IN THE NAME OF GOD

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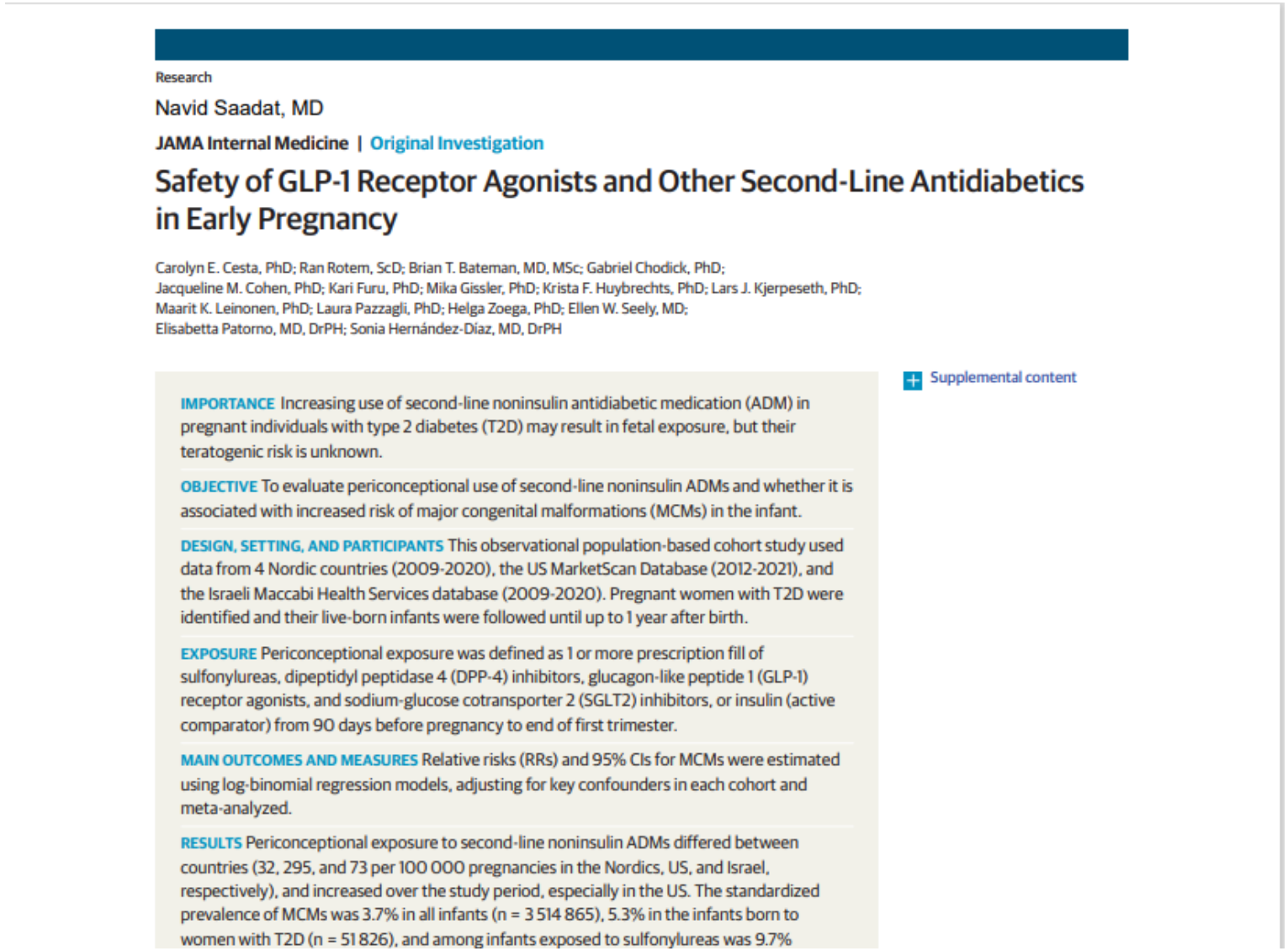

Research

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JAMA Internal Medicine | Original Investigation

Safety of GLP-1 Receptor Agonists and Other Second-Line Antidiabetics in Early Pregnancy

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Supplemental content

IMPORTANCE Increasing use of second-line noninsulin antidiabetic medication (ADM) in pregnant individuals with type 2 diabetes (T2D) may result in fetal exposure, but their teratogenic risk is unknown.

OBJECTIVE To evaluate periconceptional use of second-line noninsulin ADMs and whether it is associated with increased risk of major congenital malformations (MCMs) in the infant.

DESIGN, SETTING, AND PARTICIPANTS This observational population-based cohort study used data from 4 Nordic countries (2009-2020), the US MarketScan Database (2012-2021), and the Israeli Maccabi Health Services database (2009-2020). Pregnant women with T2D were identified and their live-born infants were followed until up to 1 year after birth.

EXPOSURE Periconceptional exposure was defined as 1 or more prescription fill of sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors, or insulin (active comparator) from 90 days before pregnancy to end of first trimester.

