table 2 Crude and adjusted relationship of diabetes status with birth outcomes

	Preterm birth				Macrosomia				Infant mortality			
	cOR	95%CI	aOR	95%CI	cOR	95%CI	aOR	95%CI	cOR	95%CI	aOR	95%CI
Non-diabetic	*ref*		*ref*		*ref*		*ref*		*ref*		*ref*	
PD-I	4.15	3.22, 5.34	2.87	2.19, 3.77	3.12	2.37, 4.11	3.01	2.26, 4.01	1.87	0.66, 5.28	1.30	0.46, 3.72
PD-NI	2.45	1.85, 3.24	1.77	1.31, 2.39	2.32	1.74, 3.10	2.12	1.57, 2.86	1.90	0.71, 5.10	1.35	0.50, 3.67
GD-I	2.54	1.91, 3.39	1.73	1.27, 2.35	2.15	1.58, 2.92	1.96	1.42, 2.70	1.62	0.54, 4.88	1.13	0.37, 3.44
GD-NI	1.41	1.27, 1.56	1.07	0.96, 1.19	1.57	1.42, 1.74	1.53	1.39, 1.70	0.51	0.29, 0.89	0.41	0.23, 0.72

aOR adjustments: Maternal age, race/ethnicity, education, paternity/marital status, adequacy of prenatal care, insurance status, smoking, hypertension, STI, previous preterm birth, body mass index, and weight gain. PD-I: Pre-pregnancy diabetes-insulin dependent; PD-NI: Pre-pregnancy diabetes-non-insulin dependent; GD-I: Gestational diabetes- insulin dependent; GD-NI: Gestational diabetes-non-insulin dependent.

were higher when there was insulin-dependence, among women with pre-pregnancy diabetes (PTB: 187% *vs* 77%; Macrosomia: 126% *vs* 57%) and among women with gestational diabetes (PTB: 73% *vs* 9%; Macrosomia: 96% *vs* 53%) in comparison with women without diabetes. The risks were significantly higher when comparing insulin dependence within the gestational categories, because the 99.8% confidence intervals did not overlap between gestational categories, and further, there was no difference in risk for preterm birth between women without diabetes and women with non-insulin dependent gestational diabetes. These results reflect similar findings among other published studies, that is, more severe adverse birth outcomes are associated with worsening glycemic control. While measures of glycemic control are not provided in the birth certificate data used for this study, glycemic control is often harder to achieve in women with absolute insulin resistance, perhaps explaining the difference in

poor birth outcomes among insulin use in comparison with non-insulin dependent women[36].

It is notable that women with GD-NI were found to be at a 59% significantly decreased odds for infant death in comparison with non-diabetic women, even after adjusting for socio-demographic, behavioral, and biological differences. This finding is consistent with a study in France, that found a 30% reduction in perinatal mortality among women with GDM in comparison with non-diabetic women[33]. Diagnosis of GDM is usually based upon results from oral glucose tolerance tests often conducted between the 24th and 28th week of gestation. Treatment is designed to lower glucose concentrations and typically involves high-risk obstetric management, including behavioral changes, nutritional plans, or insulin, as needed[37]. In the large population-based study from France discussed earlier, when their sample was limited to full-term deliveries that excluded cases of undiagnosed pregestational diabetes, the odds of perinatal mortality reversed from being decreased to being increased when compared with non-diabetic women. This led the authors to speculate that the timing and delivery of treatment may play a pivotal role in reducing risks for infant mortality. We similarly speculate that timing and intensity of GDM treatment play an important role in infant mortality among our study participants in the United States.

There are a number of limitations to this study, which include the possible misclassification of diabetes. First, women with PD-I or PD-NI may have first been diagnosed during pregnancy, and thus their DM status was wrongly classified as gestational. While extremely unlikely for women with PD-I, given the significant symptoms and typical younger age at onset associated with this condition, it is possible that women with PD-NI were undiagnosed before pregnancy and thus classified as GDM. In addition, it is possible that there are some women in the non-diabetic group who were diabetic. Prediabetes is also a growing population-level concern (women with prediabetes have higher blood glucose levels than normal, but not high enough to be medically diagnosed with diabetes[38]), but that data is not provided on birth certificates. Women with prediabetes are at increased risk for developing both GD and non-insulin dependent diabetes mellitus (PD-NI) later in life; this may distort the risk in the non-diabetic group, as individuals labeled as non-diabetic could be pre-diabetic (with increased risk for adverse birth outcomes). In addition, while the result for infant mortality was not significant in the PD-I, PD-NI, and GD-I categories, the point estimates were higher when compared to non-diabetic women and this may be due to the small number of people in those categories. Furthermore, there is potential for residual confounding within the data due to unmeasured behavioral risk factors, income levels, as well as other unmeasured c, that may impact the overall outcomes for these women and their babies. Also, due to the sample only coming from the state of Missouri, there is limited generalizability. Because the data set includes all Missouri births from 2010-2012, this study has strong internal validity with respect to risks of adverse birth outcomes by category of DM for women in Missouri.

