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RESEARCH LETTER

Pregnancies Complicated by Diabetes and Effect on Fetal Growth in Patients With Congenital Heart Disease

As more patients with congenital heart disease (CHD) are becoming pregnant and there is a shift toward advanced maternal age, more maternal and neonatal comorbidities are being recognized.[1] Simultaneously, the prevalence of diabetes mellitus (DM) in pregnancy continues to increase, following the rising trend in obesity in the United States. In 2020, the overall rate of gestational diabetes mellitus (GDM) among women giving birth was 7.8%, a 30% increase from 2016.[2] GDM offers its own set of obstetric and neonatal complications. Patients with GDM have increased risk of caesarean delivery, hypertensive disorders, preterm delivery, low 1-minute Apgar score, and large for gestational age (LGA) compared to patients without DM.[3] Increased risk of LGA persists among patients with GDM treated with insulin.[3] To date, there have been no studies evaluating the prevalence of DM in pregnant patients with CHD.

We performed a retrospective chart review of all subjects included in the STORCC (STandardized Outcomes of Reproductive Cardiovascular Care) initiative from November 2011 to June 2022 to explore the prevalence of DM among patients with CHD during pregnancy. Data collected at the first visit included baseline demographics, cardiac anatomy, surgical history, comorbid conditions, and medications. New cardiac or obstetric symptoms, changes in clinical status, medications, and cardiac and obstetric outcomes were collected prospectively at each clinic visit, during all admissions, and for up to 1 year following delivery. Patients could have more than one pregnancy included over the study period. Preexisting DM was diagnosed prior to conception based on a combination of plasma glucose and A1C criteria. Preexisting type 1 DM (T1DM) refers to insulin deficiency resulting from autoimmune destruction of insulin-producing cells in the pancreas. One patient in our cohort was diagnosed with T1DM during pregnancy. Preexisting T2DM is classified as the progressive loss of insulin secretion often due to insulin resistance based on life-style factors. GDM refers to diabetes diagnosed during pregnancy in patients without clear diabetes prior to gestation.[4] At our institution, screening and diagnosis of GDM are performed at 24 to 28 weeks with the Carpenter-Coustan criteria. Prediabetes is defined in early pregnancy as patients whose glucose levels are higher than normal but fall below the criteria for diabetes (A1c 5.7-6.4).[4] Patient characteristics and pregnancy outcomes are summarized for patients with CHD and DM, as well as a cohort of patients with CHD alone who were followed over the same time period. All patients provided informed consent, and this protocol was approved by the Institutional Review Boards at the Brigham and Women's Hospital and Boston Children's Hospital.

Table 1 characterizes the clinical characteristics of this cohort. Among the CHD and DM cohort, 1 patient had prediabetes, 1 patient had T1DM with 2 pregnancies, 3 patients had T2DM with 4 pregnancies, and 17 patients had GDM with 22 pregnancies. The majority of these patients had moderately complex CHD (68.2%) with physiologic stage C classification (68.2%). The most common cardiac diagnoses were tetralogy of Fallot (27.3%) and pulmonary stenosis (27.3%). The median prepregnancy body mass index across all pregnancies was 28.4 kg/m^2 and the median gestational weight gain was 9.2 kg across all pregnancies. The most common cardiac medication preconception was beta-blockers (6.9%), the use of which doubled by the end of pregnancy (13.8%). Of the 22 pregnancies complicated by GDM, 40.9% required insulin during gestation. The mother's median age at delivery was 33 years (23-44 years). The most common mode of delivery was vaginal delivery (58.7%) and the median GA of the fetus at delivery was 38.7 weeks (35.4-40 weeks). There were no major cardiac adverse events. No patient had preexisting hypertension, yet hypertension developed in 6.9% of the pregnancies. Polyhydramnios was found on ultrasound in 13.8% of pregnancies and oligohydramnios in 10.3%. The majority of neonates fell within a normal birth weight percentile. However, 3.3% of the neonate population was LGA (>90th) and 10% were small for gestational age (SGA) (<10th). All pregnancies resulting in neonates born outside of the

