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Positive effects of thyroid replacement therapy on ART outcomes in women with subclinical hypothyroidism with TPO positive antibodies

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Short Running: Subclinical hypothyroidism and IVF outcomes
Disclosures: No disclosures
Abstract

Objective: To study the beneficial effects of Thyroid replacement therapy (TRT) on pregnancy outcomes in patients with subclinical hypothyroidism (SCI hypoT) with respect to thyroid peroxidase autoantibodies (TPO).

Design: Retrospective study of 706 patients

Setting: Not applicable

Patients: Study evaluated 706 patients, which were defined into three cohorts: a) euthyroid, with pre-IVF thyroid stimulating hormone (TSH) levels < 2.5 uI/mL, b) SCI hypoT defined as TSH levels > 2.5 uI/mL and <4 uI/mL who were not treated and c) SCI hypoT who received thyroid replacement therapy. The three cohorts were further subclassified into two groups each based on TPO antibody levels.

Interventions: The cohorts were compared for the effects of TRT on pregnancy outcomes.

Main Outcome Measures: Identification of effects of thyroid replacement therapy on ART outcomes

Results: Results showed that SCI hypoT patients had a significantly fewer positive pregnancy outcomes compared to euthyroid patients. Importantly, low dose TRT was found to be beneficial in improving IVF success rates and pregnancy outcomes in SCI hypoT patients. The original cohort of patients, further classified into two subgroups based on antithyroid (TPO) antibodies showed that low dose TRT was associated with improved pregnancy outcomes in women with SCI hypoT and TPO positive antibodies.

Conclusions: Our findings demonstrate that low dose TRT may be beneficial in improving IVF success and pregnancy outcomes in women with SCI hypoT and positive TPO antibodies.

Key words: Subclinical hypothyroidism, invitro fertilization, thyroid replacement therapy
Introduction

The hypothalamus releases thyrotropin releasing hormone (TRH), which in turn stimulates the pituitary gland to release thyroid stimulating hormone (TSH), the primary marker for thyroid function (1). TSH stimulates the release of thyroxine (T4) and tri-iodothyronine (T3) from the thyroid gland, which exert the metabolic effects of the thyroid gland throughout the body (1). Low levels of T4 stimulate the release of more TSH via negative feedback on the hypothalamic-pituitary-axis. Thyroid function is critical to optimal reproductive function in women, and thyroid disease may exert negative effects on ovulation, menstrual function, and pregnancy success (2, 3). Due to the strong inverse log-linear relationship between serum TSH and serum-free T4, serum TSH concentrations are generally regarded as a reliable measure to indicate thyroid function and abnormalities and are routinely screened in women with infertility (4-6). Even small changes in T4 concentrations produce very large changes in serum TSH, making TSH a very reliable and sensitive indicator of thyroid function abnormalities (4-6).

With regard to reproductive function, thyroid hormone exerts its effects at multiple levels, including estradiol metabolism, ovulation, embryo implantation, pregnancy and live births (7-10). Hypothyroidism can manifest as overt or subclinical hypothyroidism (SCI hypoT)(11). In overt hypothyroidism, TSH levels are elevated, T4 levels are decreased, and symptoms of hypothyroidism, such as cold intolerance and constipation, may occur. In SCI hypoT, TSH levels are increased with normal T4 levels (i.e. TSH levels >2.5 uIU/mL and < 4 uIU/mL; T4 levels 5.0 to 12.0μg/dL), and there are mild to no evident symptoms of hypothyroidism (12, 13). However, studies have indicated that SCI hypoT patients may have additional comorbidities, including increased total cholesterol level and low-density lipoprotein (LDL), greater risk of atherosclerosis, disturbed blood coagulation, increased chronic heart failure risk, and even increased incidence of depressive disorders compared to euthyroid patients (14).

It is well established that overt hypothyroidism negatively affects reproduction and pregnancy outcomes via increased miscarriage rates, menstrual irregularities, subfertility, ovulation failure, and altered ovulatory function (15, 16). However, it is unclear to what extent SCI hypoT affects pregnancy outcome. Though this subject remains controversial, some studies have shown that pregnant patients with SCI hypoT have a significantly higher risk of placental abruption, preterm birth, stillbirths, and miscarriage (15-18). Treatment of SCI hypoT in pregnant patients has been found to positively impact miscarriage and live birth rates for those undergoing in vitro fertilization (IVF) and is associated with a decrease in obstetric and neonatal complications. (19).
In the current study, we evaluated the impact of thyroid replacement therapy on pregnancy outcomes and whether thyroid replacement therapy can overcome the adverse effects of antithyroid antibodies on pregnancy outcome in women with SCi hypOT.

