Problem Solving in Obstetrics and Gynaecology: Antenatal Diagnosis

Declan Byrne, 6th Year Medicine

As part of the Obstetrics and Gynaecology course at Trinity in 5th Year, students are given clinical problems to solve. The aim of the exercise is to encourage critical thinking with the application of Evidence Based Medicine- skills and attitudes that are crucial in achieving ‘Best Practice’ in years to come.

Introduction

This case addresses the issue of antenatal diagnosis. The patient in question is a 40-year-old psychologist who is pregnant for the first time. Since the death of her mother 2 years ago she has taken care of her 35-year-old sister who has Down Syndrome. She wants answers to the following questions pertaining to antenatal diagnosis of Down Syndrome and other chromosomal abnormalities:

1. What is the accuracy of the available tests?
2. What are the pros and cons of first versus second trimester testing?
3. What method of termination should be used if the diagnosis was not made for certain until 19 completed weeks of gestation and she wished to have the pregnancy terminated?

In addition to these specific requests I believe it would be prudent to describe the more common chromosomal abnormalities to this lady, outlining the range of severity. Furthermore, in counselling her I feel one should be cognisant of the fact that having her Down Syndrome sister living with her could be colouring her view of how to handle an affected pregnancy.

Literature Review Methodology

A number of sources were consulted to find answers to the questions posed above:

1. Reference textbooks of Obstetrics and Gynaecology, and Medical Genetics were reviewed to acquire an overview of the issues involved.
2. MedLine was accessed via the PubMed Internet site. An advanced literature review was conducted including the period 1990 to the present day (September 1999). Search terms included: antenatal diagnosis; prenatal diagnosis; first trimester; second trimester; amniocentesis; chorionic villus sampling; Down Syndrome; Edward’s Syndrome; Patau Syndrome; and Chromosomal Abnormality. This search was further narrowed to include only review articles in the English language.
3. The Cochrane Database was accessed and articles prepared by the pregnancy and childbirth group were reviewed. Two relevant articles were found, ‘Chorionic villus sampling versus amniocentesis for prenatal diagnosis’, and ‘Early amniocentesis versus transabdominal chorionic villus sampling for prenatal diagnosis’.
4. The most recent ‘Current World Literature’ section of the journal Current Opinion in Obstetrics and Gynaecology was reviewed. Relevant articles collected under the heading ‘Prenatal diagnosis’ were reviewed.
5. Relevant legal material pertaining to abortion law was collected from the Berkeley library in Trinity College, Dublin.

Chromosomal Abnormalities

Approximately 20% of all conceptions have a chromosomal disorder, but most of these fail to implant or are spontaneously aborted. Thus the birth frequency is 0.6%.

Table 1 outlines the commonest chromosomal disorders in the newborn.

<table>
<thead>
<tr>
<th>Trisomy 21: Down Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall birth incidence is 1 in 700 live births. The incidence at conception is much greater, but more than 60% are spontaneously aborted and at least 20% are stillborn. The incidence increases with increasing maternal age (see Table 2).</td>
</tr>
<tr>
<td>The overall birth incidence is 1 in 700 live births. The incidence at conception is much greater, but more than 60% are spontaneously aborted and at least 20% are stillborn. The incidence increases with increasing maternal age (see Table 2).</td>
</tr>
<tr>
<td>The clinical features include: upslanting palpebral fissures; speckling of the iris; small nose; flat facial profile; neonatal hypotonia; brachycephaly; missshapen low set ears; single palmar crease; clinodactyly; wide gap between first and second toes; mental handicap; duodenal atresia; congenital heart defects; cataracts; epilepsy; hypothyroidism; atlantoaxial instability; increased incidence of acute leukaemia.</td>
</tr>
<tr>
<td>The clinical features include: upslanting palpebral fissures; speckling of the iris; small nose; flat facial profile; neonatal hypotonia; brachycephaly; missshapen low set ears; single palmar crease; clinodactyly; wide gap between first and second toes; mental handicap; duodenal atresia; congenital heart defects; cataracts; epilepsy; hypothyroidism; atlantoaxial instability; increased incidence of acute leukaemia.</td>
</tr>
<tr>
<td>Most of these children will walk and develop simple language. Puberty is often delayed and incomplete. Presenile dementia commonly supervenes after 40 years of age.</td>
</tr>
<tr>
<td>Most of these children will walk and develop simple language. Puberty is often delayed and incomplete. Presenile dementia commonly supervenes after 40 years of age.</td>
</tr>
<tr>
<td>95% of cases are regular trisomy 21 arising from non-dysjunction at meiosis. The mother contributes the extra chromosome in 85% of cases.</td>
</tr>
<tr>
<td>95% of cases are regular trisomy 21 arising from non-dysjunction at meiosis. The mother contributes the extra chromosome in 85% of cases.</td>
</tr>
</tbody>
</table>
In 4% of cases the child receives the extra copy of chromosome 21 from a parent who is a carrier of a balanced translocation involving chromosome 21 or who has a de novo translocation. The final 1% has mosaicism with normal and trisomy 21 lines.

