

# With new prenatal testing, will babies with Down syndrome slowly disappear?

Brian G Skotko

An expansive menu of prenatal tests for Down syndrome (DS) is already available to pregnant women around the globe, but new tests are likely to become the most popular entrées. Presently, pregnant women can choose among the many prenatal screening tests – triple screen, quadruple screen, first-trimester combined screen, stepwise sequential screens, and fully integrative screens – to receive statistical chances that their fetuses have DS, to varying degrees of detection (table 1).<sup>1</sup> For a definitive prenatal diagnosis of DS, however, women currently have just two options, both of which are invasive: chorionic villus sampling (CVS), generally performed between 9 and 12 weeks of gestation, and amniocentesis, traditionally offered between 15 and 20 weeks of gestation. By nature of being invasive, both of these diagnostic tests carry small, albeit real, risks of spontaneous abortions.<sup>2–7</sup>

Professional organisations in the USA – such as the American College of Obstetrics and Gynecology (ACOG) and the American College of Medical Genetics (ACMG) – and many similar organisations around the world such as the Fetal Anomaly Screening Programme in the UK now recommend that all pregnant women, regardless of age, be offered a selection of these available tests.<sup>8–11</sup> Most pregnant women seeking prenatal confirmation of DS start with a prenatal screen, learn the statistical chances that their fetus has DS, and then decide whether to proceed with CVS or amniocentesis. Pregnant women in the UK seeking prenatal confirmation of DS typically start with one of these recommended screens, receive a result that is pre-interpreted as “high risk” or “low risk”, and are then offered CVS or amniocentesis only if they fall in the “high risk” category.

A forthcoming option, to be made available first in the USA but already

welcomed and anticipated in the UK, will be a non-invasive serum test that might provide a definitive diagnosis of DS in the first trimester at no risk to the fetus.<sup>12</sup> Some researchers are claiming that the most common genetic variation of DS – trisomy 21 – can be identified by isolating cell-free fetal DNA or RNA in the maternal serum and using a method called “allele ratio analysis”.<sup>13–17</sup> In this method, researchers first identify genes expressed exclusively on chromosome 21 and specific to the fetus. Then, they exploit polymorphic differences – that is, subtle genetic variations – between maternally and paternally inherited alleles. Fetuses with trisomy 21 would be expected to have a 2:1 or 1:2 ratio, opposed to the normal 1:1 ratio, since they have inherited two copies of chromosome 21 alleles from one parent and one copy from the other. Preliminary studies have predicted that up to 95% of fetuses will have enough polymorphic differences to render a definitive diagnosis with near 100% sensitivity and specificity.<sup>18</sup>

Other researchers are claiming that two genetic variations of DS – trisomy 21 and translocation DS – can be identified by another method in the first trimester called “shotgun sequencing”.<sup>19</sup> In this method, researchers place a genetic tag on each fragment of maternal and fetal cell-free DNA. By mapping these tags to each of the chromosomes, these researchers suggest that an over-representation of chromosome 21 tags would indicate that a fetus has DS. Preliminary results suggest that this method would be applicable to all fetuses, regardless of the amount of polymorphic differences; however, the sensitivity and specificity still need to be tested in larger trials.

## WHAT HAS BEEN THE IMPACT OF PRENATAL TESTING ON THE BIRTH INCIDENCE OF DS?

### Impact of current testing

Since no prenatal therapeutic interventions currently exist for DS, pregnant women pursue prenatal identification for one of three reasons: (1) they wish to

terminate the pregnancy if the fetus has DS; (2) they desire an advanced awareness about DS prior to the birth of a child they intend to raise; or (3) they would begin to pursue adoption strategies. In an international meta-analysis using data from the USA, UK, New Zealand, France, and Singapore, approximately 92% of women who receive a definitive prenatal diagnosis of DS choose to terminate their pregnancies.<sup>20</sup>

Birth trends worldwide suggest that women are waiting longer to have children. Because advanced maternal age is associated with increased chances of having a child with DS, the birth incidence of DS would have been expected to climb. However, the worldwide birth incidence of DS has actually decreased from what it could have been by 2–18% per year (table 2).<sup>21–34</sup> For example, in the USA, there would have been a 34% increase in the number of babies born with DS between 1989 and 2005, in the absence of prenatal testing.<sup>32–35</sup> Instead, there were 15% fewer babies born, representing a 49% decrease between the expected and observed rates. In the UK, there would have been a 58% increase in the number of babies born with DS between 1989 and 2006, in the absence of prenatal testing. Instead, there was only a 4% increase, representing a 54% decrease between expected and observed rates.<sup>34</sup> Trends like these, in the USA, UK, and abroad, are mostly attributable to the availability of prenatal testing and maternal preference for selective terminations.

