

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

**Impact of preconception androgen levels and conception method
on obstetric outcomes in women with polycystic ovary syndrome**

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common female endocrine disorder. Its clinical presentation is highly heterogeneous. Its prevalence largely depends on the varying diagnostic criteria; it is generally estimated to be around 10-13%, but some studies suggest it may reach as high as 20%. In typical adult cases, this complex endocrine and metabolic disorder is characterized by polycystic ovarian morphology, hyperandrogenemia (with its clinical and/or biochemical features), and chronic amenorrhea/anovulation.

PCOS not only affects the reproductive system but also impacts the entire body and persists throughout an individual's lifetime. The onset and symptoms of the disease are diverse. Lifestyle and body weight significantly influence its course. Its development begins in utero due to epigenetic effects. The etiology is multifactorial, and familial clustering is observed. Currently, the broadest interpretation of the disease's symptomatology is based on the Rotterdam criteria for PCOS diagnosis. A fundamental requirement of this classification is to exclude conditions that cause hyperandrogenemia, oligomenorrhea, and/or anovulation, including late-onset congenital adrenal hyperplasia, hyperprolactinemia, Cushing's syndrome, androgen-producing tumors (adrenal, ovarian), cortisol resistance, primary hypothyroidism/hyperthyroidism.

PCOS should be suspected in all women of reproductive age who present with irregular menstruation, acne, or hirsutism. The presence of male-pattern hair loss and menstrual irregularities should also prompt consideration of polycystic ovary disease. PCOS frequently manifests in adolescence. In this age group, the diagnosis is established based on ovulatory dysfunction and clinical and/or laboratory evidence of androgen excess. Polycystic ovarian morphology is not included in the diagnostic criteria during adolescence, as menstrual irregularities and hyperandrogenemia dominate the clinical picture and are necessary for diagnosis at this stage.

To prevent long-term complications, early diagnosis and avoidance of overdiagnosis are key objectives.

Patients with PCOS frequently experience metabolic abnormalities. Among others, they exhibit increased insulin resistance, hyperinsulinemia, dyslipidemia, and hypertension, which ultimately elevate the risk of cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea syndrome (OSA), diabetes, metabolic syndrome, and endometrial carcinoma. Psychological issues, including anxiety and depression, are also more prevalent in affected individuals.

The development of PCOS is influenced by both genetic and environmental factors. Genetic mutations associated with gonadotropin secretion, folliculogenesis, insulin secretion and/or action, and androgen biosynthesis regulation have been identified. It is also undeniable that environmental factors such as diet, occupation, lifestyle, and obesity play a significant role in the manifestation of the disease.

Insulin resistance (IR) and the compensatory hyperinsulinemia it induces affect a significant proportion of PCOS patients, with estimates reaching 50-90%. Elevated insulin levels synergistically interact with luteinizing hormone (LH), stimulate androgen secretion from theca cells, and inhibit the production of sex hormone-binding globulin (SHBG) and insulin-like growth factor-binding protein-1 (IGFBP-1). This ultimately leads to an increase in free androgen levels. Reduced IGFBP-1 levels result in elevated insulin-like growth factor-1 (IGF-1) levels, further contributing to excessive ovarian androgen production.

Most research indicates that obesity and metabolic syndrome are highly prevalent in PCOS patients. The prevalence of metabolic syndrome in individuals with PCOS is estimated to be between 33-47%. Obesity affects approximately 50% of PCOS patients, according to some studies. Obesity exacerbates insulin resistance, increases hyperinsulinemia, worsens ovulatory dysfunction, and aggravates menstrual irregularities. It also heightens the risk of cardiovascular issues, endometrial carcinoma, and diabetes.

A significant proportion of women with PCOS, around 40-50%, struggle with fertility issues. PCOS accounts for approximately 80% of cases of infertility caused by anovulation. Although the syndrome is a highly complex reproductive-metabolic disorder, the main target of ovulation induction therapy is the hypothalamic-pituitary axis.

As a first-line treatment, lifestyle modifications should be attempted in obese PCOS patients. Weight loss can improve and even restore ovulation without pharmacological intervention. Before initiating treatment, patients should be screened for impaired glucose tolerance, as glucose metabolism disorders increase pregnancy-related complications and worsen perinatal outcomes. Even modest weight loss of 5-10% can improve metabolic status, reduce androgen levels, and enhance ovulation.

Previously, it was suggested that insulin resistance in PCOS patients could be managed with metformin combined with lifestyle changes. Metformin alone can also be used to improve ovulation rates and may be combined with clomiphene citrate or letrozole. The primary goal of treatment is to restore normal ovulation with single follicle maturation, as this reduces the risk of multiple pregnancies. Women seeking pregnancy can undergo pharmacological ovulation

stimulation using clomiphene citrate, letrozole, or gonadotropins, or surgical intervention such as ovarian drilling.

