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Preconceptional, gestational and pospartum carbohydrate metabolic disorders

Ph.D. Thesis

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"The future belongs to those who believe in the beauty of their dreams."

Eleanor Roosevelt

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1. LIST OF ABBREVATIONS

PCOS: polycystic ovary syndrome

GDM: gestational diabetes mellitus

RCT: randomized controlled trial

BMI: body mass index

AUC: area under the curve

OGTT: oral glucose tolerance test

DCI: D-chiro-inositol

GLUT4: Glucose transporter type 4

FSH: follicle-stimulating hormone

SHBG: sex hormone binding globulin

IR: insulin resistance

HOMA-IR: Homeostatic Model Assessment insulin resistance

DHEAS: dehydroepiandrosterone-sulfate

PICO: Population, Intervention, Comparator, Outcome

LGA: large for gestational age

IUGR: intrauterine growth restriction

SD: standard deviation

RoB 2: Risk-of-bias tool for randomized trials

MD: mean difference

CI: confidence interval

RR: risk ratio

REML: Restricted maximum likelihood

GRADE: Grades of Recommendation, Assessment, Development, and Evaluation

Cycle norm.: cycle normalization

TT: total testosterone

FT: free testosterone

A: androstenedione

FG-score: Ferriman-Gallwey score

mFG-score: modified Ferriman- Gallwey score

AUC-Glu: Area under the curve- glucose

AUC-ins: Area under the curve – insulin

MYO: myoinositol

FPG: fasting plasma glucose

FPI: fasting plasma insulin

Glu/ins ratio: glucose / insulin ratio

MI: myoinositol

IADPSG: International Association of Diabetes and Pregnancy Study Groups

T2DM: type-2 diabetes mellitus

1h-OGTT: one-hour glucose tolerance test

2h-OGTT: two-hour glucose tolerance test

NICU: neonatal intensive care unit

PIP2: inositol triphosphate

G6P: glucose-6-phosphate

IP3: Inositol triphosphate

DHEA: dehydroepiandrosterone

IVF: in vitro fertilization

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2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to increase fertility and complication-free pregnancy rates, to lead families to experience the joy of parenthood with the highest levels of health and wellbeing.

My mission is to pioneer innovative prevention strategies and deepen our understanding of carbohydrate metabolism to improve reproductive health.

My specific goals include the investigation the preventive and therapeutic effects of inositol administration in polycystic ovary syndrome (PCOS) and gestational diabetes mellitus (GDM).

2.2. Scientometrics

Number of all publications:	3
Cumulative IF:	15.5
Av IF/publication:	5.16
Ranking (SCImago):	D1: 3
Number of publications related to the subject of the thesis:	2
Cumulative IF:	9
Av IF/publication:	4.5
Ranking (SCImago):	D1: 2
Number of citations on Google Scholar:	61
Number of citations on MTMT:	46
H-index:	2

2.3. Future plans

My future plans include expanding research on inositols to determine the optimal doses, long-term effects, and potential benefits in diverse populations. Additionally, I plan to investigate the role of carbohydrate metabolism in reproductive health, with the goal of identifying new therapeutic targets for improving fertility and reducing pregnancy complications. Finally, I aim to develop nutritional and lifestyle intervention programs that support healthy carbohydrate metabolism, enhance fertility, and reduce the risk of pregnancy complications.

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3. SUMMARY OF THE PH.D.

Inositol, a naturally occurring sugar alcohol, has gained significant attention in reproductive medicine due to its potential therapeutic effects on various aspects of polycystic ovary syndrome (PCOS) and its associated complications, including gestational diabetes mellitus (GDM).

Two meta-analyses were conducted with the purpose of evaluating the safety and efficacy of inositol administration in PCOS and in the prevention of GDM and related complications. To meet the eligibility criteria, randomized controlled trials (RCTs) were required to focus on the comparison of any inositol with metformin or placebo in the treatment of patients with a diagnosis of PCOS, on the one hand; and on the efficacy of inositol compared to that of a placebo in pregnant patients with a high risk of gestational diabetes mellitus, on the other hand.

Results indicate that inositol treatment increased the chance of a regular menstrual cycle by 1.79 when compared to a placebo. In addition, inositol, in this regard, displayed non-inferiority to metformin. With regard to BMI, levels of free testosterone, total testosterone, androstenedione as well as AUC insulin, a more significant reduction was achieved with inositol treatment than in the case of a placebo. Inositol caused a considerably higher increase in sex-hormone-binding globulin than the placebo. Regarding GDM, incidence rates significantly dropped (halved) in patients treated with inositol in comparison with those receiving a placebo. More specifically, a significant decrease was observed in fasting, 1-hour, and 2-hour OGTT glucose levels due to inositol. Myoinositol can also reduce the need for insulin, the risk of preterm birth, gestational hypertension and neonatal hypoglycemia. No significant beneficial effect was observed regarding C-section rate, shoulder dystocia, birthweight, or neonatal intensive care unit admission. PCOS can safely and effectively be managed with inositol. Myoinositol can be used to reduce the incidence of GDM in high-risk pregnancies. Furthermore, myoinositol supplementation decreases the risk of insulin need, gestational hypertension, preterm birth, and neonatal hypoglycemia as well.

Preventing GDM and effectively managing PCOS can lower the risk of complications for both mothers and their offspring, leading to better pregnancy outcomes and long-term health outcomes for the whole family.

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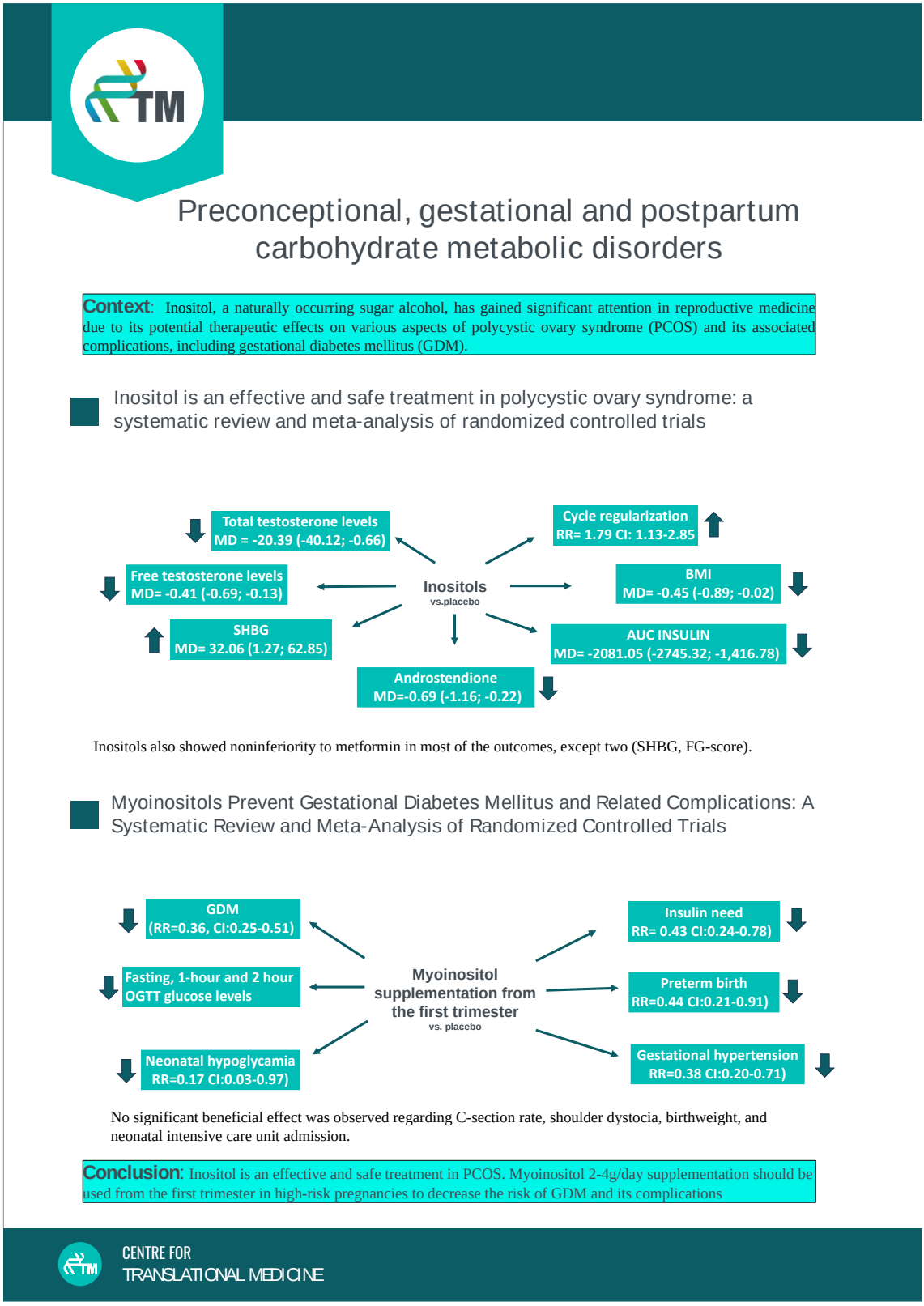
4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

Our main focus is the assessment of the safety and efficacy of inositol administration in PCOS and in the prevention of 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 (1-4). There is a need for alternative treatments, like inositol supplementation, that are effective but have fewer side effects (5-9).

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 (10-12). 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 (13).

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 (14). 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 (15, 16).

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 (15, 16).

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.

5.2. Inositol

Inositols are cyclic polyols which can be synthesized by the human body and are also naturally found in foods such as fruits, vegetables, whole grains and nuts (17, 18). They have nine stereoisomers, including myoinositol and D-chiro-inositol (DCI) as the most important ones (19, 20). Since inositol modulates the members of insulin signaling pathways, they are regarded as insulin sensitizers (21). Inositol administration can have a beneficial effect on insulin resistance through the stimulation of the translocation of GLUT4 to the plasma membrane, thereby resulting in higher glucose uptake (22). Inositol, especially myoinositol, plays a role in FSH-mediated pathways affecting the proliferation and maturation of granulosa cells (19). It is suggested that myoinositol also promotes aromatase synthesis in granulosa cells, consequently reducing androgen production (21). Inositol improves carbohydrate metabolism, the regularity of the menstrual cycle as well as the clinical and laboratory symptoms of hyperandrogenism, such as free testosterone, total testosterone, SHBG (23). Nevertheless, so far there has been no satisfactory evidence to justify their inclusion in the guidelines as standard treatment (2).

5.3. Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is known as the most frequently occurring endocrine disorder as well as a common cause of infertility in women (24), which affects about 5 to 20% of women of reproductive age (24, 25). Since the symptoms of PCOS are highly variable, establishing the diagnosis can be difficult (26). In accordance with the latest clinical guidelines, the diagnosis of polycystic ovary syndrome is based on the Rotterdam criteria, requiring the presence of at least two of the following three diagnostic criteria: ovulatory dysfunction, hyperandrogenism, and polycystic ovary morphology (2).

The pathogenesis of the syndrome is, to some extent, still unclear. It has been established, however, that insulin resistance (IR) plays a central role in it (21, 27, 28). As indicated by a cross-sectional study, 75% of normal-weight women as well as 95% of overweight women with PCOS have insulin resistance (29). At the same time, 60-70% of PCOS patients are overweight (30). Insulin resistance is also more severe in patients who are

obese (28). IR and compensatory hyperinsulinemia may result, directly or indirectly, in menstrual cycle irregularities and hyperandrogenism. Elevated levels of insulin lead to a decrease in the sex hormone binding globulin (SHBG) production of the liver. Lower SHBG levels, in turn, increase the free testosterone levels, exacerbating the signs and symptoms of hyperandrogenism. Moreover, hyperinsulinemia contributes to the androgen overproduction of ovarian theca cells (1).

Long-term consequences of untreated PCOS include an increased risk of type 2 diabetes, increased prevalence of metabolic syndrome and fertility problems (31, 32). If pregnancy occurs in PCOS, numerous complications can still arise during pregnancy, such as gestational diabetes, gestational hypertension, preeclampsia, etc. (33).

5.4. Gestational Diabetes Mellitus (GDM)

Gestational diabetes mellitus (GDM) is one of the health conditions that most frequently affect pregnant women. It is defined as a form of glucose intolerance newly diagnosed in the pregnant patient (34). The prevalence of GDM is highly variable depending on the applied diagnostic criteria and population, but globally the prevalence is around 14-16% (35-37). In healthy pregnancy, endocrinological changes induce the development of insulin resistance, causing hyperinsulinemia. In the case of insufficient β-cell function, the pregnancy-associated chronic insulin resistance results in GDM (38). Preventing GDM has long-term benefits for both the mother and the child; therefore, it would be advisable to place it in the focus of pregnancy care. Recently, there have been numerous studies focusing on GDM prevention by means of the beneficial properties of vitamin D, probiotics, zinc, dietary fiber as well as lifestyle changes (37, 39, 40). Despite these efforts, with regard to prevention programs, no real breakthrough has occurred. Inositol administration in early pregnancy may offer an innovative, new way of GDM prevention strategies.

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6. OBJECTIVES

6.1. Study I. – Investigating the safety and efficacy of inositol administration in PCOS

The purpose of our study was to conduct 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 to support the relevant guidelines. Additionally, we aimed to compare inositol supplementation with both placebo and the gold standard treatment, metformin, in women with PCOS.

6.2. 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 (RCTs) concerning the effect of different inositols in preventing GDM and its complications.

7. METHODS

The systematic reviews and meta-analyses were conducted using the PRISMA 2020 guideline (41) and in accordance with the Cochrane Handbook (42). The study protocols were registered on PROSPERO (registration numbers: Study I.: CRD42021283275 and Study II.: CRD42021284939).

7.1. Eligibility criteria

7.1.1. Study I.- Investigating the safety and efficacy of inositol administration in PCOS

RCTs that met the inclusion criteria investigated the safety and the efficacy of various inositols comparing them to those of either metformin or placebo in patients diagnosed with polycystic ovary syndrome. There were no restrictions on age. The diagnosis of PCOS had to be based on the Rotterdam criteria in eligible studies (43), as a basic rule; but studies with no specific mention of the Rotterdam criteria were also selected provided they included the PCOS diagnosis based on diagnostic criteria corresponding to the Rotterdam criteria. The interventions included either any inositol in monotherapy or inositol combined with dietary supplements or with aromatase inhibitors, irrespective of treatment duration or dosage. Comparators included placebo (C1) or metformin (C2) in monotherapy; or placebo or metformin in combination (C3) with dietary supplements or with aromatase inhibitors.

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, SHBG), as well as the side effects resulting from the intervention.

The exclusion criteria were as follows: (1) case reports and case-control, cohort, cross-sectional studies, as well as reviews and animal studies, (2) studies where inositol and metformin interventions were combined, and (3) studies focusing on pregnant women.

7.1.2. Study II.- Investigating the preventive effect of inositol administration in GDM

The PICO framework was the following: Treatment with inositol supplementation was compared (I) with placebo (C) in pregnant women (P) with the purpose of preventing GDM or other GDM-related outcomes (O) by means of eligible randomized controlled trials (RCTs). No prior exclusion criteria relating to the pregnant women or to the applied inositol treatment were specified. Eligible inositol treatments included myoinositol and/or D-chiro inositol, either as monotherapy or combined with other dietary supplements. Comparators included no treatment or a placebo (e.g., dietary supplements, etc.).

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 28th gestational week). No studies were excluded on the basis of the diagnostic methods since there are significant changes and regional differences in algorithms of OGTT and thresholds of glucose concentration.

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.

With regard to study type, in the current research only RCTs have been examined; therefore, we excluded non-randomized interventional studies, reviews, cohorts, case reports, case-controls, as well as case series.

7.2. Sources of information and search strategies

The systematic search was conducted in MEDLINE (via PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) from the inception until October 20th, 2021, in the case of the PCOS study and until December 15th, 2022, in the case of the GDM study. Furthermore, we also checked the reference lists of the studies to identify further eligible randomized controlled trials.

The systematic search was performed using the predefined search keys listed below:

I. (PCOS OR PCOD OR polycystic ovar* disease OR "polycystic ovary syndrome" OR polycystic ovar* syndrom*) AND (inositol OR inositols OR metformin OR myoinositol OR chiroinositol)
II. ("gestational diabetes" OR GDM OR "gestational diabetic" OR "gestational diabetes mellitus" OR pregnancy OR LGA OR macrosomia OR "large for gestational age") AND (inositol* OR myoinositol OR chiroinositol OR DCI)

The search did not involve the use of filters or language restrictions.

7.3. Selection process

In case of both the systematic review and the meta-analysis, publications were chosen by two independent review authors applying the EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) reference manager program. The screening method first concentrated on the titles and the abstracts of the articles, after which the entire text was reviewed, using the eligibility criteria. Any controversial issues arising in the course of the selection were decided by a further independent review author.

7.4. Data items and the process of data collection

Two independent review authors collected data from the eligible articles on a standardized data collection sheet which had been prepared in accordance with the consensus of clinical and methodological experts.

The extracted data included: title, first author, year of publication, countries, number of centers, study design, main study findings, patient demographics, inclusion and exclusion criteria, details regarding the PICO (population, intervention, comparator, outcome), and the event rates or the means of outcomes in the studied cohorts.

For continuous variables, baseline and after treatment mean and standard deviation (SD) values were extracted, and, in the case of missing SD p-values from paired t-test were collected as well. For dichotomous data, events for the outcomes and total numbers of patients were used on both arms.

7.5. Study risk of bias assessment

We evaluated the risk of bias on the basis of the Cochrane Collaboration’s recommendations, applying the Cochrane risk-of-bias tool for randomized trials (RoB 2) (44). Any controversial issues arising between the two data extractors were decided with

the involvement of a further reviewer. There were five main domains in which bias was assessed, including the process of randomization, any deviations from the intended interventions detected, outcome measurement, missing data regarding the outcome, the selection process of the findings presented.

