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TSH in unexplained infertility

Higher TSH levels within the normal range are associated with unexplained infertility

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Context: Unexplained infertility (UI)—defined as the inability to conceive after 12 months of unprotected intercourse with no diagnosed cause—affects 10-30% of infertile couples. An improved understanding of the mechanisms underlying UI could lead to less invasive and less costly treatment strategies. Abnormalities in thyroid function and hyperprolactinemia are well-known causes of infertility, but whether TSH and prolactin levels within the normal range are associated with UI is unknown.

Objective: To compare TSH and prolactin levels in women with UI and women with a normal fertility evaluation except for an azoospermic/severely oligospermic male partner

Design, Setting and Participants: Cross-sectional study including women evaluated at a large academic health system between 1/1/2000-12/31/2012 with normal TSH (levels within the normal range of the assay and at least <5 mIU/L) and normal prolactin levels (<20 ng/ml) and either UI (n=187) or no other cause of infertility other than an azoospermic/severely oligospermic partner (n=52)

Main outcome measures: TSH and prolactin

Results: Women with UI had significantly higher TSH levels than controls (UI: 1.95mIU/L [1.54, 2.61] versus severe male factor: 1.66mIU/L [1.25, 2.17]; p=0.003). This finding remained significant after controlling for age, BMI and smoking status. Nearly twice as many women with UI (26.9%) had a TSH >2.5mIU/L compared to controls (13.5%; p<0.05). Prolactin levels did not differ between the groups.

Conclusions: Women with UI have higher TSH levels compared to a control population. Further studies are warranted to determine if treatment of high-normal TSH levels decreases time to conception in couples with UI.

In women with no known thyroid disease and TSH levels within the normal range, we demonstrate an association between TSH levels greater than 2.5 mIU/L and the diagnosis of unexplained infertility.

Introduction:

Infertility, defined as the inability to conceive after 12 months of regular unprotected intercourse(1), affects approximately 7-15.5% of reproductive aged women in the US(2). Although a cause for infertility is identified in the majority of couples, approximately 10-30% have unexplained or idiopathic infertility, which is defined as infertility in the setting of regular ovulation, tubal patency, a normal uterine cavity and normal semen analysis(3-6). Unexplained infertility is associated with significant emotional and economic costs; annual US expenditures...
for all forms of infertility total $3-4 billion/year(7) and couples with unexplained infertility have higher conception rates with in vitro fertilization (IVF), one of the most expensive forms of treatment(8). Therefore, gaining a greater understanding of potential hormonal factors that may contribute to unexplained infertility may lead to more economical and effective treatment strategies for these couples.

Known causes of infertility include hyperprolactinemia and thyroid dysfunction(9,10). Hyperprolactinemia is a common cause of amenorrhea and infertility, due to impaired gonadotropin secretion and pulsatility, likely due to impaired GnRH secretion(11,12). Treatment with dopamine agonist therapy has been shown to restore ovulation and fertility in women with hyperprolactinemia(13-16). Importantly, even hyperprolactinemic women with regular menstrual cycles may experience decreased fertility due to a shortened luteal phase(17-19), but whether high-normal levels of prolactin in individuals with no known history of hyperprolactinemia may affect fertility remains unknown.

Murine and in vitro studies suggest that thyrotropin and thyroid hormone are important factors during oocyte development and implantation(20-23). In humans, an in vivo model also suggests the importance of TSH for oocyte development, as TSH levels ≥2.5 mIU/L in oocyte donors inversely predict clinical pregnancy independent of the recipient’s TSH level(24). Both hyperthyroidism(25) and hypothyroidism are associated with menstrual irregularity(26) and rates of infertility have been reported to approach 50% in women with Hashimoto’s thyroiditis and Graves’ disease(27). A higher percentage of women with infertility have also been shown to have frankly abnormal TSH levels as compared to controls(28) and the recent American Thyroid Association Thyroid and Pregnancy Guidelines recommend checking a TSH in all women seeking evaluation for infertility(29). However, whether higher TSH levels in a population of women with a normal TSH and no known history of thyroid disease are part of the unexplained infertility phenotype remains an unanswered question.

