

# **Preconceptional, gestational and postpartum carbohydrate metabolic disorders**

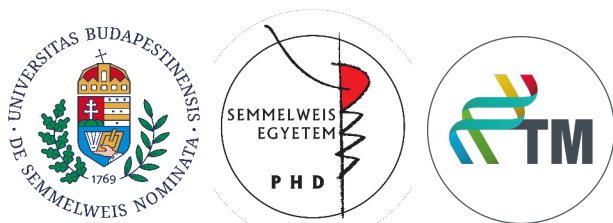
**Ph.D. Thesis Booklet**

**Dorina Greff MD**

Translational Medicine Program

Doctoral School of Theoretical and Translational Medicine

SEMMELWEIS UNIVERSITY



Supervisors: Szabolcs Várbió, M.D., Ph.D., D.Sc.

Mária Eszter Horváth, M.D., Ph.D.

Official reviewers:

Head of the Complex Examination Committee: Zsolt Molnár M.D., Ph.D.

Members of the Complex Examination Committee: Péter Fehérvári, Zoltán Németh M.D., Ph.D., Zoltán Pál M.D., Ph.D., Andrea Párniczky M.D., Ph.D.

Budapest

2024

# **1.Introduction**

## **5.1.1. What is the topic?**

Our main focus is the assessment of the safety and efficacy of inositol administration in polycystic ovary syndrome (PCOS) and in the prevention of gestational diabetes mellitus (GDM) and related complications.

## **5.1.2. What is the problem to solve?**

Metformin, the gold standard treatment for PCOS, often causes mild to severe gastrointestinal side effects, making it difficult for some patients to tolerate. There is a need for alternative treatments, like inositol supplementation, that are effective but have fewer side effects.

Gestational diabetes mellitus leads to serious short- and long-term complications for both mothers and their offspring, including gestational hypertension, neonatal hypoglycemia, and higher risks of obesity, type-2 diabetes, and pancreatic cancer. Current management focuses on treating diagnosed cases rather than preventing GDM. There is a need for generally accepted medical

treatments to prevent GDM, which could significantly improve health outcomes for mothers and their children.

### **5.1.3. What is the importance of the topic?**

According to Hungarian Central Statistical Office (KSH) in Hungary the birth rate declined over the past few years. Several factors contribute to this, including health challenges. Providing effective and well-tolerated treatments for PCOS enhances the quality of life for affected patients. By preventing complications associated with PCOS and GDM, such as diabetes and cardiovascular diseases, we can reduce the economic burden on healthcare systems and society as a whole.

Addressing these conditions contributes to overall public health by improving reproductive health outcomes, reducing the risk of chronic diseases in future generations, and promoting equitable access to healthcare for all individuals.

### **5.1.4. What would be the impact of our research results?**

Providing evidence-based recommendations for alternative treatments to metformin in PCOS management and preventive strategies for GDM. Lowering the burden of these conditions can lead to healthier populations, reduced healthcare costs, and improved societal well-being.

## **2. Objectives**

### **2.1. Study I. – Investigating the safety and efficacy of inositol administration in PCOS**

The purpose of our study included:

1. a systematic review of the available randomized controlled trials (RCTs) concerning the efficacy and safety of inositols in the management of PCOS, while also presenting evidence for the following guidelines in this respect
2. the comparison of inositol supplementation with placebo as well as with the gold standard treatment, i.e., metformin, in women with PCOS.

### **2.2. Study II.-Investigating the preventive effect of inositol administration in GDM**

The goal of our study can be defined as a systematic review of the available randomized controlled trials concerning the effect of different inositols in preventing GDM and its complications.

### **3.Methods**

The systematic reviews and meta-analyses were conducted using the PRISMA 2020 guideline and in accordance with the Cochrane Handbook. The study protocol was registered on PROSPERO (registration numbers: Study I. : CRD42021283275 and Study II. : CRD42021284939).

#### **3.1. Study I. – Investigating the safety and efficacy of inositol administration in PCOS**

The systematic search was conducted in MEDLINE (via PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) from the inception until October 20<sup>th</sup>, 2021. Eligible randomized controlled trials (RCTs) included women diagnosed with PCOS and compared any inositols with metformin or placebo. Ovarian function improvement served as the primary outcome, which was measured by menstrual cycle normalization rates, defined as the number of women with normal menstrual cycle in the study groups. There were several secondary outcomes, relating to pregnancy rates,

i.e., the number of pregnancies occurring in the study groups, carbohydrate metabolism (fasting glucose, fasting insulin, oral glucose tolerance test - OGTT, Homeostatic Model Assessment insulin resistance – HOMA-IR index), body mass index (BMI), clinical and laboratory hyperandrogenism (hirsutism, testosterone, androstenedione, dehydroepiandrosterone-sulfate – DHEAS, sex hormone-binding globulin – SHBG), as well as the side effects resulting from the intervention. Results are reported as risk ratios or mean differences (MDs) with 95% confidence intervals (CIs).

