What’s new in O&G?

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Leading the way in GP education
Learning objectives:

Topics to be discussed:

1. Non-invasive prenatal testing
2. Pertussis immunisation in pregnancy
3. Changes to GDM diagnosis
4. The future of cervical screening?
Non-invasive prenatal testing (NIPT)

- Testing of the fetal genome through a maternal blood sample
- “Non-invasive” – poses no risk to the pregnancy
- Idea is to reduce rates of invasive testing (CVS/amnio), which carry pregnancy loss rate of up to 1%
- Available in Australia since late 2012
Tell me more...

- Placental DNA
- Several tests available
  - All sent overseas
  - Turnaround time 7-14d
  - Test 21, 18, 13, X and Y; some do others...
  - No head-to-head trials
  - Overall sensitivity 99.5% and specificity 99.8% for T21 (Vs CFTS: 90% and 95%)

- Non-diagnostic – positive results require confirmatory invasive test
What’s new in 2014?

- Validated in low-risk populations
  - Outperforms CFTS:
    - Lower false positive rate (0.3% vs. 3.6%)
    - Higher PPV (46% vs. 4.2%)
- Removal of “obstetrician-only” referral by most providers
- Implementation strategy in Australian context yet to be determined
- Getting cheaper...
## Costs and access

- *No Medicare rebate*

<table>
<thead>
<tr>
<th>Test (company)</th>
<th>Provider in Brisbane</th>
<th>Chromosomes tested</th>
<th>GA (wks)</th>
<th>Sn</th>
<th>Sp</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verifi(^\d)</td>
<td>SNP</td>
<td>21,18,13 (X&amp;Y optional)</td>
<td>10+</td>
<td>&gt;99.9</td>
<td>99.8</td>
<td>595</td>
</tr>
<tr>
<td>iGeneScreen(^\d)</td>
<td>QML</td>
<td>21,18,13</td>
<td>12+</td>
<td>99</td>
<td>99</td>
<td>850</td>
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<tr>
<td>MaterniT21(^{plus})</td>
<td>Healthscope</td>
<td>21,18,13, 16, 22, X, Y, microdeletions</td>
<td>10+</td>
<td>99.1</td>
<td>99.9</td>
<td>1’250</td>
</tr>
<tr>
<td>Harmony</td>
<td>so+gi</td>
<td>21,18,13,X,Y</td>
<td>10+</td>
<td>&gt;99</td>
<td>&gt;99.9</td>
<td>470</td>
</tr>
<tr>
<td>Panorama(^\d)</td>
<td>Virtus Health (QFG)</td>
<td>21,18,13,X,Y</td>
<td>9+</td>
<td>&gt;99</td>
<td>100</td>
<td>895</td>
</tr>
</tbody>
</table>

\(^\d\): Obstetrician-only

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Possible applications

- Offer to everyone?
- Adjunct to CFTS (if high-risk)?
- “Contingent” model, redefining place role of CFTS?
- No trials evaluating cost-effectiveness of various approaches
- No guidelines in Australia (RANZCOG – draft form)
Use as adjunct

Normal process of risk assessment
e.g. Combined first trimester screening (cFTS)

Low risk women
cFTS Risk <1 in 300

High risk women
cFTS Risk ≥1 in 300

choice of

NIPT

'negative'

No further testing

'positive'

Invasive test

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Contingent model

All women offered cFTS as primary test
Risks interpreted in three rather than two groups

Low risk women
cFTS Risk <1 in 1000
(estimate 86.5% of women)

Intermediate risk women
cFTS Risk <1 in 10 to ≥1 in 1000
(estimate 13% of women)

High risk women
cFTS Risk ≥1 in 10
(estimate 0.5% of women)

NIPT
‘negative’
(estimate 98%)

NIPT
‘positive’
(estimate 2%)

No further testing
(a total of 99.2% of women)

Invasive test
(a total of 0.8% of women)
In summary:

- Most accurate prenatal screening for T21/18/13
- Expensive, with no Medicare rebate
- Does not replace invasive testing
- Patient access set to increase:
  - Costs reducing
  - Validated in low-risk women
  - Australian Guidelines in development (RANZCOG)