According to the latest guidelines, the first-choice medication for anovulatory infertility treatment is letrozole, where available. As an aromatase inhibitor, it prevents estrogen synthesis from androgens, thereby eliminating negative feedback and increasing follicle-stimulating hormone (FSH) secretion. Unlike clomiphene citrate, it does not affect estrogen receptors centrally or in the endometrium and is associated with a lower incidence of multiple pregnancies. Letrozole results in higher cumulative ovulation rates and live birth rates compared to clomiphene citrate (CC). Although previously used as a primary therapy, CC remains effective for ovulation induction, either alone or in combination with metformin. However, it carries a higher risk of multiple follicle development, ovarian hyperstimulation syndrome (OHSS), and twin pregnancies. If these treatments fail, gonadotropin therapy can be employed. Laparoscopic ovarian drilling is considered a second-line therapy for PCOS patients. However, due to the success of ovulation induction treatments, its use has declined. Disadvantages include the risk of adhesions, surgical complications, and inevitable depletion of ovarian reserve, potentially leading to premature ovarian failure.

If conventional ovulation induction therapies and/or ovarian drilling fail, assisted reproductive techniques such as intrauterine insemination (IUI), in vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI) may be necessary. Since PCOS patients typically have a high number of antral follicles, IVF treatments carry an increased risk of OHSS and multiple pregnancies. The goal is to achieve maximum oocyte yield while minimizing the risk of OHSS. Strategies such as single embryo transfer or frozen embryo transfer are recommended to reduce these risks.

IVF is a highly effective procedure; however, PCOS patients face heightened risks, including ovarian hyperstimulation syndrome and increased likelihood of multiple pregnancies and obstetric complications. Assisted reproductive techniques, particularly IVF, pose risks not only to the mother but also to the fetus and newborn. It remains uncertain whether these risks stem from PCOS itself, high BMI, or the procedures involved. These risks include early miscarriage, multiple pregnancies, low birth weight, gestational hypertension, gestational diabetes, placental abnormalities (placenta previa, placental abruption), and preterm birth. The exact causes of adverse outcomes remain unclear, but contributing factors may include pre-existing conditions, body weight, sperm quality, laboratory conditions, maternal/oocyte age, obstetric practices, prenatal genetic testing, embryo biopsy, and the “vanishing twin” phenomenon.

The presence of PCOS increases the risk of pregnancy complications, primarily due to higher androgen levels, insulin resistance, and the more frequent occurrence of metabolic disorders. These factors can contribute to an increased incidence of obstetric and neonatal complications. Women affected by PCOS have a significantly higher risk of miscarriage due to obesity, hyperinsulinemia, elevated LH levels, and endometrial dysfunction, with studies indicating that the rate of spontaneous miscarriages is 20-40% higher compared to the general population. However, it remains unclear to what extent the techniques used for obesity and/or infertility management independently contribute to these factors. The incidence of gestational diabetes is three times higher, while the risk of gestational hypertension and preeclampsia can be three to four times greater in women with PCOS, and the risk of preterm birth is twice as high compared to healthy women. There is a higher prevalence of small-for-gestational-age (SGA) newborns, which can be attributed to placental dysfunction, twin pregnancies, and preterm birth. Operative delivery is required more frequently, and both elective and non-elective cesarean sections occur more often in women with PCOS.

OBJECTIVE

Pre-Pregnancy Serum Androgen Levels, Free Androgen Levels, Androgen Level Ratios, and Their Association with Obstetric Outcomes in PCOS Patients

We sought to answer the following questions:

1. Is there an association between preconceptional androgen levels and the mode of delivery?
2. Is there an association between preconceptional androgen levels and the risk of miscarriage?
3. Is there a relationship between preconceptional androgen levels and the development of pregnancy-related complications, including gestational diabetes mellitus (GDM) and preeclampsia?
4. Is there a correlation between preconceptional androgen levels and neonatal birth weight and/or weight percentile?
5. Is there an association between preconceptional androgen levels and fetal sex determination?
6. Is there a relationship between preconceptional androgen levels and the mode of conception?

Analysis of Preconceptional Endocrine Parameters in Successful Pregnancies Conceived via IVF and Non-IVF in PCOS Patients

1. What proportion of PCOS patients require IVF to achieve pregnancy?
2. Is there a significant difference in maternal age and gestational age between pregnancies conceived via IVF and those conceived naturally in PCOS patients?
3. Are there any preconceptional laboratory parameters that can predict the need for IVF in PCOS patients?
4. Are specific obstetric outcomes more prevalent in patients requiring IVF, independent of maternal age?

