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CREATION OF THE PREGNANCY MICE MODEL TO STUDY THE EFFECT OF GLP-1/GIP AGONISTS

Galiya Akylzhanova[1], https://orcid.org/0009-0004-7485-9544
Omirgul Bakenova[1,2], https://orcid.org/0009-0009-9825-1513
Danysh Abetov[1], https://orcid.org/0000-0003-2440-060X
Arslan Umarov[3], https://orcid.org/0009-0005-0255-5573
Zhanna Musaeva[4], https://orcid.org/0009-0003-1333-8107
Gulbanu Akilzhanova[5], https://orcid.org/0000-0002-0286-8386
Dos Sarbassov[1,2], https://orcid.org/0000-0002-6848-1133
Ainur Akilzhanova[1,4], https://orcid.org/0000-0001-6161-8355

[1] Center for Life Sciences, National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan;
[2] School of Science and Humanities, Nazarbayev University, Astana, Kazakhstan;
[3] Department of Chemical & Materials Engineering, School of Engineering and Digital Sciences, Nazarbayev University, Astana, Kazakhstan;
[4] Department of Biology and Genomics, Faculty of Natural Sciences, Eurasian National University, Astana, Kazakhstan;
[5] Semey Medical University, Pavlodar branch, Pavlodar, Kazakhstan.

Abstract

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists represent a novel class of antidiabetic and anti-obesity agents. Despite their growing clinical relevance, little is known about their safety and potential effects during pregnancy. Here we describe the development of a pregnancy mouse model to study the impact of GLP-1/GIP dual agonists, with a focus on maternal metabolic changes, embryonic development, and organ-specific outcomes.

Introduction. The use of GLP-1 and GIP receptor agonists has expanded significantly due to their efficacy in improving glycemic control and reducing body weight. Tirzepatide, a dual GLP-1/GIP agonist, has shown remarkable clinical outcomes in type 2 diabetes and obesity. However, its safety profile during pregnancy remains poorly understood. Pregnancy is a unique physiological state characterized by altered glucose homeostasis, increased insulin resistance, and complex hormonal regulation. Drug exposure during this period can impact both maternal health and fetal development. Current clinical guidelines recommend discontinuing GLP-1 receptor agonists during pregnancy, but preclinical data are limited.

Aim. This work aims to establish a reproducible mouse pregnancy model to evaluate the effects of GLP-1/GIP agonists, such as Tirzepatide, on maternal physiology and embryonic outcomes.

Materials and Methods. Animals: C57BL/6 female mice, aged 8–10 weeks, were used. Females were mated overnight, and pregnancy was confirmed by vaginal plug observation (defined as embryonic day 0.5, E0.5). Experimental Groups: Control group – intraperitoneal injections of PBS, GLP-1/GIP agonist group – intraperitoneal injections of Tirzepatide. Treatment Protocol: Injections were administered daily starting from E13.5 until E17.5. On embryonic day 17.5, pregnant mice were sacrificed, and maternal organs, placenta, and embryos were collected for further analysis. Endpoints: Maternal body weight and food intake; Fetal number, size, and weight; Placental weight and morphology; Maternal organ collection for histological and molecular studies.

Results. A reproducible mouse pregnancy model to evaluate the effects of GLP-1/GIP agonists (Tirzepatide) on maternal physiology and embryonic outcomes was created. Pregnant mice were successfully treated with PBS, Tirzepatide according to the protocol. On E17.5, animals were sacrificed, and maternal/fetal samples were collected. Data analysis, including weight measurement, morphological assessment, and molecular profiling, is ongoing.

Conclusion. We established a pregnancy mouse model suitable for studying the impact of GLP-1/GIP dual agonists. This approach will generate critical preclinical data to evaluate maternal-fetal safety and mechanistic insights.