MAIN OUTCOMES AND MEASURES Relative risks (RRs) and 95% CIs for MCMs were estimated using log-binomial regression models, adjusting for key confounders in each cohort and meta-analyzed.

RESULTS Periconceptional exposure to second-line noninsulin ADMs differed between countries (32, 295, and 73 per 100 000 pregnancies in the Nordics, US, and Israel, respectively), and increased over the study period, especially in the US. The standardized prevalence of MCMs was 3.7% in all infants (n = 3 514 865), 5.3% in the infants born to women with T2D (n = 51 826), and among infants exposed to sulfonylureas was 9.7%

IMPORTANCE

- Type 2 diabetes (T2D) is an increasingly common condition in female individuals of reproductive age, which has resulted in increased use of antidiabetic medication (ADM) during pregnancy.

IMPORTANCE

- Increasing use of second-line noninsulin antidiabetic medication (ADM) in pregnant individuals with type 2 diabetes (T2D) may result in fetal exposure, but their teratogenic risk is unknown.

For patients with T2D who are planning pregnancy

- or who are already pregnant, the **guideline-recommended** treatment has traditionally been **insulin**, due to the **limited data** on the safety of **noninsulin ADM** for fetal development.

Unintentional pregnancy

- Unintentional pregnancy exposure arises because a proportion of pregnancies are unplanned, and therefore the discontinuation of these medications often occurs during or after **organogenesis**.

- Hence, **studies are urgently** needed to be able to advise patients, clinicians, and regulatory bodies on the **potential teratogenic risk** of these medications.

- To generate evidence on the teratogenic risk of second line noninsulin ADM, we combined data from **6 large population-based health care** databases
- from 4 Nordic countries,
- the US, and
- Israel
- to identify a cohort of pregnant women with pharmacologically treated T2D around the time of conception.

- First, we described the **time trends** of second-line noninsulin ADM use in pregnancy over time.
- Next, we compared the risk of major congenital malformations (**MCMs**) overall, and **cardiac MCMs** specifically, in infants born to women with periconceptional use of second-line noninsulin ADM vs insulin.

Methods

Data Sources and Pregnancy Cohorts

- This study was conducted within the ***International Pregnancy Safety Study (InPreSS) Consortium***, a collaboration among research groups in several countries, including the **Nordic countries**, the **US**, and **Israel**, all of whom have access to high-quality prospectively collected health care databases and registers.

Nordic cohort

- **All pregnancies** resulting in **singleton live-born** infants in
- **Finland, Iceland**, **Norway**, and **Sweden** from **2009** to the end of available data in each country (**2016-2020**)
- The individual-level data from the 4 countries were pooled and **harmonized** using a common data **model**.

US cohort	**commercially insured pregnant women linked to their live-born (singleton and multiple) infants included in the MarketScan Researc(2012-2021), one of the largest national health care administration databases**	**to have continuous insurance coverage from at least 6 months before pregnancy to 1 month after delivery; infants were required to have coverage from birth until 90 days after birth, unless they died sooner.**
The Israeli cohort	singleton live-born Maccabi Health Services (MHS) database 25% of the Israeli population	singleton live-born infant (2010-2020) from women continuously enrolled for **at least 1 year preconception** in the Maccabi Health Services (**MHS**) database; **infants** were required to have at **least 1 year** of complete follow-up postbirth, unless they died sooner.

Exclusion criteria

- Pregnancies with a diagnosis of a **fetal chromosomal abnormality** or with exposure to a **known teratogenic medication** were excluded from each cohort.

Table 1. Known Teratogenic drugs

Drug	US MarketScan (identified by generic drug names)	Nordic cohort and Israel-MHS (ATC Codes)
Warfarin	Yes	B01AA03
Antineoplastic drugs:	Yes	L01DA L01AB01 L01AA02 M04AC01 L01AA01 L01DB01 L01BB02 L01BA01, L04AX03 L01CA01 L01CA02
Lithium	yes	N05AN01
Topical or systemic retinoids, including isotretinoin	yes	D10BA01 D10AD54 D10BA04 D05BB D11AH04
Misoprostol	yes	A02BB01, G02AD06 M01AE56 M01AB55
Thalidomide	yes	L04AX02
Valproic acid	yes	N03AG01
Carbamazepine	yes	Nordics: not included[a] Israel: N03AF01

[a] based on recent evidence of no teratogenic effect of carbamazepine in Nordic populations(1)

Study Population

- Women with pregestational T2D linked to live-born infants
- validated algorithm
  - positive predictive value of 87% compared with electronic medical records
  - The algorithm was adapted for use in the Nordic and MHS data, and optimized based on the best available information, including laboratory measurements in MHS

- Maccabi Health Services (MHS)

- In this study, we refer to **biologic sex** and use the term pregnant woman to define pregnant human females of any **gender identity**. Gender identity was not recorded in the databases

Exposure

- **Periconceptional** exposure was defined based on the filling of **1** or **more prescriptions** of the respective drug class from **90 days before** the **first day of the last menstrual period (LMP)** to the **end of the first trimester** because drug supplies for chronic illness often **cover 1 to 3months**.
- A **secondary** exposure definition for **sensitivity analyses** required the filling of **1** or **more prescriptions** from **LMP** to the end of the **first trimester**

