



# Management of the patient circulating elevated b-HCG with no clinical findings

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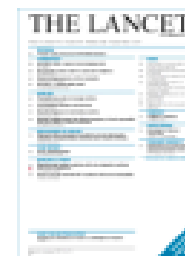
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## Case 1: The hCG-scandal. (Previously described by Rotmensch and Cole<sup>20</sup>)

In the late 1990s, a 22-year old woman with irregular menstrual bleeding had repeatedly elevated measurements of serum  $\beta$ -hCG on the Abbott AxSym platform. Pregnancy was excluded,

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Fast track — Early Report

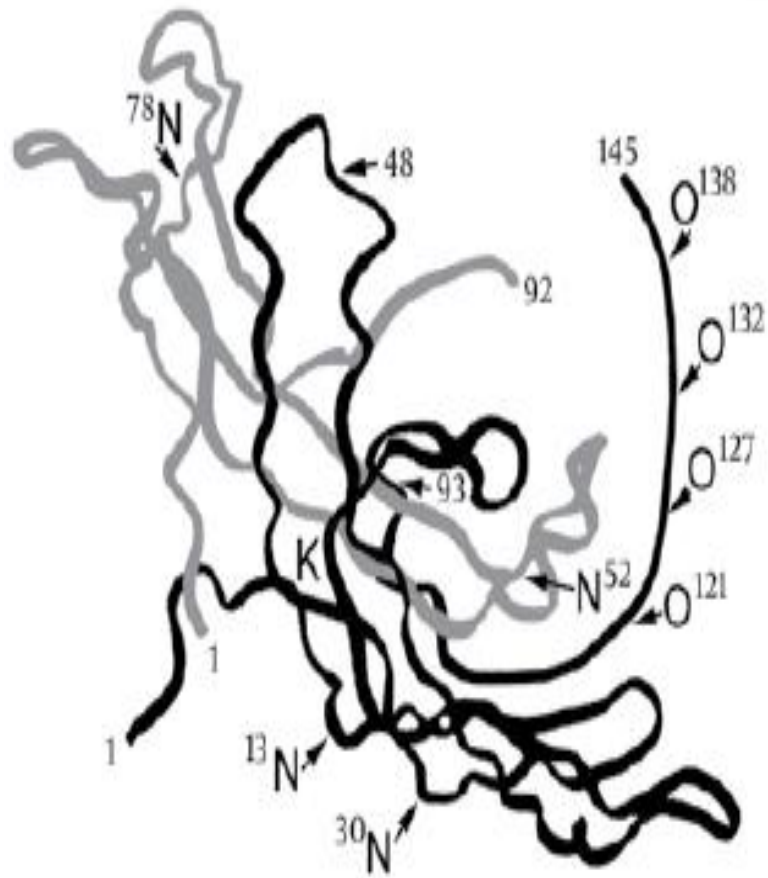
## False diagnosis and needless therapy of presumed malignant disease in women with false-positive human chorionic gonadotropin concentrations

Prof Sigi Rotmensch MD <sup>a, b</sup>, Prof Laurence A Cole PhD <sup>a, c</sup>  

caused by the unnecessary treatment. The jury allocated equal responsibility for the tragedy to Abbott Laboratories, the manufacturer of the test, and the hospital where she was treated. Several similar cases involving the AxSym  $\beta$ -hCG-assay were revealed, and Abbott Laboratories were forced to improve the heterophilic antibody resistance of their assay.