MATERIALS AND METHODS

With the approval of the Ethics Committee of the University of Debrecen, a retrospective review of electronic medical records was conducted for all patients diagnosed with polycystic ovary syndrome (PCOS) treated at the Department of Obstetrics and Gynecology, University of Debrecen, between 2012 and 2019. A total of 738 PCOS patients were identified, and their medical records were examined. Inclusion criteria for the study required patients to have had at least one successful delivery beyond the 23rd gestational week at our clinic. Based on these criteria, the study cohort comprised 160 PCOS patients who had at least one viable delivery, with a total of 232 pregnancies analyzed, including data on the newborns. The diagnosis of PCOS was established according to the Rotterdam criteria. Data were retrospectively collected from the electronic medical database system (E-medsolution).

This study was structured into two main sections:

Pre-Pregnancy Serum Androgen Levels, Free Androgen Levels, Androgen Level Ratios, and Their Association with Obstetric Outcomes in PCOS Patients

Parameters Assessed

The following clinical and demographic data were extracted from the medical history of PCOS patients: mode of conception, history of miscarriage, maternal age, body mass index (BMI), length of pregnancy, mode of delivery (vaginal delivery or cesarean section), neonatal sex, birth weight, and pregnancy complications, including gestational diabetes mellitus (GDM), preeclampsia, and preterm birth. Birth weight percentiles were calculated using the newborn's birth weight and gestational age, referencing standard percentile tables and databases.

Laboratory Assessments

Baseline pre-pregnancy serum levels of total testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEAS), sex hormone-binding globulin (SHBG), and thyroid-stimulating hormone (TSH) were recorded. The following hormonal ratios were also computed: testosterone/SHBG (T/SHBG), androstenedione/SHBG (AD/SHBG), DHEAS/SHBG, and testosterone/androstenedione (T/AD). Hormone levels, including total testosterone (nmol/L), dehydroepiandrosterone sulfate (μ mol/L), sex hormone-binding globulin (nmol/L), and androstenedione (μ g/L), were measured before conception and prior to initiating any endocrine treatment. Blood samples for hormone measurements were collected in the morning between days 3 and 5 of the menstrual cycle. Anthropometric data, including

age, height, and weight, were obtained from pre-pregnancy medical records, and BMI was calculated using the metric formula ($\text{BMI} = \text{kg/m}^2$).

Analysis of Preconceptional Endocrine Parameters in PCOS Patients With IVF and Non-IVF Pregnancies

Parameters Assessed

Collected data included mode of conception, maternal age, gestational age at delivery, birth weight, birth weight percentile, and baseline hormone levels (follicle-stimulating hormone [FSH], TSH, estradiol [E2], prolactin, luteinizing hormone [LH]). Androgen parameters (testosterone, androstenedione, DHEAS), SHBG, vitamin D levels, and progesterone levels measured in the mid-luteal phase (cycle days 21-23) were also evaluated. The endocrinological symptoms examined included hyperandrogenism, irregular menstrual cycles, insulin resistance, andrological abnormalities, and the initiation of thyroxine substitution or metformin therapy prior to conception. Among obstetric outcomes, mode of delivery, neonatal sex, and pregnancy complications, such as preeclampsia, GDM, and preterm birth, were analyzed.

Laboratory Analysis

Serum levels of thyroid-stimulating hormone, dehydroepiandrosterone sulfate, sex hormone-binding globulin, and testosterone were measured using electrochemiluminescence (ECLIA) immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). Serum androstenedione concentrations were determined using a chemiluminescence (CLIA) immunoassay (DiaSorin Inc., Stillwater, MN, USA).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 25 software. Normality of data distribution was assessed using the Kolmogorov-Smirnov test, while Levene's test was applied to evaluate variance homogeneity. For normally distributed data, comparisons were conducted using independent samples t-tests, and Pearson's correlation analysis was employed to determine associations. Non-normally distributed data were analyzed using the non-parametric Mann-Whitney U test. Nominal variables were compared using the Chi-square test or Fisher's Exact test. Binary and multinomial logistic regression analyses were used to determine odds ratios (ORs), adjusted odds ratios (aORs), and 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant. Data are presented as mean $\pm$ standard deviation (SD), ORs, and aORs with 95% CIs.

RESULTS

Examination of the Association Between Pre-Pregnancy Serum Androgen Levels, Free Androgen Levels, Androgen Level Ratios, and Obstetric Outcomes in PCOS Patients

A retrospective analysis was conducted on data from 9,787 patients treated at the Department of Endocrinology and Obstetrics of the DEKK Clinic of Obstetrics and Gynaecology. Among these, 738 patients were diagnosed with PCOS, and 160 patients had at least one delivery beyond 23 weeks of gestation. The final analysis included data from these 160 patients and a total of 232 deliveries. Measurement of androgen levels was not performed in all cases, as the diagnosis of PCOS was established based on clinical criteria, including hyperandrogenism or ovulatory dysfunction with polycystic ovarian morphology (PCOM), without the necessity of laboratory confirmation. Consequently, preconceptional androgen parameters were available for 73 patients.