- **CFTS remains acceptable standard of care in high- and low-risk women (RANZCOG)**
- Until Guidelines available, onus is on clinician to consider and counsel regarding benefits and limitations
- May become incorporated into a wider, well-defined screening program (with equity of access?)
Bordetella pertussis

- Highly contagious respiratory infection
  - Spreads to 90% of susceptible household contacts
- The least well-controlled of all vaccine-preventable diseases
  - Highly prevalent in Australia, epidemics every 3 years
  - Natural infection and immunisation does not provide lifelong protection
  - Waning immunity means a significant reservoir even in immunised communities
Mortality

- Infection may be lethal in children, especially newborns
  - 90% *pertussis* deaths occur in infants <2mo
  - In >50% cases, parents are source of infection

- Australian Immunisation Schedule begins *pertussis* vaccination at 2mo
  - *Children cannot be vaccinated during the highest-risk period of their lives*
Limiting newborn morbidity

- “Cocoon” strategy: indirect protection by immunising parents and close adult contacts
- Direct protection by maternal immunisation during pregnancy (passive immunity)
Concerns with vaccination in pregnancy

- Safety
  - (All formulations acellular since 1999)
  - (Extensive safety data from USA)
- “Protective levels” of antibodies in newborn’s blood not well-understood
- Do maternal antibodies dampen baby’s immune response to their own childhood vaccinations?
What’s new?

- Updated Immunisation Handbook (10th Ed, 2013) suggests pregnant women may be vaccinated in third trimester
  - Booster if >5 years
  - Recent evidence suggests increased neonatal protection may result from this approach
- RCT, women randomised to vaccination at 30-32 weeks, or postpartum
- Measured antibody levels in mums near delivery, and babies at birth, 2mo, and after completion of childhood pertussis program
- Findings:
  - Vaccination during pregnancy did not dampen children’s response to routine childhood vaccination
- 4-5 fold increase in protective antibodies in newborns when mum was vaccinated during pregnancy
In summary:

- Pertussis remains an important infection to be aware of in Australia
- Newborns are particularly susceptible
- Vaccination in third trimester is safe, and may reduce risk of newborn pertussis compared to postpartum vaccination
Gestational diabetes

- Onset, or first recognition, of abnormal glucose tolerance in pregnancy
- Intervention studies have demonstrated benefits from treatment, even in “mild” hyperglycaemia
- Reduced rates LGA, shoulder dystocia, C/S
Recent changes

- Universal OGTT (GCT becoming obsolete)
- Changes to diagnostic criteria
- Change to treatment targets
Why the changes?

  - Reviewed results of studies examining association between maternal hyperglycaemia and perinatal outcomes
- Landmark papers such as HAPO (NEJM 2008):
  - Strong, continuous association of adverse birth outcomes with maternal glucose levels below those currently diagnostic of GDM
Why the changes?

- Recognition of the importance of impaired fasting glucose
  - Not measured with GCT
  - Under-diagnosed by old OGTT criteria
  \[ \rightarrow 25\%+ \text{ of GDM missed} \]
- Observational data on associations with varying levels of impaired glucose tolerance
Outcome of workshop

- IADPSG Consensus Panel recommended revised diagnostic criteria:

<table>
<thead>
<tr>
<th>75g OGTT</th>
<th>Fasting</th>
<th>1hr</th>
<th>2hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old (1999)</td>
<td>≥7.0</td>
<td>--</td>
<td>≥7.8</td>
</tr>
<tr>
<td>New (2013)</td>
<td>≥5.1</td>
<td>≥10.0</td>
<td>≥8.5</td>
</tr>
</tbody>
</table>

- Endorsed by WHO, ADIPS, ADS in 2013
  - Not yet SOMANZ or Endocrine Society of Aus
Locally (Australia)

- RANZCOG-convened multidisciplinary working party (Nov 2013)
- Recommendations:
  - GCT be phased out by 1\textsuperscript{st} July 2014
  - Adoption of new IADPSG diagnostic criteria by 1\textsuperscript{st} January 2015
Revised treatment targets (ADIPS)

- Largely based on 2SD above normal values in low-risk obstetric population
- Fasting target chosen from observational data
- 1hr based on normal BGL in small number of non-diabetic pregnant women
Further research

