Association between testosterone, semen parameters, and live birth in men with unexplained infertility in an intrauterine insemination population

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Objective: To determine whether men with unexplained infertility and low total T (TT) have abnormal spermatogenesis and lower fecundity.

Design: Secondary analysis of the prospective, randomized, multicenter clinical trial, Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS).

Setting: Infertility clinics.

Patient(s): Nine hundred couples with unexplained infertility enrolled in AMIGOS. Semen analysis with an ejaculate of at least 5 million total motile sperm was required for enrollment. For inclusion in this secondary analysis, a fasting TT was required.

Intervention(s): None.

Main Outcome Measure(s): Logistic regression, adjusted for age and body mass index, assessed the association between low TT (defined as <264 ng/dL), semen parameters, and pregnancy outcome.

Result(s): Seven hundred eighty-one men (mean age, 34.2 ± 5.7 years) with a median (interquartile range) TT of 411 (318–520) ng/dL were included. Men with TT <264 ng/dL were less likely to have normal (≥4% strict Kruger) morphology (unadjusted odds ratio [OR], 0.56; 95% confidence interval [CI], 0.34, 0.92; adjusted OR, 0.59; 95% CI, 0.35, 0.99). There was no association between low TT and semen volume < 1.5 mL, sperm concentration < 15×10^6/mL, or motility < 40%. Among couples whose male partner had low TT,

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21 (18.8%) had a live birth, compared with 184 (27.5%) live births in couples with a male partner having TT > 264 ng/dL. The odds of live birth decreased by 40% in couples whose male partner had low TT (unadjusted OR, 0.60; 95% CI, 0.36, 1.00; adjusted OR, 0.65; 95% CI, 0.38, 1.12).
Conclusion(s): In couples with unexplained infertility, low TT in the male partner was associated with abnormal sperm morphology and lower live birth rates.
Clinical Trial Registration Number: NCT01044862. (Fertil Steril® 2019;111:1129–34. ©2019 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Testosterone, infertility, male, semen analysis, live birth

A significant male factor is found in 50% of infertile couples and is implicated as the sole cause for infertility in up to 30% of couples (1). Low T is found in approximately 15% of male factor infertility cases (2); however, the impact of low T on a man's fecundity is less known. In animal models, the presence of a minimum T level within the testis is clearly shown to be necessary for spermatogenesis (3), with rising serum T concentrations associated with increasing sperm production (4). In humans, low serum total T (TT), a surrogate for intratesticular levels, has previously been linked (sometimes inconsistently) (5) to abnormal semen parameters such as lower sperm concentration and total sperm motility (6). Furthermore, studies evaluating the relationship between low TT and pregnancy or live birth outcomes are lacking.

To address the relationship between TT, semen parameters, and live birth rate in couples with unexplained infertility, we performed a secondary analysis of the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) trial. This large, multicenter clinical trial determined pregnancy, live birth, and multiple gestation rates following up to four cycles of ovarian stimulation with IUI in couples with unexplained infertility (7, 8). We tested the hypothesis that low TT would be associated with abnormal semen parameters (sperm concentration, total sperm motility, and Kruger strict morphology) and lower live birth rate.

MATERIALS AND METHODS

Study Sample

The AMIGOS trial was designed to discern whether ovarian stimulation with letrozole would result in a significantly lower frequency of multiple gestations when compared with gonadotropins and/or clomiphene citrate (7, 8). This Institutional Review Board–approved study enrolled 900 couples with unexplained infertility. The female partner was required to be between 18 and 40 years of age, with regular menstrual cycles, a normal uterus, and at least one patent fallopian tube (8). Male partners were required to have a baseline semen analysis with at least 5 million motile sperm, recorded within 1 year of study initiation (7). This minimum required sperm count was considered sufficient for sperm washing and IUI—which was performed in all AMIGOS treatment cycles. While fasting, male partners also provided blood samples, which were processed for TT levels at the University of Virginia Ligand Assay and Analysis Core (Charlottesville, VA). TT was determined by radioimmunoassay (Siemens; functional sensitivity = 10 ng/dL; intra-assay coefficient of variation = 4.3%; interassay coefficient of variation = 7.4%). The assay performance was validated with determination of accuracy, linearity, precision, and functional sensitivity (i.e., the lowest concentration with accuracy to a known standard within 20% and intra-assay coefficient of variation <20%).

