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Androgenicity and Fertility Treatment in Women with Unexplained Infertility

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Abstract

Objective: To determine whether biochemical or clinical markers of androgenic activity predict live birth rate with ovarian stimulation in the unexplained infertility population.

Design: Secondary analysis of the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation clinical trial.

Setting: Multicenter university-based clinical practices

Patients: Nine-hundred couples with unexplained infertility were included. Women were 18–40 years old with regular menses, a normal uterine cavity, at least one patent fallopian tube, and a male partner with ≥5 million motile sperm. Women were randomized to receive gonadotropin, clomiphene, or letrozole with intrauterine insemination for ≤4 four treatment cycles. Women were evaluated for biochemical (total testosterone TT, DHEAS, and free androgen index FAI) and clinical markers of androgenic activity (sebum, acne, and hirsutism). Multivariable logistic regression models adjusting for treatment group, maternal age, and body mass index were performed.

Interventions: none

Main Outcome Measures: The primary outcome was live birth. Secondary outcomes included conception, clinical pregnancy, and pregnancy loss.

Results: When comparing 900 women in the AMIGOS trial based on quartiles of serum TT, women were of younger age (P=0.002), higher BMI (P<0.001), and higher waist circumference (P<0.001) with increasing TT. Increasing quartiles of TT also showed increasing DHEAS and FAI values (P<0.001). Serum androgens were not associated with outcomes of live birth, conception, clinical pregnancy or pregnancy loss. Clinical androgen markers were not associated with pregnancy outcomes.

Conclusions: In a randomized cohort of women with unexplained infertility, biochemical and clinical measures of androgens did not predict live birth rate after ovarian stimulation treatment.

Clinical Trial Registration Number: NCT01044862.

Keywords

androgens; unexplained infertility; testosterone

Introduction

Androgens appear to play an important role in early follicular development and granulosa cell proliferation. In female rhesus monkeys treated with testosterone (T), the number of primary follicles significantly increased over time, suggesting that androgens recruit resting, primordial follicles into the actively growing pool (1, 2). Androgens augment follicle-stimulating hormone (FSH) receptor expression on granulosa cells and increase the number of pre-antral and antral follicles (3, 4). Although a critical minimum amount of androgen exposure is needed for folliculogenesis, there is also evidence that excess androgens may be detrimental to follicle development (5, 6).

Pharmacologic treatment with T has been primarily studied in women who respond poorly to conventional FSH-based gonadotropin stimulation for *in vitro* fertilization (IVF). Results have been inconsistent (7–10), but a recent meta-analysis of seven randomized controlled trials concluded that T administration before or during ovarian stimulation for poor responders resulted in a higher live birth rate compared to controls (10).

Little is known about the effects of physiologic, endogenous androgens in a non-PCOS population. Baseline T levels in non-PCOS women may be positively correlated with ovarian response and number of oocytes retrieved for IVF (11, 12); however, it has also been shown that non-PCOS women who conceive in their first IVF treatment cycle have lower T compared to controls (13). To date, there are no data available on the association of androgen markers in a non-PCOS population and non-IVF fertility treatment outcomes. Thus, we sought to investigate whether biochemical or clinical markers of androgen activity, collectively termed ‘androgenicity’, are associated with pregnancy outcomes in a rigorously defined cohort of women with unexplained infertility (UI) undergoing non-IVF fertility treatment. We hypothesized that higher androgenicity would be associated with higher live birth rates.

Materials and Methods

We performed a secondary analysis of deidentified data from the Eunice Kennedy Shriver National Institute of Child Health and Human Cooperative Reproductive Medicine Network (RMN) clinical trial “Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation” (AMIGOS), which was conducted at 12 sites in the United States. Women enrolled in AMIGOS were between the ages of 18 and 40 and had unexplained infertility, defined as one or more years of infertility with regular menstrual cycles, evidence of a normal uterine cavity, at least one patent fallopian tube, and a male partner with at least 5 million motile sperm in the ejaculate. The protocol was approved by the Institutional Review Board at each study site, and the study design and main outcome of the AMIGOS trial have been previously published (14, 15).

At the screening visit, participants underwent a physical exam, including height, weight, and waist circumference. Hirsutism was assessed in all participants using the Ferriman-Gallwey (FG) scoring scale (16). An acne assessment was performed by trained personnel using an Investigators Global Assessment and an acne lesion count (17). Sebum was measured in the middle forehead using a Sebumeter (SM 815, CK Electronic GMBH, Koln Germany) (18). Fasting blood was obtained for hormone assays, which were conducted by the University of Virginia Ligand Assay and Analysis Core Laboratories, as previously described (19). Serum androgens measured included total testosterone (TT), DHEAS, and SHBG (Siemens Immulite 2000 platform). Free androgen index (FAI) was calculated as TT (in nmol/L) / SHBG (in nmol/L). For TT, intraassay and interassay %CVs were 4.3% and 7.4%, respectively. For DHEAS, intraassay and interassay %CVs were 5.4% and 6.5%, respectively (19).

