ULTRASOUND AND EARLY PREGNANCY: IS THE DISCRIMINATORY ZONE OBSOLETE?

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CONVENTIONAL WISDOM

“...25% of all pregnancies bleed; and of those 1/2 will proceed and 1/2 will fail, so go home and put your feet up and you have a 50/50 chance”
R/O ECTOPIC

- Every patient who is pregnant with ANY bleeding (and a closed cervical os) is a “R/O ectopic”
TRANSVAGINAL ULTRASOUND HAS CHANGED THINGS TOTALLY
Prior to the vaginal probe, sonography was a tool of the obstetrician. Early equipment had barely enough resolution to localize placenta, find fetal lie and measure BPD.
SONOMICROSCOPY

Vaginal sonography provides a degree of image magnification that is as if we were doing ultrasound through a low power microscope.
EARLY PREGNANCY: A CHANGING PLAYING FIELD
LET’S START WITH…

WHAT IS A PREGNANCY?
In the simplest of terms... when an egg meets a sperm!
Process of conception, implantation, development and birth is a long arduous journey (odyssey)
INFERTILITY

• multitude of reasons why the process never initiates

PREGNANCY FAILURE

• reasons why losses occur after conception prior to the birth process
When and why do pregnancies fail?
What is the prognostic significance of pregnancy failure?
INCIDENCE OF EARLY LOSS OF PREGNANCY

Wilcox et al. *NEJM* 318:189, 1988

- 221 women attempting to conceive
- daily ucg by radioimmunoassay
- 22% of pregnancies detected by assay were lost prior to clinical recognition ("Chemical Pregnancy")
- of these, 35% became *clinically* pregnant the next cycle, 65% *clinically* pregnant by the third cycle, 83% by the sixth cycle, and 95% within 2 years
• THIS IS EXTREMELY IMPORTANT NOW THAT PATIENTS CAN DIAGNOSE A PREGNANCY EVENT WITH OTC (“HOME TESTS”) AT THE TIME OF THE MISSED MENSES (30 mIU/ml hCG)

• BASED ON WILCOX 22% OF THESE CAN BE EXPECTED TO FAIL

• THIS HAS CAUSED AN EPIDEMIC OF PULs (MORE ON THAT LATER)
CHEMICAL PREGNANCY

Previously: Loss occurs prior to clinical recognition

Current: Loss prior to the onset of embryonic period
CHEMICAL PREGNANCIES

REASONS FOR LOSS (SPECULATIVE)

- hormonal (inadequate luteal phase)
- chromosomal (? type and incidence compared to embryonic losses)
- defective implantation
EMBRYONIC LOSSES – CHROMOSOMAL ABNORMALITIES

- 144 spontaneous abortions
- direct prep of villi
- 69.4% had abnormal chromosomes, of which…
  - autosomal trisomy (64%)
  - polyploidy (9%)
  - monosomy x (7%)
  - structural rearrangements (6%)
CHROMOSOMAL PREGNANCY FAILURE: (70% of embryonic losses)

- errors of gonadogenesis during meiosis (autosomal trisomies)
- errors of fertilization (triploidy form dispermy)
- errors of the first division of zygote (tetraploidy, mosaicism)
- would not be expected to be repetitive (except in very rare instances of balanced translocations or inversions in one parent)
NON CHROMOSOMAL PREGNANCY FAILURE (30% OF LOSSES)

- uterine abnormalities  
  (septa, myomas, incompetent cervix)
- luteal phase defects (?) 
- autoimmune factors  
  (antiphospholipid syndrome, thrombophelias?)
- infectious agents: T strain mycoplasmas
- alcohol
- smoking
- molecular genetic abnormalities with NORMAL karyotypes
PREGNANCY FAILURE: Can ultrasound findings predict those cases with abnormal karyotypes

Karyotyping of a failed pregnancy that produces abnormal chromosomes
  - allows for no further workup at that time
  - gives the parents a definitive diagnosis

Karyotyping of a failed pregnancy that produces normal chromosomes
  - can result in work up of the various other causes without first having to have a subsequent loss.
MATERIALS AND METHODS

- 102 patients
- Sonographic evidence of early pregnancy failure
- Elective dilatation & curettage
- Products of conception sent for karyotyping
RESULTS

