Human Chorionic Gonadotropin: Clinical Utility & Diagnostic Considerations

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April 13, 2009

Disclosures

David G. Grenache has no relevant financial interests regarding the material presented today.

Objectives

- Describe the structure, synthesis and function of hCG
- Discuss the clinical utility of hCG testing in the diagnosis and management of pregnancy, malignancy, and Down syndrome
- Discuss the causes of false-positive hCG results and persistently low hCG concentrations and explain investigations that can be used to identify each

Outline

- hCG structure and isoforms
- hCG assays and issues
- Clinical utility
- Persistent, low hCG

Human Chorionic Gonadotropin (hCG)

- Glycoprotein hormone family

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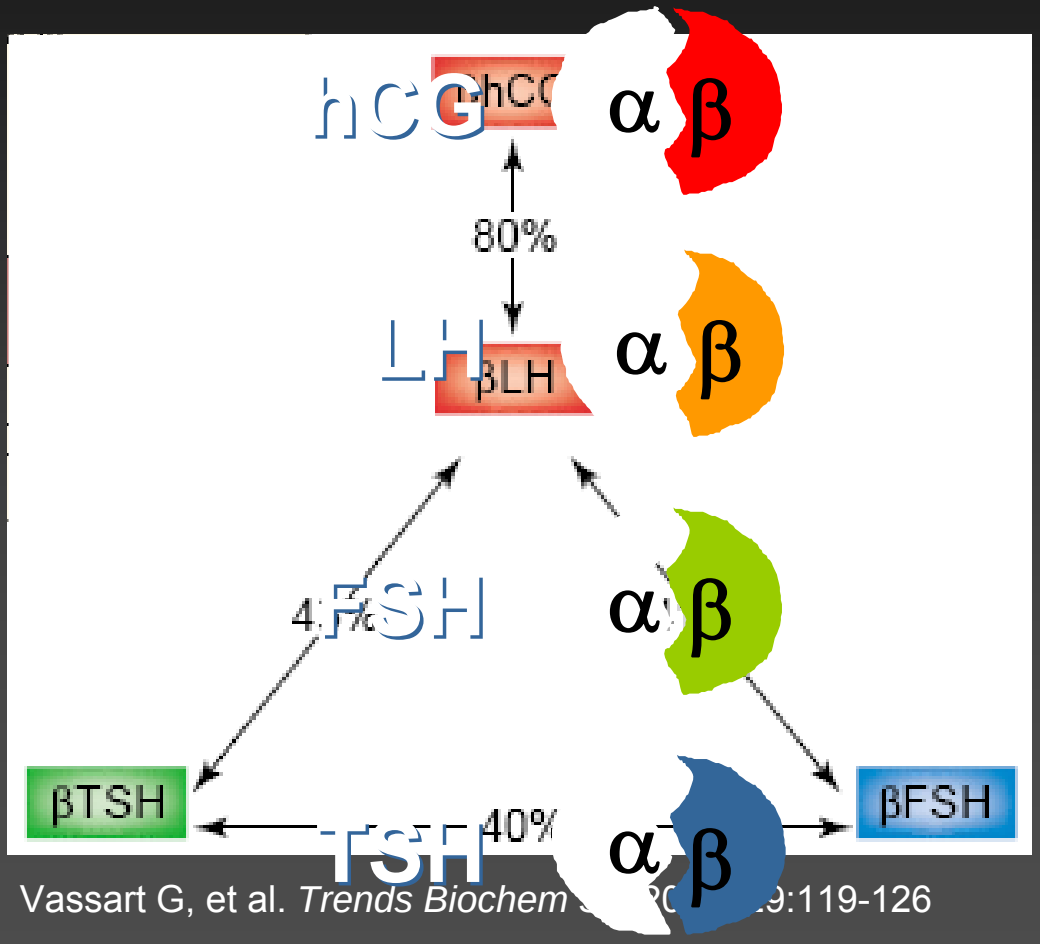
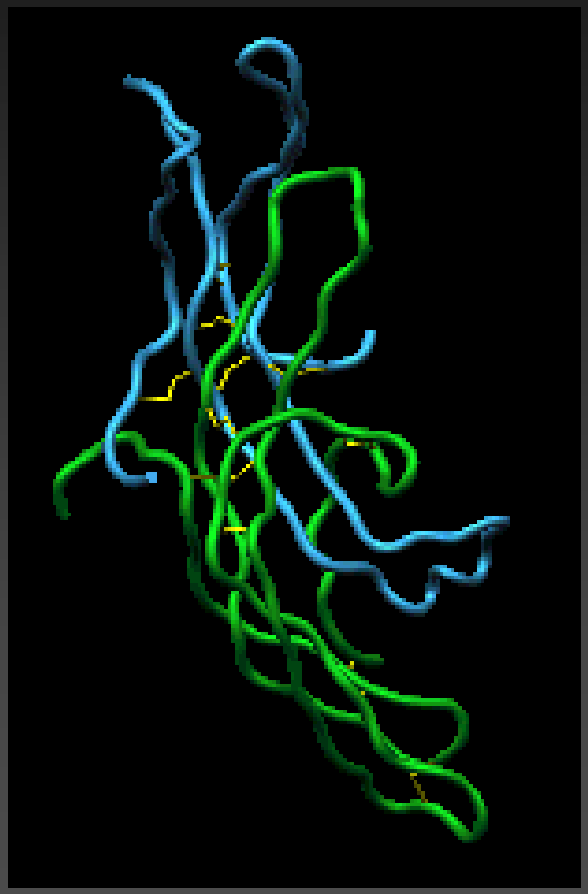


Vassart G, et al. *Trends Biochem* 19:119-126

hCG Structure

- Dimer is ~38,000 daltons
  - 30% of weight due to carbohydrate
- Alpha subunit
  - 92 amino acids
  - 2 N-linked carbohydrate chains
  - 5 disulfide bridges
- Beta subunit
  - 145 amino acids
  - 2 N-linked & 4 O-linked carbohydrate chains
  - 6 disulfide bridges



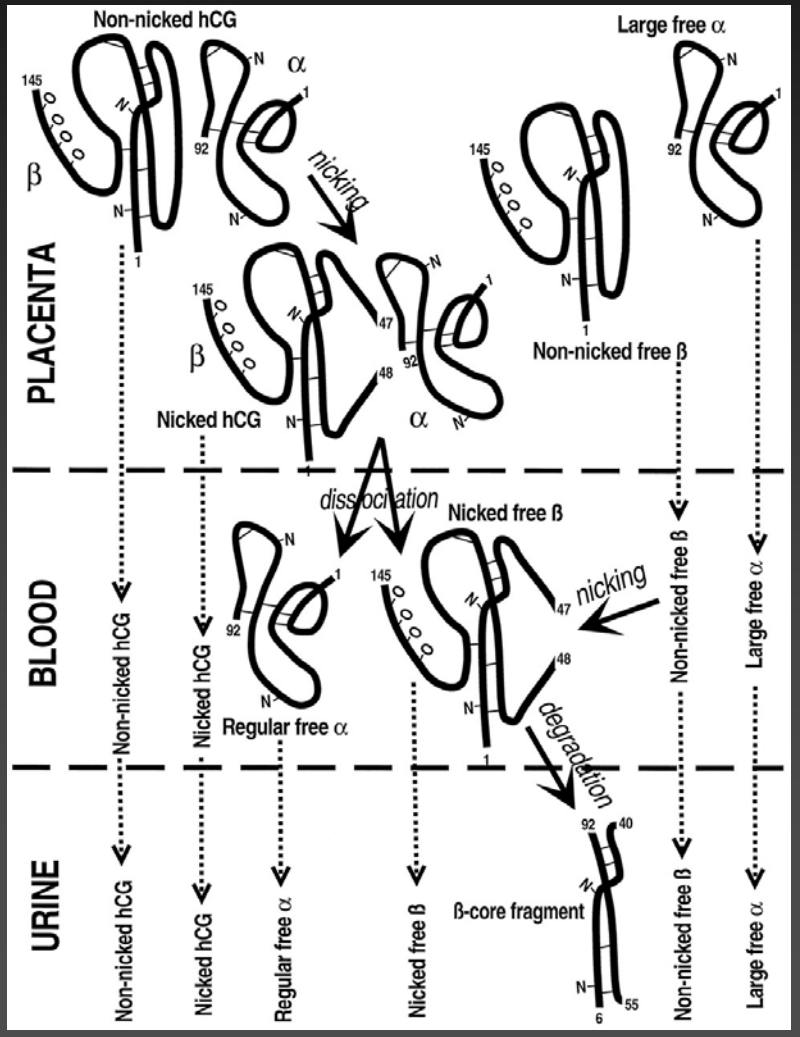
http://www.chem.gla.ac.uk/protein/glyco/hyper/hcg_act.html

Physiology of hCG

- Extends functional life of corpus luteum
- Maintains high progesterone concentrations in early pregnancy
- Thyrotropic at very high concentrations

hCG Heterogeneity

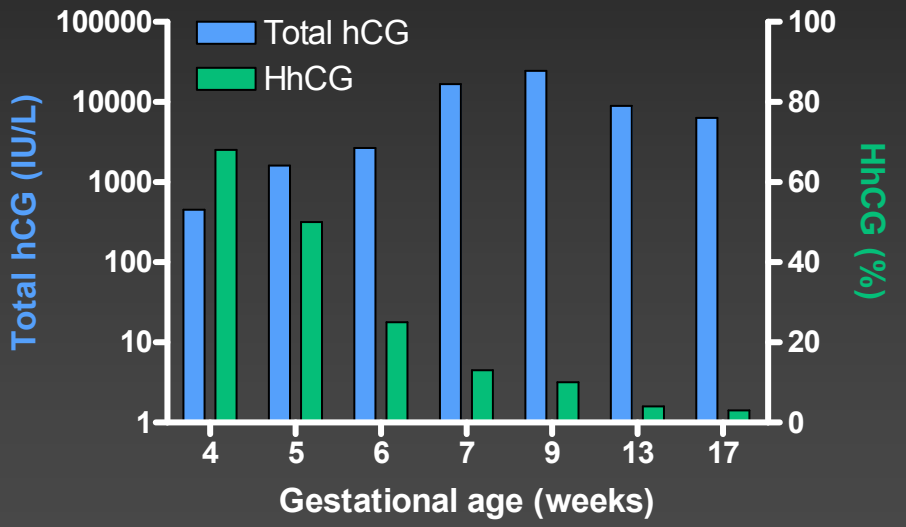
- Numerous molecular forms of hCG present in pregnancy serum
  - Dissociated or degraded molecules with no biological activity
- Key β-containing isoforms
  - Intact hCG
  - Nicked hCG
  - Free β subunit
  - Nicked free β subunit
  - β-core fragment (urine)



Cole, LA. *Clin Chem* 1997;43:2233-2243

Hyperglycosylated hCG (HhCG)