Participants in the AMIGOS trial were randomized to receive daily, subcutaneous gonadotropin injections (Menopur, Ferring Pharmaceuticals), orally administered

clomiphene, or orally administered letrozole. Randomization was stratified according to study site and age group. Medications were initiated on day 3, 4, or 5 of the menstrual cycle, with ovarian stimulation and human chorionic gonadotropin (HCG)-triggered ovulation, followed by timed intrauterine insemination for up to four treatment cycles. The primary outcome for this analysis was live birth. Secondary outcomes included conception (positive βHCG), clinical pregnancy (fetal heart motion detected on ultrasound performed at 4–6 weeks gestation), and pregnancy loss (defined as spontaneous loss or biochemical pregnancy). Pregnancy loss did not include ectopic pregnancies.

Descriptive statistics were used to compare baseline characteristics by quartiles of serum TT, using analysis of variance (ANOVA), Chi-square test, or Fisher's exact test as appropriate. We conducted multivariable logistic regression analysis to determine if serum androgens (TT, DHEA-S, FAI), sebum score, acne score, and FG score as continuous variables were associated with live birth, conception, clinical pregnancy, and pregnancy loss. Analyses were adjusted for maternal age, maternal BMI, and treatment group. For this analysis, participants with serum TT greater than the upper limit of normal (>73 ng/dL) were excluded as it is possible, though unlikely, that the unexplained infertility cohort inadvertently included some women with polycystic ovary syndrome (PCOS). We did not use serum androgens as categorical variables as a trend analysis of the primary outcome for TT, DHEAS, and FAI did not demonstrate categories that would be helpful or necessary. Analyses were performed with SAS software, version 9.4 (SAS institute). Statistical significance was defined as a two-sided P value of less than 0.05.

Results

When comparing 900 women in the AMIGOS trial based on quartiles of serum TT, women were of younger age (P=0.002), higher BMI (P<0.001), and higher waist circumference (P<0.001) with increasing TT (Table 1). Increasing quartiles of TT also showed increasing DHEAS and FAI values (P<0.001) (Table 1). The median acne count was 0 and the median FG score was 7 across all quartiles of TT. There was no difference in treatment group allocation or pregnancy outcomes based on quartiles of TT.

In a multivariable analysis excluding 10 participants with TT greater than the reference range (N=890), serum androgens were not associated with outcomes of live birth, conception, clinical pregnancy or pregnancy loss (Table 2). A one unit increase (ng/dL) in TT was associated with an OR 1.005 (95% CI 0.99, 1.019) for live birth, which is not statistically significant. The clinical markers of androgenicity, including sebum score, acne score, and FG score, also were not associated with outcomes of live birth, conception, clinical pregnancy, or pregnancy loss (Table 2).

In a secondary analysis focused on DHEAS levels in this cohort, nulliparous women had higher DHEAS levels compared to those who had a prior live birth – median 123 (Q1 87, Q3 171) μg/dL vs 111 (77, 147) μg/dL, P=0.002.

Discussion

In a rigorously defined cohort of women with unexplained infertility undergoing non-IVF fertility treatment, biochemical and clinical markers of androgenicity were not associated with live birth or other pregnancy outcomes such as conception, clinical pregnancy, or pregnancy loss. Thus far, most research on androgens and fertility focuses on either hyperandrogenic women with PCOS or women determined to be poor ovarian responders. We chose a clinically normal population in which to study androgen levels – women with unexplained infertility – to determine if subtle differences in androgens across the physiologic range are associated with pregnancy outcomes. Our findings suggest that there is no clinically significant role of endogenous androgens in predicting fertility outcomes of women with unexplained infertility using currently recommended treatment modalities.

In this study, we used multiple measures of androgens to assess the association with pregnancy outcomes. Although we measured serum androgens with immunoassays (20) instead of mass spectrometry, we have previously demonstrated in a blinded comparison that our TT immunoassay is as precise as mass spectrometry (21). Additionally, our TT measurements do appear to be clinically meaningful. The TT measurements are correlated with DHEAS and FAI measurements as we would expect. Participants in the highest quartile of TT had the lowest mean age, which is consistent with the knowledge that androgens decline with age (22, 23). Furthermore, participants in the highest quartile of TT also had the highest mean BMI and waist circumference, which has been shown previously in community-based cohorts (24).