Keywords. *Pregnancy model, mice, GLP-1, GIP, dual agonist, tirzepatide, embryonic development, maternal metabolism*

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Резюме

СОЗДАНИЕ МОДЕЛИ У БЕРЕМЕННЫХ МЫШЕЙ ДЛЯ ИЗУЧЕНИЯ ВЛИЯНИЯ АГОНИСТОВ GLP-1/GIP

Галия Акильжанова[1], https://orcid.org/0009-0004-7485-9544
Омиргуль Бакенова[1,2], https://orcid.org/0009-0009-9825-1513
Даныш Абетов[1], https://orcid.org/0000-0003-2440-060X
Арслан Умаров[3], https://orcid.org/0009-0005-0255-5573
Жанна Мусаева[4], https://orcid.org/0009-0003-1333-8107
Гульбану Акильжанова5, https://orcid.org/0000-0002-0286-8386
Дос Сарбасов[1,2], https://orcid.org/0000-0002-6848-1133
Айнур Акильжанова[1,4], https://orcid.org/0000-0001-6161-8355

[1] Центр наук о жизни, National Laboratory Astana, Назарбаев Университет, г. Астана, Республика Казахстан;
[2] Школа естественных и гуманитарных наук, Назарбаев Университет, г. Астана, Республика Казахстан;
[3] Кафедра химической инженерии и материаловедения, Школа инженерии и цифровых наук, Назарбаев Университет, г. Астана, Республика Казахстан;
[4] Кафедра биологии и геномики, Факультет естественных наук, Евразийский национальный университет, г. Астана, Республика Казахстан;
[5] Медицинский университет Семей, Павлодарский филиал, г. Павлодар, Республика Казахстан.

Агонисты рецепторов глюкагоноподобного пептида-1 (GLP-1) и глюкозозависимого инсулинотропного полипептида (GIP) представляют собой новый класс противодиабетических препаратов. Несмотря на растущее клиническое значение, их безопасность и возможные эффекты во время беременности изучены недостаточно. В данной работе описывается разработка модели беременности на мышах для изучения воздействия двойных агонистов GLP-1/GIP с акцентом на изменения материнского метаболизма, эмбриональное развитие и органоспецифические эффекты.

Введение. Применение агонистов рецепторов GLP-1 и GIP значительно расширилось благодаря их эффективности в улучшении гликемического контроля и снижении массы тела. Тирзепатид, двойной агонист GLP-1/GIP, продемонстрировал выдающиеся клинические результаты при лечении сахарного диабета 2 типа и ожирения. Однако его профиль безопасности во время беременности остаётся малоизученным. Беременность представляет собой уникальное физиологическое состояние, характеризующееся изменением гомеостаза глюкозы, повышенной инсулинорезистентностью и сложной гормональной регуляцией. Воздействие лекарственных средств в этот период может повлиять как на здоровье матери, так и на развитие плода. Согласно действующим клиническим рекомендациям, при беременности рекомендуется прекращать приём агонистов GLP-1, однако доклинических данных крайне мало.

Цель данной работы — создать воспроизводимую модель беременности на мышах для оценки влияния агонистов GLP-1/GIP, таких как тирзепатид, на физиологию матери и эмбриональные показатели.

Материалы и методы. Животные: Использовали самок мышей линии C57BL/6 в возрасте 8–10 недель. Самок подсаживали к самцам на ночь, беременность подтверждали по наличию вагинальной пробки (обозначено как эмбриональный день 0,5 — E0.5). Экспериментальные группы. Контрольная группа — внутрибрюшинные инъекции PBS. Группа GLP-1/GIP агониста — внутрибрюшинные инъекции тирзепатида. Протокол лечения. Инъекции проводились ежедневно, начиная с E13.5 и до E17.5. На 17,5-й день беременности (E17.5) беременные мыши подвергались эвтаназии, после чего собирались органы матери, плаценты и эмбрионы для дальнейшего анализа. Конечные точки. Масса тела матери и потребление пищи. Количество, размер и вес плодов. Масса и морфология плаценты. Сбор органов матери для гистологических и молекулярных исследований.

Результаты. Была создана воспроизводимая модель беременности на мышах для оценки влияния агонистов GLP-1/GIP (тирзепатида) на физиологию матери и эмбриональные исходы. Беременные мыши успешно получали PBS или тирзепатид в соответствии с протоколом. На E17.5 животные были эвтаназированы, и были собраны образцы от матерей и плодов. В настоящее время проводится анализ данных, включающий измерение массы, морфологическую оценку и молекулярное профилирование.

Заключение. Нами создана модель беременности у мышей, подходящая для изучения воздействия двойных агонистов GLP-1/GIP. Данный подход позволит получить важные доклинические данные для оценки материнско-плодной безопасности и механистических аспектов их действия.