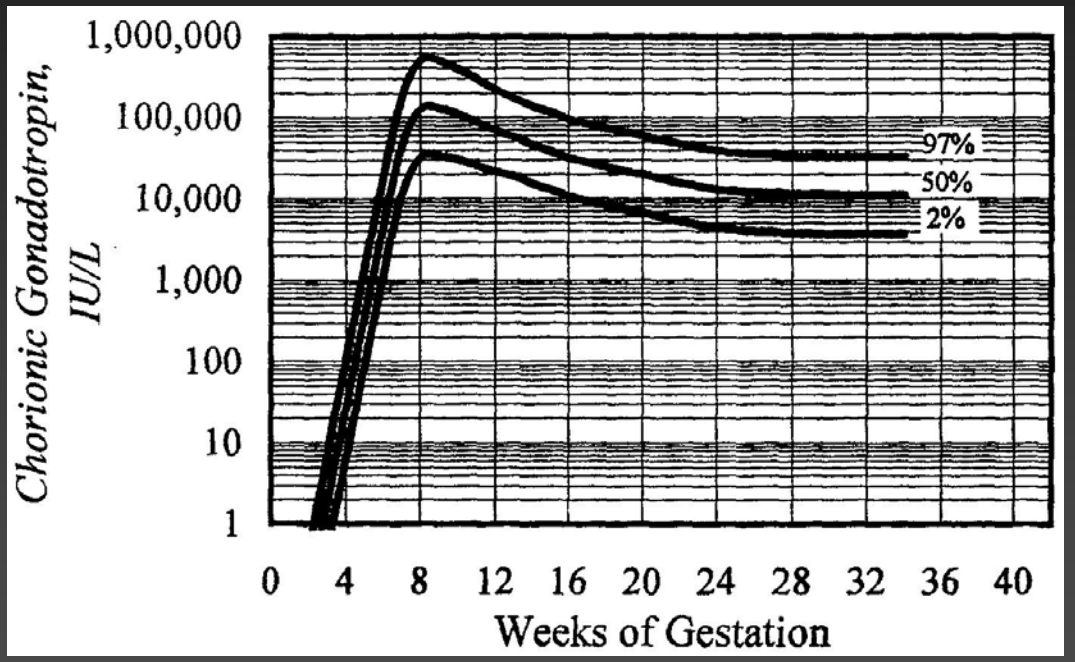
- O-linked carbohydrates on β chain larger than normal
  - 74% vs. 16% hexasaccharides
- Synthesized by invasive cytotrophoblasts
  - Implantation blastocysts
  - Choriocarcinoma
- Principal isoform produced in early gestation



Adapted from Cole, et al. *Clin Biochem* 2003;36:647-655

Intact hCG

- Synthesized by syncytiotrophoblasts
- Serum concentrations increase progressively in early pregnancy
  - Peak at 7 – 9 weeks of gestation
- Decrease until ~24 weeks then plateau



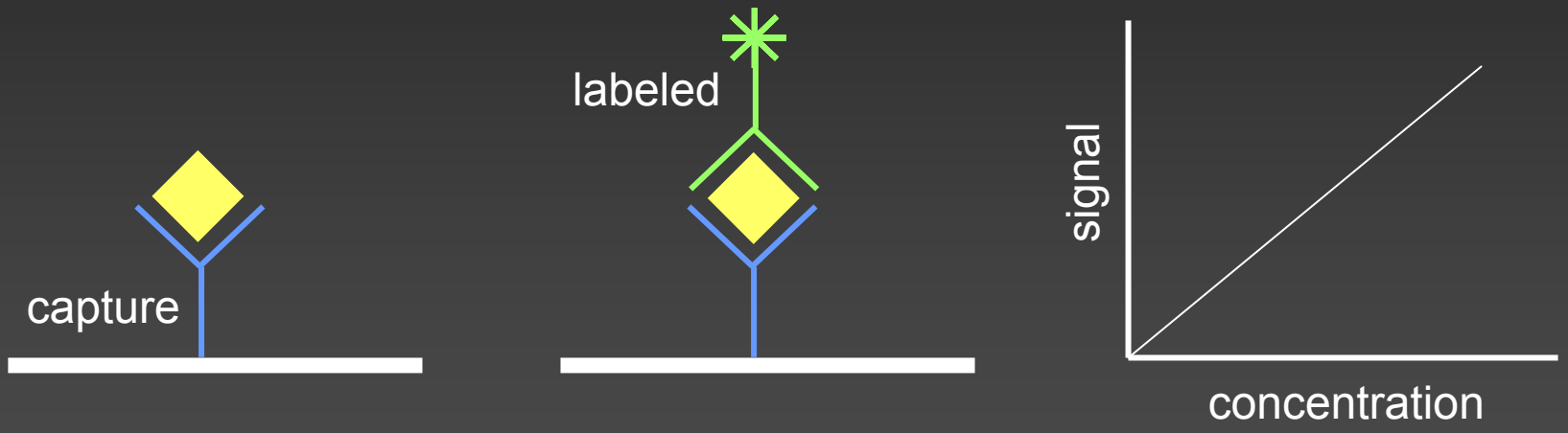
Tietz Textbook of Clinical Chemistry, 3rd ed, 1998

hCG Assays

- All are FDA approved for assessment of pregnancy status only
- Approximately half of all hCG tests performed for this reason
  - 35% for maternal serum screening for Down's syndrome
  - 15% for use as a tumor marker
- Quantitative tests should detect intact hCG *and* free beta subunit

Quantitative Assays

- Immunometric methods designed for use with serum



- Molecular heterogeneity influences assay performance

Assay Antibodies

Table 1. Commonly identified antibody binding sites (epitopes) on hCG, its free subunits, and degradation products.

		Reactivity						
Epitope	Descriptions	Nonnicked hCG	Nicked hCG	hCG-terminal	Nonnicked free β	Nicked free β	β-core fragment	Regular or large free α
Anti-hCG dimer	Site at subunit interface on nonnicked hCG	✓						
Anti-common β1	Mutual site on hCG, free β, and β-core	✓	✓	✓	✓	✓	✓	
Anti-common β2	Separate mutual site on hCG and free β (β-core?)	✓	✓	✓	✓	✓	±[a]	
Anti-β C-terminal	Mutual site on hCG and free β only	✓	✓		✓	✓		
Anti-common α	Mutual site on hCG and free α	✓	✓	✓				
Anti-free β	Free subunit-specific site, hidden on hCG				✓	✓		
Anti-nonnicked free β	Free subunit-specific site, close to nicking site				✓			
Anti-free β + β-core	Mutual site on free β and β-core fragment				✓	✓	✓	
Anti-β-core fragment	β-core fragment-specific site, hidden on free β						✓	
Anti-free α	Free subunit-specific site, hidden on LCG							✓

[a] Some anti-common β antibodies also recognize β-core fragment.

Cole, LA. *Clin Chem* 1997;43:2233-2243

Assay Antibodies

Intact only

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Anti-free β	Free subunit-specific site, hidden on hCG				✓	✓		
Anti-nonnicked free β	Free subunit-specific site, close to nicking site				✓			
Anti-free β + β-core	Mutual site on free β and β-core fragment				✓	✓	✓	
Anti-β-core fragment	β-core fragment-specific site, hidden on free β						✓	
Anti-free α	Free subunit-specific site, hidden on LCG							✓

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Assay Antibodies

Intact + Nicked

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Cole, LA. *Clin Chem* 1997;43:2233-2243

Assay Antibodies

Intact + Nicked + free β

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Anti-free α	Free subunit-specific site, hidden on LCG							✓

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Cole, LA. *Clin Chem* 1997;43:2233-2243

Assay Antibodies

Free β

Table 1. Commonly identified antibody binding sites (epitopes) on hCG, its free subunits, and degradation products.

Epitope	Descriptions	Reactivity						
		Nonnicked hCG	Nicked hCG	hCG-terminal	Nonnicked free β	Nicked free β	β-core fragment	Regular or large free α
Anti-hCG dimer	Site at subunit interface on nonnicked hCG	✓						
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Anti-free β	Free subunit-specific site, hidden on hCG				✓	✓		
Anti-nonnicked free β	Free subunit-specific site, close to nicking site				✓			
Anti-free β + β-core	Mutual site on free β and β-core fragment				✓	✓	✓	
Anti-β-core fragment	β-core fragment-specific site, hidden on free β						✓	
Anti-free α	Free subunit-specific site, hidden on LCG							✓