Pregnancies were then classified into the following exposure groups:

- **periconceptional** use of
- **no ADM**,
- metformin only,
- insulin (with or without coprescriptions of metformin, but no other ADM),
- sulfonylureas,
- DPP-4 inhibitors,
- GLP-1 receptor agonists, or
- SGLT2 inhibitors.
- Women in the latter 4 exposure groups were allowed to have coprescriptions of any other ADM during the periconception period

Major Congenital Malformations (MCM)

- Briefly, MCMs were defined using infant diagnoses from the **date of birth to 1 year after birth** in the Nordic and Israeli cohorts, and using claims in the infant and the women's records from date of birth to 90 days after birth in the US cohort.

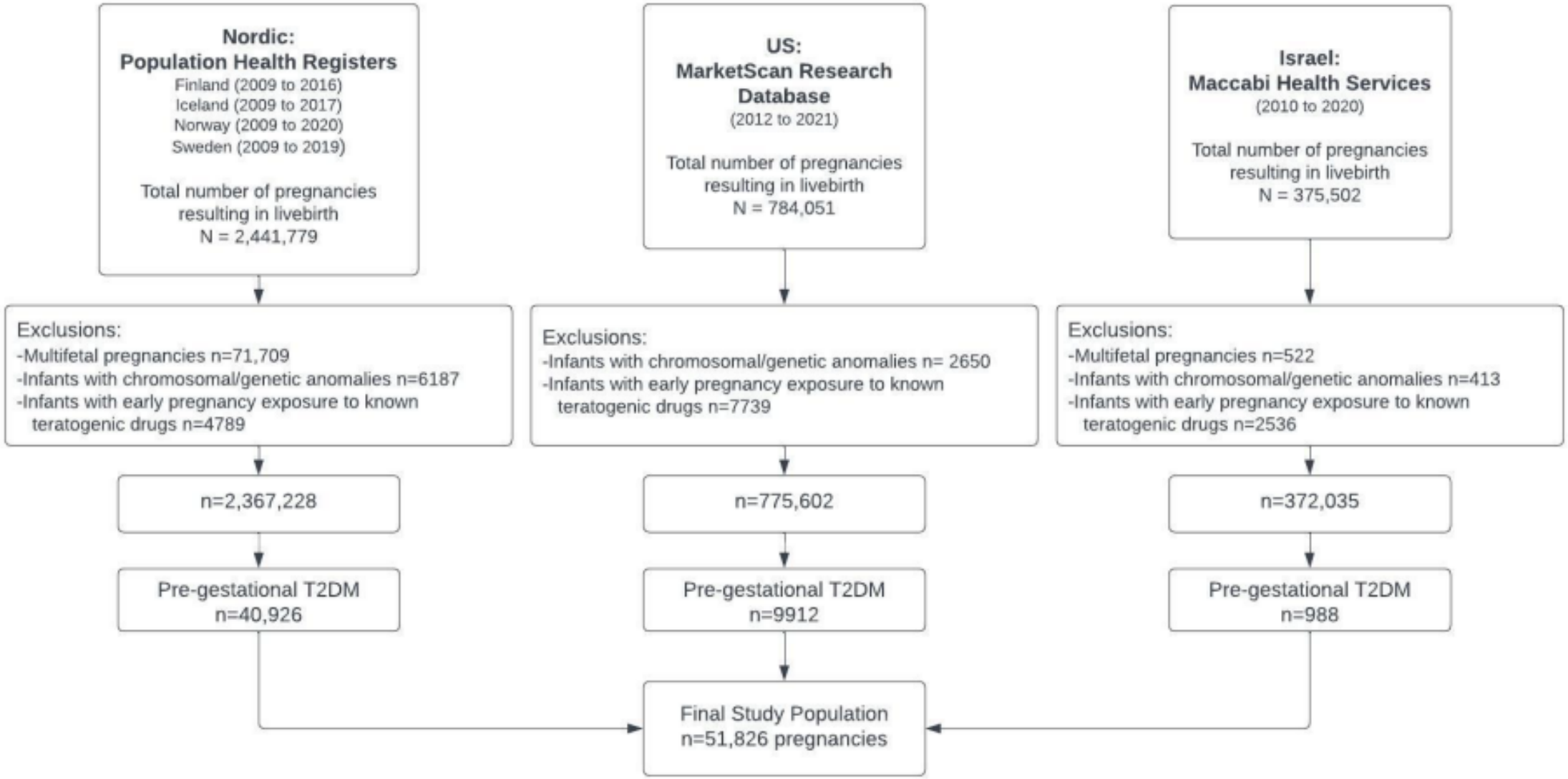
Covariates

- Key baseline **characteristics** were described for pregnant women with **periconceptional use of the second-line ADM**, including maternal age, comorbidities (ie, obesity, hypertension, cardiovascular disease, diabetic complications, polycystic ovary syndrome [PCOS]) and other prescription medication (ie, antihypertensive medication, lipid modifying agents; defined in eTable 5 inSupplement 1). Hemoglobin A1c (HbA1c) levels, which are a measure of glycemic control over the previous 3 months, were available for a subset of pregnancies in the US and Israeli cohorts (eTable 6 in Supplement 1). The mean (SD) and median (IQR) were calculated for each exposure group (HbA1c unit = %) with linked laboratory test results for **HbA1c levels from between 90 days before LMP to the end of the first trimester**