In PCOS patients with a history of miscarriage, pre-pregnancy androstenedione levels were significantly elevated (3.60 ± 1.97 vs. 2.68 ± 1.22 , $p=0.04$). A one-unit increase in androstenedione levels was associated with a 1.513-fold increased risk of miscarriage (95% CI: 0.988-2.317, $p=0.057$); however, after adjusting for maternal age, the association reached statistical significance (aOR: 1.555, 95% CI: 1.005-2.407, $p=0.047$).

Patients requiring in vitro fertilization (IVF) treatment were significantly older (32.00 ± 5.26 years vs. 28.83 ± 4.44 years, $p=0.027$). Each additional year of maternal age increased the probability of requiring IVF treatment by 1.157-fold (95% CI: 1.006-1.336, $p=0.041$).

No significant differences were observed in androgen levels, SHBG levels, androgen/SHBG ratios, or TSH levels between PCOS patients who developed gestational diabetes mellitus (GDM) or preeclampsia. Although SHBG levels were lower in the GDM group, this difference did not reach statistical significance (SHBG: 38.51 ± 22.5 vs. 61.86 ± 44.43 , $p=0.18$). However, the mean age of GDM patients was significantly higher (32.22 ± 4.06 years vs. 28.85 ± 4.70 years, $p=0.044$), whereas BMI did not differ significantly between groups.

Pre-pregnancy androstenedione levels were significantly higher in patients who delivered a female neonate (3.57 ± 1.96 vs. 2.58 ± 1.12 , $p=0.01$). A one-unit increase in androstenedione levels increased the likelihood of delivering a female neonate by 1.512-fold (95% CI: 1.037-2.207, $p=0.03$). This association remained significant after adjusting for maternal age (aOR: 1.495, 95% CI: 1.016-2.198, $p=0.04$).

No significant differences in pre-pregnancy androgen, SHBG, and TSH levels or androgen/SHBG ratios were observed between patients who delivered at term and those who experienced preterm birth. However, the testosterone/androstenedione (T/AD) ratio was significantly higher in those who later had a preterm birth (0.82 ± 0.61 vs. 0.55 ± 0.31 , $p=0.05$). After adjusting for maternal age, this association was no longer statistically significant but maintained a notable trend (OR: 4.531, 95% CI: 0.834-24.612, $p=0.08$; aOR: 4.173, 95% CI: 0.727-23.960, $p=0.10$).

Maternal age at delivery exhibited a significant negative correlation with pre-pregnancy DHEAS levels ($r= -0.40$, $p=0.001$) and the DHEAS/SHBG ratio ($r= -0.32$, $p=0.01$). However, no significant correlations were observed between age and pre-pregnancy androgen levels, androgen/SHBG ratios, the T/AD ratio, or TSH levels. Similarly, no significant associations were found between gestational age at delivery and pre-pregnancy androgen levels, androgen/SHBG ratios, the T/AD ratio, or TSH levels.

Preconception androgen levels and TSH were not associated with birth weight or birth weight percentiles. However, pre-pregnancy SHBG levels showed a weak but significant negative correlation with birth weight ($r= -0.30$, $p=0.02$). Conversely, androgen/SHBG ratios exhibited a weak positive correlation with birth weight: T/SHBG ($r= 0.28$, $p=0.03$), AD/SHBG ($r= 0.24$, $p=0.06$), and DHEAS/SHBG ($r= 0.26$, $p=0.04$). Similar findings were observed for birth weight percentiles: pre-pregnancy SHBG levels negatively correlated with birth weight percentiles ($r= -0.27$, $p=0.04$), whereas androgen/SHBG ratios showed a positive correlation: T/SHBG ($r= 0.28$, $p=0.03$), AD/SHBG ($r= 0.25$, $p=0.05$), and DHEAS/SHBG ($r= 0.27$, $p=0.03$).

Preconceptional Endocrine Parameters in PCOS Patients with IVF and Non-IVF Pregnancies

Pregnancies were stratified based on the mode of conception. Assisted reproductive techniques (ART) were utilized in 46% of cases, comprising ovulation induction (23%), intrauterine insemination (8%), and in vitro fertilization (IVF) (15%). The remaining 54% of patients conceived spontaneously without ovulation induction, achieving pregnancy through metabolic-endocrine therapy and lifestyle modifications alone.

Androstenedione levels (2.20 ± 1.11 vs. 3.16 ± 1.66 , $p=0.05$) and dehydroepiandrosterone sulfate (DHEAS) levels (6.11 ± 3.13 vs. 8.09 ± 3.37 , $p=0.05$) were significantly lower in the IVF group compared to the non-IVF group.

