

# The Role of Serum Testosterone in Early Pregnancy Outcome: A Comparison in Women With and Without Polycystic Ovary Syndrome

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## Abstract

**Objective:** Hyperandrogenic conditions in women are associated with increased rates of miscarriage. However, the specific role of maternal testosterone in early pregnancy and its association with pregnancy outcome is unknown. The purpose of this study was to compare serum testosterone levels during early pregnancy in women with and without polycystic ovary syndrome (PCOS) who either had successful pregnancies or miscarried.

**Method:** We collected serum samples from women attending a university-based fertility centre at the time of their first positive serum beta human chorionic gonadotropin pregnancy test. The samples were subsequently assayed for total testosterone level. We used logistical regression modelling to control for PCOS diagnosis, BMI, and age.

**Results:** Total testosterone levels were available for 346 pregnancies, including 286 successful pregnancies and 78 first trimester miscarriages. We found no difference in total testosterone levels between women who subsequently had an ongoing pregnancy (mean concentration  $3.6 \pm 2.6$  nmol/L) and women with a miscarriage (mean  $3.6 \pm 2.4$  nmol/L). Using the Rotterdam criteria to identify women with PCOS, we also found no differences in serum testosterone between women who had ongoing pregnancies or miscarriages, either with PCOS ( $P = 0.176$ ) or without PCOS ( $P = 0.561$ ).

**Conclusions:** Our findings show that early pregnancy testosterone levels do not predict pregnancy outcome, and they call into question the role of testosterone in causing miscarriage in populations of women with PCOS. Further research is needed to elucidate the normal progression of testosterone levels during pregnancy and to investigate further the relationship between PCOS and miscarriage.

**Key Words:** Testosterone, spontaneous abortion, infertility, pregnancy, androgens, polycystic ovary syndrome

Competing Interests: None declared.

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## Résumé

**Objectif :** Chez les femmes, les troubles liés à l'hyperandrogénie sont associés à des taux accrus de fausse couche. Toutefois, le rôle particulier que joue la testostérone maternelle aux débuts de la grossesse et l'influence qu'elle exerce sur l'issue de la grossesse restent inconnus. L'objectif de la présente étude était de comparer les taux sériques de testostérone aux débuts de la grossesse chez des femmes qui, en présence ou non d'un syndrome d'ovaires polykystiques (SOPK), avaient connu soit une grossesse réussie, soit une fausse couche.

**Méthode :** Nous avons prélevé des échantillons sériques chez des femmes qui fréquentaient un centre de fertilité universitaire, au moment de l'obtention de leur premier résultat positif au test de grossesse fondé sur le taux sérique de bêta-gonadotropine chorionique humaine. Les échantillons ont ensuite été analysés en vue d'établir le taux total de testostérone. Nous avons utilisé un modèle de régression logistique pour neutraliser l'effet du diagnostic de SOPK, de l'IMC et de l'âge.

**Résultats :** Des taux totaux de testostérone étaient disponibles pour 346 grossesses (286 grossesses réussies et 78 fausses couches au premier trimestre). Nous n'avons constaté aucune différence en matière de taux total de testostérone entre les femmes qui ont été en mesure de poursuivre leur grossesse (concentration moyenne de  $3,6 \pm 2,6$  nmol/l) et les femmes qui ont connu une fausse couche (moyenne de  $3,6 \pm 2,4$  nmol/l). En ayant recours aux critères de Rotterdam pour identifier les femmes présentant un SOPK, nous avons constaté qu'il n'existait également aucune différence en matière de taux sérique de testostérone entre les femmes qui ont pu poursuivre leur grossesse et celles qui ont connu une fausse couche, qu'il y ait eu présence d'un SOPK ( $P = 0,176$ ) ou non ( $P = 0,561$ ).

**Conclusions :** Les résultats que nous avons obtenus démontrent que les taux de testostérone présents aux débuts de la grossesse ne permettent pas de prévoir l'issue de la grossesse et remettent en question l'influence qu'exerce la testostérone sur la survenue d'une fausse couche chez les femmes qui présentent un SOPK. Des recherches plus poussées sont nécessaires pour élucider l'évolution normale des taux de testostérone pendant la grossesse, ainsi que pour explorer plus à fond le lien qui existe entre le SOPK et la fausse couche.

