A global method for pregnancy dating: results from the INTERGROWTH-21st Project

Aris Papageorghiou

on behalf of:

The International Fetal and Newborn Growth Consortium for the 21st Century

Oxford Maternal & Perinatal Health Institute
Green Templeton College
Accurate pregnancy dating

Important at individual level

Important at population level to correctly define rates of preterm birth; and rates of small for gestational age (SGA).

The lack of accurate GA estimation, in particular in those areas of the world at greatest risk of these conditions, means that preterm birth and SGA rates are merely estimates in much of the world (Blencowe 2012, De Onis 1998)
Dating by ultrasound measurement of CRL
<table>
<thead>
<tr>
<th>Formula</th>
<th>Difference in days (measurement error)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td><strong>CRL formulae (n = 167)</strong></td>
<td></td>
</tr>
<tr>
<td>Selbing and Fjällbrant 1984&lt;sup&gt;3&lt;/sup&gt; (formula a)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>−0.041</td>
</tr>
<tr>
<td>Koornstra et al. 1990&lt;sup&gt;4&lt;/sup&gt; (formula a)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>−0.136</td>
</tr>
<tr>
<td>Vollebergh et al. 1989&lt;sup&gt;5&lt;/sup&gt;&lt;sup&gt;*&lt;/sup&gt;</td>
<td>−0.302</td>
</tr>
<tr>
<td>Izquierdo et al. 1991&lt;sup&gt;6&lt;/sup&gt;</td>
<td>−0.188</td>
</tr>
<tr>
<td>Hadlock et al. 1992&lt;sup&gt;7&lt;/sup&gt;</td>
<td>0.285</td>
</tr>
<tr>
<td>Rossavik et al. 1988&lt;sup&gt;8&lt;/sup&gt;</td>
<td>−0.614</td>
</tr>
<tr>
<td>MacGregor et al. 1987&lt;sup&gt;9&lt;/sup&gt; (formula a)</td>
<td>0.691</td>
</tr>
<tr>
<td>Nelson 1981&lt;sup&gt;10&lt;/sup&gt;</td>
<td>0.887</td>
</tr>
<tr>
<td>Selbing and Fjällbrant 1984&lt;sup&gt;3&lt;/sup&gt; (formula b)</td>
<td>−0.893</td>
</tr>
<tr>
<td>Drumm et al. 1976&lt;sup&gt;11&lt;/sup&gt;</td>
<td>1.222</td>
</tr>
<tr>
<td>Robinson and Fleming 1975&lt;sup&gt;12&lt;/sup&gt;</td>
<td>−1.309</td>
</tr>
<tr>
<td>von Kaisenberg et al. 2002&lt;sup&gt;13&lt;/sup&gt;</td>
<td>−1.332</td>
</tr>
<tr>
<td>Daya 1993&lt;sup&gt;14&lt;/sup&gt;</td>
<td>−2.117</td>
</tr>
<tr>
<td>Wisser et al. 1994&lt;sup&gt;15&lt;/sup&gt;</td>
<td>−2.126</td>
</tr>
<tr>
<td>MacGregor et al. 1987&lt;sup&gt;9&lt;/sup&gt; (formula c)</td>
<td>2.174</td>
</tr>
<tr>
<td>Selbing 1982&lt;sup&gt;16&lt;/sup&gt;</td>
<td>2.427</td>
</tr>
<tr>
<td>Grisolia et al. 1993&lt;sup&gt;17&lt;/sup&gt;</td>
<td>2.912</td>
</tr>
<tr>
<td>Goldstein et al. 1991&lt;sup&gt;18&lt;/sup&gt;</td>
<td>2.966</td>
</tr>
<tr>
<td>Koornstra et al. 1990&lt;sup&gt;4&lt;/sup&gt; (formula b)</td>
<td>−3.422</td>
</tr>
<tr>
<td>MacGregor et al. 1987&lt;sup&gt;9&lt;/sup&gt; (formula b)</td>
<td>3.876</td>
</tr>
<tr>
<td>Silva et al. 1990&lt;sup&gt;19&lt;/sup&gt;</td>
<td>3.922</td>
</tr>
</tbody>
</table>

Modified from Sladevicius et al, 2005
Articles selected from CINAHL, embase, medline & science citation index search (n = 1851)

Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 1142)

Records screened at title/abstract review (n = 1142)

Records excluded (n = 1080)

Full-text articles assessed for eligibility (n = 62)

Full-text articles excluded, with reasons (Table S2) (n = 33)

Studies included in qualitative synthesis (Table 1) (n = 29)
Systematic review: Results from 29 studies selected
Systematic review: Results from 29 studies selected

Napolitano et al, BJOG, 2014
Existing equations relating CRL to Gestational Age

Napolitano et al, BJOG, 2014
“Healthy” environment criteria for selection of sites in Fetal Growth Longitudinal Study

• Low birth weight rate <10%
• Mean birth weight >3100g
• Perinatal mortality <20 per 1000 live births
• >75% mothers have attained an educational level/socio-economic status indicator greater than the locally defined cut-off points
• Lack of known, major, non-microbial environmental contaminants
• Altitude <1600m

Villar et al. *BJOG*, 2013
All pregnancies in 8 sites
n = 58,989
“Healthy” mother criteria for Fetal Growth Longitudinal Study

| a) | aged ≥18 and ≤35 years; |
| b) | BMI ≥18.5 and <30 kg/m²; |
| c) | height ≥ 153 cm; |
| d) | singleton pregnancy; |
| e) | a known LMP with regular cycles (defined as a 26-30 day cycle in the previous 3 months), without hormonal contraceptive use, pregnancy or breastfeeding in the 3 months before pregnancy; |
| f) | natural conception |

Criteria defining a low-risk study population as healthy and well-nourished (both before and during pregnancy) to ensure that fetal growth is optimal

- no clinically significant atypical red cell alloantibodies;
- negative urinalysis;
- systolic blood pressure <140 mmHg and diastolic blood pressure < 90 mmHg;
- haemoglobin ≥11 g/dl;
- negative syphilis test and no clinical evidence of any other sexually transmitted diseases, including clinical Trichomoniasis;
- not in an occupation with risk of exposure to chemicals or toxic substances, or very physically demanding activity to be evaluated by local standards. Also women should not be conducting vigorous or contact sports, as well as scuba diving or similar activities.