Maternal age was significantly higher in PCOS patients requiring IVF intervention. This association was evident when considering all pregnancies (33.58 ± 4.36 vs. 29.83 ± 4.38 ,

$p < 0.001$) and persisted when restricting the analysis to singleton pregnancies (33.57 ± 4.26 vs. 29.94 ± 4.26 , $p < 0.001$).

In assessing predictive factors for the necessity of IVF, no significant association was found between the onset of endocrinological symptoms and the requirement for therapeutic interventions. Although not statistically significant, the presence of a hematological disorder increased the likelihood of requiring IVF.

Binary logistic regression analyses were conducted to evaluate odds ratios (ORs) associated with the need for IVF. Each additional year of maternal age increased the likelihood of IVF treatment by 22% (OR: 1.222, 95% CI: 1.11-1.35, $p < 0.001$). Conversely, a one-unit increase in DHEAS levels ($\mu\text{mol/L}$) was associated with an 18% reduction in the probability of requiring IVF (OR: 0.82, 95% CI: 0.66-1.01, $p = 0.06$), while a one-unit increase in androstenedione levels ($\mu\text{g/L}$) was associated with a 42% reduction in IVF necessity (OR: 0.58, 95% CI: 0.33-1.02, $p = 0.056$). The latter two associations were marginally above the threshold of statistical significance.

Preterm birth and cesarean section rates were significantly elevated in IVF-conceived pregnancies, both when considering singleton pregnancies and the total cohort, including twin pregnancies. Overall, IVF pregnancies were associated with a more than fourfold increase in the risk of preterm birth (OR: 4.53, 95% CI: 1.75-11.70, $p = 0.002$). A similar, albeit non-significant, upward trend was observed in singleton pregnancies (OR: 3.12, 95% CI: 0.89-10.92, $p = 0.07$). Likewise, the incidence of cesarean section was significantly higher in the IVF group (all pregnancies: OR 3.22, 95% CI: 1.4-7.4, $p = 0.006$; singleton pregnancies: OR 2.55, 95% CI: 1.02-6.35, $p = 0.04$). These associations remained significant after adjusting for maternal age. Following maternal age adjustment, the risk of preterm birth remained significantly elevated in IVF pregnancies (aOR: 5.06, 95% CI: 1.81-14.18, $p = 0.002$), with a similar, though non-significant, trend in singleton pregnancies (aOR: 3.38, 95% CI: 0.88-12.88, $p = 0.075$). The odds of cesarean section were also significantly higher in the IVF cohort (aOR: 2.82, 95% CI: 1.19-6.71, $p = 0.019$), while in singleton pregnancies, the difference approached but did not reach statistical significance (aOR: 2.25, 95% CI: 0.87-5.81, $p = 0.09$).

A significant difference in neonatal birth weight was observed only in the total pregnancy cohort (3069 ± 683 vs. 3362 ± 638 , $p = 0.02$). The presence of twin pregnancies within the IVF group likely contributed to the lower birth weight, as no significant difference was detected between IVF and non-IVF singleton pregnancies (3289.13 ± 496.08 vs. 3376.62 ± 628.71 , $p = 0.52$). Additionally, no significant difference was found in birth weight percentiles

between IVF and non-IVF pregnancies (all pregnancies: 51.37 ± 33.67 vs. 54.85 ± 29.82 , $p = 0.56$; singleton pregnancies: 54.09 ± 32.63 vs. 55.11 ± 29.83 , $p = 0.88$).

DISCUSSION

Polycystic ovary syndrome (PCOS) is the most significant endocrine disorder among women of reproductive age. The condition often begins in adolescence, with a prevalence reaching up to 20% among adult women. Its significance extends beyond menstrual irregularities, hyperandrogenemia, and polycystic ovarian morphology observed via ultrasound. The impact of PCOS on fertility is undeniable, and in the long term, it is associated with various health issues, including an increased prevalence of cardiovascular diseases, endometrial cancer, and obstructive sleep apnea disorder (OSAD).

In recent years, a substantial amount of knowledge has accumulated regarding polycystic ovary syndrome. To our knowledge, we were the first to examine the detailed preconception androgen levels and their ratios in PCOS patients and their associations with obstetric outcomes. Additionally, we pioneered the comparison of endocrine parameters measured before successful pregnancies in PCOS patients, conceived naturally and through in vitro fertilization (IVF).