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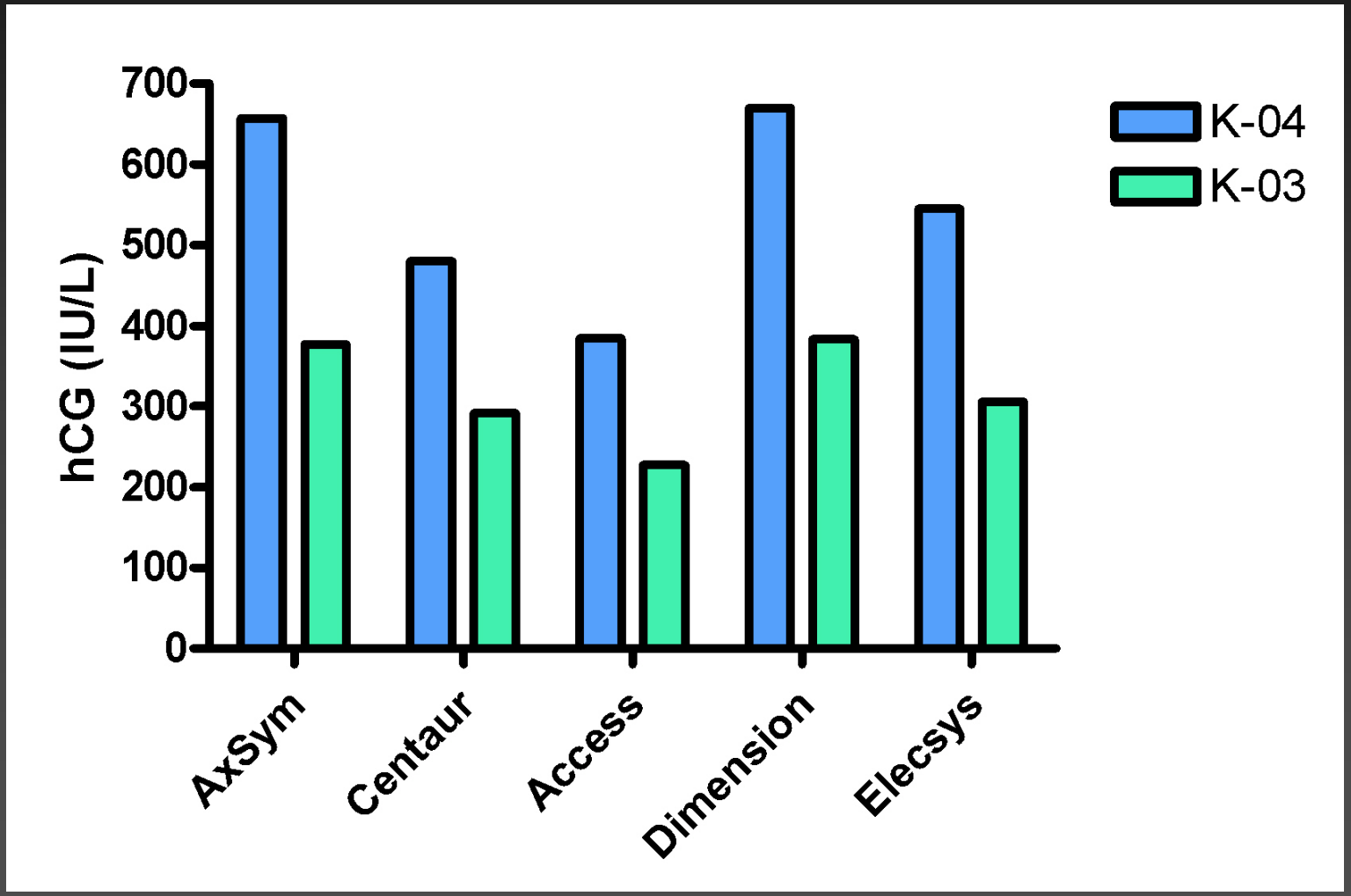
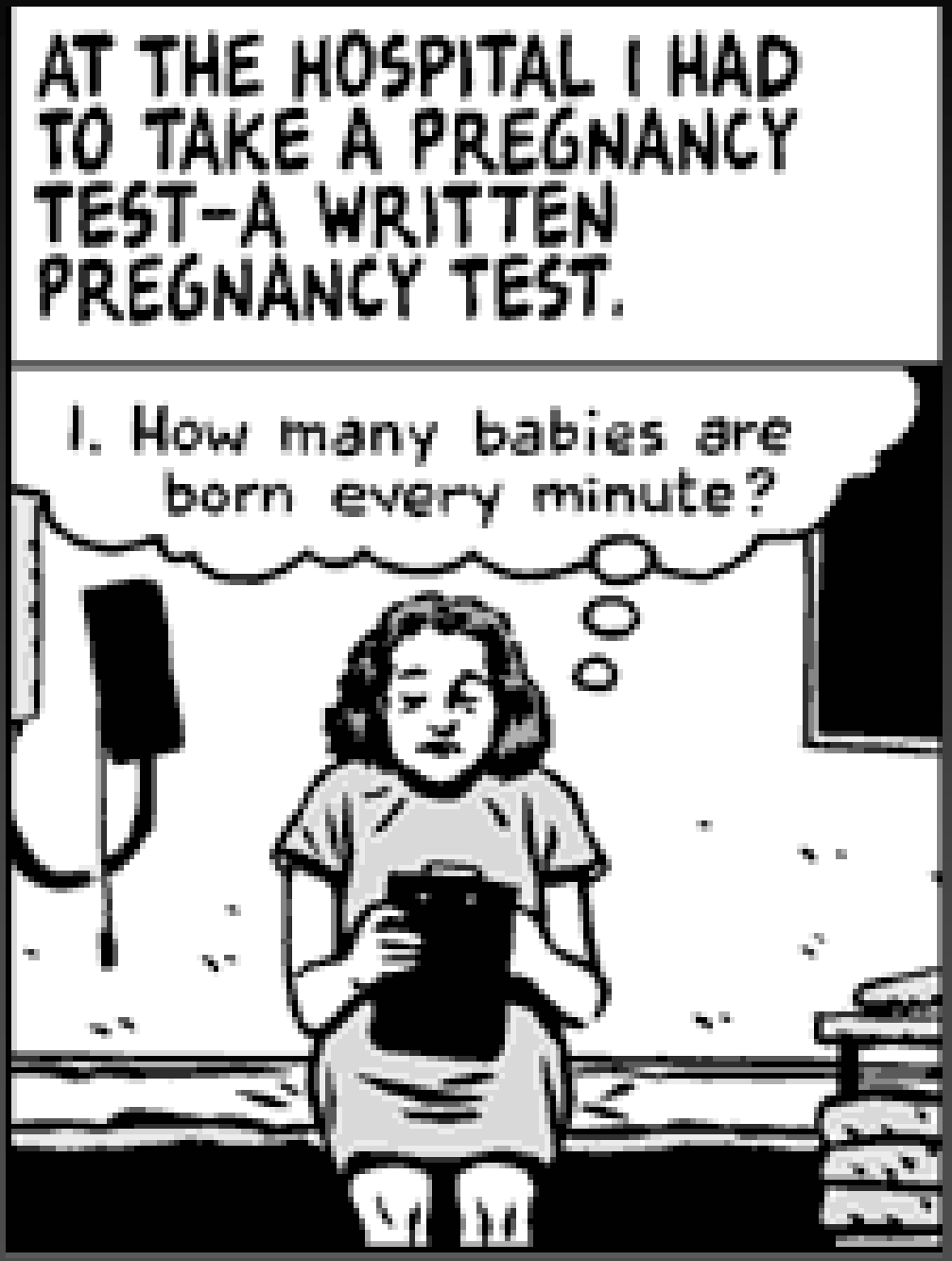
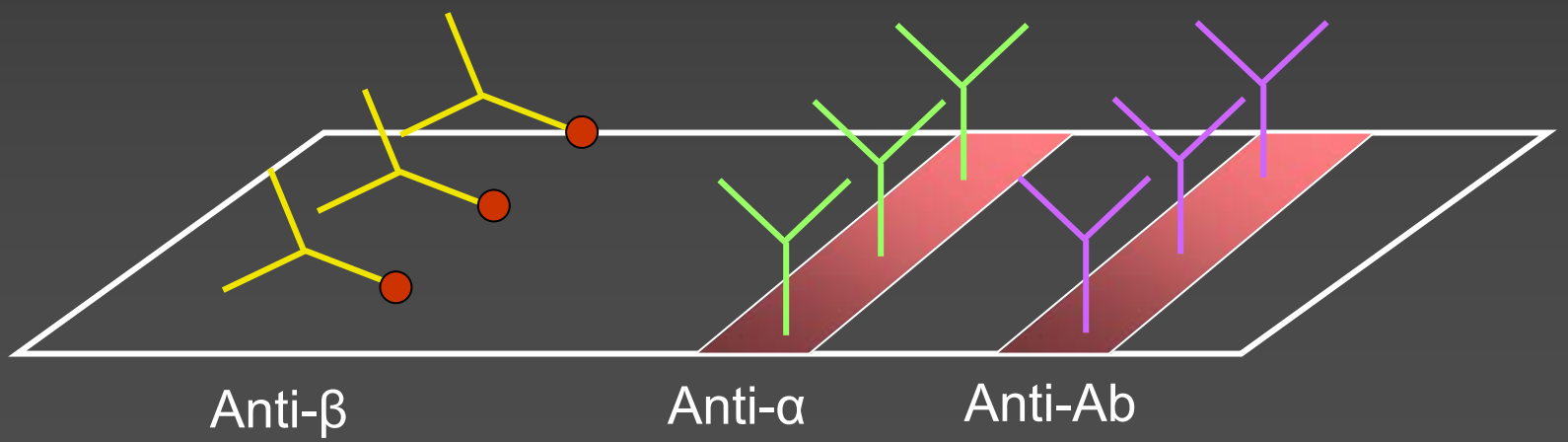
CAP Survey (2005)



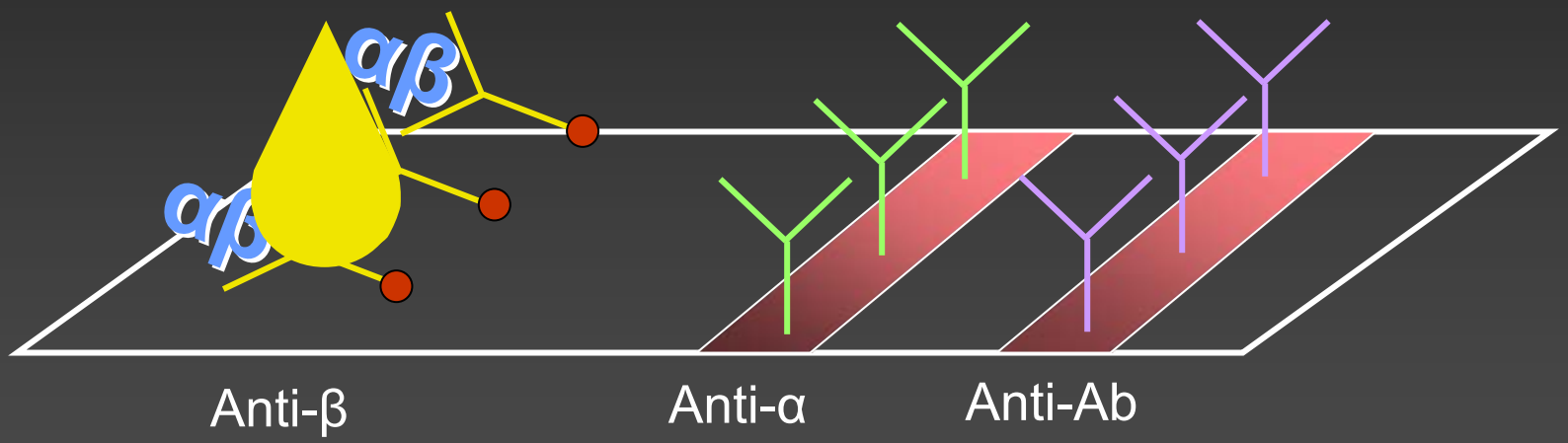

AT THE HOSPITAL I HAD TO TAKE A PREGNANCY TEST-A WRITTEN PREGNANCY TEST.
1. How many babies are born every minute?