7.6. Synthesis methods

7.6.1. Study I. Investigating the safety and efficacy of inositol administration in PCOS

An analysis of the effect of inositol interventions in comparison with placebo or metformin treatments was carried out. Subgroup analysis was also conducted, whenever it was possible, on the basis of various inositol isomers and their combinations (i.e., D-chiro-inositol, myoinositol, or their combination).

The presentation of the continuous results was performed by calculating mean differences (MD) with 95% confidence intervals (CIs) for continuous variables from the changes between the baseline value and the after-treatment value. Due to the missing correlation of before and after values, we assumed a 0 correlation when calculating the SD of change. With regard to missing SD and presence of p-value, the Cochrane handbook recommendations were observed (45). In order to pool MDs, we used the random-effects model with the inverse variance method; while the restricted maximum-likelihood method was applied to estimate variance measure τ^2 (46). In the case of dichotomous categorical outcomes, pooled risk ratios (RRs) were calculated with 95% CIs using the random-effects model with the Mantel-Haenszel method, whereas in order to obtain τ^2, the Paule-Mandel estimator was applied (47).

In each model, a p-value that was lower than 0.05 was regarded as statistically significant. Statistical heterogeneity was evaluated by means of the I^2 statistics and the Cochran Q test, where significant heterogeneity is indicated by $p<0.1$. Where applicable, the prediction intervals (i.e., the expected range of effects of future studies) of the findings were presented in accordance with the recommendations of IntHout et al (48). Forest plots were applied for the graphical representation of all results. To pool MDs, metacont was used, and for RR metabin functions from the meta R package v. 5.5-0 (49). Statistical calculations were invariably conducted by means of the R language (50).

7.6.2. Study II. – Investigating the preventive effect of inositol administration in GDM

When the identified studies were deemed adequately homogenous on the basis of the PICO, we conducted both qualitative and quantitative data synthesis. In order to carry out a meta-analysis, at least three studies were required.

We performed all statistical calculations by means of the R programming language (R Core Team, 2022, Vienna, Austria, R v4.2.1) using the meta v6.0-0, metafor v3.8-1 and dmetar v0.0.9000 packages (51-53). The presentation of quantitative results was performed by calculating mean differences (MD) with 95% confidence intervals (CIs) for continuous variables. For dichotomous outcomes, risk ratios (RRs) were calculated with 95% CIs. All analyses were conducted with the application of the random-effects models and illustrated by forest plots. In order to pool binary outcome data, for instance preterm birth, we used the Mantel-Haenszel method with the Paule-Mandel method to estimate the between-study variance (47, 54, 55). However, in the case of continuous outcomes, such as birth weight, we applied Restricted maximum likelihood methods (REML) in order to estimate the between-study variance and inverse variance for weighting (56). A $p<0.05$ value was regarded as statistically significant. When applicable, prediction intervals of the pooled estimates were also presented (57).

We tested statistical heterogeneity using the I^2 statistics and the Cochrane Q test; with $p<0.1$ indicating significant heterogeneity. However, the evaluation of publication bias was not possible since the number of studies was not high enough.

Subgroup analysis based on inositol stereoisomers was also carried out.

7.5. Evaluation of the level of evidence

In order to assess the quality of the evidence, we complied with the recommendations of the "Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)" workgroup (58).

8. RESULTS

8.1. Study I. - Investigating the safety and efficacy of inositol administration in PCOS

8.1.1. Search and selection

As shown in **Figure 1**, out of a total of 4676 records, 26 randomized controlled trials were selected for inclusion, reporting on 1691 PCOS patients. The quantitative synthesis covered twenty-four studies (5-9, 59-77), while two studies were excluded from the meta-analysis since the data reporting was not appropriate (78, 79).

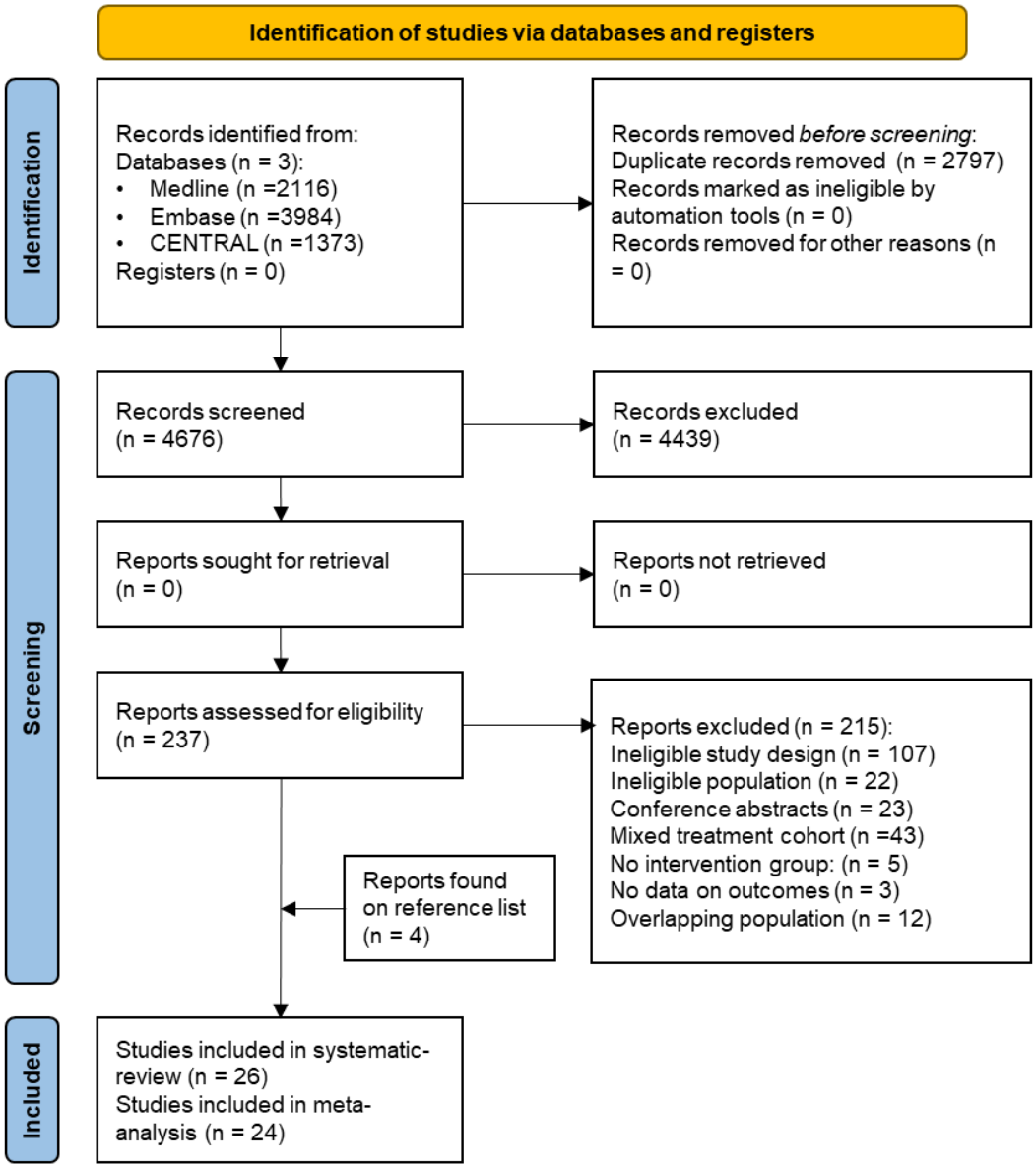

Figure 1. PRISMA 2020 flowchart representing the study selection process (80).

8.1.2. Basic characteristics of the included studies

Table 1 represents baseline characteristics of the studies included in the analysis. Most women participating in the studies were in their 30s and had a mean body mass index below 30 kg/m2. There were two studies, however, where BMI served as an inclusion criterion, i.e., only obese and overweight PCOS patients participated (71, 79). The details of the inclusion and exclusion criteria of the analyzed studies can be found in the supplementary material of the original publication, together with further data on the intervention described by each study as well as on the corresponding control group. Only studies that reported on interventions applying either myoinositol or D-chiro-inositol were eligible, but the dosage and the duration of the administration varied from study to study. There was one RCT that used combinations of myoinositol and inositol and compared them to dietary intervention (8). We also included a single three-arm trial that compared myoinositol to metformin and placebo (72).

Table 1. Basic characteristics of the included studies (80).

Study (year)	**Country**	**Study period**	**Population (I/C) ***	**Age[1]**	**BMI[1]**	**Intervention**	**Control**	**Outcomes**
Angik, 2015 (74)	India	09.2012-08.2014	50/50	NR	23.7	MI 1000mg 24w	MET 1000mg	cycle norm., BMI, pregnancy rate, FPI, FPG, HOMA, TT, m-FG score, side effect
Benelli, 2016 (59)	Italy	NR	21/25	24.1	31.5	MI (1100mg) +DCI (27,6 mg) 24w	FA 400mcg	BMI, FPI, FPG, HOMA index, FT, SHBG, DHEAS, A, side effect
Brusco, 2013 (60)	Italy	06.2012-05.2013	58/91	NR	NR	MI (2000mg) +DCI (400mg) 12w	FA 400mcg	pregnancy rate
Chirania, 2017 (75)	India	08.2015-07.2016	26/28	23.8	25.1	MI 1000mg 16w	MET 1000mg	cycle. norm., BMI, pregnancy rate, FPI
Chhabra, 2018 (61)	India	NR	31/32	29.7	NR	MI 4000mg 12w	MET 1700mg	cycle norm., m-FG score, acne
Costantino, 2009 (62)	Italy and France	NR	23/19	28.3	22.7	MI 4000mg 12-16w	FA 400 mcg	BMI, FPI, FPG, AUC-glu, AUC-ins, TT, FT, SHBG, DHEAS, A
Doná, 2012 (63)	Italy	NR	18/8	23.5	21.7	MI 1200mg 12w	Placebo powder	BMI, FPI, FPG, AUC-ins, AUC-glu, HOMA, TT, A

Donne, 2019 (8)	Italy	11.2015-06.2016	22/21	26.7	32	1. MI 4000mg 24w 2. MI 1100mg +DCI 27,6mg 24w	diet	cycle norm., BMI, FG-score
Fruzetti, 2016 (64)	Italy	2014-2015	24/22	21.9	27.8	MI 4000mg 24w	MET 1500mg	BMI, HOMA, AUC-ins, A, hirsutism, acne
Genazzani, 2008 (65)	Italy	NR	10/10	NR	28.4	MI 2000mg 12w	FA 200mcg	BMI, FPI, HOMA, glu/ins ratio, TT, A, FG-score
Gerli, 2007 (66)	Italy	NR	45/47	29.4	34.4	MI 4000mg 14w	FA 400mcg	BMI, pregnancy rate, FPI, FPG, AUC-ins,
H.Jamiliam, 2017 (68)	Iran	06.2016-12.2016	30/30	28.1	27.9	MI 4000mg 12w	MET 1500mg	BMI
Iuorno, 2002 (67)	Venezuela	NR	10/10	27.4	24.5	DCI 600mg 7w	NR	BMI, FPI, FPG, AUC-glu, AUC-ins, TT, FT, SHBG, DHEAS, A, side effect
Leo, 2013[2] (78)	Italy	NR	20/20	NR	27,5	MI 3000mg 24w	MET 1700mg	BMI, FPI, FPG, HOMA, TT, FT, SHBG, A, FG-score
M.Jamiliam, 2017 (69)	Iran	11.2016-02.2017	30/30	26.8	26.5	MI 4000mg 12w	MET 1500mg	BMI, TT, SHBG, mFG-score
Nehra, 2017(70)	India	NR	30/30	23.5	26.3	MI 2000mg 24w	MET 1500mg	BMI

Nehra J., 2017 (9)	India	NR	30/30	23.5	26.3	MI 2000mg 24w	MET 1500mg	FPI, FPG, Glu/ins ratio, HOMA, TT
Nestler, 1999 (71)	Venezuela	NR	22/22	27.5	31.2	DCI 1200mg 7w	Placebo	BMI, AUC-glu, AUC-ins, TT, FT, SHBG, DHEAS, A, side effect, presence of ovulation
Pourghasem, 2018 (72)	Iran	2015-2016	50/50/50	30.9	28.3	MI 4000mg 12w	1.MET 1500mg 2.FA 400mcg	cycle norm., pregnancy rate, side effect
Shokrpour, 2021 (7)	Iran	09.2017-12.2017	26/27	28	27.7	MI 4000mg 12w	MET 1500mg	BMI, FPG, Insulin, HOMA
Raffone, 2010 (77)	Italy	06.2006-06.2008	60/60	29.4	25	MI 4000mg 24w	MET 1500mg	cycle norm., pregnancy rate
Rajasekaran, 2021 (6)	India	05.2018-03.2020	50/50	30.5	26.5	MI 4000mg 12w	MET 1700mg	cycle norm., BMI, pregnancy rate, FPI, FPG, HOMA, TT, SHBG, side effect
Schihalli, 2012 (73)	Italy	01.2010-09.2010	9/8	30.6	NR	MI 4000mg NR w	FA 400mcg	pregnancy rate
Shokrpour, 2021 (7)	Iran	09.2017-12.2017	26/27	28	27.7	MI 4000mg 12w	MET 1500mg	BMI, FPG, Insulin, HOMA
Singh, 2020 (76)	India	04.2013-08.2014	66/66	NR	31.8	MI 4000mg 12w	FA 500mcg	BMI, FPI, FPG, TT

Soldat-Stankovic, 2021 (5)	Bosnia-Herzegovina	11.2017-05.2019	30/30	NR	26.1	MI 4000mg 24w	MET 1500mg	BMI, FPI, FPG, AUC-glu, AUC-ins, HOMA, TT, SHBG, DHEAS, FG-score,side effect
Tagliaferri, 2017[2] (79)	Italy	NR	14/20	25.6	32.6	MI 1000mg 24w	MET 1700mg	BMI, pregnancy rate, AUC-ins, AUC-glu, TT, SHBG, DHEAS, A, FG-score, side effect,

[1]Age (years) and BMI (kg/m2) are expressed in mean. [2] studies included only in the systematic review part

*I/C intervention/ control

MI: myoinositol, MET: metformin, NR: not reported. Cycle norm.: cycle normalization; TT: total testosterone; FT: free testosterone; SHBG: sex-hormone binding globulin; A: androstenedione; DHEAS: dehydroepiandrosteron- sulfate; FG-score: Ferriman-Gallwey score; mFG-score: modified Ferriman- Gallwey score; AUC-Glu: Area under the curve- glucose; AUC-ins: Area under the curve – insulin; FPG: fasting plasma glucose; FPI: fasting plasma insulin; Glu/ins ratio: glucose / insulin ratio.

8.1.3. Synthesis of the results

8.1.3.1. The normalization of the ovarian cycle and increased weight loss resulting from inositol supplementation

The findings of the pooled analysis are detailed in **Table 2 and 3**. Two eligible studies report that cycle normalization has a higher rate in the inositol-treated group than in the placebo group (RR=1.79, CI: 1.13; 2.85, **Figure 2.**).

The pooled analysis based on eight randomized controlled trials indicates that body mass index was more effectively reduced in the inositol-treated group than in the placebo group (MD=-0.45 kg/m^2, CI: -0.89; -0.02, **Figure 3.**). In this respect, especially myoinositol appears to be highly beneficial (MD=-0.71 kg/m^2 (CI: -1.00; -0.43 kg/m^2, **Figure 3**.).

The efficacy of myoinositol is comparable to that of metformin with regard to both ovarian cycle normalization (RR=1.42 CI: 0.8; 2.53, **Figure 2)** and BMI reduction (MD=-0,11kg/m2, CI: -0.25; 0.04, **Table 3.**).

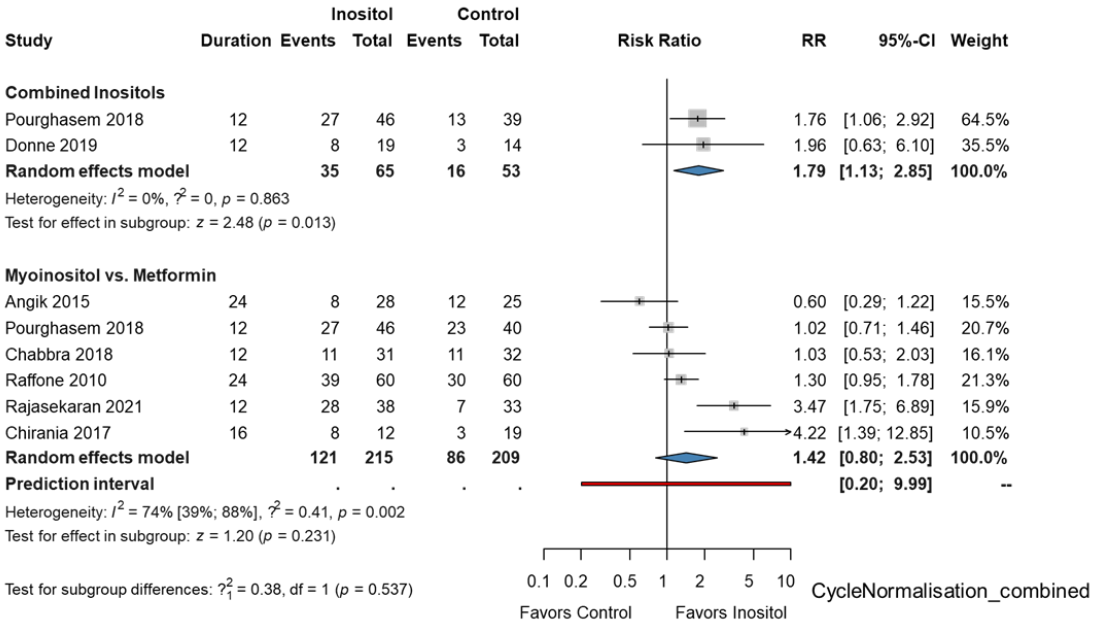

Figure 2. Forest plots illustrating the rate of ovarian cycle normalization in patients receiving inositol treatment in comparison with placebo or metformin intervention (80).