Pre-Pregnancy Serum Androgen Levels, Free Androgen Levels, Androgen Ratios, and Their Association with Obstetric Outcomes in PCOS Patients

In our study, only the preconception androstenedione level was significantly higher in PCOS patients with a history of at least one miscarriage. This association was found to be independent of age and BMI as confounding factors. The effect of androgens on endometrial receptivity—defined as the ability of the endometrium to support embryo implantation—is well known. If endometrial receptivity is impaired, it can lead to miscarriage and infertility. Identified genes and proteins that influence endometrial receptivity in hyperandrogenic states include the Wnt and CDK signaling pathways, HOXA genes, integrin $\alpha V\beta 3$, MECA-79, and MAGEA-11. Furthermore, early in vitro studies suggest that androstenedione may inhibit the growth of human endometrial cells (as indicated by reduced (3)H-thymidine uptake and Ki67 expression) and their secretory activity (glycodelin A secretion). However, testosterone (T), dihydrotestosterone (DHT), and dehydroepiandrosterone sulfate (DHEAS) did not produce similar alterations. No significant differences were found in other measured androgen parameters between the groups.

In our study, PCOS women requiring IVF treatment were significantly older. This trend is also observed in the presence of other endocrine disorders (e.g., diminished ovarian reserve [DOR], hypothyroidism, and Hashimoto's thyroiditis). A one-year increase in maternal age raised the necessity for IVF treatment by 1.157 times. This finding is not surprising, as it is well known that maternal age significantly increases the need for IVF treatment, and this also proved to be true in our PCOS patient cohort.

There was no significant difference in baseline preconception androgen levels, androgen/sex hormone-binding globulin (SHBG) ratios, or testosterone/androstenedione ratios between PCOS patients who conceived naturally and those who required IVF. However, DHEAS and androstenedione levels tended to be lower, while SHBG levels tended to be higher, in those who ultimately conceived through IVF, though these differences were not statistically significant. The differences in preconception androgen levels remained nonsignificant even though the IVF population had a significantly higher age, and age correlates with DHEAS levels.

Maternal age showed a significant negative correlation with DHEAS and the DHEAS/SHBG ratio among preconception androgen levels. The pattern of circulating dehydroepiandrosterone sulfate (DHEAS) levels follows a characteristic trajectory throughout human life: fetal DHEAS levels gradually rise during pregnancy, followed by a rapid decline in the neonatal period. A subsequent increase occurs during adrenarche, reaching its peak in early adulthood, after which DHEAS levels progressively decline with age.

We found no significant association between preconception androgen levels, SHBG levels, and the development of gestational diabetes mellitus (GDM) or preeclampsia during pregnancy. According to the literature, low SHBG levels are strong predictors of insulin resistance and gestational diabetes, and SHBG levels gradually increase with age after reaching their lowest point in adolescence (in contrast to DHEAS levels). Our gestational diabetes group was significantly older, which may explain why no significant difference was observed in SHBG levels, consistent with the aforementioned trends.

We found significantly higher androstenedione levels in those who gave birth to female newborns. A 1 µg/L increase in AD levels increased the likelihood of having a female newborn by 51%, and this association was independent of maternal age. The testosterone/androstenedione (T/AD) ratio was also lower and approached statistical significance, although it did not reach the threshold.

The T/AD ratio is commonly used as an indicator of 17-β-hydroxysteroid dehydrogenase (17-β-HSD) enzyme activity, which catalyzes the conversion of androstenedione to testosterone. A

low T/AD ratio may indicate reduced enzyme activity, while a higher ratio suggests increased activity. The T/AD ratio has been studied in relation to PCOS, and recent research has used a low T/AD ratio to identify 17- β -HSD type 3 deficiency following hCG stimulation. This deficiency plays a role in male under-masculinization and can be associated with disorders of sexual development (DSD).

To the best of our knowledge, this is the first study demonstrating that preconception maternal AD levels and the T/AD ratio differ by offspring sex in PCOS patients. We hypothesize that altered 17- β -HSD enzyme activity may be present in some PCOS patients and that this altered enzymatic activity may be inherited by the fetus, influencing sex determination or potentially favoring fertilization by sperm carrying a specific chromosome. It is unlikely that altered maternal hormone levels directly influence fetal sex, as placental aromatase protects the fetus from excessive androgen exposure.

Among PCOS patients who later experienced preterm birth, we also found a higher T/AD ratio, while androgen levels showed no significant differences. We did not find any prior literature investigating the relationship between the T/AD ratio and preterm birth. Existing studies on testosterone and hyperandrogenism as predictors of preterm birth have yielded contradictory results, with some showing an association while others have not.

Our findings suggest that although preconception androgen levels were similar between preterm and full-term birth groups, the T/AD ratio—and consequently maternal or even inherited fetal 17- β -HSD enzyme activity—may influence the risk of preterm birth.

Preconception androgen levels did not show a significant association with birth weight or birth weight percentiles. However, preconception SHBG levels exhibited a negative correlation with birth weight, while the preconception androgen/SHBG ratio demonstrated a positive correlation. Among the correlations with birth weight, the SHBG-birth weight association was the strongest and most significant compared to the T/SHBG, AD/SHBG, and DHEAS/SHBG ratios.