Qualitative Assays

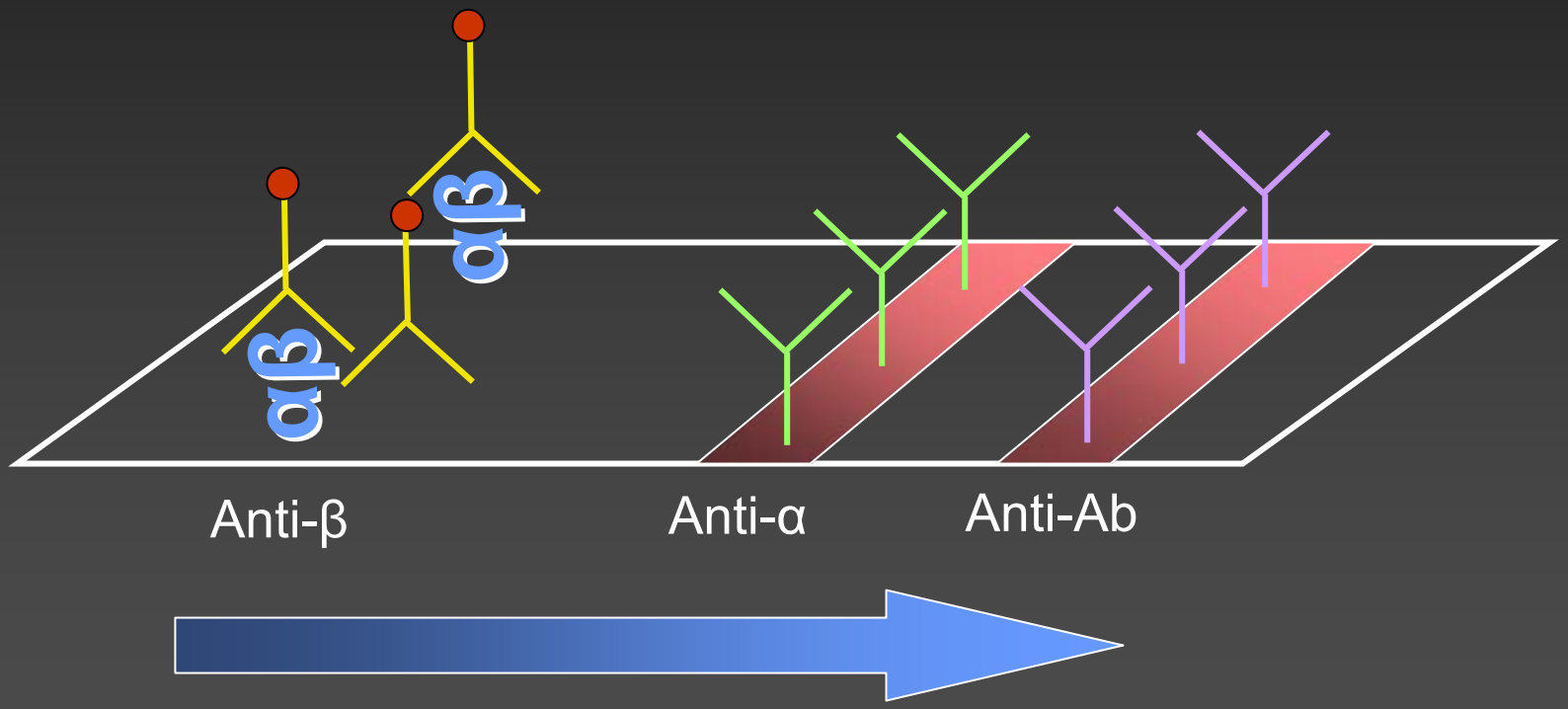
- All can be performed with urine (waived) and some with serum (moderately complex)
- Majority of current tests are immunochromatographic



Qualitative Assays



Qualitative Assays



Variation Among Qualitative Assays

- Used for pregnancy detection so are designed to detect dimeric hCG isoforms
- Some detect additional, unexpected isoforms

Case Report

- 24-year-old female with endometrial adenocarcinoma presents to clinic to begin radiation therapy
- Reports being sexually assaulted 2 weeks prior
- Serum hCG of 56 IU/L so no therapy received
- Follow-up hCG tests
  - 4 weeks later: 45 IU/L
  - 6 weeks later: 60 IU/L
- False-positive hCG?

Case Report

Qualitative Serum and Urine hCG Results From Different Assays*

Device Name (Manufacturer)	Serum	Urine	hCG Detection Limits in Serum/Urine (mIU/mL)†
Sure-Vue (Fisher Healthcare, Houston, TX)	Negative	Positive	10/20
Poly-Stat (Polymedco, Cortlandt Manor, NY)	Negative	Negative	20/20
QuickVue (Quidel, San Diego, CA)	Negative	Positive	25/25
Signify (Genzyme Diagnostics, Cambridge, MA)	Negative	Negative	20/20

hCG, human chorionic gonadotropin.
* Performed on week 10 samples (Table 1).
† To calculate Système International units for serum values (IU/L), multiply by 1.0.

hCG Results From Different Quantitative Assays*

Sample	DPC Immulite	DPC Free beta	Nichols Advantage ITA	Intact hCG Dimer	Nicked hCG	β Core Fragment
Serum	165	155	<5	<5	<5	ND
Urine	683	249	<5	<5	<5	1,360†

hCG, human chorionic gonadotropin; ND, not done.
* Performed on week 10 samples (Table 1). All results are in mIU/mL; to calculate Système International units for serum values (IU/L), multiply by 1.0. DPC Immulite and DPC Free beta from Diagnostic Products, Los Angeles, CA; and the Nichols Advantage ITA, Nichols Institute Diagnostics, San Clemente, CA.
† The β core fragment is detected only partially by the DPC Immulite assay.

Grenache, et al. *AJCP* 2004;121:748-753

Qualitative hCG Device

	Sure-Vue	Clinitest	QuickVue+	Osom	hCG Combo	ICON II	Elecsys (IU/L)
Capture Ab	anti-α	anti-hCG dimer	proprietary	anti-α	anti-α	anti-α	anti-β
Label Ab	anti-hCG dimer	anti-β	anti-β	anti-β	anti-β	anti-β	anti-β
Intact hCG	Pos	Pos	Pos	Pos	Pos	Pos	1220
hCGn	Pos	Pos	Pos	Pos	Pos	Pos	2263
HCGβ	Pos	Pos	Pos	Neg	Pos	Pos	2336
hCGβn	Pos	Pos	Pos	Neg	Pos	Pos	630
hCGβcf	Neg	Pos	Pos (weak)	Neg	Pos	Neg	815
hCGα	Neg	Neg	Neg	Neg	Neg	Neg	<2.0

Sigel, et al. *Clin Chem* 2007;53:989-990

Diagnosing Pregnancy – Home Tests

"More than 99% accurate when used on the day of the expected period"

"Use as early as 4 days before your expected period."

"Test anytime of day. You do not have to use the first morning urine."

Diagnosing Pregnancy – Home Tests

Table. Estimated Day of Implantation of Clinical Pregnancies Relative to the Expected Onset of the Next Menstrual Period

Estimated Day of Implantation Relative to First Day of the Expected Period	Estimated No. of Conceptions Implanting on This Day	Cumulative %
–7 and earlier	55	40
–6	15	51
–5	14	62
–4	9	68
–3	7	74
–2	8	79
–1	8	85
Day of expected period	6	90
+1	1	90
+2	3	93
+3	3	95
+4	2	96
+5	1	97
+6	0	97
+7	0	97
+8	1	98
+9	0	98
+10	1	99
+11 and later	2	100
Total	**136**	

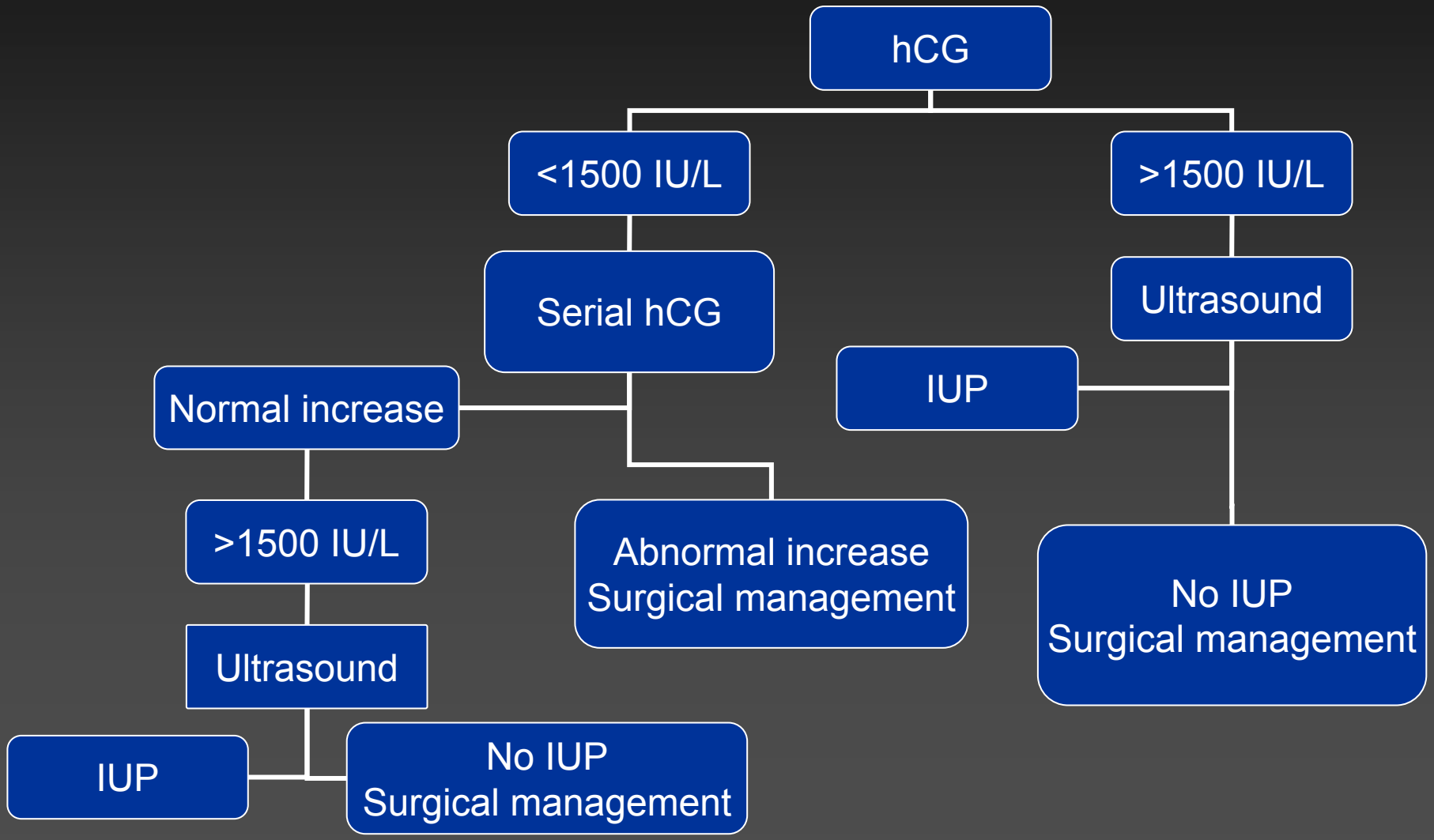
Wilcox, et al., *JAMA* 2001;286:1759-1761

- 221 women planning to conceive kept menstrual diaries and froze daily urine for later analysis (151 pregnancies)
- Quantitative hCG determined by high-sensitive assay (0.13 IU/L detection limit)
  - Onset of pregnancy defined as earliest day of sustained hCG elevation
- 90% of pregnancies occurred by the day of the expected period
  - Detecting 99% of pregnancies required +10 days

Ectopic Pregnancy

- Extrauterine implantation of blastocyst
  - 98% occur in fallopian tube
- Incidence is estimated at 2% of all pregnancies
- Leading cause of maternal mortality in the 1st trimester
  - 1 death per 2000 ectopic pregnancies
- Diagnostic tools
  - Serial hCG (prolonged doubling time, 87% sensitive)
  - Transvaginal ultrasound (90% sensitive)

