

# The Impact of Anti-thyroid Peroxidase Antibodies on Maternal Outcome in Pregnancy with Subclinical Hypothyroidism

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## ABSTRACT

Numerous studies worldwide have found inconsistent associations between subclinical hypothyroidism (SCH) in pregnancy and adverse obstetrical outcomes including miscarriage, fetal death, preterm delivery, gestational diabetes (GDM), hypertensive disorders of pregnancy (HDP), placental abruption. This study aimed to further evaluate and discuss on the outcomes of pregnancy with Anti-TPO antibodies in patients with proven subclinical hypothyroidism and whether supplementation with levothyroxine potentially reduces the adverse outcomes.

Patients with deranged TSH levels, normal free T<sub>4</sub> levels, with either positive or negative Anti-TPO antibodies were recruited in this study and followed till delivery/miscarriage. It was found that the median S. TSH values in 1st trimester in Anti-TPO positive women was 5.91 μIU/ml while, in Anti-TPO negative women it was 4.87 μIU/ml. Out of 150 Anti-TPO positive pregnant women, 51 (34%) developed GDM and 8 (5.3%) developed HDP while out of 150 Anti-TPO negative pregnant women, 39 (26%) developed GDM and only 1 (0.7%) developed HDP. Amongst Anti-TPO positive mothers, 7 (4.7%) had missed abortion in first trimester, 13 (8.7%) had RPL and 14 (9.3%) had threatened abortion, while none of these complications were observed in the Anti-TPO negative mothers.

Thus, timely diagnosis and adequate supplementation can reduce the associated maternal and fetal morbidity and improve the pregnancy outcomes even in women with thyroid autoimmunity.

## Introduction

Thyroid hormones T<sub>4</sub> and T<sub>3</sub> affect almost every metabolic process of the body. Pregnancy is considered to be a physiologically altered state of metabolism as the body tries to cater to the needs of

the growing fetus. The requirement of iodine increases in pregnancy, as demand for synthesis of excess thyroid hormones is there during pregnancy. This is because of fetal dependency on maternal thyroid hormones till 12 weeks of gestation as fetal thyroid tissue is not matured enough to produce adequate amount of hormones for the growing fetus. Hence, the gland becomes over stimulated and hyperactive to secrete more T<sub>4</sub> and T<sub>3</sub> to meet the increased

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demand. Human Chorionic Gonadotropin (hcg) is known to have a Thyroid stimulating hormone (TSH) stimulating effect and hence attributes to raise the thyroid hormone synthesis to meet the increased demand via its thyrotrophic effect.<sup>1</sup> Therefore, dietary iodine deficiency or intake of excess goitrogens in diet can be the major cause of overt and subclinical hypothyroidism in pregnancy.

Overt hypothyroidism is an increase in serum TSH (more than 10 mIU/L) as a result of decrease thyroxine and negative feedback, while subclinical hypothyroidism is serum TSH level in the range of 4-10 mIU/L with normal thyroxine (T4) levels.

Apart from this, autoimmune basis of overt and sub clinical hypothyroidism is also equally important in pregnant women. Data shows presence of antibodies like anti thyroperoxidase antibody (anti TPO antibody) and anti-thyroglobulin antibody (anti Tg antibody) in pregnancy is associated with increased prevalence of overt and sub clinical hypothyroidism and aggravation of the symptoms associated with it.<sup>1</sup>

On a worldwide scale, numerous studies with variable methodological quality have found inconsistent associations between subclinical hypothyroidism (SCH) in pregnancy and adverse obstetrical outcomes including miscarriage, fetal death, preterm delivery, gestational diabetes (GDM), hypertensive disorders of pregnancy (HDP) and placental abruption.<sup>2</sup> This study aims to further evaluate and discuss on the outcomes of pregnancy with positive Anti-TPO antibodies in patients with proven subclinical hypothyroidism and whether supplementation with levothyroxine potentially reduces the adverse outcomes.

