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Outcomes of Pregnancy in Women with TPO Positive Status after Appropriate Dose Adjustments of Thyroxin: A Prospective Cohort Study

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***Abstract*—**This study aimed to analyse the pregnancy outcomes in patients with TPO positivity after appropriate L-Thyroxin supplementation with close surveillance. All pregnant women attending the antenatal clinic at Milann-The Fertility Center, Bangalore, India- from Aug 2013 to Oct 2014 whose booking TSH was more than 2.5 mIU/L were included along with those pregnant women with prior hypothyroidism who were TPO positive. Those with TPO positive status were vigorously managed with appropriate thyroxin supplementation and the doses were readjusted every 3 to 4 weeks until delivery. Women with recurrent pregnancy loss were also tested for TPO positivity and if tested positive, were monitored serially with TSH and fT4 levels every 3 to 4 weeks and appropriately supplemented with thyroxin when the levels fluctuated. The testing was done after an informed consent in all these women. The statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data. 460 pregnant women were screened for thyroid dysfunction at booking of which 52% were hypothyroid. Majority of them (31.08%) were subclinically hypothyroid and the remaining were overt. 25% of the total no. of patients screened were TPO positive. The various pregnancy complications that were observed in the TPO positive women were gestational glucose intolerance [60%], threatened abortion [21%], midtrimester abortion [4.3%], premature rupture of membranes [4.3%], cervical funneling [4.3%] and fetal growth restriction [3.5%]. 95.6% of the patients who followed up till the end delivered beyond 30 weeks. 42.6% of these patients had previous history of recurrent abortions or adverse obstetric outcome and 21.7% of the delivered babies required NICU admission. Obstetric outcomes in our study in terms of midtrimester abortions, placental abruption, and preterm delivery improved for the better after close monitoring of the thyroid hormone [TSH and fT4] levels every 3 to 4 weeks with appropriate dose adjustment throughout pregnancy. Euthyroid women with TPO positive status enrolled in the study incidentally were those with recurrent abortions/infertility and required thyroxin supplements due to elevated Thyroid hormone (TSH, fT4) levels during the course of their pregnancy. Significant associations were found with age>30 years and Hyperhomocysteinemia [p=0.017], recurrent pregnancy loss or previous adverse obstetric outcomes [p=0.067] and APLA [p=0.029]. TPO antibody levels >600 I U/ml were significantly associated with development of gestational hypertension [p=0.041] and fetal growth restriction [p=0.082]. Euthyroid women with TPO positivity were also screened periodically to counter fluctuations of the thyroid hormone levels with appropriate thyroxin supplementation. Thus, early identification along with aggressive management of thyroid dysfunction and stratification of these patients based on their TPO status with appropriate thyroxin supplementation beginning in the first trimester will aid risk modulation and also help avert complications.

***Keywords*—**Antinuclear antibody, Subclinical hypothyroidism, Thyroxin, TPO antibody.

I. Introduction

THE fetal thyroid begins to function at twelve weeks of gestation. This makes the fetus completely dependent on the maternal thyroid gland for its requirement in the first trimester. Pregnancy initiates physiological changes in the maternal thyroid gland to help suffice this increased demand. This function is impaired in maternal hypothyroid states which warrant additional extrinsic supplementation of L-Thyroxin to the pregnant mother to meet this requirement.

Thyroid hormone is required for normal placentation. It is evidence based presently to link preterm delivery and vascular diseases like preeclampsia to faulty early placentation [1], [2]. These adverse effects are more common in those with overt hypothyroidism as compared to those with the subclinical variety [3].