**Materials and Methods**

**Patient Population**

Our retrospective study was approved by our institutional review board, the ethics committee of Clinical Research ART data gathering complies with US law on assisted reproductive technologies (The Fertility Clinic Success Rate Act 1992 (Wyden bill)). The study analyzed data from 706 patients undergoing ART between year 2017-18 at South Florida Institute for Reproductive Medicine (IVFMD). Of 706 patients, total number of patients with Preimplantation Genetic Testing for Aneuploidy (PGTA) were 217, and the number of patients with non PGTA cases were 489. Patients were categorized into three groups. Group 1, euthyroid, consisted of patients who had pre-IVF TSH levels <2.5 uIU/mL. Patients with SCi hypOT (TSH levels > than 2.5 uIU/mL but ≤4 uUI/mL) were divided into two groups (Groups 2 and 3) based on whether they were given low dose thyroid supplementation (treatment): group 2 included patients with SCi hypOT who were not treated, and group 3 included patients who were treated. The information on thyroid antibodies (TPO) was used to classify each of the three groups (euthyroid, SCi hypOT untreated, SCi hypOT treated) into two subgroups of thyroid antibodies (TPO): Negative (<11 IU/ml) or Positive (>11 IU/ml). Serum TSH and TPO antibodies were measured in serum within 1-2 months prior to treatment initiation. All women underwent standard controlled ovarian stimulation protocols following the typical practice in our IVF center.

**Oocyte Retrieval, Embryo Biopsy, and Culture Conditions**

Patients underwent controlled ovarian stimulation using standardized protocols. When at least two follicles had reached ≥ 18 mm in diameter, human chorionic gonadotropin (hCG) and/or gonadotropin releasing hormone agonist was administered, and oocyte retrieval was scheduled 35-36 hours later. Conventional insemination or intracytoplasmic sperm injection was performed, and embryo culture proceeded to the blastocyst stage, at which time embryo transfer, embryo cryopreservation, or embryo biopsy was performed, as previously described (20, 21).

Preimplantation genetic testing for aneuploidy (PGT-A) was performed for different indications (recurrent miscarriage, repetitive implantation failure, advanced maternal age, or male factor infertility). All patients subsequently underwent embryo transfer pregnancy, miscarriage and ongoing pregnancy rates were recorded. There was a total of 220 patients who underwent PGTA,
of which 3 were fresh embryo transfers and 217 were frozen embryo transfers. The number of non PGTA cases were 486, of which 274 were fresh embryo transfers and 212 were frozen embryo transfers (Supplementary Table 1).

Statistical analysis and sample size calculation

Variables are presented as mean and standard deviation or as median and interquartile values based on sample distribution. Intrinsic and extrinsic variables with fixed and random effects are considered in the analysis. GraphPad Prism (GraphPad Software) was used for statistical analysis. All data are presented as the means ± SEM. The statistical significance between two groups was estimated by unpaired two-tailed t test. Multiple group comparisons were performed using a one-way analysis of variance with least significant difference test. In all cases, $p < 0.05$ was considered statistically significant.

Results

Impact of thyroid replacement therapy on pregnancy outcomes

To study the impact of thyroid replacement therapy on pregnancy outcomes, a total of 706 patients were considered. Among these, total number of patients with Preimplantation Genetic Testing for Aneuploidy (PGT-A) were 210, of which 3 were fresh embryo transfers and 207 were frozen embryo transfers. The number of patients with non-PGT-A cases were 486, of which 274 were fresh embryo transfers and 212 were frozen embryo transfers. The number of patients with non PGTA patients with fresh embryo transfer were greater (significantly; $p<0.05$) than number of non PGTA or PGTA patients with frozen embryo transfer. On the contrary, the number of non PGTA patients with frozen embryo transfer were not significantly different ($p>0.05$) than number of PGTA patients with frozen embryo transfer (confirming that PGTA and non PGTA as classes does not confound the ART outcomes). (Supplementary Table 1). After excluding the 3 patients with fresh embryo transfers from PGTA category, patients were stratified into 3 classes based on treatment and pre-retrieval TSH levels of less than or greater than 2.5 uIU/ml. Group 1 (n=525 patients) consisted of euthyroid women, with pre-retrieval TSH of less than 2.5 uIU/ml who did not receive thyroid replacement therapy. Group 2 (n=50 patients) consisted of SCI hypoT women, with pre-retrieval TSH of greater than 2.5 uIU/ml who did not received thyroid replacement therapy. Group 3 (n=131 patients) consisted of SCI hypoT women, with pre-retrieval TSH of greater than 2.5 uIU/ml who received thyroid replacement therapy. These three groups were compared for pregnancy outcomes. Results showed that the overall pregnancy rate was significantly lower in women with SCI hypoT without treatment (compared to Euthyroid ($p<0.05$). On the contrary, treated women
with SCI hypot, group 3 showed no significant differences compared to Euthyroid, group 1 (p>0.05) (Table 1) (Figure 1).