Preconception SHBG concentration has been shown not to be an independent predictor of GDM risk when obesity is taken into account. However, independent of GDM and preconception BMI, SHBG is a significant predictor of neonatal birth weight. Since differences in birth weight can be attributed either to actual size variations or to differences in gestational age (as fetal weight gain can range from 200–400 g per week near term with adequate placental function), we also calculated birth weight percentiles to obtain information on true growth potential, unaffected by the exact timing of birth.

When examining birth weight percentiles, the previously analyzed parameters (T/SHBG, AD/SHBG, and DHEAS/SHBG ratios and SHBG) remained statistically significant, but the T/SHBG ratio (also known as the free androgen index, FAI) correlated more strongly and significantly with birth weight percentiles than SHBG alone. Thus, the T/SHBG ratio may serve as a slightly better overall indicator of fetal growth potential than SHBG alone. In our population, preconception BMI did not show a significant correlation with either birth weight or birth weight percentiles.

Preconceptional Endocrine Parameters in PCOS Patients with IVF and Non-IVF Pregnancies

To our knowledge, in the second phase of our study, we were the first to examine preconception endocrine parameters, endocrine symptoms and treatments, as well as obstetric outcomes in PCOS patients who achieved successful pregnancies with or without IVF treatment. The potential complications of IVF are well known, as is the fact that IVF should be avoided in PCOS patients whenever possible due to the increased risk of OHSS and multiple pregnancies. According to WHO data, 17.5% of the global adult population (approximately one in six people) struggles with infertility. The primary cause of anovulatory infertility is PCOS. In our study, 15% of PCOS pregnancies were conceived through IVF. After treating endocrine and metabolic disorders associated with PCOS, 54% of patients conceived naturally, while the remaining 31% required ovulation induction, insemination, or a combination of these to achieve conception.

During the examination of preconception clinical and laboratory parameters, we found that, as expected, maternal age was significantly higher in the IVF group. Maternal age over 31 years increased the likelihood of requiring IVF treatment by 3.89 times. Our study revealed that PCOS patients in both groups were overweight; however, there was no significant difference in BMI between the IVF and non-IVF treatment groups. Considering that the patients were neither too old compared to the average Hungarian reproductive-age population nor severely obese, we can assume that neither extreme age nor BMI values distorted the results.

The LH/FSH ratio tended to be higher in the non-IVF group. When dichotomizing LH/FSH data and setting a threshold value of 1.3, we found that an LH/FSH ratio below 1.3 increased the likelihood of requiring IVF treatment by 3.58 times. Studies indicate that changes in the LH/FSH ratio may influence the outcomes of IVF procedures. This may be explained by the fact that an increasing LH/FSH ratio indicates more significant ovulatory dysfunction, which can be effectively treated with ovulation-supporting treatments (endocrine, metabolic,

ovulation induction). However, in cases of a lower LH/FSH ratio, other non-ovulatory dysfunction-related causes of infertility may be suspected, which naturally increases the likelihood of requiring IVF in the future. A recent study suggests that patients with a higher basal LH/FSH ratio are more likely to develop OHSS and have a higher incidence of GDM in PCOS cases.

Our study established that progesterone levels measured in the luteal phase, though not reaching statistical significance, were nearly twice as high in the IVF group. This result clearly shows that among those who did not require IVF, ovulatory function was poorer, and pregnancies achieved through ovulation induction and/or insemination treatments made IVF unnecessary.

Among preconception androgen levels, DHEAS and AD levels were significantly lower in the IVF group. A 1 $\mu\text{mol/L}$ increase in DHEAS levels reduced the likelihood of being in the IVF group by 18%, while a 1 $\mu\text{g/L}$ increase in androstenedione decreased this likelihood by 42%. Additionally, DHEAS levels below 6.5 $\mu\text{mol/L}$ increased the probability of requiring IVF treatment by 3.86 times. These differences can only partially be explained by the fact that DHEAS levels decrease with age in both women and men. This declining trend is also observed in PCOS patients. However, the 25-50% difference in DHEAS levels between the two groups cannot be fully explained by the average 3.5-year age difference, as the annual decline in DHEAS levels starting in the 20s-30s is only 2-3% per year. DHEA supplementation is frequently used in IVF for low ovarian reserve, and several studies support its positive effects, although the issue is not yet fully clarified. However, a clear relationship between androgen levels and IVF success has not yet been confirmed.