Considering the potentially increased obstetric risks associated with subclinical hypothyroidism, it seems prudent for clinicians to consider appropriate L-Thyroxin supplementation in these pregnant women. Trimester specific reference ranges for TSH should guide supplementation [4] which are as follows; First Trimester- 0.1 to 2.5 m IU/L. Second Trimester- 0.2 to3 m IU/L. Third Trimester- 0.3 to 3 m IU/L. Auto antibody associations with thyroid dysfunction and its influence on pregnancy outcomes have been vastly studied in recent times. Association with TPO antibody has been considered as a high risk for pregnancy complications which warrants close maternal and fetal surveillance to improve perinatal outcomes [5]. Pregnant mothers with positive thyroid autoantibodies seem to have a greater risk of preeclampsia, fetal growth restriction and low first minute Apgar scores of which both preeclampsia and fetal growth restriction have been attributed to the additive effect of thyroid dysfunction [6]. A recent study has also shown that TPO positive hypothyroid women are significantly at high risk for mid trimester abortions compared to the TPO negative hypothyroid women [5]. The present study primarily aimed at analyzing

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the maternal and perinatal outcomes of TPO positive pregnant women after appropriate dose adjustments of L-Thyroxin with close surveillance. The secondary objectives were to establish the prevalence of TPO antibody positivity in pregnant mothers with subclinical hypothyroidism and also to establish its associations with other co-morbidities like antinuclear antibody (ANA) positivity, other autoimmune disorders, and thrombophilias (antiphospholipid antibody syndrome i.e. APLA and hyperhomocysteinemia).

II. Material and Methods

This study was a prospective observational study conducted at Milann –The Fertility Center, Bangalore; India between August 2013 to October 2014.All pregnant women attending the antenatal clinic at Milann-The Fertility Center with a booking TSH of more than 2.5 mIU/L and those who were already diagnosed with hypothyroidism were tested for TPO antibody positivity after an informed consent. A positive TPO antibody level was considered to be more than or equal to 35 IU/ml. Those with TPO positivity with elevated TSH [as per the trimester specific ranges] were aggressively managed with oral L-Thyroxin supplementation in the dose of 1 to 2 microgram/kg body wt. with appropriate dose adjustment made every 3to 4 weeks as per TSH and fT4 levels unlike the TPO negative cohort who were monitored every 4 to 6 weeks with corresponding dose adjustments.

III. Results

This was an observational single group clinical study. The data was tabulated as follows;

TABLE I
AGE DISTRIBUTION OF PATIENTS

Age in years	No. of patients	%
21-25	7	6.1
26-30	49	42.6
31-35	41	35.7
36-40	10	8.7
41-45	7	6.1
46-50	1	0.9
Total	115	100.0

Mean ± SD: 31.26±4.74

TABLE II
TPO ANTIBODY (AB) LEVELS OF PATIENTS STUDIED

TPO AB Levels	No. of patients	%
<40	22	19.1
40-80	51	44.3
80-160	11	9.6
>160	31	27.0
Total	115	100.0

Descriptive and inferential statistical analysis was carried out in the present study. Results on continuous measurements were presented on Mean ± SD (Min-Max) and results on categorical measurements were presented in Number (%). The level of significance was assessed at 5 %. The following assumptions on data were made, Assumptions: 1. Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, Cases of the samples should be independent.

TABLE III
ADVERSE OUTCOMES IN PREGNANT WOMEN WITH TPO POSITIVITY

Adverse outcomes	No. of patients (n=115)	%
Gestational glucose intolerance/ Gestational Diabetes	69	60.0
Hyperhomocystenemia	50	43.5
Bad obstetric history/Recurrent Pregnancy Loss	49	42.6
Threatened abortion	25	21.7
Gestational hypertension	17	14.8
Antinuclear antibody positive	17	14.8
Antiphospholipid antibody positive	14	12.2
Oligohydramnios	6	5.2
2nd trimester abortion	6	5.2
Funneling of cervix	5	4.3
Premature rupture of membranes	5	4.3
Missed abortion	5	4.3
Fetal growth restriction	4	3.5

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures were interpreted on the following basis;

- +Suggested significance- (p value: $0.05<p<0.10$),
- Moderately significant -(P value: $0.01<p \leq 0.05$),
- ** Strongly significant- (p value: $p \leq 0.01$).

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

460 pregnant women attending the antenatal clinic at Milann- The Fertility Center which is a tertiary center catering to high risk pregnancies between August 2013 and October 2014 were screened for thyroid dysfunction with Serum TSH and fT4 at booking. 240 (52%) out of 460 pregnant were hypothyroid. Amongst the hypothyroid cohort, 97 (21.08%) were overtly hypothyroid and 143 (31.08%) were subclinically hypothyroid.115 patients (25%) were diagnosed as TPO positive. 88 patients of the TPO positive cohort were subclinically hypothyroid while 23 were overtly hypothyroid. 4 TPO positive women were euthyroid at the booking visit. A diagnosis of euthyroid TPO positive status was made in 4 pregnant women who were evaluated for the same in view of previous history of recurrent pregnancy loss or prolonged period of infertility.