Results

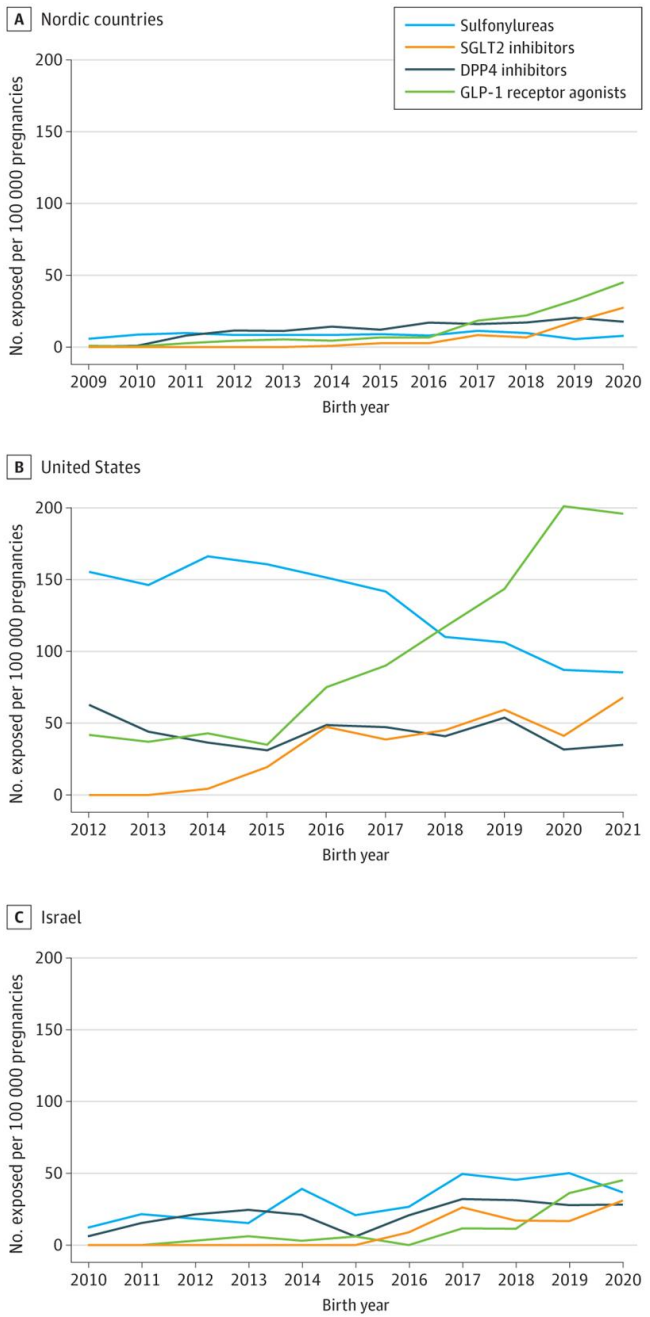
- Study Population and Exposure Groups In a total of **3 514 865 pregnancies** from the 3 data sources combined, **51 826 (1.5%)** were in women with pregestational T2D, of whom **15 148 (29.2%)** were treated with ADM in the periconceptional period (Nordics, 9693; US, 4778; Israel, 677) (eFigure in Supplement 1).

Supplementary Figure 1: Flow chart outlining the derivation of the study population



- Among these pregnancies, 7440 (50%) used metformin only,
- 5078 (34%) insulin,
- 1352 (9.0%) sulfonylureas,
- 687 (4.5%) DPP-4 inhibitors,
- 938 (6.2%) GLP-1 receptor agonists,
- and 335 (2.2%) SGLT2 inhibitors.
- Periconceptional use of second-line noninsulin ADM increased over time, particularly in the US for GLP-1 receptor agonists, and except for sulfonylureas, which remained low in the Nordic countries, decreased in the US, and increased slightly in Israel (Figure 1). Use of other ADM classes such as glitazones, meglitinides, and α-glucosidase inhibitors remained very low.

Figure 1. Prevalence of Periconceptional Second-Line Noninsulin Antidiabetic Medication Exposure Over Time in the Nordics, US, and Israel



GLP1RA

The denominator contains all live-born infants per year per database. Nordic results are based on pooled data from national health registers in Finland, Iceland, Norway, and Sweden. US results based on data from the MarketScan database. Israel results based on data from Maccabi Health Service database. DPP-4 indicates dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2.

