In The Name of God

Case Presentation

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A 39-year-old woman with

Recurrent Pregnancy Loss and Altered Thyroid Function Tests

Patient ID

- 39-year-old woman
- Born & live in Qazvin
- Source of History : patient
- Education: Master of Marketing Management
- Occupation: Director of the airline agency

Chief complaint

Recurrent Pregnancy Loss and Altered Thyroid Function Tests

Present Illness

A 39-year-old woman

The first time in the ***checkup tests*** 5 years ago, She noticed high TT3 and TT4 in the Presence of normal TSH

No history of tremor, palpitation, profuse sweating, heat intolerance

7 months later, the tests were rechecked:

	97/9/25	98/4/19
Laboratory	خاتم	رازی
TSH	4.03	3.79
T4	19.22 (µg/dl) (5-14)	19.4 (µg/dl) (5-14)
T3	3.04 (ng/ml) (0.8-2)	348 (ng/dl) (83-200)

Present Illness

referred to an endocrinologist: Additional tests and family investigation were done and the results of the father's tests were similar

	98/5/2
Laboratory	بهار
TSH	4.33
T4	233 (60-160) (nmol/l)
T3	3.5 (1.3-3.1)(nmol/l)
FTI	264.8 (60-160) (nmol/l)

Present Illness

A year later, the decision to get pregnant again: Three consecutive miscarriages at 11, 8 and 8 weeks

After the first miscarriage:

	99/3/1
TSH	1.7
T4	24 (5-14) (µg/dl)
T3	2.8 (0.8-2)(ng/ml)
FTI	18.4 (5-14) (µg/dl)
Anti-TPO	63 (0-34)(IU/ml)

Present Illness

In the third pregnancy, at 5 weeks :levothyroxine is started (250 mcg/weekly) →
Miscarriage at 8 weeks → Continued levothyroxine → Cardiac arrhythmia: AF

	99/10/7 (5th week of pregnancy)
TSH	2.74
T4	22.7 (5-14) (µg/dl)
Anti-TPO	107.3

Present Illness

In the fourth pregnancy → Miscarriage at 8 weeks → Evaluations for hypercoagulation states and autoimmune diseases and hysterosalpingography

1401/5/31

Immunoassays-CLIA

Test	Result	Unit	Method	Normal Range
Anti Cardiolipin Ab (IgG)	Negative [1.0]	U/ml	ELISA	Negative: <10 Positive: >=10
Anti Cardiolipin Ab (IgM)	Negative [1.6]	U/ml	ELISA	Negative: <10 Positive: >=10
Anti-thyroid peroxidase(Anti TPO) H	139.80	IU/ml	ECL	Up to 34

H=High

The test(s) was performed by LIASION fully automated analyser adopts "Flash" chemiluminescence technology (CLIA) with a paramagnetic micro particle solid phase (Diasorin-Italy, CE).

Immunoassays-A

Test	Result	Unit	Method	Normal Range
Anti Phospholipid Ab (IgG)@	Negative [1.6]	U/ml	ELISA	Normal : <10 Elevated : >=10
Anti Phospholipid Ab (IgM)@	Negative [1.6]	U/ml	ELISA	Normal : <10 Elevated : >=10

This section test(s) was performed by fully automated ALEGRIA instrument (ORGENTEC diagnostic, Germany, CE) based on SMC(R) technology represents the newest dimensions in the field of autoimmune diagnostics.

Biochemical -immunoassay

Test	Result	Unit	Method	Normal Range
CD55	99.9	%		>80
CD59	95.0	%		>80
Inter Leukin 6(IL-6)	<2.0	pg/ml	CLIA	Up to 5.9

Indirect immunofluorescenc assay or ELISA

Test	Result	Unit	Method	Normal Range
Antinuclear Antibody (ANA)	Negative		IF&ELISA	ELISA Method Normal range:Negative : <1.0(Index) Positive :>=1.0(Index) IF Method Normal range: Negative : <1/40(Titer) Positive :>or=1/40 (Titer)

Comment: IF method

1401/8/3

Protein-C	118	%	65-145
Protein-S	135	%	60-140
CD56	10.3	%Lymph	Adult: 3-15
CD16	8.7	%Lymph	Adult: 5-19
CD19	7.0	%Lymph	Adult: 3-14
			2-8 years:9-38
CD5	81.9	%Lymph	Adult: 42-82
CD(16+56)	6.3	%Lymph	
CD(5+19)	0.3	%Lymph	

MTHFR C677T	Heterozgote C/T
MTHFR A1298C	Normal A/A
Prothrombin20210A	Normal G/G
Fibrinogen PCR	Normal G/G
PAI 844	Heterozygote A/G
PAI 675	4G/5G