There is currently no consensus on the definition of subclinical hypothyroidism in non-pregnant women who are attempting to conceive. Subclinical hypothyroidism is defined as an elevated TSH level in the setting of normal thyroid hormone levels but what the upper limit of normal should be for TSH is controversial. Based on the National Health and Nutrition Examination (NHANES) III survey including a sampling of 8,619 females (≥12 years of age) in the US without a history of thyroid disease, the median TSH level is 1.50 mIU/L with an upper 97.5 percentile of 6.10 mIU/L(30), whereas others argue that the upper limit of normal for TSH should be 2.5 mIU/L based on data from the National Academy of Clinical Biochemistry which indicate that 95% of individuals without evidence of thyroid autoimmunity and without a personal or family history of thyroid disease have a TSH level ≤2.5 mIU/L(31) and the fact that subclinical hypothyroidism may be associated with adverse obstetrical outcomes including increased risk of pregnancy loss(32). Therefore, there is poor consensus regarding the normal range for non-pregnant women who are attempting to conceive, although current guidelines provide an upper limit of normal for TSH of 4 mIU/L for women in their first trimester of pregnancy – a time when TSH levels should be at their lowest because of HCG stimulation of thyroid hormone(29) – suggesting that the upper limit of normal for non-pregnant women is >4 mIU/L. Furthermore, current guidelines do not recommend treating women with subclinical hypothyroidism, who are attempting to conceive naturally, with thyroid hormone replacement for the purposes of improving the likelihood of conception(29,33). Our goal in performing this study was to understand whether thyroid function, as estimated by TSH, is associated with infertility in individuals with a completely normal fertility evaluation and who do not have any history of
thyroid disease or abnormal thyroid function tests. We hypothesized that women with unexplained infertility would have higher TSH and higher prolactin levels, within the normal range, as compared to a control group of women who had a similarly normal infertility evaluation but whose partners were found to be azoospermic or severely oligospermic.

Methods:

Study Population:
Using the patient database registry at a large academic health system [the Research Patient Data registry (RPDR) of Partners HealthCare System], we obtained data on all female patients between the ages of 18-39 years of age who presented to the Partners HealthCare System with the diagnosis of infertility and without a disorder of menstruation between 1/1/2000 and 12/31/2012. All electronic records were then individually reviewed to ensure that individuals met our inclusion and exclusion criteria. Women were included who did not conceive after ≥1 year with appropriate exposure to sperm (unexplained infertility group) or who had inadequate exposure to sperm due to a male partner with azoospermia (n=39) or severe oligospermia (n=13) with a sperm count <1 million/mL (severe male factor). Inclusion criteria for all women included regular menstrual cycles every 21-35 days with no more than 5 days of inter-cycle variability, normal uterine cavity evaluation, menstrual cycle day 3 FSH < 10 IU/mL with concomitant estradiol level of ≤ 80 pg/mL(34), TSH level within the normal range of the assay and at least ≤ 5 mIU/L and prolactin level ≤ 20 ng/mL. Male partners of individuals with unexplained infertility had semen concentration ≥15 million/mL, motility ≥40% and normal forms ≥4% (where strict Tygerberg analysis was available), based on World Health Organization 2010 criteria(35), regardless of the year of evaluation. If strict Tygerberg(36) evaluation of sperm was not available, subjects were not excluded based on percentage of abnormal forms. Male partners of individuals in the severe male factor group had semen concentration <1 million/mL on at least two occasions. We excluded women with history of hypo- or hyperthyroidism (including postpartum thyroiditis or history of an abnormal TSH level), history of a high prolactin level, BMI < 18.5 kg/m² or ≥40 kg/m², individuals with recurrent pregnancy loss (≥3 miscarriages), individuals with abnormalities that may be associated with reproduction (e.g., complex ovarian cysts, prior ovarian surgery, cervical stenosis, endometriosis or endometritis), or a strong suspicion by the evaluating physician of an endocrine disorder, including polycystic ovary syndrome (PCOS). This study was approved by the Partners HealthCare institutional review board.