**METHODS AND ACCURACY OF ANTENATAL DIAGNOSTIC TESTS**

Pre-natal diagnostic techniques may be divided into 2 groups, invasive and non-invasive. Invasive techniques include amniocentesis, chorionic villus sampling, cordocentesis, and foetal skin and liver biopsy. Non-invasive techniques include ultrasonography, other imaging techniques and analysis of foetal cells found in the maternal circulation.

This essay will concentrate on the techniques of amniocentesis and chorionic villus sampling. A short description of both techniques follows.

**Amniocentesis**

This technique involves the withdrawal of amniotic fluid. It is usually performed at 16-18 weeks of gestation when there is about 180 ml of liquor and the ratio of viable to non-viable cells is maximal. However, early amniocentesis performed between 12-15 weeks of gestation is increasingly being performed.

It is an aseptic technique that is usually performed under the guidance of ultrasound. Around 10-20 ml of liquor is removed. Amniocentesis allows foetal sexing, karyotyping, foetal enzyme assay, amniotic fluid biochemistry and foetal DNA diagnosis.

For the purposes of karyotyping amniotic fluid cells are grown in culture and results are usually available in 2-3 weeks.

**Chorionic Villus Sampling**

Sampling of chorionic villi from the foetus is performed from 10 weeks of gestation. The biopsy is usually taken under ultrasound guidance via a transabdominal approach. Alternatively the cervical approach may be utilised. Each biopsy yields 5-30 mg of tissue that can be used for foetal sexing, karyotyping, biochemical studies and DNA analysis. A direct foetal chromosomal analysis on cultured cells is possible within 24 hours. However, given the problem with mosaicism in CVS samples, this should always be followed by chromosomal analysis on cultured cells from the sample 2-3 weeks later. An advantage of CVS is that termination can be completed in the first trimester when it is technically easier.

**Accuracy**

The Canadian Trial was a multicentre randomised trial comparing diagnostic accuracy of CVS and second trimester amniocentesis. In this study amniocentesis achieved an accuracy of 99.4%. CVS achieved an accuracy of 97.5%. However, the higher rates of mosaicism seen in CVS adversely affects the positive predictive value (PPV) of this procedure with the Canadian Collaborative study determining the PPV of amniocentesis to be 0.909 whilst that of CVS was only 0.525.

**COMPARISON OF TESTS: PROS AND CONS**

a) The best evidence relating to chorionic villus sampling versus amniocentesis for prenatal

**Table 1: Common Chromosomal Disorders found in the Newborn**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Birth Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balanced Translocation</td>
<td>1 in 500</td>
</tr>
<tr>
<td>Unbalanced Translocation</td>
<td>1 in 2000</td>
</tr>
<tr>
<td>Pericentric Inversion</td>
<td>1 in 100</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>1 in 700</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>1 in 3000</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>1 in 5000</td>
</tr>
<tr>
<td>47, XXY</td>
<td>1 in 1000 males</td>
</tr>
<tr>
<td>47, XYY</td>
<td>1 in 1000 males</td>
</tr>
<tr>
<td>47, XXX</td>
<td>1 in 1000 females</td>
</tr>
<tr>
<td>45, X</td>
<td>1 in 5000 females</td>
</tr>
</tbody>
</table>

