Comparison between disclosure and non-disclosure approaches for trisomy 21 screening tests

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BACKGROUND: First-trimester nuchal translucency (NT) and second-trimester triple test (TT) are common screening programmes for trisomy 21. The aim of this study was to compare disclosure and non-disclosure approaches of combining those tests. METHODS: Likelihood ratios of both NT and TT tests, among 508 normal and 23 trisomy 21-affected pregnancies, were used for calculating population-adjusted risks. Disclosure approach incorporated all cases which, by either NT or TT, exhibited a risk ≥1:250 whereas non-disclosure approach generated a new integrated figure ≥1:250. RESULTS: Among women aged ≤34 years, the disclosure and non-disclosure approaches were associated with false positive rates of 4.3 and 1.1%, detection rates of 76.4 and 61.2%, positive predictive value (PPV) of 1:53 and 1:17, and false negative rate of 1:3129 and 1:1985 respectively. CONCLUSIONS: The disclosure approach resulted in considerably higher detection rates. The non-disclosure approach, however, was four times better regarding the number of invasive procedures required to detect one case of trisomy 21. However, the positive predictive value associated with the disclosure policy was still much more beneficial than that obtained in women aged ≥37 years, who are routinely referred to fetal karyotyping.

Key words: disclosure/non-disclosure/nuchal translucency/triple test/trisomy 21

Introduction

Screening approaches for the detection of trisomy 21 have undergone remarkable changes during the last decade. The traditional second trimester serum screening, introduced in the 1980s (Cuckle and Wald, 1984), had been improved to detect about 60% of trisomy 21 cases, yielding a false positive rate (FPR) of ~5% (Haddow et al., 1992; Wald and Hackshaw, 1997). A decade ago, first-trimester ultrasound screening programmes broke through (Nicolaides et al., 1992) and their feasibility and effectiveness were reconfirmed by numerous reports (Snijders et al., 1998; Hafner et al., 1998; Thilaganathan et al., 1999). Except for the advantage of being able to apply it at an earlier stage of gestation, the overall performance of nuchal translucency (NT) in detecting trisomy 21 was quite similar to that of the second-trimester test (Wald and Hackshaw, 1997; Hafner et al., 1998; Thilaganathan et al., 1999). When the NT approach was first introduced, it was met with some reluctance because of the possibility that the addition of yet another screening modality could cause confusion due to potentially contradictory results of the various tests. The main argument against its routine incorporation, however, was the apparently higher FPR that it yielded. To overcome this problem, Wald et al. recently proposed integrating the results of the first-trimester and second trimester screening tests and generating a single risk. By using non-disclosure statistical modelling of different studies, the authors (Wald et al., 1999) showed the potential benefit of reaching a detection rate above 85%, associated with a low FPR of ~1%. Cuckle recently discussed at length the question of how to combine different screening modalities, and concluded that this question needs to be evaluated in terms of efficiency, without overlooking the issues of individual choice (Cuckle, 2001). The dilemma which bothers many investigators and clinicians alike is which modality to use: (i) disclosure approach (in which the tests are performed sequentially)—this approach leads to relatively high FPR and, probably, a better detection rate (DR); or (ii) non-disclosure approach—an approach which expresses the risk in one figure and is associated with much lower FPR, but its clinical performance still requires validation.

The aim of the present study was to compare the results of the disclosure and non-disclosure approaches, using the clinical data of first-trimester ultrasound and second trimester serum screening tests, among the same groups of normal and trisomy 21-affected pregnancies.

Materials and methods

The study included 508 consecutive normal pregnancies and 23 trisomy 21-affected pregnancies. All underwent both first-trimester
ultrasound screening (operated at Assaf Haroheh Medical Center, Israel, since 1997) and second-trimester maternal serum screening.

First-trimester ultrasound screening was principally based on nuchal translucency (NT) measurements between 10 and 14 weeks gestation, according to the method described by others (Nicolaides et al., 1992). Institutional review board approval was obtained for this study and each subject gave her signed informed consent to participate in it. Trisomy 21 risk calculation was based on the software provided by the Fetal Medicine Foundation. Second-trimester biochemical screening was performed at 16–19 weeks gestation and included the three components of the ‘triple test’ (TT), i.e. alpha-fetoprotein, intact human chorionic gonadotrophin and unconjugated estriol.

The methodology of collecting data among the 508 normal pregnancies was previously published by us (Herman et al., 2000). The detailed information of the 23 cases with trisomy 21 was obtained from various sources: eight cases from our local first-trimester ultrasound screening programme, 11 cases which were scanned elsewhere and referred to our facility for termination of pregnancy, two cases from neighbouring hospitals and two cases which were identified as trisomy 21 after birth. Only those cases for which the NT images were of sufficiently good quality, as defined elsewhere (Herman et al., 1998), were included. Second-trimester serum test results were available in all cases and, whenever amniocentesis was performed, blood was drawn before the invasive procedure was undertaken.