# human chorionic gonadotropin (hCG)



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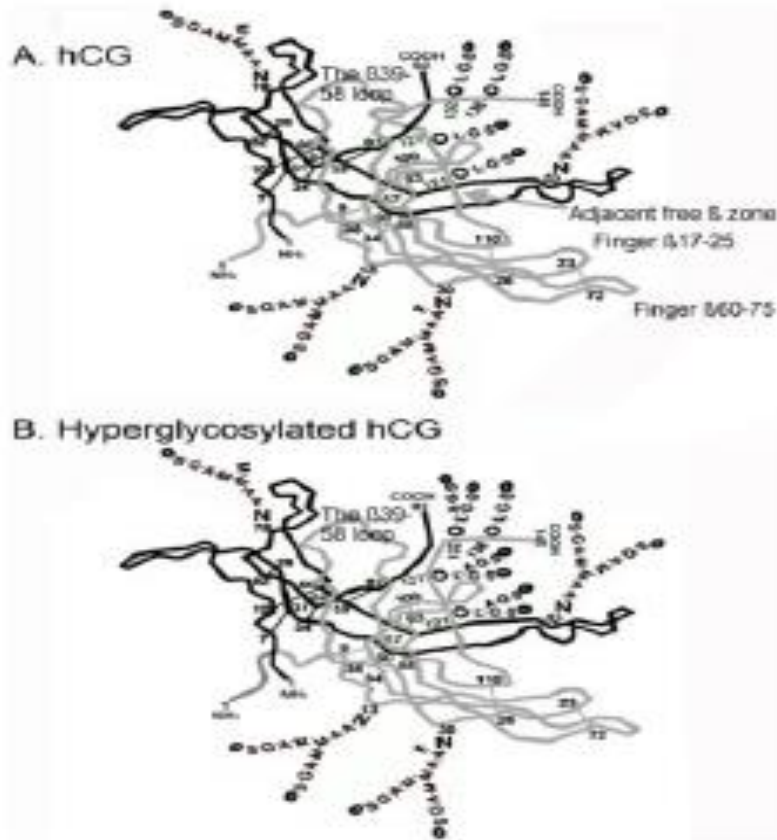
- Chorion comes from the Latin chordata meaning afterbirth;
- Gonadotropin because the hormone was considered a gonadotropic molecule, or a stimulator of gonad (or ovary) steroid production.

# hCG

- The hormone and autocrine dealt with today are produced by placenta cells and cells other than placenta cells.
- The hormone and autocrine do not act primarily on gonad cells. Considering that it is both a hormone (hCG) and a autocrine (hyperglycosylated hCG).
- human pregnancy glycoprotein or human acidicglycoprotein



# Hyperglycosylated hCG



Hyperglycosylated hCG had an identical  $\alpha$  and  $\beta$ -subunit amino acid sequence to the hormone hCG, identical N linked sugar structures, but at least 3 of 4 very different O-linked carbohydrate side chains.

Signal Molecule	Function
hCG	<ol style="list-style-type: none"><li>1. Promotion of corpus luteum progesterone production</li><li>2. Angiogenesis of uterine vasculature</li><li>3. Cytotrophoblast differentiation</li><li>4. Immuno-blanding and blockage of phagocytosis of invading trophoblast cells</li><li>5. Growth of uterus in line with fetal growth</li><li>6. Quiescence of uterine muscle contraction</li><li>7. Promotion of growth and differentiation of fetal organs</li><li>8. Blastocysts signal decidua prior to implantation</li><li>9. Umbilical cord growth and development</li><li>10. hCG in sperm and receptors found in fallopian tubes suggesting pre-pregnancy communication</li><li>11. hCG receptors in brain hippocampus, hypothalamus and brain stem, cause of pregnancy nausea/vomiting</li></ol>
Hyperglycosylated hCG	<ol style="list-style-type: none"><li>1. Blocks apoptosis in cytotrophoblast cells</li><li>2. Promotes invasion process by cytotrophoblast cells</li><li>3. Promotes implantation of pregnancy</li><li>4. Promotes growth of cytotrophoblast cells</li></ol>



- The hormone hCG acts on an hCG/LH joint hormone receptor,
- while the autocrine nicked hyperglycosylated hCG  $\beta$ -subunit act on an ancestral TGF- $\beta$ -II receptor.