Androgens are known to play an important role in early follicular development, facilitating the transition of follicles from the resting to the growing pool. Thus, biologic plausibility exists for manipulating androgen levels in IVF cycles to improve outcomes in certain populations with androgen “dysfunction”. It can be speculated that a balance of androgen action in the ovary is needed. Zollner *et. al.* demonstrated that women who conceive in their first IVF cycle had lower T levels than those who did not (13), whereas other studies concluded that baseline T levels ≤20 ng/dL are associated with poor IVF success rates in women with normal ovarian reserve (25). It may be the case that androgen action is more critical in women with diminished ovarian reserve as androgen levels decline with age (26). Indeed, Qin *et. al.* analyzed IVF cycles in over 1200 women, showing that baseline T levels predict the number of dominant follicles with ovarian stimulation and pregnancy outcome in women with diminished ovarian reserve (FSH >10 IU/L), but not in women with normal reserve (FSH ≤10 IU/L) (27).

The finding of higher DHEAS levels in nulliparous women in this study was somewhat unexpected. In one small cohort study, serum DHEAS was found to be elevated in 19% of infertile women with regular ovulation (28). Higher DHEAS may suggest a subtle adrenal dysfunction contributing to impaired folliculogenesis and spontaneous conception. However, this subtle dysfunction, if present, appears to be readily overcome by routinely used medications for ovarian stimulation, such as clomiphene, letrozole, and gonadotropin.

It is also possible, though unlikely, that the unexplained infertility cohort in this study inadvertently included some women with PCOS. To address this possibility, the logistic regression analysis excluded women with TT greater than the upper limit of normal for the assay used (N=10). More importantly, recruitment was targeted toward women with regular cycles without clinical complaints of hyperandrogenism, and therefore women with PCOS would be unlikely to meet eligibility criteria for the study. Nonetheless, the possibility remains that a very small proportion of the sample could have had mild PCOS. Their inclusion in the final analysis is unlikely to have changed any of our findings.

Strengths of this study include a large sample of rigorously defined women with UI and a thorough assessment of their androgenicity--both biochemical and clinical. This study also focuses on non-IVF fertility treatment, which is under-represented in the research on fertility treatment outcomes. Thus, these findings contribute novel data to the existing body of literature, confirming that endogenous androgens do not affect live birth rates in women with unexplained infertility undergoing non-IVF fertility treatment.

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Capsule

In a randomized cohort of women with unexplained infertility, biochemical and clinical measures of androgens did not predict live birth rate after treatment with gonadotropin, clomiphene, or letrozole.

Table 1

Baseline characteristics by quartiles of serum total testosterone (TT)