**Negative effects of antithyroid antibodies on pregnancy outcomes in hypothyroid and SCI hypot women**

Recent studies suggest that thyroid autoimmunity may adversely impact pregnancy outcome (22, 23). Though the adverse effects of antithyroid antibodies have been well studied in hypothyroid pregnant women, their effects in euthyroid and SCI hypot women are not well evaluated. As a first step we studied the effects of thyroid peroxidase antibody (TPO) on ART outcomes following embryo transfer in all women. For this purpose, patients were classified into two groups based on the thyroid antibodies (TPO): Negative (<11 IU/ml) or Positive (>11 IU/ml) and compared for ART outcomes. Among 582 TPO negative patients, 450 were pregnant (P) and 132 were not pregnant (NP) which were found not to be significantly different (p>0.05) from 124 patients who were TPO positive of which 94 were P and 30 were NP. As a first step we studied the effects of thyroid peroxidase antibody (TPO) on ART outcomes following embryo transfer in all women. For this purpose, patients were classified into two groups based on the thyroid antibodies (TPO): Negative (<11 IU/ml) or Positive (>11 IU/ml) and compared for ART outcomes. Among 582 TPO negative patients, 450 were pregnant (P) and 132 were not pregnant (NP) which were found not to be significantly different (p>0.05) from 124 patients who were TPO positive of which 94 were P and 30 were NP. Next, we studied the effects of thyroid replacement therapy on ART outcomes following embryo transfer in women with SCI hypot with respect to the presence of TPO antibodies. For this purpose, patients in three groups (euthyroid, SCI hypot who did not or did receive thyroid replacement therapy) were further classified into two subgroups based on the thyroid antibodies (TPO): Negative (<11 IU/ml) or Positive (>11 IU/ml). Among 525 women in Group 1 (euthyroid), 453 were TPO negative (358 P, 95 NP) and 72 patients were TPO positive (54 P, 18 NP). Group 2 included 50 women with SCI hypot who were not treated. Of these, 42 patients were TPO negative (28 P, 14 NP) and 8 patients were TPO positive (3 P, 5 NP). Group 3 included 131 women who were treated. Of these, 87 patients were TPO negative (64 P, 23 NP) and 44 patients were TPO positive (37 P, 7 NP). Pregnancy outcomes were compared in each of the subgroups via three-way ANOVA analyses. Results showed that women with SCI hypot and TPO positive had significantly fewer pregnancies compared to women with SCI hypot and TPO negative (p<0.05) (Table 2) (Figure 2). Additionally, thyroid replacement therapy was able to significantly improve the pregnancy outcomes in patients with SCI hypot and TPO positive.
Moreover, the difference between pregnancy outcomes between patients in Group 1 versus Group 3 was non-significant (p>0.05).

Discussion
SCI hypothyroidism (SCl hypot) is an early and mild form of hypothyroidism (24, 25). Recently published guidelines of the American Thyroid Association, prior guidelines from the Endocrine Society and the European Thyroid Association, recommend the treatment of SCl hypothyroidism in the mother during pregnancy.

However, the benefits of treating SCl hypothyroidism with thyroid replacement therapy preconception and in pregnancy are unclear and are controversial (11). For instance, some studies suggest that SCl hypothyroidism during pregnancy is associated with multiple adverse maternal and neonatal outcomes however no association is reported between recurrent pregnancy loss and SCl hypothyroidism, nor does levothyroxine improve subsequent pregnancy outcomes (11, 26). On the other hand, some studies showed that the effects of levothyroxine in SCl hypothyroidism pregnant women are not the same for all pregnancy outcomes and can indeed reduce pregnancy loss in some patients (27). Recently published guidelines of the American Thyroid Association, prior guidelines from the Endocrine Society and the European Thyroid Association, recommend the treatment of SCl hypothyroidism in the mother during pregnancy. Our study focus is on evaluating if 1) SCl hypothyroidism may negatively impact IVF success and pregnancy outcomes, 2) low dose thyroid replacement therapy may be beneficial in improving IVF success and pregnancy outcomes in women with SCl hypothyroidism, 3) antithyroid antibodies have any deleterious effects on pregnancy outcomes in women with SCl hypothyroidism, and 4) low dose thyroid replacement therapy may be beneficial in improving IVF success and pregnancy outcomes in women with SCl hypothyroidism with positive TPO antibodies.

