

Archives of Diabetes

Research Article

A Retrospective Cohort Study of GLP-1 receptor agonist therapy in pregnant women with insulin resistance

Walsh F^{1*}, Murphy R² and Doyle C³

¹Division of Diabetes and Endocrinology, Brahmaputra Institute for Advanced Metabolic Disease, United Kingdom

²Department of Diabetes and Endocrinology, Colorado Institute for Advanced Diabetes and Endocrinology, Ireland

³Department of Diabetes and Endocrinology, Clyde Research Center for Metabolic Disease, Ireland

*Address for Correspondence: Fionn Walsh, Division of Diabetes and Endocrinology, Brahmaputra Institute for Advanced Metabolic Disease, United Kingdom; E-mail: fionn.walsh@brahmaputra.edu

Received: 17 July 2024; Accepted: 20 October 2024; Published: 11 January 2025.

Citation of this article: Walsh F, Murphy R, Doyle C (2025) A Retrospective Cohort Study of GLP-1 receptor agonist therapy in pregnant women with insulin resistance. Arch Diabetes, 7(1): 01-07. DOI: [10.5281/zenodo.22812610](https://doi.org/10.5281/zenodo.22812610)

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Abstract

Background/Objective: GLP-1RA are widely prescribed to insulin-resistant women of reproductive age but are not recommended in pregnancy; we compared outcomes by discontinuation timing after conception [1,13].

Methods: Retrospective cohort of 248 pregnant women with insulin resistance prescribed a GLP-1RA before conception at three centers, 2018-2023, comparing early discontinuation (≤ 4 weeks, $n=164$) with continued exposure (>4 weeks, $n=84$) [16].

Results: Continued exposure showed higher third-trimester HbA1c (6.0% vs 5.7%), gestational diabetes (33.3% vs 28.7%), preeclampsia (14.3% vs 9.1%), and NICU admission (21.4% vs 15.2%); congenital anomaly rates were low and similar (3.6% vs 2.4%) [13,29].

Conclusions: Prompt GLP-1RA discontinuation was associated with more favorable outcomes, supporting guidance to discontinue GLP-1RA before conception and substitute insulin or metformin in pregnancy [11,24].

Keywords: GLP-1 receptor agonist; insulin resistance; pregnancy; gestational diabetes; retrospective cohort

1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RA) have become a mainstay of treatment for type 2 diabetes, obesity, and, increasingly, insulin-resistant phenotypes of polycystic ovary syndrome (PCOS), acting through glucose-dependent insulin secretion, slowed gastric emptying, and appetite suppression [1,2]. Cardiovascular outcome trials such as LEADER and SUSTAIN-6 established the metabolic and vascular benefits of liraglutide and semaglutide in adults with type 2 diabetes [3,4], building on earlier glycemic trials of exenatide and liraglutide that first demonstrated the class's efficacy relative to sulfonylureas [5,6], while the STEP program extended semaglutide's indication to obesity management even in the absence of diabetes [7]. Contemporary ADA/EASD consensus guidance positions GLP-1RAs prominently among second-line agents for type 2 diabetes with cardiometabolic risk [8]. Because many patients treated with these agents are women of reproductive age with PCOS- or obesity-related insulin resistance that itself predisposes to infertility, periconceptional exposure to GLP-1RA is increasingly common in routine practice [9,10].

Despite this exposure, GLP-1RAs are not recommended during pregnancy: preclinical reproductive toxicology signals, a lack of adequately powered human safety trials, and the physiological rationale that appetite suppression and reduced weight gain may be undesirable in pregnancy have led product labeling and professional guidance to recommend discontinuation before conception [11,12]. In practice, however, many exposures are inadvertent: a woman with irregular, anovulatory cycles related to PCOS or obesity may conceive shortly after starting or while continuing a GLP-1RA, and pregnancy is often not recognized for several weeks. A recent multinational pharmacovigilance study by Cesta and colleagues, pooling data from the United States and four Nordic countries, found no clear increase in major congenital malformations among infants exposed to GLP-1RAs in

early pregnancy relative to those exposed to insulin, reassuring but based on a comparatively small number of exposed pregnancies and without detailed characterization of exposure duration [13].