Ectopic Pregnancy

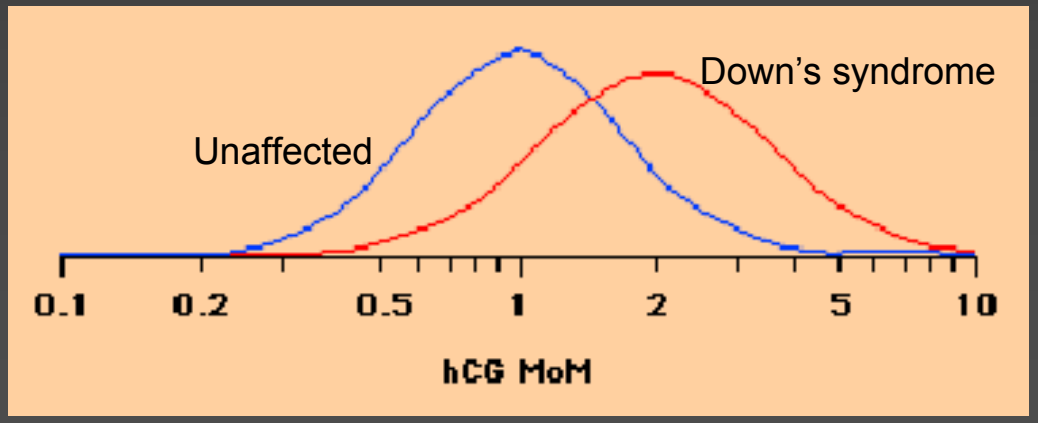


Barnhart, et al. *Obstet Gynecol* 1994;84:1010-1015

Maternal Serum Screening for Down's Syndrome

- 2nd trimester screening (16-18 weeks)
  - Triple screen: hCG, AFP, uE3
  - Quadruple screen: hCG, AFP, uE3, Inhibin A

- 1st trimester screening (11-13 weeks)
  - hCG or free beta subunit, PAPP-A, nuchal translucency (ultrasound)



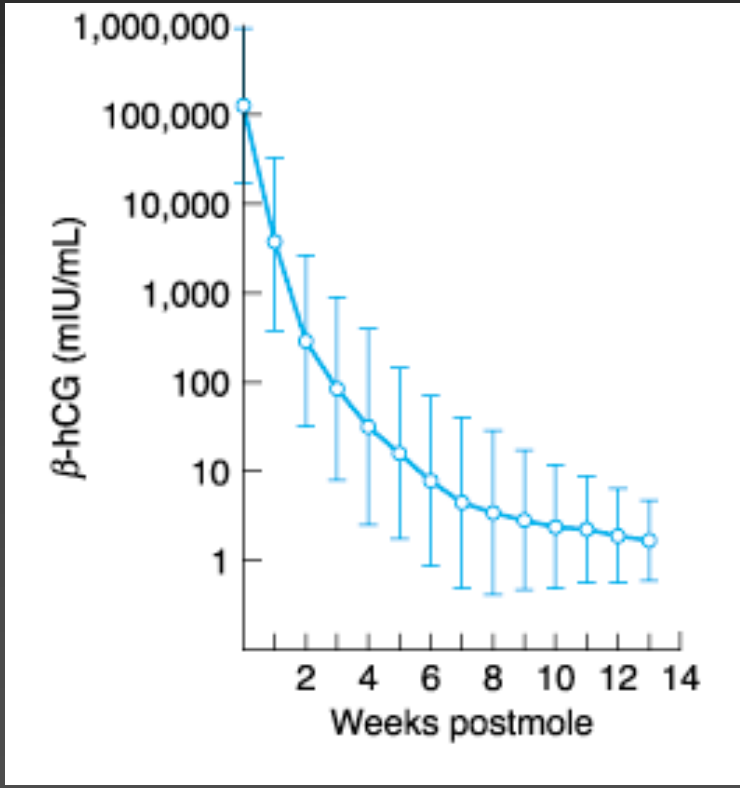
UpToDate, 2007

Gestational Trophoblastic Disease (GTD)

- Heterogeneous group of interrelated lesions derived from an aberrant fertilization event
  - Hydatidiform mole (partial and complete)
  - Persistent/invasive GTD
  - Choriocarcinoma
- All produce hCG and hormone is used in diagnosis and to monitor response to therapy
- Very responsive to chemotherapy and treatment is most often single-agent therapy with methotrexate

hCG in GTD

- Concentrations may exceed 100,000 IU/L
- Assess tumor mass
  - Serum concentration correlates with the number of viable tumor cells
- Monitor therapy
  - Successful treatment leads to progressive decline of hCG, usually within 14 weeks
  - A rise or plateau suggests recurrence or persistence of disease
- Detect recurrence
  - ACOG recommends f/u hCG for 6 months



Schlaerth et al., *Obstet Gynecol* 1981;58:478

Persistent Low hCG

- Low concentrations of hCG that persist for months to years
  - hCG often <50 IU/L
- Uncommon event attributed to
  - False-positives
  - Pituitary hCG

Persistent Low hCG – The Clinical Problem

- hCG tests performed on women prior to interventions that could harm fetus
  - hCG cutoff of <5.0 IU/L used for pregnancy diagnosis
- Standardized protocols result in the use of hCG testing even in women who are unlikely to be pregnant (e.g. menopausal, hysterectomy)
- Positive results create clinical fusion, may delay needed therapies, or result in unnecessary therapy

Jury awards $15.5 million to woman misdiagnosed with cancer. UW and drug company share blame

Seattle Post-Intelligencer

Saturday, June 30, 2001

False-positive hCG

- Patient consulted doctor about irregular bleeding between menstrual periods
  - Positive serum hCG but no apparent intra-uterine pregnancy
- 11 month ordeal to identify cause
- Treatments
  - Laparoscopy for presumed ectopic pregnancy (none)
  - D&C (normal)
  - Chemotherapy, single and multi-agent (no hCG change)
  - Hysterectomy (no hCG change)
  - Surgery for removal of lung nodules found by CT (no disease)
- hCG eventually found to be false-positive due to interfering antibody in patient's serum
- http://www.legalwa.org/ (docket number 99-2-27090-8)

Interfering Antibodies

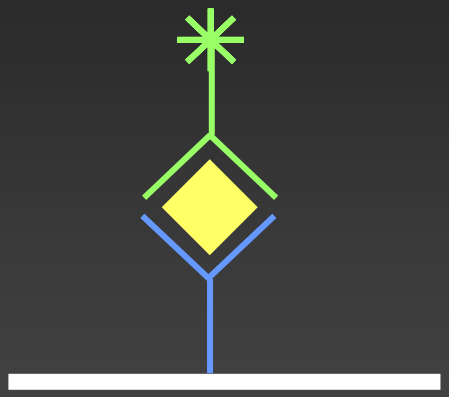
Heterophile antibodies

- Antibodies with broad but weak reactivity for many different antigens
- Naturally occurring and originate from early stages of B-cell immunoglobulin synthesis
- Distinct from antibodies produced against specific animal immunoglobulins

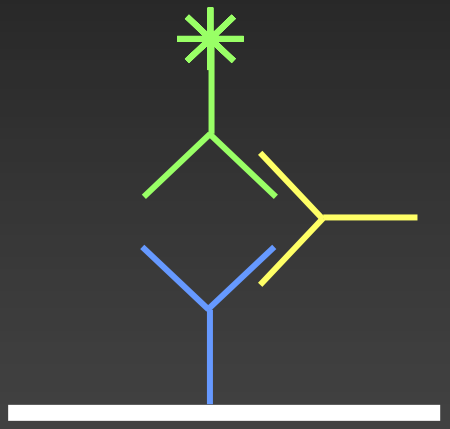
Human anti-animal antibodies (HAAA)

- Produced after exposure to a defined antigen
- Exposure to therapeutic animal immunoglobulin or pharmaceutical agents derived from animal sources
- Immunogen is often unknown and its source remains unclear
- Human anti-mouse antibody (HAMA) is the most common HAAA

Mechanism of Interference - Positive



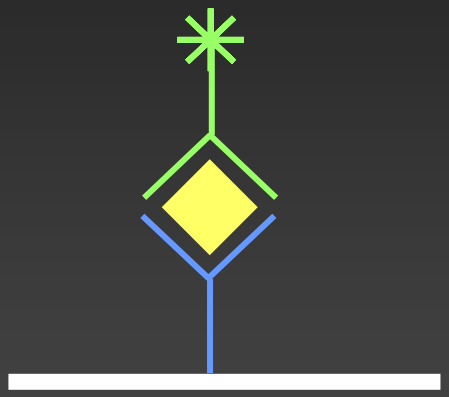
Real hCG present



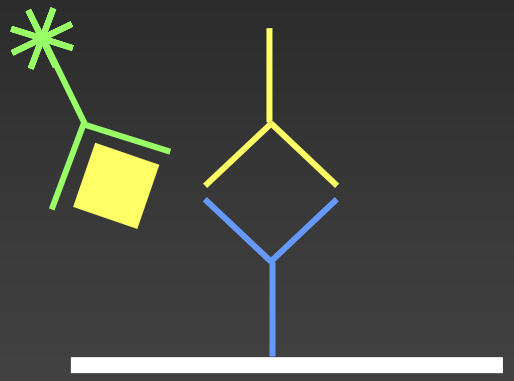
Interfering antibody cross-links reagent antibodies

Falsely increased result

Mechanism of Interference - Negative



Real hCG present



Interfering antibody binds only 1 reagent antibody and prevents binding of hCG

Falsely decreased result

Detection

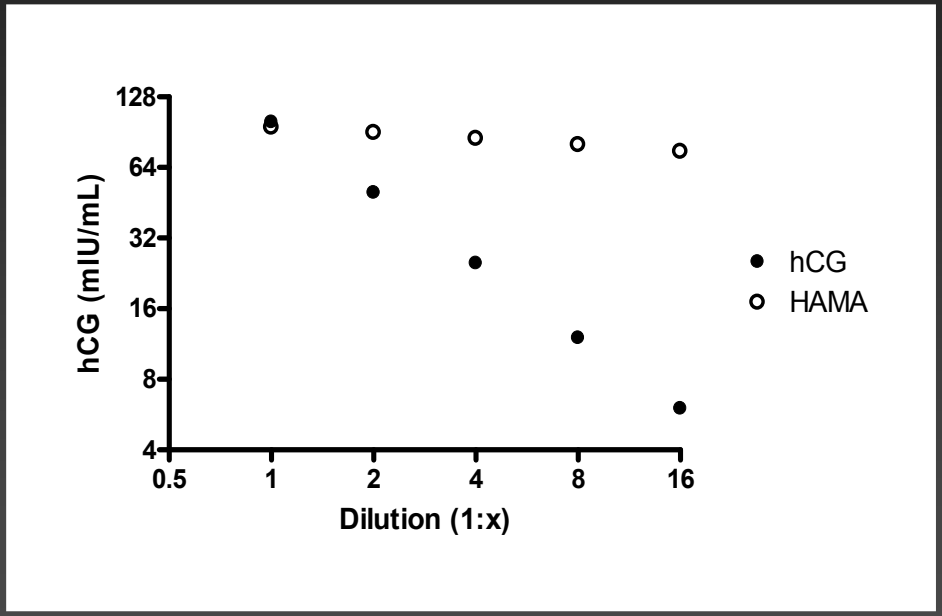
- Suspicion of interfering antibodies should be high when immunoassay results are inconsistent with the clinical scenario
- Lab personnel are frequently unaware of clinical condition of patient
  - Difficult for lab to identify independently
- What to do when asked “could this result be falsely increased?”

