EPH24

Sodium glucose co-transporter 2 inhibitor exposure and the risk of congenital malformations: nationwide birth cohort study

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INTRODUCTION

- Diabetes is increasingly common in pregnancy, and poorly controlled maternal blood glucose levels are associated with a higher risk of congenital malformations and adverse fetal outcomes. Current guidelines recommend insulin as the standard pharmacologic therapy during pregnancy.
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors, although beneficial for cardiovascular and renal protection, lack sufficient safety data in pregnant women.
- This study aimed to evaluate the association between SGLT2 inhibitor exposure during pregnancy and the risk of congenital malformations.

METHODS

Study Design: Retrospective cohort study

Data Source

- The Health Insurance Review and Assessment database representative of the Korean population from January 1, 2016, to December 31, 2022

Study Population

- Mothers who gave birth between 2018 and 2021 (*Figure 1*)
- Inclusion criteria: aged between 19 to 45
- Exclusion criteria: exposure to known teratogen during pregnancy

Exposure

- Assessment window: first trimester of pregnancy
- Intervention: 1+ prescription of SGLT2 inhibitor (±metformin, insulin)
- Active comparator: 1+ prescription of insulin (±metformin)
  (without other oral antidiabetic medication)

Outcomes

- Major congenital malformations (ICD-10: Q00-Q89)
- Heart defects (ICD-10: Q20-Q28)
- Definition of outcome: ≥2 diagnoses or ≥1 diagnosis plus death in 1 year

Statistical Analysis

- Descriptive analysis: t-test, chi-square test
- 1 : 5 Propensity score matching: Logistic regression
- Relative risk: Generalized linear regression

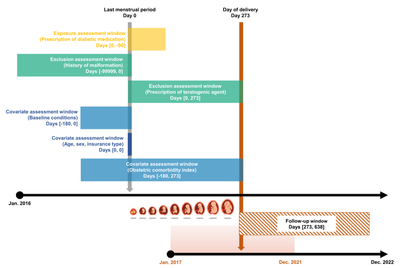


Figure 1. Study scheme

RESULTS

Patient selection

- A total of 121 SGLT2-exposed patients and 2,007 comparator patients were identified in the full unmatched cohort. After 1:5 propensity score matching, the final matched cohort comprised 115 patients in the SGLT2 group and 515 patients in the comparator group.

Baseline characteristics

- After propensity score matching, baseline characteristics between the two groups were well balanced across key variables including age, and comorbidities.
- Mean age at delivery (SD) was 34.9 (4.20), and 35.17 (3.93) in patients with SGLT2 inhibitor exposure, and insulin exposure (*Table 1*).

Table 1. Baseline characteristics of study cohort before and after propensity score matching

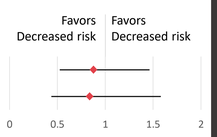
	Full unmatched			Propensity scores matched		
	Exposed to SGLT2 inhibitors	Exposed to insulin	SMD	Exposed to SGLT2 inhibitors	Exposed to insulin	SMD
Total number of delivery	121	2007		115	515	
Age at delivery, mean (SD)	35.07 (4.26)	34.89 (4.28)	0.042	34.92 (4.20)	35.17 (3.93)	0.061
Aged over 35, N (%)	69 (57.0)	1149 (57.2)	0.005	64 (55.7)	309 (60.0)	0.088
Maternal medical conditions, N (%)						
Diabetic renal disease	20 (16.5)	220 (11.0)	0.162	20 (17.4)	84 (16.3)	0.029
Diabetic neuropathy	13 (10.7)	112 (5.6)	0.189	13 (11.3)	43 (8.3)	0.099
Diabetic retinopathy	16 (13.2)	245 (12.2)	0.03	15 (13.0)	68 (13.2)	0.005
Prescription drug use, N (%)						
Lipid lowering agent	10 (8.3)	351 (17.5)	0.278	9 (7.8)	42 (8.2)	0.012
Antihypertensives	10 (8.3)	174 (8.7)	0.015	10 (8.7)	47 (9.1)	0.015
Comorbidity indices, mean (SD)						
Charlson comorbidity index	2.09 (1.26)	1.53 (1.40)	0.422	2.10 (1.29)	1.98 (1.20)	0.092
Diabetes complication severity index	0.56 (1.10)	0.49 (1.07)	0.068	0.55 (1.09)	0.59 (1.06)	0.036
Obstetric comorbidity index score	3.26 (2.81)	2.97 (2.23)	0.114	3.10 (2.56)	3.11 (2.37)	0.003
Healthcare resource utilization, mean (SD)						
Number of outpatient visits	12.54 (8.80)	11.14 (9.26)	0.154	11.70 (7.08)	11.93 (7.47)	0.031
Number of hospitalizations	0.22 (0.56)	0.17 (0.50)	0.109	0.19 (0.49)	0.16 (0.47)	0.071

