Amniocentesis and chorionic villus sampling for prenatal diagnosis

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On safety grounds, second-trimester amniocentesis is better than transcervical CVS and early amniocentesis. For prenatal diagnosis in the first trimester, transabdominal CVS and transcervical CVS should be considered, in that order of preference. The effectiveness of amniocentesis and CVS depends on the technical proficiency of operators for invasive prenatal diagnosis.

RHL Commentary by Oladapo OT

1. INTRODUCTION

The burden of genetic disorders is heavy in all parts of the world, but the impact is most felt in under-resourced settings owing to lack of preventive measures and specialized health and social services to care for affected individuals. As a result of the high birth rate, consanguinity and procreation till later reproductive years, a large number of infants with genetic disorders are born each year to families in underserved populations. In India for instance, approximately half a million children are born annually with congenital malformations, most of which are related to genetic or chromosomal aberration (1). It is estimated that about 9000 babies with thalassaemia major, 5200 babies with sickle cell disease and 21 000 babies with Down syndrome are born in India each year (1). Of all single-gene disorders of public health importance in developing countries, only sickle cell anaemia has an incidence greater than 1 per 1000 in any ethnic group. The high frequency of the carrier status of the disease among the African populations, particularly those from West African countries, has ensured the persistence of the sickle cell gene. For instance, in Nigeria, where the prevalence of the gene carriers is approximately 25% (2), about 1%–2% of children are born with sickle cell anaemia.

As a result of the social, psychological and economic implications of caring for children born with genetic and chromosomal disorders, most pregnant women with affected offspring would wish to be reassured that their unborn baby is healthy. Access to safe, accurate and affordable screening and diagnostic tests for the unborn baby at a time that avails the mother an option of pregnancy termination is therefore essential to limit the proliferation of abnormal genes and chromosomes in under-resourced populations. Presently, the definitive and accurate diagnosis for most disorders can only be made from fetal cells obtained through first trimester amniocentesis (usually performed between 9 weeks and 14 weeks of gestation). Second-trimester amniocentesis (at 16-18 weeks of gestation) and chorionic villus sampling (CVS) by transabdominal or transcervical route. However, there are concerns about the safety and diagnostic accuracy in relation to timing and techniques of these procedures. It was against this background that this review (3) was conducted to compare the safety and diagnostic accuracy of all types of amniocentesis (both early and late) and CVS (transabdominal or transcervical) for prenatal diagnosis.
2. METHODS

The review authors used the Cochrane Pregnancy and Childbirth Trial Register to identify all randomized comparisons of late amniocentesis (after 15 weeks of gestation), early amniocentesis (before 15 weeks of gestation) and CVS (either transabdominally or transcervically) with each other or with no testing. The participants were pregnant women requesting invasive prenatal diagnostic testing for fetal chromosomal or genetic disorders. Outcomes considered in the review included those related to (i) technical difficulties in sampling, (ii) cytogentic analysis, (iii) pregnancy complications, (iv) pregnancy outcome, and (v) neonatal complications.

The criteria employed in the review for selection of eligible studies allowed relevant trials to be identified. However, the outcome measures included a wide range of variables and were not designated as primary and secondary outcomes. Fewer outcome variables that portray safety and diagnostic accuracy of the techniques would allow users of the review to weigh and appreciate their clinical significance. In addition, infectious morbidity as an outcome measure that depicts safety should be considered for the benefits of users of the review in under-resourced settings.

The basis for the use of total pregnancy loss (which included all terminations of pregnancy) to illustrate safety in the comparison of invasive prenatal tests is not clear since the aim of these interventions is to identify genetically abnormal fetuses for subsequent pregnancy termination. Though it can be argued that pregnancy terminations would balance out in a properly randomized controlled trial of two interventions, it is unlikely that such a balance would be achieved when an invasive technique is compared with no intervention (e.g. Second-trimester amniocentesis versus control). Trials that reported only total pregnancy losses without specifying the number of spontaneous miscarriages may not have conclusively provided evidence on the comparative safety of the interventions.

Most of the included studies in the review were of high methodological quality as indicated by the proportion of the trials with adequate allocation concealment (13 out of 16). Appropriate statistical methods were used to summarize the findings and data were clearly presented under different subheadings for easy understanding. However, exclusion of randomized trials on the basis of inadequate allocation concealment as performed in this review has been questioned on the grounds that some included trials with uncertain allocation concealment would have also fallen into this category if full information were available. In future updates, it might be better to make the inclusion/exclusion decisions on whether or not trials were randomized (and exclude quasi-randomized trials) rather than making the inclusion decision on allocation concealment (as currently advised by the Cochrane Pregnancy and Childbirth Group).