Homocystein	9.5	micmol/L	5 - 15
APCR(Leiden factor)	2.3	Sec	2.18-3.38

1401/8/3

ANA	0.17	ISR	ELISA	Neagative: <0.8 Positive : >1.2 Borderline : 0.8-1.2
Anti dsDNA	0.16	ISR	ELISA	Negative : < 0.8 Positive :> 1.2 Doubtful :0.8-1.2
Anti Sperm Antibody	Negative	Titer		Less than 1/16
Anti Thyroglobulin Antibody H	277.00	IU/ml	ELFA	Up to 18.0
Anti TPO-IgG H	175	IU/ml	ELFA	<8.0
Anti lupus	37	Sec		31-45
Anti Thrombin III	120	%		75-125
B2 Glycoprotein IgM	0.21	U/ml	ELISA	<0.7 Negative =>0.7 Positive
B2 Glycoprotein Ab(IgG)	0.24	U/ml	ELISA	<0.7 Negative =>0.7 Positive

1401/8/1

هیستروسالپنگوگرافی:

در کلیشه کنترل کلسیفیکاسیون اینتراپلویک دیده نمی‌شود.

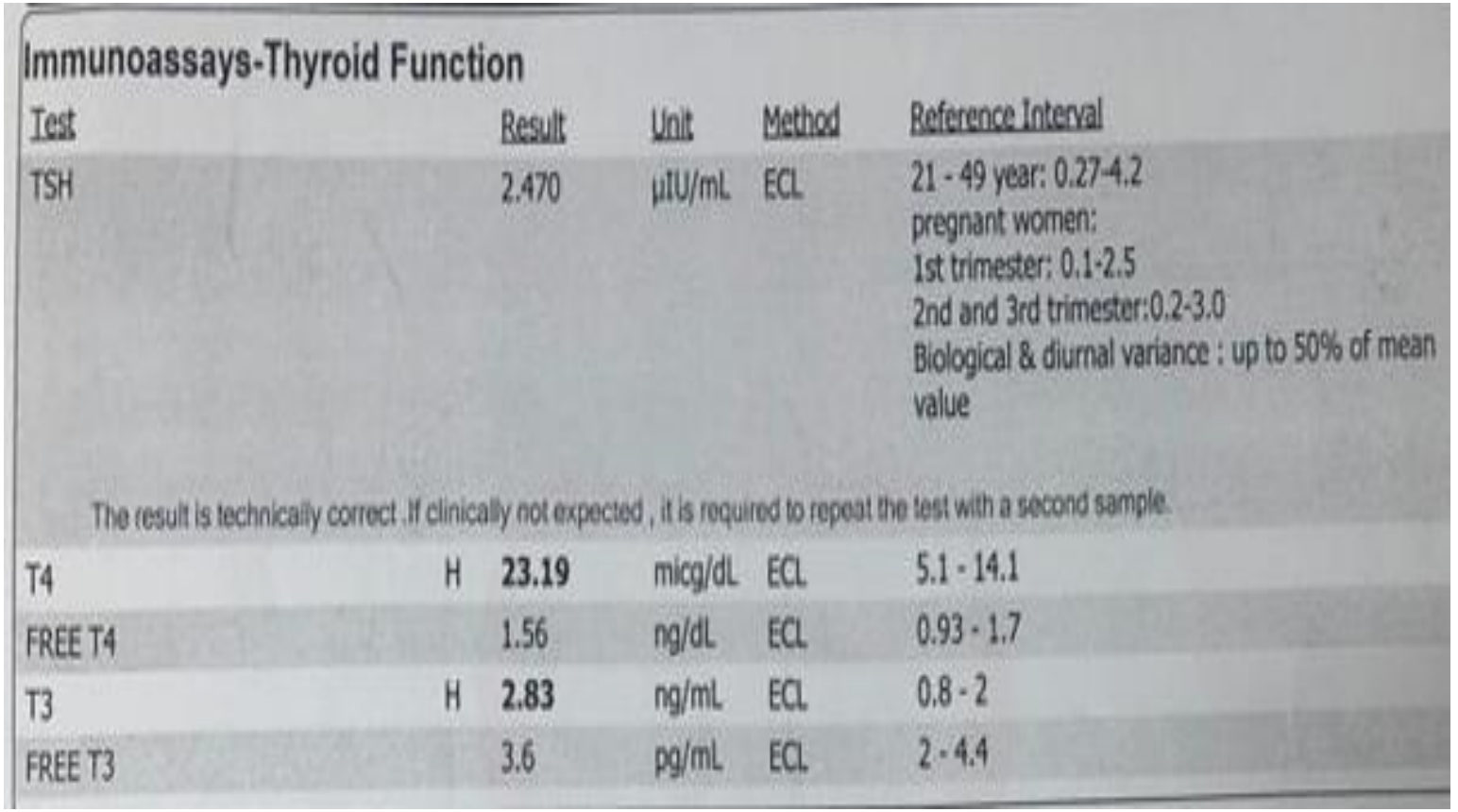
پس از تزریق CM کاویته رحم نمایان شده و علائم واضحی دال بر ضایعهٔ فضاگیر و یا adhesion دیده نمی‌شود.