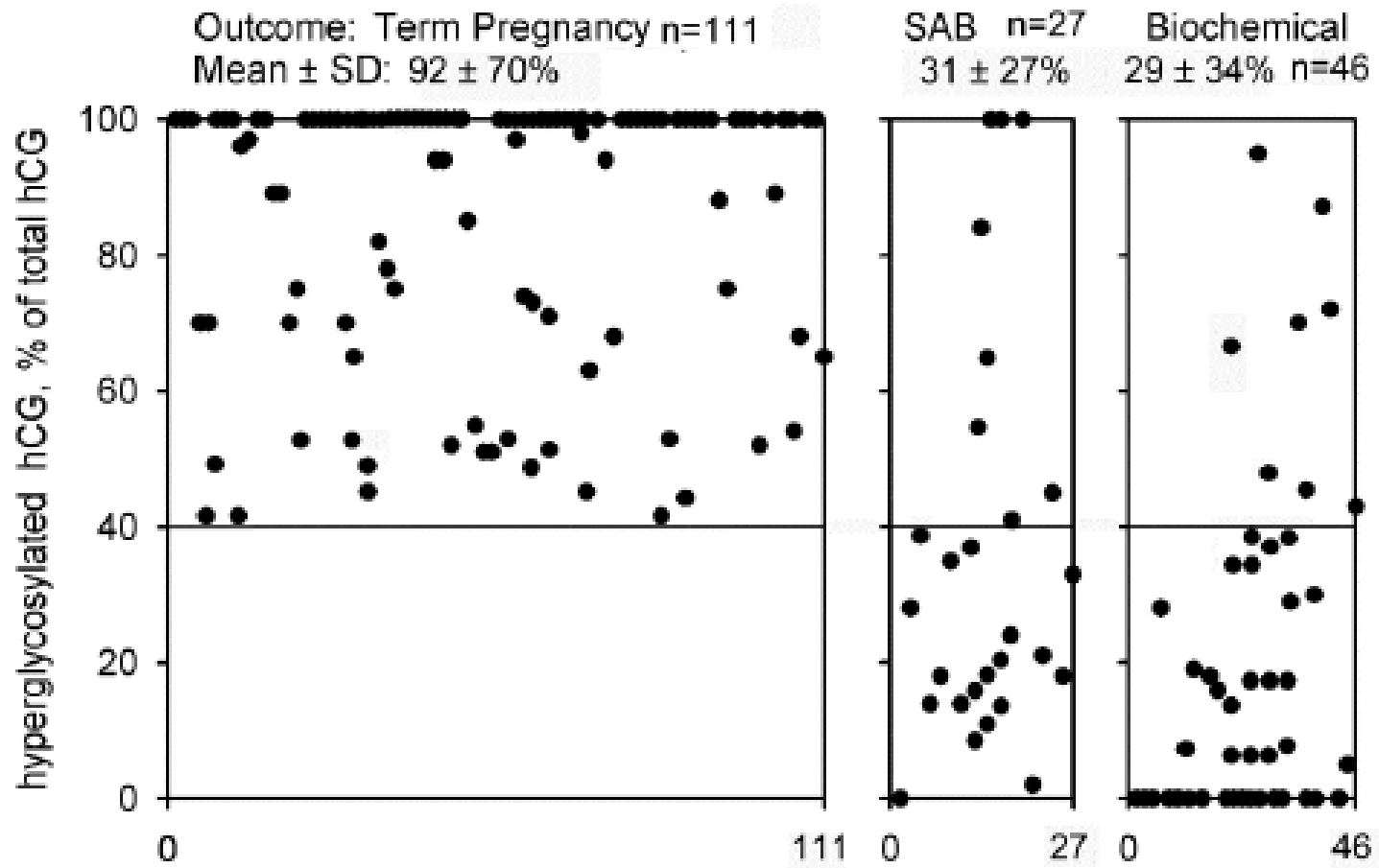
Parameter	Placental Hormone hCG	Placental glycosylated hCG	Hyper- Pituitary Sulfated	Cancer glycosylated hCG	hyper- Cancer hyperglycosylated $\beta$ -subunit	free	Ovarian hyper-glycosylated hCG	Fetal hCG
Source cells	Syncytiotrophoblast cells	Cytotrophoblast cells	Pituitary Gonadotropin cells	Trophoblastic malignancy cells	Non-trophoblastic malignancy cells	cancer	Ovarian Theca cell	Fetal kidney & liver cells
Mode of action	Endocrine	Autocrine	Endocrine	Autocrine	Autocrine		Autocrine	Endocrine
Total MW	36525	39149	35943	40461	26271		Not determined	Not determined
Site of action	LH/hCG receptor	TGF $\beta$ antagonism	LH/hCG receptor	TGF $\beta$ antagonism	TGF $\beta$ antagonism		Ovarian follicle	Fetal organ

Cole LA. Human chorionic gonadotropin (hCG) and hyperglycosylated hCG, seven semi-independent critical molecules: A review. J Mol Oncol Res. 2017;1(1):22-44.