### Impact of future testing

An open question remains: with the forthcoming availability of new DS diagnostic tests, will the birth incidence of DS decrease even further? Several factors suggest so. First, the new tests will be offered in the first trimester before women begin to show any physical signs of their pregnancies. Consequently, women will be able to receive a DS diagnosis and make a decision about the continuation of their pregnancies in private. If desired, a woman could decide to terminate without anyone ever knowing that she was pregnant. Diagnosis at the present time is rarely made before 12 weeks and frequently not until 18 weeks, when the expectant mother shows obvious signs of pregnancy to family and friends. Second, the new tests are non-invasive, carrying no risk to the fetus, unlike CVS and amniocentesis. As such, many more – if not the majority – of women can be expected to request these

**Correspondence to:** Brian Skotko, Children’s Hospital Boston, 300 Longwood Ave, Boston, Massachusetts 02115, USA; [Brian.Skotko@childrens.harvard.edu](mailto:Brian.Skotko@childrens.harvard.edu)

**Table 1** Down syndrome detection rates with screening tests (using 5% false positive rate)

Screening test	Detection rate (%)	Recommended by
First-trimester combined screen* (NT measurement, PAPP-A, fβhCG)	87	ACOG, ACMG, NICE, NSC
Second-trimester triple screen† (AFP, hCG, unconjugated oestriol)	69	ACOG, ACMG, NICE
Second-trimester quadruple screen† (AFP, hCG, unconjugated oestriol, inhibin A)	81	ACOG, ACMG, NICE, NSC
Stepwise sequential screening*† (disclosed first-trimester combined screen and second-trimester quadruple screen)	95	ACOG, ACMG
Fully integrative screening*† (non-disclosed first-trimester combined screen and second-trimester quadruple screen)	96	ACOG, ACMG, NSC

\*Using 1 in 150 as a "positive result" at 11 completed weeks of gestation.

†Using 1 in 300 as a "positive result" in the second trimester.

ACMG, American College of Medical Genetics; ACOG, American College of Obstetrics and Gynecology; AFP, alpha-fetoprotein; fβhCG, free beta-human chorionic gonadotropin; NICE, National Institute for Health and Clinical Excellence; NSC, National Screening Committee; NT, ultrasonographic nuchal translucency; PAPP-A, pregnancy-associated plasma protein A.

tests, resulting in more prenatal discoveries of DS. Consequently, the numbers of elective terminations would likely increase, depending on a society's laws, culture, and religious values.

Third, in countries like the UK, where women are only offered CVS or amniocentesis if their screening test is deemed "high risk", the new tests would afford everyone an opportunity to know definitively if their fetus has DS, potentially meaning more fetuses could be electively terminated. This would further obviate concerns that the UK's current screening system does not respect the patient's autonomy in decision-making and results in too many spontaneous procedure-related terminations from CVS or amniocentesis.<sup>36 37</sup>

Fourth, the new tests are projected to cost less than amniocenteses or CVS.<sup>19</sup> As a result, health insurance plans might readily shift to covering the new tests, making their uptake more universal. The UK's PHG Foundation convened an

expert working group that has already called the implementation of the tests into the UK's National Health System "desirable".<sup>12</sup> Not impossible in the near future, then, will be the offering of these tests during routine obstetric care visits.