Urine hCG

- Real hCG should be detectable in the urine
- Antibodies too large to be filtered by kidney
- Negative urine hCG suggests interfering antibody present

Serial Dilution

- Interfering antibodies are reactive against the assay reagents and not the measured analyte
- Serial dilution of specimen may not produce the expected linear response



Different Assay

- Repeat test using an immunoassay that utilizes antibodies produced from a different animal species

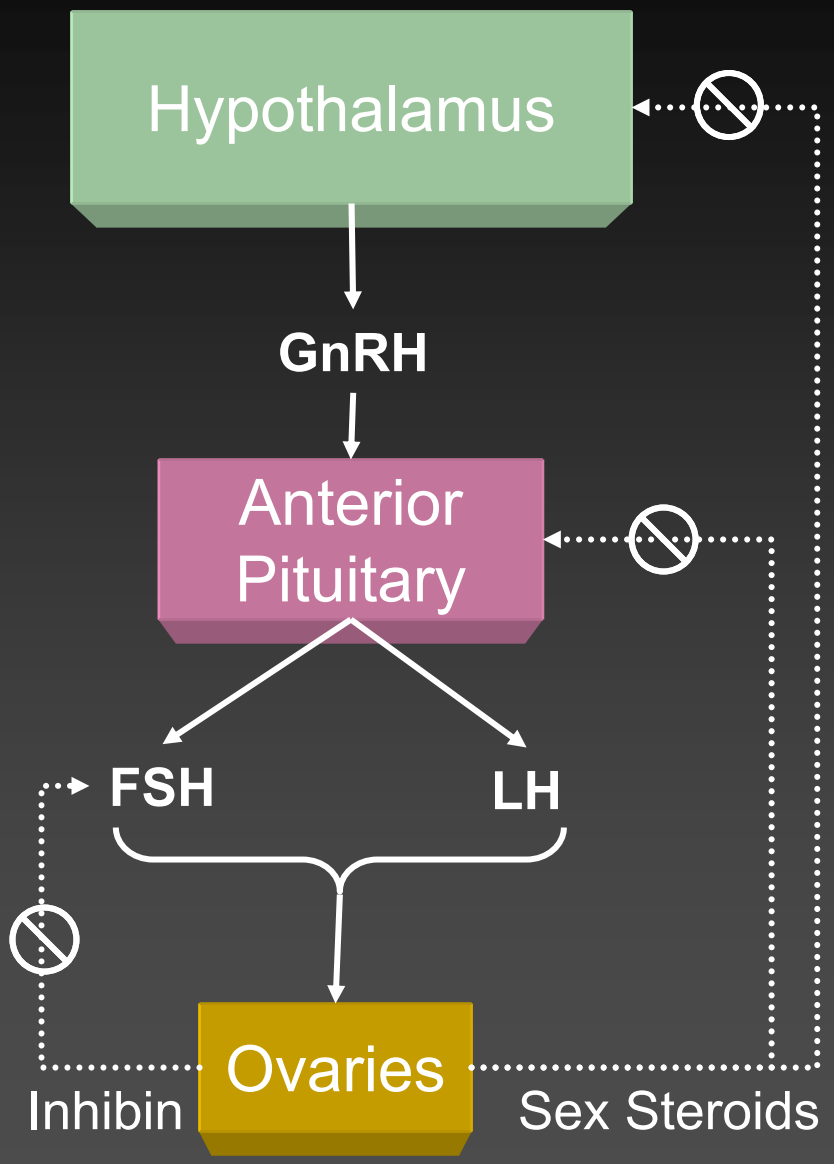
- Not fool-proof as some interfering antibodies are not species-specific
  - May cross react with multiple animal species and interfere with multiple assays

Blocking Agents

- Remove interfering antibody through use of material that binds to it
  - Substantial change in concentration after use suggests interfering antibody present
- Non-immune globulin from the same species of animal used to produce the assay antibodies
- Effectiveness depends on interfering antibody class, specificity, and concentration
- Immunoassay reagents often contain blocking agents

Pituitary hCG

- First reported 30 years ago
- Gonadotrope cells of pituitary gland produce small amounts of hCG



Pituitary hCG

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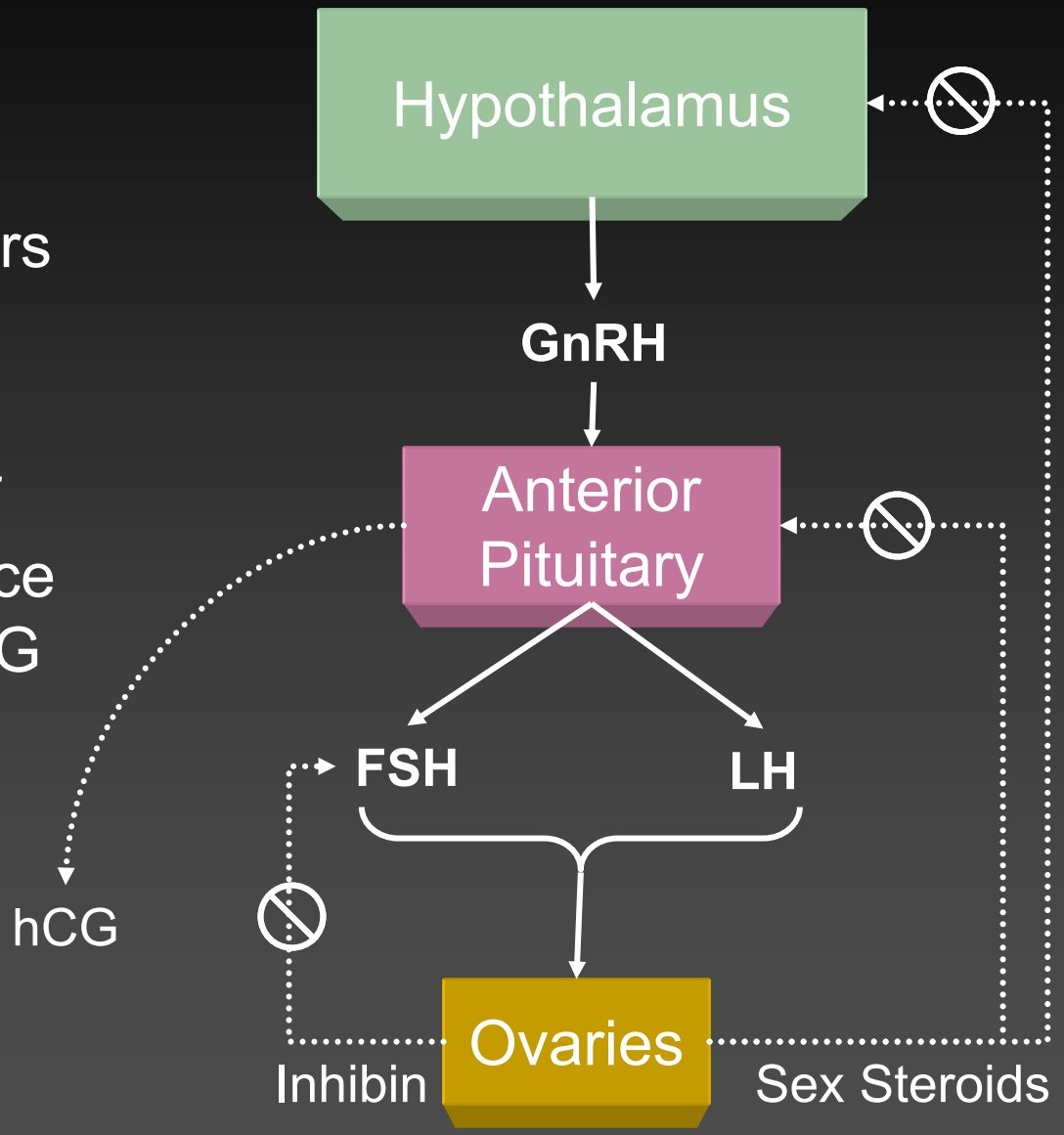


Pituitary hCG – The Clinical Problem

- JP is a 49-year-old female with ESRD secondary to polycystic kidney disease. She has been on peritoneal dialysis for 2 years and is admitted for a deceased-donor renal transplant.

- Pre-transplant screening reveals an hCG of 12 IU/L.

- The renal team calls to ask what this means.

hCG in Aging Women

1. Determine upper hCG limit in peri- and post-menopausal women

2. Evaluate the utility of serum FSH to assist in the interpretation of a positive hCG result

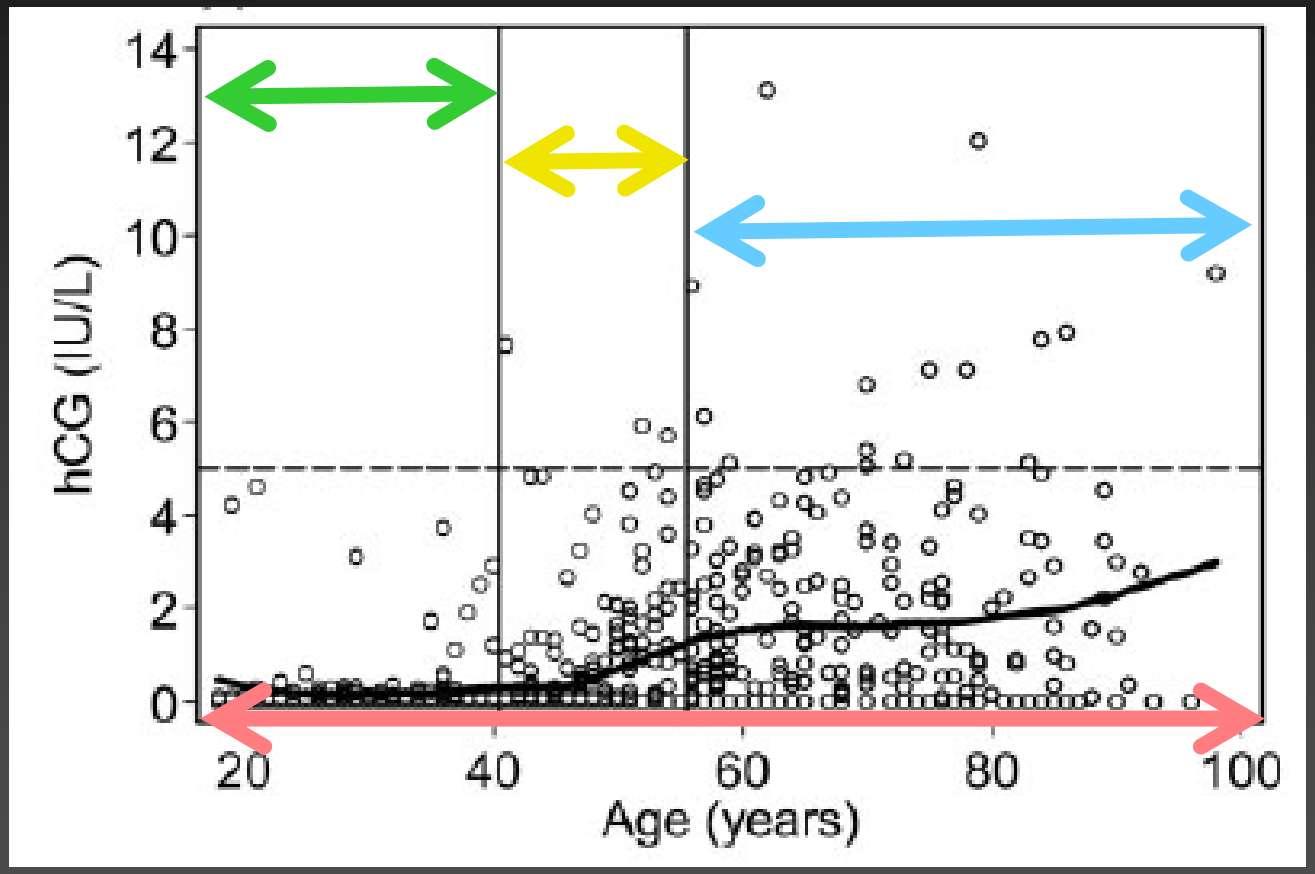
Snyder, et al. *Clin Chem* 2005;51:1830-1835

hCG in Aging Women

- 4 cohorts
  - Pregnant (≥18 y)
  - Non-pregnant, pre-menopausal (18 – 40 y)
  - Non-pregnant, peri-menopausal (41 – 55 y)
  - Non-pregnant, post-menopausal (>55 y)
- No history of trophoblastic disease or ectopic pregnancy
- Menopause status defined by age alone