# Placental Hormone hCG

- The placental hormone hCG is the original form of hCG as discovered by Aschner, Fellner, and Ascheim and Zondek at the turn of the twentieth century.
- The principal function is to drive growth and maintenance of hemochorial placentation, the fetal feeding system during pregnancy.

## Placental hyperglycosylated hCG and pregnancy failure.



# Pituitary sulfated hCG

hCG is produced in low concentrations (0.1–10 mIU/ml) by pituitary gonadotrope cells during the menstrual cycle.

It is called pituitary sulfated hCG because the sulfated side chains terminate in a sulfated N acetylgalactosamine residues.

It is believed that pituitary sulfated hCG supplement and guarantees LH biological activity.

Pituitary sulfated hCG taking over enhancing ovulation and enhancing steroidogenesis, ovulation and luteogenesis whenever LH production is insufficient.

# Fetal hcg

- hCG is independently produced in the pregnancy fetus, by fetal liver and fetal kidney cells.
- It was demonstrated that this variant of hCG controls fetal organ growth and development.
- It was also demonstrated that production of fetal hormone hCG is halted at parturition

# Ovarian Autocrine Hyperglycosylated hCG

- The final step of ovulation is that metalloproteinases and collagenase make holes in the ovary and the follicle to permit oocyte ovulation.
- It is inferred since hyperglycosylated hCG drives such proteolytic actions in implantation and deep implantation, that this is driven by a theca cells hyperglycosylated hCG.



# Cancer Autocrine Hyperglycosylated hCG and Cancer Hyperglycosylated hCG free $\beta$ -subunit

- Hyperglycosylated hCG and its free  $\beta$ -subunit are useful tumor markers for cancer.
- They are best measured as their urinary degradation product,  $\beta$ -core fragment. 100% of cancer expressed hyperglycosylated hCG or hyperglycosylated hCG free  $\beta$ subunit.

	Abbott Architect	Abbott AxSYM	Beckman Access 2	Beckman Dxl 800	Ortho Vitros ECIQ	Roche Elecsys hCG + $\beta$	Siemens Centaur	Siemens Dimension	Siemens Immulite	Siemens Stratus	Tosoh A1A
Serum standards											
hCG	96%	103%	103%	100%	112%	109%	104%	96%	96%	92%	95%
Hyperglycosylated hCG	86%	85%	120%	98%	<u>68%</u>	78%	81%	<u>67%</u>	105%	<u>66%</u>	ND
Nicked hCG	<u>70%</u>	99%	84%	<u>71%</u>	80%	<u>69%</u>	<u>66%</u>	<u>65%</u>	115%	<u>8%</u>	ND
Nicked hCG missing CTP	<u>0%</u>	<u>0%</u>	<u>0%</u>	<u>0%</u>	<u>0%</u>	<u>12%</u>	<u>0%</u>	<u>10%</u>	109%	<u>28%</u>	<u>16%</u>
Nicked hyperglycosylated hCG	<u>40%</u>	<u>46%</u>	<u>46%</u>	<u>51%</u>	80%	100%	<u>40%</u>	80%	103%	88%	<u>70%</u>
Asialo hCG	<u>35%</u>	<u>69%</u>	<u>48%</u>	<u>46%</u>	85%	<u>46%</u>	<u>39%</u>	<u>65%</u>	114%	<u>73%</u>	<u>59%</u>
hCG $\beta$	87%	94%	<u>142%</u>	<u>136%</u>	<u>47%</u>	102%	<u>47%</u>	<u>47%</u>	111%	<u>73%</u>	<u>66%</u>
Nicked hCG $\beta$	<u>33%</u>	<u>51%</u>	<u>56%</u>	<u>63%</u>	<u>19%</u>	<u>53%</u>	<u>19%</u>	<u>41%</u>	107%	<u>70%</u>	<u>60%</u>
$\beta$ -core fragment	<u>1%</u>	<u>1%</u>	<u>1%</u>	<u>1%</u>	<u>1%</u>	<u>16%</u>	<u>1%</u>	<u>1%</u>	<u>35%</u>	<u>1%</u>	<u>1%</u>
<b><u>Bold underline</u></b> poor detection	6 of 9	5 of 9	6 of 9	7 of 9	5 of 9	5 of 9	7 of 9	7 of 9	1 of 9	7 of 9	6 of 7
LH crossreactivity	0.01%	0.01%	0.01%	0.01%	0.32%	0.01%	0.01%	0.01%	0.04%	0.53%	0.01%

