

ISCHEMIA-MODIFIED ALBUMIN AND THYROID HORMONE LEVELS IN FIRST-TRIMESTER ABORTIONS: A RELATIONSHIP?AMIT R BARAPATRE¹, PALLAVI ANIL RATHOD², VENKATESH RATHOD³, AVINASH NAMDEO JADHAO^{4*}

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ABSTRACT

Objectives: The objectives are to estimate maternal thyroid hormone levels and ischemia-modified albumin (IMA) levels in first-trimester pregnancy loss and to study the correlation between the maternal thyroid hormone levels and the IMA.

Methods: We recruited 45 pregnant women with recurrent pregnancy loss (RPL) from our obstetric clinic as cases and 45 healthy pregnant women with the same gestational age and successful pregnancy outcomes as controls.

Results: There is no correlation between the maternal thyroid hormone levels and the IMA levels in first-trimester pregnancy loss. Maternal IMA levels appear to be elevated in women with early RPL.

Conclusion: In cases of first-trimester pregnancy loss, there is no association between maternal thyroid hormone levels and IMA levels. IMA cannot be used for the diagnosis and follow-up of early RPL because maternal IMA levels appear to be higher in women with early RPL.

Keywords: Abortion, IMA, Thyroid profile.

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INTRODUCTION

Recurrent pregnancy loss (RPL), also known as recurrent miscarriage or habitual abortion, is historically defined as three or more than three successive pregnancies before 20 weeks of gestation from the last menstrual period [1]. This description takes into consideration the fact that women who are over 35 years are more inclined than women under 25 years to go through pregnancy loss [2]. One of the least understood disease mechanisms is spontaneous abortion. A battery of tests, including genetic parental screening, hystero-grams, hysteroscopies, immunological testing, uterine assessments, and antibody testing, will come back negative in a 50% or higher female who has recurrent spontaneous abortion. Most women who experience recurrent spontaneous abortions would not have a definitive diagnosis [3].

According to research by Regan *et al.* and Wilcox *et al.*, clinically recognized intrauterine pregnancy loss affects 12–14% of pregnancies and is caused by a variety of reasons, including hormonal instability and chromosomal abnormality [4,5]. Hormonal variations play a significant role in both first- and second-trimester pregnancy losses. Women in their reproductive years are affected by thyroid disorders. They are the most prevalent endocrine ailments that affect pregnancy Ramprasad *et al.* [6] Maternal ischemia-modified albumin (IMA) levels in the first trimester are higher than the threshold used to identify myocardial ischemia in people who are not pregnant, supporting the idea that proper placentation is associated with relative intrauterine hypoxia [7]. The discovery that maternal serum IMA levels are elevated at such a young gestational age lends more evidence to the idea that IMA may serve as a marker for aberrant placental development, which may be connected to early pregnancy loss of clinically confirmed pregnancies, up to 15% experience first-trimester pregnancy loss [8]. In reality, RPL patients make up 40–50% of those who do not have a known reason for their losses [9]. There is currently no information on any

relationship between maternal thyroid hormone levels and IMA levels in first-trimester pregnancy loss. In this study, we compared recurrent miscarriage women to healthy pregnant as control to assess the levels of circulating thyroid hormone and IMA in the mothers.

Study design and subject selection

We conducted a case-control study from January 2008 to September 2012 at our institute's Department of Biochemistry. The Institutional Ethics Committee approved the study protocol and we obtained informed consent from all participants. We recruited 45 pregnant women with RPL and hypothyroidism from our obstetric clinic as cases and 45 healthy pregnant women with the same gestational age and successful pregnancy outcomes as controls.

Case inclusion standards

We included cases that met the following criteria: History of two or more unexplained spontaneous abortions; diagnosis of cervical dilatation with curettage and symptoms of pelvic pain and vaginal bleeding; absence of gestational sac and fetal cardiac activity on ultrasound; and spontaneous abortions up to 12 weeks of gestation. Both parents had normal karyotypes and the male partner had normal sperm count and morphology.

Case exclusion standards

Cases of ischemic heart disease, hypertension, diabetes smokers and chewers of tobacco, drinking alcohol, cases of toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus case positivity, polycystic ovarian syndrome, abnormal husband semen analysis, antiphospholipid antibody syndrome, and ectopic conception.

Criteria for controls' inclusion

We selected 45 healthy pregnant women with the same gestational age and successful pregnancy outcomes as controls. They had no chronic diseases and did not take any medications.