CONCLUSION

As categories of diabetes differed, so too did risk for poor birth outcomes, with having insulin use among women with pre-pregnancy diabetes putting women at the highest risk for the poorest birth outcomes. Clinical management of DM and healthy lifestyle behaviors before pregnancy have been shown to improve birth outcomes, suggesting that access to preconceptional care plays an important role in reducing risks for poor birth outcomes. Clinical implications from these findings should recognize the increased risk for adverse birth outcomes for all categories of diabetes, especially for preterm birth and macrosomia. The classification schema of insulin-dependent, non-insulin dependent, and gestational diabetes may be outdated[6], yet the risks for poor birth outcomes were significantly increased based upon timing of DM onset (*i.e.*, prepregnancy or gestational) and insulin use. We now have a better understanding of the spectrum of factors associated with different forms of DM, including age, weight, metabolic syndrome, autoimmune disease, inflammation, and c-peptide[39]. Future research should focus on maintaining proper glycemic control before pregnancy and throughout pregnancy to help reduce the risk for adverse birth outcomes. Further, findings from a large systematic review found that a diet high in fruits and vegetables, legume, nuts, whole grains, and fish before pregnancy may reduce one's risk for developing GDM during pregnancy[40]. Future research should consider how non-pregnant women of childbearing age are assessed and provided education on management and prevention of DM, specifically as it relates to pregnancy. Increased knowledge and implementation of evidence-based standards of care during the preconceptional period could result in reduced rates of DM among women, and in turn, healthier moms and babies.

ARTICLE HIGHLIGHTS

Research background

Diabetes mellitus (DM) rates in the United States have been increasing and women with diabetes in pregnancy have high rates of congenital anomalies, preeclampsia, preterm delivery, macrosomia, and perinatal mortality. In the United States, approximately seven percent of pregnancies are affected by DM, a condition in which a woman's blood glucose levels are above normal. The effect of insulin resistance on birth outcomes has been well documented. There is an important gap in the published literature, however, regarding population level studies of diabetes during pregnancy. For example, several large cohort studies of birth certificate data have reported an association between diabetes and birth outcomes, although differences in birth outcomes between diabetes types have rarely been reported.

Research motivation

Understanding the differential impact of prepregnancy diabetes with and without insulin dependence and GDM can offer important clues to understanding the population impact of insulin dependence on birth outcomes in the United States. This study explores how birth outcomes vary for women exposed based upon timing of diabetes (pre-gestational or gestational) and insulin-dependence, building upon previous studies by including potentially important confounders like BMI (a reliable measure for population-based surveillance).

Research objectives

To investigate differences in birth outcomes (preterm birth, macrosomia, and infant mortality/) by diabetes status.

Research methods

Cross-sectional design, using linked Missouri birth and death certificates [singleton births only), 2010 to 2012 (n = 204057). Exposure was diabetes (non-diabetic, pre-pregnancy diabetes-insulin dependent (PD-I), pre-pregnancy diabetes-non-insulin dependent (PD-NI), gestational diabetes- insulin dependent (GD-I), and gestational diabetes-non-insulin dependent (GD-NI)]. Outcomes included preterm birth, macrosomia, and neonatal death. Confounders included demographic characteristics, adequacy of prenatal care, BMI, smoking, hypertension, and previous preterm birth. Bivariate and multivariate logistic regression assessed differences in outcomes by diabetes status.

Research results

Women with PD-I, PD-NI, and GD-I remained at a significantly increased odds for preterm birth (aOR 2.87; aOR 1.77; and aOR 1.73, respectively) and having a very large baby (macrosomia) (aOR 3.01, aOR 2.12; aOR and 1.96;, respectively); in reference to non-diabetic women. Women with GD-NI were at a significantly increased risk for macrosomia (aOR1.53), decreased risk for their baby to die before their first birthday (aOR 0.41) and no difference in risk for preterm birth in reference to non-diabetic women.

Research conclusions

As categories of diabetes differed, so too did risk for poor birth outcomes, with having insulin use among women with pre-pregnancy diabetes putting women at the highest risk for the poorest birth outcomes.