***Ключевые слова**. Модель беременности, мыши, GLP-1, GIP, двойной агонист, тирзепатид, эмбриональное развитие, материнский метаболизм*

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Түйіндеме

GLP-1/GIP АГОНИСТЕРІНІҢ ӘСЕРІН ЗЕРТТЕУ ҮШІН ЖҮКТІ ТЫШҚАН МОДЕЛІН ҚҰРУ

Ғалия Ақылжанова[1], https://orcid.org/0009-0004-7485-9544
Өміргүл Бакенова[1,2], https://orcid.org/0009-0009-9825-1513
Даныш Абетов[1], https://orcid.org/0000-0003-2440-060X
Арслан Умаров[3], https://orcid.org/0009-0005-0255-5573
Жанна Мұсаева[4], https://orcid.org/0009-0003-1333-8107
Гүлбану Ақылжанова[5], https://orcid.org/0000-0002-0286-8386
Дос Сарбасов[1,2], https://orcid.org/0000-0002-6848-1133
Айнұр Акильжанова[1,4], https://orcid.org/0000-0001-6161-8355

[1] Өмір туралы ғылымдар орталығы, National Laboratory Astana, Назарбаев Университеті, Астана қ., Қазақстан Республикасы;
[2] Ғылым және гуманитарлық ғылымдар мектебі, Назарбаев Университеті, Астана қ., Қазақстан Республикасы;
[3] Химиялық инженерия және материалтану кафедрасы, Инженерлік және цифрлық ғылымдар мектебі, Назарбаев Университеті, Астана қ., Қазақстан Республикасы;
[4] Еуразия ұлттық университеті, жаратылыстану факультеті, биология және геномика кафедрасы, Астана қ., Қазақстан Республикасы;
[5] Семей медицина университеті, Павлодар филиалы, Павлодар қ., Қазақстан Республикасы.

Глюкагонға ұқсас пептид-1 (GLP-1) және глюкозаға тәуелді инсулинотропты полипептид (GIP) рецепторларының агонисттері қант диабетіне және артық салмаққа қарсы жаңа дәрілер класына жатады. Олардың клиникалық маңызы артып келе жатқанына қарамастан, жүктілік кезеңіндегі қауіпсіздігі мен ықтимал әсерлері жеткілікті зерттелмеген. Бұл жұмыста GLP-1/GIP қос агонисттерінің жүктілік кезіндегі әсерін зерттеу үшін тышқандардың жүктілік моделін құру сипатталады. Зерттеу ананың метаболикалық өзгерістеріне, эмбрион дамуына және ағзаларға әсеріне бағытталған.

Кіріспе. GLP-1 және GIP рецепторларының агонисттерін қолдану соңғы жылдары айтарлықтай кеңейді, себебі олар гликемиялық бақылауды жақсартуда және артық дене салмағын азайтуда тиімді. GLP-1/GIP қос агонисті болып табылатын тирзепатид 2 типті қант диабеті мен артық салмақты азайтуда жоғары клиникалық нәтижелер көрсетті. Алайда, оның жүктілік кезіндегі қауіпсіздігі аз зерттелген. Жүктілік – глюкоза гомеостазының өзгеруімен, инсулинге төзімділіктің артуымен және күрделі гормондық реттелумен сипатталатын ерекше физиологиялық жағдай. Осы кезеңде дәрі-дәрмек қабылдау ананың денсаулығына да, ұрықтың дамуына да ықпал етуі мүмкін. Қазіргі клиникалық нұсқаулықтар жүктілік кезінде GLP-1 агонисттерін тоқтатуды ұсынады, бірақ доклиникалық деректер шектеулі.

Бұл жұмыстың мақсаты — ананың физиологиясына және эмбриондық көрсеткіштеріне GLP-1/GIP агонисттерінің, мысалы тирзепатидтің әсерін бағалау үшін қайталанбалы тышқан жүктілік моделін жасау.