### **3.2. Study II.-Investigating the preventive effect of inositol administration in GDM**

Systematic search was performed in CENTRAL, MEDLINE, and Embase until 13 September 2023. Eligible randomized controlled trials (RCTs) compared the efficacy of inositols to placebo in pregnant women at high risk for GDM. The primary outcome can be defined as the diagnosis of gestational diabetes mellitus in accordance with the diagnostic oral glucose tolerance test (taken not later than the 28<sup>th</sup> gestational week). Due to the

changes and regional differences of OGTT algorithm and glucose concentration thresholds, no study was excluded. Secondary outcomes related to OGTT test results (fasting, 1- and 2-hour post-load plasma glucose concentration), the necessity of treatment with insulin, the presence of preeclampsia and / or gestational hypertension, as well as preterm birth, C-section, gestational age at birth, birth weight, and conditions such as macrosomia, large for gestational age (LGA), intrauterine growth restriction (IUGR), shoulder dystocia, diabetic fetopathy, neonatal hypoglycemia, and neonatal intensive care unit admission. Results are reported as risk ratios or mean differences (MDs) with 95% confidence intervals (CIs).



## **4.Results**

### **4.1. Study I. – Investigating the safety and efficacy of inositol administration in PCOS**

Twenty-six randomized controlled trials were selected for inclusion, reporting on 1691 PCOS patients (806 inositol, 311 with placebo, and 509 metformin groups). In patients treated with inositols, the risk of having a regular menstrual cycle was found by 1.79 higher than in the case of placebo. Moreover, the inositols showed non-inferiority compared to metformin regarding cycle normalization. In the case of BMI (MD= -0.45; CI: -0.89; -0.02), free testosterone (MD=-0.41, CI: -0.69; -0.13), total testosterone (MD= -20.39, CI: -40.12; -0.66), androstenedione (MD= -0.69, CI: -1.16; -0.22), and AUC insulin (MD= -2081.05, CI: -2745.32; -1416.78) inositol treatment induced greater decrease compared to placebo. Inositol supplementation increased sex-hormone-binding globulin significantly compared to placebo (MD=32.06, CI:1.27; 62.85). Compared to metformin SHBG levels was significantly increased due to myoinositol (MD=2.78

nmol/l, CI: 0.02; 5.54). In contrast, metformin decreased FG-score more effectively than inositol (MD= 0.60, CI:0.24-0.96).

### **3.2. Study II.-Investigating the preventive effect of inositol administration in GDM**

Eight eligible RCTs were detected, including the data of 1361 pregnant women. The incidence of GDM was halved by inositol compared to placebo (RR=0.42, CI: 0.26-0.67). Fasting (MD= -0.17, CI: -0.26- -0.09), 1-hour (MD= -0.44, CI: -0.74--0.14), and 2-hour OGTT (MD= -0.37, CI: -0.69- -0.06) glucose levels were significantly decreased by inositol. Myoinositol can also reduce the risk of insulin need (RR=0.29, CI: 0.13-0.68), pregnancy-induced hypertensive disorders (RR=0.38, CI: 0.2-0.71), preterm birth (RR=0.44, CI: 0.22-0.88), and neonatal hypoglycemia (RR=0.12, CI: 0.03-0.55). No significant beneficial effect was observed regarding C-section rate (RR=0.90, CI:0.78-1.03), shoulder dystocia (RR=0.59, CI: 0.12-2.82) birthweight (MD= - 4.83, CI: -96.88- 87.21), and neonatal intensive care unit admission (RR=0.55, CI:0.25-1.2).

## 5. Conclusions

Our study focused on the following questions:

1. On the basis of our results, inositols have a beneficial effect on several outcomes of PCOS. First of all, inositols effectively decrease serum total and free testosterone and androstenedione levels, elevate SHBG levels, and normalize cycle length in comparison with placebo. Furthermore, a significant decrease was found in AUC insulin levels and BMI in the inositol-treated groups. Of the analyzed isomers, myoinositol has the most supported benefit.
2. On the other hand, in almost all the parameters, inositols were not inferior to metformin except two. Compared to metformin, myoinositol caused a significant increase in SHBG levels, while metformin apparently reduced FG-score more effectively than inositol. Finally, inositols caused fewer side effects than metformin.

3. Inositol, especially myoinositol, halves the risk of GDM in high-risk pregnancies. Inositols significantly decreased the fasting, 1-hour, and 2-hour OGTT glucose levels. Moreover, the effects inositols exercised on various GDM-related outcomes were also beneficial. Inositol can reduce the need for insulin treatment as well as decrease the risk of hypertensive disorders, preterm birth and neonatal hypoglycemia.

## 6. Bibliography

-Publications related to the thesis:

-**Dorina Greff**, Anna E. Juhász, Szilárd Váncsa, Alex Váradi, Zoltán Sipos, Julia Szinte, Sunjune Par, Péter Hegyi, Péter Nyirády, Nándor Ács, Szabolcs Várbíró, Eszter M. Horváth: Inositol is an effective and safe treatment in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials **Reprod Biol Endocrinol.** 2023 Jan 26;21(1):10. doi: 10.1186/s12958-023-01055-z.

**D1, IF: 4,2**

- **Dorina Greff**, Szilárd Váncsa, Alex Váradi, Julia Szinte, Sunjune Park, Péter Hegyi, Péter Nyirády, Nándor Ács, Eszter M. Horváth, Szabolcs Várbíró: Myoinositols prevent gestational diabetes mellitus and related complications: a systematic review and meta-analysis of randomized controlled trials. **Nutrients.** 2023 Sep 30;15(19):4224.

**D1, IF: 4,8**