## Material and Methods

**Study Area:** Department of Obstetrics and Gynecology, The Fatima Hospital, Lucknow.

**Ethical Approval:** The research method was approved by Institutional Ethical Committee vide no. IEC/FH/22/0002 dated 15/07/2022

**Study Population:** Pregnant women attending OPD of The Fatima Hospital in the first trimester. Their thyroid function tests were done. Patients with deranged TSH levels, normal free T4 levels, with either positive or negative Anti- TPO antibodies after

obtaining consent form were recruited in this study. Patients were followed up till delivery.

**Study Design:** Prospective observational study (Case control study)

### Inclusion Criteria:

1. Mothers with a singleton pregnancy without any known previous thyroid disorder
2. Women with deranged thyroid function tests upto 13 weeks of gestation (1st trimester)

### Exclusion Criteria:

1. Mothers with pregnancy in congenitally malformed uterus, fibroid uterus, known cervical incompetence
2. Previous history of any thyroid abnormalities
3. H/o any autoimmune diseases
4. Chronic hypertensive and diabetic patients
5. Subjects not willing to participate in the study
6. Subjects not coming for regular follow-up

**Methodology For Data Collection:** Total 300 pregnant women satisfying the above criteria were chosen for the above-mentioned study after taking written and informed consent. All the pregnant women selected experienced regular menstrual cycles and precisely recorded the dates of their last menstrual periods. If menstrual history and examination findings were not correlating, then ultrasonography was done to find the exact gestation period.

A proper detailed obstetric history including demographic characteristics and systemic examination was done. Women were evaluated for risk factors for adverse perinatal outcome and any associated underlying disorders.

Depending on the levels of TSH, free T4 and Anti-TPO antibodies, patients were supplemented with levothyroxine therapy and followed up with regular ante-natal check-ups and required biochemical and radiological tests. Tests were repeated at an interval of 4-6 weeks. Patients were followed up throughout the course of pregnancy for various associated maternal complications like HDP, GDM and pre-term labour. While conducting the study, the patient was informed of her condition and the risks associated, to enforce the drug compliance.

Regular follow up was done and confidentiality of the subjects maintained. Data for the study was recorded on Performa and shall be disclosed only to the ethics committee or appropriate authorities.

ATA Guidelines (2017) recommended establishing population-based trimester-specific reference ranges for serum thyroid-stimulating hormone (TSH) levels. In our study, we used the following criteria to supplement the patients with levothyroxine irrespective of their antibody status.

TRIMESTER	UPPER LIMIT OF TSH RANGE
1st trimester	2.5 mIU/L
2nd trimester	3 mIU/L
3rd trimester	3 mIU/L

The cut-off for Anti- TPO antibodies were:

>34 IU/L – POSITIVE

< 34 IU/ L- NEGATIVE

## Results and Discussion

### 1) AGE GROUP

The age of the hypothyroid women studies varied from 20- 40 years. In the Anti- TPO positive group, 14 (9.3%) women were in age group 20-24 years, 62 (41.3%) in age group of 25- 29 years, 46 (30.7%) in age group of 30-34 years and 28 (18.7%) in age group of 35-40 years. In the Anti- TPO negative group, 15 (10%) women were in age group of 20- 24 years, 80 (53.3%) in age group of 25-29 years, 47 (31.3%) in age group of 30-34 years and 8 (5.3%) in age group of 35- 40 years.

### 2) PARITY

In women with Anti- TPO positive, 69 (46%) were primigravida and 81 (54%) were multigravida. In women with Anti- TPO negative, 89 (59.3%) were primigravida and 61 (40.7%) were multigravida.

### 3) 1ST TRIMESTER TSH VALUES

The median S. TSH values in 1st trimester in Anti-TPO positive women was 5.91µIU/ml while, in Anti- TPO negative women the median S. TSH was 4.87 µIU/ml. In a study done by Bhattacharyya et al<sup>3</sup>, the mean serum TSH level was significantly ( $p < 0.0001$ ) higher (2.31 vs. 1.73 µIU/ml) among TPO-Ab positive than negative mothers.