Statistical Analysis

Bivariate analyses were conducted to examine the relationship between baseline demographics and low TT using χ^2, Fisher's exact, *t*-tests, or nonparametric Wilcoxon rank-sum test where appropriate. We defined low TT as <264 ng/dL, based on recently published data that represent the reproductive age group of our cohort (9). Normal semen parameters were defined as semen volume ≥1.5 mL, sperm concentration ≥15 × 10^6/mL, total sperm motility ≥40%, and Kruger strict morphology ≥4%. Conception was defined as having a rising serum level of hCG on two consecutive tests. Clinical pregnancy was defined as an intrauterine pregnancy with fetal heart motion detected by transvaginal ultrasound. Lastly, live birth was defined as the delivery of a viable infant. Logistic regression was used to investigate the relationship between low TT (<264 ng/dL) and the outcomes of normal semen parameters and pregnancy including conception, clinical pregnancy, and live birth. The logistic regression analyses were adjusted for age and body mass index (BMI). The pregnancy outcome models were adjusted for treatment group (i.e., clomiphene citrate, letrozole, and gonadotropins). All hypothesis tests were two-sided, and all analyses were performed using SAS software, version 9.4 (SAS Institute).

RESULTS

Of the 900 couples enrolled, 781 men with both TT and a baseline semen analysis with at least 5 million total motile sperm were included in our present study, whereas 119 men were excluded due to missing TT. The male partners had a mean age of 34.2 (±5.7) years, with a mean BMI of 28.9 (±5.7) kg/m^2. Over half of the male partners were nonsmokers and had obtained a college or graduate degree (Table 1). Men with low TT had higher BMIs. There were no statistically

TABLE 1

Patient characteristics of male partners of couples with unexplained infertility.

Characteristic	All	TT < 264 ng/dL	TT ≥ 264 ng/dL	*P* Value
Age, y	34.2 (±5.7)	34.6 (±4.9)	34.2 (±5.8)	.45
BMI, kg/m^2	28.9 (±5.7)	31.7 (±6.8)	28.4 (±5.3)	< .001
Reporting secondary infertility	286 (37.2)	34 (31.5)	252 (38.2)	.18
College/graduate degree	426 (55.6)	62 (57.4)	364 (55.3)	.69
Smoker				.53
Never	414 (54.0)	53 (49.1)	361 (54.8)	
Past	253 (33.0)	40 (37.0)	213 (32.3)	
Current	100 (13.0)	15 (13.9)	85 (12.9)	

Note: Data are reported as mean ± standard deviation or n (%), unless stated otherwise.

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significant differences in age, smoking status, or education level between those in the lower and higher TT groups. There was also no difference in the age of the female partners.

The median (interquartile range) TT for the cohort was 411 (318–520) ng/dL. There were 112 subjects (14.3%) with a TT < 264 ng/dL. Baseline median (interquartile range) sperm parameters included semen volume 2.8 (2.0–3.7) mL, sperm concentration 49 (27–85) × 10^6/mL, motility 56% (49%–65%), and strict morphology 9% (5%–18%). Of these 781 couples, 295 (37.8%) conceived, 234 (30.0%) had a clinical pregnancy, and 205 (26.3%) had a live birth.

Men with low TT and at least 5 million total motile sperm were less likely than men with TT ≥264 ng/dL to have normal Kruger strict morphology (unadjusted odds ratio [OR] 0.56; 95% confidence interval [CI], 0.34, 0.92; Table 2; Fig. 1). The result remained statistically significant after adjusting for age and BMI (OR, 0.59; 95% CI, 0.35, 0.99). This corresponds to 41% decreased odds of normal morphology in men with low TT. No association between low TT and semen volume, sperm concentration, or sperm motility was found.