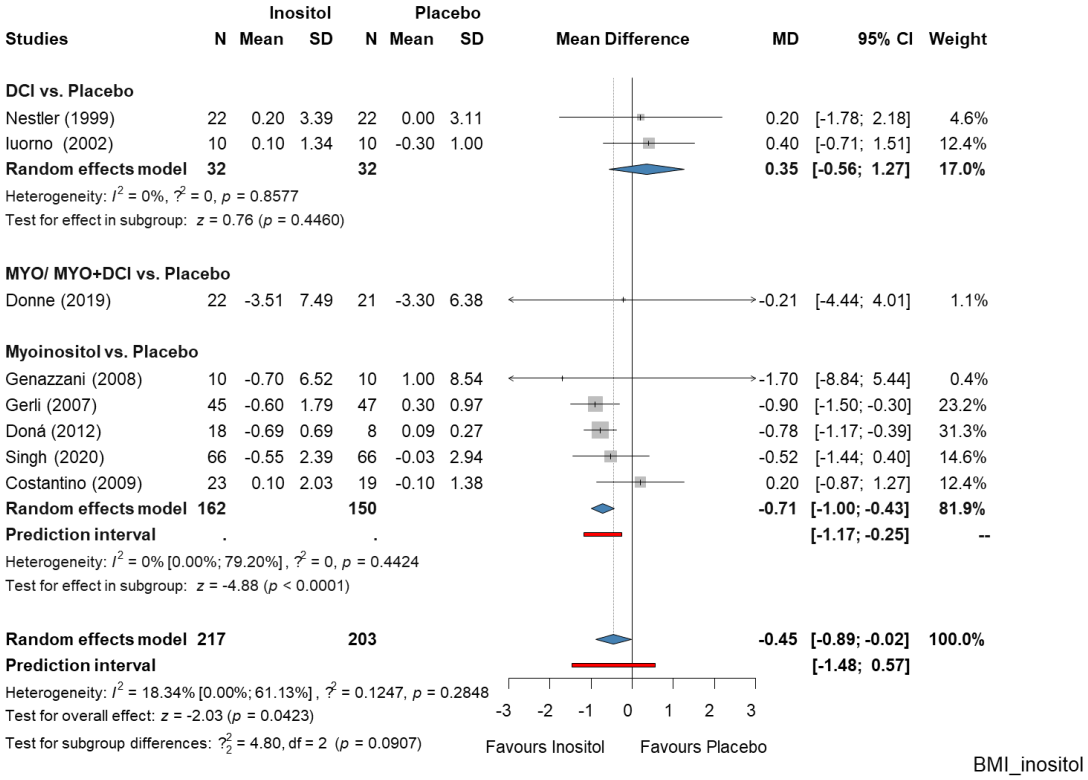

Figure 3. Forest plots summarizing the mean difference of weight loss in the groups treated with different inositol stereoisomers in comparison with placebo (80).

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Table 2. Summary of studies comparing inositol stereoisomers to placebo (80).

Outcomes	**Inositol vs Placebo**			**Myoinositol vs Placebo**			**DCI vs Placebo**			**Inositol combination vs Placebo**		
	N^0 of studies (N^0 of pts)	**RR/ MD (95% CI)**	**GRADE**	**N^0 of studies (N^0 of pts)**	**RR/ MD (95% CI)**	**GRADE**	**N^0 of studies (N^0 of pts)**	**RR/ MD (95% CI)**	**GRADE**	**N^0 of studies (N^0 of pts)**	**RR/ MD (95% CI)**	**GRADE**
Total testosterone (ng/dl)	**6 (284)**	**-20.39 (-40.12; -0.66)**	**moderate**	4 (220)	-11.38 (-29.48; 6.72)	moderate	**2 (64)**	**-41.71 (-70.09; -13.34)**	**high**	-	-	-
Free testosterone (ng/dl)	**4 (152)**	**-0.41 (-0.69; -0.13)**	**moderate**	1 (42)	-0.57 (-1; -0.14)	high	**2 (64)**	**-0.58 (-0.89; -0.28)**	**high**	1 (46)	-0.12 (-0.28; 0.04)	low
SHBG (nmol/L)	**4(152)**	**32.06 (1.27; 62.85)**	**moderate**	1 (42)	37.6 (-43.97; 119.17)	moderate	**2(64)**	**55.45 (25.99; 84.91)**	**high**	1 (46)	10.82 (-1.7; 23.34)	moderate
Androstenedione (ng/ml)	**6 (198)**	**-0.69 (-1.16; -0.22)**	**moderate**	**3 (88)**	**-0.89 (-1.56; -0.22)**	**very low**	**2 (64)**	**-0.52 (-1.13; -0.09)**	**low**	1 (46)	0.12 (-1.3; 1.54)	low
DHEAS (µg/dl)	4 (152)	-92.54 (-206.31; 21.22)	low	1 (42)	-114 (-294.53; 66.53)	high	**2 (64)**	**-168.48 (-281.15; -55.82)**	**moderate**	1 (46)	42.4 (-89.68; 174.48)	low

Ferriman-Gallwey score	1(43)	-1.23 (-5.37; 2.92)	low	-	-	-	-	-	-	1 (43) †	-1.23 (-5.37; 2.92)†	low†
AUC Glucose (mg/dl/min)	4 (132)	-763.3 (-1925.05; 398.45)	moderate	2 (68)	-550.98 (-2182.91; 1080.95)	low	2 (64)	-1502.41 (-3406.31; 401.48)	low	-	-	-
AUC insulin (µU/ml/min)	**4 (132)**	**-2081.05 (-2745.32; -1,416.78)**	**high**	**2 (68)**	**-2034.05 (-2706.3; -1361.81)**	**high**	2 (64)	-4027.17 (-8352.7; 298.33)	moderate	-	-	-
BMI (kg/m2)	**8 (419)**	**-0.45 (-0.89; -0.02)**	**high**	**5 (312)**	**-0.71 (-1.00; -0.43)**	**high**	2 (64)	0.35 (-0.56; 1.27)	low	1 (43) †	-0.21 (-4.44; 4.01) †	low†
cycle normalization	**2 (118)**	**1.79 (1.13; 2.85)**	**very low**	1(85)	1.76 (1.06; 2.92)	moderate	-	-	-	1 (33) †	1.96 (0.63; 6.1) †	low†
pregnancy rate	4 (308)	1.24 (0.85; 1.81)	very low	3 (159)	0.92 (0.53; 1.61)	very low	-	-	-	1 (149)	1.45 (1.06; 1.98)	low
pregnancy rate (no other treatment)	1 (42)	3.3 (0.4; 27.13)	low	1 (42)	3.3 (0.4; 27.13)	very low	-	-	-	-	--	-

† means MI and MI+DCI treated group is pooled into one group (8)

Numbers referring to significant results have been bolded.

Table 3. Summary of studies comparing myoinositol treatment to metformin (80).

Outcomes	**Inositol vs Metformin**		
	N^0 of studies (N^0 of pts)	**RR/ MD (95% CI)**	**GRADE**
Total testosterone (ng/dl)	4 (320)	0.2 (-5.72; 6.12)	moderate
Free testosterone(ng/dl)	-	-	-
SHBG (nmol/L)	**3 (220)**	**2.78 (0.02; 5.54)**	**moderate**
Androstenedione (ng/ml)	-	-	-
DHEAS (μg/dl)	1 (60)	17.31 (-17.84; 52.46)	low
Ferriman-Gallwey score	**3 (220)**	**0.6 (0.24; 0.96)**	**high**
AUC Glucose (mg/dl/min)	1 (60)	1218.76 (-812.79; 3250.3)	moderate
AUC insulin (μU/ml/min)	1 (60)	1593.71 (-2802.06; 5989.5)	moderate
BMI (kg/m2)	9 (593)	-0,11 (-0.25; 0.04)	high
cycle normalisation	6 (424)	1.42 (0.8; 2.53)	very low
pregnancy rate	5 (383)	1.22 (0.84; 1.78)	very low
pregnancy rate (no other treatment)	3 (183)	1.38 (0.88; 2.15)	very low

Numbers referring to significant results have been bolded.

8.1.3.2. Androgens in PCOS

Total testosterone levels showed significant reductions as a result of inositol interventions in comparison with placebo (MD=-20.39 ng/dl, CI: -40.12; -0.66, **Figure 4.**). At the same time, free testosterone levels became significantly lower due to treatment with inositol when compared to the placebo (MD=-0.41 ng/dl, CI: -0.69; -0.13, **Figure 5.**). As another result of inositol treatment, SHBG levels rose considerably (MD=32.06 nmol/l, CI: 1.27; 62.85, **Figure 6.**). A significant reduction in androstenedione levels was observable as well, following treatment with inositol (MD=-0.69 ng/ml, CI: -1.16; -0.22, **Figure 7.**).

The positive effect of myoinositol on androstenedione can also be observed when compared to a placebo (MD=0.89 ng/ml, CI: -1.56; -0.22, **Figure 7.**). DCI decreased DHEAS levels (MD=-168.48 µg/dl, CI-281.15; -55.82, **Figure 8**.). On the other hand, the combined analysis of various inositols did not reach the level of significance. Finally, there was only one study reporting on the effect that inositol had on the FG-score (**Figure 9.**) (8). SHBG levels demonstrated a significantly higher increase due to myoinositol than in the case of metformin treatment (MD=2.78 nmol/l, CI: 0.02; 5.54, **Figure 6.**). Nevertheless, metformin decreased FG-score more effectively (MD=0.6, CI: 0.24; 0.96, **Figure 9.**) than inositol. With regard to total testosterone levels, inositol proved to be non-inferior when compared to metformin (**Table 3.**). It should be mentioned that only one RCT investigating DHEAS was detected, while there were no studies making a comparison between inositol and metformin interventions regarding the levels of free testosterone and androstenedione (5).

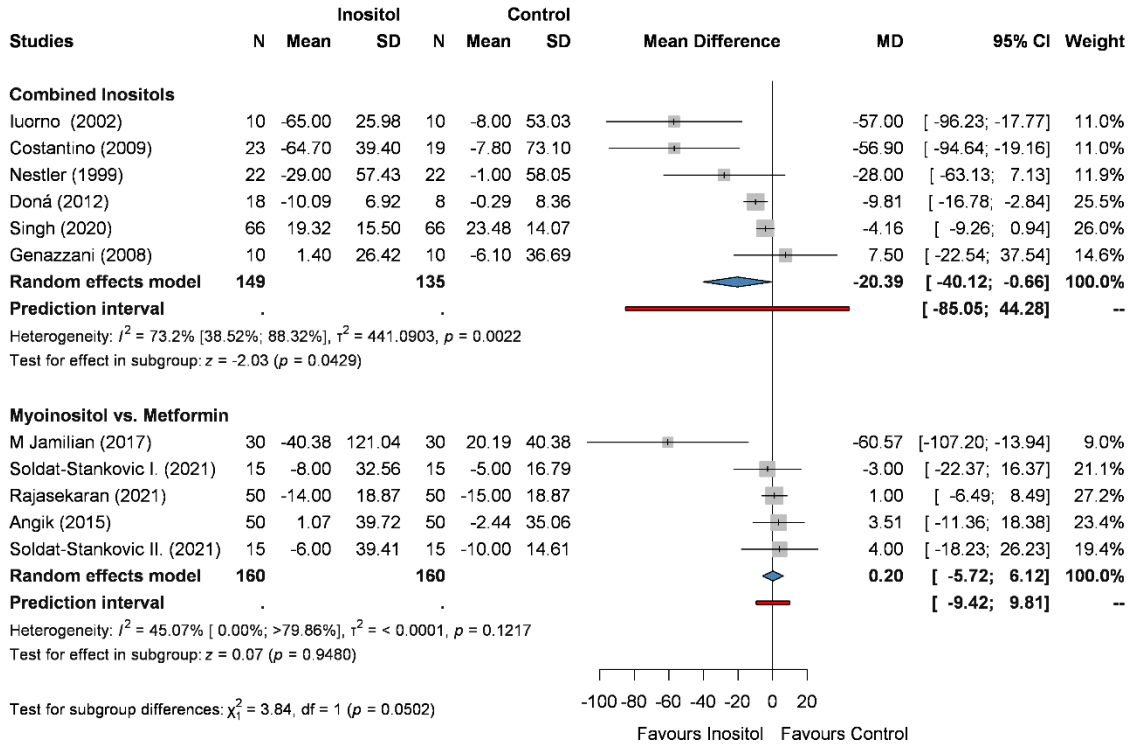

Figure 4. Forest plots representing the mean difference of total testosterone levels in the inositol-treated groups as compared to placebo or metformin (80). Soldat-Stankovic I. (2021) : BMI < 25kg/m2 ; Soldat-Stankovic II. (2021): BMI > 25kg/m2 .

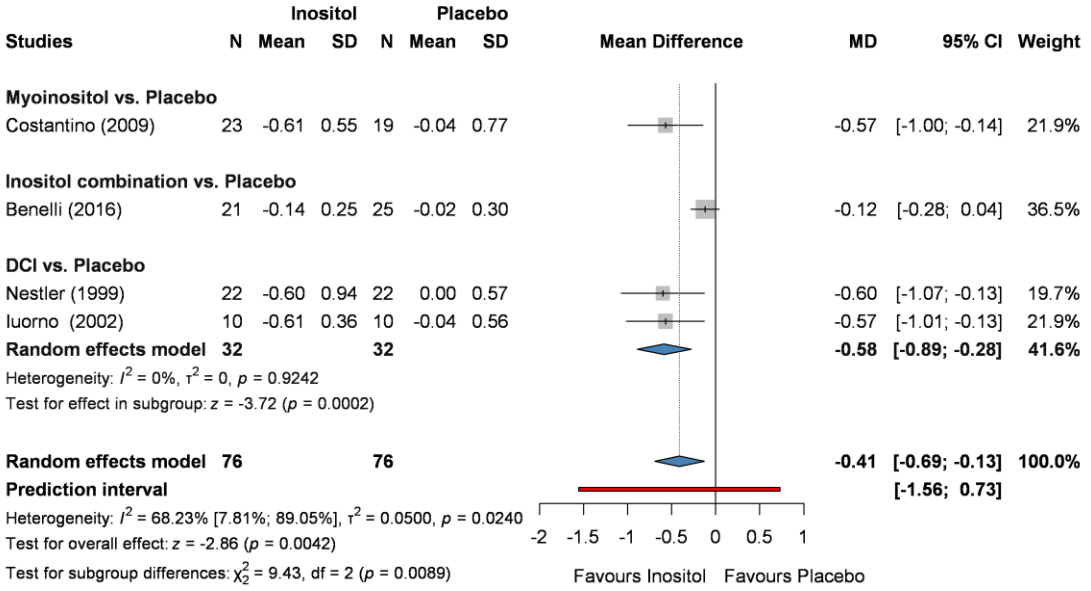

Figure 5. Forest plots presenting the mean difference of free testosterone levels in the groups treated with inositols compared to placebo (80).

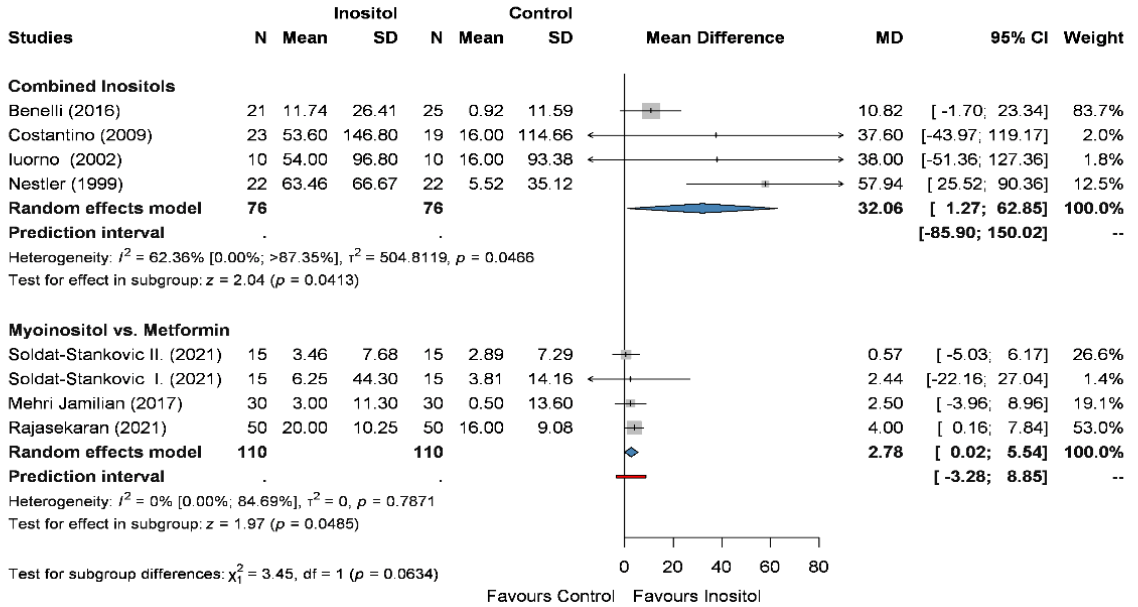

Figure 6. Forest plots representing the mean difference of SHBG levels in the groups treated with inositols compared to placebo or metformin (80). Soldat-Stankovic I. (2021) : BMI < 25kg/m2 ; Soldat-Stankovic II. (2021): BMI > 25kg/m2

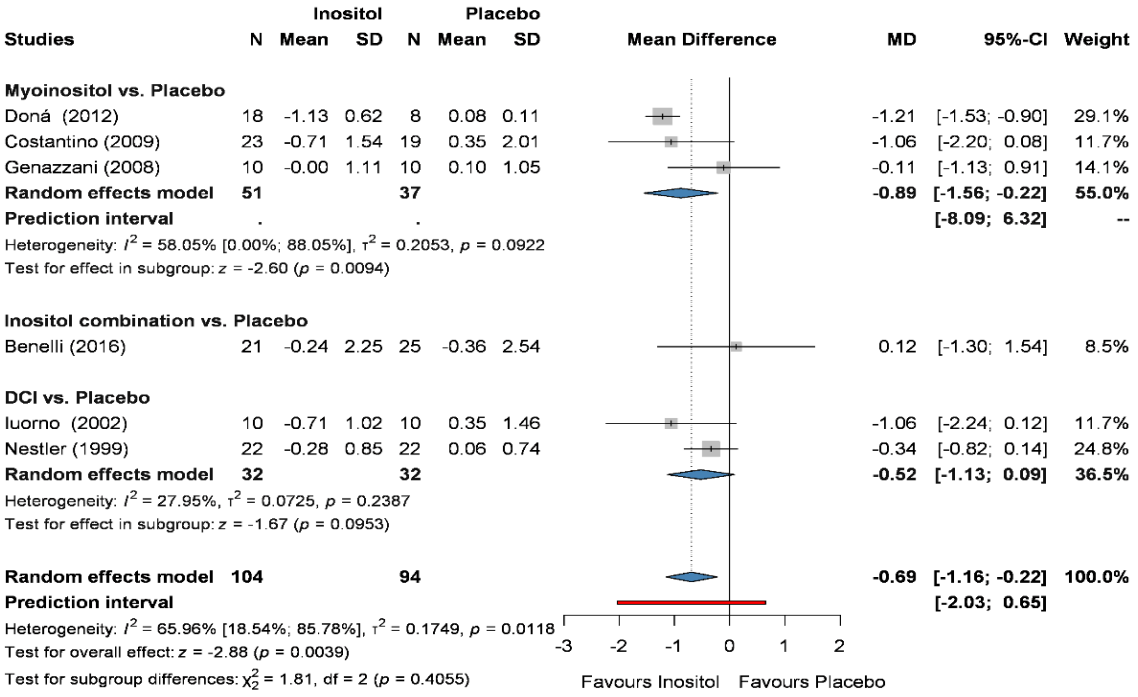

Figure 7. Forest plots representing the mean difference of androstenedione levels in the groups treated with inositols compared to placebo (80).