58 had NORMAL KARYOTYPES (57%) of which
  52 were 46XX
  6 were 46XY

AVG Age 36.8 years
AVG Gestational Age 9.1 weeks by dates
RESULTS

44 had ABNORMAL KARYOTYPES (43%): these were:

- 33 trisomies (75%) including 24 autosomal trisomies, 4 double trisomies, 1 triple trisomy, 3 mosaics and 1 translocation

- 11 (25%) included 4 triploidy, 1 tetraploidy, 2 monosomy X, 4 others (isochromosome, unbalanced complement etc.)
An abnormal yolk sac (> 6mm and/or abnormal morphology) was a non specific sign present in 17.2% of normal karyotypes and 18.2% of abnormal karyotypes.
EMBRYONIC TRENDS IN ABNORMAL KARYOTYPES

Trisomy 22: 3/4 developed embryos with cardiac activity (11mm, 11mm, 18mm)

Mosaic Trisomies: 3/3 developed embryos with cardiac activity (9mm, 19mm, 16mm)

Monsomy x: 2/2 developed embryos with cardiac activity (14mm, 24mm)
EMBRYONIC TRENDS IN ABNORMAL KARYOTYPES

Trisomy 16: 6/8 developed no embryonic structure, largest embryo 4mm, no cardiac activity

Multiple trisomies: 4/5 developed no embryonic structure

Isolated Variants: 4/4 developed no embryonic structure
CONCLUSIONS

Expertise in separation of villi with attached chorion from decidua will reduce the incidence of maternal contamination (46XX) which results from merely submitting “products of conception” for karyotyping.
NEW INSIGHTS: WHERE DID THEY COME FROM?

- assisted reproductive technologies
- high resolution endovaginal ultrasound
- ability to detect minute levels of hCG
- PULs: gap between biochemical detection and sonographic confirmation
hCG

- Produced by trophoblastic tissue
- Detectable 8 days post conception
- Erroneously still referred to as “Beta Sub Unit” or simply “Beta” to distinguish it from alpha subunit shared with TSH and other molecules
- Current tests however measure INTACT hCG molecule
hCG LEVELS

- OTC Home pregnancy tests turn “positive” at 30 mIU/ml (time of missed menses)
- hCG normally rises a MINIMUM of 53-66% every 48 hours (often doubles every 48 hours)
- 15-20% of ectopics follow NORMAL doubling times of hCG (ones that usually end up with an embryo +/- heartbeat)
- Pregnancy seen on TV U/S by hCG >1000mIU (modern “discriminatory” zone)
RATE OF RISE OF hCG IN ULTIMATELY VIABLE PREGNANCY
"GRAND DADDY" STUDY

- MINIMUM rate of rise = 66% in 48 hrs (was dictum for many years)
- Based on 20 patients !!!
- TA U/S !!!
- Represents 85% confidence limit
MORE UPDATED APPROACH...

53% MINIMUM rate of rise in 48 hours...
• HOWEVER LET’S TAKE A CLOSER LOOK AT THAT NUMBER…
Based on 287 patients with pain or bleeding and initial non diagnostic ultrasound who ultimately were viable IUGs
RATE OF RISE OF hCG

Barnhart, et al  Obstet Gynecol 2004;104:50

- AVERAGE increase at 48 hours = 2.24 fold (more than double)
- MINIMUM increase at 48 hours = 1.53 (53% increase) (99% confidence interval)
- GREATEST increase at 48 hours = 3.28 fold (more than triple)
Remember these were “symptomatic” patients that ultimately proved normal. May not be applicable to asymptomatic patients who present early.
Also a subnormal rate of rise does not diagnose an ectopic pregnancy. It will diagnose a non normal gestation but says nothing about location.
DISCRIMINATORY vs. THRESHOLD LEVEL

- Threshold level is the EARLIEST you sometimes see something (e.g. gestational sac, yolk sac, cardiac activity)
- Discriminatory level is the point at which a structure MUST be visualized if it is normal
ORIGINAL DISCRIMINATORY ZONE OF hCG
(Kadar, Romero, et al.)