#### WHAT INFLUENCES A MOTHER'S DECISION AFTER RECEIVING A PRENATAL DIAGNOSIS?

Mothers from the USA, Spain, and the Netherlands who have received a prenatal diagnosis of DS and chose to continue their pregnancies have indicated that their physicians often provided incomplete, inaccurate, and, sometimes, offensive information about DS.<sup>38-41</sup> Mothers in the Netherlands who have terminated their pregnancies after receiving a prenatal diagnosis of DS mostly based their decisions on an understanding that DS was "an abnormality too severe" and a "burden" that was "too heavy" for the child.<sup>42</sup> As a result, some have even questioned

whether mothers are making informed clinical decisions about their pregnancies.<sup>43</sup> Physicians' training and personal opinions might underscore this conclusion.

#### Are today's physicians competently trained?

In a survey conducted in 2004 of 2500 medical school deans, students, and residency directors in the USA, 81% of medical students report that they "are not getting any clinical training regarding individuals with intellectual disabilities", and 58% of medical school deans say such training is not a high priority.<sup>44</sup> In a questionnaire completed by 532 ACOG fellows and junior fellows in 2004, 45% rated their training regarding how to deliver a prenatal diagnosis as "barely adequate or non-existent", and only 28% felt "well qualified" in general prenatal genetic counselling.<sup>45</sup> A survey of 507 ACOG fellows and junior fellows

**Table 2** Worldwide effects of prenatal testing on the birth incidence of Down syndrome (DS)

Reference	Location	Timeframe	Observed change in DS incidence (%)	Expected change in DS incidence* (%)	Realised change† (%)	Average realised change/year‡ (%)
O'Leary <i>et al</i> 1996 <sup>21</sup>	Western Australia	1980-1994	↓ 9	↑ 63	↓ 72	↓ 5
Caruso <i>et al</i> 1998 <sup>22</sup>	Boston, USA	1972-1974 to 1993-1994	↓ 24	↑ 90	↓ 114	↓ 6
Carothers <i>et al</i> 1999 <sup>23</sup>	Scotland	1990-1991 to 1992-1994	↓ 29	↑ 7	↓ 36	↓ 18
Wortelboer <i>et al</i> 2000 <sup>24</sup>	Northern Netherlands	1987-1996	↑ 15	↑ 29	↓ 14	↓ 2
Rösch <i>et al</i> 2000 <sup>25</sup>	Eastern Germany	1980-1997	↑ 75	↑ 220	↓ 145	↓ 9
Cheffins <i>et al</i> 2000 <sup>26</sup>	South Australia	1982-1996	↓ 42	↑ 60	↓ 102	↓ 7
Verloes <i>et al</i> 2001 <sup>27</sup>	South Belgium	1987-1992	↓ 4	↑ 12	↓ 16	↓ 3
Iiyasu <i>et al</i> 2002 <sup>28</sup>	Glasgow, Scotland	1980-1996	↓ 6	↑ 29	↓ 35	↓ 2
Bell <i>et al</i> 2003 <sup>29</sup>	North England	1985-1999	0	↑ 43	↓ 43	↓ 3
Khoshnood <i>et al</i> 2004 <sup>30</sup>	Paris, France	1981-2000	↓ 57	↑ 190	↓ 247	↓ 13
Ekelund <i>et al</i> 2008 <sup>31</sup>	Denmark	2000-2006	↓ 50	↑ 12	↓ 62	↓ 10
NDSCR <sup>34</sup>	England and Wales	1989-2006	↑ 4	↑ 58	↓ 54	↓ 3
Egan <i>et al</i> 2008 <sup>32</sup>	USA	1989-2005	↓ 15	↑ 34	↓ 49	↓ 3
Halliday <i>et al</i> 2009 <sup>33</sup>	Victoria, Australia	1988-1990 to 1998-2000	↓ 28	NA	≥ ↓ 28	≥ ↓ 3

\*Predicted or calculated change in the incidence of babies born with DS, reflecting advancing maternal age of pregnant women, absent prenatal testing. Not all papers adjusted for small changes attributable to spontaneous terminations between prenatal diagnosis and birth.

†Difference between observed change and predicted change in incidence of babies born with DS.

‡Average realised change per year based on the timeframe of the study.

NA, not available.

conducted 4 years later showed little progress – approximately 40% thought their training was “less than adequate”, and only 36% felt “well qualified” in counselling an expectant mother whose prenatal screen suggests a high chance for DS.<sup>46</sup> Taken together, these studies suggest that today’s and tomorrow’s physicians are not adequately prepared.