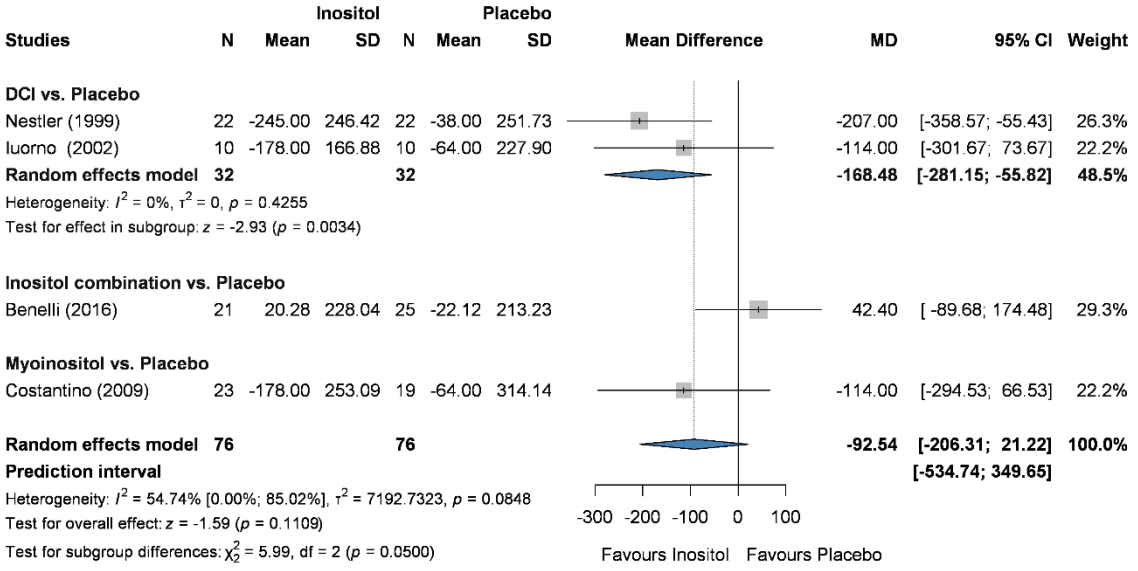

Figure 8. Forest plots representing the mean difference of DHEAS levels in the groups treated with different inositol stereoisomers compared to placebo (80).

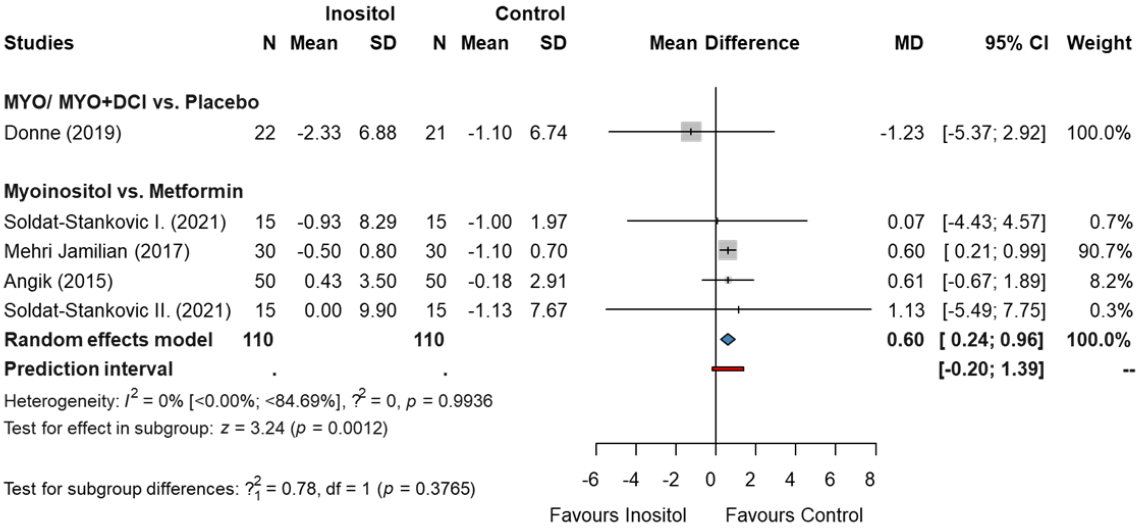

Figure 9. Forest plots representing the mean difference of Ferriman–Gallwey score in the groups treated with inositols compared to placebo or metformin (80). Soldat-Stankovic I. (2021): BMI < 25kg/m2; Soldat-Stankovic II. (2021): BMI > 25kg/m2

8.1.3.3. Glucose metabolism in PCOS

In the case of AUC-glucose, inositol did not display any beneficial effects in comparison with placebo (**Figure 10**.). Essentially, AUC-insulin levels were considerably decreased by inositol (MD=-2081.05 μU/ml/min, CI: -2745.32; -1416.78, **Figure 11.**). The subgroup analysis, on the other hand, indicates a beneficial effect exercised by myoinositol on AUC-insulin levels in comparison with placebo (MD=-2034.05 μU/ml/min, CI: -2706.3; -1361.81, **Figure 11.**).

With regard to the examined glycemic outcomes, non-inferiority of inositol to metformin is indicated by the fact that no significant differences could be detected between the inositol and the metformin interventions in this respect (**Table 3.**).

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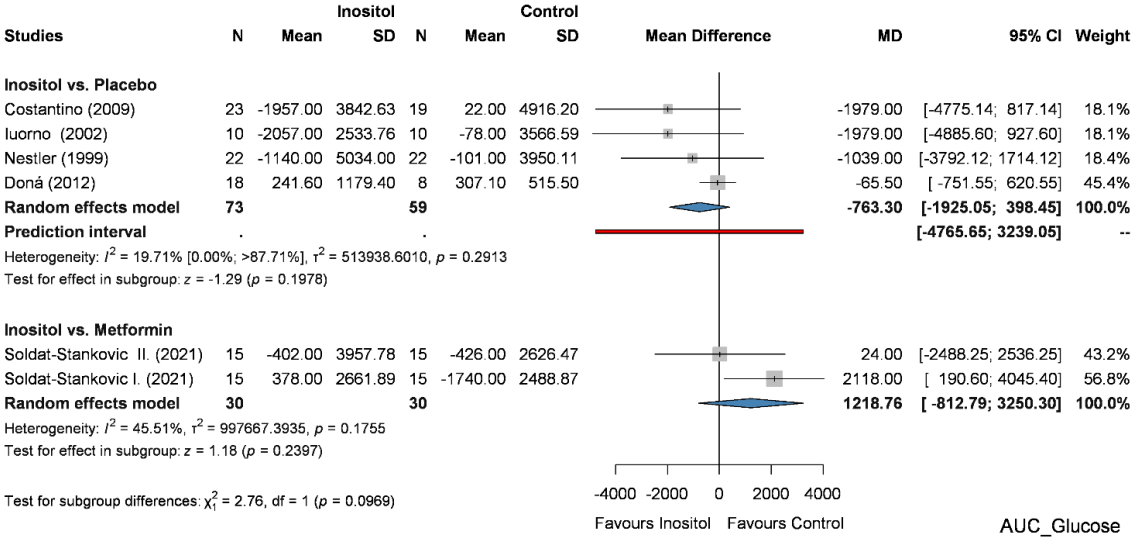

Figure 10. Forest plots representing the mean difference of AUC Glucose in the groups treated with inositols compared to placebo or metformin (80). Soldat-Stankovic I. (2021) : BMI < 25kg/m2; Soldat-Stankovic II. (2021): BMI > 25kg/m2.

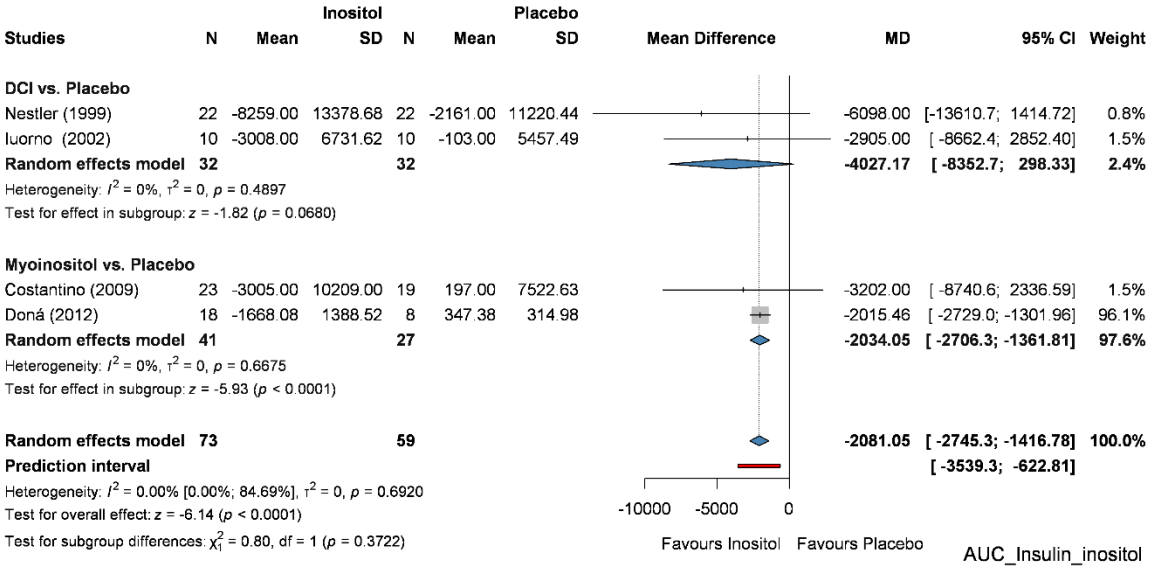

Figure 11. Forest plots representing the mean difference of AUC insulin in the groups treated with different inositol stereoisomers compared to placebo (80).

8.1.3.4. Pregnancy in PCOS

Eight of the randomized controlled trials provided information on pregnancy rates, whereas four studies reported on inositol therapy followed by additional therapy, e.g., letrozole or a combination of rFSH and HCG injection. The outcome related to pregnancy was generally heterogenous in terms of definition, therefore the risk of bias can be considered significant.

Pregnancy rates in the context of the inositol versus placebo comparison without additional therapy were provided by only one article, where no difference was detected in this regard (RR=3.3 CI: 0.4; 27.13, **Figure 12**.) (66). Likewise, the pool of studies in which inositol therapy was followed by additional therapy detected no significant difference in the rate of pregnancy compared to placebo (RR=1.24, CI: 0.85; 1.81, **Figure 13**.).

Both in the presence (RR=1.22, CI: 0.84; 1.78**, Figure 14.**) and in the absence (RR=1.38, CI: 0.88; 2.15, **Figure 12.**) of additional therapy, inositol demonstrated results comparable to those of metformin therapy.

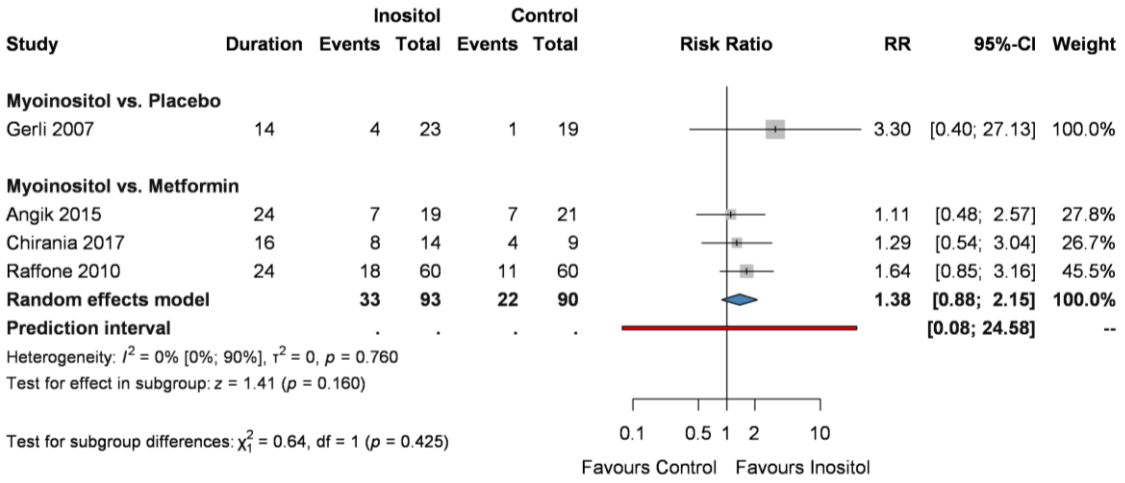

Figure 12. Forest plots representing the risk of pregnancy in the groups treated with inositols compared to placebo or metformin (without any other additional treatment) (80).

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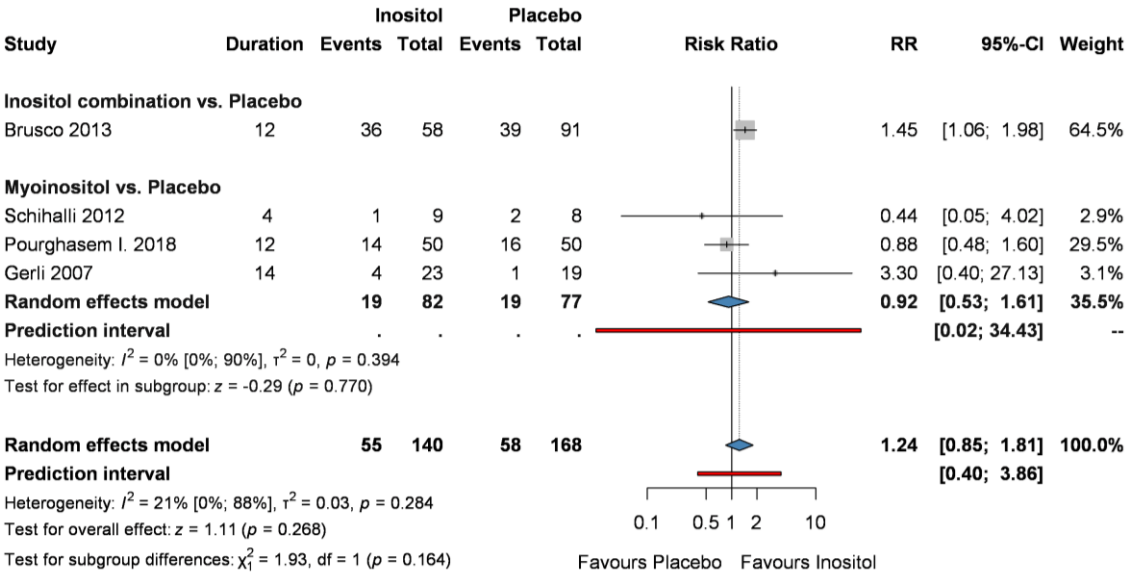

Figure 13. Forest plots representing the risk of pregnancy in the groups treated with different inositol stereoisomers compared to placebo (80). Pourghasem I.: Myoinositol and placebo treated group were compared.