Several studies have suggested that the effects of treated subclinical or overt hypothyroidism on IVF success are variable. Interestingly, Scoccia et al. showed that even treated patients with hypothyroidism had worse pregnancy outcomes (decreased implantation, clinical pregnancy, and live birth rates) than euthyroid patients (28). In contrast, Busnelli et al. showed that treated hypothyroid patients had no difference in pregnancy rate and live births compared to euthyroid patients (29).

There are several potential mechanisms which can contribute to these differing findings. For example, the controlled ovarian hyperstimulation causes higher estradiol (E2) levels, which in turn lead to elevated thyroid-binding globulin levels. This decreases the levels of free T4 and increases TSH levels due to the hypothalamic-pituitary feedback mechanism. Euthyroid patients have
appropriate control of this feedback loop and can synthesize more T4 to compensate for this
response; however, patients with hypothyroidism who are on fixed doses of thyroid replacement
therapy may be unable to adequately compensate and may actually be undertreated, leading to
lower pregnancy success rates (28). Additionally, hCG administration to trigger ovulation can
affect thyroid hormone levels. TSH and hCG share 85% homology as they have a common α-
subunit. This leads to cross reaction of hCG on TSH receptors, which increases T4 levels. In
euthyroid patients, the increase in free T4 due to hCG cross reactivity and the decrease in free
T4 due to increased TBG levels are balanced (28). However, these mechanisms are not intact in
patients with hypothyroidism and can affect IVF success depending on the adequacy of thyroid
replacement therapy. Therefore, close monitoring of TSH levels during treatment for subclinical
or clinical hypothyroidism are critical in determining successful pregnancy outcomes.

Our study focused on patients with SCI hypot treated with thyroid replacement therapy. Although
different studies suggest reference ranges for SCI hypot which vary drastically from 0.45-4.5
uUI/ml (30-32), for selecting the patients with SCI hypot, we considered a TSH range levels of
2.5-4.0 uUI /mL based on over 30 years of clinical practice experience. We evaluated the
implications of thyroid replacement therapy, TSH and TPO antibodies on improving the pregnancy
success rates in these patients. We found that SCI hypot negatively impacts IVF success and
pregnancy outcomes. Patients with SCI hypot benefit from low dose of thyroid replacement
therapy with improved IVF success and pregnancy outcomes. Moreover, we found that antithyroid
antibodies have deleterious effects on pregnancy outcomes in women with SCI hypot, and low
dose thyroid replacement therapy improves IVF success and pregnancy outcomes in these
women. However, our study has limitations which are but not limited to 1) Group 2 which
represents patients with SCI hypot which did not receive thyroid replacement therapy is a small
group with limited number of patients. The existence of this group is influenced by individual
clinician discretion on whether to give thyroid replacement therapy, which could be important but
are beyond the scope of analysis in the present study; 2) Upon comparing the pregnancy
outcomes in patients with SCI hypot with negative TPO antibodies, which did not receive any
thyroid replacement therapy, we could not observe a significant difference with that of patients
with SCI hypot with negative TPO antibodies which received therapy. This suggest up to some
extent that the treatment efficacy is influenced by the TPO antibodies. However, to validate this
observation, more detailed analysis on other factors that could potentially confound the outcomes
which are but not limited to BMI, percent body fat, HS-CRP, elevated estradiol etc would be
required. Further in-depth studies are ongoing to evaluate parameters such as the presence of
ATG antibodies and other specific treatment strategies which may have an additional effect on successful IVF outcomes.

Conclusion

Serum TSH is often screened in women planning to conceive to evaluate thyroid function, given its association with adverse neonatal and obstetric outcomes. Thyroid hormone replacement (levothyroxine) is the standard of care for women with clinical hypothyroidism, and it can be consumed daily or as otherwise prescribed (33, 34). The general recommendation is to target a TSH of <2.5 mIU/L with levothyroxine treatment for optimal outcomes for patients with primary hypothyroidism (35-37). However, no specific TSH value within the recommended ≤2.5 mIU/L range for pregnancy has been found to predict better IVF outcomes (38). Our study showed that thyroid replacement therapy has significant positive effects on ART outcome in SCI hypoT women. Additionally, we found that TPO antibodies can have deleterious effects on pregnancy outcomes in SCI hypoT women. Thyroid replacement therapy can improve the overall pregnancy outcomes in SCI hypoT women with positive TPO antibodies. Our findings are consistent with the updated recommendations for thyroid replacement in pregnant women by the American Thyroid Association. Further in-depth studies are ongoing considering parameters such as the AMH, BMI, and additional specific treatment strategies which may have additional effects on successful IVF outcomes (33, 34).