- No randomised treatment trial has been conducted using the new IADPSG diagnostic criteria for inclusion
- No RCT has defined the optimal treatment targets
  - Targets based on consensus discussions and “best available” data
  - Validity needs to be tested
- Cost-effectiveness?
In summary:

- Revised criteria for diagnosing GDM
- Revised treatment targets
- Largely by consensus; based on extrapolation from observational and some randomised trials
- Further research needed to evaluate magnitude of benefits (versus costs)
Cervical screening

- Current approach to prevention of CaCx prevention and early detection:
  - HPV vaccination (12-13yo girls since 2007; boys since 2013)
  - National Cervical Screening Program
- Medical Services Advisory Committee (MSAC) is currently undertaking NCSP renewal
Cervical screening

Aims of the NCSP Renewal

1. Assess evidence for:
   a. Screening tests and pathways
   b. Screening interval
   c. Commencement age, and age range

2. Determine cost-effective screening pathway

3. (Investigate options for improving data collection)

4. (Assess feasibility and acceptability of renewed program)
Cervical screening

Tests considered

- Conventional cytology (CC = Paps)
- Liquid-based cytology (LBS)
- HPV testing
- Intervals:
  - 2 vs 3 vs 5-yearly
- Based on HPV/cancer science and modelling
Pathways considered

- LBC as primary “triage” test
- HPV and LBC “co-test”
- HPV “triage” test, with “reflex” LBC if (+)
  - Specific HPV typing
  - High-risk typing only (16, 18, 45), with remainder grouped together as (+) or (−)
Cost-effectiveness analyses

- Participation rates
  - Ability to self-collect HPV test
  - More acceptable interval
- Costs of tests and subsequent colposcopy
  - Higher unit price c.f. CC but fewer tests
- Effect on cancer mortality
Considerations

- Sensitivity HPV > LBC for HG lesions (esp. glandular)
- Specificity LBC > HPV
- Therefore HPV first (fewer false negatives), with “reflex” LBC on same sample (weed out false positives)
Recommendations

- HPV as primary test – every 5 years
- ALL positives → LBC on same sample
  - Self-collected HPC test patients will need to see GP for LBC specimen collection
- High-risk HPV (+) → colposcopy regardless of LBC result
- Other HPV (+) → Manage by LBC:
  - LSIL/normal → repeat HPV test 12 months
    - Remains positive → colposcopy
    - Negative → recall 5 years
  - HSIL → colposcopy
Cervical screening

HPV Test with partial genotyping

- Positive HPV other types
  - Reflex LBC
    - Negative Cytology
      - Repeat HPV test in 12 months
        - Negative HPV: Test was negative (normal) → Recall for screening in 5 years
        - Any positive HPV: Indicates HPV infection still present → Refer to colposcopy
    - p/d LSIL
      - Repeat HPV test in 12 months
        - Negative HPV: Test was negative (normal) → Recall for screening in 5 years
        - Any positive HPV: Indicates HPV infection still present → Refer to colposcopy
    - HSIL
      - Repeat HPV test in 12 months
        - Any positive HPV: Indicates cellular changes present that may require tx → Refer to colposcopy
        - Unsatisfactory test for technical reasons
          - Reauthenticate test for technical reasons

Positive HPV 16,18 +/- 45
  - Reflex LBC

Unsatisfactory test
Screening age range

- Commencement age to change from 18 to 25
- High rate of regression in 18-25yo group (43% and 32% for CIN2 and CIN3, respectively)
- Risk of obstetric complications from “unnecessary” treatment
- Cancer mortality hasn’t changed in this group since introduction of NCSP – screening not effective
- “Exit testing” aged 69-74yo
Cervical screening

Forecasted implications (modelling)

- Improved program participation (presently ~67%)
- Increased colposcopy referrals in younger women (<35yo)
  - Higher HPV prevalence
  - Expected to fall as the proportion of HPV-vaccinated cohort increases
- Reduced CaCx mortality by up to 18%
  - 232 deaths in Aus in 2010
- Costs savings est. $50M
When?

- MSAC Recommendations at proposal stage, awaiting government agreement
- Implementation likely by 2016
Further reading