Various pregnancy complications and associations observed in TPO positive pregnant women were: threatened abortion (21.7%), missed abortion (4.3%), cervical funneling (4.3%) midtrimester abortion (5.2%), fetal growth restriction (3.5%), oligohydramnios (5.2%), premature rupture of membranes (4.3%), gestational diabetes/gestational glucose intolerance (60%), gestational hypertension (14.8%) and bad obstetric history/recurrent pregnancy loss (42.6%). Bad obstetric history was defined as any previous adverse pregnancy outcome like preeclampsia, fetal growth restriction,

midtrimester abortion, and intrauterine fetal demise [Table III]. Other comorbidities that were studied included; ANA positivity (14.8%), APLA syndrome (17%) and Hyperhomocysteinemia (43.5%) [Table III].

Significant associations were found with pregnant women aged above 30 years of age who were TPO positive and Hyperhomocysteinemia (p=0.017) those with bad obstetric history/recurrent pregnancy loss (p=0.067) and APLA (p=0.029) [Table IV]. Those with TPO antibody levels more than 600 IU/ml (15 pregnant women) showed significant associations with gestational hypertension (p=0.041) and fetal growth restriction (p=0.082) [Table V].

46 out of 115 were followed up till delivery of which 44 (95.6%) delivered beyond 30 weeks. The NICU admissions for the delivered babies were 10 (21.7%), but there were no intrauterine fetal deaths or neonatal deaths.

TABLE IV
ADVERSE OUTCOMES IN PREGNANT WOMEN WITH TPO POSITIVITY ACCORDING TO AGE

Adverse outcomes	No. of patients (n=115)	Age in years <30 years (n=56)	>30 years (n=59)	p value
Gestational glucose intolerance/Gestational Glucose Intolerance	69	32(46.4%)	37(53.6%)	0.542
Hyperhomocystenemia	50	18(36%)	32(64%)	0.017*
Bad obstetric history/Recurrent Pregnancy Loss	49	19(38.8%)	30(61.2%)	0.067+
Threatened abortion	25	9(36%)	16(64%)	0.112
Gestational hypertension	17	8(47.1%)	9(52.9%)	0.884
Antinuclear antibody positive	17	8(47.1%)	9(52.9%)	0.884
Antiphospholipid antibody positive	14	3(21.4%)	11(78.6%)	0.029*
Oligohydramnios	6	2(33.3%)	4(66.7%)	0.680
2nd trimester abortion	6	4(66.7%)	2(33.3%)	0.431
Funnelling of cervix	5	2(40%)	3(60%)	1.000
Premature rupture of membranes	5	3(60%)	2(40%)	0.674
Missed abortion	5	3(60%)	2(40%)	0.674
Fetal growth restriction	4	1(25%)	3(75%)	0.619

TABLE V
ADVERSE OUTCOMES IN PREGNANT WOMEN WITH TPO POSITIVITY AS PER ANTIBODY LEVELS

Adverse outcomes	No. of patients (n=115)	TPO-AB levels <600 (n=100)	>600 (n=15)	p value
Gestational glucose intolerance/Gestational Diabetes	69	61(88.4%)	8(11.6%)	0.572
Hyperhomocystenemia	50	45(90%)	5(10%)	0.395
Bad obstetrics history	49	45(91.8%)	4(8.2%)	0.181
Threatened abortion	25	23(92%)	2(8%)	0.518
Gestational hypertension	17	12(70.6%)	5(29.4%)	0.041*
Antinuclear antibody positive	17	15(88.2%)	2(11.8%)	1.000
Antiphospholipid antibody positive	14	13(92.9%)	1(7.1%)	0.690
Oligohydramnios	6	4(66.7%)	2(33.3%)	0.175
2nd trimester abortion	6	4(66.7%)	2(33.3%)	0.175
Funneling of cervix	5	4(80%)	1(20%)	0.509
Premature rupture of membranes	5	4(80%)	1(20%)	0.509
Missed abortion	5	5(100%)	0(0%)	1.000
Fetal growth restriction	4	2(50%)	2(50%)	0.082+