All the women were given a complete clinical examination at the institute after giving their signed, informed consent. 5–6 mL of blood from the study and control groups were taken. For thyroid hormones and ischemia-modified albumin, serum is centrifuged to separate the two components and is then kept in small aliquots at -20°C . Using commercially available competitive immunoassay kits (ACCUBIND, USA) on a microplate reader, serum total T3 (TT3), total T4 (TT4), TSH, free T3 (fT3), and free T4 (fT4) concentrations were calculated in the cases and control group. Measurement of ischemia-modified albumin was performed spectrophotometrically as per the method explained by Bar-Or et al. (albumin cobalt-binding assay) as shown in Table 1.

RESULTS

A total of 90 participants were enrolled in our study – Group A: 45 (cases of first-trimester abortion) and Group B: 45 (control of normal pregnancy).

The mean age group in our study was 24 (19–32 years) and 24 (20–34 years) for cases and controls, respectively. The mean body mass index (kg/m^2) was 23.84 (21.4–24.5) and 22.3 (20.3–23.3) for cases and controls, respectively. The gestational age in week was 10.23 ± 1.09 and 10.29 ± 0.92 for cases and controls, respectively. The gravida with 2 (1–4) and 2 (1–5) for cases and controls, respectively, and parity was 1 (0–2) and 1 (0–3) for cases and controls, respectively. Demographic and clinical data of participants are expressed in Table 2.

The mean value of TT3 in first-trimester abortion group and control group of normal pregnancy was 2.234 ± 1.42 ng/mL and 2.624 ± 0.9786 ng/mL, respectively. The mean value of TT4 in first-trimester abortion group and control group was 4.88 ± 1.53 $\mu\text{g}/\text{dL}$

and 5.726 ± 1.234 $\mu\text{g}/\text{dL}$, respectively. Thus, we found mean value of TT3 at lower range in first-trimester abortion group as compared to controls, and difference is statistically significant ($p < 0.0001$). We also observed mean value of TT4 at lower range in first-trimester abortion group as compared to controls, and difference is statistically significant ($p < 0.002$). The mean value of fT3 in first-trimester abortion group was 4.687 ± 1.89 pmol/l, and in control group, it was 5.116 ± 1.876 pmol/l. Thus, fT3 was significantly lower in first-trimester abortion group as compared to control group. Decrease in fT3 level was found to be statistically highly significant ($p < 0.05$). The mean fT4 value in abortion and control group was 14.60 ± 5.23 pmol/l and 18.35 ± 5.234 pmol/l, respectively. Thus, fT4 was significantly lower in first-trimester abortion group as compared to control group. This decrease in fT4 level was found to be statistically highly significant ($p < 0.0001$). Mean TSH value in first-trimester abortion group was 9.297 ± 3.09 $\mu\text{IU}/\text{L}$ and in control group, it was 7.351 ± 3.234 $\mu\text{IU}/\text{L}$. Thus, mean TSH value was significantly higher first-trimester abortion group as compared to control group with ($p < 0.001$). The ischemia-modified albumin value in first-trimester abortion group was 0.8232 ± 0.453 which was higher than control group, i.e., 0.6926 ± 0.543 expressed in ABSU unit, which is statistically significant. Laboratory findings of the participants are shown in Table 3.

There is no significant correlation between total T3 and ischemia-modified albumin as shown in Fig. 1.

There is no significant correlation between free total T3 and ischemia-modified albumin as shown in Fig. 2.

There is no significant correlation between total T4 and ischemia-modified albumin as shown in Fig. 3.

There is no significant correlation between free total T3 and ischemia-modified albumin as shown in Fig. 4.

There is no significant correlation between TSH and ischemia-modified albumin as shown in Fig. 5.

DISCUSSION

Thyroid disorders are common in women of reproductive age and can affect their fertility and pregnancy outcomes. As a result of thyroid dysfunction, hormonal imbalances, autoimmune reactions, and oxidative stress may occur, which may impair ovulation, implantation, placental function, and fetal development [10]. Furthermore, thyroid disorders can also increase the risk of miscarriage, pre-term delivery, pre-eclampsia, fetal growth restriction, congenital anomalies, and neurodevelopmental problems in the offspring [11]. We conducted

Table 1: Albumin cobalt-binding assay

Steps		
1	Patients serum sample	200 microliter
2	0.1% cobalt chloride (CoCl_2)	50 microliter
	Vigorous mixing was done	
3	Incubation for 10 minutes	
4	Add 50 microliter dithiothreitol (DTT) solution in water (1.5 mg/mL)	
5	After 2 min 1 mL of 0.9% NaCl is added	