Table 1. Selected Characteristics of Pregnant Women With Pregestational Type 2 Diabetes and Periconceptional Use of Second-Line Antidiabetic Medication[a]

Characteristic	Nordic countries					US					Israel				
	Insulin	Sulfonylureas	DPP-4 inhibitors	GLP-1 receptor agonists	SGLT2 inhibitors	Insulin	Sulfonylureas	DPP-4 inhibitors	GLP-1 receptor agonists	SGLT2 inhibitors	Insulin	Sulfonylureas	DPP-4 inhibitors	GLP-1 receptor agonists	SGLT2 inhibitors
Total pregnancies, No.	3269	198	266	214	82	1387	1049	341	681	218	422	115	80	43	35
Maternal age at delivery, y, %															
<30	28.8	27.3	18.0	31.3	22.0	12.5	16.9	16.4	17.8	13.3	8.8	15.7	15.0	20.9	11.4
30-34	32.6	26.3	33.8	34.6	28.1	36.2	35.7	34.0	33.9	34.9	30.3	26.1	18.8	27.9	25.7
35-39	27.3	29.8	33.5	22.4	34.2	36.2	33.5	36.4	36.3	36.7	32.5	32.2	25.0	27.9	31.4
≥40	11.4	16.7	14.7	11.7	15.9	15.1	14.0	13.2	12.0	15.1	28.4	26.1	41.3	23.3	31.4
Comorbidities and comedication, %															
Overweight/ obesity	43.9	42.4	54.9	60.3	54.9	33.4	28.3	32.6	47.9	45.4	39.1	25.2	33.8	65.1	45.7
Chronic hypertension	10.9	14.1	15.4	13.6	13.4	29.1	28.6	35.8	28.9	38.5	18.0	11.3	25.0	11.6	11.4
Diabetic complications	14.2	17.7	16.5	22.4	28.1	12.3	5.7	9.7	7.6	18.8	28.0	13.0	20.0	11.6	22.9
Cardiovascular disease	0.5	0.0	NA[b]	NA[b]	17.1	0.8	0.4	2.3	0.6	1.4	4.3	1.7	3.8	0	2.9
Polycystic ovary syndrome	9.3	8.1	11.3	22.0	16.9	10.9	7.3	10.0	19.4	12.4	24.2	18.3	23.8	20.9	17.1
Antihypertensive drugs	7.1	10.6	12.8	12.2	9.8	17.2	20.4	27.9	25.3	38.5	15.9	8.7	12.5	18.6	25.7
Lipid modifying agents	4.0	12.6	13.2	11.2	17.1	5.6	9.2	15.5	12.2	21.1	9.2	8.7	28.8	20.9	40.0
Other ADM prescription fills, %															
Insulin	100	74.2	67.7	62.2	81.7	100	36.6	58.4	38.5	61.0	100	33.9	67.5	44.2	68.6
Metformin	35.9	65.2	63.2	55.6	59.8	61.7	56.8	81.2	49.3	81.2	46	25.2	90.0	39.5	71.4
Sulfonylureas	0	100	12.0	4.2	7.3	0	100	24.9	7.6	20.6	0	100	8.8	9.3	2.9
DPP-4 inhibitors	0	9.6	100	2.3	19.5	0	8.1	100	4.3	16.5	0	6.1	100	4.7	25.7
GLP-1 receptor agonists	0	4.6	1.9	100	11.0	0	5.0	8.5	100	22.9	0	3.5	2.5	100	11.4
SGLT2 inhibitors	0	2.5	6.0	4.2	100	0	4.3	10.6	7.3	100	0	0.9	11.3	NA[b]	100

Abbreviations: ADM, antidiabetic medication; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2.

[a] Separately for the Nordic countries (pooled Finland, Iceland, Norway, Sweden); US, MarketScan; and Israel, Maccabi Health Services databases.

[b] Percentages based on counts <5 are not shown for data privacy policies in the Nordic countries.

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Characteristic	Nordic countries					US					Israel				
	Insulin	Sulfonylureas	DPP-4 inhibitors	GLP-1 receptor agonists	SGLT2 inhibitors	Insulin	Sulfonylureas	DPP-4 inhibitors	GLP-1 receptor agonists	SGLT2 inhibitors	Insulin	Sulfonylureas	DPP-4 inhibitors	GLP-1 receptor agonists	SGLT2 inhibitors
Total pregnancies, No.	3269	198	266	214	82	1387	1049	341	681	218	422	115	80	43	35
Maternal age at delivery, y, %															
<30	28.8	27.3	18.0	31.3	22.0	12.5	16.9	16.4	17.8	13.3	8.8	15.7	15.0	20.9	11.4
30-34	32.6	26.3	33.8	34.6	28.1	36.2	35.7	34.0	33.9	34.9	30.3	26.1	18.8	27.9	25.7
35-39	27.3	29.8	33.5	22.4	34.2	36.2	33.5	36.4	36.3	36.7	32.5	32.2	25.0	27.9	31.4
≥40	11.4	16.7	14.7	11.7	15.9	15.1	14.0	13.2	12.0	15.1	28.4	26.1	41.3	23.3	31.4
Comorbidities and comedication, %															
Overweight/ obesity														65.1	45.7
Chronic hypertensio														11.6	11.4
Diabetic complicatio														11.6	22.9
Cardiovascular disease	0.5	0.0	NA[b]	NA[b]	17.1	0.8	0.4	2.3	0.6	1.4	4.3	1.7	3.8	0	2.9
Polycystic ovary syndrome	9.3	8.1	11.3	22.0	16.9	10.9	7.3	10.0	19.4	12.4	24.2	18.3	23.8	20.9	17.1
Antihypertensive drugs	7.1	10.6	12.8	12.2	9.8	17.2	20.4	27.9	25.3	38.5	15.9	8.7	12.5	18.6	25.7
Lipid modifying agents	4.0	12.6	13.2	11.2	17.1	5.6	9.2	15.5	12.2	21.1	9.2	8.7	28.8	20.9	40.0
Other ADM prescription fills, %															
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Sulfonylureas	0	100	12.0	4.2	7.3	0	100	24.9	7.6	20.6	0	100	8.8	9.3	2.9
DPP-4 inhibitors	0	9.6	100	2.3	19.5	0	8.1	100	4.3	16.5	0	6.1	100	4.7	25.7
GLP-1 receptor agonists	0	4.6	1.9	100	11.0	0	5.0	8.5	100	22.9	0	3.5	2.5	100	11.4
SGLT2 inhibitors	0	2.5	6.0	4.2	100	0	4.3	10.6	7.3	100	0	0.9	11.3	NA[b]	100