فلکسیون جسم رحم دیده می شود.

لوله‌ها نمایان شده و Spillage مادهٔ حاجب از هر دو طرف به خوبی انجام شده است.

در کلیشه تخلیه پخش CM در حفرهٔ‌پریتوئن به طور یکنواخت انجام شده است.

Present Illness



Immunoassays-Thyroid Function

Test		Result	Unit	Method	Reference Interval
TSH		2.470	µIU/mL	ECL	21 - 49 year: 0.27-4.2 pregnant women: 1st trimester: 0.1-2.5 2nd and 3rd trimester:0.2-3.0 Biological & diurnal variance : up to 50% of mean value

The result is technically correct .If clinically not expected , it is required to repeat the test with a second sample.

T4	H	**23.19**	micg/dL	ECL	5.1 - 14.1
FREE T4		1.56	ng/dL	ECL	0.93 - 1.7
T3	H	**2.83**	ng/mL	ECL	0.8 - 2
FREE T3		3.6	pg/mL	ECL	2 - 4.4

1401/9/26

TSH	2.47
TT4 (µg/dl) (5-14)	23.19
fT4 (ng/dl) (0.9-1.7)	1.56
TT3 (ng/ml) (0.8-2)	2.83
fT3 (pg/ml) (2-4.4)	3.6

کد بیمار: 42011133

[redacted]

تاریخ: 1402/01/18

[redacted]

Dynamic Pituitary Study M.R.I:

With and without IV contrast

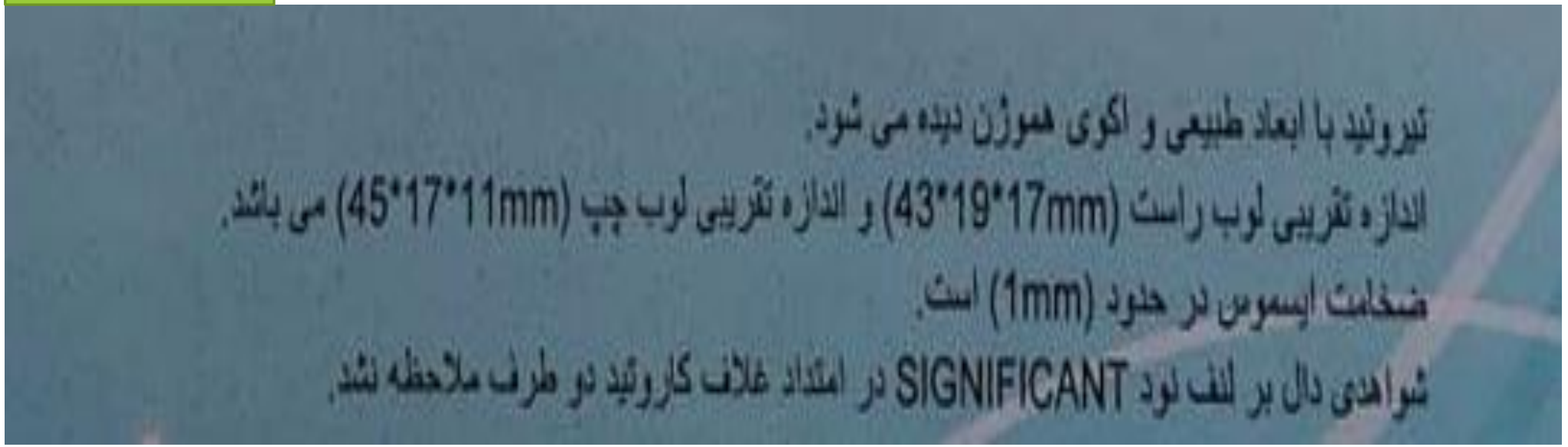
Protocols: Multiplanar images at different M.R.I sequences.

Dynamic Pituitary Study M.R.I reveals:

- **Small (3.5 mm)late enhancing focus in the left side pituitary gland suggestive for microadenoma causing no sellar roof bulging.**

Cerebral ventricles and major intracranial vascular structures are normal.
Parasellar regions, orbits, optic nerves and 7/8 nerve complexes are normal.

1402/3/20


تیروئید با ابعاد طبیعی و اکوی هموژن دیده می شود.
اندازه تقریبی لوب راست (43*19*17mm) و اندازه تقریبی لوب چپ (45*17*11mm) می باشد.
ضخامت ایسموس در حدود (1mm) است.
شواهدی دال بر لنف نود SIGNIFICANT در امتداد غلاف کاروتید دو طرف ملاحظه نشد.