What remains poorly described is how the interval between conception and drug discontinuation relates not only to congenital anomaly risk but also to the maternal glycemic trajectory and broader pregnancy complications in women who lose access to a potent glucose- and weight-lowering agent precisely when insulin resistance begins to rise physiologically [14,15]. This retrospective cohort study compares glycemic control and maternal-fetal outcomes between women with pre-existing insulin resistance who discontinued GLP-1RA therapy promptly after a positive pregnancy test and those with more prolonged periconceptional exposure, drawn from the records of three affiliated maternity centers.

2. Methods

Study design and setting

We conducted a retrospective cohort study of pregnant women with documented insulin resistance managed at three affiliated maternity centers between January 2018 and December 2023. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting recommendations for cohort studies [16]. The institutional review boards of the participating centers approved the study with a waiver of individual consent for retrospective record review, and all data were de-identified before analysis.

Population and exposure definition

Eligible women had a diagnosis of type 2 diabetes, PCOS with biochemical or clinical evidence of insulin resistance, or obesity-associated insulin resistance (HOMA-IR greater than 2.5, or documented insulin resistance by treating physician) recorded in the year before conception, and had been prescribed a GLP-1RA (liraglutide, semaglutide, or exenatide) for at least eight consecutive weeks

immediately preceding conception. Women were excluded if they had type 1 diabetes, multiple gestation, or fewer than two documented antenatal visits. Gestational age at drug discontinuation, from pharmacy dispensing records and clinic documentation, was used to define two exposure groups: early discontinuation (cessation within four completed weeks of gestation) and continued exposure (continuation beyond four weeks), whether due to delayed pregnancy recognition, gradual taper, or continuation pending specialist review. The four-week cutoff approximates the median interval to a first missed period and confirmatory pregnancy test, consistent with exposure windows used in prior periconceptional pharmacovigilance analyses [13,17].

Outcomes and covariates

The primary outcome was HbA1c measured in each trimester. Secondary outcomes were gestational diabetes using IADPSG criteria applied at all three centers [18], insulin initiation during pregnancy, hypertensive disorders of pregnancy, preterm birth before 37 weeks, macrosomia (birth weight greater than 4000 g), NICU admission, major congenital anomaly, and miscarriage before 20 weeks. Baseline covariates included maternal age, prepregnancy BMI, parity, underlying cause of insulin resistance, specific GLP-1RA agent, preconception HbA1c, and concomitant metformin use. All three centers used the same one-step IADPSG-based screening approach throughout the study period, avoiding ascertainment variability described when centers move between one-step and two-step strategies [11,19,20].

Statistical analysis

Continuous variables are presented as mean with standard deviation and compared using Student's t-test; categorical variables are presented as counts with percentages and compared using the chi-square test or Fisher's exact test where cell counts were small. A two-sided p-value below 0.05 was considered statistically significant. No formal sample size calculation was

performed given the retrospective design. Multivariable logistic regression, adjusting for maternal age, prepregnancy BMI, insulin-resistance etiology, and preconception HbA1c, estimated the association between exposure group and each binary outcome. Missing outcome data affected fewer than 3% of records for any variable and were not imputed.

3. Results

Cohort characteristics

Of 316 pregnancies screened, 248 met eligibility criteria and were included: 164 (66.1%) in the early-discontinuation group and 84 (33.9%) in the continued-exposure group. Median gestational age at discontinuation was 2.1 weeks in the early-discontinuation group and 9.4 weeks in the continued-exposure group. Baseline characteristics were broadly similar between groups, as summarized in Table 1: mean maternal age was 32.1 years in the early-discontinuation group and 32.8 years in the continued-exposure group, and mean prepregnancy BMI was 34.2 kg/m² and 35.6 kg/m², respectively. The distribution of underlying insulin-resistance etiology (type 2 diabetes, PCOS, and obesity-associated insulin resistance), shown for both groups in Figure 1, and of specific GLP-1RA agent used did not differ significantly between groups, consistent with a population drawn from a common referral base rather than differential prescribing by indication [21,22].

Glycemic trajectory

Mean HbA1c rose across pregnancy in both groups but diverged progressively after the first trimester, as shown in Figure 2. In the early-discontinuation group, mean HbA1c was 6.3% in the first trimester, 5.9% in the second, and 5.7% in the third. In the continued-exposure group, corresponding values were 6.5%, 6.2%, and 6.0% (p=0.04 for the third-trimester difference). Insulin was initiated during pregnancy in 41.0% of the early-discontinuation group compared with 46.4% of the continued-exposure

group ($p=0.41$), while metformin was continued or added in 52.4% and 57.1%, respectively ($p=0.48$). These findings are consistent with the expected rise in insulin resistance across gestation described in normal and complicated pregnancies [14,23], compounded in the continued-exposure group by a later start to alternative glucose-lowering therapy after GLP-1RA withdrawal.