Risk of congenital malformation

- After propensity score matching, the risk estimates (95% confidence interval, 95% CI) were 0.88 (0.52-1.46) for major congenital malformations, and 0.83 (0.44-1.58) for congenital heart defects(*Figure 2*).

Figure 2. Risk of Congenital Malformations Following Exposure to Sodium Glucose Co-Transporter Inhibitor during First Trimester of Pregnancy

	Event in SGLT2 inhibitors, N (%)	Event in insulin, N (%)	Risk ratio (95% CI) Before matching	Risk ratio (95% CI) After matching
Congenital malformation	15 (13.0)	77 (15.0)	0.87 (0.55-1.40)	0.88(0.52-1.46)
Heart defect	10 (8.7)	54 (10.5)	0.88 (0.49-1.57)	0.83(0.44-1.58)



Sensitivity analysis

- Sensitivity analyses using different exposure windows and exposure definitions were conducted, and no significant associations were observed, except during the organogenesis period(*Table 2*).

Table 2. Sensitivity Analysis of Association Between Sodium Glucose Co-Transporter Inhibitor Exposure in Pregnancy and Risk of Congenital Malformations

	Event in SGLT2 inhibitors, N (%)	Event in insulin, N (%)	Risk ratio (95% CI) After matching
Major congenital malformations			
Exposed between -40 weeks and -12 weeks before delivery	15 (13.0)	92 (13.6))	1.13 (0.72-1.76)
Last menstrual period defined as 36 weeks before delivery	12 (14.1)	60 (14.5)	0.97 (0.52-1.79)
Exposure limited to organogenesis period (weeks 4–10)	11 (22.0)	25 (10.0)	2.04 (0.97-4.26)
Restricted to patients with ≥2 prescriptions	2 (11.8)	7 (9.3)	1.51 (0.31 – 7.48)
Heart defects			
Exposed between -40 weeks and -12 weeks	14 (8.8)	68 (10.1)	0.85 (0.48 – 1.52)
Last menstrual period as 36 weeks before	9 (10.6)	43 (10.4)	1.00 (0.49 – 2.06)
Exposure in organogenesis period (week 4 - week 10)	8 (16.0)	16 (6.4)	2.79 (1.16-7.06)
Restricted to patients with ≥2 prescriptions	2 (11.8)	5 (6.7)	1.93 (0.36 – 10.31)

DISCUSSION

Strengths

- Nationwide, population-based data in South Korea
- Confounding adjusted through propensity score matching
- Consideration of uncertainty in estimating last menstrual period

Limitations

- Glycemic control status (e.g., blood glucose, HbA1c) not available
- Relatively small sample size limited the ability to assess rare outcomes, such as nephrological malformations.

CONCLUSION

- In this study, SGLT2 inhibitor use during the first trimester of pregnancy was not associated with an increased risk of major congenital malformations.
- Sensitivity analyses suggest that SGLT2 inhibitors are unlikely to pose a major teratogenic risk.
- Given the increasing number of patients with diabetes, our findings may help guide clinicians and patients in decision-making regarding the use of SGLT2 inhibitors during the first trimester.

Acknowledgment

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