Research perspectives

Diabetes is associated with the poor birth outcomes. Clinical management of diabetes during pregnancy and healthy lifestyle behaviors before pregnancy can reduce the risk for diabetes and poor birth outcomes.

ACKNOWLEDGEMENTS

This project was completed in the epidemiology capstone course as part of the MPH degree requirements at Saint Louis University, College for Public Health and Social Justice, a course co-instructed by Pamela K Xaverius, PhD, MBA and Joanne Salas, MPH.

FOOTNOTES

Author contributions: Xaverius PK oversaw all aspects of this project including developing the research question, collecting and analyzing the data, and writing the overall manuscript; Xaverius PK and Kiel D designed the research study; Wankum E, Carter C, Fang C, and Carriere R analyzed the data; and Xaverius PK, Howard SW, and Thurman JE wrote the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: This study has been granted an exemption by the Institutional Review Board at Saint Louis University.

Conflict-of-interest statement: The authors have no financial or non-financial competing interests or conflicts of interests associated with this manuscript.

Data sharing statement: The data used in this manuscript were acquired from the Missouri Department of Health and Senior Services (MODHSS) and are not available for public access due to MODHSS guidelines. The contents of this document including data analysis, interpretation or conclusions are solely the responsibility of the authors and do not represent the official views of DHSS.

STROBE statement: The authors have read the STROBE Statement, and the manuscript was prepared and revised according to the STROBE Statement.

Country/Territory of origin: United States

ORCID number: Pamela K Xaverius 0000-0001-8824-2933; Steven W Howard 0000-0003-0056-6680; Deborah Kiel 0000-0003-0081-1252; Jerry E Thurman 0000-0003-3752-816X; Ethan Wankum 0000-0001-8470-1688; Catherine Carter 0000-0002-3839-4346; Clairy Fang 0000-0002-3570-2112; Romi Carriere 0000-0002-7157-4576.

S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

REFERENCES

1 **Bardenheier BH**, Imperatore G, Devlin HM, Kim SY, Cho P, Geiss LS. Trends in pre-pregnancy diabetes among deliveries in 19 U.S. states, 2000-2010. *Am J Prev Med* 2015; **48**: 154-161 [PMID: 25326417 DOI: 10.1016/j.amepre.2014.08.031]
2 **Bardenheier BH**, Imperatore G, Gilboa SM, Geiss LS, Saydah SH, Devlin HM, Kim SY, Gregg EW. Trends in Gestational Diabetes Among Hospital Deliveries in 19 U.S. States, 2000-2010. *Am J Prev Med* 2015; **49**: 12-19 [PMID: 26094225 DOI: 10.1016/j.amepre.2015.01.026]
3 **Correa A**, Bardenheier B, Elixhauser A, Geiss LS, Gregg E. Trends in prevalence of diabetes among delivery hospitalizations, United States, 1993-2009. *Matern Child Health J* 2015; **19**: 635-642 [PMID: 24996952 DOI: 10.1007/s10995-014-1553-5]
4 **Dodd JM**, Crowther CA, Antoniou G, Baghurst P, Robinson JS. Screening for gestational diabetes: the effect of varying blood glucose definitions in the prediction of adverse maternal and infant health outcomes. *Aust N Z J Obstet Gynaecol* 2007; **47**: 307-312 [PMID: 17627686 DOI: 10.1111/j.1479-828X.2007.00743.x]
5 **Feig DS**, Hwee J, Shah BR, Booth GL, Bierman AS, Lipscombe LL. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada, 1996-2010. *Diabetes Care* 2014; **37**: 1590-1596 [PMID: 24705609 DOI: 10.2337/dc13-2717]
6 **Knight KM**, Thornburg LL, Pressman EK. Pregnancy outcomes in type 2 diabetic patients as compared with type 1 diabetic patients and nondiabetic controls. *J Reprod Med* 2012; **57**: 397-404 [PMID: 23091986]
7 **Weeks JW**, Major CA, de Veciana M, Morgan MA. Gestational diabetes: does the presence of risk factors influence perinatal outcome? *Am J Obstet Gynecol* 1994; **171**: 1003-1007 [PMID: 7943062 DOI: 10.1016/0002-9378(94)90023-x]
8 **American Diabetes Association**. Erratum. Classification and diagnosis of diabetes. Sec. 2. In Standards of Medical Care in Diabetes-2016. Diabetes Care 2016;39(Suppl. 1):S13-S22. *Diabetes Care* 2016; **39**: 1653 [PMID: 27555625 DOI: 10.2337/dc16-er09]
9 **Lawrence JM**, Contreras R, Chen W, Sacks DA. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999-2005. *Diabetes Care* 2008; **31**: 899-904 [PMID: 18223030 DOI: 10.2337/dc07-2345]
10 **Ogden CL**, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA* 2014; **311**: 806-814 [PMID: 24570244 DOI: 10.1001/jama.2014.732]