	Quartile 1 TT ≤ 15.7 ng/dL (n=216)	Quartile 2 15.8 ng/dL ≤ TT ≤ 22.2 ng/dL (n=221)	Quartile 3 22.3ng/dL ≤ TT ≤ 30.1 ng/dL (n=216)	Quartile 4 TT ≥30.2 ng/dL (n=220)	P-value
Age, years	33.0 (30.0, 37.0)	32.0 (30.0, 36.0)	32.0 (29.0, 35.0)	31.0 (29.0, 35.0)	0.002
BMI, kg/m^2	24.4 (21.6, 28.9)	24.8 (21.9, 29.9)	25.0 (21.6, 29.9)	27.5 (23.2, 33.2)	<0.001
Waist circumference, cm	81.0 (74.0, 91.0)	83.0 (74.0, 96.0)	84.0 (73.0, 97.0)	88.0 (77.0, 100.5)	<0.001
Education, n(%)					0.0191
High school graduate or less	10 (4.6)	24 (10.9)	15 (6.9)	21 (9.6)	
College graduate or some college	138 (63.9)	143 (64.7)	138 (63.9)	157 (71.4)	
Graduate degree	68 (31.5)	54 (24.4)	63 (29.2)	42 (19.1)	
Annual household income, n(%)					0.462
<=50,000	33 (15.3)	44 (19.9)	31 (14.4)	43 (19.6)	
>=50,000	148 (68.5)	144 (65.2)	144 (66.7)	135 (61.4)	
Wish to not answer	35 (16.2)	33 (14.9)	41 (19.0)	42 (19.1)	
Current smoking, n(%)	8 (3.7)	14 (6.3)	20 (9.3)	26 (11.8)	0.010
Ethnicity, n(%)					0.289
Not Hispanic or Latino	197 (91.2)	190 (86.0)	194 (89.8)	199 (90.5)	
Hispanic or Latino	19 (8.8)	31 (14.0)	22 (10.2)	21 (9.6)	
Race, n(%)					0.857
White	172 (79.6)	181 (81.9)	175 (81.0)	178 (80.9)	
Black	22 (10.2)	14 (6.3)	23 (10.65)	20 (9.1)	
Asian	16 (7.4)	16 (7.2)	12 (5.6)	11 (5.0)	
American Indian	1 (0.5)	3(1.4)	2 (0.9)	3 (1.4)	
Native Hawaiian	0 (0)	0 (0)	0 (0)	0 (0)	
Mixed race	5 (2.3)	7 (3.2)	4 (1.9)	8 (3.6)	
Prior live birth, n(%)	48 (22.2)	49 (22.2)	34 (15.7)	47 (21.4)	0.274
Prior conception, n(%)	92 (42.6)	98 (44.3)	74 (34.3)	95 (43.2)	0.126
Acne score, count	0.0 (0.0, 2.0)	0.0 (0.0, 3.0)	0.0 (0.0, 3.0)	0.0 (0.0, 4.0)	0.096
Sebum, μg/cm^2	74.0 (53.0, 99.0)	85.0 (63.0, 123.0)	81.0 (56.0, 112.0)	79.0 (60.0, 126.0)	0.018
Ferriman-Gallwey score	7.0 (2.0, 11.0)	7.0 (4.0, 12.0)	7.0 (2.0, 11.0)	7.0 (3.0, 12.0)	0.187
DHEAS, μg/dL	90.4 (63.9, 127.5)	115.0 (77.7, 151.0)	130.5 (96.9, 179.0)	156.5 (104.0, 215.0)	<0.001
SHBG, nmol/L	54.2 (37.3, 72.3)	55.3 (39.0, 73.9)	58.3 (41.8, 76.8)	53.8 (35.9, 78.1)	0.644
Free androgen index	0.8 (0.5, 1.1)	1.2 (0.9, 1.7)	1.6 (1.1, 2.1)	2.6 (1.7, 4.0)	<0.001
Treatment group					0.934
Clomiphene	75 (34.7)	75 (33.9)	72 (33.3)	71 (32.3)	
Letrozole	75 (34.7)	74 (33.5)	68 (31.5)	70 (31.8)	
Gonadotropins	66 (30.6)	72 (32.6)	76 (35.2)	79 (35.9)	
Conception, n (%)	70 (32.4)	77 (34.8)	80 (37.0)	96 (43.6)	0.088

	Quartile 1 TT ≤ 15.7 ng/dL (n=216)	Quartile 2 15.8 ng/dL ≤ TT ≤ 22.2 ng/dL (n=221)	Quartile 3 22.3ng/dL ≤ TT ≤ 30.1 ng/dL (n=216)	Quartile 4 TT ≥30.2 ng/dL (n=220)	P-value
Clinical Pregnancy, n (%)	58 (26.9)	59 (26.7)	59 (27.3)	77 (35.0)	0.158
Live Birth, n (%)	49 (22.7)	53 (24.0)	53 (24.5)	64 (29.1)	0.437
Pregnancy Loss: spontaneous + biochemical, n (%)	15 (6.9)	15 (6.8)	23 (10.7)	23 (10.5)	0.291

Median (Interquartile range), n (%)

P-value by ANOVA, Chi square test or Fisher's exact test

Table 2 -

Association of androgen markers as continuous variables and pregnancy outcome

	Conception	Clinical Pregnancy	Live Birth	Pregnancy Loss
Total testosterone	1.011 (0.999, 1.024)	1.007 (0.994, 1.021)	1.005 (0.990, 1.019)	1.017 (0.996, 1.039)
DHEAS	0.999 (0.996, 1.001)	0.999 (0.996, 1.001)	0.998 (0.996, 1.001)	1.001 (0.997, 1.005)
Free androgen index	1.033 (0.954, 1.117)	1.024 (0.973, 1.078)	1.025 (0.977, 1.075)	1.000 (0.954, 1.048)
Sebum score	0.999 (0.996, 1.002)	1.000 (0.997, 1.003)	0.999 (0.996, 1.003)	0.998 (0.993, 1.003)
Acne score	0.995 (0.973, 1.018)	0.997 (0.973, 1.021)	0.994 (0.969, 1.020)	1.012 (0.980, 1.046)
Ferriman-Gallwey score	1.003 (0.979, 1.028)	0.992 (0.967, 1.018)	0.988 (0.962, 1.016)	1.034 (0.994, 1.076)

Values shown represent Odds Ratio (95% Confidence Interval).

Analyses adjusted for age, BMI, and treatment group.