Villar et al. *BJOG*, 2013
Maternal inclusion criteria to date pregnancy

Gestational age based on last menstrual period (LMP) if:

- Known certain LMP
- Regular 26-30 day menstrual cycles
- No hormonal contraception, pregnancy or breastfeeding in 3 months preceding LMP
- Ultrasound measurement of fetal crown-rump length (CRL) at 9+0 to 14+0 weeks consistent with LMP, i.e. any discrepancy between LMP and CRL < 7 days

Villar et al. BJOG, 2013
INTERGROWTH-21\textsuperscript{st} populations

Low-risk pregnancies
n = 20,324
INTERGROWTH-21st populations

Low-risk pregnancies
n = 20,324

Medium-high risk pregnancies

Fetal Growth Longitudinal Study
n = 4,607
INTERGROWTH-21st populations

Low-risk pregnancies
n = 20,324

Medium-high risk pregnancies

Fetal Growth Longitudinal Study
n = 4,607

International Fetal Growth Standards
Scans every 5 ± 1 weeks

Measurements at each scan >14° weeks:

- Biparietal diameter
- Occipito-frontal diameter
- Head circumference
- Transverse abdominal diameter
- Anterio-posterior abdominal diameter
- Abdominal circumference
- Femur length

Measurements obtained 3 times from 3 separately obtained images of each structure in blinded fashion (no measurement visible) and submitted electronically

Papageorghiou et al. BJOG, 2013
Ultrasound Manual of Operations

Detailed instructions on:

• Measurement techniques
• Equipment
• Step-by-step guide
• Data management
• Local standardisation and training exercises

Papageorghiou et al, BJOG, 2013
INTERGROWTH-21st Standardised Training for FGLS across all study sites

INCORRECT: the wings of the sphenoid bone (3) and cerebral peduncles (4) are demonstrated: this section is too low in the fetal head

Sarris et al, BJOG, 2013
Standardisation: Improves agreement

Sarris et al. Ultrasound Obstet Gynecol 2011
Ongoing quality control and audit

• **Image review**
  • Self review
  • External review (random 10%)

• **Data monitoring**
  • Intra-observer agreement
  • Consistency & bias
  • CUSUM charts
  • Re-measurement (random 10%)
Using data for Quality Control

Sarris et al, BJOG, 2013
Standardised anthropometric measurements at birth and follow-up to 2 years

Cheikh Ismail et al. *BJOG*, 2013
Fetal size $<14^{+0}$ weeks by crown-rump length
FGLS distribution by country

- 34% high-income countries
- Italy 12%
- USA 7%
- UK 15%
- Oman 14%
- Kenya 15%
- Brazil 9%
- China 14%
- India 14%
Early fetal size: CRL by gestational age for UK, USA & Italy

Villar et al. Lancet Diab Endocrin, 2014
Early fetal size: CRL by gestational age for UK, USA, Italy & China

Early fetal size: CRL by gestational age for UK, USA, Italy, China & India

Early fetal size: CRL by gestational age for UK, USA, Italy, China, India & Kenya

Early fetal size: CRL by gestational age for UK, USA, Italy, China, India, Kenya & Oman

Early fetal size: CRL by gestational age for UK, USA, Italy, China, India, Kenya, Oman & Brazil

Regression model fit for CRL data by gestational age (weeks) according to study site (3rd, 50th and 97th percentiles)

Fitting same model for each site's data

CRL centiles by gestational age:
All 8 sites

Sensitivity analysis for CRL measures:
All sites, excluding UK, India, Kenya & China separately

Villar et al. Lancet Diab Endocrin, 2014
### Variance component analysis for fetal CRL and HC, and newborn length

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variance among study sites</strong></td>
<td>1.9%</td>
<td>2.6%</td>
<td>3.5%</td>
<td>3.4%</td>
</tr>
<tr>
<td><strong>Unexplained variance</strong></td>
<td>98.1%</td>
<td>97.4%</td>
<td>96.5%</td>
<td>96.6%</td>
</tr>
</tbody>
</table>

**Villar, Lancet Diabetes Endocrinol. 2014**
Conclusions

• We have developed a new, international CRL equation for estimating gestational age based on a study of 4,500 healthy, well-nourished women in 8 countries across 4 continents who have been monitored up until infancy.

• There were no major discrepancies between our international data and those previously published from good quality studies in developed countries.

• This tool allows all pregnancies around the world to be dated in the same way.

Papageorghiou et al, UOG 2014
International standards for early fetal size and pregnancy dating based on ultrasound measurement of crown-rump length in the first trimester


UOG, 2014; 44: 641–648

International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project

José Villar, Leila Cheikh Ismail, Cesar G Victoria, Eric O Ohuma, Enrico Bertino, Doug G Altman, Ann Lambert, Aris T Papageorghiou, Maria Carvalho, Yasmin A Jaffer, Michael G Gravett, Manorama Purwar, Ihunnaya O Frederick, Alison J Noble, Ruyan Pang, Fernando C Barros, Cameron Chumlea, Zulfiqar A Bhutta*, Stephen H Kennedy*, for the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st)

Lancet, 2014; 384:869-79

Lancet, 2014; 384:857-68