Laboratory assessment:
All diagnostic and laboratory testing was performed as part of routine clinical care. TSH and/or prolactin levels were measured in one of four hospital laboratories within the Partners HealthCare system for >75% of patients. The remaining patients had a TSH and/or prolactin level checked at a known outside laboratory for which methodology information was available or an outside facility for which assay/methodology information was not available (14.6% of patients). The upper limit of normal for two of the TSH assays was <5 mIU/L and in this case, we only included patients who had a TSH within the normal range of the assay. There were two TSH assays with an upper limit of normal of >5mIU/L and in this case, we only included patients with a TSH ≤5mIU/L.

Statistical Analysis:
Statistical analysis was performed using JMP Pro 11.0 (SAS Institute, Cary, NC) software. Means and standard deviation (SD) measurements are reported and compared using the Student’s
t-test unless the data were non-normally distributed, in which case medians and first and third quartile ranges are presented and compared using the Wilcoxon rank-sum test. Percentages were compared using the Fisher’s exact test or the Pearson’s chi-squared test. Least-squares linear regression modeling was performed to control for clinically relevant covariates. TSH was log transformed for the regression analyses due to non-normality. A p-value of <0.05 on a two-tailed test was used to indicate statistical significance.

Results:

Clinical Characteristics:
A total of 239 women met our inclusion and exclusion criteria: 187 individuals with unexplained infertility and 52 with severe male factor infertility. Subjects in the two groups were similarly distributed across the 13-year study period (p=0.69). Characteristics of the study participants are listed in Table 1. Subjects in the unexplained infertility group were slightly older than subjects in the severe male factor group (mean age±SD: unexplained infertility: 31.5±2.7 years versus severe male factor: 30.1±3.7 years; p=0.01). Median BMI was lower in the unexplained infertility group as compared to the severe male factor group (median [interquartile range]: unexplained infertility: 23.0 kg/m² [20.9, 26.2] versus severe male factor: 24.4 kg/m² [22.2, 27.0]; p=0.04) and the percentage of individuals with a BMI >25 was lower in the unexplained infertility group as compared to those with severe male factor, although this difference was not statistically significant (p=0.24). Median duration of infertility and median FSH levels were similar in both groups.

TSH and Prolactin Levels:

TSH
Median TSH levels were significantly greater in the unexplained infertility group as compared to the severe male factor group (unexplained infertility: 1.95 mIU/L [1.54, 2.61] versus severe male factor: 1.66 mIU/L [1.25, 2.17]; p=0.003) (Figure 1). TSH levels remained significantly higher in the unexplained infertility group when controlling for both BMI (p<0.02) and age (p<0.01), variables that have been positively associated with TSH in previous studies(37-41). Although smoking status was not significantly different between the groups, both past as well as a current history of cigarette smoking are associated with lower TSH levels(42). Therefore, we also controlled for both current history of smoking and past or current history of smoking and TSH remained significantly higher in the unexplained infertility group as compared to the severe male factor group (p<0.01 for both).

After excluding individuals from the unexplained infertility group whose partner had a low morphology based on methodology that did not use strict (Tygerberg) criteria (n=19), TSH levels remained significantly greater in the unexplained infertility group as compared to the severe male factor group (unexplained infertility: 1.96 mIU/L [1.54, 2.61] versus severe male factor: 1.66 mIU/L [1.25, 2.17]; p<0.01) and regression analyses similarly remained significant (p≤0.01 for all).

Significantly more individuals in the unexplained infertility group had TSH values >2.5 mIU/L as compared to individuals in the severe male factor group (Figure 2). The percentage of individuals in the unexplained infertility group with a TSH >2.5 mIU/L was nearly double the percentage in the severe male factor group (unexplained infertility: 26.9% versus severe male factor: 13.5%; p<0.05). Of the 57 total patients who had a TSH ≥2.5 mIU/L, 22.3% (13 patients) were started on thyroid hormone replacement therapy after their initial evaluation, although it is...
not known if patients were initiated on thyroid hormone replacement to prevent adverse obstetrical outcomes if they were to conceive or in an attempt to improve the likelihood of conception.