Compared with those using insulin, women using second-line noninsulin ADMs were slightly younger in the US and Israel and slightly older in the Nordic countries.

Abbreviations: ADM, antidiabetic medication; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2.

[a] Separately for the Nordic countries (pooled Finland, Iceland, Norway, Sweden); US, MarketScan; and Israel, Maccabi Health Services databases.

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≥40	11.4	16.7	14.7	11.7	15.9	15.1	14.0	13.2	12.0	15.1	28.4	26.1	41.3	23.3	31.4
Comorbidities and comedication, %															
Overweight/ obesity	43.9	42.4	54.9	60.3	54.9	33.4	28.3	32.6	47.9	45.4	39.1	25.2	33.8	65.1	45.7
Chronic hypertension	10.9	14.1	15.4	13.6	13.4	29.1	28.6	35.8	28.9	38.5	18.0	11.3	25.0	11.6	11.4
Diabetic complications	14.2	17.7	16.5	22.4	28.1	12.3	5.7	9.7	7.6	18.8	28.0	13.0	20.0	11.6	22.9
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Antihypertensive drugs	7.1	10.6	12.8	12.2	9.8	17.2	20.4	27.9	25.3	38.5	15.9	8.7	12.5	18.6	25.7
Lipid modifying agents	4.0	12.6	13.2	11.2	17.1	5.6	9.2	15.5	12.2	21.1	9.2	8.7	28.8	20.9	40.0
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SGLT2 inhibitors	0	2.5	6.0	4.2	100	0	4.3	10.6	7.3	100	0	0.9	11.3	NA[b]	100

The prevalence of obesity and PCOS was highest in women using GLP-1 receptor agonists; chronic hypertension, cardiovascular disease, and use of antihypertensive and lipid-modifying agents were highest in SGLT2 inhibitor users.

Diabetic complications were highest among women using insulin and SGLT2 inhibitors.

Abbreviations: ADM, antidiabetic medication; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2.

[a] Separately for the Nordic countries (pooled Finland, Iceland, Norway, Sweden); US, MarketScan; and Israel, Maccabi Health Services databases.

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Antihypertensive drugs	7.1	10.6	12.8	12.2	9.8	17.2	20.4	27.9	25.3	38.5	15.9	8.7	12.5	18.6	25.7
Lipid modifying agents	4.0	12.6	13.2	11.2	17.1	5.6	9.2	15.5	12.2	21.1	9.2	8.7	28.8	20.9	40.0
Other ADM prescription fills, %															
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Metformin	35.9	65.2	63.2	55.6	59.8	61.7	56.8	81.2	49.3	81.2	46	25.2	90.0	39.5	71.4
Sulfonylureas	0	100	12.0	4.2	7.3	0	100	24.9	7.6	20.6	0	100	8.8	9.3	2.9
DPP-4 inhibitors	0	9.6	100	2.3	19.5	0	8.1	100	4.3	16.5	0	6.1	100	4.7	25.7
GLP-1 receptor agonists	0	4.6	1.9	100	11.0	0	5.0	8.5	100	22.9	0	3.5	2.5	100	11.4
SGLT2 inhibitors	0	2.5	6.0	4.2	100	0	4.3	10.6	7.3	100	0	0.9	11.3	NA[b]	100

Among second-line noninsulin ADM users, coprescription fills of insulin were common (37%-82%), as were coprescription fills of metformin (25%-90%)

Abbreviations: ADM, antidiabetic medication; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2.

[a] Separately for the Nordic countries (pooled Finland, Iceland, Norway, Sweden); US, MarketScan; and Israel, Maccabi Health Services databases.

[b] Percentages based on counts <5 are not shown for data privacy policies in the Nordic countries.