3. RESULTS

A total of 16 trials were included in the review.

3.1. Second-trimester amniocentesis versus control (no testing)

The review shows that second-trimester amniocentesis significantly increased the risk of spontaneous miscarriage in women who underwent the procedure compared with those who did not [one trial, 4606 women; relative risk (RR) 1.60; 95% confidence interval (CI) 1.02–2.52]. This evidence is essentially based on the findings of a large 1980s multicentre trial involving Danish women at low risk of pregnancy loss.

3.2. Second-trimester amniocentesis versus early amniocentesis

Second-trimester amniocentesis was found to be comparatively safer than early amniocentesis for invasive prenatal diagnosis. Early amniocentesis was associated with increased total pregnancy loss (one trial, 4334 women; RR 1.29; 95% CI 1.03–1.61) and congenital abnormalities (one trial, 4334 women; RR 1.73, 95%
CI 1.26–2.38) compared with second-trimester amniocentesis. It was also technically more demanding as evident from the increased risks of multiple needle insertions (one trial, 4368; RR 2.79; 95% CI 1.92–4.04) and insufficient yield of viable fetal cells required for chromosomal diagnosis (one trial, 4368; RR 9.76; 95% CI 3.49–27.26).

3.3. Second-trimester amniocentesis versus transcervical CVS

Four trials (6527 women) showed that the risk of total pregnancy loss was higher with transcervical CVS compared with second-trimester amniocentesis (RR 1.40; 95% CI 1.09–1.81). Although this finding appears plausible considering the technicality involved in the two procedures, the result needs to be interpreted cautiously as these trials demonstrated statistically significant heterogeneity due to inconsistencies in the findings of the largest two of the four trials. In addition, the trial that reported the highest rate of total pregnancy loss in the transcervical CVS group (19.5%) also recorded a significant loss to follow up (33.5%) (4).

3.4. Second-trimester amniocentesis versus transabdominal CVS

Evidence on the comparative safety of transabdominal CVS and second-trimester amniocentesis is provided by the subgroup analysis of one trial (2234 women), which showed no significant difference in the risks of total pregnancy loss between the two procedures.

3.5. Second-trimester amniocentesis versus CVS by any route

The total pregnancy loss was higher after CVS compared to second-trimester amniocentesis (two trials, 6503 women; RR 1.43; 95% CI 1.22–1.67) and increase in spontaneous miscarriage after CVS was the main contributing factor (two trials, 6280 women; RR 1.51; 95% CI 1.23–1.85).

3.6. Early amniocentesis versus transabdominal CVS

There was no difference in the total pregnancy loss but there were more spontaneous miscarriages after early amniocentesis (four trials, 5491 women; RR 1.76, 95% CI 1.17–2.64). Early amniocentesis was not as technically difficult as evident from the reduced risk of multiple insertions (three trials, 4445 women; RR 0.47; 95% CI 0.29–0.74) and second test performed (four trials 5566 women; RR 0.59; 95% CI 0.36–0.98). Although there was no significant difference in the overall incidence of anomalies in the newborn, there were more cases of talipes equinovarus with early amniocentesis compared to transabdominal CVS (four trials, 5305 women; RR 4.61; 95% CI 1.82–11.66).

3.7. Transcervical versus transabdominal CVS

The comparison of transcervical and transabdominal CVS does not show statistically significant differences in the risks of total pregnancy loss and spontaneous miscarriage. However, transcervical CVS appeared to be technically more demanding as indicated by the increased risks of multiple insertions (two trials, 1314 women; RR 2.73; 95% CI 1.78–4.17).

3.8. Diagnostic accuracy of procedures

Most of the trials were not well designed to assess adequately the diagnostic accuracy of invasive prenatal testing and therefore could not provide a satisfactory answer to the second question of the review. With the currently available data, it is not possible to weigh the benefits of the various amniocentesis and CVS procedures for prenatal testing against the risks of diagnostic imprecision of these procedures.

4. DISCUSSION
4.1. Applicability of the results

The authors concluded that, on safety grounds, second-trimester amniocentesis is better than transcervical CVS and early amniocentesis, and in situations where prenatal diagnosis in the first trimester becomes essential, options to be considered should be transabdominal CVS and transcervical CVS, in that order of preference. Expectedly, this conclusion was essentially based on the comparative effect of the procedures on continuation of pregnancy and neonatal structural anomalies.