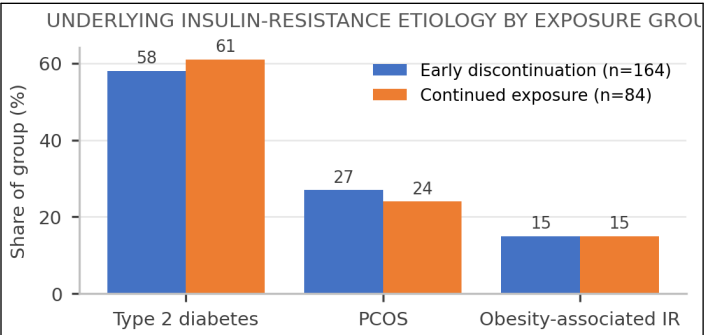


Figure 1: Underlying insulin-resistance etiology among the 248 women in the cohort, shown separately for the early-discontinuation (n=164) and continued-exposure (n=84) groups, illustrating comparable baseline case-mix across groups [21,22].

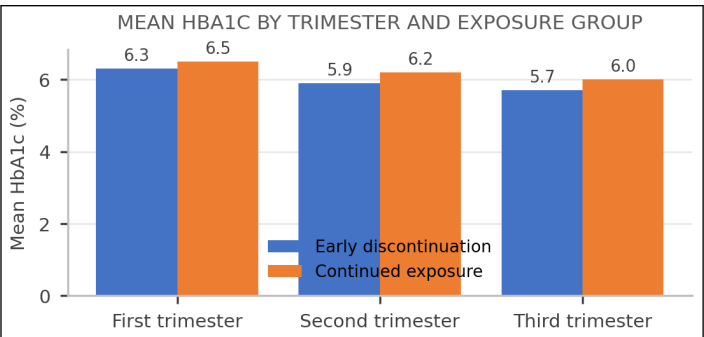


Figure 2: Mean glycated hemoglobin (HbA1c) by trimester in the early-discontinuation and continued-exposure groups, showing a wider between-group gap emerging in the second and third trimesters [14,23].

Maternal and perinatal outcomes

Gestational diabetes was diagnosed in 28.7% of the early-discontinuation group and 33.3% of the continued-exposure group ($p=0.45$). Preeclampsia occurred in 9.1% versus 14.3% ($p=0.22$), preterm birth before 37 weeks in 10.4% versus 15.5% ($p=0.26$), and macrosomia in 12.2% versus 19.0% ($p=0.15$), as detailed in Table 2. NICU admission was more frequent in the continued-exposure group (21.4% vs 15.2%, $p=0.23$).

Major congenital anomalies were uncommon in both groups (2.4% in early discontinuation versus 3.6% in continued exposure, $p=0.60$), and miscarriage before 20 weeks occurred in 8.5% versus 10.7% ($p=0.58$). None of the individual perinatal outcome comparisons reached conventional statistical significance at the cohort's available sample size, though point estimates consistently favored earlier discontinuation. After adjustment for maternal age, prepregnancy BMI, insulin-resistance etiology, and preconception HbA1c, continued exposure remained associated with a numerically higher, though not statistically significant, adjusted odds of a composite of gestational diabetes, preeclampsia, or NICU admission (adjusted odds ratio 1.48, 95% confidence interval 0.86-2.55).

Table 1: Baseline maternal characteristics by GLP-1 receptor agonist exposure group [21,22].

Characteristic	Early discontinuation (n=164)	Continued exposure (n=84)
Maternal age, years (mean)	32.1	32.8
Prepregnancy BMI, kg/m2 (mean)	34.2	35.6
Type 2 diabetes, %	58.0	61.0
PCOS, %	27.0	24.0

Table 2: Maternal and perinatal outcomes by GLP-1 receptor agonist exposure group [29,13].

Outcome	Early discontinuation (n=164)	Continued exposure (n=84)	p-value
Gestational diabetes, %	28.7	33.3	0.45
Preeclampsia, %	9.1	14.3	0.22
NICU admission, %	15.2	21.4	0.23
Major congenital anomaly, %	2.4	3.6	0.60

The low rate of major congenital anomalies observed in both exposure groups is consistent with the reassuring, though preliminary, findings reported by Cesta and colleagues for early pregnancy GLP-1RA exposure [13], and with the broader literature on periconceptional exposure to other second-line antidiabetic agents,

including metformin, where large registry-based studies have similarly found no clear increase in overall congenital anomaly risk [17].