HbA1c levels

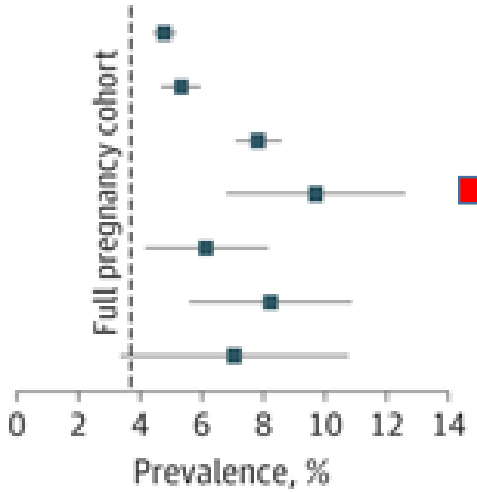
- For the subsample of pregnant women in the US (n = 397) and Israel (n = 575) with available laboratory data, the median periconceptional HbA1c levels were highest among those using either **insulin** or the second-line noninsulin ADM, particularly **DPP-4** inhibitors and **SGLT2** inhibitors, relative to other pregnant women with T2D treated with *metformin* or *not treated* pharmacologically

Prevalence of Malformations

There were 132 283 infants born with an **MCM** in the full pregnancy cohort (3.76%), and 2584 infants born with an MCM in the study population of women with T2D (5.28%).
For **cardia cmalformations**, the prevalence was similarly elevated among infants born to women with T2D (2.25% vs 1.31% in the full pregnancy cohort)

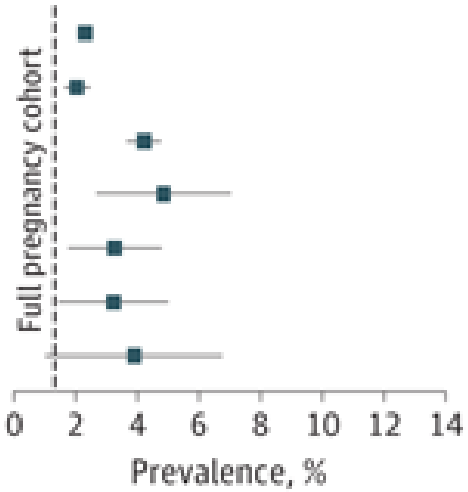
A Any major congenital malformation

Medication	Pooled prevalence, % (95% CI)
No ADM	4.77 (4.42-5.12)
Metformin only	5.32 (4.68-5.95)
Insulin	7.83 (7.09-8.57)
Sulfonylureas	9.71 (6.80-12.62)
DPP-4 inhibitors	6.14 (4.15-8.14)
GLP-1 receptor agonists	8.23 (5.58-10.88)
SGLT2 inhibitors	7.04 (3.35-10.73)



B Cardiac malformations

Medication	Pooled prevalence, % (95% CI)
No ADM	2.30 (2.07-2.53)
Metformin only	2.04 (1.62-2.46)
Insulin	4.20 (3.64-4.76)
Sulfonylureas	4.85 (2.65-7.04)
DPP-4 inhibitors	3.26 (1.75-4.78)
GLP-1 receptor agonists	3.22 (1.43-5.01)
SGLT2 inhibitors	3.88 (1.01-6.75)



The corresponding number of exposed, number of cases, prevalence, and 95% CIs combined and for each study cohort are reported in eTable 7 in Supplement 1. ADM indicates antidiabetic medication; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2.

Relative Risks of Malformations

Table 2. Risk for Any and Cardiac Major Congenital Malformations in Infants Born to Women With Type 2 Diabetes and Periconceptional Use of Second-Line Noninsulin Antidiabetic Medications Compared With Insulin[a]

Treatment	No. of exposed cases/ No. of exposed (%)[b]	Crude relative risk (95% CI)	Adjusted relative risk (95% CI)[c]
Any major congenital malformation			
Insulin	400/5078 (7.8)	1 [Reference]	1 [Reference]
Sulfonylureas	121/1362 (9.7)	1.14 (0.91-1.42)	1.18 (0.94-1.48)
DPP-4 inhibitors	50/687 (6.1)	0.91 (0.67-1.24)	0.83 (0.64-1.06)
GLP-1 receptor agonists	75/938 (8.2)	1.02 (0.78-1.33)	0.95 (0.72-1.26)
SGLT2 inhibitors	30/335 (7.0)	1.13 (0.76-1.67)	0.98 (0.65-1.46)[d]
Cardiac malformations			
Insulin	212/5078 (4.2)	1 [Reference]	1 [Reference]
Sulfonylureas	50/1362 (4.8)	1.05 (0.75-1.47)	1.05 (0.75-1.48)
DPP-4 inhibitors	24/687 (3.3)	0.91 (0.59-1.41)	0.90 (0.58-1.39)
GLP-1 receptor agonists	23/938 (3.2)	0.67 (0.42-1.06)	0.68 (0.42-1.12)
SGLT2 inhibitors	15/335 (3.9)	1.22 (0.70-2.13)	1.10 (0.63-1.92)[d]

Abbreviations: DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2.

[a] Individual study cohort estimates are reported in eTable 8 in Supplement 1.