References

7. Sohn SY, Joung JY, Cho YY, Park SM, Jin SM, Chung JH et al. Weight Changes in Patients with Differentiated Thyroid Carcinoma during Postoperative Long-Term Follow-up under Thyroid Stimulating Hormone Suppression. Endocrinol Metab (Seoul) 2015;30:343-51.


TABLE 1. Distribution of patients with respect to the pre-retrieval TSH levels, PGTA status, age of the patients and pregnancy outcomes (non-pregnant, SAB, Biochem, Delivered, Ectopic) into three groups (gp1-Euthyroid, gp2- SCI hypoT untreated and gp3- SCI hypoT which received treatment).

TABLE 2. Distribution of patients with respect to the TPO antibodies, pre-retrieval TSH levels, treatment, PGTA status, age of the patients and pregnancy outcomes (non-pregnant, SAB, Biochem, Delivered, Ectopic) into three groups (gp1-Euthyroid, gp2- SCI hypoT untreated and gp3- SCI hypoT which received treatment).

FIGURE 1. Impact of treatment on thyroid replacement therapy on pregnancy outcomes in three groups (gp1-Euthyroid, gp2- SCI hypoT untreated and gp3- SCI hypoT which received treatment). Asterisks denote p values asterisks (e.g., *p<0.05).

FIGURE 2. Impact of treatment on thyroid antibodies and thyroid replacement therapy on pregnancy outcomes in three groups with respect to each other (gp1-Euthyroid, gp2- SCI hypoT untreated and gp3- SCI hypoT which received treatment). Asterisks denote p values asterisks (e.g.****p<0.0001)

SUPPLEMENTARY TABLE 1. Distribution of patients with respect to number of fresh, frozen embryo transfers, PGTA, non-PGTA status, age of the patients and pregnancy outcomes.
## GROUP 1

**Pre, TSH<2.5, Non Treated**

<table>
<thead>
<tr>
<th>Pregnancy Outcome</th>
<th>PGTA</th>
<th>NPGTA</th>
<th>Mean Age</th>
<th>S.Dev</th>
</tr>
</thead>
<tbody>
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<td>27</td>
<td>86</td>
<td>97.50</td>
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<td>16</td>
<td>42</td>
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<tr>
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<tr>
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<td>189</td>
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<td>0.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>172</td>
<td>353</td>
<td>100</td>
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</table>

## GROUP 2

**Pre, TSH≥2.5, Non Treated**

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<tr>
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<th>PGTA</th>
<th>NPGTA</th>
<th>Mean Age</th>
<th>S.Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Pregnant</td>
<td>5</td>
<td>14</td>
<td>34.49</td>
<td>1.60</td>
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<tr>
<td>BIOCHEM</td>
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<td>DELIVERED</td>
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<td>19</td>
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<td>0.00</td>
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<tr>
<td><strong>Total</strong></td>
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## GROUP 3

**Pre, TSH≥2.5, Treated**

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<th>Pregnancy Outcome</th>
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<th>NPGTA</th>
<th>Mean Age</th>
<th>S.Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Pregnant</td>
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<td>25</td>
<td>35.66</td>
<td>1.18</td>
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<tr>
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<td>2.58</td>
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<tr>
<td><strong>Total</strong></td>
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<td>100</td>
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### GROUP 1

<table>
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<th>Pregnancy Outcome</th>
<th>No of Patients</th>
<th>%</th>
<th>No of PGTA</th>
<th>%</th>
<th>Mean Age</th>
<th>S.Dev</th>
<th>No of Patients</th>
<th>%</th>
<th>No of NPGTA</th>
<th>%</th>
<th>Mean Age</th>
<th>S.Dev</th>
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<tr>
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<td>55</td>
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### GROUP 2

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<th>Pregnancy Outcome</th>
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<th>%</th>
<th>No of Patients</th>
<th>%</th>
<th>Mean Age</th>
<th>S.Dev</th>
<th>No of Patients</th>
<th>%</th>
<th>No of Patients</th>
<th>%</th>
<th>Mean Age</th>
<th>S.Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Pregnant</td>
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<td>44.44</td>
<td>10</td>
<td>30.30</td>
<td>35.57</td>
<td>1.08</td>
<td>1</td>
<td>100</td>
<td>4</td>
<td>57.14</td>
<td>33.4</td>
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