Each test was analysed by eliminating the maternal age-derived background risk and obtaining its likelihood ratio (LR). Those LR were used to calculate age-adjusted FPR and DR for: NT alone, TT alone, the disclosure and the non-disclosure approaches. Age-adjusted risk was calculated for maternal age between 20 and 44 years in 1 year increments. Age-related (prior) odds during the second trimester, expressed in 1:, was derived from previous studies (Snijders et al., 1994; Nyberg et al., 1998) using a threshold value of 1:250. Data for calculating FPR were obtained from normal pregnancies group, and the DR were calculated from the data of the trisomy 21-affected pregnancies group. Positive predictive values (PPV) and false negative rates (FNR) were calculated from both groups in conjunction.

Calculations of NT alone and TT alone were straightforward, using the age-derived background risks and the LR of the tests, but the application of the non-disclosure and disclosure modalities requires further explanation. The disclosure approach means that a single case was considered ‘positive’ if either the NT and/or the TT age-adjusted risk was $\geq$1:250. The non-disclosure approach involves the generation of a new integrated risk derived from the multiplication of the LR (\(LR_{\text{integrated}} = LR_{\text{NT}} \times LR_{\text{TT}}\)) (Orlandi et al., 1997; Cuckle and Sehmi, 1999) and was considered as ‘positive’ only if this integrated age-adjusted risk was $\geq$1:250.

Comparison of the disclosure versus the non-disclosure approach was examined by evaluating population-adjusted figures including: FPR, DR, PPV (odds of being affected given a positive result) and FNR (odds of being affected given a negative result). The methodology of population-adjusted calculations was described previously (Pandya et al., 1995; Biagiotti et al., 1997) and since the calculations require overall maternal age distribution, we used information provided (The Central Bureau of Statistics, Israel, 2000) on maternal age distribution. The comparison referred to three populations: patients of $\leq$34 years, all patients of $\leq$39 and the total population.

Results

Age-adjusted figures—FPR and DR for NT alone, TT alone, disclosure approach and non-disclosure approach—are presented in Table I. Although the calculations used later for population-adjusted results referred to maternal ages at yearly increments, Table I presents the results between 20 and 30 years in 5 year increments and between 30 and 44 years in 2 year increments. Both the FPR and the DR could quite clearly be seen to increase in parallel to maternal age for each of the tests. The DR of both NT and TT analyses were $<50\%$ in the youngest group of patients and it approached 100% in the oldest ones. The reason for the last feature is that when the prior odds are very high (e.g. 1:20), even a low LR of 0.15 will still result in a final risk that is $>1:250$. The disclosure approach was consistently associated with a four-fold higher FPR compared with the non-disclosure approach. Those FPR were still reasonable for young patients: 3.5, 6.3 and 7.5% for patients of 20, 30 and 32 years of age respectively. However, this modality was associated with the extremely high FPR of 29.3 and 42.7% for the 38 and 40 year old patients respectively. Compared with each test alone the non-disclosure approach was associated with lower FPR and higher DR. It demonstrated remarkably low FPR, across most maternal ages, starting with 0.8% for 20 year old patients, 1.8% for patients of 30 years of age, 4.9% for patients of 36 years of age and reaching 10.2% for patients of 40 years of age. The DR of the disclosure approach were consistently higher than those obtained by the non-disclosure approach. Whereas they were $\geq80\%$ for patients of $>30$ years of age by the first method, they reached this figure only for patients of $>38$ years of age by the second approach.

Population-based calculations, i.e. dividing the screened population according to age groups, are presented in Table II. In patients of $\leq34$ years the non-disclosure approach was associated with a low FPR (1.1%) and a remarkably high PPV (1:17) but with relatively low DR of 61.2% and an FNR of 1:1985. The disclosure approach in this group resulted in a much higher FPR (4.3%), a lower PPV (1:53), higher DR (76.4%) and a much lower FNR (1:3129). The figures for the total population showed that disclosure approach was associated with highest DR close to 90% and FNR of 1:2640. The non-disclosure approach was associated with low FPR of 2.4% and higher PPV of 1:12.

Discussion

Our present results validate theoretical calculations performed (Wald et al., 1999) and statistical modelling presented (Cuckle, 2001), that the non-disclosure approach concomitantly improves trisomy 21 detection and lowers the FPR, compared with each test alone. Although our findings fall short of being absolutely accurate, because of a bias that will be discussed later, they do faithfully incorporate the major properties of each of the two approaches. This is the first report of such an undertaking, based on clinical findings, and we hope that our data will help diagnostic centres to solve the dilemma of choosing the most appropriate modality.