	97/9/25	98/4/19	98/5/2	99/3/1	99/10/7	00/1/23	99/12/2	00/9/23	01/7/28	01/9/26	02/3/16
TSH	4.03	3.79	4.33	1.7	2.74	3.03	2.02	3.59	1.94	2.47	4.47
TT4 (µg/dl) (5-14)	19.22	19.4	233 (60-160) (nmol/l)	24	22.7	22.64	24.8		24.8	23.19	23.77
fT4 (ng/dl) (0.9-1.7)								1.69		1.56	1.48
TT3 (ng/ml) (0.8-2)	3.04	348 (83-200) (ng/dl)	3.5 (1.3-3.1) (nmol/l)	2.8						2.83	3
fT3 (pg/ml) (2-4.4)										3.6	3.6
FTI (µg/dl) (5-14)			264.8 (60-160) (nmol/l)	18.46					19.07		16.06
Anti TPO				63	107				173		116

	TSH	T4	fT4	T3	fT3	FTI	Anti TPO
Father (77 yr)	1.4	20 (µg/dl) (5.1-14.1)	1.5 (ng/dl) (0.9-1.7)	2.45 (ng/ml) (0.8-2)	3.4 (pg/ml) (2-4.4)	13.6	4.2
Mother (77 yr)	0.43	130 (nmol/l) (60-160)	15.7 (pmol/l) (9-19)	0.9 (nmol/l) (0.8-2)	2.12 (pg/ml) (2-4.4)	125 (60-160)	
Brother 1 (52 yr)	0.9	7 (µg/dl)	1.37 (ng/dl)	1.5 (ng/ml)	3.4		19.7
Brother 2 (49 yr)	1.07	8.5 (µg/dl)	1.45 (ng/dl)	1.4 (ng/ml)	3.2		10.4
Brother 3 (44 yr)	0.9	7.85 (µg/dl)	1.35 (ng/dl)	1.46 (ng/ml)	3.2		12.9
Daughter (6.5 yr)	2.05	12.3 (µg/dl)	1.5 (ng/dl)	2.31 (ng/ml)	4		18

آزمایشگاه خاتم خرداد 1402	TSH	T4 (µg/dl) (5.1-14.1)	fT4 (ng/dl) (0.9-1.7)	T3 (ng/ml) (0.8-2)	fT3 (pg/ml) (2-4.4)	FTI (µg/dl) (5.1-14.1)	Anti TPO
Patient	4.4	23.77	1.48	3	3.6	16.06	116
Father	1.4	20	1.5	2.45	3.4	13.60	4.2

Past History

PMH: Migraine

DH: Sumatriptan (PRN)

Aspirin 80 (Daily/ After the third miscarriage)

Letrozole 20 (Since three months ago)