### 4) ASSOCIATED MEDICAL DISORDERS

Out of 150 Anti- TPO positive pregnant women, 51 (34%) developed GDM, 8 (5.3%) developed HDP and 13 (8.7%) developed IHCP.

Out of 150 Anti- TPO negative pregnant women, 39 (26%) developed GDM, 1 (0.7%) developed HDP and 19 (12.7%) developed IHCP.

There is documented evidence that shows thyroid hormones are required for the decidual angiogenesis, trophoblastic invasion and the placental hormones secretion. Therefore, improper placentation is associated with higher prevalence of pre- eclampsia and other hypertensive disorders in patients with thyroid dysfunction.<sup>4</sup> Similar results were reported in studies done by Saki F et al<sup>5</sup> in 2014 and Sitoris et al<sup>6</sup> in 2020.

### 5) MATERNAL COMPLICATIONS

Out of 150 Anti- TPO positive women, 7 (4.7%) had missed abortion in first trimester while out of 150 Anti- TPO negative women, none had this complication.

In the Anti- TPO positive group, 14 (9.3%) had threatened abortion. Pregnancy was continued on levothyroxine; dose adjusted every trimester. 13 (8.7%) had RPL.

9 (6%) Anti- TPO positive women developed PPROM while 3 (2%) Anti- TPO negative developed PPROM.

In Anti- TPO positive group, 19 (12.7%) had preterm labour. In Anti- TPO negative group only 1(0.7%) had this complication. The p value is <0.005 for the maternal which is statistically significant. The t value is 2.77.

Various studies done previously have found similar results. In the meta-analysis done by Shakila T et al<sup>7</sup> in, results showed that there was a tripling in the odds of miscarriage with the presence of thyroid autoantibodies. Raghunath et al<sup>3</sup> found similar results in their prospective study done. Also, Pradhan et al<sup>8</sup> reported higher incidence of threatened and spontaneous abortions in their study. James E Haddow et al<sup>9</sup> in their prospective study found that, women with elevated levels of thyroperoxidase, thyroglobulin antibodies, or both in the first trimester have a higher

rate of preterm delivery before 37 weeks of gestation than antibody negative women (7.5% compared with 6.4%, odds ratio [OR] 1.18; 95% confidence interval [CI] 0.95-1.46). Yan Han et al<sup>10</sup> in their prospective birth cohort study done in 2018 in iodine sufficient area of China, found that TPO-Ab positivity in the second trimester was associated with a 1.863-fold higher risk of premature birth (OR = 1.863, 95% CI 1.009, 3.441), after adjustment for potential confounding factors.

## Summary

This study was done with an aim to determine the prevalence of subclinical hypothyroidism in pregnancy with positive Anti-TPO antibodies and study the course of pregnancy. Pregnancy course was evaluated in terms of any association with miscarriage, HDP, GDM, pre-term labour. This was a prospective observational study done over a period of 2 years on pregnant women attending our OPD. First trimester booking is the ideal time to screen for hypothyroidism, this was done by measuring FT<sub>4</sub>, TSH and subsequently Anti-TPO. The patients were supplemented with levothyroxine depending on the S. TSH levels and thereafter, measured at 6 weeks interval for necessary dose adjustments. ATA guidelines were followed for the trimester specific S.TSH values. All the mothers were followed till delivery/ miscarriage in both anti-TPO negative and positive and the adverse outcome was recorded.