Table 9: Detection of serum hCG-related molecules by different automated total hCG tests (40,41).  $\beta$ CTP is  $\beta$ -subunit C-terminal peptide, RIA is radioimmunoassay. Percentage values are the result in nmol/L expressed as a percentage of the actual concentration of the standard, ND is not determined. A poor detection, <75% or >125% of standard concentration is shown by **bold underlined** numbers.

# Total 440 cases (1985-2017)

- Quiescent disease n=184 (41%)
- Pituitary hCG n=134
- Heterophilic antibodies n=86
- Familial hCG syndrome n=20
- Gestational trophoblastic disease n=6
- Cancer n=7
- Munchausen's syndrome n=3

False-positive hCG cases, 440 cases total, examined by the USA hCG Reference Service.

# Quiescent disease n=184 (41%)

Quiescent disease n= 184	Median hCG mIU/ml	Range hCG mIU/ml	Proportion H-hCG ng/ml
Quiescent pregnancy	16	6.0 - 256	<5% total hCG
Quiescent hydatidiform mole	19	1.7 - 207	<5% total hCG
Quiescent choriocarcinoma	8	2.0 - 117	<5% total hCG

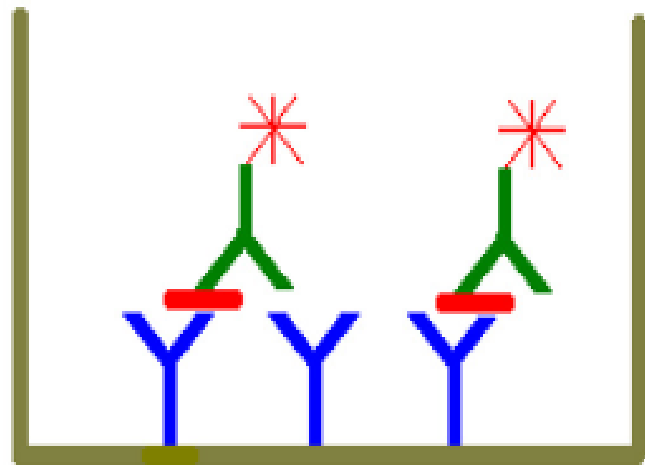
# Pituitary hCG

	Number Cases	Median hCG mIU/ml	Range hCG mIU/ml	Median H-hCG ng/ml	Median FSH mIU/ml
Perimenopause, age 38-51	60	8.4	1.4 - 28	<0.05	69.9
Postmenopause, age 52-70	47	11.4	2.5 – 33	<0.05	68
Bilateral oophorectomy cases	14	10.1	1.8 - 39	<0.05	59
Amenorrhea cases	1	6.1		<0.05	55.7
hCG peak	10	2.5	<1.0 – 11.8	<0.05	