## INTRODUCTION

The establishment of a successful pregnancy requires both a healthy endometrial environment and a competent embryo. Whereas fetal causes of pregnancy loss (e.g. fetal aneuploidy) are well known, factors affecting endometrial competence are poorly understood. Under normal circumstances, the endometrium goes through a series of changes under steroid hormone regulation to become receptive to implantation by an embryo. For example, studies in mouse models and donor oocyte populations have shown that estrogen priming before progesterone treatment is necessary for endometrial receptivity.<sup>1-3</sup>

Androgens and estrogens demonstrate an intricately balanced relationship in the normal control of endometrial cell growth and gene expression. Testosterone has been shown to inhibit estrogen-related gene expression in the endometrium, and elevated androgen levels have been proposed as a mechanism for miscarriage related to implantation defects rather than aneuploidy.<sup>4</sup> Conditions associated with elevated testosterone levels, such as polycystic ovary syndrome and obesity, have been shown to have higher than expected miscarriage rates.<sup>5-9</sup> To date there is no evidence of higher aneuploidy rates in the embryos of women with PCOS who miscarry,<sup>10</sup> and no increase in rates of miscarriage has been observed when women with PCOS act as oocyte donors.<sup>11</sup> These findings suggest that the effects of elevated androgen levels on the endometrial environment may be the cause of miscarriage in women with PCOS.<sup>5,12</sup> Yet human studies have not shown a significant correlation between pre-pregnancy testosterone levels and pregnancy outcomes.<sup>13</sup> However, testosterone levels have not been carefully examined during early pregnancy and implantation. In a small study of 53 women undergoing IVF, Takeuchi et al. did not find testosterone levels at three days and at 14 days after embryo transfer to be predictive of pregnancy rates using logistic regression analysis, but they did find a higher mean testosterone level at day 14 in women who became pregnant.<sup>14</sup> However, it is unclear in that study how testosterone was measured and whether birth outcome was recorded.

The objective of this study was to examine serum testosterone levels at four to six weeks' gestational age in both successful pregnancies and those ending in miscarriage, and also in women with and without PCOS.

## ABBREVIATIONS

β-hCG	beta human chorionic gonadotropin
PCOS	polycystic ovary syndrome
SHBG	sex hormone binding globulin

It was hypothesized that women who miscarried would demonstrate significantly higher total testosterone levels in early pregnancy than women with ongoing pregnancies.

## METHODS

Women attending our Northern California university-based fertility clinic for management of infertility who had a possible pregnancy were approached for participation in this study. In addition to having blood drawn for quantitative β-hCG assessment at this time, women who gave informed consent had an additional aliquot of serum drawn and frozen at -20°C. In this study, an initial serum sample was collected from these women at the time of first positive serum pregnancy test, at between four and six weeks' gestation. For most participants (287/346, 83%), we collected a follow-up serum sample on average two days after the initial sample (minimum 2 days, maximum 6 days). In this study, samples from women with single ongoing pregnancies or first trimester miscarriages during a three-year period were later analyzed for total testosterone.

All subjects, regardless of method of conception, were excluded from the analysis if they had thyroid dysfunction (TSH ≥ 2.5 mU/L), hyperprolactinemia on two samples (serum prolactin above the upper limit of normal for the assay used), ovarian or adrenal tumours, congenital adrenal hyperplasia, or hypothalamic amenorrhea. All subjects underwent hysteroscopy before treatment. Women with submucous fibroids, endometrial polyps, or intrauterine synechiae had these surgically corrected before treatment was initiated. Women with uterine anomalies or intramural fibroids > 3 cm in diameter were excluded from the evaluation.

During the study period, a total of 445 infertile women who conceived with or without ovarian stimulation were considered for inclusion. Forty-two women who conceived after oocyte donation or frozen embryo transfer and 61 women with multiple gestations were excluded from the analysis. Four women underwent oocyte donation and conceived a multiple gestation. In total, 99 women were excluded using these criteria; the remaining 346 women were included in the final analysis.

Study participants with increasing serum β-hCG levels were scheduled for ultrasound examination to confirm pregnancy viability at six to seven weeks' gestation, with a repeat ultrasound one to two weeks later. If no cardiac activity was detected at transvaginal ultrasound on two occasions, missed abortion was diagnosed, and dilatation and curettage was offered. All women who chose to undergo suction curettage for a missed abortion were offered cytogenetic testing of the products of

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