11 **Fong A**, Serra A, Herrero T, Pan D, Ogunyemi D. Pre-gestational *vs* gestational diabetes: a population based study on clinical and demographic differences. *J Diabetes Complications* 2014; **28**: 29-34 [PMID: 24094665 DOI: 10.1016/j.jdiacomp.2013.08.009]

12 **Lavery JA**, Friedman AM, Keyes KM, Wright JD, Ananth CV. Gestational diabetes in the United States: temporal changes in prevalence rates between 1979 and 2010. *BJOG* 2017; **124**: 804-813 [PMID: 27510598 DOI: 10.1111/1471-0528.14236]

13 **Centers for Disease Control and Prevention**. Diabetes Basics. 2021. Available from: https://www.cdc.gov/diabetes/basics/index.html

14 **Lynch CP**, Baker N, Korte JE, Mauldin JG, Mayorga ME, Hunt KJ. Increasing prevalence of diabetes during pregnancy in South Carolina. *J Womens Health (Larchmt)* 2015; **24**: 316-323 [PMID: 25786128 DOI: 10.1089/jwh.2014.4968]

15 **Vahratian A**. Prevalence of overweight and obesity among women of childbearing age: results from the 2002 National Survey of Family Growth. *Matern Child Health J* 2009; **13**: 268-273 [PMID: 18415671 DOI: 10.1007/s10995-008-0340-6]

16 **Klemetti M**, Nuutila M, Tikkanen M, Kari MA, Hiilesmaa V, Teramo K. Trends in maternal BMI, glycaemic control and perinatal outcome among type 1 diabetic pregnant women in 1989-2008. *Diabetologia* 2012; **55**: 2327-2334 [PMID: 22752076 DOI: 10.1007/s00125-012-2627-9]

17 **Jensen DM**, Korsholm L, Ovesen P, Beck-Nielsen H, Moelsted-Pedersen L, Westergaard JG, Moeller M, Damm P. Peri-conceptional A1C and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes. *Diabetes Care* 2009; **32**: 1046-1048 [PMID: 19265024 DOI: 10.2337/dc08-2061]

18 **Callec R**, Perdriolle-Galet E, Sery GA, Morel O. Type 2 diabetes in pregnancy: Rates of fetal malformations and level of preconception care. *J Obstet Gynaecol* 2014; **34**: 648-649 [PMID: 24922555 DOI: 10.3109/01443615.2014.925856]

19 **Middleton P**, Crowther CA, Simmonds L. Different intensities of glycaemic control for pregnant women with pre-existing diabetes. *Cochrane Database Syst Rev* 2016; CD008540 [PMID: 27142841 DOI: 10.1002/14651858.CD008540.pub4]

20 **Miranda JA**, Mozas J, Rojas R, Esteva G, Muñoz C, Herruzo Nalda AJ. Strict glycemic control in women with pregestational insulin-dependent diabetes mellitus. *Int J Gynaecol Obstet* 1994; **47**: 223-227 [PMID: 7705526 DOI: 10.1016/0020-7292(94)90565-7]

21 **Rackham O**, Paize F, Weindling AM. Cause of death in infants of women with pregestational diabetes mellitus and the relationship with glycemic control. *Postgrad Med* 2009; **121**: 26-32 [PMID: 19641265 DOI: 10.3810/pgm.2009.07.2026]

22 **Sacks DA**, Feig DS, Liu IL, Wolde-Tsadik G. Managing type I diabetes in pregnancy: how near normal is necessary? *J Perinatol* 2006; **26**: 458-462 [PMID: 16761010 DOI: 10.1038/sj.jp.7211546]

23 **Hunt KJ**, Marlow NM, Gebregziabher M, Ellerbe CN, Mauldin J, Mayorga ME, Korte JE. Impact of maternal diabetes on birthweight is greater in non-Hispanic blacks than in non-Hispanic whites. *Diabetologia* 2012; **55**: 971-980 [PMID: 22237686 DOI: 10.1007/s00125-011-2430-z]

24 **Shan X**, Chen F, Wang W, Zhao J, Teng Y, Wu M, Teng H, Zhang X, Qi H, Liu X, Tan C, Mi J. Secular trends of low birthweight and macrosomia and related maternal factors in Beijing, China: a longitudinal trend analysis. *BMC Pregnancy Childbirth* 2014; **14**: 105 [PMID: 24641671 DOI: 10.1186/1471-2393-14-105]