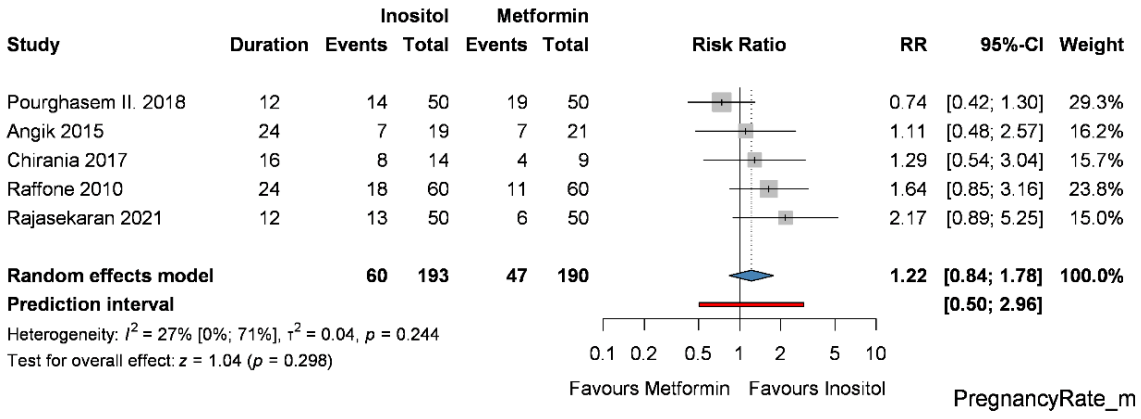

Figure 14. Forest plots representing the risk of pregnancy in the groups treated with inositols compared to metformin (80). Pourghasem II.: Myoinositol and metformin treated group were compared.

8.1.3.5. Side effects

No side effects were mentioned in the case of inositol in any of the four articles that compared inositol with placebo. In addition, four articles comparing inositol and metformin interventions reported that the side effect rate was lower in the inositol-treated group than in the control group (7 vs. 53%, RR=0.16, CI: 0.09; 0.28, **Figure 15.**). The side effects of metformin therapy included nausea, bloating, as well as generalized weakness.

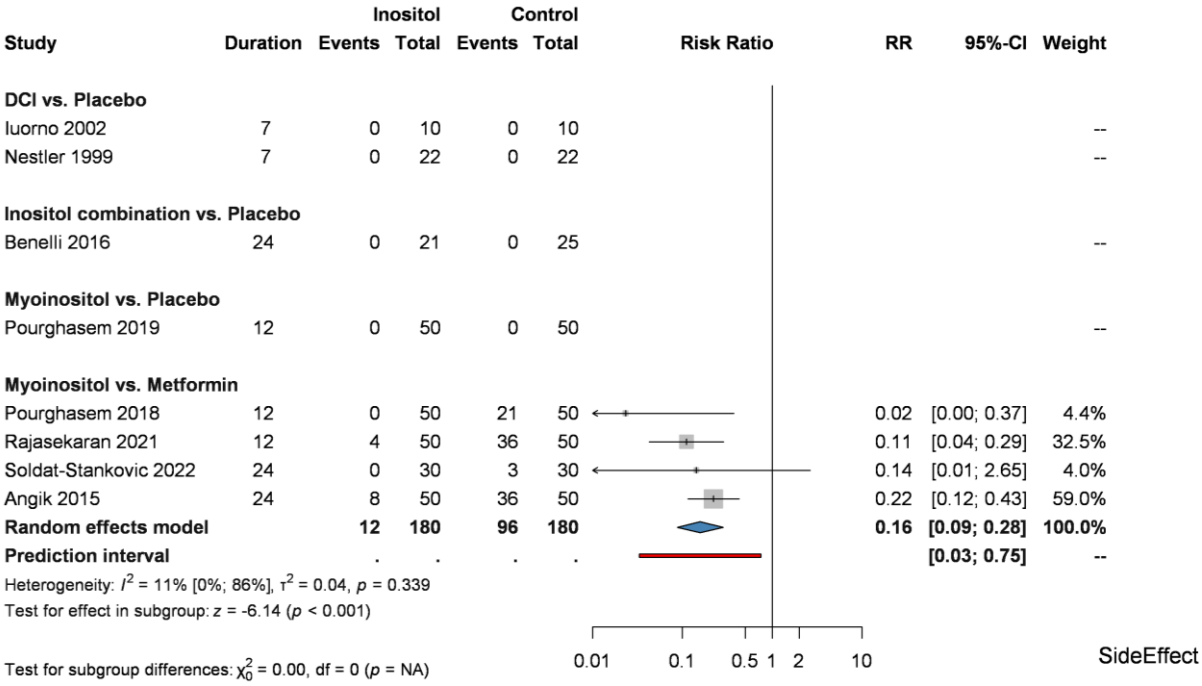

Figure 15. Forest plots representing the risk of side effect in the groups treated with inositols compared to placebo or metformin (80).

8.1.4. Risk of bias assessment, quality of evidence

The RoB 2 risk of bias assessment is summarized in the supplementary material of the original publication (80). Most of the outcomes were ranked as low or moderate risk of bias. The risk of bias was low in 120 outcomes, moderate in 151 outcomes and high risk in 12 investigated outcomes. Attrition rates, confounding factors, statistical analysis and reporting were indentified as common methodological limitations. The level of evidence can be viewed in Tables 2 and 3 and in the supplementary material of the original publication. The level of evidence tended to be moderate in relation to the outcomes.

8.2. Study II.- Investigating the preventive effect of inositol administration in GDM

8.2.1. Search and selection

After the duplicates had been removed, 1795 references were screened by title and abstract. Next, we examined the entire contents of 88 articles. In the end, the selection process yielded eight eligible randomized control trial studies, which reported altogether on 1361 pregnant women, to be included in the present meta-analysis (**Figure 16.**) (81-88).

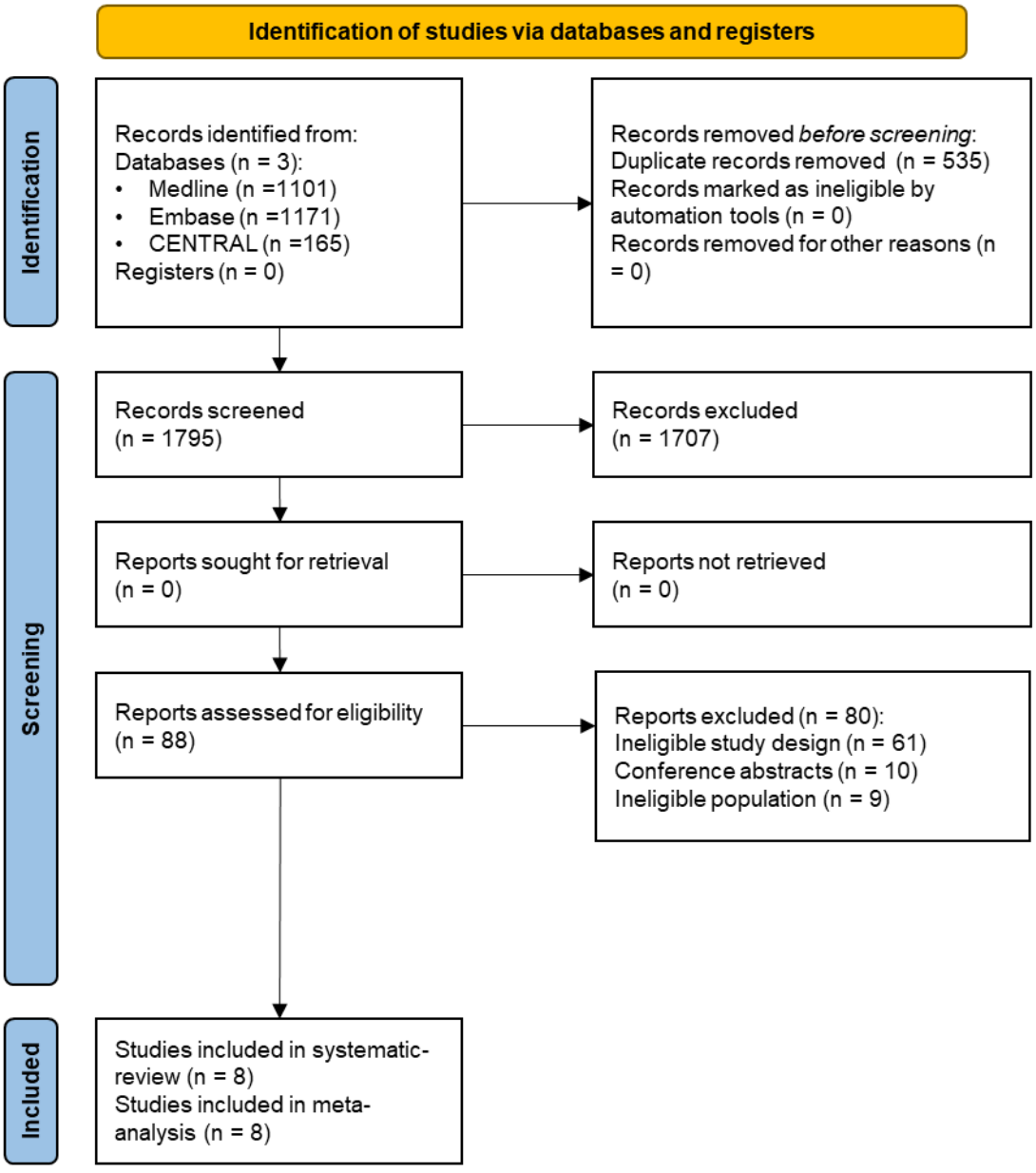

Figure 16. PRISMA 2020 flowchart representing the study selection process (89).

8.2.2. Basic characteristics of the included studies

Table 4. represents the baseline characteristics of the selected analyses. In the course of the trials, myoinositol supplementation, DCI supplementation, a combined therapy of myoinositol and DCI as well as placebo were administered to 515, 32, 154 and 660 pregnant patients, respectively. There was one RCT that examined myoinositol, DCI and inositol combination separately (81), while six RCTs compared the effect of myoinositol with that of placebo (82, 83, 85-88), and finally one RCT reported on the benefits of a combination of myoinositol and DCI in comparison with placebo (84).

In all of the RCTs, the diagnosis of GDM was understood in accordance with the recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG), and each of the studies had inositol supplementation commenced during the 12^{th} or 13^{th} gestational week. According to the recommendations of IADPSG, GDM is diagnosed when one of the fasting, 1h and 2h post-load glucose level, after the consumption of 75g of glucose, is higher than the expected threshold of 92, 180 and 153 mg/dl, respectively, between the 24^{th} and 28^{th} gestational weeks (36).

Participants in each of the eligible studies were patients with high risk for GDM. Four trials focused specifically on overweight (86-88) and obese patients (82). Matarelli (85) and Celenatano (81) conducted examinations of pregnant women with elevated blood glucose levels in the first trimester, whereas there were two further RCTs focusing on pregnant women whose family history involved type-1 or type-2 diabetes (83, 84). Inclusion and exclusion criteria are detailed in the supplementary material of the original publication (89).

Table 4. Basic characteristics of included studies (89).

Author (year)	Country	Number of patients (I/ C)	Age (year) (I/ C)‡	BMI (kg/m2) (I/ C)‡	Risk factors/ inclusion criteria	Intervention	Outcomes	Baseline fasting glucose (mg/dl) ‡
Celentano, 2018 (81)	Italy	105/52	33.8 / 33.9	23.8/24.4	elevated fasting glucose at first trimester blood exams.	4g MI+400mcg FA; 500mg DCI+400mcg FA; 1100mg MI+27,6mg DCI	GDM, OGTT, insulin therapy, preeclampsia or pregnancy-induced hypertension, C-section, preterm birth, neonatal hypoglycemia, NICU admission	97.2/ 97.2
D'Anna, 2013 (83)	Italy	99/98	31 / 31.6	22.8/ 23.6	family history of type 2 DM	4g MI+40mcg FA	GDM, gestational hypertension, C-section, shoulder dystocia, preterm delivery, gestational age at delivery, neonatal hypoglycemia.	-
D'Anna, 2015 (82)	Italy	97/104	30.9 / 31.7	33.8/ 33.8	prepregnancy BMI 30 or greater	4g MI+40mcg FA	GDM, OGTT, insulin treatment, gestational hypertension, C-section, shoulder dystocia, preterm birth, gestational age at delivery, macrosomia, birth weight, neonatal hypoglycemia, NICU admission	83.1/ 82.3
Esmaeilzadeh, 2022 (88)	Iran	27/29	27.8/ 29.3	27.3/ 26.9	overweight patients (prepregnancy BMI above 25 and under 30), age 18-40	2g MI + 200mcg FA	GDM, fasting blood sugar, fasting blood insulin, insulin treatment, preeclampsia or pregnancy-induced hypertension, shoulder dystocia, C-section, preterm delivery, NICU admission	84/ 85.2
Farren, 2017 (84)	Ireland	120/120	31.1 / 31.5	26 / 26.2	patients with a family history in a first-degree relative of	1100mg MI+27,6mg DCI+400mcg FA	GDM, OGTT, preeclampsia or pregnancy-induced hypertension, C-section, shoulder dystocia, preterm	-

					diabetes, either type 1 or type 2.		delivery, gestatational age at delivery, macrosomia, birth weight, hypoglycemia, NICU admission	
Matarelli, 2013 (85)	Italy	35/38	33 / 33.8	23.5/ 24.7	elevated fasting glucose and BMI under 35	4g MI+400mcg FA	GDM, OGTT, insulin therapy, gestational age at delivery, birth weight, neonatal hypoglycemia	97.2/ 97.2
Santamaria, 2015 (86)	Italy	95/102	32.1 / 32.7	26.9 / 27.1	overweight patients (prepregnancy BMI above 25 and under 30)	4g MI+400mcg FA	GDM, OGTT, insulin treatment, gestational hypertension, shoulder dystocia, C-section, preterm delivery gestational age at delivery, macrosomia, neonatal hypoglycemia, NICU admission	81.08 / 78.63
Vitale, 2020 (87)	Italy	110/113	27.18 / 27.95	27 / 26.68	overweight patients (prepregnancy BMI above 25 and under 30)	4g MI+400mcg FA	GDM, OGTT, gestational hypertension	82.2/ 83.1

‡ **parameters represented as mean,** I/C – intervention and control group (BMI: body mass index; DCI: d-chiro-inositol; FA: folic acid; GDM: gestational diabetes; OGTT: oral glucose tolerance test; MI: myoinositol; NICU: neonatal intensive care unit)

8.2.3. Synthesis of the results

8.2.3.1. Inositol treatment can prevent GDM

A total of 1357 pregnant patients were involved in the analysis focusing on the occurrence of GDM. The results show that administration of inositol, commencing in the course of the 12th or 13th gestational week, achieved a significant decrease in the risk of GDM developing (RR=0.42, CI: 0.26-0.67) in comparison with placebo (**Figure 17**). Seven RCTs carried out research into myoinositol supplementation, and all of them indicate that myoinositol has the potential of significantly decreasing the risk of GDM (RR=0.3, CI: 0.18-0.48). One article on DCI administration was identified, and it reported that DCI contributed to the prevention of GDM (RR=0.56, CI: 0.33-0.94) (81). However, two articles indicated that myoinositol and DCI in combination did not contribute to GDM prevention any better than the placebo (RR=0.89, CI: 0.44-1.79). See details in the supplementary material of the original publication (89).

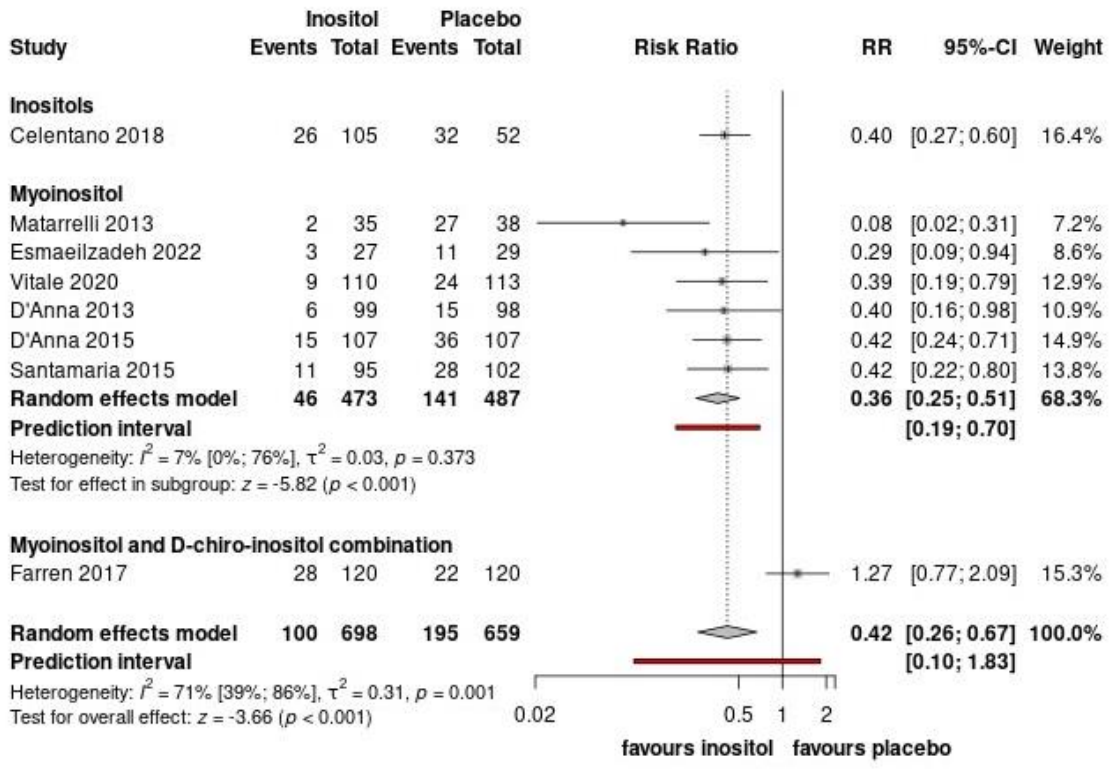

Figure 17. Forest plots representing the risk of developing GDM (89).