It was found that the median S. TSH values in 1st trimester in Anti-TPO positive women is 5.91  $\mu$ IU/ml while, in Anti-TPO negative women the median S. TSH is 4.87  $\mu$ IU/ml. Out of 150 Anti-TPO positive pregnant women, 51 (34%) developed GDM and 8 (5.3%) developed HDP while out of 150 Anti-TPO negative pregnant women, 39 (26%) developed GDM and only 1 (0.7%) developed HDP. In our study, out of 150 Anti-TPO positive mothers, 7 (4.7%) had missed abortion in first trimester, 13 (8.7%) had RPL and 14 (9.3%) had threatened abortion, while none of these complications were observed in the Anti-TPO negative mothers. Amongst 150 Anti-TPO positive women, 19 (12.7%) had preterm labour and 9 (6%) developed PPRM while amongst Anti-TPO negative women only 1 (0.7%) had preterm labour while 3 (2%) developed PPRM.

## Conclusion

Thyroid autoimmunity is an important etiology for the development of hypothyroidism in pregnancy and is associated with adverse maternal and fetal outcome. First trimester is the ideal time for screening for hypothyroidism however, every woman should be screened for it whenever she first visits a doctor, irrespective of her gestational age. Anti-TPO screening must be offered to women with a history of recurrent miscarriages and preterm labour to start levothyroxine supplementation at an earlier gestational age. Similarly, woman with other pregnancy associated disorders like hypertensive disorders of pregnancy and gestational diabetes mellitus must also be screened for this.

Woman who are at a high risk or have been identified to have positive titers for antibodies must be educated about their adverse effects and encouraged to ask relevant questions so as to improve the medication adherence.

Timely diagnosis and adequate supplementation can reduce the associated maternal and fetal morbidity and improve the pregnancy outcomes even in women with thyroid autoimmunity

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**Conflict of Interest:** There is no conflict of interest in the study.

## Bibliography

- 1) Autoimmune Basis of Sub Clinical Hypothyroidism in Pregnancy-- Prakruti Dash and Rajlaxmi Tiwari.
- 2) The Impact of Subclinical Hypothyroidism on Adverse Perinatal Outcomes and the Role of Thyroid Screening in Pregnancy--Mei-Qin Wu, Jin Liu, Ya-Qian Wang, Ying Yang, Chong-Huai Yan and Jing Hua.
- 3) Anti-thyroid peroxidase antibody positivity during early pregnancy is associated with pregnancy complications and maternal morbidity in later life — Raghunath Bhattacharyya, Kasturi Mukherjee, Anjan Das, Madhuri Ranjana Biswas, Sandip Roy Basunia, and Anindya Mukherjee.
- 4) The interplay between thyroid hormones and the placenta: a comprehensive review†-Enoch Appiah Adu-Gyamfi, Ying-Xiong Wang, Yu-Bin Ding -Biology of Reproduction, Volume 102, Issue 1, January 2020, Pages 8– 17, <https://doi.org/10.1093/biolre/ioz182>.