[b] Standardized prevalence.

[c] Adjusted for birth year, maternal age, obesity, and specific Nordic country (in the pooled Nordic cohort only; Finland, Iceland, Norway, Sweden).

[d] US model only adjusted for birth year and obesity.

Discussion

Discussion

- In this cohort study by the **InPreSS consortium** including more than **50 000 pregnancies** in women with pregestational T2D from **6 countries**, we observed **no elevated risk** of **MCMs** after periconceptional exposure to GLP-1 receptor agonists or any of the second-line noninsulin ADM classes evaluated compared with insulin, another second-line ADM and the traditional treatment for T2D in pregnancy

Discussion

- Further, we showed an **increase in periconceptional** use of second-line noninsulin ADMs, **particularly GLP-1 receptor** agonists in the **US**, highlighting that there has been a shift in how T2D in reproductive aged women is treated.
- Although this study **did not suggest** that these medications have **strong teratogenic effects**, there is a ***need*** for further research to ***fully evaluate the safety*** of these medications in pregnancy

Discussion

- In-line with previous studies, we found an **elevated prevalence** (5.3%) of **MCMs** in infants born to women with **pregestational T2D**, compared with the general population (3.7%).
- The **effect of T2D** is believed to be at least partially mediated by ***hyperglycemia*** because poor glycemic control during pregnancy is associated with an increased risk of MCMs and other adverse pregnancy outcomes.
- This supports the importance of **glycemic control** and having safe and effective medications available during pregnancy.

Discussion

- Although **insulin** does not cross the **placenta** and is considered **nonteratogenic**, little to no data are available on what risks, if any, noninsulin ADMs may pose when used during the time of embryogenesis.

Discussion

- However, use of metformin may be considered according to some guidelines.
- Because metformin use in pregnant women with T2D has increased over time and is also used for treatment of **infertility** and **PCOS**, there is some information on the safety of metformin exposure during the first trimester.

Strengths and Limitations

- Although the study design optimized clinical equipoise between comparison groups, **residual bias** due to the **channeling of T2D** patients with specific characteristics to **specific second-line ADM** treatments is expected because these medications are recommended based on the presence of **comorbidities** such as **obesity, cardiac**, and **kidney** diseases.The clinical characteristics (eg, comorbidities and comedication use)of the exposure groups were in line with these treatment recommendations.

Strengths and Limitations

- Confounding by obesity and cardiovascular conditions would preferentially affect **GLP-1 receptor agonists** and **SGLT2 inhibitors**, and **bias** the **RR** estimates for MCMs upward.

Strengths and Limitations

- Reassuringly, **adjusting** for **obesity** in this study **did not** substantially affect the **RRs**, and given the expected direction of confounding, adjustment for additional and maternal comorbidities would likely attenuate the estimates toward the null

Strengths and Limitations

- Moreover, the **HbA1c levels** were slightly higher in some of the **second-line noninsulin** ADM groups compared with insulin, indicating that confounding by **glycemic control could**, if any thing, bias the RR for MCMs upward.
- Despite the likely overestimation of the RRs due to residual confounding, they were most compatible with a ***null effect*** relative to insulin.

Strengths and Limitations

- Filled **prescriptions around conception** might not result in exposure during embryogenesis, particularly for those filled before LMP. Among second-line noninsulin ADM users, coprescription fills of insulin or metformin were common in the periconceptional period, indicating scenarios that are difficult to **disentangle** in our data: concomitant use or adherence to guideline recommendations for switching to metformin or insulin.

Strengths and Limitations

- If there are increased risks conferred by use of second-line noninsulin ADM throughout the first trimester, then early pregnancy **switching** among the exposed groups could lead to an **underestimation** of those risks. We conducted a **sensitivity analysis** including only pregnant women with prescription fills during the **first trimester**. Fewer pregnancies were included in this analysis, yet the conclusion that there was **not a substantial increased risk** of MCMs overall or cardiac malformations remained.

Strengths and Limitations

- The study population was restricted to pregnancies resulting in **live births** because **information** on MCM was **not available** or was only partially available for pregnancies that resulted in ***stillbirth***, ***miscarriage***, or ***termination***.

Strengths and Limitations

- Conditioning on livebirth might introduce **selection bias** and potentially underestimate the RRs only if MCMs were **more lethal** or preferentially terminated in pregnancies exposed to specific ADMs relative to those exposed to insulin; however, to our knowledge, there are currently no studies that have investigated whether there is evidence toward this. Evaluating the potential effect of noninsulin ADM on fertility, miscarriages, or pregnancy termination is challenging and beyond the scope of this study

Conclusions

- In this study, infants born to women with pregestational T2D were associated with having a higher prevalence of MCMs, including cardiac malformations, compared with infants in the general population.

Conclusions

- However, in infants born to women with T2D treated with second-line ADM, we didnot observe a greater risk of MCMs after periconceptional exposure to sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, or SGLT2 inhibitors compared with insulin.
- Although reassuring, confirmation from other studies is needed, and continuous monitoring will provide more precise risk estimates in the future as data accumulate.