In couples with a male partner with low TT, 21 (18.8%) had a live birth, compared with 184 (27.5%) in couples with a male partner having a TT ≥ 264 ng/dL. This difference demonstrated a lower live birth for couples with a male partner with low TT (unadjusted OR, 0.60; 95% CI, 0.36, 1.00; adjusted OR, 0.65; 95% CI, 0.38, 1.12; Table 2; Fig. 1). Similarly, conception and clinical pregnancy rates were lower in women partnered with a male with low TT; however, these differences did not reach statistical significance (Table 2).

DISCUSSION

In this cohort of couples with unexplained infertility, men with low TT (<264 ng/dL) and at least 5 million total motile sperm had greater odds of having abnormal strict morphology sperm when compared with men with TT ≥ 264 ng/dL. Additionally, low TT was associated with lower live birth rates than those observed in couples with a male partner with normal TT (>264 ng/dL). These data suggest that optimal spermatogenesis and fecundity may require a minimum level of T and underscore the importance of identifying men with low TT in couples with unexplained infertility.

The group of men with lower TT had a higher median BMI. This inverse relationship between T and BMI is well established (1), yet complex. BMI is potentially on the causal pathway to developing low T but was not independently associated with AMIGOS pregnancy outcomes (10). While we reported the OR both unadjusted and adjusted for age and BMI, we believe the unadjusted data are actually the best representation of the relationship we sought to describe. Both increasing BMI and age are associated with lower T levels. However, neither were independently associated with pregnancy outcomes in the original AMIGOS trial (10). Therefore, adjusting for one or both may attenuate the relationship between serum T and treatment outcomes.

Low TT is present in approximately 15% of infertile men (2). Consistent with these previously published data, the present analysis found that 14% of the male partners in couples with unexplained infertility had TT levels < 264 ng/dL. Both the American Urological Association's best practice statement and the American Society for Reproductive Medicine's Committee Opinion regarding the evaluation of the infertile male recommend testing total T as part of the routine workup when the sperm concentration is low, a degree of sexual dysfunction is present, or other findings suggest an endocrinopathy. Many experts advocate that all infertile males should have endocrine testing (5, 6).

Serum TT is a surrogate marker for intratesticular levels. In humans, intratesticular T concentrations are 30–100 times higher than serum levels (11–15), and this elevated T concentration is necessary for spermatogenesis to occur. Although testing in some animal models has shown that minimum T levels are needed for spermatogenesis (3), a minimum level for human spermatogenesis is not well defined. Along this line, studies have not shown a consistent pattern of abnormal semen parameters in men whose T is low but adequate for spermatogenesis to occur (5). One of the primary aims of the present study was to determine whether semen parameters were associated with lower serum T. Aside from idiopathic infertility, the main inclusion criterion for these men was to have a minimum total motile sperm count of 5 million, which potentially selects men with higher sperm concentrations and/or motility compared with unselected group of men with infertility. No association was seen with sperm concentration or motility, but sperm morphology was decreased in the men with low TT.

More important than any semen parameter for couples with infertility are reproductive outcomes, such as pregnancy and live birth. Unfortunately, studies relating these outcomes to the male partner's endocrine status are lacking. To our knowledge, this is the first study evaluating the association of T to reproductive outcomes. Conception, clinical pregnancy, and live birth rates were all lower when male partners had lower T. A lower live birth rate for couples with a male partner with low TT is a compelling finding that merits further study.

TABLE 2

Semen analysis and pregnancy outcomes (n = 781).