Snyder, et al. *Clin Chem* 2005;51:1830-1835

hCG is Correlated with Age



r = 0.034, p = 0.60
r = 0.156, p = 0.02
r = 0.038, p = 0.55

r = 0.333, p <0.0001

Snyder, et al. *Clin Chem* 2005;51:1830-1835

hCG Reference Intervals by Age

hCG >5.0 IU/L

Peri-menopausal, N=3

Post-menopausal, N=16

Table 1. hCG concentration ranges and the 97.5 percentile values for the nonpregnant cohorts in the study.

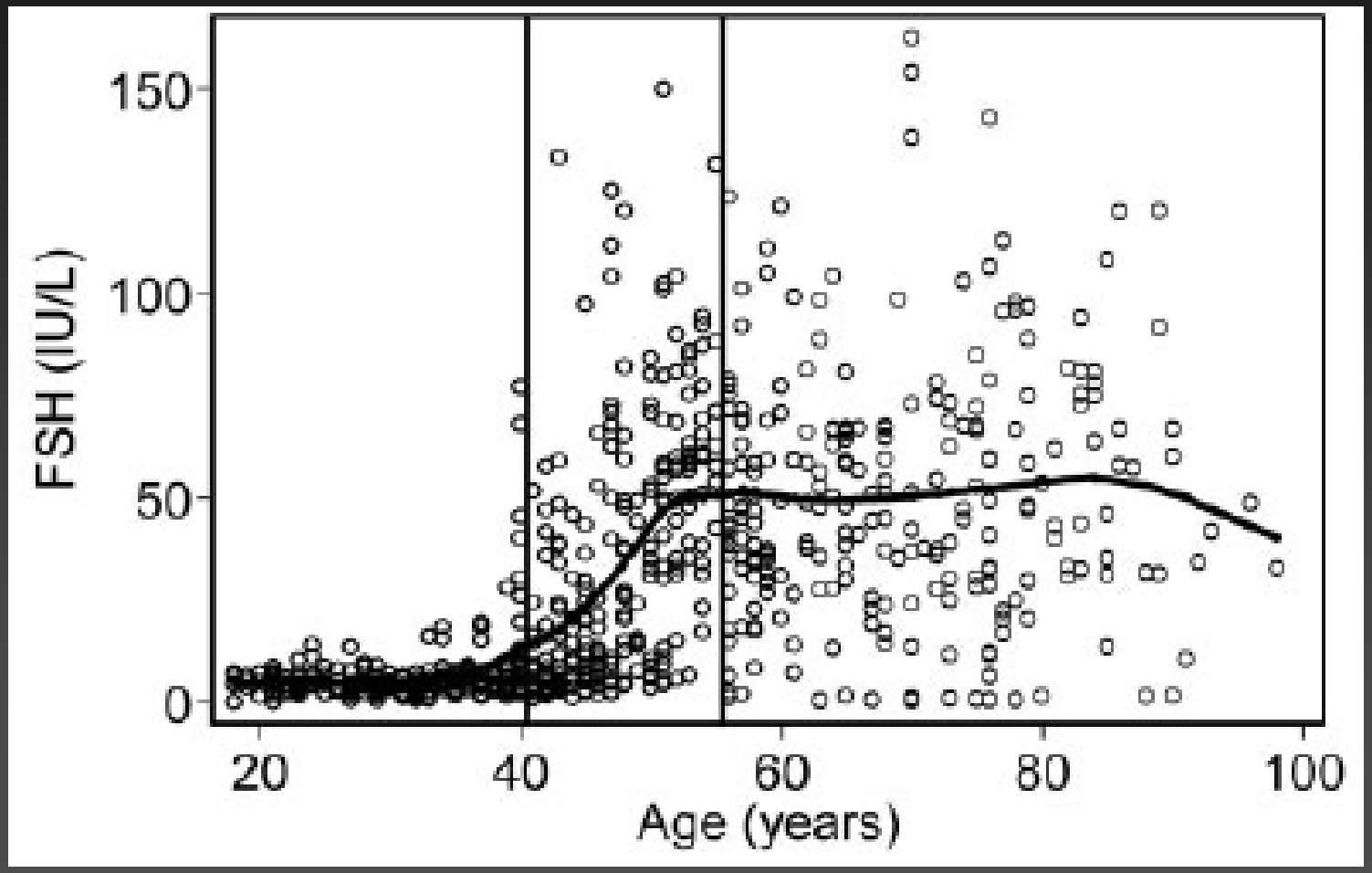
Nonpregnant cohort	n	hCG range, IU/L		97.5 percentile, IU/L	*P*
Premenopausal, 18–40 years	240	<2.0 to 4.6	**5**	2.5	
Perimenopausal, 41–55 years	240	<2.0 to 7.7	**8**	4.8	0.07[a]
Postmenopausal, >55 years	240	<2.0 to 13.1	**14**	7.7	<0.0001[b]

[a] Compared with the nonpregnant premenopausal cohort.

[b] Compared with the nonpregnant premenopausal and nonpregnant perimenopausal cohorts.

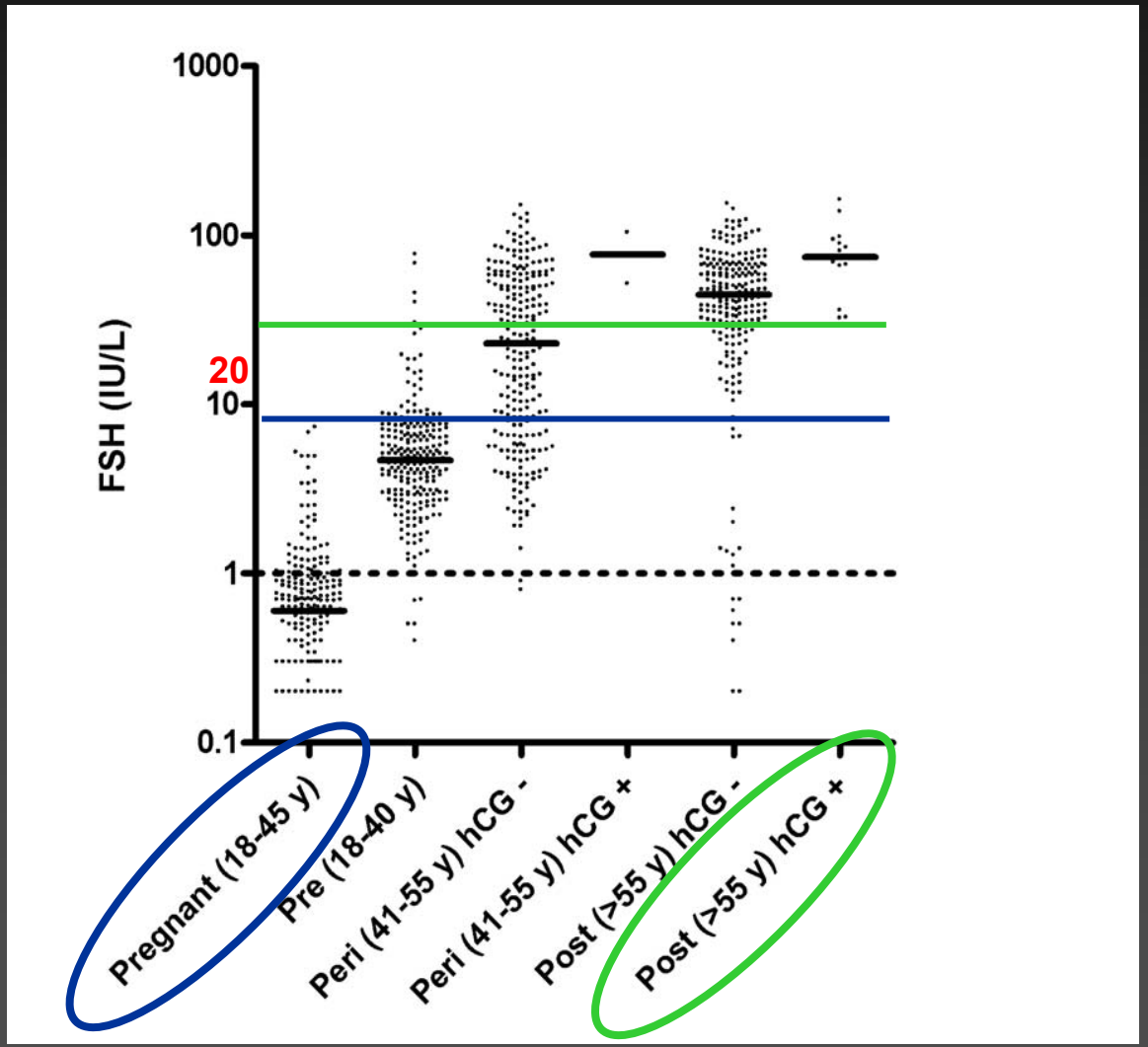
Snyder, et al. *Clin Chem* 2005;51:1830-1835