The absorbance of assay mixture was measured with spectrophotometer set at 470 nm. A sample without dithiothreitol addition was used as the blank for each measurement. There is a substantial degree of variation between the units of expression of both ACB and IMA in different clinical studies [14]. In our study, the values of IMA were expressed in ABSU

Table 2: Demographic and clinical data of participants

S. No		Group A: 45 (cases of first-trimester abortion) Mean \pm SD	Group B: 45 (control of normal pregnancy) Mean \pm SD	p-value
1.	Age in years	24 (19–32)	24 (20–32)	0.672
2.	Body mass index (kg/m^2)	23.84 (21.4–24.5)	22.3 (20.3–23.3)	0.297
3.	Gestational age in week	10.23 ± 1.09	10.29 ± 0.92	0.241
4.	Gravida (range)	2 (1–4)	2 (1–5)	0.825
5.	Parity (range)	1 (0–2)	1 (0–3)	0.764

Table 3: Laboratory findings of the participants

S. No	Parameters	Group A: 45 (cases of first-trimester abortion)	Group B: 45 (control of normal pregnancy)	p-value
1.	TT3 (ng/mL)	2.234 ± 1.42	2.624 ± 0.9786	$< 0.0001^{****}$
2.	TT4 ($\mu\text{g}/\text{dL}$)	4.975 ± 1.53	5.726 ± 1.234	0.0002^{***}
3.	fT3 (p mol/l)	4.687 ± 1.89	5.116 ± 1.876	$< 0.0001^{****}$
4.	fT4 (p mol/l)	14.6 ± 5.23	18.35 ± 5.234	$< 0.0001^{****}$
5.	TSH ($\mu\text{IU}/\text{L}$)	9.297 ± 3.09	7.351 ± 3.234	$< 0.0001^{****}$
6.	IMA	0.8232 ± 0.453	0.6926 ± 0.543	$< 0.0001^{****}$

