EARLY PREGNANCY: WHEN YOU SEE IT, WHEN YOU DON’T

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WHEN YOU DON’T SEE IT…

There is a widening GAP between biochemical detection of a pregnancy (30-50mIU/ml hCG) and sonographic confirmation (what is an appropriate “discriminatory zone?”)
THIS HAS LED TO AN NEW ENTITY….PUL (PREGNANCY OF UNKNOWN LOCATION)

SO IF A PUL IS A +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”)

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

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

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 V I A B L E 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...

RATE OF RISE OF hCG

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 DISCRIMINATORY LEVEL
Doubilet and Benson, JUM, 2011

- Reviewed 10 years of scans at Brigham and Womens
- 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)
FURTHER EVIDENCE AGAINST THE RELIABILITY OF hCG DISCRIMINATORY LEVEL
Doubilet and Benson, JUM, 2011

- 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!

**VERY EARLY PREGNANCY DETECTION WITH ENDOVAGINAL ULTRASOUND**

GOLDSTEIN, ET AL. Obstet Gynecol 1988;72:200

- 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.
SO WHAT CONSTITUTES A DEFINITIVE INTRAUTERINE PREGNANCY?
(COROLLARY: BEST WAY TO EXCLUDE ECTOPIC IS TO PROVE AN INTRAUTERINE)

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?

- 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)
Most clinical trials (especially RCTs) are well designed, tightly controlled, performed by better trained clinicians often with State-of-the-art equipment.

VS.

Practice in the field by well meaning health care providers without the same level of quality control, equipment, or expertise but still expected to duplicate the data from the trials used to create guidelines.
IMPORTANT PREMISE

- Huge difference between calling a definitive pregnancy failed and getting follow-up scans if there is still any chance if ectopic pregnancy.

- Clearly no one wants even a single wanted pregnancy to be interrupted by overzealous diagnosis of pregnancy failure.

- “Give early pregnancy the benefit of the doubt. Once ectopic pregnancy has been excluded follow-up scan depends on the fact that the G.S. grows ≈ 1mm/day and the embryo grows ≈ 1mm/day.”
I wrote that slide 26 years ago and I believe it is still the cornerstone of management.

The multicenter observational study from the Imperial Group (Abdallah, et al.) is a landmark paper which is the basis for the UK revised Green Top Guidelines guidelines.

I have never been comfortable with MSD. The sac seems to me to be compressible, affected by focal myometrial contractions, interobserver variations, and just not as reproducible as embryonic size.
• Thus, in Abdallah, et al. Although 100% of the time by MSD of 21mm with or without y.s. failed pregnancy was accurately diagnosed...

...coupled with the reality that in the field the quality of scans cannot consistently match the research...

...makes liberalizing the “cut off” to MSD of ≥25mm “on the basis of a single measurement” as is stated in the article a very reasonable approach.
HOWEVER

- Just as we may be concerned about misdiagnosis of intrauterine failed pregnancy in the hands of clinicians in the community...

- I am concerned about misdiagnosis of ectopic when there is a fluid collection that is mistaken for a G.S.

International Consensus Panel: Assessing Early Pregnancy Failure
NEJM 10/2013

Stringent Criteria of Failed Pregnancy
- CRL $\geq$ 7 mm with NO cardiac activity
- MSD $\geq$ 25 mm with NO embryo.
- Absence of embryo with cardiac activity $\geq$ 2 weeks after a scan that showed a gest sac WITHOUT a y.s.
- Absence of embryo with cardiac activity $\geq$ 11 days after a scan that showed a gestational sac WITH a y.s.
SO WHY DO PREGNANCIES FAIL AFTER THEY REACH THE EMBRYONIC STAGE?

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, thrombophilies?)
- infectious agents: T strain mycoplasmas
- alcohol
- smoking
- molecular genetic abnormalities with NORMAL karyotypes

PREGNANCY FAILURE: Can ultrasound findings predict those cases with abnormal karyotypes


THESIS

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 monsomy 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.

SO IN THINKING ABOUT EARLY PREGNANCY...

- 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)

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

- EVEN ACOG GOT IT WRONG FOR 10 YEARS!!!
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 >3.5 cm 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
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)
- 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 \textit{NORMALLY} a pregnancy is developing - not \textit{WHERE} it is located.

\begin{itemize}
\item What constitutes a pregnancy
\item What early pregnancy looks like and why it looks that way
  \begin{itemize}
  \item Pregnancy failure, its recognition, and reasons for it
  \end{itemize}
\end{itemize}

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\item Biochemical detection of hCG at 30-50 mIU/ml
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IN SUMMARY

- Management issues regarding D&C vs. empiric Methotrexate in such cases are still unresolved