**Table 2: Age specific incidence of Trisomy 21**

<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>Frequency of Trisomy 21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At Birth</td>
</tr>
<tr>
<td>20</td>
<td>1 in 1560</td>
</tr>
<tr>
<td>25</td>
<td>1 in 1350</td>
</tr>
<tr>
<td>35</td>
<td>1 in 380</td>
</tr>
<tr>
<td>39</td>
<td>1 in 150</td>
</tr>
<tr>
<td>41</td>
<td>1 in 85</td>
</tr>
<tr>
<td>45</td>
<td>1 in 28</td>
</tr>
</tbody>
</table>
diagnosis is found in the Cochrane Database of Systematic Reviews. The studies included in this review included women requesting invasive prenatal diagnostic testing for foetal chromosome or genetic disorders. First trimester CVS was compared to second trimester amniocentesis with respect to foetal and pregnancy outcomes, antenatal complications and diagnostic accuracy. All randomised controls of two prenatal diagnostic procedures were included. The trials were evaluated for methodological quality and appropriateness for inclusion, without consideration of their results. This paper reported on three large studies of good quality. Over 9000 women were included. All were randomised centrally. The safety of the procedures was adequately addressed by collecting the relevant obstetric and neonatal data.

- NONE OF THE TRIALS WERE DESIGNED TO ADEQUATELY ASSESS THE DIAGNOSTIC ACCURACY OF PREGNATAL TESTING. Complete follow-up of all randomised pregnancies with cytogenetic confirmation would be necessary to accurately determine the number of false-negative and false-positive results.

- Compliance was less with amniocentesis. Fewer women underwent this procedure than CVS (Odds Ratio 0.44, 95% Confidence Interval 0.38, 0.51). This was a reflection of both spontaneous miscarriage and parental change of mind.

- CVS is technically more difficult with significantly more sampling failures, multiple insertions, repeated procedures, laboratory failures and maternal contamination.

- There were more false positives in the CVS group (OR 3.7, CI 1.87, 7.7). This was due to more ambiguous findings including mosaics. The only false negatives obtained occurred in the CVS group (OR 8.08, CI 1.13, 57.54).

- Maternal side effects and complications were uncommon after both procedures. There were no reports that either were life threatening. Vaginal bleeding was more common after CVS (OR 5.37, CI 4.28, 6.75), although there was no difference in the incidence of vaginal bleeding later in pregnancy. There was no significant difference in the leakage of amniotic fluid following CVS (odds ratio contains 1) or preterm spontaneous rupture of the membranes before 28 weeks. Nor was there any effect on antenatal admission to hospital.

- Pregnancy Outcome: there was an increase of 30% in the number of preterm deliveries and small for gestational age babies in the CVS group. Pregnancy loss was more common after allocation to the CVS group (OR 1.33, CI 1.17, 1.52). There were an increased number of terminations for abnormal prenatal tests in the CVS group - this could be due to the higher number of false positives. Furthermore there is a worrying but NOT statistically significant increase in the number of stillbirths and neonatal deaths following CVS.

- Neonatal Complications: The hypothesis of increased limb deformities and adverse effect on respiratory function after CVS was NOT supported.

- Transabdominal CVS vs. Amniocentesis: there was no differential effect on total pregnancy loss, spontaneous loss before viability, number of stillbirths and neonatal deaths, and number of congenital anomalies. However there were more abnormal karyotypes in the transabdominal CVS group (1.93, CI 1.31, 2.84).