- 6500 mIU/ml
- Transabdominal ultrasound (only used real time equipment to identify heart motion)
- Early 1980’s
- Of 383 patients clinically suspected to have an ectopic, hCG > 6500 mIU/ml had 100% sensitivity and 96% specificity with a prevalence for ectopic of 18%
FURTHER EVIDENCE AGAINST THE RELIABILITY OF hCG

Doubilet and Benson, JUM, 2011

- Reviewed 10 years of scans at Brigham and Women's
- There were 9 scans with hGC >2000 mIU/ml that initially only had a fluid collection but ultimately were “viable”, with five resulting in live singleton births and one a twin birth (the other 3 miscarried)
They concluded “The hCG discriminatory level should not be used to determine the management of a hemodynamically stable patient with suspected ectopic pregnancy, if sonography demonstrates no findings of an intrauterine gestation or an ectopic pregnancy”
• NOT SURE I AGREE TOTALLY
● They had no mention of what their denominator was (i.e., how many women were scanned).

● Nor did they mention how many ectopics were picked up and treated whose initial scan was “No IUG” but hCG > 2,000.

● As radiologists I think they underestimate the potential morbidity and even mortality associated with ruptured ectopic.
- I would agree that there are many potential shortcomings from a SINGLE hCG determination and its corresponding ultrasound.
- We pointed this out 24 years ago!
235 patients requesting termination
hCG measured when gestational sac < 1.0cm or was not seen
Conclusions
1) All normal gestations had sac visualized when sac > 4mm
2) All normal pregnancies had a sac visualized when hCG was >1025 mIU/ml. (If the uterus was normal and had homogenous echo pattern)
3) 3 cases with coexisting fibroids or an IUD had hCG > 1025 and no sac seen (ONE AT 5544 MIU
● POTENTIAL PROBLEMS WITH OVER RELIANCE ON “DISCRIMINATORY ZONE” OF hCG

● SITUATIONS WHERE hCG MIGHT BE >1,000 mIU/ml and IUG NOT SEEN BUT STILL BE “NORMAL”
DISCRIMINATORY LEVEL OF hCG POSSIBLY A “MOVING TARGET”

● With the vaginal probe approx. 1000 -2000 mIU/ml BUT…

● Depends on issues like: equipment, frequency, magnification, coexisting myomas, marked obesity, axial uterus and most dangerous, multiple gestations!!!
SERIAL DETERMINATIONS OF hCG

- If hCG is less than a discriminatory level it should be repeated when it is expected to have surpassed that level (approx 1000 mIU/ml)

- The EM, while lacking a gestational sac, should at least have an appearance COMPATIBLE with an early normal pregnancy, (lush, homogenous, decidualized/secretory in appearance)
ENDOMETRIAL ECHO ("Lose the word stripe") THICKNESS AND PREGNANCY OUTCOME


- 576 patients presenting to ER without definitive IUG on TV U/S
- EM thickness and ultimate outcome
- Average EM thickness in ectopic 9.6 ± 4.9mm
- Average EM thickness in viable IUGs 12.1 ± 6.0mm
- Average EM thickness in spontaneous Abs 10.2 ± 6.1mm
- Take home message: In patients with bleeding EM thickness is not a reliable predictor of outcome BUT EM < 6mm is rarely compatible with ongoing viable IUG.
GESTATIONAL SAC

- sonographic not anatomic term
- first definitive sign of pregnancy
- echogenic rind around a sonolucent center
- recognized by its appearance, not its location
WHEN SHOULD YOU SEE A GESTATIONAL SAC?

- Usually by 5 weeks LMP (3 weeks post conception)
- Should not usually go by dates...often notoriously unreliable
- hCG levels...Concept of a Discriminatory level vs. Threshold level
YOLK SAC

- Not appreciated originally by TA U/S
- First structure visualized within the gestational sac
- Round, bright rim
- < 6mm
- When enlarged (“hydropic”), solid or duplicated, it is a very poor prognostic sign
WHEN SHOULD YOU SEE A YOLK SAC?

- Threshold Level
WHEN SHOULD YOU ABSOLUTELY SEE A YOLK SAC? (DISCRIMINATORY LEVEL)

- TA U/S (Nyberg): MSD = 20mm
- TV U/S (Filly): MSD 13mm
- TV U/S (Bree, 1989): MSD = 8mm
WHEN SHOULD YOU ABSOLUTELY SEE A YOLK SAC?

- Rowlins et al, 1999
  MSD = 13 mm (5 MHz transducer)
  MSD = 5 mm (9-5 MHz transducer)

The sac size at which a yolk sac is DEFINITIVELY seen will depend on frequency, as well as other potential factors.
WHY IS THIS IMPORTANT?