Материалдар мен әдістер. Жануарлар. 8–10 апталық C57BL/6 ұрғашы тышқандар қолданылды. Ұрғашыларды түнде аталықтармен шағылыстырды, жүктілік вагинальды тығын арқылы расталды (эмбрионалды күн 0,5 — E0.5 деп белгіленді). Эксперименттік топтар. Бақылау тобы — PBS иньекциясы. GLP-1/GIP агонист тобы — тирзепатид иньекциясы. Емдеу протоколы. Инъекциялар E13.5-тен бастап E17.5-ке дейін күнге дейін жүргізілді. E17.5 күні жүкті тышқандар эвтаназия жасалып, аналықтар, плацента және эмбриондар кейінгі талдауға алынды. Соңғы нүктелер. Аналықтың дене салмағы мен тамақ қабылдауы. Ұрық саны, өлшемі және салмағы. Плацентаның салмағы мен морфологиясы. Аналық ағзаларын гистологиялық және молекулалық зерттеулерге жинау.

Нәтижелер. GLP-1/GIP агонистінің (тирзепатид) ана физиологиясы мен ұрықтың нәтижелеріне әсерін бағалау үшін тінтуірдің жүктілігінің қайталанатын үлгісі құрылды. Жүкті тышқандарға PBS және тирзепатидпен емдеу протоколына сәйкес жүргізілуде. E17.5 күні жануарларға эвтаназия жасалып, аналық және ұрық үлгілері жиналды. Мәліметтерді талдау (салмақ өлшеу, морфологиялық бағалау және молекулалық зерттеу) жалғасуда.

Қорытынды. Біз GLP-1/GIP қос агонисттерінің әсерін зерттеуге мүмкіндік беретін жүктілік моделі құрдық. Бұл тәсіл аналық-плацентарлық-ұрық жүйесінің қауіпсіздігін және әсер ету механизмдерін бағалауға қажетті маңызды доклиникалық деректер береді.

***Негізгі сөздер**. Жүктілік моделі, тышқан, GLP-1, GIP, қос агонист, тирзепатид, эмбрион дамуы, аналық метаболизмі*

Дәйексөз үшін:

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Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists, as well as dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, have emerged as highly effective therapies for type 2 diabetes and obesity. Among them, Tirzepatide, a first-in-class dual GLP-1/GIP agonist, has demonstrated remarkable improvements in glycemic control, weight reduction, and metabolic regulation in clinical trials [1,2]. However, despite their therapeutic promise, the safety and potential consequences of GLP-1/GIP agonists during pregnancy remain poorly understood.

Pregnancy represents a unique physiological state characterized by profound metabolic adaptations, including increased insulin resistance, altered glucose homeostasis, and complex hormonal changes [3,4]. These adaptations are essential for ensuring proper fetal growth and development, but they may also interact with pharmacological agents in unpredictable ways. Since GLP-1 receptor agonists cross the maternal circulation and can influence metabolic and hormonal pathways, there is a critical need to evaluate their potential impact on both maternal health and embryonic development [5].

Current clinical recommendations advise discontinuation of GLP-1 receptor agonists during pregnancy, largely due to the lack of sufficient preclinical and clinical data [6]. To address this knowledge gap, the development of robust animal models is essential. Mouse models, particularly the C57BL/6 strain, provide a well-established system for studying pregnancy-related physiology and drug effects [7].

The present study aims to establish a pregnancy mouse model to investigate the effects of GLP-1/GIP agonists, with a focus on maternal metabolic outcomes, fetal development, and placental function. This model will serve as a preclinical platform to generate critical insights into the safety and mechanisms of these agents during gestation.

Materials and Methods

Animals and Housing

C57BL/6 female mice (8–10 weeks old, average body weight 18–22 g) were obtained from the animal facility of National Laboratory Astana. Mice were housed in groups of 3–5 per cage under specific pathogen-free (SPF) conditions with a controlled 12 h light/dark cycle, temperature of 22 ± 2 °C, and relative humidity of 50–60%. Standard rodent chow and water were provided *ad libitum*. All animal procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Nazarbayev University, in accordance with the ARRIVE guidelines and the European Directive 2010/63/EU for animal experiments.

Mating Procedure and Establishment of Pregnancy Model

Females were paired overnight with proven fertile C57BL/6 males (1:1 ratio). The presence of a vaginal plug was checked the next morning and recorded as embryonic day 0.5 (E0.5). Pregnancy progression was monitored by weight gain and abdominal palpation.

Experimental Groups and Drug Administration

Pregnant mice were randomly assigned to two groups:

Control group (PBS) – received intraperitoneal (IP) injections of sterile phosphate-buffered saline once daily.