In order to exclude the possibility that the observed differences were due to changes in assay methods or laboratory procedures, we divided patients into groups depending on where their TSH level was measured (which hospital/laboratory) and which assay was used. In one case, two laboratories used the same TSH assay but patients who had their TSH measured using this assay were divided into two separate groups as there may have been systematic differences between the hospital labs that could have led to differences in TSH levels. Table 2 shows the percentage of individuals with unexplained infertility and severe male factor in each of the laboratory/assay groupings. Although the overall chi-squared test did not detect a difference between the groups with respect to where and how TSH was measured (p=0.48), we performed individual significance testing to ensure that we were not missing differences. With individual testing, we found a significantly higher percentage of subjects in the severe male factor group had a TSH level measured in one laboratory/assay (group 4) compared to subjects with unexplained infertility (p=0.04). When we excluded patients from laboratory/assay group 4 and those who had their TSH measured in an unknown assay, the observed differences in TSH levels remained significant; the TSH level in the unexplained infertility group (n=130) was significantly higher compared to the severe male factor group (n=30): 1.94 mIU/L [1.52, 2.54]) versus 1.72 mIU/L [1.32, 2.00], p=0.01 and a significantly higher percentage of individuals with unexplained infertility had a TSH ≥2.5 mIU/L compared to those with severe male factor infertility: 25.4% versus 6.7%, p<0.03.

**Thyroid peroxidase (TPO) antibodies**

Only 19 of the 239 women in the study had TPO antibodies assessed around the time of their infertility evaluation. Of these 19 individuals, six had an elevated TPO antibody level (three in the unexplained infertility group and three in the severe male factor group). Median TPO antibody levels were significantly higher in the severe male factor group as compared to the unexplained infertility group (unexplained infertility: 13.3 IU/mL [10.2, 18] versus severe male factor: 90.4 IU/mL [18.4, 2994.3] p=0.03). When the six subjects with a positive TPO antibody were excluded from the TSH analyses, the results remained significant with a higher median TSH level in the unexplained infertility group (1.95 mIU/L [1.52, 2.58]) as compared to the severe male factor group (1.69 mIU/L [1.22, 2.16]; p<0.01) and a significantly higher percentage of subjects with a TSH ≥2.5 mIU/L in the unexplained infertility group (26%) as compared to the severe male factor group (12%; p<0.04).

**Prolactin**

Prolactin levels were similar in the unexplained infertility group as compared to the severe male factor group (unexplained infertility: 10.4 ng/mL [7.7, 13.4] versus severe male factor: 11 ng/mL [8.5, 13.7]; p=0.36). As prolactin levels may vary during the menstrual cycle(43,44), we performed an analysis including only individuals who had prolactin measured on day 3 of their menstrual cycle (n=180) and the results were similar (unexplained infertility: 10.8 ng/mL [8.1, 13.7] versus severe male factor: 12.5 ng/mL [9.2, 14.5]; p=0.20). There were no significant differences between the groups with respect to method of prolactin measurement (p=0.82; Supplemental Table 1).

**Discussion:**
We have shown that women with unexplained infertility have significantly higher TSH levels as compared to a control group of women with a comparatively normal fertility evaluation except for an azoospermic/severely oligospermic partner. Similarly, nearly twice as many women with unexplained infertility have TSH levels ≥2.5 mIU/L as compared to the control group. Importantly, all of the subjects in this study had TSH levels within the normal, pre-pregnancy reference range, suggesting that even mild variations of thyroid dysfunction within the normal range may be an important factor in fertility in women who have no known cause for their infertility.

Thyroid disease is a known cause of menstrual irregularity and infertility(9). A number of prior studies have investigated the relationship between TSH and conception rates or time to pregnancy with conflicting results; a TSH ≥2.5 mIU/L has not been associated with increased time to pregnancy in women with proven fecundity (and without a history of infertility)(45) or with adverse intrauterine insemination outcomes(46), whereas in a large population-based study including women with thyroid dysfunction, higher TSH levels were associated with fewer total pregnancies(47).