- Transcervical CVS vs. Amniocentesis: there were significantly more pregnancy losses following transcervical CVS than amniocentesis (1.32, CI 1.12, 1.55). It also yielded more abnormal karyotypes (1.68, CI 1.42, 2.5). The number of spontaneous miscarriages reached statistical significance and a trend was noticed in the number of perinatal deaths.

b) The best evidence relating to Early amniocentesis versus transabdominal chorionic villus sampling for prenatal diagnosis is found in the Cochrane Database of Systematic Reviews. They tested the hypothesis that: Amniocentesis performed before 14 weeks gestation is as safe and accurate in obtaining correct prenatal diagnosis of foetal karyotype as transabdominal chorionic villus sampling (CVS) performed during the same gestational age interval. The participants were pregnant women requesting invasive prenatal diagnostic testing for foetal chromosome or genetic disorders before 14 weeks gestation. All randomised comparisons of early amniocentesis and transabdominal CVS were eligible. Three studies satisfied the inclusion criteria, specific details are available in the review. Data was analysed according to the allocated intervention allowing ‘intention-to-treat’ analysis. The statistical handling of the data was good.

- Technical Difficulties in Sampling: Sampling failure, multiple insertions, and need for a second test occurred more frequently in the CVS group, although the overall incidence of these complications was low. Sampling failure was 0.4% in the early amniocentesis group compared with 2% in the CVS group (RR 0.23, CI 0.08, 0.65).

- Cytogenetic Analysis: there were no statistically significant differences in the rate of laboratory failures (RR 0.43, CI 0.17, 1.10) or number of women with various chromosomal abnormalities (RR 0.51, CI 0.26, 1.04), however less than 1.8% (33) of the trial population had abnormal karyotype making meaningful analysis difficult.
There were no false negatives in either group and only one false positive in the CVS group, but this was not statistically, nor likely to be clinically, significant.

- **Pregnancy Complications:** fewer women bled after early amniocentesis (RR 0.57, CI 0.35, 0.94) but they did experience more amniotic fluid leakage (RR 48.83, CI 2.98, 801.12).
- **Pregnancy Outcome:** combined total pregnancy loss in the early amniocentesis group was 6.2% (57/915) compared with 5% (46/917) in the CVS group (RR 1.24, CI 0.85, 1.81). There were more spontaneous miscarriages after early amniocentesis (4.4% v. 2.3%, RR 1.92, CI 1.14, 3.23).
- **Neonatal Outcome:** There was no difference in the incidence of neonatal respiratory distress (RR 1.06, CI 0.64, 1.76). There was no difference in the overall incidence of anomalies in the newborn infants (RR 1.70, CI 0.90, 3.2). The incidence of talipes in the early amniocentesis group was 1.8% compared with 0.2% in the CVS group (RR 6.43, CI 1.68, 24.64). Haemangiomas were more common in the CVS group (0.1% in the early amniocentesis group compared with 1.3% in the CVS group (RR 0.18, CI 0.04, 0.79). Finally none of the infants had abnormal results when assessed for development using the Denver developmental screening test at 6 and 9 months.

**Laws in Relation to Termination of Pregnancy**

The legal position regarding abortion in the UK and Ireland is summarised as follows:

**Ireland**

DeVries reviews this topic very well. Article 40.3.3 of the Irish Constitution deals with the issue of abortion. Following referenda in 1987 and 1993, the latter following the infamous X case, it now reads:

‘The state acknowledges the right to life of the unborn and, with due regard to the equal right to life of the mother, guarantees in its laws to respect, and, as far as practicable, by its laws to defend and vindicate that right.

This subsection shall not limit freedom to travel between the state and another state.

This subsection shall not limit freedom to obtain or make available, in the state, subject to such conditions that may be laid down by law, information relating to services lawfully available in another state.’

Effect is given to paragraph 3 of Article 40.3.3 by the Regulation of Information Services Outside the State for Termination of Preganancies Act, 1995. It allows doctors to provide patients with names and addresses of abortion clinics abroad. They cannot advocate abortion, nor can they make arrangements on behalf of their patients.

**United Kingdom**


1. The continuance of the pregnancy would involve risk to the life of the pregnant woman greater than if the pregnancy were terminated.

2. The termination is necessary to prevent grave permanent injury to the physical or mental health of the pregnant woman.

3. The pregnancy has not exceeded its 24th week and the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, or injury to the physical or mental health of the pregnant woman.

4. The pregnancy has not exceeded its 24th week and the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the existing children of the family of the pregnant woman.

5. There is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped.

A certificate of opinion is given by two medical practitioners before the commencement of treatment for the termination of pregnancy to which it refers.