- DOES A YOLK SAC NEED TO BE PRESENT TO MAKE A DEFINITIVE DX OF AN IUG?
- NO UNANIMITY…DIFFERENCES BETWEEN EUROPE/UK AND USA
WHAT ABOUT CARDIAC ACTIVITY?
CARDIAC ACTIVITY:
THRESHOLD LEVEL

- Realize that any pregnancy whose outcome is ultimately normal had cardiac activity present in the early embryo prior to our ability to image it.
CARDIAC ACTIVITY

Abaid LN, J Reprod Med 2007;52:375

- Retrospective analysis, 179 gestations
- 8-MHz vaginal transducer
- Embryo > 3.1 mm (with or without bleeding) and no discernable cardiac activity was 100% predictive of embryonic demise
• BUT MORE RECENTLY NEW DATA AND THEN NEW GUIDELINES CAME OUT OF BRITAIN, WHERE THEY HAVE SPECIALIZED “EARLY PREGNANCY UNITS”
REVISED “Green Top Guidelines” of ROYAL COLLEGE OF OBGYN

- Issued October 19th, 2011
- In response to an article by Abdallah, et al. in the White Journal
- Raised the threshold for diagnosing “miscarriage”
  - To a MSD > 25mm with no obvious yolk sac (was > 20mm)
  - To a CRL > 7mm without evidence of cardiac activity (was ≥ 6mm)
BUT MORE ON THESE NEW BRITISH GUIDELINES IN THE NEXT TALK...
HEART RATE

- (Benson and Doubilet, 1994)…40 patients <8 weeks gestation
- Embryonic heart rate < 90 resulted in 80% death in 1st trimester, when HR between 70-79 = 91% died (n=11), HR < 70 = 100% death (n=7)
- BE CAUTIOUS! Shenker et al, 1986 showed PRIOR to 7 weeks before maturing of the SA node HR often less than 70 bpm!
WHEN ARE SERIAL hCG DETERMINATIONS APPROPRIATE

- For R/O ectopic pregnancy...utilizing hCG and discriminatory zone
- Once ectopic pregnancy is excluded, embryonic well being depends on serial U/S examinations NOT serial hCG determinations!
ONCE ECTOPIC RULED OUT

UTILIZE...

- EMBRYO GROWS 1MM/DAY
- GESTATIONAL SAC GROWS 1MM/DAY
PUL: A RISING EPIDEMIC
PREGNANCY OF
UNKNOWN LOCATION
● The patient who presents to us with biochemical evidence of a pregnancy event will fall into one of three categories:
PATIENTS WHO ARE PREGNANT...

- **Definitive** IUG
- **Definitive** Ectopic
- Everything else (PULs)
  - quantitative hCG (often serial
  - discriminatory zone
  - villi vs. decidua
NORMAL IUG
DEFINITIVE IUG THAT MAY NOT BE NORMAL
PATIENTS WHO ARE PREGNANT...

- **Definitive** IUG
- **Definitive** Ectopic
- Everything else (PULs)
  - quantitative hCG (often serial
  - discriminatory zone
  - villi vs. decidua
PATIENTS WHO ARE PREGNANT…

- **Definitive** IUG
- **Definitive** Ectopic
- Everything else in the middle (PULs):
  - quantitative hCG (often serial
  - discriminatory zone
EARLY PREGNANCY OF UNKNOWN LOCATION (PUL)

- It is this “everything else in the middle” category that is on the rise because of the widening gap between biochemical detection (hCG = 30-50 mIU/ml) and the ability to see a sac on TV U/S (discriminatory level around 1000 mIU/ml).
+hCG and no IUG on U/S....

- What does this potentially represent?
  - Early IUG too early to visualize
  - Failed IUG without definitive sonographic confirmation
  - Ectopic pregnancy (which may or may not be “thriving”)
WHAT IF THE hCG > DISCRIMINATORY LEVEL AND THERE IS “NO IUG” ON U/S?

- Original approach: D&C to look for villi vs. decidua (villi proves an IUG)
- This approach was also advocated in the original description of methotrexate for medical management of ectopic
WHAT IF THE hCG > DISCRIMINATORY LEVEL AND THERE IS “NO IUG” ON U/S?