Family history

She was born of a consanguineous marriage

3 Healthy brothers

ROS

NEGATIVE

Palpitation

Weight loss

Tremors

Anxiety

Insomnia

Irregular menses

blurred vision

POSITIVE

Headache

Physical Exam

General appearance: A 39 y/o female, Awake & alert

Body Weight: 64 kg , **Height**: 159 cm, ***BMI** = 25.39 kg/m2*

***BP**: 120/80, **PR**: 74*

***Thyroid**: NL size & Rubbery , No palpable nodule*

Problem list

Recurrent Pregnancy Loss

TSH: NL, ↑TT4 (1.3-1.7 ULN), ↑ TT3 (1.4-1.7 ULN), ↑FTI (1.18-1.3 ULN), Nl FT4 and FT3

Anti TPO: +, Anti Tg: +

Family History:+

Euthyroid Hyperthyroxinemia

AGENDA

DDx Of Euthyroid Hyperthyroxinemia

FDH and Risk of Miscarriages

Thyroid autoantibody positivity and Risk of Miscarriages

Plan

DDx Of Euthyroid Hyperthyroxinemia

- ***Euthyroid Hyperthyroxinemia Due to Binding Protein Abnormalities***

  Familial dysalbuminemic hyperthyroxinemia

  Abnormal TTR bindindg of T4

  Hereditary TBG excess

- ***Anti-T4 immunoglobulins***

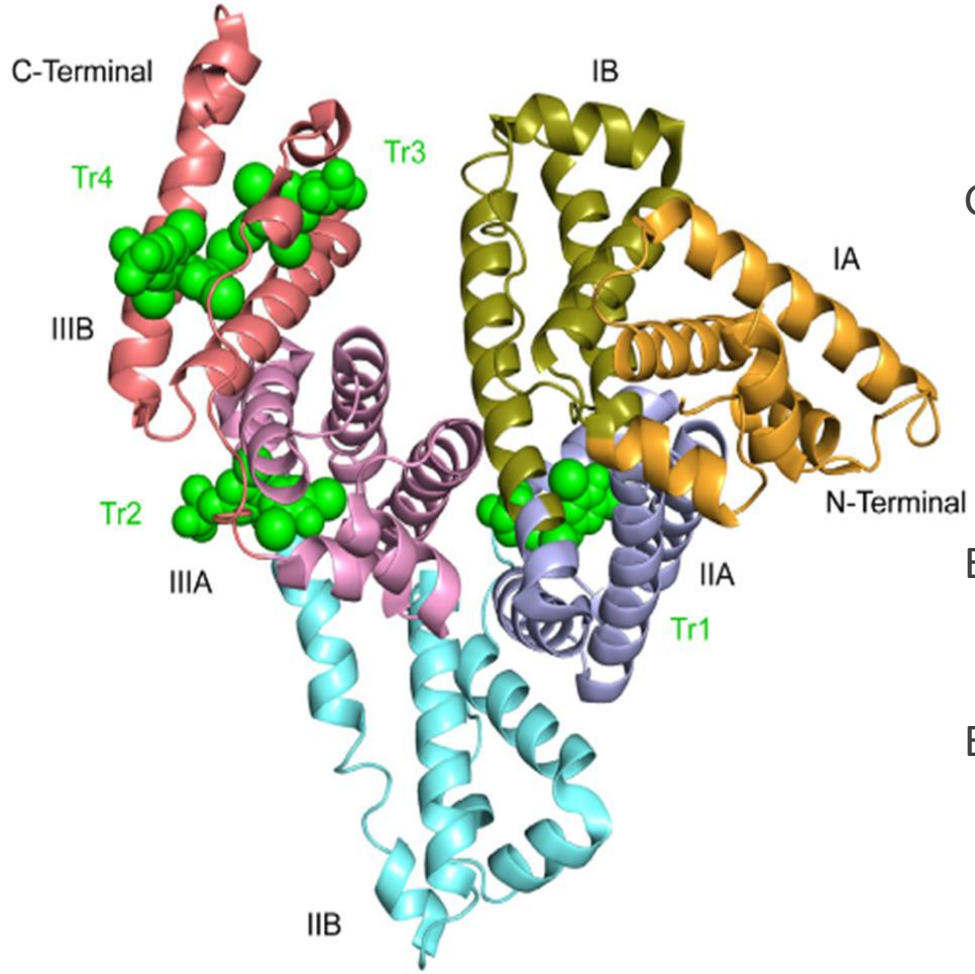
- ***RTH***

The most liklely Diagnosis:

FDH

Defect	T4	T3	rT3	T3/rT3 ratio	TSH	FT4 Dialysis	Other Common Manifestations
RTHβ	↑	↑ or N	↑	N	N or ↑	↑	Tachycardia, goiter ADHD
RTHα	N or sl ↓	N or sl ↑	N sl ↓	↑	N or sl ↑	N or sl ↓	Growth and mental delay, constipation
TSHoma	↑	↑	↑	N	sl ↑ or N	↑	Thyrotoxicosis
MCT8 mut	N or ↓	↑↑	↓↓	↑↑	N or sl ↑	↓	Neuropsychomotor retardation
SBP2 mut[a]	↑	↓	↑	↓↓	N or sl ↑	↑	Growth delay
FDH (*ALB* mut)	↑	N or sl ↑[b]	↑	↓	N	N or ↑	None
TBG excess	↑	↑	↑	N	N	N	None
Acute NTI	↑	↓↓	↑	↓	N	N or ↑	Variable depending on illness

*F*amilial *D*ysalbuminemic *H*yperthyroxinemia



Gain-of-function sequence variants in the ALB gene increase the *affinity*

Major clinical consequence of altered TBP is that of *misdiagnosis*

Effect of FDH on *total & free hormone* assays: both assays can return *high results*

Effects on *fTH* assays are *method dependent* and *artifactual*

The Thyroid. Lewis E. Braverman. 11th Edition.

Familial Dysalbuminemic Hyperthyroxinemia

The clinician must be wary if the free T4 result by any method does not agree with the clinical state and the TSH: Another method should be used to estimate the free T4

Familial Dysalbuminemic Hyperthyroxinemia

Caveats in the interpretation of FTI (labeled T3) results:

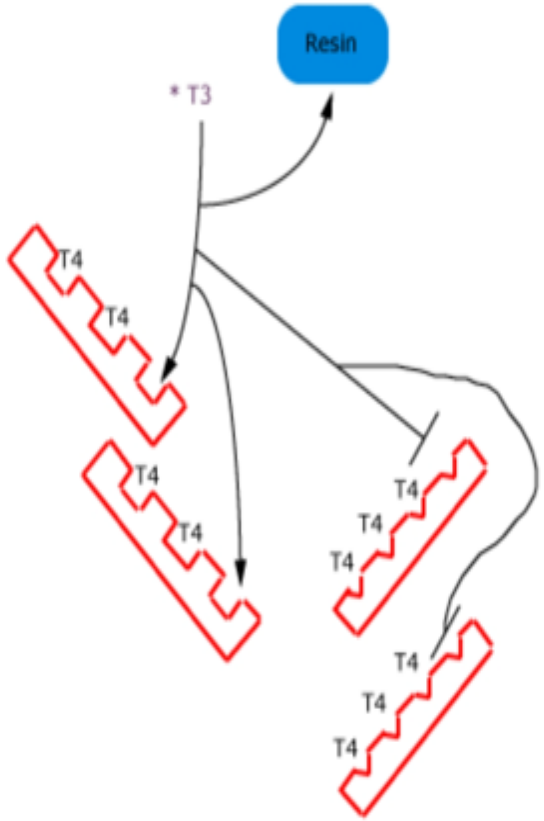
(1) In cases of familial dysalbuminemic hyperthyroxinemia (FDH)

(2) In the presence of endogenous antibodies directed against T3

(3) In sick patients

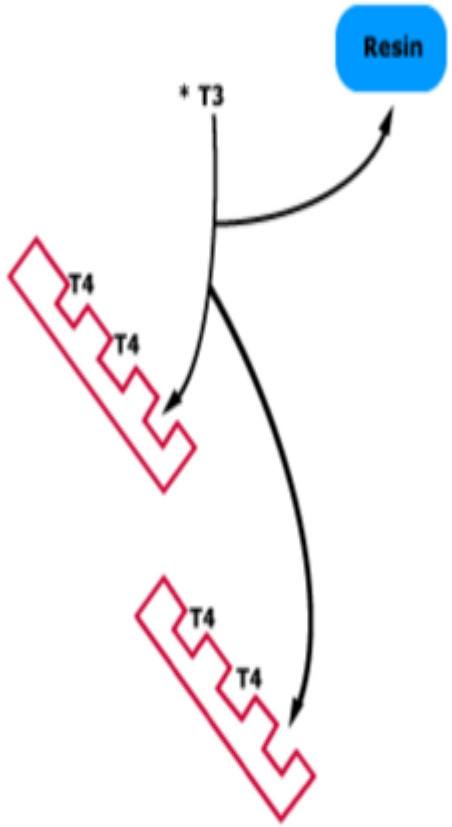
T3-resin test in familial dysalbuminemic hyperthroxinemia

T3-resin test in familial dysalbuminemic hyperthroxinemia



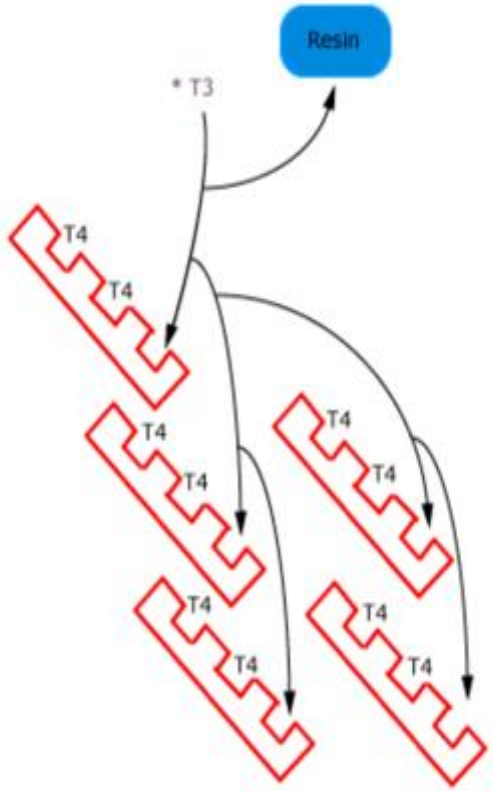
Normal T3 resin test

Normal T3 resin test



T3-resin test in TBG excess

T3-resin test in TBG excess



Familial Dysalbuminemic Hyperthyroxinemia

The prevalence of FDH is dependent on the population studied with high prevalence in Hispanic populations (1:55 to 1:100) and 1:10,000 in Europeans, but *very rare in Asian individuals*

The Thyroid. Lewis E. Braverman. 11th Edition.

TABLE 1 | Molecular, clinical, and ethnic characteristics of familial dysalbuminemic hyperthyroxinemia (FDH-T4) (1–20) and FDH-T3 (21) causing mutations.