Sequential screening means that patients identified as being at an increased risk by the first test undergo karyotyping and the rest are referred to a second test and act upon its results. However, the absence of data of both screening tests simultaneously, for those undergoing early karyotyping, may
Table I. Age-adjusted false positive rate (FPR) and detection rate (DR) according to trisomy 21 screening test and approach of combination using a threshold of 1:250

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Prior oddsa</th>
<th>NT alone</th>
<th>TT alone</th>
<th>Disclosure approach</th>
<th>Non-disclosure approach</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FPR (%)</td>
<td>DR (%)</td>
<td>FPR (%)</td>
<td>DR (%)</td>
</tr>
<tr>
<td>20</td>
<td>1:1176</td>
<td>0.8</td>
<td>47.8</td>
<td>2.8</td>
<td>39.1</td>
</tr>
<tr>
<td>25</td>
<td>1:1040</td>
<td>1.0</td>
<td>56.5</td>
<td>3.3</td>
<td>39.1</td>
</tr>
<tr>
<td>30</td>
<td>1:690</td>
<td>1.6</td>
<td>60.9</td>
<td>4.7</td>
<td>43.5</td>
</tr>
<tr>
<td>32</td>
<td>1:508</td>
<td>2.2</td>
<td>60.9</td>
<td>5.3</td>
<td>47.8</td>
</tr>
<tr>
<td>34</td>
<td>1:342</td>
<td>2.6</td>
<td>60.9</td>
<td>8.1</td>
<td>52.2</td>
</tr>
<tr>
<td>36</td>
<td>1:216</td>
<td>3.9</td>
<td>65.2</td>
<td>15.6</td>
<td>78.3</td>
</tr>
<tr>
<td>38</td>
<td>1:129</td>
<td>7.9</td>
<td>69.6</td>
<td>23.8</td>
<td>78.3</td>
</tr>
<tr>
<td>40</td>
<td>1:74</td>
<td>13.0</td>
<td>69.6</td>
<td>35.2</td>
<td>82.6</td>
</tr>
<tr>
<td>42</td>
<td>1:42</td>
<td>80.3</td>
<td>100</td>
<td>90.6</td>
<td>100</td>
</tr>
<tr>
<td>44</td>
<td>1:23</td>
<td>100</td>
<td>100</td>
<td>93.5</td>
<td>100</td>
</tr>
</tbody>
</table>

aAge-derived background risk of being affected during the second trimester.
NT = nuchal translucency; TT = ‘triple test’.

Table II. Population-based calculated false-positive rate (FPR), trisomy 21 detection rate (DR), positive predictive value (PPV) and false-negative rate (FNR), according to screened population and using a threshold of 1:250

<table>
<thead>
<tr>
<th>Screened population</th>
<th>Disclosure approach</th>
<th>Non-disclosure approach</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FPR (%)</td>
<td>DR (%)</td>
</tr>
<tr>
<td>Patients ≤34 years old</td>
<td>4.3</td>
<td>76.4</td>
</tr>
<tr>
<td>Patients ≤39 years old</td>
<td>7.2</td>
<td>83.8</td>
</tr>
<tr>
<td>All patients</td>
<td>9.5</td>
<td>88.7</td>
</tr>
</tbody>
</table>

prohibit any comparison between the approaches. Recently, others (Audibert et al., 2001; Schuchter et al., 2001) reported on results of sequential screening by first-trimester ultrasound and second-trimester biochemistry. In those studies the FPR among 4130 and 9342 low-risk patients were between 5 and 7.2% respectively; and trisomy 21 DR, among 12 and 19 affected cases, were around 90%. Nevertheless, their methodology could not allow a meaningful comparison between the disclosure policy, utilized by them, and the non-disclosure one. In order to compare between the two approaches a prospective mass population study, for whom results of both tests are available simultaneously, is needed. Since such a study is not yet available we applied an age-adjustment risk technique that might help to close the gap between a theoretical statistical model and such a large undertaking. This method uses the net results of the tests, i.e. their LR, and its utilization is based on the fact that the distributions of the tests’ results are not influenced by maternal age in normal or trisomy 21 pregnancies. In essence, this constitutes the principle of ‘calculated risk’ which uses the maternal age-derived background risk and the test’s LR. Thus, the major possible bias that should be considered in the current study concerns the selection of our cases: normal pregnancies on the one hand and trisomy 21 on the other.