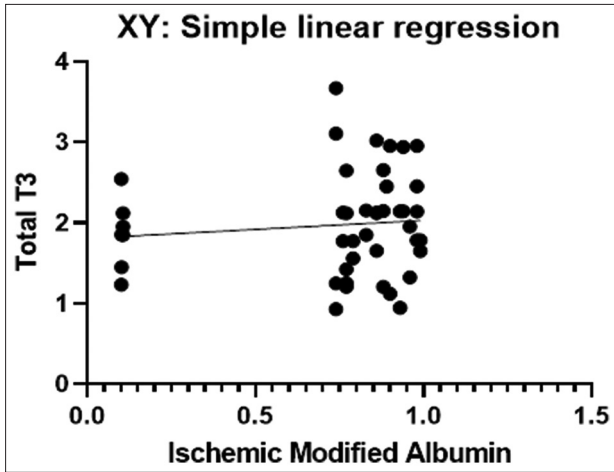


Fig. 1: Correlation between total T3 and ischemia-modified albumin

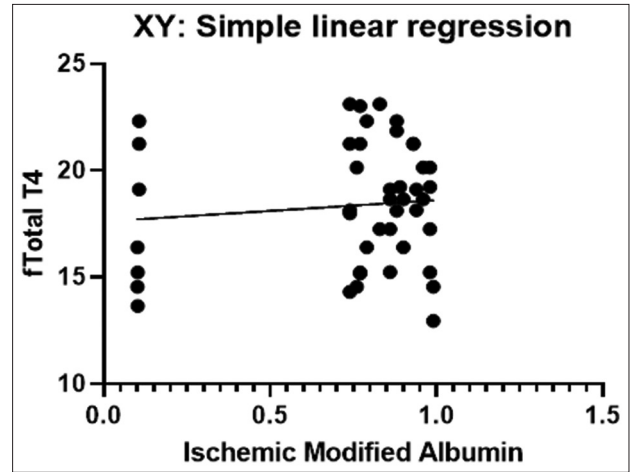


Fig. 4: Correlation between free total T4 and ischemia-modified albumin

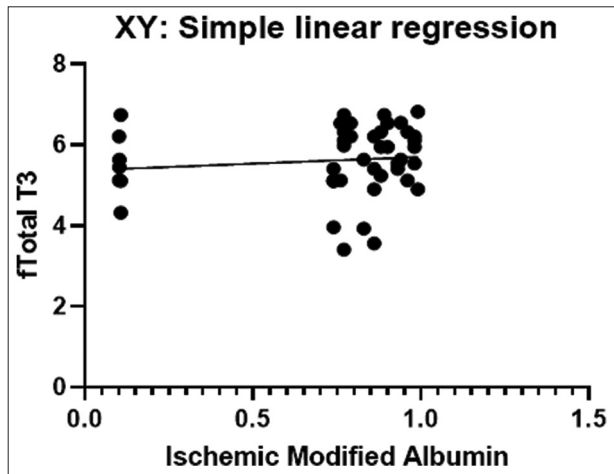


Fig. 2: Correlation between free Total T3 and ischemia-modified albumin

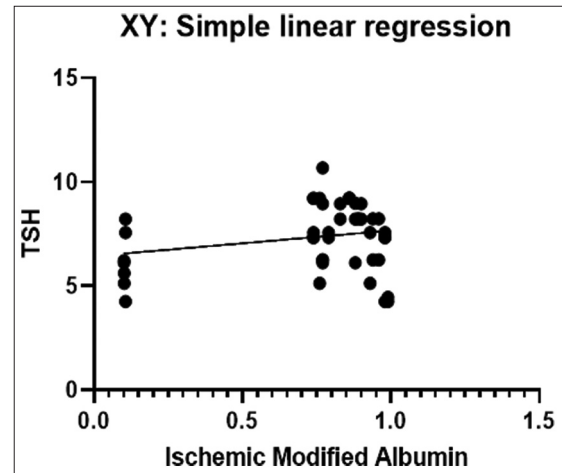


Fig. 5: Correlation between TSH and ischemia-modified albumin

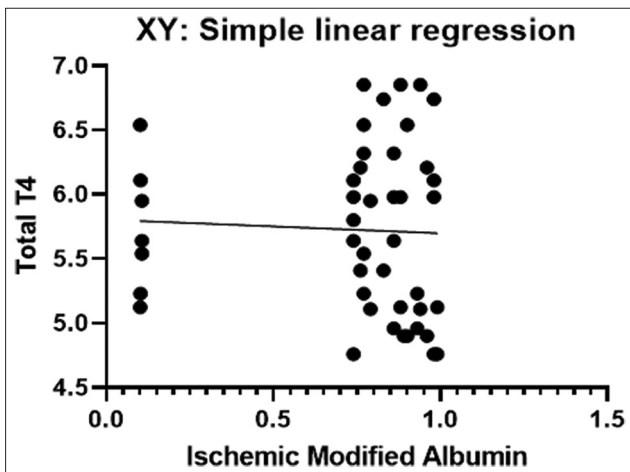


Fig. 3: Correlation between total T4 and ischemia-modified albumin

a study to evaluate the prevalence and impact of hypothyroidism in recurrent spontaneous abortions. Out of 45 cases, we detected overt clinical hypothyroidism in 15 cases (33%). Sharma *et al.* (2007) reported an incidence of hypothyroidism (1.15%) in pregnancy and a

higher rate of spontaneous abortion (14.63%) compared to euthyroid women (4.96%). They also found that thyroxine therapy improved the pregnancy outcome in hypothyroid women. Ramachandra *et al.* also observed a significant association between hypothyroidism (4.29%) and RPL in the first trimester. They concluded that early diagnosis and treatment of hypothyroidism could increase the chances of a successful pregnancy in women with RPL [11]. We also evaluated the role of serum IMA as a marker of oxidative stress and ischemia in pregnant women with endocrine disorders. We found that serum IMA levels were significantly higher in women with endocrine disorders than in healthy women and that they were associated with placental histopathological changes and fetomaternal outcomes. Our results suggest that serum IMA may be a useful biomarker for early diagnosis and management of endocrine disorders and their complications in pregnancy. Serum IMA may also reflect the underlying mechanisms of these disorders and their impact on placental function and fetal health. Further studies are needed to confirm our findings and to explore the potential therapeutic implications of serum IMA modulation in pregnancy.

Hyperthyroidism is a condition that causes more oxidative stress in the body. Oxidative stress is when there are too many harmful molecules that can damage cells and tissues. To measure oxidative stress, researchers often look at how these molecules affect the levels and activity of some substances in the body, such as lipid peroxides, glutathione, and antioxidant enzymes [12]. However, no one has studied how oxidative stress damages the proteins in the blood of mother with RPL in the first 3 months of pregnancy. A study by Sankha *et al.* showed

that hyperthyroid patients had more carbonylated proteins in their blood than normal patients. This means that their blood proteins were more affected by oxidative stress [13].

We wanted to find if there was any statistical relationship between maternal thyroid hormone levels and IMA levels in first-trimester pregnancy loss. There is no correlation between the maternal thyroid hormone levels and the IMA levels in first-trimester pregnancy loss. Maternal IMA levels appear to be elevated in women with early RPL. This finding may suggest that an abnormally high hypoxic intrauterine environment may be associated with abnormal placental development that contributes to early miscarriage but in our study, maximum patients were euthyroid and 15% are hypothyroid.