- 5) Thyroid autoimmunity in pregnancy and its influences on maternal and fetal outcome in Iran (a prospective study) -Forough Saki, Mohammad Hossein Dabbaghmanesh, Seyede Zahra Ghaemi, Sedighe Forouhari, Gholamhossein Ranjbar Omrani & Marzieh Bakhshayeshkaram
- 6) The Impact of Thyroid Disorders on Clinical Pregnancy Outcomes in a Real World Study Setting -Georgiana Sitoris, Flora Veltri, Pierre Kleynen, Alexandra Cogan, Julie Belhomme, Serge Rozenberg, and Kris Poppe.
- 7) Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence--Shakila Thangaratnam, senior lecturer/consultant in obstetrics and gynaecology and clinical epidemiology<sup>1</sup>, Alex Tan, academic foundation trainee, Ellen Knox, consultant obstetrician/subspecialist in fetal medicine, Mark D Kilby, professor of fetal medicine, Jayne Franklyn, professor of medicine, Arri Coomarasamy, reader/consultant gynaecologist /subspecialist in reproductive medicine and surgery.
- 8) Thyroid peroxidase antibody in hypothyroidism: Its effect on pregnancy Mandakini Pradhan, Bhavna Anand, Neeta Singh & Manasi Mehrotra
- 9) Haddow JEC-GJ, McClain MR, Palomaki GE, Neveux LM, Lambert-Messerlian G, Canick JA, Malone FD, Porter TF, Nyberg DA, Bernstein PS, D'Alton ME. Thyroperoxidase and thyroglobulin antibodies in early pregnancy and preterm delivery. *Obstet Gynecol.* 2010;116(1):58–62.
- 10) Impact of maternal thyroid autoantibodies positivity on the risk of early term birth: Ma'anshan Birth Cohort Study -- Yan Han, Lei-Jing Mao, Xing Ge, Kun Huang, Shuang-Qin Yan, Ling-Ling Ren, Shu-Qing Hong, Hui Gao, Jie Sheng, Yuan Yuan Xu, Wei-Jun Pan, Peng Zhu, Jia-Hu Hao, De-Fa Zhu & Fang-Biao Tao.
- 11) Overt and subclinical thyroid dysfunction among Indian pregnant women and its effect on maternal and fetal outcome -- Meenakshi Titoria Sahu, Vinita Das, Suneeta Mittal, Anjoo Agarwal, Monashis Sahu.
- 12) Prevalence and impact of thyroid disorders on maternal outcome in Asian-Indian pregnant women- Vimal Nambiar, Varsha S Jagtap, Vijaya Sarathi, Anurag R Lila, Sadishkumar Kamalanathan, Tushar R Bandgar, Padmavathy S Menon, Nalini S Shah.
- 13) Treatment of recurrent pregnancy loss by Levothyroxine in women with high Anti-TPO antibody -- Mohammad Hosein Mosaddegh, Pharm D, Ph.D., Nasrin Ghasemi, M.D., Ph.D., Tahere Jahaninejad, M.Sc., Fatemeh Mohsenifar, M.D., and Abbas Afatoonian, M.D.

**Table 1: Tabular representation of age of enrolled women**

ANTI TPO	Positive		Negative	
	Number	%	Number	%
Age (years)				
20-24	14	9.3%	15	10.0%
25-29	62	41.3%	80	53.3%
30-34	46	30.7%	47	31.3%
35-40	28	18.7%	8	5.3%
Total	150	100.0%	150	100.0%

**Table 3: Tabular representation of parity of enrolled women**

ANTI TPO	Positive		Negative	
	Number	%	Number	%
Parity				
Primigravida	69	46.0%	89	59.3%
Multigravida	81	54.0%	61	40.7%
Total	150	100.0%	150	100.0%

**Table 5: Tabular representation of associated medical disorders**

ANTI TPO	Positive		Negative	
	Number	%	Number	%
Medical Disorder				
GDM	51	34.0%	39	26.0%
HDP	8	5.3%	1	0.7%
IHCP	13	8.7%	19	12.7%

**Table 2: Statistical analysis of age of women in each group**

Statistics	Age	
	Positive	Negative
Number	150	150
Mean	29.92	28.58
Median	29	28
SD	4.13	3.61