Our data on normal pregnancies were gathered prospectively in a consecutive manner and the FPR found were within the acceptable ranges. The only bias that could not be overcome resides in the fact that we are dealing with two tests that had been performed during substantially different time periods. This refers mainly to cases with a markedly thickened NT, which involve women who opt for early karyotyping or even termination of pregnancy. A non-disclosure policy would not appear to be practical in all cases in such circumstances. First-trimester ultrasound screening is not an anonymous test whose results are usually mailed days later, as is the case for TT results. The women undergoing real-time ultrasound examination invariably carefully scrutinize both the ultrasound screen and the examiner’s face, and are highly sensitive to any hint of some abnormality. Neither the examiner nor the woman’s obstetrician can or should overlook the meaning of test results, nor attempt to shield them from her. This is especially true in light of the fact that a thickened NT may also suggest an increased risk for other aneuploidies, cardiac anomalies as well as a variety of syndromes that warrant genetic counselling. Therefore, a method which requires complete data, of both tests for all cases, will inevitably miss some of those that are screen-positive by the first-trimester ultrasound test. The fact that disclosure approach resulted in a similar FPR of 7.2% in another study (Schuchter et al., 2001) as well as this one, among similar populations, points to minimal bias on this part.

The issue of possible bias among the trisomy 21-affected pregnancies requires further clarification. The fact that most
of the cases were screened elsewhere does not introduce a bias as long as both tests were performed according to the same protocol that was applied to the originally screened group (Wald and Hackshaw, 1997). The findings obtained from the trisomy 21 group are not intended to serve for the comparison between the screening programmes but rather for the examination of interrelationship between the net results of the tests in the same affected individuals. These data are utilized for the calculations of the DR, adjusted to different maternal ages or populations, as had been done in other studies (Snijders et al., 1994; Pandya et al., 1995; Biagiotti et al., 1997; Nyberg et al., 1998).

Healthcare planners would probably prefer the non-disclosure approach, which may save costs by performing less invasive procedures, identify more cases of trisomy 21 (compared with each test performed alone), and reduce the number of post-testing abortions. Nevertheless, besides the already mentioned unique features associated with first-trimester NT examinations, our current findings provide relevant information which may affect the clinician’s attitude. The overall results of the disclosure approach show that the trade-off of the high FPR are its reasonable PPV between 1:40–50. This is a ratio which is much more fruitful than the prior odds of 1:250 or 1:300 in patients of 37 or 35 years old, who are routinely referred for invasive testing. In light of the fact that genetic counselling is aimed towards helping patients to come to their own decisions and respecting their autonomy (Holzgreve and Miny, 1993), this finding may prove a non-disclosure policy to be a problematic one.

Another issue that deserves attention is that of non-indicated karyotyping among young women. In an earlier study (Herman et al., 2000), we showed that 20% of women aged 30–34 years underwent amniocentesis despite receiving reassuring results of both screening tests. A previous study, also carried out in our country, reported that one case of trisomy 21 was detected for 917 amniocenteses procedures performed in women with a negative triple test (Shohat et al., 1995). This shows a lack of confidence in the screening tests, on the part of our population, and our present study’s results may contribute to a change in this trend. We have found that the odds of being affected given a negative result (FNR), of both approaches, were much lower than the values obtained by a single screening test. This was 1:1478 for the non-disclosure approach and almost one-half, 1:2640, with the disclosure policy. Thus, the latter approach affords another advantage by possibly helping to reassure young women that their individual risk of having a trisomy 21 fetus is, indeed, very low. The issue of elevating the maternal age threshold for routine karyotyping is beyond the scope of the current study. However, in pregnancies with correct dating of gestational age, our findings may support considering an elevation of the threshold to the age of 40 years when all the screening tests are reassuring.

It has already been shown that pregnancies achieved by assisted reproduction presented high serum screening FPR compared with natural pregnancies, whereas results of NT screening were unaffected by the mode of conception (Maymon et al., 1999). Here, a semi-sequential approach may prove to be beneficial and low risk NT results may serve as a buffer that balance the high positive TT results. Namely, following a disclosure approach of the NT test a non-disclosure approach, integrating low risk NT results with TT, may be utilized. A different study, among pregnancies achieved by assisted reproduction, may clarify the properties associated with each approach.

In summary, the results of this study validate previous theoretical calculations that the non-disclosure approach decreases the FPR and improves the DR compared with each test alone. The yield of this approach in terms of high PPV is most favourable. Although the PPV of the disclosure approach are three times worse, they are still much more fruitful than the current policy of referring all patients who are 35 or 37 years old for routine karyotyping. Serious ethical aspects and other implications make the non-disclosure approach less attractive and sometimes impractical. The disclosure approach overcomes these problems, is associated with higher detection and may contribute to the avoidance of unnecessary invasive testing. More studies are needed to supplement objective data to resolve the controversy surrounding prenatal screening.

References


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