### Do physicians knowingly insert their own personal opinions?

Explaining DS to expectant parents is as much of an art, as it is science. While academic societies across the globe subscribe to non-directive counselling – equipping expectant parents with non-biased facts so that they can make informed decisions in the context of their own beliefs and values – do individual physicians honestly practise this? The only known study, to date, examined 499 physicians and 1084 genetic professionals from the USA who were involved in presenting a prenatal diagnosis of DS to expectant couples.<sup>47</sup> On anonymous surveys, 63% of physicians and 86% of genetic professionals claim that they try to adhere to non-directive counselling. By contrast, 13% of physicians and 13% of genetic professionals admit to overemphasising the negative aspects of DS in hopes that pregnant women would seek a termination. Further, 10% of physicians said that they actively “urge” mothers to terminate. On the flip side, 10% of physicians and 2% of genetic professionals indicate that they overemphasise the positive aspects of DS in hopes that pregnant women will continue with their pregnancies. An additional 4% of physicians said that they actively “urge” mothers to continue. This one study suggests that not all pregnant mothers are receiving unbiased information from their healthcare providers.

### URGENT IMPROVEMENTS NEEDED PRIOR TO THE ARRIVAL OF NEW DS TESTS

A collision can be anticipated: unprepared, untrained obstetricians and midwives will need to grapple with new, first-trimester tests that might be quickly adopted, once made commercially available. Preparations are needed in targeted realms:

- Obstetric, midwifery, and genetic professional organisations across the world need to develop guidelines on how their country’s health professionals should deliver a prenatal diagnosis of DS to expectant parents. Research studies have already offered

many recommendations, including providing up-to-date information and referrals to DS parent support groups, when desired.<sup>38–41</sup>

- Current and accurate informational packets on DS need to be assembled by a collaborative of medical organisations and parent support organisations. When an expectant couple receives the news that their fetus has DS, what printed materials will be given? Wide variation exists both within and between countries.
- Comprehensive training on how to deliver a non-directive prenatal diagnosis of DS should be offered to all obstetricians, geneticists, midwives, genetic counsellors, neonatologists, family medicine physicians, and other healthcare professionals involved in prenatal care. Online simulation has already been developed for physicians to practise these skills.<sup>48</sup> The Human Genetics Commission, an advisory group to the UK’s government, has called for a heightened awareness and education among midwives and obstetricians.<sup>49</sup>
- Medical, nursing, and genetic counselling students need a richer understanding about DS, beyond the statistics cited in their texts. Some schools are now inviting people with DS and their families to give lectures, and others are offering creative opportunities for students to interact with people who have DS.<sup>50</sup>

In countries where women can choose to terminate their pregnancies, the birth incidence of children with DS should ideally reflect societal mores and not the interventions of physicians or medical technology. Until the above measures are implemented, the evidence suggests that we cannot say this is true.

### ETHICAL DECISIONS ABOUT OUR GENETIC FUTURES

While DS might be the first genetic condition that can be definitively diagnosed in the first trimester on a population basis, others will undoubtedly follow. Countries and their people will be challenged to answer: what forms of human genetic variation are valuable? In the USA, for example, ACOG issued an opinion opposing obstetric practices that perform terminations based on fetal sex alone.<sup>51</sup> Barring work-up for sex-limited genetic conditions, sex selection could be interpreted as “condoning sexist values” and creating a “climate in which sex discrimination can more easily flourish”. By contrast, in its support for DS prenatal

screening, has ACOG endorsed a climate in which disability discrimination could more easily flourish?

Where should our professional organisations draw the line? Should expectant parents be able to select out fetuses with an undesired sex? Should fetuses with genes that predispose them to adult breast cancer be prenatally identified?<sup>52</sup> Should couples in the future be supported if they wish to terminate fetuses with genes correlated with sexual preferences? The age is swiftly coming where not all possible technologic advances may bring welcomed change. Parents who have children with DS have already found much richness in life with an extra chromosome.<sup>53</sup> Now is the time for the rest of us to discuss the ethics of our genetic futures.

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