GLP-1/GIP agonist group – received IP injections of Tirzepatide (4 mg/kg), prepared freshly each day in PBS, once daily. Treatment began on embryonic day 13.5 (E13.5), corresponding to late organogenesis, and continued until E17.5. Injections were performed at the same time each day to minimize circadian variability. The number of mice per group was n = 3.

Monitoring of Pregnancy and Body Weight

Maternal body weight was measured at baseline (E0.5) and then on E7.5, E10.5, E14.5, and E17.5 to assess pregnancy progression and treatment effects. Any abnormal behaviors, pregnancy loss, or maternal mortality were recorded.

Sample Collection and Processing

On E17.5, pregnant females were euthanized by CO_2 inhalation followed by cervical dislocation. The uterine horns were dissected under sterile conditions. The number of implantation sites, resorptions, and live fetuses was recorded.

Fetal measurements: body weight and crown-rump length were measured for each fetus.

Placental analysis: placentas were weighed and macroscopically examined.

Tissue collection: maternal tissues (liver, heart, brain, pancreas) and fetal tissues (liver, heart, brain, placenta) were collected. Samples were divided for:

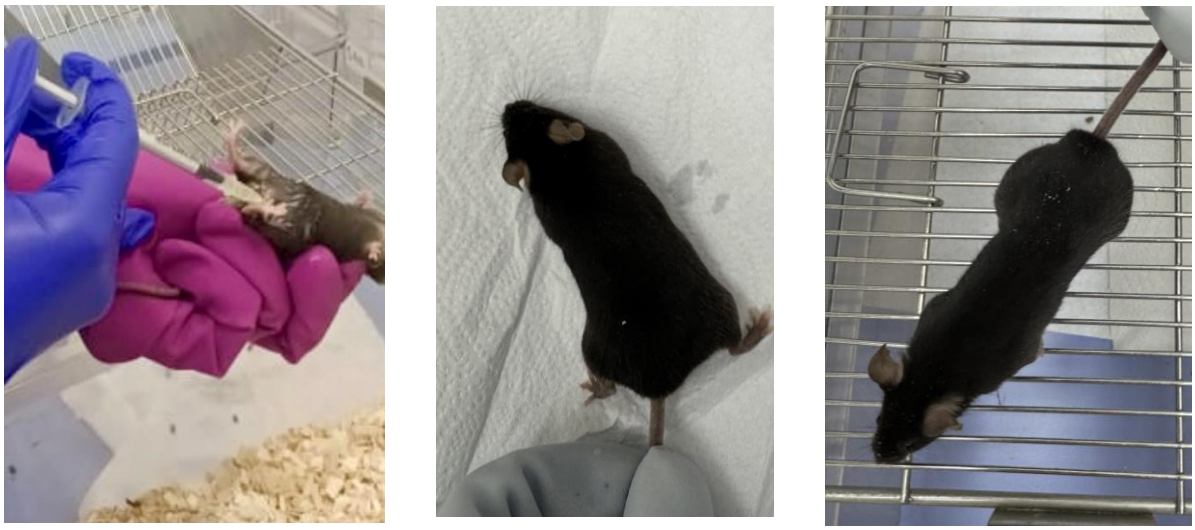
Fixation in 4% paraformaldehyde, followed by paraffin embedding for histological analysis (H&E staining, immunohistochemistry).

Snap-freezing in liquid nitrogen and storage at –80 °C for subsequent molecular studies (RNA, protein, or metabolite extraction).

Results

Preliminary observations from our pregnancy mouse model treated with Tirzepatide demonstrated notable changes compared to the control group. Pregnant mice receiving Tirzepatide exhibited a reduction in maternal body weight during gestation. In addition, the embryos collected at gestational day 17 were smaller in size compared to those from the PBS-treated control group.