Variable	TT < 264 ng/dL (n = 112), n (%)	TT ≥ 264 ng/dL (n = 669), n (%)	TT < 264 vs. TT ≥ 264, unadjusted OR (95% CI)	*P* Value	TT < 264 vs. TT ≥ 264, adjusted for age and BMI OR (95% CI)	*P* Value
Normal semen volume (≥ 1.5 mL)	97 (86.6)	592 (88.5)	0.84 (0.46, 1.52)	.57	0.79 (0.43, 1.45)	.45
Normal sperm concentration (≥ 15 × 10^6/mL)	104 (92.9)	599 (89.5)	1.52 (0.71, 3.25)	.28	1.45 (0.66, 3.15)	.35
Normal total sperm motility (≥ 40%)	94 (83.9)	585 (87.4)	0.75 (0.43, 1.30)	.31	0.73 (0.40, 1.33)	.31
Normal strict morphology (≥ 4%)	71 (72.4)	474 (82.4)	0.56 (0.34, 0.92)	.02	0.59 (0.35, 0.99)	.05
Conception[a]	34 (30.4)	261 (39.0)	0.67 (0.43, 1.04)	.08	0.67 (0.42, 1.06)	.09
Clinical pregnancy (heart beat)[a]	27 (24.1)	207 (30.9)	0.70 (0.44, 1.12)	.14	0.74 (0.45, 1.22)	.24
Live birth[a]	21 (18.8)	184 (27.5)	0.60 (0.36, 1.00)	.05	0.65 (0.38, 1.12)	.12

[a] OR (95% CI) and *P* value for pregnancy outcomes are adjusted for treatment group.

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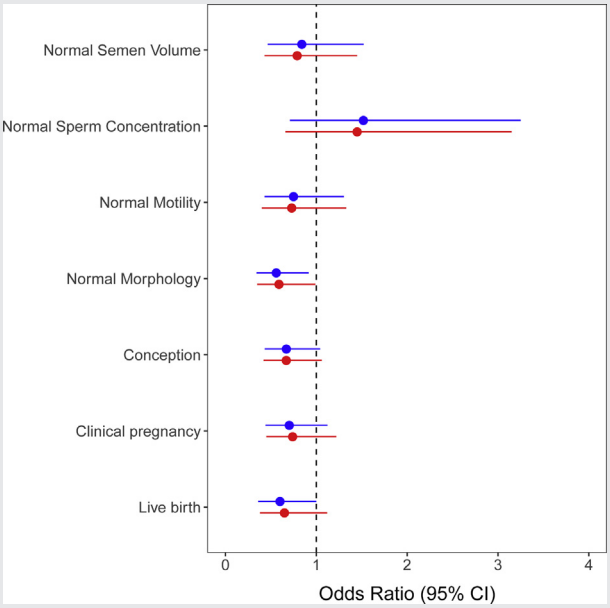
FIGURE 1



Comparison of TT < 264 vs. TT ≥ 264 with respect to semen analysis and pregnancy outcomes. Blue represents unadjusted models for semen parameters and models adjusted for treatment for pregnancy outcomes. Red represents models adjusted for age and BMI for semen parameters and models adjusted for treatment, age, and BMI for pregnancy outcomes.

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This study has several limitations. As a secondary analysis of a previously completed, randomized controlled trial performed with a different purpose in mind, many of the limitations for this present study are simply for this reason alone. Both male and female participants came in for blood draws in a fasting state, which predominantly occurred in the morning hours, but were not strictly controlled for time of day. This may have affected TT measurements, as male patients with later blood draws may be falsely identified as having low TT due to the diurnal secretion of T production in men. Additionally, only one baseline TT was collected, and symptoms of hypogonadism were not assessed. Therefore, we cannot assign the diagnosis of symptomatic hypogonadism. Further limitations include an absence of free T or calculated bioavailable T from the present analysis. The AMIGOS study did not query for possible use of selective estrogen receptor modulators or other androgenic agents that could artificially raise the serum TT level. Moreover, our cohort excluded 119 male partners who were missing a baseline TT. Therefore, we considered multiple imputation to account for missing data. Although the association with the outcomes of morphology and live birth was slightly weaker after imputation ($P=.04$ and $P=.07$, respectively), the results were relatively consistent with the analysis of 781 men with measured TT (Supplemental Table 1). Moreover, although men were required to have 5 million total motile sperm for enrollment, a physical exam or additional evaluation of

men with oligoasthenozoospermia was not a part of the AMIGOS protocol. Lastly, this study was not specifically designed to address outcomes on a per-cycle (IUI) basis, and variations in the total motile sperm count for each IUI cycle may affect fecundity.