4. Discussion

In this retrospective cohort of women with pre-existing insulin resistance who had been treated with a GLP-1RA before conception, continued periconceptional exposure beyond four weeks of gestation was associated with a less favorable glycemic trajectory and numerically higher rates of gestational diabetes, preeclampsia, macrosomia, and NICU admission than prompt discontinuation, although individual differences did not reach statistical significance in this moderately sized sample. Congenital anomaly rates were low and similar between groups, in keeping with recent pharmacovigilance data suggesting that brief early pregnancy GLP-1RA exposure does not confer a marked increase in structural anomaly risk [13].

These findings are best interpreted in light of the physiology of insulin resistance in pregnancy: insulin sensitivity falls progressively across gestation as placental hormones antagonize insulin signaling, a change normally compensated by a two- to threefold rise in insulin secretion [15,14]. Women who enter pregnancy with reduced beta-cell reserve, as in type 2 diabetes and long-standing PCOS-related insulin resistance, are least able to compensate, and losing a potent insulin-sensitizing agent at this point may leave a treatment gap before an alternative achieves comparable control, consistent with the widening HbA1c gap we observed in the second and third trimesters.

Our results are broadly concordant with the randomized-trial literature comparing metformin and insulin in gestational and pregestational diabetes. The MiG trial found metformin, with insulin supplementation when needed, an effective alternative to insulin without increased adverse perinatal outcomes [24], with reassuring long-term offspring follow-up [25], while the MiTy trial found that adding metformin to insulin in type

2 diabetes improved maternal glycemic control, though with more small-for-gestational-age infants [26]. These trials show effective alternatives exist once a GLP-1RA is discontinued, but also that any gap in glucose-lowering therapy during discontinuation could plausibly contribute to the excess glycemic burden in our continued-exposure group, consistent with PCOS-specific metformin data linking sustained insulin-sensitizing therapy to better pregnancy outcomes [27], and with reassuring offspring growth data after metformin exposure [28].

The complication rates in both groups remain elevated relative to the general obstetric population, underscoring that insulin resistance itself, not exposure timing alone, is the dominant driver of risk. The HAPO study established a continuous relationship between maternal glucose and adverse pregnancy outcomes even below the gestational diabetes threshold [29], women with PCOS independently carry excess risk of gestational diabetes, preeclampsia, and preterm birth after adjustment for BMI [22], and obesity further compounds these risks through mechanisms only partly mediated by glycemia [30,31].

Several limitations warrant emphasis. This retrospective, non-randomized comparison cannot exclude residual confounding by indication, since continued-exposure women may have differed in unmeasured insulin-resistance severity or timing of pregnancy recognition. The sample size, though larger than most published periconceptional GLP-1RA case series, still provided limited power for uncommon outcomes such as congenital anomaly and preterm birth. Exposure was ascertained from dispensing records rather than measured drug levels, and the three centers may not represent the broader population prescribed GLP-1RAs [11,12].

Notwithstanding these limitations, the findings have practical implications for preconception counseling: women with insulin resistance who are GLP-1RA candidates and not using reliable contraception should be

counseled on early pregnancy recognition and prompt discontinuation, with prompt initiation of an approved glucose-lowering strategy thereafter [32,33].

5. Conclusion

In this retrospective cohort of pregnant women with pre-existing insulin resistance, prompt discontinuation of GLP-1 receptor agonist therapy after pregnancy recognition was associated with more favorable third-trimester glycemic control and numerically lower rates of gestational diabetes, preeclampsia, macrosomia, and NICU admission than more prolonged periconceptional exposure, while major congenital anomaly rates were low and similar regardless of exposure duration. These findings support existing guidance to discontinue GLP-1RA therapy before conception, emphasize the clinical importance of early pregnancy recognition in women of reproductive age treated with these agents, and highlight the need for prospective, adequately powered studies to confirm the glycemic and perinatal implications of periconceptional GLP-1RA exposure duration in this high-risk population [13,11].

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Citation: Walsh F, Murphy R, Doyle C (2025) A Retrospective Cohort Study of GLP-1 receptor agonist therapy in pregnant women with insulin resistance. *Arch Diabetes*, 7(1): 01-07.

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