8.2.3.2. Inositol decreases fasting, 60', and 120' glucose levels during OGTT

During the 24th-28th gestational week, a significant reduction in fasting glucose levels was achieved by means of inositol supplementation (MD=-0.17 mmol/L, CI: -0.26; -0.09, **Figure 18**.). With regard to the 60' and 120' post-load plasma glucose levels, inositol performed significantly better than the placebo. On average, it reduced OGTT 60' glucose levels by MD=-0,44 mmol/l (CI: -0.74; -0.14, **Figure 19.)** and OGTT 120' glucose levels by MD=-0.37 mmol/l (CI: -0.69; -0.06, **Figure 20).**

All glucose levels during OGTT were successfully decreased by myoinositol to a significant extent, as indicated by the subgroup analysis. On average, fasting glucose concentrations were reduced by MD=-0.21 mmol/l (CI: -0.3; -0.11), 1h post-load glucose levels were reduced by MD=-0.53 mmol/l (CI: -0.79; -0.27), and 2h post-load glucose concentrations were reduced by MD=-0.5 mmol/l (CI: -0.77; -0.23) as a result of myoinositol intervention (see the supplementary material of the original publication) (89).

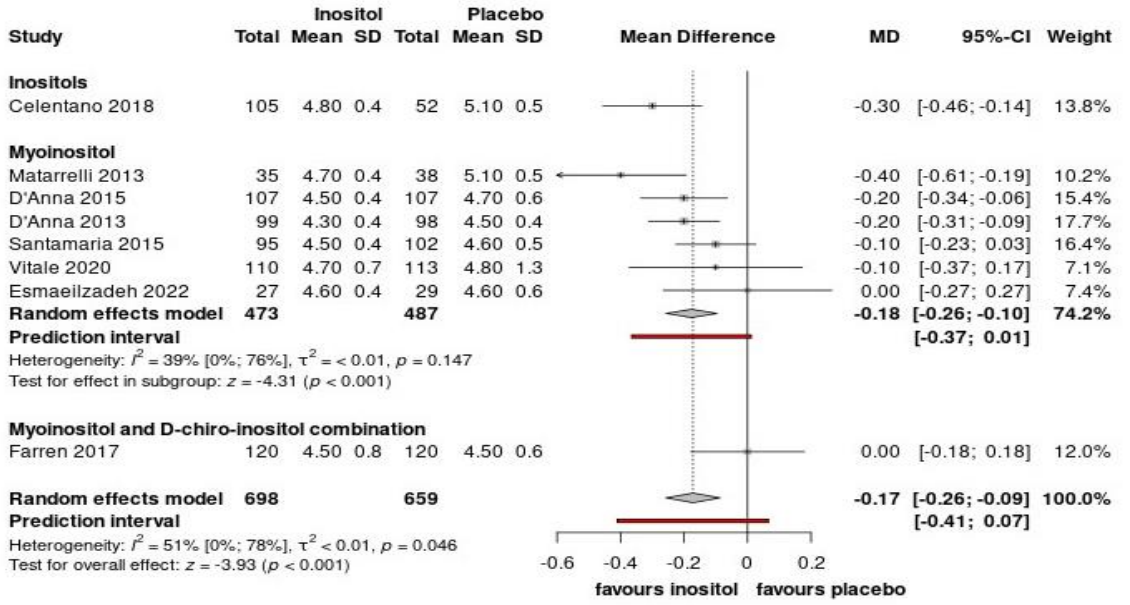

Figure 18. Forest plots representing the mean differences of fasting glucose (89).

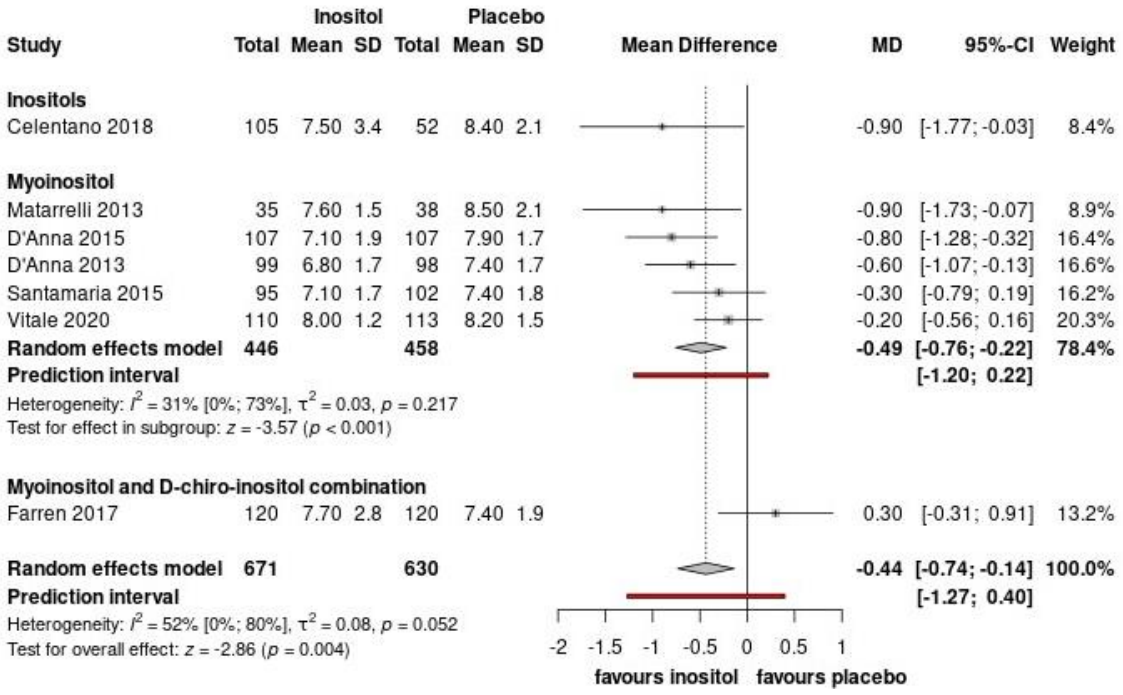

Figure 19. Forest plots representing the mean differences of 1h-OGTT (89).

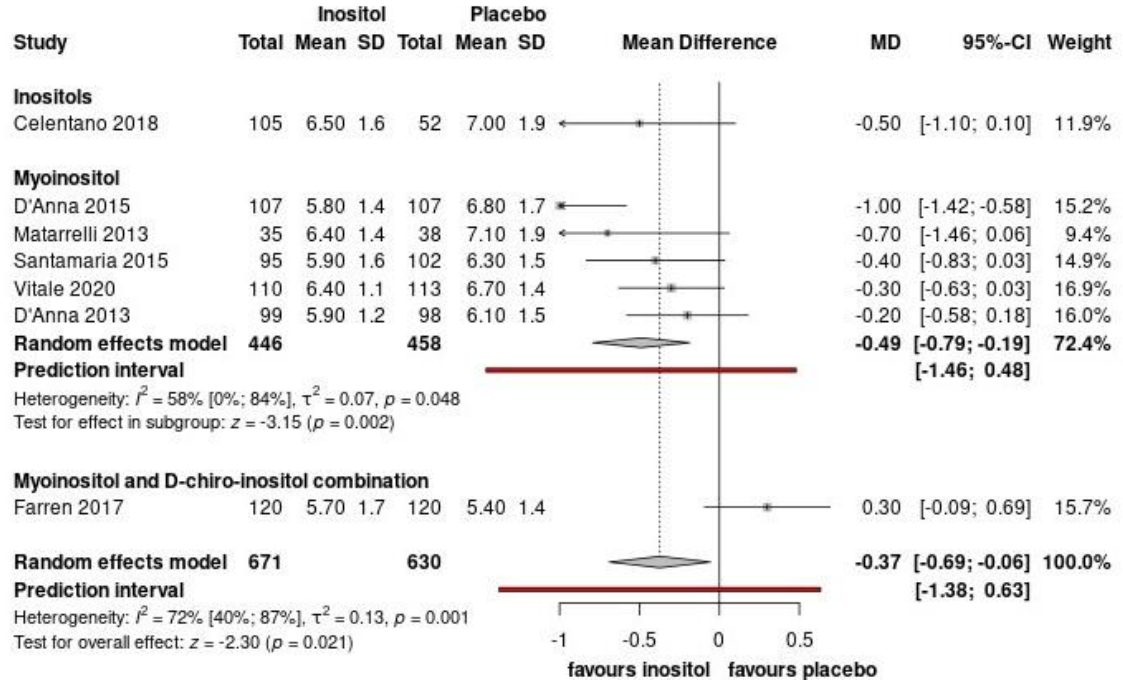

Figure 20. Forest plots representing the mean differences of 2h-OGTT (89).

8.2.3.1. Maternal health outcomes

A significantly higher number of pregnant women required insulin treatment in the non-treated group than in the group which received treatment with inositol. (RR=0.45, CI: 0.28-0.73, **Figure 21**.). Similarly, preeclampsia or pregnancy-induced hypertension as well was significantly rarer in the intervention group than in the control group (RR=0.39 CI:0.22-0.69, **Figure 22.**). There was only one RCT (Esmaeilzadeh et al. (88)) that indicated the presence of a side effect, i.e., headache, which was experienced by one patient only, even though all eight studies included the examination of possible side effects.

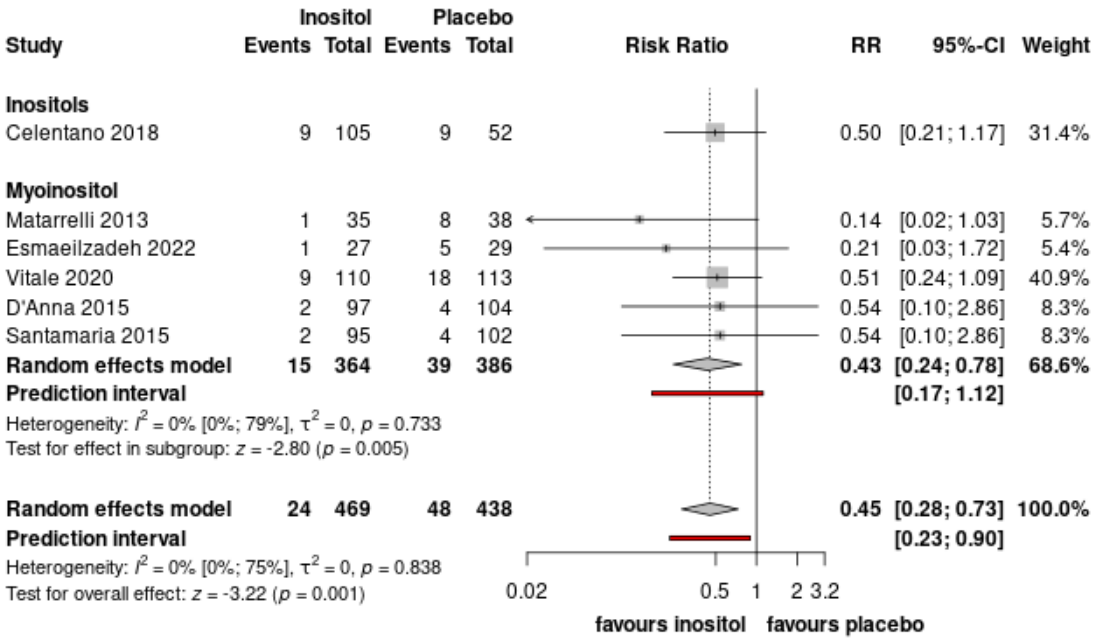

Figure 21. Forest plots representing the risk of insulin need (89).

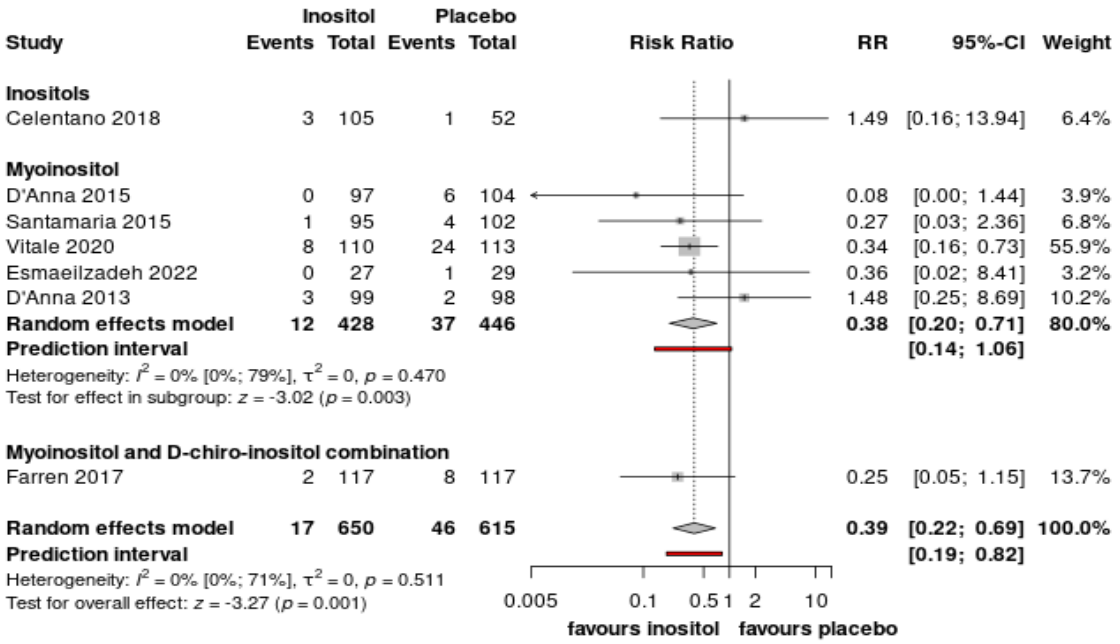

Figure 22. Forest plots representing the risk of hypertensive disorders (89).

8.2.3.4. Delivery outcomes

As the present analysis has shown, inositol supplementation can play a significant role in decreasing the risk of preterm birth (RR=0.41, CI: 0.22-0.75, **Figure 23.**). On the other hand, no significant difference could be detected concerning gestational age at birth (MD=0.52, CI: -0.03; 1.08, **Figure 24.**). The findings of two RCTs (81, 84) suggest that a combination of myoinositol and DCI could have a beneficial effect on gestational age at birth (MD=0.36, CI: 0.00-0.71, see supplementary material of the original publication) (89). The studies did not report any significant differences regarding C-section incidence (RR=0.9, CI: 0.78-1.03, **Figure 25.**) or the risk of shoulder dystocia (RR=0.59, CI: 0.12-2.82, **Figure 26.**) between the inositol-treated patients and the control group.

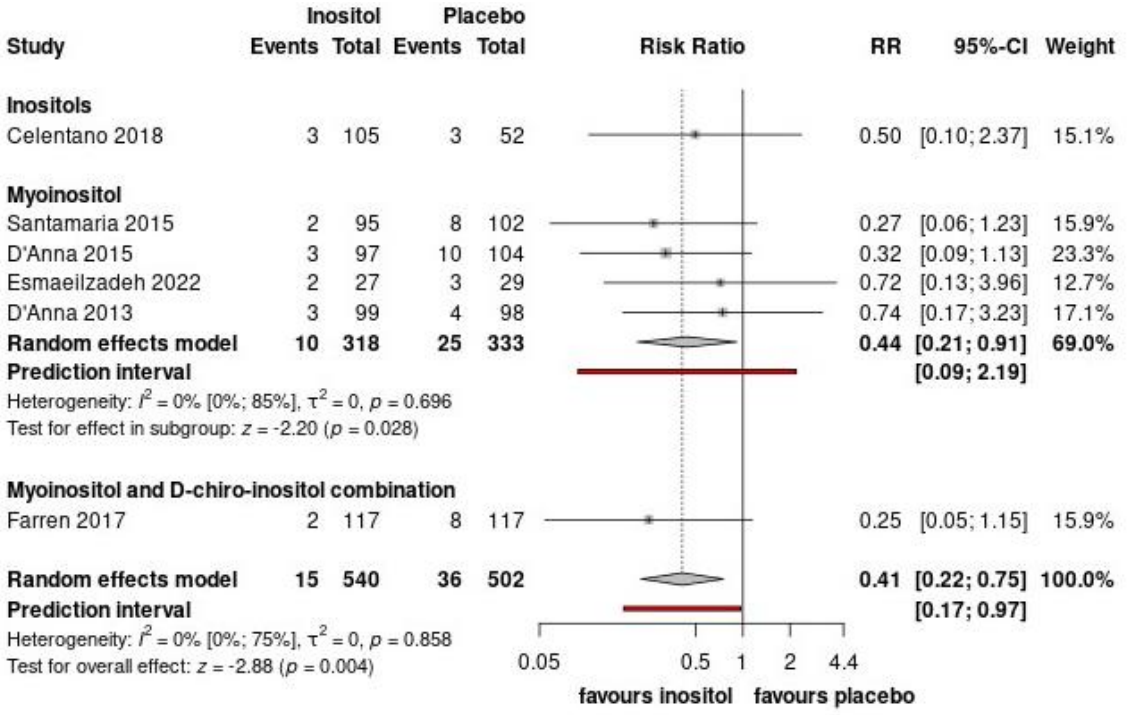

Figure 23. Forest plots representing the risk of preterm birth (89).