The study had many strengths, including a randomized controlled trial setting, a large sample size, systematic male partner phenotyping, and a standardized methodology for conducting semen analyses that was adopted across all study sites. Serum T measurements were performed in a centralized, high-volume laboratory of excellence. Additionally, all participant couples were carefully followed through pregnancy and delivery, with complete capture of study endpoints.

This study highlights the importance of T for male reproduction, not only for male sexual function, but also for semen quality and ultimately reproductive outcomes. The results underscore the importance of a complete evaluation of the subfertile male, which should include a physical examination, an endocrine assessment, and treatment of underlying endocrinopathies. Efforts to further evaluate and optimize even asymptomatic low T levels in male partners should be considered in the treatment of the infertile couple. Future studies should seek to determine whether there is a threshold of TT below which semen parameters are more negatively impacted or whether there are other male factor variables that may expand the predictive value of total T and the semen analysis.

CONCLUSION

In couples with unexplained infertility and baseline semen analyses with at least 5 million total motile sperm, low TT (<264 ng/dL) in the male partner was associated with low sperm morphology and a lower live birth rate.

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Asociación entre la testosterona, los parámetros seminales, y los nacidos vivos en hombres con infertilidad inexplicable en una población de inseminación intrauterina

Objetivo: Determinar si los hombres con infertilidad inexplicable y testosterona total (TT) baja tienen espermatogénesis anormal y menor fecundidad.

Diseño: Análisis secundario del ensayo clínico prospectivo, aleatorizado, multicéntrico, *Evaluación de Gestaciones Intrauterinas Múltiples a partir de Estimulación Ovárica* (AMIGOS).

Entorno: Clínicas de infertilidad.

Paciente(s): Novecientas parejas con infertilidad inexplicada inscritas en AMIGOS. Análisis de semen con una eyaculación con al menos 5 millones de espermatozoides móviles totales para la participación en el estudio. Para su inclusión en este análisis secundario, se requirió una muestra en ayunas de TT.

Intervención (es): Ninguna.

Principales medidas de resultados: Regresión logística, ajustada por edad e índice de masa corporal, evaluando la asociación entre TT baja (definido como $<$264 ng/dL), parámetros del semen y resultado del embarazo.

Resultado(s): Se incluyeron setecientos ochenta y un hombres (edad media, 34.2 $\pm$ 5.7 años) con una mediana (rango intercuartil) de TT de 411 (318–520) ng / dL. Los hombres con TT $<$264 ng / dL tuvieron menos probabilidades de tener una morfología normal ($\geq$4% Kruger estricto) (odds ratio [OR] sin ajustar 0.56; Intervalo de confianza del 95% [IC], 0.34, 0.92; OR ajustado, 0.59; IC del 95%, 0.35, 0.99). No hubo asociación entre la TT baja y el volumen de semen $<$1.5 mL, la concentración de esperma $<15x10^6$ / ml, o la motilidad $<$40%. Entre las parejas cuyo compañero masculino tenía TT baja, 21 (18.8%) tuvieron un nacido vivo, en comparación con 184 (27.5%) nacidos vivos en parejas con compañero masculino que tenía TT$>$ 264 ng/dL. Las probabilidades de nacidos vivos disminuyeron en un 40% en las parejas cuyo compañero masculino tenía TT baja (OR no ajustada, 0.60; IC del 95%, 0.36; 1.00; OR ajustada, 0.65; IC del 95%, 0.38; 1.12).

Conclusión(es): En parejas con infertilidad inexplicable, la TT baja en la pareja masculina se asoció con una morfología anormal de los espermatozoides y menores tasas de nacidos vivos.