The findings from the review have significant implications on the practice of obstetric specialists involved in prenatal testing in the developing countries. This is corroborated by several observational studies that attempt to provide local information on the safety of CVS in some developing settings like Nigeria (5, 6). It should be noted, however, that all the included trials that generated the evidence for this review were conducted in developed countries. Since the indication and scope for prenatal genetic testing, as well as infrastructural and technical capabilities, may considerably differ between the developed- and developing-country settings, the results need to be considered with caution. The operators in all the trials included in the review were generally experienced and were required to have done at least 20 procedures before participating in the trial. The level of experience and expertise of operators in under-resourced settings (most of whom are still on their "learning curve") may not produce similar results in such settings. Likewise, the interventions in the included trials were conducted in conditions and circumstances that may not be readily available in many under-resourced settings. A study in Nigeria highlights the difficulty associated with inadequate provision of basic infrastructural facilities such as power supply in the provision of high-quality prenatal diagnostic services (5).

Another important aspect to consider is the baseline risks of the participants in the reviewed studies and that of the potential clients in under-resourced populations. Some of the large trials that influenced the results of the review randomized women with low risk of genetic disorders. As most women presenting for invasive prenatal testing in developing-country settings are more likely to be those at high risk of genetic disorders (as a result of prohibitive costs and other factors), it is uncertain whether similar or worse outcomes would be expected in these populations.

4.2. Implementation of the intervention

The effectiveness of amniocentesis and CVS depends on the availability of appropriate diagnostic tools and technical proficiency for invasive prenatal diagnosis. Besides the expertise required for the collection of the sample, the procedure requires a highly technical laboratory support that may not be readily available in under-resourced settings. Presently, prenatal diagnosis in many developing countries is still in its infancy and services, where they exist, are still rudimentary (5). This may be connected with the poor awareness of the existence of such services within the population and the financial implications for individuals who need them. In Nigeria for instance, CVS and amniocentesis cost approximately US$ 1290, which is beyond the reach of most couples at risk of having genetically abnormal offspring. Besides costs, religious, social, infrastructural, political and cultural barriers may also restrict the feasibility of incorporating invasive prenatal screening of all at-risk pregnant women into the existing health-care services. As a result of these factors, routine screening of pregnant women aged 35 years and above as practiced in developed countries is unlikely to be a common practice in Nigeria and other similarly under-resourced countries for some time to come.
Nevertheless, as second-trimester amniocentesis and transabdominal CVS are technically less demanding compared with early amniocentesis and transcervical CVS, translating the evidence from this Cochrane review into clinical practice among operators in developing countries should not be problematic. The generally late presentation of their obstetric population for antenatal care also makes second-trimester amniocentesis a more feasible option for women who need them. Availability of non-invasive triple marker testing for detection of Down syndrome, however, is likely to restrict the uptake of invasive methods by women over the age of 35 years where both types of service are available.

Therefore, implementation of this intervention has to be balanced against the specific needs of the population needing obstetric interventions, its feasibility and cost-effectiveness as well as views of the potential clients. Pregnant women who request invasive prenatal testing should be counselled appropriately on the various available approaches to make an informed choice. Clinicians and operators alike should not take advantage of the weak medico-legal systems in under-resourced settings to coerce women to accept techniques that contravene what is suggested by available evidence, but with which they are more familiar. In the present situation, the financial and emotional savings of detecting a specific genetic disorder must be able to justify the high cost of any invasive prenatal test employed. Mechanisms for quality assurance have to be put in place to maintain standards and deviation from evidence-based approach should be met with some form of sanction. Introduction of invasive prenatal testing services in settings where there are strong cultural, religious and political barriers to prenatal diagnosis needs to be gradual and should be preceded by education of the populace on the benefits and risks. Necessary measures must be taken to prevent the abuse of this technology in settings where they are readily accessible. For instance, the use of amniocentesis or CVS for fetal sex determination and selective abortion of female fetuses as practised in some developing countries should be discouraged (7).

### 4.3. Research

Subsequent trials should address the issue of diagnostic accuracy of the methods as it has to be balanced with their safety concerns for women to make an informed choice. New trials should include centres from developing countries to improve their external validity and universal applicability. Outcome measures should include infectious morbidity to provide information for settings where postoperative infection is still a major problem. The cost-effectiveness of introducing the intervention in individual populations, amidst other pressing needs, could be researched to prepare grounds for a successful implementation.

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