A single practitioner may give an emergency certificate before termination or, where not reasonably practical, within 24 hours of termination and terminate a pregnancy if it is necessary to save the life of the pregnant woman or to prevent grave permanent injury to her physical or mental health.

**Methods of Terminating Pregnancy**

There is a lack of randomised controlled trials comparing methods of termination in the 2nd trimester. An accepted method of medical induction of abortion after 14 weeks of gestation is the combination of prostaglandin-2 applied to the cervix and oxytocin given intravenously. This technique (Extra-Amniotic Prostaglandin Termination) involves the slow instillation of PGE2 into the cervix through a Foley catheter at a rate not exceeding 2.5 ml per hour. After 6-8 hours of PGE2 the cervix will be soft enough to allow the action of oxytocin given intravenously in gradually increased dosage up to 150 mU/minute. Abortion should occur within 24 hours and the uterus should then be curetted under general anaesthesia. The risks of medical damage include infection and cervical damage.

An alternative approach involves the use of mifepristone. Ashok et al reviewed 500 cases of mid-trimester termination of pregnancy using a regimen combining mifepristone followed by a combination of the vaginal and oral administration of misoprostol. Each woman received an oral dose of mifepristone followed 48 hours later by misoprostol. Three hours
following the first dose of misoprostol further doses were given orally at 3 hourly intervals to a maximum of four doses. Ninety-seven percent aborted successfully (within 5 doses of misoprostol or 15 hours of first dose of misoprostol).

**SUMMARY**

When advising this woman I would adopt the following strategy:

- I would outline the types and effects of the common chromosomal anomalies that are screened for on testing.
- Although not mentioned in this essay, I would outline the option of antenatal screening, based on analysis of blood alpha-fetoprotein, oestriol and beta-HCG levels, as a non-invasive first step prior to undertaking the invasive antenatal diagnostic tests.
- I would outline the availability of first and second trimester testing. I would strongly recommend second trimester amniocentesis unless she had a particularly strong desire to proceed with first trimester testing.
- When discussing second trimester testing I would emphasise:
  - amniocentesis is accurate and less likely to result in a false-positive result.
  - amniocentesis is technically simpler than CVS.
  - Maternal complications are uncommon and foetal loss is less common after amniocentesis (loss rate 0.5-1%) compared with CVS (1-1.8%).
  - CVS is highly operator dependent. The transabdominal route is safer than the transcervical. The postulated relationship between CVS and limb deformities is much exaggerated.

When discussing first-trimester testing, the points I would develop are:

- First trimester amniocentesis is technically easier than CVS
- Fewer women bleed after amniocentesis but they experience more amniotic fluid leakage.
- Early amniocentesis is associated with a 6.2% pregnancy loss rate whilst CVS has a 5% loss rate. This difference was not statistically significant.
- Talipes deformity occurs in approximately 2% of children assessed by amniocentesis. This is 10 times the rate in those assessed by CVS.
- Haemangiomas occurred in 1.3% of the CVS group. This is 13 times the rate in the amniocentesis group.
- There is no long-term developmental problem as a result of first-trimester testing as assessed by either method.

With respect to the issue of termination:

- Abortion is not available in Ireland. Information may be given about centres in Britain that perform them. In Britain one can avail of an abortion on the basis that the child will suffer from incapacitating handicap.
- An abortion beyond 19 weeks is best procured by a procedure based on pre-treating with mifepristone, followed 48 hours later by regular doses of misoprostol. Ninety-seven percent abort within 15 hours of the first dose of misoprostol.

**REFERENCES**


**Editor’s note:** Please note the lack of emphasis on non-invasive methods of prenatal diagnosis of Down Syndrome which would be employed more frequently in clinical practice. The question posed was with regard to diagnosis – i.e. the only way to definitely diagnose Down Syndrome prenatally would be via amniocentesis or chorionic villous sampling. We do not wish to present a skewed representation of clinical practice to the general medical reader and hence have included a short segment on screening tests for Down Syndrome.
Screening Tests for Down Syndrome

_Tze Y Kong, Sub-Editor TSMJ_

The basic principle of antenatal screening for Down Syndrome is to adequately detect pregnancies that are at high risk of the condition. This target population can then be subjected to diagnostic tests for the condition; diagnostic tests that would be otherwise of an unacceptable risk-benefit ratio if applied to the general population. Characteristics of an ideal screening test thus include ease of use, low cost, low risks to mother and foetus, with results bearing high sensitivity and specificity for the condition. The aims of antenatal Down Syndrome screening hence endeavour to approximate these ideals. This is achieved by using multiple approaches and a combination of their results.