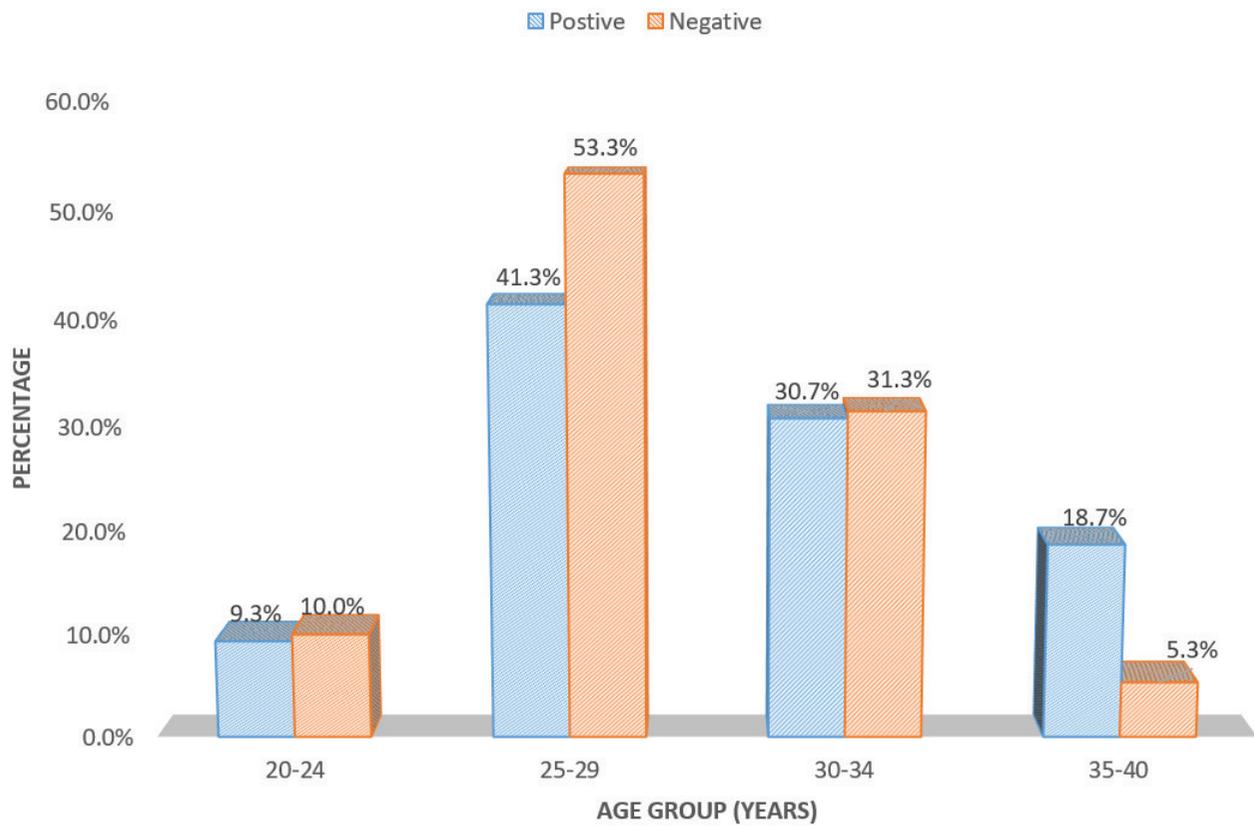
**Table 4: Tabular representation of TSH values of enrolled women**

Statistics	1st Trimester TSH	
	Positive	Negative
Number	150	150
Mean	5.91	5.13
Median	5.71	4.87
SD	1.53	1.27