Prior studies have also investigated the percentage of individuals with abnormal TSH levels or subclinical hypothyroidism in different types of infertility. Abalovich et al found a higher rate of subclinical hypothyroidism (defined as a TSH >4.22 mIU/L or a TSH >26.6 mIU/L in response to 200 mcg of IV TRH stimulation) in individuals with premature ovarian insufficiency, tubal disease and ovulatory dysfunction compared to fertile women but none of the individuals diagnosed with unexplained infertility was diagnosed with subclinical hypothyroidism(48). A second study from Finland looked at the rate of frankly abnormal TSH levels in individuals diagnosed with infertility and found that 6.3% of individuals in the ovulatory dysfunction group and 4.8% of individuals in the unexplained infertility group had an elevated TSH(28). Our study differs from these prior studies in that we used very strict criteria to ensure our subjects had completely normal fertility evaluations (other than azoospermia/severe oligospermia in the control group) and no known history of thyroid disease or abnormal thyroid function tests. All subjects in both groups in our study had regular menstrual cycles, <35 days in length, with no more than 5 days of inter-cycle variability, normal uterine evaluations and normal hormonal profiles. In the unexplained infertility group, male partners had a normal semen analysis(35). The purpose of our strict inclusion/exclusion criteria was to assess whether mild variations in thyroid function and/or circulating prolactin levels contribute to the phenotype of unexplained infertility.

As we did not require proven fecundity as a criterion for the severe male factor group, our choice of control group likely biased our result towards the null hypothesis, as it is possible that some of the women in the severe male factor group would have been classified as having unexplained infertility had they been with a partner with a normal semen profile. Therefore, we believe that the fact that we found a difference in TSH levels, despite this choice of control group, only adds to the strength of our findings. We also did not use a population of individuals with less severe forms of male factor infertility as our control group, which would have yielded a much larger number of controls. The definition of male factor infertility has changed over the years with the lower limit of most semen parameters being lower in current as compared to prior reference ranges(35). Therefore, including a population of individuals over a span of 13 years, with a changing definition of male infertility, would have been problematic. Secondly, a prior study found that in a population of couples who underwent IVF, TSH levels were significantly higher in women with a male partner with male factor infertility as compared to other types of
infertility, including ovulatory and tubal factors(49). The authors hypothesized that this is likely
due to the fact that in couples diagnosed with mild male factor infertility, female factors also
contribute to the diagnosis of infertility, supported by prior studies demonstrating that female
partners of males with poor semen factors have lower fertilization rates using donor sperm as
compared to female partners of azoospermic males(49-51). Given the complicated relationship
between mild male factor infertility and female hormonal status, we included only couples with
azoospermia/severe oligospermia in our analysis.

We also hypothesized that women with unexplained infertility would have higher prolactin
levels (within the normal range) as compared to the control group. A prior study demonstrated
higher prolactin levels in ovulating women with infertility of an unknown cause as compared to a
control group of fertile women, and treatment with a dopamine agonist resulted in conception in
16 out of the 40 infertile women during the 10 months of follow-up(52). On the other hand, a
more recent Cochrane review combining data from three double-blind, randomized trials of 127
women with unexplained infertility treated with bromocriptine or placebo found no benefit in
conception rates in the bromocriptine-treated group(53). In our study, we did not find a
significant difference in prolactin levels in women with unexplained infertility as compared to
severe male factor infertility. Importantly, prolactin levels are exquisitely sensitive to
environmental influences including stress(54), food intake(55) and have been shown to be
highest during the ovulatory and luteal phases of the menstrual cycle(43,44). We attempted to
control for some of this potential variability by only including prolactin levels measured on day 3
of the menstrual cycle, but it is possible that even if there was a difference between groups, we
did not detect it because of the variability we were not able to control for. In order to determine if
prolactin levels contribute to the phenotype of unexplained infertility, future studies will need to
measure prolactin levels in a carefully controlled setting.