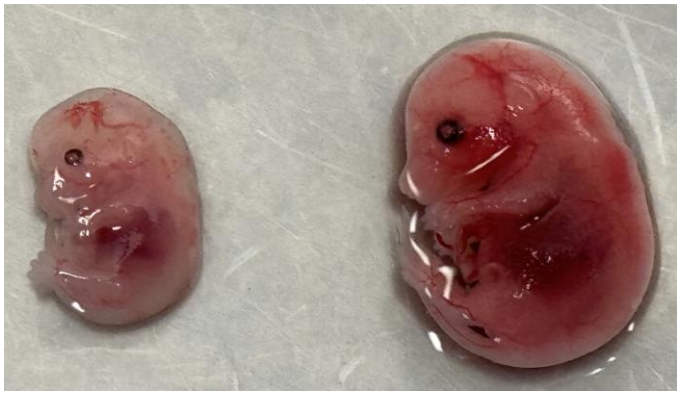
Although these findings suggest a potential effect of Tirzepatide on maternal physiology and embryonic development, the study is still ongoing. Further analyses are currently in progress, including histological evaluation of collected tissues and RNA-based molecular studies, which will provide deeper insights into the mechanisms underlying these observed phenotypic change.



A B C

Fig.1 Mouse treated with Tirzepatide. A) Start injection (body weight 27.5 g. B) During pregnancy 32.7 g. C) Before sacrifice (body weight 26.1 g)

Left: tirzepatide treatment; Right: vehicle treatment



A B

Fig.2 Embryos collected from pregnant mice after dissection A) Tirzepatide 17.5 day B)Control 17.5 day

Although our data remain preliminary, they highlight the necessity of cautious consideration when translating incretin-based therapies to pregnant populations. The smaller embryonic size observed in the Tirzepatide-treated group may indicate potential risks to fetal development, warranting further systematic investigation. Our study is currently progressing toward histological assessment of maternal and embryonic tissues, as well as RNA-based analyses, to uncover molecular and cellular pathways that might underlie these phenotypic changes.

Future directions will include expanding the sample size, performing detailed histopathological examinations of placental and embryonic tissues, and integrating molecular assays such as qPCR or RNA-seq to identify alterations in gene expression associated with maternal treatment. Such data will provide more definitive insights into whether GLP-1/GIP agonists may interfere with fetal growth, and could help inform clinical decision-making regarding their use in women of reproductive age.

So, our initial findings support the feasibility of the established pregnancy mouse model and suggest that tirzepatide exposure during pregnancy has measurable effects on maternal and fetal outcomes. Continued analyses will be essential to clarify the mechanisms involved and to evaluate the translational significance of these findings for human health.

Discussion

The present study describes the establishment of a pregnancy mouse model to evaluate the effects of the dual GLP-1/GIP receptor agonist Tirzepatide during gestation. Preliminary findings revealed that maternal administration of Tirzepatide in late pregnancy was associated with reduced maternal weight gain and smaller fetal size compared with control animals. These results suggest that modulation of incretin signaling during pregnancy may influence maternal–fetal metabolic interactions and potentially alter fetal growth trajectories.

The observed reduction in maternal body weight is consistent with the known pharmacological actions of GLP-1 and GIP receptor agonists, which reduce appetite, delay gastric emptying, and enhance insulin sensitivity [1,2]. While these effects are therapeutically beneficial in obesity and type 2 diabetes, during pregnancy they may lead to relative maternal undernutrition or altered nutrient allocation

to the fetus. Reduced nutrient availability or placental transport efficiency could, in turn, contribute to the smaller fetal size observed in the Tirzepatide-treated group. It is also possible that direct effects of GLP-1/GIP signaling on placental tissues modulate trophoblast differentiation, angiogenesis, or nutrient transporter expression, thereby influencing fetal growth. Previous studies have shown that GLP-1 receptors are expressed in placental and decidual tissues, supporting the hypothesis that incretin agonists may act locally within the maternal–fetal interface [8,9].

Another potential mechanism underlying the observed phenotype involves altered maternal insulin and lipid metabolism. GLP-1 and GIP agonists enhance glucose-stimulated insulin secretion and promote lipid oxidation, which may shift the maternal metabolic profile toward a catabolic state. During late gestation, however, normal pregnancy requires increased insulin resistance to ensure adequate glucose supply to the fetus [3,4]. Interference with this adaptive mechanism might disturb the balance between maternal and fetal energy demands, leading to growth restriction or other developmental consequences. Future biochemical and molecular analyses—including insulin and leptin measurements, placental transporter gene expression, and histological assessment of placental morphology—will be necessary to delineate these pathways.