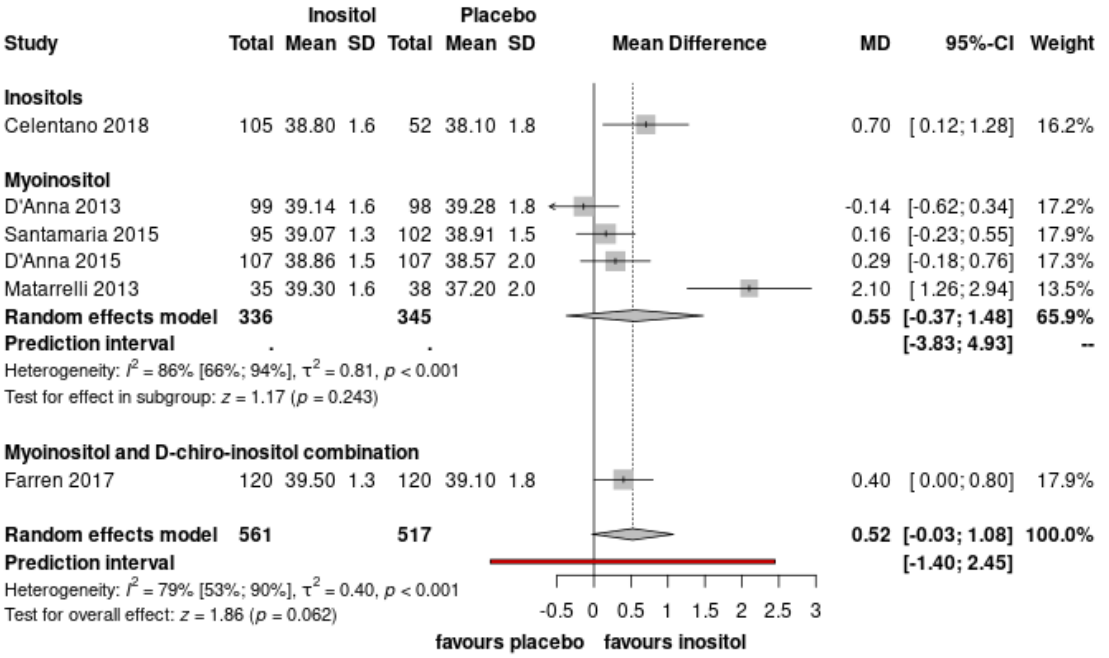

Figure 24. Forest plots representing the mean difference of gestational age at birth (89).

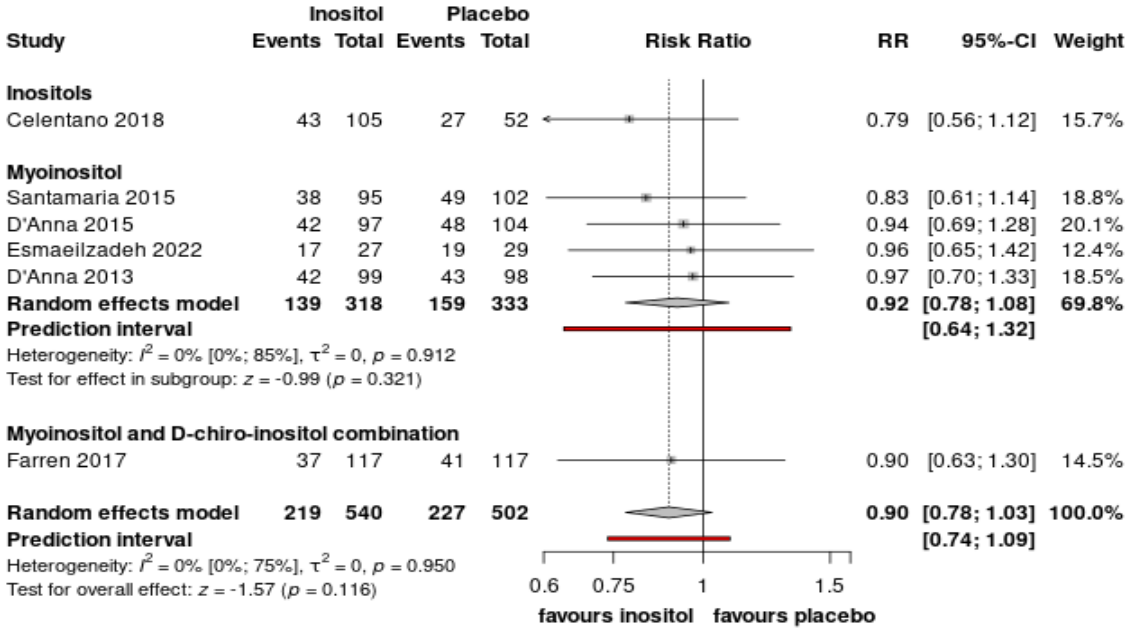

Figure 25. Forest plots representing the risk of C-section rate (89).

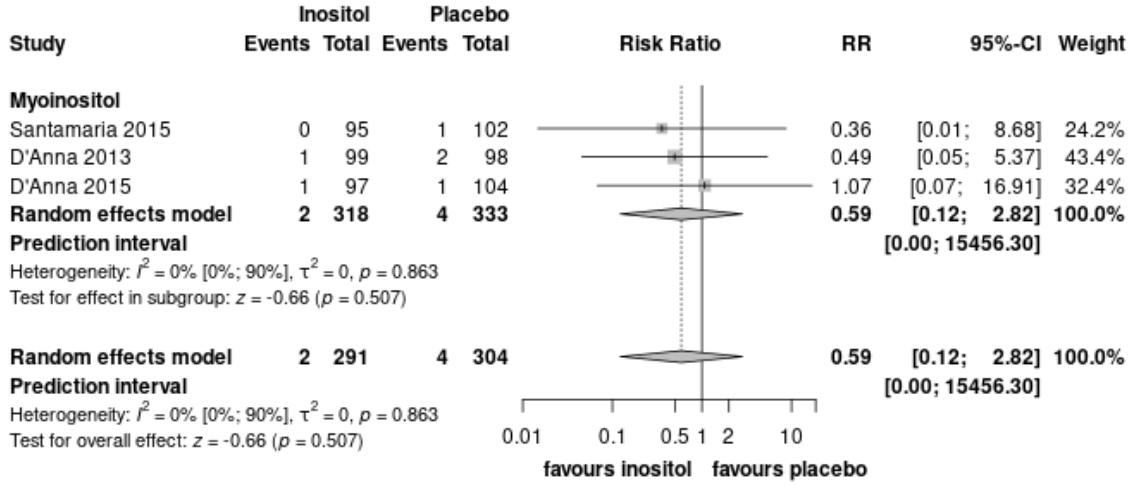

Figure 26. Forest plots representing the risk of shoulder dystocia (89).

8.2.2.5. Fetal-neonatal health outcomes

Six of the trials included birthweight**,** while five included macrosomia in the research, and the authors came to the conclusion that inositol supplementation has no effect on these parameters **(Figure 27-28.**). Concerning neonatal hypoglycemia, the beneficial effect of myoinositol on this condition was confirmed as well as its significant potential in the prevention of hypoglycemia (RR=0.12, CI: 0.03-0.55, **Figure 29.**). Nevertheless,

inositol does not seem to have an effect on the need for neonatal intensive care unit (NICU) admission, based on five of the articles reporting on this outcome **(Figure 30.**) (81, 82, 84, 86, 88). Finally, the available data concerning IUGR and diabetic fetopathy proved to be insufficient to draw conclusions based on them. A single study provided data on LGA and it confirmed the potential positive effect of myoinositol (81).

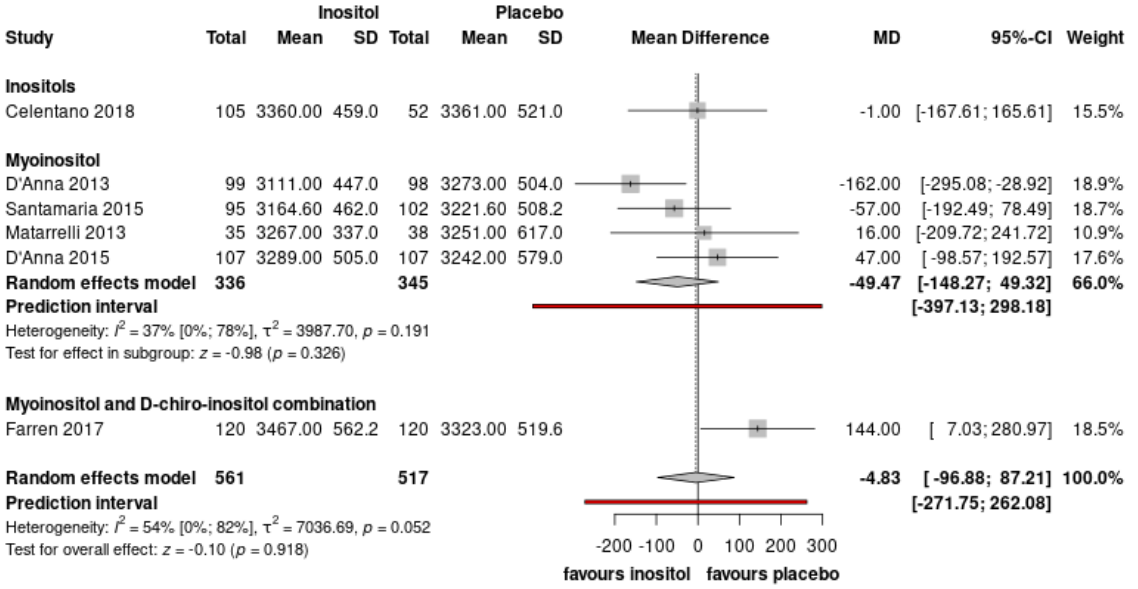

Figure 27. Forest plots representing the mean difference of birthweight (89).

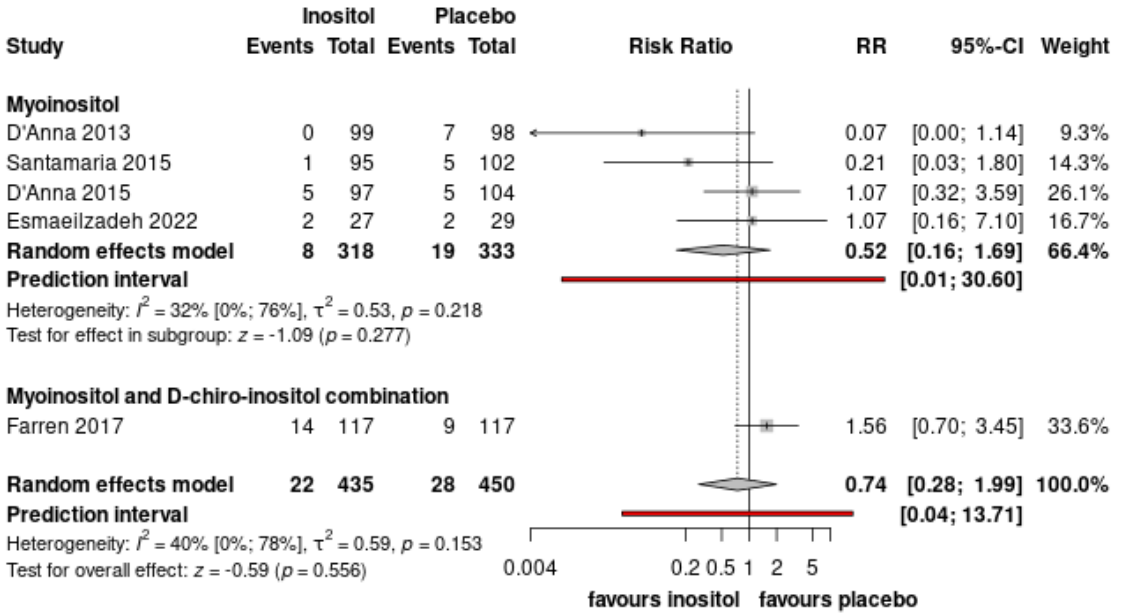

Figure 28. Forest plots representing the risk of macrosomia (89).

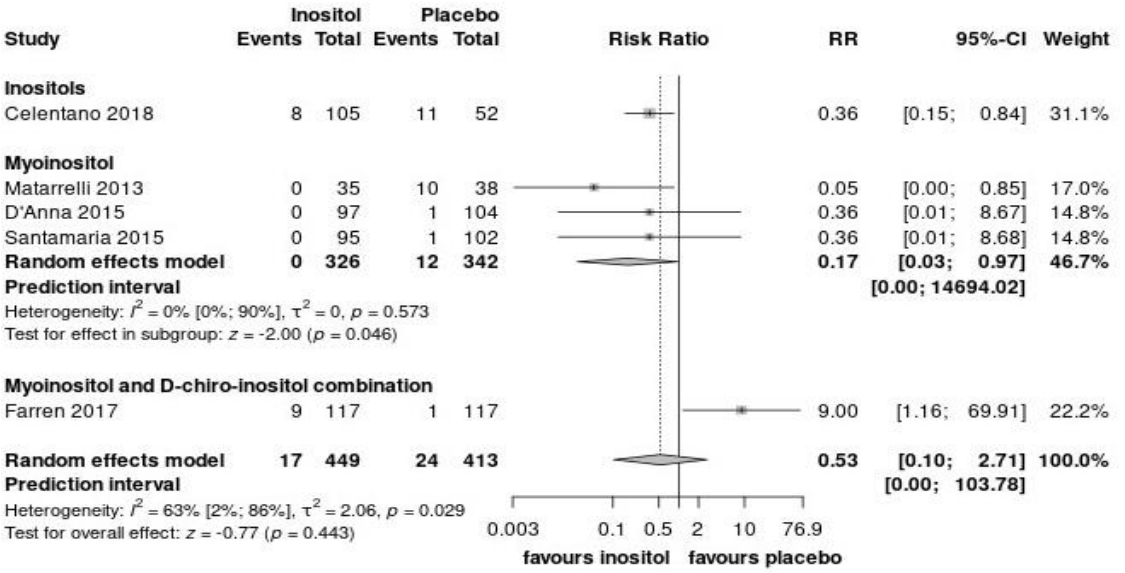

Figure 29. Forest plots representing the risk of neonatal hypoglycemia (89).

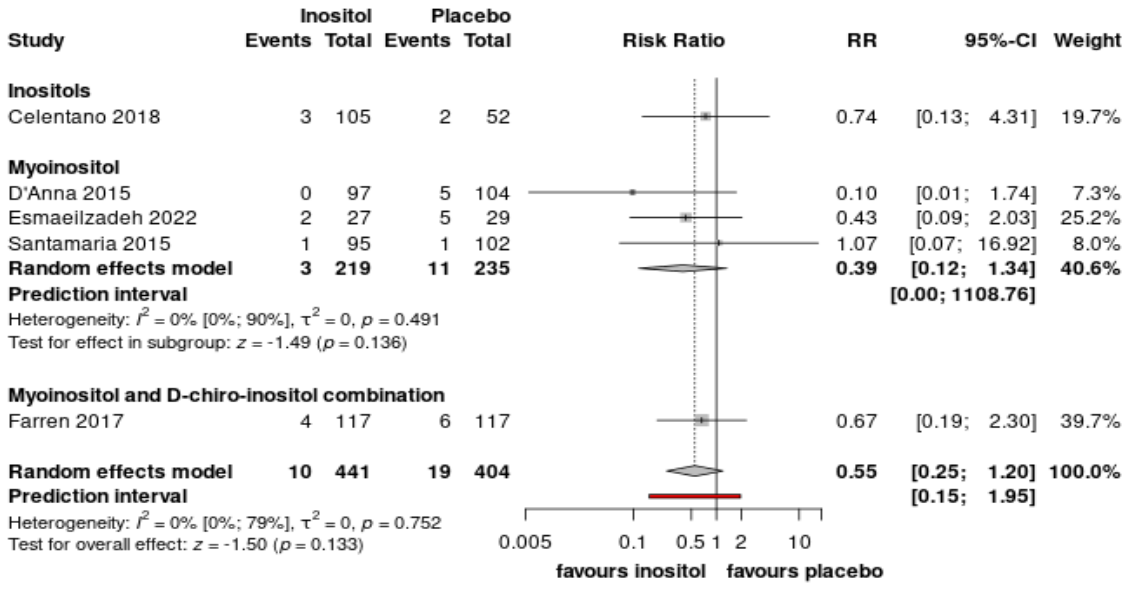

Figure 30. Forest plots representing the risk of NICU admission (89).

8.2.3. Risk of bias assessment, quality of evidence

In general, in the case of GDM, 2h-OGTT, gestational age at birth, and neonatal hypoglycemia outcomes, a high level of heterogeneity can be observed, whereas in the case of insulin therapy, C-section rate, preterm birth, neonatal intensive care unit admission, shoulder dystocia, and gestational hypertension outcomes, heterogeneity was low. Heterogeneity derives from the different inositol stereoisomers, which were applied

in varying dosage (2 -4g MI or 500mg DCI or 27.6mg DCI and 1100mg MI in combination), and differences in body mass index characterizing the participating patients. The results of the risk of bias assessment can be found in the supplementary material of the original publication (89). The absence of blinding methods caused a moderate risk of bias. Most of the RCTs were open-label trials, except for Matarelli's and Esmaeilzadeh's studies, which were double-blinded (85, 88). The level of evidence covers a wide range from very low to moderate. A high level of evidence was manifested with regard to one outcome, which was preterm birth. Further details concerning the level of evidence can be viewed in the supplementary material of the original publications (89).

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9. DISCUSSION

9.1. Summary of findings, international comparisons

Based on our study, every examined aspect of PCOS can be improved with inositol interventions. Primarily, inositols successfully contribute to the reduction of serum total, free testosterone and androstenedione levels, to an increase in SHBG levels, as well as to the normalization of cycle length, in comparison with placebo. Inositols have also proved to be not inferior to metformin regarding all the above-mentioned parameters. In addition, a significant reduction in AUC insulin levels and BMI was detected in the patients receiving inositol treatment. The research included various isomers, of which myoinositol was reported to be the most beneficial. Lastly, the side effects of inositols were fewer than those of metformin. Beside these favorable effects, it is also possible to decrease the prevalence of gestational diabetes by applying inositol supplementation. Furthermore, as a result of inositol intervention, the necessity of insulin therapy, preeclampsia or pregnancy-induced hypertension, the risk of preterm birth and neonatal hypoglycemia can be decreased. Fasting, 1-hour, and 2-hour OGTT glucose levels were also considerably reduced by inositol. At the same time, there were no significant effects relating to the other investigated parameters observed; this can be due to the fact that most of those parameters, including, for instance, macrosomia, NICU admission, and shoulder dystocia, displayed low event rates and were experienced by relatively few patients.