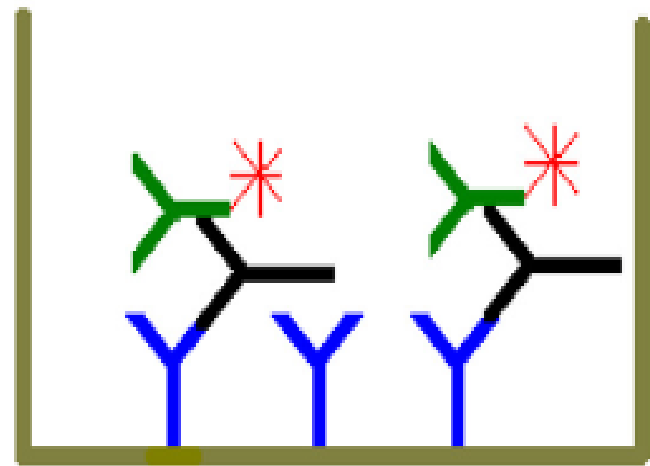
# Heterophilic antibodies n=86

	Number Cases	False Positive hCG, mIU/ml	False Positive Range, mIU/ml	hCG Immulite mIU/ml	hCG range mIU/ml
Abbott AxSYM, 1998-2005	45	81	6.0 - 1010	12.5	0 – 179
All methods, 2006-2016	38	24	7.1 - 404	4	0 – 74

correct measurement of hCG



falsely elevated measurement due to interference from heterophilic antibodies



— hCG      Y solid phase antibody      Y\* tracer antibody with tag      Y heterophilic antibody



# Familial hCG syndrome n=20

	Median hCG mIU/ml	Range hCG mIU/ml	Median free $\beta$ ng/ml	Mean free $\beta$ % of total hCG
	29.5	<1.0 - 287	0.45	0.68

# Gestational trophoblastic disease n=6

	Median hCG mIU/ml	Range hCG mIU/ml	Median H-hCG ng/ml	Range H-hCG ng/ml
	239	60 - 2362	9.8	0.36 - 283

# Cancer n=7

	Median hCG mIU/ml	Range hCG mIU/ml	Median free $\beta$ ng/ml	Mean free $\beta$ % of total hCG
	8	<1.0 - 274	1.3	0.88

# Munchausen's syndrome n=3

	Median hCG mIU/ml	Range hCG mIU/ml
	44150	7900 – 80400

# Detecting positive hCG cases outside of pregnancy

Diagnosis	Supporting data
Quiescent gestational trophoblastic disease	<ol style="list-style-type: none"><li>1. Has history of molar pregnancy or miscarriage</li><li>2. Negative (&lt;10% total hCG) in hyperglycosylated hCG test</li></ol>
Pituitary hCG	<ol style="list-style-type: none"><li>1. FSH test &gt;30 mIU/ml</li><li>2. Hyperglycosylated hCG not detected</li><li>3. Three weeks treatment with high estrogen pill suppresses hCG</li></ol>
False positive hCG test	<ol style="list-style-type: none"><li>1. In quantitative hCG test, hCG detected in serum but not urine</li><li>2. Multiple serum hCG tests give widely varying results</li></ol>