No.	Mutation	Base change[a]	Total T4 (µg/dL)[b]	Total T3 (ng/dL)[c]	Total rT3 (ng/dL)[d]	Persons (families)	Country	Ethnicity	Reference
1	R218H	c.725G>A	13.3–21.5	103–218	21.3–44.2	21 (8)	USA	Mainly European	(29)
2	R218H	c.725G>A	NI[e]	NI	NI	3 (3)	HI, USA	Caucasian	(32)
3	R218H	c.725G>A	15.4	147	28.6	22 (1)	USA	Amish (Swiss)	(30)
4	R218H	c.725G>A	15.4–18.8	130–150	NI	1 (1)	Taiwan	Chinese	(33)
5	R218H	c.725G>A	15.6	138	26.9	2 (1)	Puerto Rico	Hispanic	(31)
6	R218H	c.725G>A	14.9–20.0	NI	NI	7 (1)	Hong Kong	Chinese	(34)
7	R218H	c.725G>A	18.5	NI	NI	1 (1)	Denmark	Danish	(28)
8	R218H	c.725G>A	NI	NI	NI	4 (4)	Western Europe	NI	(35)
9	R218H	c.725G>A	13.7	119	43.6	1 (1)	USA	NI	(27)
10	R218H	c.725G>A	14.6	NI	NI	2 (2)	New Zealand/Sri Lanka	Caucasian/NI	(14)
11	R218H	c.725G>A	14.5	99	NI	3 (1)	Korea	Korean	(36)
12	R218P	c.725G>C	182	225	164	6 (1)	Japan	Japanese	(37)
13	R218P	c.725G>C	NI	NI	NI	2 (2)	Japan	Japanese	(38)
14	R218P	c.725G>C	102–120	214–312	156–177	4 (1)	Switzer-land	Swiss	(39)
15	R218P	c.725G>C	99.1	338	NI	1 (1)	Japan	Japanese	(40)
16	R218P	c.725G>C	>30	387	NI	3 (1)	Japan	Japanese	(41)
17	R218P	c.725G>C	24.9[f]	232	NI	4 (3)	Japan	Japanese	(42)
18	R218P	c.725G>C	>24.9	NI	NI	1 (1)	Japan	Japanese	(43)
19	R218S	c.724C>A	85	288	86.2	2 (1)	Canada	Bangla-deshi	(44)
20	R222I	c.737G>T	15.9-23.5	–[g]	–[g]	9 (4)	UK	Somali/Croatian	(45)
21	L66P	c.269T>C	8.4	256	NI	8 (1)	Thailand	Thai	(46)

The hormone concentrations are usually given for the probands.

[a]*Codon numbering according to HGVS rules and based on the cDNA sequence NM_000477.12.*

[b]*Normal concentration: 4.5–12 µg/dL (55–144 nmol/L).*

[c]*Normal concentration: 90–180 ng/dL (0.9–2.8 nmol/L).*

[d]*Normal concentration: 15–32 ng/dL (0.2–0.5 nmol/L).*

[e]*No information available.*

TT4: 19.2-24.8 µg/dl
TT3: 280-348 ng/dl

Ulrich K-Hansen. Clinical. Genetic, and Protein Structural Aspects of Familial Dysalbuminemic Hyperthyroxinemia and Hypertriiodothyroninemia., *Frontiers in Endocrinology*. (2017) 8: article 297.

TABLE 2 | Summary of mutations and phenotypes.

Mutation	Factors by which hormone concentrations are increased[a]		
	Total T4	**Total T3**	**Total rT3**
R218H	1.1–1.8	0.6–1.2	0.7–1.4
R218P	8–15	1.2–2.1	5
R218S	7	1.6	2.4
R218C[b]	–	–	–
R222I	1.3–2.0	NI[c]	40–70
L66P	0.7	1.4	NI
L66V[b]	–	–	–

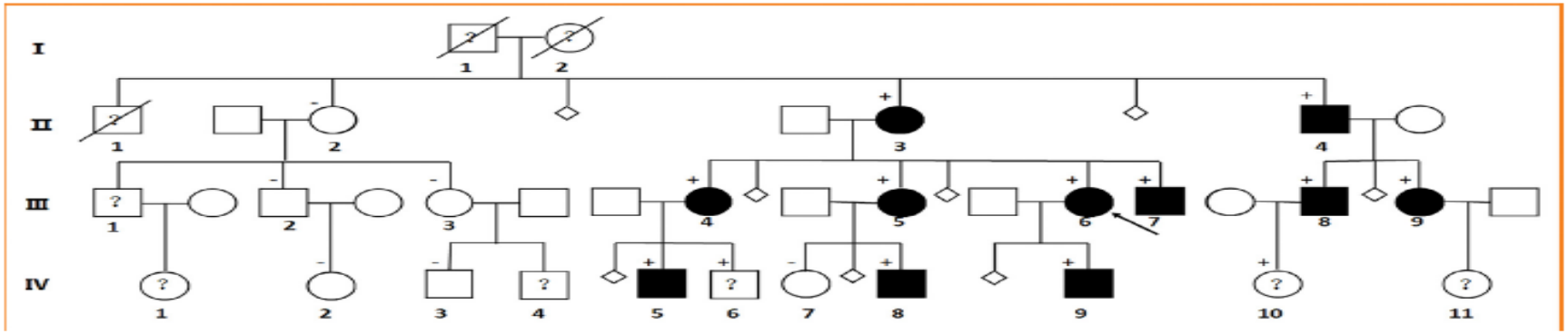
[a]*Concentrations are related to the upper limit of the normal concentration range.*
[b]*These variants are included in the Exome Aggregation Consortium Website (47), but they have not been reported to case FDH-T4 or FDH-T3.*
[c]*No information available.*