IV. DISCUSSION

52% i.e. 240 out of 460 pregnant women screened were hypothyroid of which 31.08% (143 patients) were subclinically hypothyroid and the remaining 21.08% (97 patients) were of the overt category. The high prevalence of hypothyroidism amongst the pregnant patients could be attributable to the fact that our center is a tertiary care facility for high risk pregnancy and infertility. 47% of the hypothyroid cohort were TPO positive which was slightly higher compared to the prevalence quoted in other studies which is 3.3% [7], [8] to 31% [9], [3].

Several studies till date have established the association of adverse pregnancy outcomes with TPO positivity. Gafoor et al. showed a higher risk of abortion and prematurity in pregnant women with TPO positivity [10]. Mannisto T. et al. found that first trimester TPO antibody positivity was a risk factor for perinatal death but not thyroid hormone status [11].

Negro et al. reported less obstetrical complications in L-Thyroxin treated TPO positive group as compared to TPO positive untreated group [12].

Feki et al. in their study on Tunisian pregnant women found that there was a significant increase in history of past gestational hypertension, late abortions and fetal death [13].

Both Casey and Abassi et al. reported a 3 fold increase in the risk of placental abruption in TPO positive women [14], [15]. 60% of pregnant patients with TPO positivity in our study were also diagnosed with either gestational diabetes or gestational glucose intolerance which correlated with findings of large for gestational age babies and higher placental weights as in [11].

21% of the TPO positive cohort in our study had threatened abortion but only 4.3% of the patients had a missed abortion. Gestational hypertension was seen in 14.8% of these patients, but only 3.5% of the TPO positive cohort had fetal growth restriction. 42.6% of pregnant mothers who were TPO positive in our study had a bad obstetric history or recurrent pregnancy loss.

Significant associations were found with pregnant women aged above 30 years and TPO positivity with Hyperhomocysteinemia (p=0.017), APLA (p=0.029) and bad obstetric history or recurrent pregnancy loss (p=0.067).

Those with TPO antibody levels of more than 600 IU/ml showed significant associations with gestational hypertension (p=0.041) and fetal growth restriction (p=0.082).

4 cases of euthyroid TPO positive women were part of the study of which 3 had a previous history of recurrent pregnancy loss/bad obstetric history along with APLA positivity. Hyperhomocysteinemia and gestational glucose intolerance were diagnosed in two patients. One patient had a history of prolonged period of infertility and also was a case of gestational glucose intolerance. All the 4 cases were followed up with serial testing for TSH and f T4 every 3 to 4 weeks and were advised supplementation only when the levels fluctuated above 2.5m IU/L. Only two of these patients required supplementation as compared to the remaining two who maintained euthyroid levels during the period of surveillance. 2 patients amongst this cohort delivered beyond 37 weeks of

gestation unlike the remaining two who had a late first trimester missed abortion in spite of maintaining euthyroid levels without any extrinsic supplementation.

Appropriate dose adjustment of L-Thyroxin with close surveillance as in our study showed a trend [Odds Ratio 2.18 (0.67-7.09; p=0.21) towards decrease in the midtrimester abortions which were known to be significantly associated with TPO positive hypothyroid pregnant women [5]. However, larger studies are required to extrapolate the above findings.

V. Conclusion

- Appropriate dose based adjustment of L-Thyroxin supplementation as in our study showed a trend towards decreasing the possibility of a midtrimester abortion which is known to be significantly associated with TPO positive hypothyroid women.
- 76.5% of the TPO positive hypothyroid women were subclinically hypothyroid in our study which emphasizes the need for appropriate surveillance and management of this cohort to avert adverse obstetric outcomes.
- TPO positive pregnant women with levels more than 600 IU /ml were significantly at risk for gestational hypertension and fetal growth restriction.
- Significant associations were found between pregnant women aged above 30 years who were TPO positive with Hyperhomocysteinemia, APLA and bad obstetric history/recurrent pregnancy loss.

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