# Detecting positive hCG cases outside of pregnancy

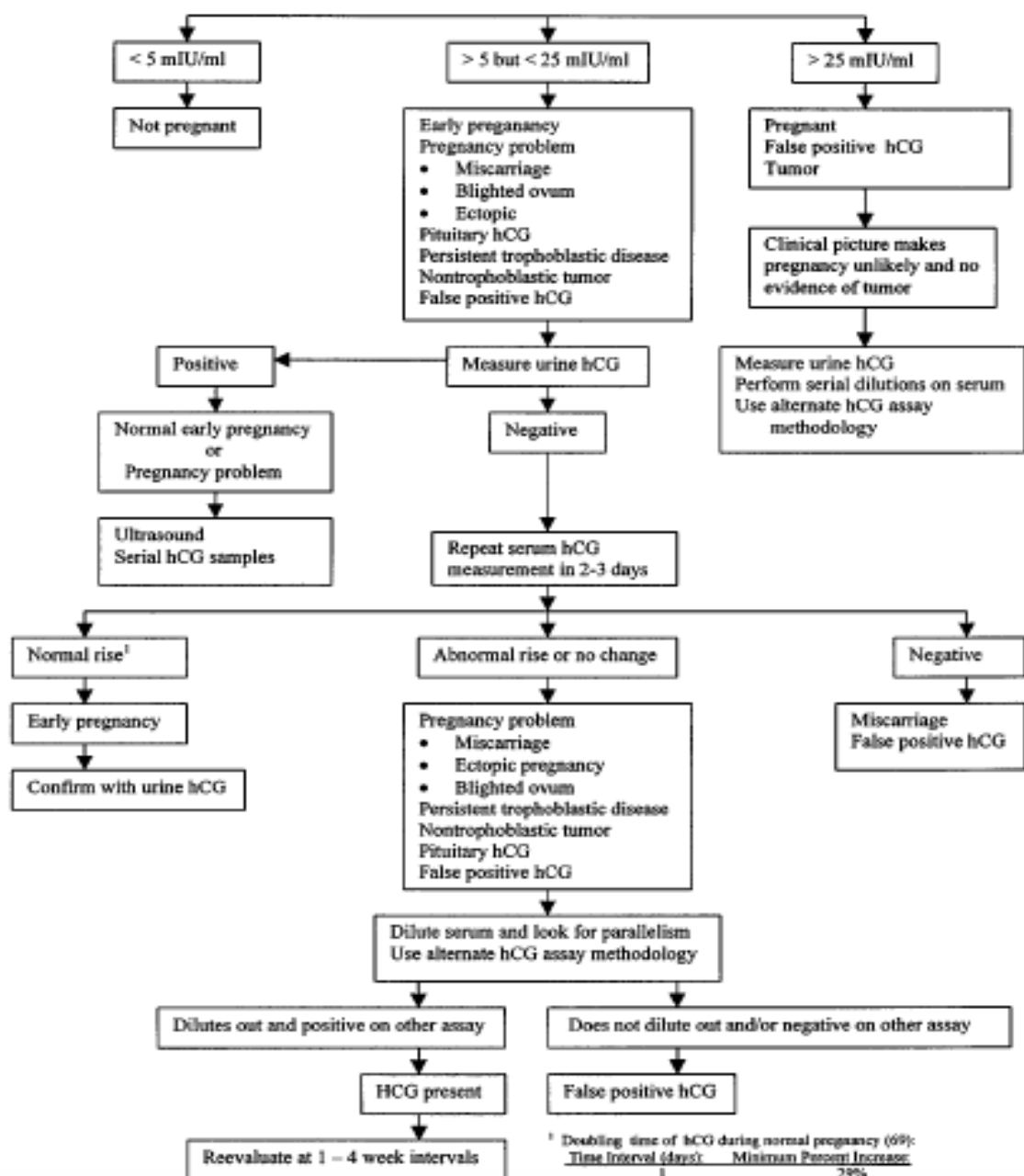
Diagnosis	Supporting data
Cancer	<ol style="list-style-type: none"><li>1. Data shows all hCG to be free <math>\beta</math>-subunit</li><li>2. Variable results in Immulite and other automated hCG tests</li></ol>
Choriocarcinoma/GTN	<ol style="list-style-type: none"><li>1. Hyperglycosylated hCG more than 50% of total hCG</li><li>2. Uterine mass</li></ol>
Familial hCG syndrome	<ol style="list-style-type: none"><li>1. Other automated assay give &lt;50% of Immulite hCG result</li><li>2. Total hCG is &gt;50% free <math>\beta</math>-subunit</li><li>3. Family members positive</li></ol>

# Detecting positive hCG cases outside of pregnancy

Diagnosis	Supporting data
Munchausen's syndrome	<ol style="list-style-type: none"><li>1. Exclude all other causes of positive hCG</li><li>2. Serum lacks hyperglycosylated hCG and hCG free <math>\beta</math>-subunit</li></ol>
Administering hCG	<ol style="list-style-type: none"><li>1. hCG levels that slowly over a month falls and then rises</li><li>2. Need confidential conversation with patient</li></ol>



Serum hCG Determination



<sup>1</sup> Doubling time of hCG during normal pregnancy (69):

Time Interval (days)	Minimum Percent Increase
1	29%
2	66%
3	114%
4	175%
5	238%

# Teşekkürler