TABLE 1 Clinical Characteristics of the Cohort

	Total DM Patients (n = 22)	Type 1 (n = 1)	Type 2 (n = 3)	GDM (n = 17)	Prediabetes (n = 1)	Non-DM Patients (n = 275)
Cardiac diagnosis						
Tetralogy of Fallot	6 (27.3%)	0 (0%)	1 (33.3%)	5 (29.4%)	0 (0%)	33 (12.0%)
Pulmonary stenosis	6 (27.3%)	0 (0%)	1 (33.3%)	4 (23.5%)	1 (100%)	15 (5.5%)
D-loop transposition of the great arteries	3 (13.6%)	0 (0%)	0 (0%)	3 (17.6%)	0 (0%)	19 (6.9%)
Coarctation of the aorta	2 (9.1%)	0 (0%)	0 (0%)	2 (11.8%)	0 (0%)	30 (10.9%)
Other	5[a] (22.7%)	1 (100%)	1 (33.3%)	3 (17.6%)	0 (0%)	178 (64.7%)
Race						
Asian	3 (13.6%)	1 (100%)	0 (0%)	2 (11.8%)	0 (0%)	15 (5.5%)
White	13 (59.1%)	0 (0%)	1 (33.3%)	12 (70.6%)	0 (0%)	229 (83.3%)
Black	3 (13.6%)	0 (0%)	1 (33.3%)	1 (5.9%)	1 (100%)	15 (5.5%)
Native American	0 (0.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0.0%)
Other or unknown	3 (13.6%)	0 (0%)	1 (33.3%)	2 (11.8%)	0 (0%)	16 (5.8%)
Ethnicity						
Hispanic	5 (22.7%)	0 (0%)	1 (33.3%)	4 (23.5%)	0 (0%)	20 (7.3%)
Non-Hispanic	17 (77.3%)	1 (100%)	2 (66.7%)	13 (76.5%)	1 (100%)	207 (75.3%)
Other or unknown	0 (0.0%)	0 (0%)	0 (0.0%)	0 (0.0%)	0 (0%)	48 (17.5%)
Anatomical class						
I	4 (18.2%)	0 (0%)	1 (33.3%)	2 (11.8%)	1 (100%)	56 (20.4%)
II	15 (68.2%)	1 (100%)	2 (66.7%)	12 (70.6%)	0 (0%)	164 (59.6%)
III	3 (13.6%)	0 (0%)	0 (0%)	3 (17.6%)	0 (0%)	55 (20.0%)
Physiological class						
A	1 (4.5%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	37 (13.5%)
B	6 (27.3%)	0 (0%)	0 (0%)	5 (29.4%)	1 (100%)	115 (41.8%)
C	15 (68.2%)	1 (100%)	3 (100%)	11 (64.7%)	0 (0%)	117 (42.6%)
D	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (2.2%)
Maternal characteristics						
Age at delivery (y)	33 (23-44)	32 (30-34)	29.5 (27-30)	34 (23-44)	26	32 (19-43)
Gestational age at delivery (wk)	38.7 (35.4-40.0)	39 (38.0-40.0)	38.5 (36.7-39.1)	38.7 (35.4-39.7)	39.4	38.9 (15.9-58.7)
Gravidity	2 (1-6)	2.5 (2-3)	1 (1-2)	2 (1-6)	1	2 (0-9)
Parity	0 (0-2)	1 (0-2)	0 (0-1)	0.5 (0-2)	0	0 (0-4)
Hemoglobin A1C (%)	5.4[b] (5.2-7.9)	7.1 (6.2-7.9)	5.6 (5.4-6.5)	5.3 (5.2-5.7)	6.4	-
Prepregnancy BMI (kg/m^2)	28.4[c] (17.4-45.0)	27.6 (27.6)	34.6 (26.3-36.3)	26.2 (17.4-41.6)	45.0	24.4 (17.5-47.5)

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normal birth weight percentile were complicated by GDM. Congenital anomalies afflicted 6.9% of neonates, with 3.3% of neonates born with CHD.

In this cohort, 40.9% of patients with CHD and GDM required insulin. Given the background rate of insulin requirement closer to 15% to 30% in patients with GDM without CHD,[5] this may be an area for future investigation as to why patients with CHD and GDM may have a higher rate of insulin use. Furthermore, although LGA is a common finding among pregnancies in patients with GDM,[3] this was not observed within this cohort. Only 4.5% of the neonate population from pregnancies affected by CHD and GDM were LGA while 13.6% of this neonate population was SGA. Our findings are similar to those from a population-based study of over 2,100 women with CHD which reported a 12.8% incidence of SGA infants.[1] It is known that SGA may be associated with pregnancies in patients with CHD.[1] Our data suggest that underlying CHD in patients with GDM may result in a higher occurrence of growth restriction rather than the more typical pattern of LGA observed in pregnancies complicated by GDM without CHD. Although our sample size is too small for meaningful conclusions when compared to our cohort of patients with CHD and no DM, similar rates of SGA among the 2 groups further support this observation. Future studies looking at the relationship between GDM and CHD during pregnancy would be useful to better understand mechanisms that can be targeted to decrease adverse complications in this group.