Strengths of our study include our very strict inclusion and exclusion criteria, which allowed
us to control for other possible factors contributing to infertility. Importantly our control group
consisted of a population of women who had a similarly rigorous fertility evaluation compared to
the unexplained infertility group. The main limitation of this study is that we relied on health
records and therefore we were limited to labs that were drawn for clinical purposes. Therefore,
we could not measure thyroid antibody levels or thyroid hormone levels in our subjects and a
prior meta-analysis demonstrated an increased rate of infertility in women who were thyroid
antibody positive(56). Of the 239 women included in our study, only 19 had TPO antibodies
checked around the time of their infertility evaluation.

In conclusion, TSH levels are significantly higher in a population of women without known
thyroid dysfunction and with unexplained infertility as compared to a control group. The fact
that nearly 27% of women with unexplained infertility have TSH levels ≥2.5 mIU/L as compared
to 13.5% of women in the control group suggests that mild abnormalities in thyroid function may
potentially contribute to some cases of unexplained infertility. It also raises the question of
whether treatment with thyroid hormone replacement for individuals with TSH levels ≥2.5
mIU/L may be an economical first step in treating unexplained infertility, especially for this
population for whom early use of IVF – a resource intensive treatment – has been shown to
result in higher conception rates(8). Although current practice guidelines do not recommend
treating individuals with a TSH ≥2.5 mIU/L who are attempting to conceive naturally(29, 33),
some practitioners use this lower cut-off to initiate treatment. Our data demonstrate that 22.8%
of patients with a TSH ≥2.5 mIU/L were started on thyroid hormone replacement after their
initial evaluation and therefore > 75% of patients were not, demonstrating the great variance in
clinical practice and the important need for more data. Therefore, future studies will be necessary to determine if treatment of high-normal TSH levels decreases time to conception in couples with unexplained infertility.

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Figure 1: The unexplained infertility group had a significantly higher median TSH as compared to the severe male factor group (p=0.003). Solid lines represent median and first and third quartiles. Dotted line represents a TSH of 2.5 mIU/L

Figure 2: A significantly higher percentage of women in the unexplained infertility group (26.9%) had a TSH level ≥ 2.5 mIU/L as compared to the severe male factor group (13.5%; p < 0.05).
Table 1: Clinical characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Unexplained infertility (n=187)</th>
<th>Severe male factor infertility (n=52)</th>
<th>p-value</th>
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<tr>
<td>Age (years)</td>
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<td>30.1 ± 3.7</td>
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<tr>
<td>BMI (kg/m²)</td>
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<td>24.4 [22.2, 27.0]</td>
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<td>Tobacco</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>-% Current use (n)</td>
<td>7.0% (13)</td>
<td>11.5% (6)</td>
<td>0.38</td>
</tr>
<tr>
<td>-% Past or present use (n)</td>
<td>15.6% (29)</td>
<td>19.2% (10)</td>
<td>0.53</td>
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<tr>
<td>Age of menarche (years)</td>
<td>13 [12, 13]</td>
<td>13 [12, 13]</td>
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<td>% Secondary infertility (n)</td>
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<td>28.9% (15)</td>
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<tr>
<td>Duration of infertility (months)</td>
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<td>18 [12,30]</td>
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<td>Day 3 FSH (IU/mL)</td>
<td>6.7 ± 1.7</td>
<td>6.6 ± 1.4</td>
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Table 2: Percentage of individuals in the unexplained infertility group and severe male factor group who had their TSH measured using a given assay within a specific laboratory (“Laboratory/Assay for TSH measurement” takes into account both the assay and the specific laboratory in which TSH was measured). TSH was measured in four separate hospital laboratories and an additional outside laboratory; three of the laboratories changed their TSH assay once during the 13-year period.

<table>
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<tr>
<th>Laboratory/Assay for TSH measurement</th>
<th>Reference range (mIU/L)</th>
<th>Unexplained infertility (%)</th>
<th>Azoospermia/Severe Oligospermia (%)</th>
<th>p-value</th>
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<td>13.5%</td>
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<td>12.9%</td>
<td>11.5%</td>
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<td></td>
<td>15.1%</td>
<td>13.5%</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Unexplained infertility

Severe male factor

TSH (mIU/L)

$p=0.003$

ADVANCE ARTICLE: Endocrinology

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% with TSH $\geq$ 2.5 mIU/L

- Unexplained infertility
- Severe male factor

p < 0.05