Myoinositol is endogenously synthesized from glucose-6-phosphate (G6P). However, it is also found in the cell membranes as phosphatidyl-myoinositol, as the precursor of inositol triphosphate (PIP2), playing a vital part (22) in the signal transduction of various receptors, such as FSH, promoting granulosa cell differentiation and follicle maturation (75). Moreover, since myoinositol contributes to the translocation of GLUT4 to the plasma membrane, leading to elevated glucose uptake (90), and it also contributes to aromatase activity, it has the potential to improve oocyte and embryo quality (27). In the course of the secondary signaling mechanisms, inositol triphosphate (IP3) is also released, which, in turn, can be converted into free myoinositol by inositol-monophosphatase (21).

9.1.1. Inositols effect on cycle regularization

When the follicules do not develop into mature eggs, because of the lack of inositol, follicular arrest leads to menstrual irregularities (amenorrhea and oligomenorrhea). In everyday clinical practice menstrual cycle regularization is a frequently required intervention among women of reproductive age. Our data relating to menstrual cycle regularization proved to be heterogeneous. It was regarded as menstrual cycle regularization when a patient initially suffering from amenorrhea or oligomenorrhea had eumenorrhea following the intervention. Therefore, since Genazzani et al. considered it improvement when an amenorrheic patient became oligomenorrheic, their results were excluded from the present analysis (65). Similar results were mentioned by Pundir et al. (23).

9.1.2. Inositols effect on androgen levels

Androgens are produced from cholesterol in ovarian theca cells and in zona reticularis in adrenal glands. The majority of testosterone is produced through the metabolism of androstenedione, with approximately 50% originating from the peripheral conversion of androstenedione, 25% from the ovaries, and the remaining 25% from the adrenal glands (91, 92). Dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEA-S) are secreted by adrenal glands primarily, with comparatively smaller amounts being secreted by the ovaries. As a result, DHEA-S serves as the most reliable marker for adrenal androgen secretion (91, 93).

We did not find any significant differences with regard to DHEAS. Most of the findings are similar to those reported by Zeng et al.; however, the present analysis included the study of other inositol stereoisomers as well (94). No statistical differences were observable between the myoinositol-treated patients and the control group in relation to total testosterone levels. Nonetheless, two studies reported reduced levels of free testosterone. In comparison with Pundir et al., the current analysis involved one more RCT (59), and no differences in DHEAS levels were detected following the treatment with inositol when compared to the placebo group (23, 59). According to, Kutenai et al., however, myoinositol was more effective than metformin in decreasing total testosterone and DHEA levels (95).

It can be concluded from the present analysis that it is primarily because of their effect exercised on insulin resistance that inositols contribute to the increase in SHBG concentration. In addition, due to being precursors of inositol triphosphate (PIP2), inositols have a vital role in insulin signal transduction. They exert dual influence on free androgen concentration: (1) on the one hand, by means of their role in follicle maturation, they are able to improve the mechanism of dominant follicle selection, thereby increasing aromatase activity, and thus effectively decreasing total androgen production, (2) on the other hand, they stimulate SHBG production as well, causing decreased levels of free androgen. While inositols apparently decrease testosterone and androstenedione levels, they do not reduce DHEA concentrations, which implies that the antiandrogen effect of inositols is essentially due to improved ovarian function. However, DCI, an aromatase inhibitor, promotes glycogen synthase, inhibiting the conversion of androgens to estrogens, which leads to the accumulation of androgens and lack of estrogens. This is the reason why administration of DCI either over a long period of time or in high dosage exacerbates PCOS symptoms. In the short term, however, it can lead to an improvement in insulin levels, encouraging the production of SHBG (21). Our data confirm that 6 to 8 weeks of treatment did not affect androgen levels adversely.

The effect of inositols on SHBG production was also researched by Zeng et al., albeit on the basis of two studies only, with the conclusion that myoinositol could exercise a more beneficial effect on SHBG than a placebo (94).

Our analysis also confirms that inositols are non-inferior to metformin concerning their effect on free and total testosterone, androstenedione, and SHBG. Fanchinetti et al. reported findings corresponding to our results regarding the improvement in testosterone, androstenedione, and SHBG levels following the administration of inositol, in comparison with metformin (26, 96).

9.1.3. Inositols and BMI

It is worth noting that 60-70% of PCOS patients are overweight (30). As observed in individuals with excess weight, higher fat content corresponds to an increased likelihood of developing hyperinsulinism and insulin resistance (IR) (97). Hyperandrogenism is a prevalent feature in PCOS, strongly promoting the deposition of visceral fat (98).

Research has suggested that testosterone plays a significant role in lipogenesis within the visceral fat deposits in women (99).

On the other hand, PCOS can occur in lean women too. In these patients, hyperandrogenism emerges as the primary driving symptom within their PCOS. Studies have confirmed that PCOS patients, despite possessing a lean body mass, frequently experience insulin resistance (100).

In contrast to our findings, the study of Zeng et al. concluded that myoinositol did not facilitate weight loss (94), but their analysis did not observe the changes in BMI, recording only the after-treatment values. At the same time, earlier published meta-analyses (Fanchinetti et al. and Zhang et al) are in agreement with our conclusion on the non-inferiority of inositols to metformin with regard to BMI reduction (26, 96).

9.1.4. Inositols effect on carbohydrate metabolism in women with PCOS

When compared with placebo, treatment with inositol led to better outcomes with regard to both hyperinsulinemia and carbohydrate metabolism. In this respect, the findings of earlier meta-analyses confirm our results (23, 94), although it must be noted that there was a partial overlap between the RCTs reviewed. Zeng et al., however, did not indicate any improvement with regard to fasting glucose as a result of inositol treatment in comparison with placebo (94). In addition, inositol appears to be non-inferior to metformin in relation to carbohydrate metabolism, concerning which Zhang et al. and Kutenaei et al. reached conclusions similar to ours (26, 95).

9.1.5. Inositols effect on pregnancy

Women with PCOS have increased risk of anovulatory infertilty and pregnancy complications, such as gestational diabetes mellitus, pregnancy induced gestational hypertension. The risk of fetal congenital heart defects, neural tube defects and omphalocele is also increased in women with PCOS (33, 101).

Inositol supplementation may help normalize menstrual cycles and promote regular ovulation, especially in women with PCOS (80). Myoinositol supplementation may have positive effects on oocyte quality and maturation, especially in women undergoing assisted reproductive technologies such as myo (IVF) (32). Some research suggests that myoinositol improve oocyte development and increase the chances of successful

fertilization and pregnancy (102). It also improve carbohydrate metabolism, which results a stabile metabolism leading to potential successful fertilization. Some research indicates that myoinositol supplementation during pregnancy may help reduce the risk of gestational diabetes, a condition that can develop during pregnancy and affect both maternal and fetal health (89).

9.1.6. Inositols effect on carbohydrate metabolism in GDM

There is an elevated risk of type-2 diabetes mellitus developing in the fertile population due to an increased prevalence of obesity and glucose metabolism disorder during adolescence and childhood (103, 104). The higher prevalence of T2DM in female patients of reproductive age, in turn, increases the prevalence of GDM as well (35). In the long term, GDM can have complications for both the mother and the child, including a higher risk for T2DM and associated cardiometabolic risk. Vounzoulaki et al. stated that mothers with GDM are at nearly tenfold higher risk of developing T2DM, while Kramer et al. calculated that the risk of cardiovascular events in GDM patients is two-fold higher (10, 12, 105). The risks in the case of the children born to mothers with GDM are estimated to be similar (106).

9.1.6.1. Inositol treatment administered from the first trimester is able to prevent the development of GDM by reducing fasting, 1-hour, and 2-hour OGTT glucose levels.

Our analysis has shown that the risk of GDM developing in pregnant mothers can be halved by starting preventive inositol administration before the 13th week of the pregnancy. This is related to the fact that the fasting, 1-hour, and 2-hour OGTT glucose levels (i.e., the basis of the diagnosis of GDM) are reduced similarly by the end of the 28th week.

The evidence identified by our research is corroborated by earlier meta-analyses and systematic reviews (107-109). According to Wei et al., Guo et al. and Chan et al. inositol supplementation can successfully prevent GDM (107, 109, 110). Wei et al. pooled all the selected studies in one group of “4 g MI group”, and although in one article only 2 g MI was administered (Vitale et al.), the conclusion was nevertheless that inositol treatment had a beneficial effect (87, 109).

Farren et al. reported that the combination of myoinositol and D-chiro-inositol did not appear to possess any preventive properties. This might be either because the combination

of the two inositol stereoisomers has no effect or because the applied dose of inositol, especially MI, was insufficient (1100mg MI+ 27,6mg DCI) (84). In the five studies where myoinositol was administered in 4-gram doses, the treatment proved to be beneficial regarding primary prevention (81-84, 86). Vitale et al. and Esmaeilzadeh et al. administered 2 grams of myoinositol, and it also proved to be effective (87, 88). Based on the available evidence, the appropriate daily dose of myoinositol should be between 2 and 4 grams in order to prevent gestational diabetes; therefore, our conclusion is that myoinositol has the potential to halve the risk of gestational diabetes provided that the dose is over 2 grams per day. Nevertheless, the combination of 1100mg MI+ 27,6mg DCI cannot successfully prevent GDM in high-risk patients whose family history includes diabetes.

Preventing gestational diabetes is a major problem to solve in prenatal care. Based on a new case-control study, GDM risk can be estimated with a 96.6% specificity and 97.5% sensitivity in the first trimester from maternal blood samples (111). Effective prediction test combined with an appropriate prevention strategy might counterbalance the year-by-year worsening statistics of GDM in the western world. Beyond our suggestion, healthy diet combined with inositol treatment would be a promising prevention. Recently, a number of innovative approaches have been presented in order to prevent GDM, most of them being based on lifestyle interventions (including dietary therapy and physical exercise) combined with dietary supplements, including, in addition to inositol, magnesium, vitamin D, and probiotics. A recent network meta-analysis reports that physical exercise (OR: 0.64 (0.46-0.88)) in combination with probiotic intake (OR: 0.57 (0.34-0.96)) can decrease the risk of gestational diabetes. Although the same analysis did not find evidence for the preventive properties of inositol, it may be because only four studies were included in the analysis, among them Farren et al. with 1100mg MI+ 27.6mg DCI intake (112). Gestational diabetes mellitus is due to multiple etiological factors. The elimination of a given potential risk factor does not necessarily have an effect on any other etiological factors that can play a role in the development of the disorder. To give a few examples, patients suffering from magnesium insufficiency benefit from magnesium supplementation, whereas vitamin D supplementation may be the most effective in patients with vitamin D insufficiency (37). In order to resolve the problem, a range of combined treatments have been tested for GDM preventive purposes. A combination of

myoinositol, DCI, zinc, methylsulfonylmethan, and methyltetrahydrofolic acid was researched by D'ell Edera et al. with the conclusion that the above-mentioned combination could prevent the development of gestational diabetes (113). In contrast with the above, Godfrey et al. concluded that treatment with myoinositol 4 g/day, vitamin D 10 μg/day, riboflavin 1.8 mg/day, vitamin B6 2.6 mg/day, vitamin B12 5.2 μg/day, zinc 10 mg/day, and probiotics (Lactobacillus rhamnosus NCC 4007 and Bifidobacterium animalis species lactis NCC 2818,folic acid 400 μg/day, iron 12 mg/day, calcium 150 mg/day, iodine 150 μg/day, and β-carotene 720 μg/day vs. folic acid, iron, calcium, iodine, and β-carotene, when commenced before conception, failed to decrease GDM incidence in a general population (114). The above findings are inconsistent with prior evidence showing that each added dietary supplement is effective on its own. A possible explanation is that the study population was highly versatile in terms of gestational diabetes risk and ethnicity, compared to earlier studies, which typically included high-risk Caucasian cohorts. A further possible explanation could be the presence of interaction between the combined supplements. For instance, folic acid supplementation has been associated with an increased risk of GDM, in particular, when vitamin B12 insufficiency is present. In addition, a relatively high prevalence of GDM (24.8% and 22.6%) was found, in spite of the general study population, while patients already diagnosed with type-2 diabetes or being treated with metformin were not included in the study (115).

9.1.7. Treatment with inositol may decrease the necessity of insulin treatment and the risk of hypertension-associated conditions

Our evidence shows that inositol supplementation halved the risk of the patients needing insulin - provided that the intervention commenced prior to the 13th week of pregnancy. This effect was not apparent in the RCTs that included only a low number of patients needing insulin treatment (81, 82, 85-88). Wei et al. have confirmed our findings with regard to insulin treatment, but their analysis did not find any difference between the inositol-treated group and the control group in relation to pregnancy-associated hypertensive disorders (109).

9.1.8. Inositol treatment reduces the risk of preterm birth and neonatal hypoglycemia.

In their meta-analysis, Vitagliano et al. reported significant improvements resulting from treatment with inositol regarding the reduction of preterm births but none with regard to neonatal hypoglycemia (108). Wei et al., however, confirm our findings, i.e., that inositol can decrease the risk of both preterm birth and neonatal hypoglycemia (109). The study of Godfrey et al., on the other hand, did not find any preventive properties of inositol administration in combination with other supplements with regard to GDM; in spite of that, they did confirm that the combined treatment resulted in a lower risk of preterm birth (114). It is worth noting that treatment with 4g of myoinositol decreases the risk of preterm delivery and the need for insulin in GDM patients. Consequently, inositol treatment does not only prevent the development of GDM but also its complications in patients already suffering from the disorder (116, 117).

9.2. Strength

The main strength of the analysis is that it adhered to a strict protocol. Examination of different stereoisomers was carried out separately as well, with the purpose of identifying the most effective one in both PCOS and the prevention of GDM. No language restrictions were applied but a rigorous methodology was consistently observed. Given the fact that various diagnostic criteria exist worldwide for GDM, a special strength of our analysis is that it was based on RCTs applying uniform criteria in the diagnosis. Another strength is that in the reviewed RCTs inositols were not only compared to a placebo but to the gold standard treatment, i.e., metformin, as well, in women with PCOS.

9.3. Limitations

What can be regarded as a limitation of the analysis is the relatively small number of studies with a small sample size. Moreover, the RCTs applied different dosages of inositols in inositol monotherapy compared to inositol combinations.

9.3.1. Study I. -Investigating the safety and efficacy of inositol administration in PCOS

In addition, the time periods for follow up showed considerable differences among the RCTs. The results concerning pregnancy rates were generalized, which was problematic

because there was only one study that specifically included women who wanted to become pregnant. Furthermore, there were no graphs of AUC-insulin and glucose. Consequently, it was difficult to interpret the findings with the purpose of evaluating the effect of various inositols and metformin on early and late insulin responses. Finally, a further limitation was the presence of a moderate and high risk of bias in some domains.

9.3.2. Study II.-Investigating the preventive effect of inositol administration in GDM

The populations were mostly Caucasian patients. The absence of blinding methods is another limitation of the studies included in the analysis.

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10. CONCLUSIONS

Our research 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 cause 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 of 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.

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11. IMPLEMENTATION FOR PRACTICE

We recommend the introduction of inositols into the treatment protocol of polycystic ovary syndrome to normalize menstrual cycles, to reduce testosterone levels and normalize carbohydrate metabolism. This approach is particularly beneficial for women experiencing side effects from metformin.

Our findings suggest that it is advisable to administer 2-4g/per day myoinositol supplementation from the first trimester in high-risk pregnancies in order to decrease the risk of gestational diabetes and its complications. Myoinositol inclusion in pregnancy vitamins should be considered.

Developing clear guidelines and protocols for using inositols in managing PCOS and high-risk pregnancies can standardize care and optimize treatment outcomes across various healthcare settings.

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12. IMPLEMENTATION FOR RESEARCH

With a view to evaluating how inositols can improve pregnancy rates, further well-designed randomized controlled trials are necessary. Research into the effect of metformin and inositol co-treatment in managing PCOS would also be useful.

Further prospective data collection is needed in order to evaluate the effects of inositol treatment on low-risk pregnancies more accurately. More RCTs with not Caucasian patients should be enrolled. In addition, the question of what dosages of inositol are the most effective requires further research in the course of double-blinded studies. More information on this topic could be provided by an international registry of pre-pregnancy inositol administration in the case of high-risk patients. Last, but not least it is imperative that, instead of a dichotomous format, insulin needs are interpreted by giving the exact amounts of insulin needed.

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13. IMPLEMENTATION FOR POLICYMAKERS

By recognizing the efficacy of inositol, healthcare systems can offer a cost-effective and accessible treatment option, potentially improving outcomes for individuals affected by these conditions. Promoting the use of inositol in clinical practice can lead to better management of PCOS and GDM, ultimately enhancing the quality of life for patients and reducing the long-term health care costs associated with these conditions. Therefore, it is recommended that policymakers prioritize the inclusion of inositol in relevant healthcare policies and programs.

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14. FUTURE PERSPECTIVES

In the management of PCOS and GDM the future holds promising opportunities for the administration of inositols. Investigate novel formulations and delivery methods for inositols to improve their bioavailability, stability, and patient adherence. Novel formulations, such as tablets instead of powder could improve the convenience of inositol supplementation.

Investigate the potential of inositol-based interventions to target specific molecular pathways and metabolic abnormalities involved in PCOS and GDM. By uncovering the precise mechanisms of action, we can develop targeted therapies that address the underlying pathophysiology of these conditions.

By embracing these future perspectives and deepening our understanding of inositols, we can unlock their full potential as safe and effective treatments for PCOS and GDM, ultimately enhancing the health and well-being of individuals affected by these conditions worldwide.

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16. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

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-**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.

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