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TABLE 1 Continued

	Total DM Pregnancies (n = 29)	Type 1 (n = 2)	Type 2 (n = 4)	GDM (n = 22)	Prediabetes (n = 1)	Non-DM Pregnancies (n = 367)
Maternal medications						
Preconception						
Beta-blocker	2 (6.9%)	0 (0%)	1 (25%)	1 (4.5%)	0 (0%)	62 (16.9%)
Insulin	1 (3.4%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	-
Metformin	2 (6.9%)	0 (0%)	2 (50%)	0 (0%)	0 (0%)	-
End of pregnancy						
Beta-blocker	4 (13.8%)	0 (0%)	2 (50%)	2 (9.1%)	0 (0%)	74 (20.2%)
Insulin	12 (41.4%)	1 (50%)	1 (25%)	9 (40.9%)	1 (100%)	-
Metformin	2 (6.9%)	0 (0%)	2 (50%)	0 (0%)	0 (0%)	-
Type of delivery						
Planned cesarean delivery	8 (27.6%)	1 (50%)	1 (25%)	6 (27.3%)	0 (0%)	58 (15.8%)
Cesarean delivery during labor	4 (13.8%)	0 (0%)	2 (50%)	1 (4.5%)	1 (100%)	67 (18.3%)
Vaginal delivery	17 (58.7%)	1 (50%)	1 (25%)	15 (68.2%)	0 (0%)	235 (64.0%)
Labor complications						
Hypertension	2 (6.9%)	0 (0%)	0 (0%)	2 (9.1%)	0 (0%)	54 (14.7%)
Chorioamnionitis	1 (3.4%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	21 (5.7%)
Placental abruption	1 (3.4%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	16 (4.4%)
Neonatal characteristics	(n = 30)	(n = 2)	(n = 5)	(n = 22)	(n = 1)	(n = 372)
Birth weight (g)	3,038.5 (2,160-4,140)	3,161 (3,062-3,260)	2,920 (2,850-3,290)	3,007.5 (2,160-4,140)	3,460	3,075 (566-4,340)
Birth weight percentile						
Normal	26 (86.7%)	2 (100%)	5 (100%)	18 (81.8%)	1 (100%)	289 (77.7%)
>90th percentile (LGA)	1 (3.3%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	40 (10.8%)
<10th percentile (SGA)	3 (10%)	0 (0%)	0 (0%)	3 (13.6%)	0 (0%)	43 (11.6%)
Apgar score at 5 min	9 (5-9)	9 (9-9)	9 (9-9)	9 (5-9)	8	9 (4-10)
Calculated mean blood glucose (mg/dL)	61[d] (30-94)	74.5 (72-77)	61 (40-65)	59 (30-94)	44	-
NICU admission	4 (13.3%)	0 (0%)	0 (0%)	3 (13.6%)	1 (100%)	100 (26.9%)
Congenital heart defect	1 (3.3%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	28 (7.5%)

Values are n (%), or median (range). [a]Aortic insufficiency, bicuspid aortic valve, partial anomalous pulmonary venous connection, Ebstein anomaly, and hypoplastic right pulmonary artery and right lung. [b]Hemoglobin A1C values were available for 21 DM pregnancies. [c]Prepregnancy BMI values were available for 26 DM pregnancies. [d]Calculated mean blood glucose values were available for 28 neonates from mothers with DM after delivery.

BMI = body mass index; DM = diabetes mellitus; GDM = gestational diabetes mellitus; LGA = large for gestational age; NICU = neonatal intensive care unit; SGA = small for gestational age.

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REFERENCES

1. Ramage K, Grabowska K, Silversides C, Quan H, Metcalfe A. Association of adult congenital heart disease with pregnancy, maternal, and neonatal outcomes. *JAMA Netw Open*. 2019;2:e193667.

2. Gregory EC, Ely DM. Trends and characteristics in gestational diabetes: United States, 2016-2020. *Natl Vital Stat Rep*. 2022;71:1-15.

3. Ye W, Luo C, Huang J, Li C, Liu Z, Liu F. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ*. 2022;377:e067946.

4. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42:S13-S28.

5. American Diabetes Association. 14. Management of diabetes in pregnancy: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42:S165-S172.