- BE CAREFUL: use of Mtx after a SINGLE seemingly elevated hCG with no IUG common source of lawsuits IF it turns out to be an IUG that was unappreciated (poorly performed scan, multiple gestation, coexisting fibroids, axial uterus…)


METHOTREXATE

- Folic acid antagonist inhibits DNA synthesis and cell reproduction primarily in actively proliferating tissue like malignant cells, trophoblast, and fetal cells.
- Widely used in cancer, psoriasis, rheumatoid arthritis, and most recently ectopic pregnancy.
- Increase in non-surgical Rx. makes tracking hospital admissions for incidence obsolete.
METHOTREXATE
(ACOG Practice Bulletin Number 3, 1998)

- Unruptured mass < 3.5 cm greatest dimension
- No cardiac activity present
- Patients whose hCG level does not exceed a predetermined value (6,000-15,000 mIU/ml)
- Patient able to return for f/u care
- No contraindications to Mtx
METHOTREXATE

- remember…works on trophoblast
- Quality and health of the trophoblastic tissue will be a more important determinant of success not just absolute size or hCG level
- For instance…
  - U/S mass >3.5cm that is mostly blood, clot and fibrin i.e. hematosalpinx will do better than a normal looking sac of 2.0 cm with a yolk sac!
  - hCG of 2000 that was 1800 48 hours ago will do better than an hCG of 1500 that was 750 48 hours ago
METHOTREXATE
(ACOG Practice Bulletin Number 94, 2008)

- No longer gives a LEVEL of hCG nor a SIZE of the mass as a criteria
- Check serum creatinine, LFTs, and R/O any blood dysrasias PRIOR to administration
- Expect a 15% drop in hCG levels from Day 4-day 7; If not additional Mtx or surgical intervention
- “not unusual ... to experience abd pain 2-3 days after administration presumably from the cytotoxic effect causing tubal abortion”
TREATMENT OF NON NORMAL GESTATIONS OF UNKNOWN LOCATION
IS A D&C ALWAYS NECESSARY?
EXAMPLE #1

- 38 Days LMP, staining, positive home test
- U/S shows homogenous decidualized EM, NO IUG
- hCG 740 mIU/ml
- 48 hours later hCG 210 mIU/ml
- Dx: Failed Pregnancy, uncertain location
- Plan: Expectant Management
DECLINE OF hCG IN SPONTANEOUS ABORTIONS IN PUL’S


- 710 patients with PUL’s that ultimately resolved spontaneously (hCG <5 mIU/ml)
- Retrospective review of database
  - Rates of decline ranged from 21% to 35% at 2 days
  - Rates of decline ranged from 60%-84% at 7 days
  - Declines LESS than this likely represent ongoing trophoblast but not necessarily ectopic pregnancy
  - Most rapid decline in those with higher initial level
DOES EVERY SPONTANEOUS ABORTION NEED hCG FOLLOWED UNTIL IT IS NEGATIVE?

- Condos et al (BJOG, 2005, 112:827-9) studied 152 women diagnosed with completed Ab using TV U/S.
- Regardless of how much bleeding occurred by history, 6% with apparent complete miscarriage ultimately proved to have ectopics.
- They concluded “A dx of complete miscarriage based on hx and scan findings alone is unreliable. These women should be managed with serum hCG follow up”
EXAMPLE #2

- 38 days LMP, staining positive home test
- U/S shows homogenous EM, No IUG
- hCG 740 mIU/ml
- 48 hours later hCG 815 mIU/ml (10% increase), 48 hours still later 906 mIU/ml (another 10% increase)
- Dx: Non Normal pregnancy, undetermined location, hCG rising i.e. some viable trophoblast
- Plan: D&C OR Single shot Methotrexate???
• AS LONG AS WE ARE TALKING ABOUT PREGNANCIES AND THEIR LOCATION...
FINAL PEARL...
What we recognize with ultrasound will depend on how *NORMALLY* a pregnancy is developing - not *WHERE* it is located.
IN SUMMARY

- What constitutes a pregnancy
- What early pregnancy looks like and why it looks that way
- Pregnancy failure, its recognition, and reasons for it
IN SUMMARY

- Biochemical detection of hCG at 30-50 mIU/ml
- TV U/S detection at approx 1000 nIU/ml
- PULs increasing issue with gap between biochemical and TV U/S detection
IN SUMMARY

- Consistent definitions of what IS a PUL and the ultimate OUTCOME will improve our ability to study and understand this new entity.
- Until then management issues regarding D&C vs. empiric Methotrexate in such cases are still unresolved.