**Table 6: Tabular representation of associated medical disorders**

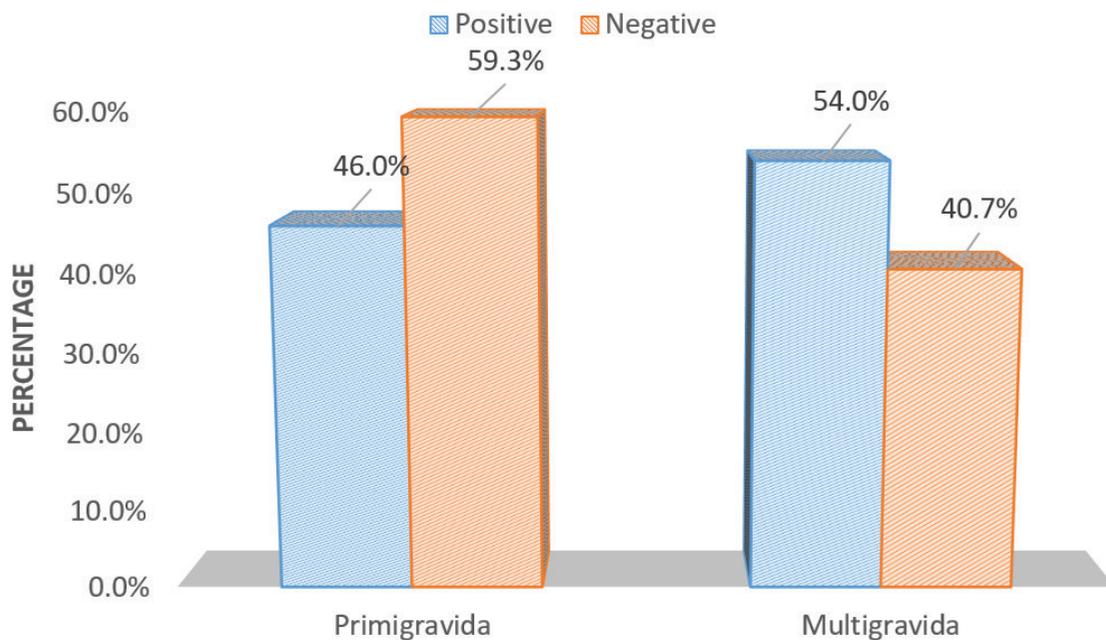
ANTI TPO	Positive		Negative	
	Number	%	Number	%
Complications				
Missed Abortion	7	4.7%	0	0.0%
Threatened Abortion	14	9.3%	0	0.0%
RPL	13	8.7%	0	0.0%
PPROM	9	6.0%	3	2.0%
PTL	19	12.7%	1	0.7%

## AGE GROUP



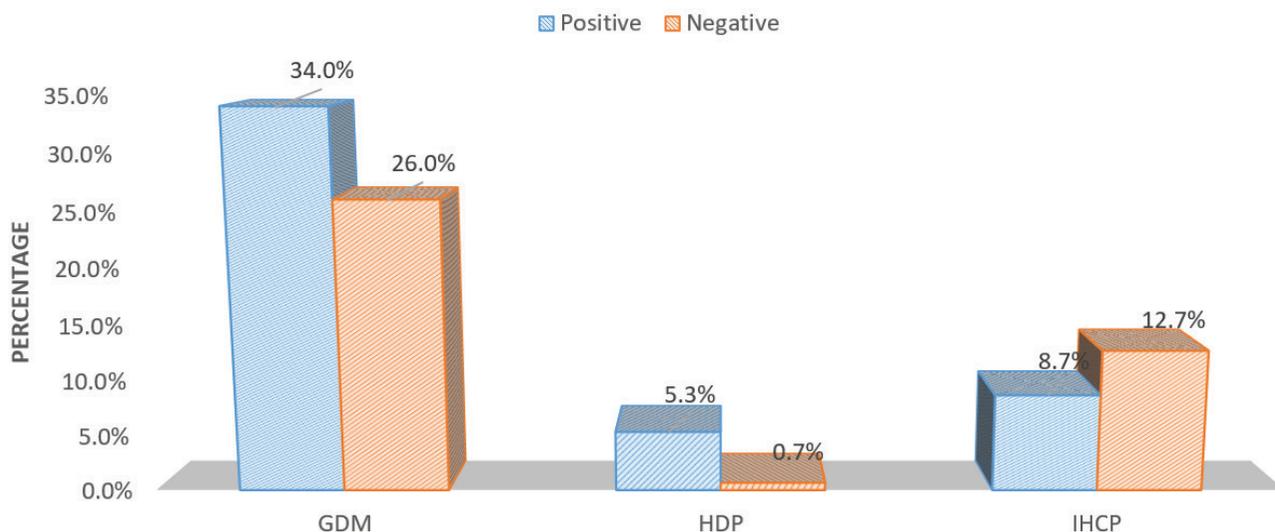
Graph 1: Graphical representation of age of enrolled women