**Serum Markers**

The principal serum markers of value between the 15th and 22nd week of pregnancy are:
- Maternal serum alpha foetoprotein (MSAFP)
- Oestriol (UE3)
- Total human chorionic gonadotrophin (total hCG) and its subunits (free a-hCG and free b-hCG)
- Dimeric inhibin A

Other markers found to be of lesser value are:
- Schwangerschaftsprotein-1 (SP1) or Pregnancy-specific b1-glycoprotein
- a inhibin

Urea-resistant neutrophil alkaline phosphatase (URNAP) is still under evaluation.

Most screening programmes utilise multiple markers, as this increases the detection rates, namely the double (maternal age, MSAFP and either total hCG or free b-hCG) and triple tests (maternal age, MSAFP, total hCG, UE3). Recently, inhibin A has been introduced into routine screening practice in the United Kingdom, forming a quadruple test. For a 5% false-positive rate, the detection rates are estimated to be 59% for the double test and 69% for the triple test. This increases to 76% for the quadruple test. Gestational age should be based on an ultrasound scan.

**Urinary Markers and Foetal Cells in Maternal Blood**

Urinary b-core hCG, a breakdown product of hCG, has shown to be elevated in affected pregnancies. When combined with maternal age, predicted detection rates range from 41-80%, due to the small sample sizes of the studies to date. Other promising markers include free urinary b-hCG and total urinary UE3.

The most successful type of foetal cell recoverable from maternal blood is the nucleated red blood cell. Given the rarity of these cells in the maternal blood, at approximately 1-2 foetal cells per 10 million maternal cells, sophisticated techniques must be used for their analysis. Fluorescent in-situ hybridisation (FISH), magnetic activated cell sorting (MACS) or polymerase chain reaction techniques to identify the extra chromosome 21 are employed. However, its widespread use is not financially feasible at this point in time.

**Ultrasound Markers**

Nuchal fold thickness is the most discriminatory ultrasound marker of Down Syndrome at 15-22 weeks gestation on its own. However, it is not discriminatory enough to be used alone for screening. Studies investigating its role in combination with serum markers have not been completed to date. Nuchal translucency has also been found to be a useful marker at 10-14 weeks gestation, but lacks proper quantification of its performance alone and in combination with serum markers.

**Cost-effectiveness and Safety**

In classic cost-benefit analyses, the costs of the screening tests are weighed against the lifetime cost of caring for people with Down Syndrome. Such comparisons however lack consideration of individual choices and the impossibility of placing a monetary value on human life. Screening for Down Syndrome aims to allow parents to prepare for the birth of their child, emotionally and mentally. In countries and societies where abortion is available, screening is utilised by some as a means of terminating the pregnancy before its completion. With this in mind, screening has to be approached with great sensitivity. Pre-screening counselling and the exploration of expectations and motives have to be undertaken with the parents-to-be. Physicians have to carefully guide parents through the implications of test results, as the predictive values are not absolute. Additionally, the choice to undergo further invasive antenatal diagnostic tests carries inherent risks towards the foetus. In this respect, more detailed screening reduces the number of women undergoing an invasive diagnostic procedure that may result in foetal loss. The number of unaffacted foetal losses per Down Syndrome birth avoided declines by 24% from 0.59 (double test) to 0.45 (quadruple test).

**Conclusion**

The current screening programmes lack uniformity. Multiple, uncoordinated step-wise screening and inequity of access to the service are the issues to be addressed. The establishment of local screening units with dedicated personnel, having full responsibility for their service has also been proposed. With the advent of more screening methods, a constantly updated protocol from a properly conducted organising body would be in order.

**References**