CONCLUSION

IMA is a new marker of ischemia produced due to hypooxygenation and increased hydroxyl free radicals in low pH-2. Thyroid disease is a common endocrine disorder affecting women of reproductive age and when untreated during pregnancy is associated with an increased risk of miscarriage. The presence of higher maternal IMA levels in women who experience early RPL raises the possibility that an unusually high degree of hypoxia within the uterus may be linked to aberrant placental development, which in turn contributes to early miscarriage. In cases of first-trimester pregnancy loss, there is no association between maternal thyroid hormone levels and IMA levels. IMA cannot be used for the diagnosis and follow-up of early RPL because maternal IMA levels appear to be higher in women with early RPL.

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AUTHORS CONTRIBUTION

Concept writing: Amit Ramesh Barapatre and Pallavi Anil Rathod, Manuscript writing and Proofreading: Venkatesh Rathod, Statistics and Proofreading: Avinash Jadhao

CONFLICTS OF INTEREST

Nil.

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REFERENCES

- Stephenson MD. Frequency of factors associated with habitual abortion in 197 couples. *Fertil Steril* 1996;66:24-9. PMID: 8752606
- Lampinen R, Vehviläinen-Julkunen K, Kankkunen P. A review of pregnancy in women over 35 years of age. *Open Nurs J* 2009;3:33-8. doi: 10.2174/1874434600903010033. PMID: 19707520; PMCID: PMC2729989
- Alves C, Rapp A. Spontaneous abortion. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK560521> [Last accessed on 2022 Jul 18].
- Regan L, Braude PR, Trembath PL. Influence of past reproductive performance on risk of spontaneous abortion. *BMJ* 1989;299:541-5. doi: 10.1136/bmj.299.6698.541. Erratum in: *BMJ* 1989;299:1082. PMID: 2507063; PMCID: PMC1837397
- Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. *N Engl J Med* 1988;319:188-94. doi: 10.1056/NEJM198807283190401. PMID: 3393170
- Ramprasad M, Bhattacharyya SS, Bhattacharyya A. Thyroid disorders in pregnancy. *Indian J Endocrinol Metab* 2012;16 Suppl 2:S167-70. doi: 10.4103/2230-8210.104031. PMID: 23565370; PMCID: PMC3603018
- Jaiswar SP, Verma S, Agrawal M, Deo S, Goel M, Mahdi AA. Association of maternal serum ischemia modified albumin (IMA) with placental histopathological changes and fetomaternal outcome: A prospective case control study in normotensive and pre-eclamptic women. *J Obstet Gynaecol India* 2022;72 Suppl 1:166-73. doi: 10.1007/s13224-021-01614-7, PMID: 35928062; PMCID: PMC9343519
- Patil M, Panchanadikar TM, Wagh G. Variation of papp-a level in the first trimester of pregnancy and its clinical outcome. *J Obstet Gynaecol India* 2014;64:116-9. doi: 10.1007/s13224-013-0481-4, PMID: 24757339; PMCID: PMC3984652
- Cho MK. Thyroid dysfunction and subfertility. *Clin Exp Reprod Med* 2015;42:131-5. doi: 10.5653/cerm.2015.42.4.131, PMID: 26816871; PMCID: PMC4724596
- Alemu A, Terefe B, Abebe M, Biadgo B. Thyroid hormone dysfunction during pregnancy: A review. *Int J Reprod Biomed* 2016;14:677-686. PMID: 27981252; PMCID: PMC5153572
- Ramachandra V, Lakshmi A, Sadhnani MD. Prevalence of hypothyroidism in recurrent pregnancy loss in first trimester. *Indian J Med Sci* 2008;62:357-61. PMID: 18923214
- Kochman J, Jakubczyk K, Bargiel P, Janda-Milczarek K. The influence of oxidative stress on thyroid diseases. *Antioxidants (Basel)* 2021;10:1442. doi: 10.3390/antiox10091442. PMID: 34573074; PMCID: PMC8465820
- Sankha S, Kumar YM, Madhuri AA, Kumar MT. Antioxidant status and oxidative stress in hypothyroidism. *J Datta Meghe Inst Med Sci Univ* 2021;16:508-14.
- Bhagavan NV, Lai EM, Rios PA, Yang J, Ortega-Lopez AM, Shinoda H et al. Evaluation of human serum albumin cobalt binding assay for the assessment of myocardial ischemia and myocardial infarction. *Clin Chem* 2003; 49:581-5.