25 **Hillman N**, Herranz L, Vaquero PM, Villarroel A, Fernandez A, Pallardo LF. Is pregnancy outcome worse in type 2 than in type 1 diabetic women? *Diabetes Care* 2006; **29**: 2557-2558 [PMID: 17065703 DOI: 10.2337/dc06-0680]

26 **Clausen TD**, Mathiesen E, Ekbom P, Hellmuth E, Mandrup-Poulsen T, Damm P. Poor pregnancy outcome in women with type 2 diabetes. *Diabetes Care* 2005; **28**: 323-328 [PMID: 15677787 DOI: 10.2337/diacare.28.2.323]

27 **Macintosh MC**, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, Golightly S, Miller A. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. *BMJ* 2006; **333**: 177 [PMID: 16782722 DOI: 10.1136/bmj.38856.692986.AE]

28 **Owens LA**, Sedar J, Carmody L, Dunne F. Comparing type 1 and type 2 diabetes in pregnancy- similar conditions or is a separate approach required? *BMC Pregnancy Childbirth* 2015; **15**: 69 [PMID: 25885892 DOI: 10.1186/s12884-015-0499-y]

29 **Billionnet C**, Mitanchez D, Weill A, Nizard J, Alla F, Hartemann A, Jacqueminet S. Gestational diabetes and adverse perinatal outcomes from 716,152 births in France in 2012. *Diabetologia* 2017; **60**: 636-644 [PMID: 28197657 DOI: 10.1007/s00125-017-4206-6]

30 **Osterman MJ**, Martin JA, Mathews TJ, Hamilton BE. Expanded data from the new birth certificate, 2008. *Natl Vital Stat Rep* 2011; **59**: 1-28 [PMID: 21848043]

31 **Park S**, Sappenfield WM, Bish C, Bensyl DM, Goodman D, Menges J. Reliability and validity of birth certificate prepregnancy weight and height among women enrolled in prenatal WIC program: Florida, 2005. *Matern Child Health J* 2011; **15**: 851-859 [PMID: 19937268 DOI: 10.1007/s10995-009-0544-4]

32 **Branum AM**, Kirmeyer SE, Gregory EC. Prepregnancy Body Mass Index by Maternal Characteristics and State: Data From the Birth Certificate, 2014. *Natl Vital Stat Rep* 2016; **65**: 1-11 [PMID: 27508894]

33 **Donner A**. The relative effectiveness of procedures commonly used in multiple regression analysis for dealing with missing values. *Am Sta* 1982; **36**: 378-381 [DOI: 10.1080/00031305.1982.10483055]

34 **Schafer JL**. Multiple imputation: a primer. *Stat Methods Med Res* 1999; **8**: 3-15 [PMID: 10347857 DOI: 10.1177/096228029900800102]

35 **Dietz P**, Bombard J, Mulready-Ward C, Gauthier J, Sackoff J, Brozicevic P, Gambatese M, Nyland-Funke M, England L, Harrison L, Farr S. Validation of selected items on the 2003 U.S. standard certificate of live birth: New York City and Vermont. *Public Health Rep* 2015; **130**: 60-70 [PMID: 25552756 DOI: 10.1177/003335491513000108]

36 **American Diabetes Association**. 13. Management of Diabetes in Pregnancy. *Diabetes Care* 2017; **40**: S114-S119 [PMID: 27979900 DOI: 10.2337/dc17-S016]

37 **Horvath K**, Koch K, Jeitler K, Matyas E, Bender R, Bastian H, Lange S, Siebenhofer A. Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. *BMJ* 2010; **340**: c1395 [PMID: 20360215 DOI: 10.1136/bmj.c1395]

38 **American Diabetes Association**. Prevention or Delay of Type 2 Diabetes. *Diabetes Care* 2017; **40**: (Suppl. 1) S44-S47 [DOI: 10.2337/dc17-S008]

39 **Schwartz SS**, Epstein S, Corkey BE, Grant SF, Gavin JR 3rd, Aguilar RB. The Time Is Right for a New Classification

System for Diabetes: Rationale and Implications of the β-Cell-Centric Classification Schema. *Diabetes Care* 2016; **39**: 179-186 [PMID: 26798148 DOI: 10.2337/dc15-1585]

40 **Schoenaker DA**, Mishra GD, Callaway LK, Soedamah-Muthu SS. The Role of Energy, Nutrients, Foods, and Dietary Patterns in the Development of Gestational Diabetes Mellitus: A Systematic Review of Observational Studies. *Diabetes Care* 2016; **39**: 16-23 [PMID: 26696657 DOI: 10.2337/dc15-0540]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com