Preconception endocrine symptoms and treatments did not significantly influence the likelihood of requiring IVF treatment. Metformin therapy, thyroxine supplementation, hyperandrogenism, andrological disorders, previous miscarriage, and insulin resistance did not show predictive value. Although it just missed statistical significance, a clear trend was observed regarding menstrual cycle regularity: the presence of irregular cycles approximately halved the likelihood of requiring IVF later. This is understandable, as irregular cycles in PCOS often indicate oligo-anovulation, which in many cases can be successfully treated with endocrine-metabolic therapy or ovulation induction, thus avoiding the need for IVF.

Our results indicate, consistent with literature data, that IVF conception may be associated with adverse obstetric outcomes. Various studies suggest that in pregnant women with PCOS, the risk of pregnancy-induced hypertension and preeclampsia is 3–4 times higher, the risk of gestational diabetes is 3 times higher, and the risk of preterm birth is twice as high. Furthermore, previous studies have indicated that in PCOS, multiple pregnancies further increase the risk of

pregnancy-induced hypertension (OR 2.030), preeclampsia (OR 2.879), gestational diabetes (OR 1.358), preterm birth (OR 8.466), and cesarean section (OR 5.146).

In IVF pregnancies, both for all pregnancies and for singleton pregnancies, the rate of preterm birth and cesarean section was 2.5–4.5 times higher compared to non-IVF-conceived pregnancies. However, we found a statistically significant difference only in overall pregnancies regarding preterm birth and cesarean section. Among singleton pregnancies, after age correction, the trend remained, but the difference was just not statistically significant.

The occurrence of gestational diabetes and preeclampsia did not show a higher prevalence depending on the mode of conception, neither among all pregnancies nor among singleton pregnancies.

There was no difference in the incidence of small-for-gestational-age (SGA) newborns or intrauterine growth restriction (IUGR) between IVF and naturally conceived pregnancies, as birth weight percentiles showed similar values for both total pregnancies and the singleton group. No cases of IUGR were observed in any of the examined subgroups.

Regarding the relationship between PCOS and IUGR, previous research has produced contradictory results: while one study suggested that PCOS increases the likelihood of IUGR by 2.62 times, other studies did not find significant differences. However, it is important to note that these studies did not compare birth weights and their percentiles between IVF and non-IVF subgroups of PCOS patients.

SUMMARY

Polycystic ovary syndrome (PCOS) is the most prevalent gynecological endocrine disorder, exerting a significant impact on female fertility and representing the primary cause of anovulatory infertility. The objective of this study was to evaluate the associations between preconception androgen levels and androgen ratios in patients with PCOS and subsequent perinatal outcomes, as well as to assess the influence of the mode of conception on obstetric outcomes in pregnant women with PCOS.

Our novel scientific findings are as follows:

- Preconception serum androstenedione (AD) concentrations were significantly elevated in PCOS patients with a history of at least one miscarriage.
- Each 1 µg/L increase in preconception AD level was associated with a 1.513-fold increase in the risk of first-trimester miscarriage in women with PCOS.

- Significantly higher preconception AD levels were observed in women who subsequently gave birth to female neonates.
- A 1 µg/L increase in AD level was associated with a 51% higher probability of delivering a female infant; this association was independent of maternal age.
- The testosterone-to-androstenedione (T/AD) ratio was lower in cases of preterm birth. Although this association did not reach statistical significance, it approached the threshold.
- To our knowledge, this is the first study to demonstrate that preconception maternal AD levels and T/AD ratios in PCOS patients are associated with offspring sex and the risk of preterm delivery.
- Maternal age was positively associated with the likelihood of requiring in vitro fertilization (IVF), increasing by 22% for each additional year of age.
- In contrast, each 1 µmol/L increase in dehydroepiandrosterone sulfate (DHEAS) concentration was associated with an 18% reduction in the likelihood of IVF treatment, while each 1 µg/L increase in AD level reduced the need for IVF by 42%.
- Maternal age above 31 years was associated with a 3.89-fold increase in the probability of undergoing IVF.
- An LH/FSH ratio below 1.3 was associated with a 3.58-fold higher likelihood of requiring IVF.
- Among patients undergoing IVF, the rates of preterm birth and cesarean section were 2.5 to 4.5 times higher than among those who conceived spontaneously, both in overall and singleton pregnancies.

Based on these findings, PCOS represents a highly complex endocrinopathy that imposes a considerable burden on women's reproductive and general health, not only due to its role in infertility but also owing to its association with increased risk of pregnancy complications and potential long-term health consequences.

PUBLICATIONS



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List of publications related to the dissertation

1. **Orosz, M.**, Borics, F., Rátonyi, D., Krasznai, Z. T., Vida, B., Herman, T., Csehely, S., Jakab, A., Lukács, L., Lampé, R., Deli, T.: Endocrine Characteristics and Obstetric Outcomes of PCOS Patients with Successful IVF and Non-IVF Pregnancies.
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IF: 3 (2023)
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