Although few studies have explored the safety of GLP-1 receptor agonists in pregnancy, available preclinical evidence raises concerns. For example, liraglutide and semaglutide have been associated with reduced fetal weight and delayed ossification in animal studies [10,11]. Human data remain limited, as clinical use of GLP-1 analogs is contraindicated during pregnancy. Our findings with Tirzepatide, a more potent dual agonist, align with these preclinical observations and emphasize the need for comprehensive evaluation of incretin-based therapies in reproductive contexts.

Limitations

This study has several limitations that must be acknowledged. First, the data presented are preliminary and based on a limited number of animals. The small sample size restricts the statistical power of our observations and prevents definitive conclusions at this stage. Second, the current analysis is largely descriptive, focusing on gross morphological changes such as maternal weight loss and reduced embryonic size. Without quantitative histological data or molecular analyses, it is not yet possible to determine the specific biological mechanisms underlying these changes.

Additionally, the duration of the experiment was limited to gestational day 17, and long-term effects on embryonic development, viability, or postnatal outcomes were not assessed. Earlier or prolonged exposure may yield different outcomes, particularly regarding implantation or early embryonic development. In addition, quantitative molecular and histological analyses are ongoing, which will provide more definitive evidence of the pathways involved. Since our model currently excludes postnatal follow-up, potential implications for offspring survival and metabolic health remain unexplored. Furthermore, only one dose and regimen of tirzepatide were tested, which may not fully reflect dose-dependent or time-dependent effects.

Finally, while mice provide a valuable model for investigating mechanisms of drug action, species differences in metabolism and placental physiology must be considered when extrapolating these findings to humans. Thus, caution is required before making translational inferences regarding the safety of GLP-1/GIP agonists during pregnancy.

Despite these limitations, the model successfully demonstrates that Tirzepatide exerts measurable physiological effects on pregnant mice and their fetuses, validating its utility for future mechanistic investigations.

Conclusion

This study presents the development of a pregnancy mouse model to investigate the impact of Tirzepatide during gestation. Our preliminary data suggest that GLP-1/GIP receptor activation during pregnancy may alter maternal metabolism and fetal growth. These findings highlight the importance of careful risk–benefit assessment when considering incretin-based therapies in women of reproductive age and underscore the need for further mechanistic and developmental studies. The established mouse model offers a valuable platform for future work aimed at elucidating the molecular and placental mechanisms underlying the maternal and fetal effects of GLP-1/GIP agonists during gestation.

Conflict of interest: *The authors declare that they have no conflicts of interest.*

Contribution of the authors: *Each of the authors made an equal contribution.*

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Author Information
Galiya Akylzhanova - Junior Researcher, Laboratory of Molecular Oncology, National Laboratory Astana, Astana, Kazakhstan, Kabanbay Batyr Avenue, 53 https://orcid.org/0009-0004-7485-9544
Omirgul Bakenova - PhD student, Nazarbayev University, School of Science and Humanities, Research Assistant, National Laboratory Astana в Laboratory of Genomic and Personalized Medicine https://orcid.org/0009-0009-9825-1513
Danysh Abetov - Researcher, Laboratory of Molecular Oncology, National Laboratory Astana, Astana, Kazakhstan, Kabanbay Batyr Avenue, 53 https://orcid.org/0000-0003-2440-060X
Arslan Umarov -Master student, Department of Chemical & Materials Engineering, School of Engineering and Digital Sciences, Nazarbayev University, Astana, Kazakhstan https://orcid.org/0009-0005-0255-5573
Zhanna Musaeva - Master student, Eurasian National University, Faculty of Natural Sciences, https://orcid.org/0009-0003-1333-8107
Gulbanu Akilzhanova - Master student, Semey Medical University, MD, https://orcid.org/0000-0002-0286-8386
Dos Sarbassov - Professor, Biology Department,Vice Dean for Research (STEM) School of Sciences and Humanities, Director of the National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan, https://orcid.org/0000-0002-6848-1133

***Corresponding author:**
Ainur R. Akilzhanova – Doctor of Medical Sciences, PhD, M.D., Professor, Head of Laboratory of Genomic and Personalized Medicine, Acting director, Center for Life Sciences, National Laboratory Astana, Astana, Kazakhstan, https://orcid.org/0000-0001-6161-8355
Post address: Kabanbay batyr avenue 53, Astana, 010000, Republic of Kazakhstan;
E-mail: akilzhanova@nu.edu.kz
Phone: +7 777 658 4089 +7(7172)70-6501