FSH vs. Age



Snyder, et al. *Clin Chem* 2005;51:1830-1835

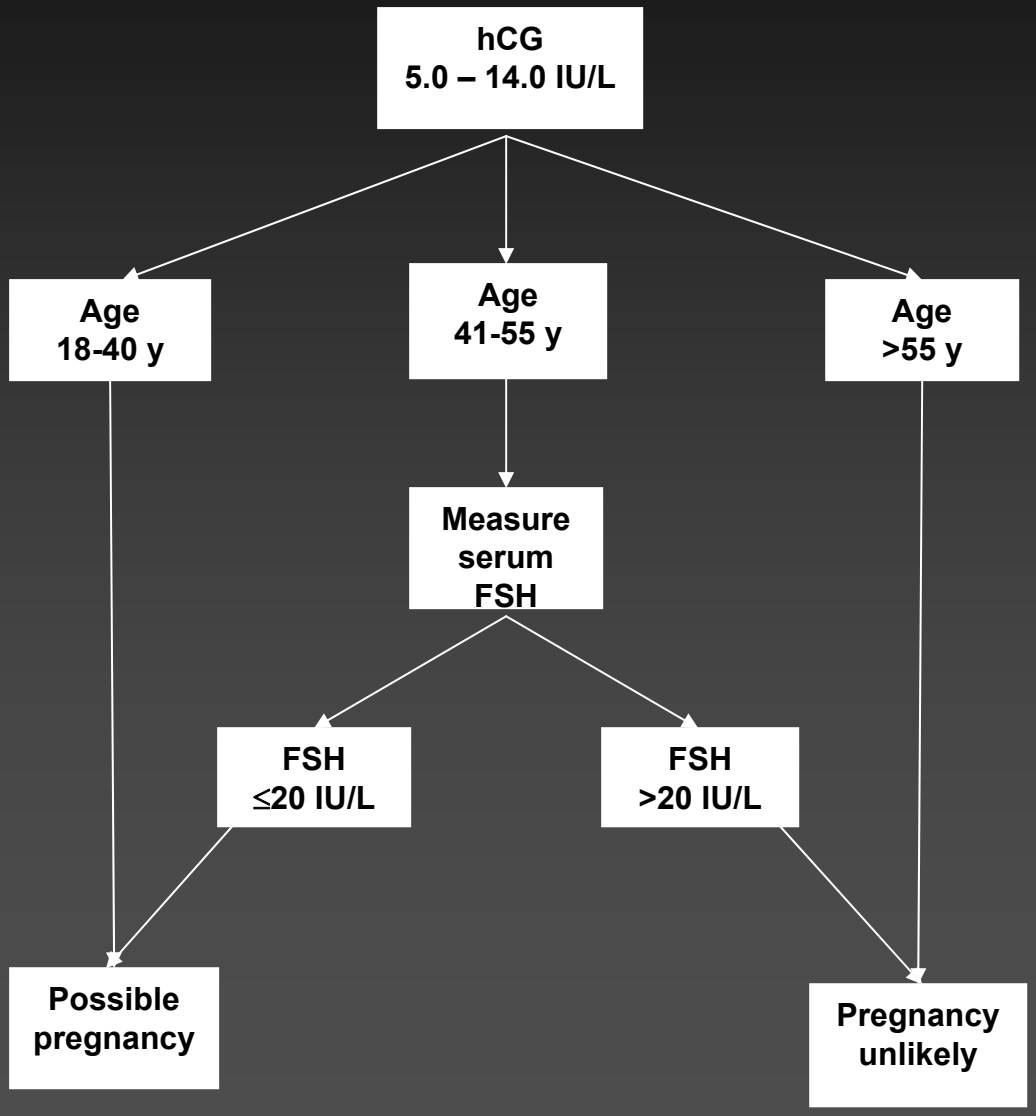
FSH by Cohort & hCG Status



- FSH cutoff of 20 IU/L differentiates hCG of pregnancy from pituitary hCG

Snyder, et al. *Clin Chem* 2005;51:1830-1835

Interpreting Low hCG Results



Study Limitations

- Analytical variation among hCG assays
- Interfering antibodies
- Age as criteria for menopause status
- Estrogen therapy
- 3 peri-menopausal patients with low pos hCG
  - Need to validate FSH of 20 cutoff in peri-menopausal group

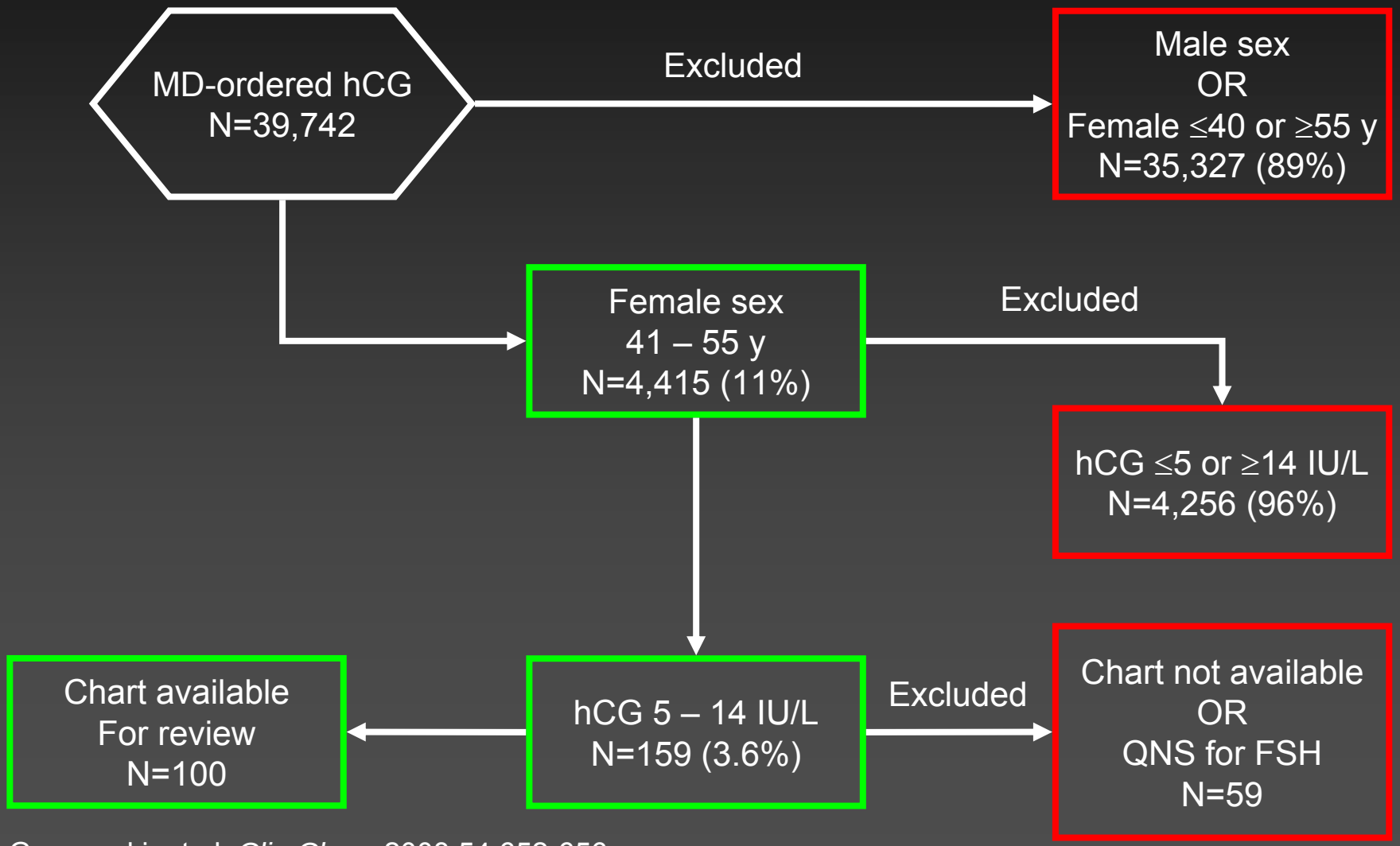
Follow-up Investigation

- Validate the 20 IU/L FSH cutoff for excluding pregnancy in 41-55 yo with hCG 5-14 IU/L

- 100 patients desired
  - Need ~25,000 hCG results
  - 7 medical center laboratories
  - 80% of hCG and FSH assays represented

Gronowski, et al. *Clin Chem* 2008;54:652-656

Inclusion/Exclusion Algorithm



Gronowski, et al. *Clin Chem* 2008;54:652-656

Results

- 77 hCG not of placental origin
- 23 hCG of placental origin
  - 17 resolving abortion/miscarriage
  - 4 GTD
  - 2 early pregnancies

Cutoff	Sensitivity	Specificity
20 IU/L	83%	84%
45 IU/L	100%	76%

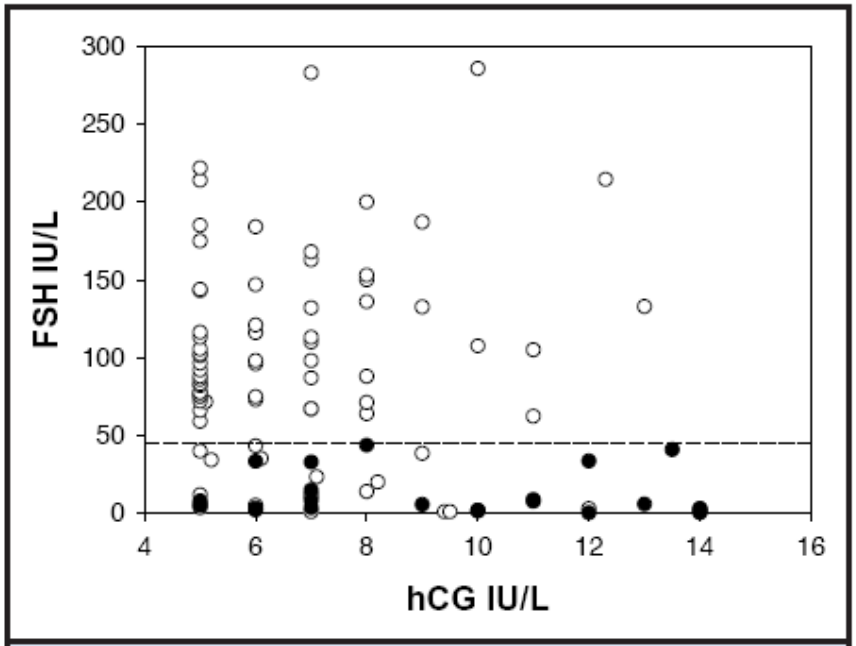


Fig. 2. Scatter plot of hCG vs FSH concentrations.
Open circles represent nonplacental hCG; n = 77. Closed circles represent placental hCG; n = 23. The dashed line represents a FSH cutoff of 45 IU/L.

Gronowski, et al. *Clin Chem* 2008;54:652-656

Summary

- hCG is a heterogeneous molecule that exists as numerous isoforms.
- hCG assays show considerable variability in the isoforms of hCG that they detect.
- There is a biological limit regarding the early detection of urinary hCG in pregnancy.
- Serum hCG is useful in conjunction with ultrasound for the diagnosis of ectopic pregnancy.
- hCG is an essential biomarker in screening for Down's syndrome and as a monitor of GTD.

Summary

- False-positive hCG tests are infrequently encountered but can have significant consequences if not recognized.
- Serum hCG increases with age in non-pregnant women.
- A cutoff of higher than the often used 5 IU/L should be utilized when interpreting hCG results in women >55 years of age.
- Pregnancy is unlikely in peri-menopausal women 41-55 years of age with an hCG between 5.0 and 14.0 IU/L if serum FSH is >45 IU/L.

Case Follow-up

49 yo renal transplant patient with hCG of 12 IU/L

- FSH = 215 IU/L
  - More consistent with menopausal status than pregnancy
- Renal transplant was performed

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