2\textsuperscript{nd} trimester Ultrasound markers and Down’s Syndrome

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John Langdon Down 1828 – 1896
1st to describe features of Down’s syndrome

Some examples relating to ultrasound markers

• “The face is flat and broad...

• The nose is small

• The skin is deficient in elasticity, giving the appearance of being too large for the body...”
2\textsuperscript{nd} trimester Ultrasound Markers

Definition
Anatomic finding
• not an abnormality
• present in a minority of normal fetuses
• Their presence gives a statistically increased risk for aneuploidy

What should we call them?
• Ultrasound sonographic marker?
• Ultrasound “soft” marker?
• Ultrasound Normal Variant?
History of ultrasound markers

• First reported from mid 1980s

Examples

– Nuchal fold /thickening (Benacerraf, 1985)
– Femur / humerus lengths (Benacerraf; Lockwood 1987)
– Pyelectesis (Benacerraf, 1990)
– Hyper echogenic bowel (Nyberg, 1990)
– Echogenic intracardiac focus, (Roberts & Genest, 1992)
– Absent nasal bone ossification (Cicero, 2001)

Plenty of others e.g. wide iliac angle, choroid plexus cysts, colour echocardiography
Nuchal Fold (NF)

- 40 – 50% of 2nd trimester Down’s fetuses have NF ≥ 6mm FPR 0.1%
- Highly specific marker (Benecerraf, 1992)
- Small observer variability (1%)
Mild pyelectasis (renal pelvic dilatation) and Down’s syndrome

Definition

• Anterior-posterior diameter of renal pelvis ≥ 4mm (or 5, 6, 7?) in Transverse section

• Present in 17-25% of Down’s fetuses, and 2-3% of normal controls (Benacerraf, 1990)

• Minor marker
Fetal hyperechogenic bowel

Definition
• Fetal bowel at least as echogenic as bone

• Present in 3 – 27% of Down’s fetuses and <1% normal controls

• Subjective finding

• Note - risk for cystic fibrosis, cytomegalovirus, growth restriction
Echogenic intracardiac focus (EIF)

Definition

• Micro-calcification of papillary muscle – must be as bright as bone
• Present in 18% of Down’s fetuses and 4.7% of normal fetuses
• Not an efficient marker
Hypoplastic / Absent Nasal Bone (NB) Ossification – the newest marker

- Absent NB ossification – first described (Cicero 2001) in 1\textsuperscript{st} trimester (73\% DS fetuses, 0.1\% normal fetuses)
- 2\textsuperscript{nd} trimester
  - 30-40\% DR for v low FPR
- Hypoplastic NB
  - 70\% DR, 5\% FPR
- Ethnicity important
  - 8.8\% Afro-carribean fetuses
  - 0.5\% Caucasian fetuses
Should all soft markers continue to be reported?

• In 1998 Boyd et al reported 6 years experience in an unselected population

“ultrasound soft markers were responsible for a 4% increase in detection of malformations (from 51% to 55%) and a 12 fold increase in false positive rate (1 in 2332 to 1 in 188)”
Implementing the use of markers – scoring systems / genetic sonogram

• Challenge of how to interpret presence / absence of markers, in particular whether to refine the risk given after a 1st or 2nd trimester screening test

• i.e. Should the prior risk for Down’s syndrome be modified?

• Different countries – different solutions
### Likelihood ratios for fetal Down’s using isolated markers

(Benacerraf 2010)

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One example – simulation study
Genetic sonogram after 1st trimester screening (Krantz et al, 2007)

• 1st trimester combined screening
  – 88.5% DR 4.2% FPR
• Applying Likelihood ratios > 1st trimester screening
  – Detection rate raised to 94.5% 5.4% FPR

• Is it worth it?
• Does it do more “harm” than good?
UK policy

• UK NSC reviewed evidence on role of minor markers to modify prior DS screening risks.

• Concluded that, with exception of nuchal thickening, minor markers should not be used to modify a prior DS screening risk, either by increasing the risk in the presence of a marker or decreasing it if the scan is normal.
FaSTER Trial (First and Second Trimester Estimation of risk)

(Aagard-Tillery et al, 2009)

• Showed that the genetic sonogram can provide benefit to patients who have had 1\textsuperscript{st} trimester screening
  – e.g. DR increased from 81% to 90% with the combined test

• BUT scan must be performed in centres with experience

• More work needed to redefine Likelihood ratios of 2\textsuperscript{nd} trimester markers on populations already screened in the 1\textsuperscript{st} trimester
The Future

- More markers, especially 1\textsuperscript{st} trimester?
- Contingency / sequential testing?
- Non-invasive prenatal detection?
Colour Doppler of Ductus Venosus

Doppler assessment of Tricuspid Flow

Reversed a-wave

Tricuspid regurgitation
Analysis of secondary ultrasound markers in the first trimester before CVS
(Molina García et al, 2010, PND)

evaluated DR and FPRs of ultrasound markers—
  • nasal bone, ductus venosus flow and tricuspid regurgitation
  • 1\textsuperscript{st} trimester
  • high risk population
  • to study the influence of how a two-stage screening policy alters previous combined screening on the rate of invasive procedures

Concluded
  • Assessment of secondary ultrasound markers is feasible in clinical practice and their use could reduce the number of unnecessary invasive procedures by 30%.
Two-stage first-trimester screening for trisomy 21 by ultrasound assessment and biochemical testing  (K. O. KAGAN et al, 2010)

Aim

to examine the performance of a contingent policy in first-trimester screening for trisomy 21

• estimated risk first derived by a combination of
  – maternal age
  – fetal NT thickness
  – presence/absence of the nasal bone
  – blood flow in the ductus venosus or flow across the tricuspid valve

• biochemical testing carried out only in those found to have an intermediate risk.

Conclusion

Effective first-trimester screening for trisomy 21 can be achieved by a contingent policy in which first-stage testing is based on ultrasound examination and second-stage biochemical testing is carried out in only 20% of the patients
Move from screening to diagnosis

Non-invasive prenatal diagnosis

Detection of free fetal DNA in maternal circulation
Non-invasive Prenatal Diagnosis (NIPD) in 2020 (Lo, 2010 Prenatal Diagnosis)

“Thus, I would predict that by 2020

• Many groups would routinely be using massively parallel sequencing technology for the NIPD of multiple monogenic diseases from maternal plasma.
• Furthermore, the same tests would also provide diagnostic information on fetal chromosomal aneuploidies...
• These developments would likely lead to a drastic reduction in the use of invasive techniques, such as amniocentesis and chorionic villus sampling.
• I would foresee that in 2020, there would be multiple articles in *Prenatal Diagnosis* debating about the ethical and social implications of the information explosion from NIPD.”
Muchísimas gracias por invitarme a Bilbao!