## PARITY



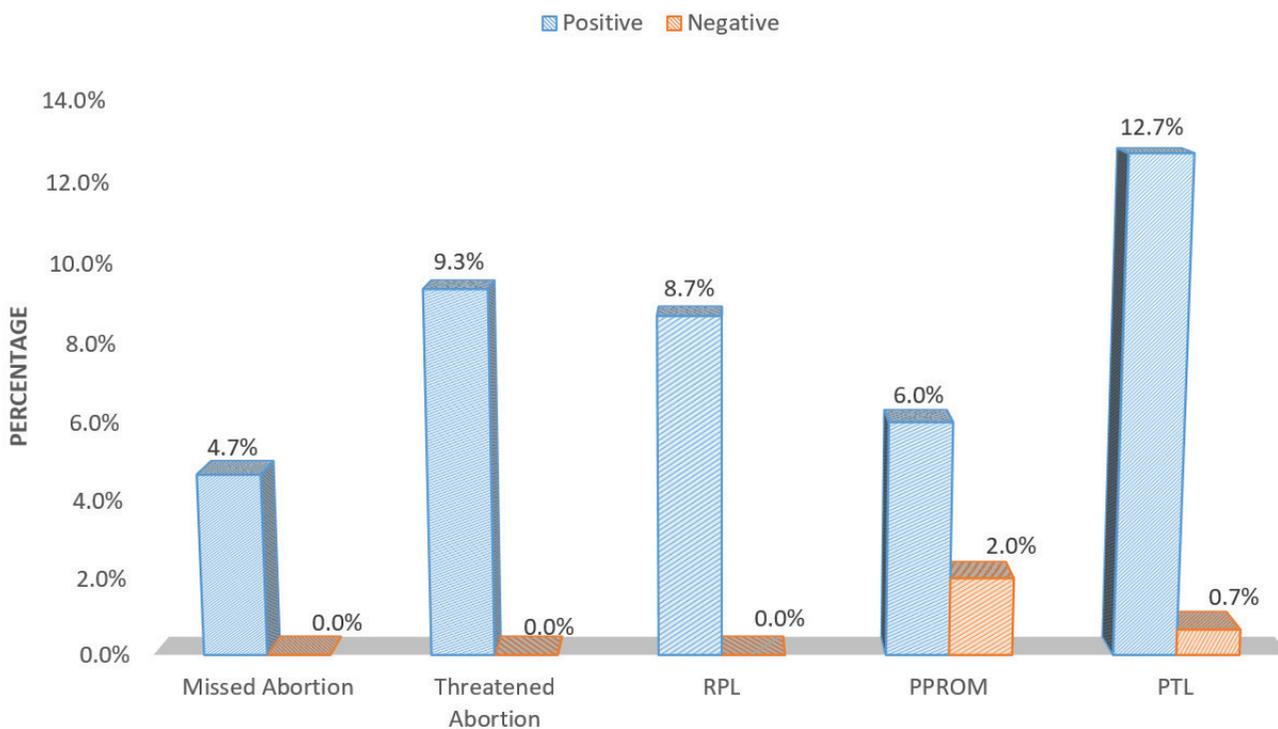
Graph 2: Graphical representation of parity of enrolled women

## ASSOCIATED MEDICAL DISORDERS



Graph 3: Graphical representation of associated medical disorders in enrolled women

## MATERNAL COMPLICATIONS



Graph 4: Graphical representation of maternal complications in enrolled women

**List of abbreviations:**

hcg- Human chorionic gonadotropin

TSH- Thyroid stimulating hormone

Anti-TPO- Anti-thyroid peroxidase antibody

Anti- Tg - Anti-thyroglobulin antibody

SCH - Subclinical hypothyroidism

TAI - Thyroid autoimmunity

GDM - Gestational diabetes mellitus

HDP - Hypertensive disorders of pregnancy

IHCP - Intrahepatic cholestasis of pregnancy

PTL - Preterm labour

PPROM - Preterm prelabour rupture of membranes

RPL - Recurrent pregnancy loss

ATA - American Thyroid association

LT4 - Levothyroxine

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