TT4: 1.3-1.7

TT3: 1.4-1.7

Ulrich K-Hansen. Clinical. Genetic, and Protein Structural Aspects of Familial Dysalbuminemic Hyperthyroxinemia and Hypertriiodothyroninemia., *Frontiers in Endocrinology*. (2017) 8: article 297.

FDH and Risk of Miscarriages



32% (95% CI 16-54%) of FDH women -Albumin gene variant (R218S)- experienced miscarriages at a rate that was substantially higher than the spontaneous abortion rate reported in the general population in China (7-14%)

Shuiqing Lai. Familial Dysalbuminemic Hyperthyroxinemia (FDH), Albumin Gene Variant (R218S), and Risk of Miscarriages in Offspring. Am J Med Sci 2020;360(5):566–574.

Thyroid autoantibody positivity and Risk of Miscarriages

While the impacts of overt thyroid dysfunction on feto-maternal morbidities have been clearly identified and its long term impact on childhood development is well known, data on the early and late complications of subclinical thyroid dysfunction during pregnancy or thyroid autoimmunity are controversial. Further studies on maternal and neonatal outcomes of subclinical thyroid dysfunction maternal are needed

Iran J Reprod Med Vol. 13. No. 7. pp: 387-396, July 2015

Review article

Thyroid dysfunction and pregnancy outcomes

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Abstract

Background: Pregnancy has a huge impact on the thyroid function in both healthy women and those that have thyroid dysfunction. The prevalence of thyroid dysfunction in pregnant women is relatively high.

Objective: The objective of this review was to increase awareness and to provide a review on adverse effect of thyroid dysfunction including hyperthyroidism, hypothyroidism and thyroid autoimmune positivity on pregnancy outcomes.

Materials and Methods: In this review, Medline, Embase and the Cochrane Library were searched with appropriate keywords for relevant English manuscript. We used a variety of studies, including randomized clinical trials, cohort (prospective and retrospective), case-control and case reports. Those studies on thyroid disorders among non-pregnant women and articles without adequate quality were excluded.

Thyroid autoantibody positivity and Risk of Miscarriages

Although the frequency of miscarriage in the AT group was greater (4.8%) than in the controls (2.9%), no significant differences were detected (P=0.181)

If thyroid function is adequately controlled, the presence and titer of thyroid autoantibodies does not negatively influence gestation. Although not significant, suboptimal thyroid hormone status seems to affect pregnancy outcomes more than thyroid autoimmunity

Francesca Orsolini,Thyroid Function Rather Than Thyroid Antibodies Affects Pregnancy and Perinatal Outcomes: Results of a Prospective Study. The Journal of Clinical Endocrinology & Metabolism. (2022): 107, e4302–e4310.

Thyroid autoantibody positivity and Risk of Miscarriages

Analysis of 22 eligible studies revealed significant association between TPO-Ab and the prevalence of RM (OR = 1.85; 95% CI, 1.38 to 2.49; P < .001)(n ≥ 3),
(OR = 1.82; 95% CI, 1.13 to 2.92; P = .01)

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REVIEW ARTICLE

AJRI American Journal of Reproductive Immunology WILEY

Effect of antithyroid antibodies on women with recurrent miscarriage: A meta-analysis

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Abstract

Problem: The effect of thyroid autoimmunity (TAI) on the prevalence of recurrent miscarriage (RM) is highly debatable. No meta-analysis has been published in the past decade to investigate the impact of TAI on women with RM.

Method of Study: Systemic literature search was conducted on PubMed, Embase, Cochrane, and Web of Science databases. English language literatures published between 1993 and 2019 were selected. We assessed the relationship between the prevalence of RM and thyroid peroxidase antibodies (TPO-Ab) or antithyroid antibodies (ATA) and evaluated the thyroid-stimulating hormone (TSH) level in TPO-Ab-positive women with RM. We also observed the treatment effect with levothyroxine (LT4) for RM. Review Manager 5.3 software was used to obtain the pooled odds ratios (OR).

Plan

Rheumatologic Consultation

Seronegative APS → ASA, LMWH

TSH in Pregnancy

Reimaging 6-12 month later


Thanks For Your Attention