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Prenatal Detection Rates of Chromosomal Aberrations by Amniocentesis, Chorionic Villus Sampling, First Trimester Screening, Non-Invasive-Prenatal Test and Triple-Test Under Everyday Conditions

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Abstract

Objective: Prenatal care entails a range of test methods for aneuploidy screening such as Amniocentesis (AC), Chorionic Villus Sampling (CVS), First Trimester Screening (FTS), and Non-Invasive Prenatal Tests (NIPT). It was the aim of this study to retrieve the detection rates of chromosomal abnormalities under real conditions in a medical practice.

Method: Pregnancies with fetal aneuploidy after 11+0 weeks of gestation were retrospectively analyzed. The findings were compared to theoretical detection rates assuming that all screenings were performed by NIPT.

Results: Forty-one cases remained for analysis, from which 18 were primarily detected by routine ultrasound prior to any other screening test.

Assuming that NIPT test strategy with or without preceding ultrasound examination would have been applied in all pregnancies, 62.5% respectively 71.5% of all chromosomal abnormalities would have been detected.

In five cases, AC and CVS were performed simultaneously. Four out of these five pregnancies were affected by mosaicism which developed placental insufficiency.

Conclusion: NIPT is not suitable to detect a wide number of chromosomal abnormalities, while about 60% of all aneuploidies are detectable solely by ultrasound examination. Placental mosaicisms offer a higher rate of NIPT without valid result, which have to be considered as test positive. This would strongly increase the false-positive-rate.

Keywords: Fetal aneuploidy; NIPT; First trimester screening; Mosaicism; Pregnancy; Chorionic villus sampling

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Introduction

Prenatal care entails a range of specialized test methods for aneuploidy screening such as amniocentesis (respectively chorionic villus sampling) [1,2], first trimester screening [3-5], the older triple-test [6-8], and Non-Invasive Prenatal Tests (NIPT) [9,10]. Prior to any diagnostic procedure, the expectant mother must be informed about its advantages and limitations [11], which also include the test performance like sensitivity and specificity. Thus, it was the aim of this study to retrieve the detection rates of chromosomal abnormalities under real conditions in a medical practice.

Methods

Pregnancies with fetal aneuploidy after 11+0 weeks of gestation which had been examined at the Women´s practice Bahnhofstrasse, Wolfenbüttel, Germany between 2003 and 2020 were retrospectively analyzed. The data were obtained from the practice documentation system and categorized according to the primary kind of genetic testing (primary conspicuous ultrasound, first trimester screening, amniocentesis, chorionic villus sampling respectively amniocentesis, NIPT, triple-test). In view of first trimester screening, it was documented whether the result was

conspicuous solely due to the ultrasound component (especially increased nuchal translucency), abnormal biochemistry, the combination of ultrasound and biochemistry, where each component was inconspicuous for itself but the combination was conspicuous, and findings, where the ultrasound, as well as the biochemistry were all conspicuous (Figure 1). The findings were compared to theoretical detection rates assuming that all screenings were performed by NIPT. Therefore, the values for sensitivity were considered according to published data as follows: Trisomy 21: 95.9%, trisomy 18: 86.5%, trisomy 13: 77.5%, sex chromosome abnormalities: 92.4% [10].

Results

Within the test cohort 40 pregnancies were affected by aneuploidies, including one twin pregnancy in which one fetus presented a free trisomy 21, while the other displayed a triple-X-syndrome. These two fetuses are considered as two separate cases. Three further cases entailed molecular genetic diseases. As this study solely focuses on cytogenetic aberrations, the latter cases were not included into further consideration. Hence, 41 cases remained for analysis.

Primary ultrasound

Out of 41 cases, 18 (43.9%) were primarily detected by routine ultrasound prior to any other screening test.

Primary first trimester screening

In 19 cases (46.3%) a first trimester screening was performed as primary test strategy. Thereof 18 were test positive, resulting in karyotyping by amniocentesis (n=6), chorionic villus sampling (n=8) or simultaneous amniocentesis with chorionic villus sampling (n=3). In one case spontaneous miscarriage occurred after first trimester screening prior to any further invasive testing. However, karyotyping could be performed in the aborted material. One case with false negative first trimester screening result was missed. In this case, a second trimester ultrasound scan at week 25+3 showed no malformation either. The diagnosis of trisomy 21 was first given after birth. In conclusion, 18 out of 19 (94.7%) chromosomal abnormalities were detected by first trimester screening. The test positive rate was 10.2% at a high-risk collective with an incidence for aneuploidies of 1:110.

Out of these 18 cases, four became test positive solely by abnormal ultrasound findings. A further five cases were detected due to abnormal biochemical values (especially low PAPP-A value). In three cases any component lead to a test positive result, while further two cases became conspicuous only by the combination of ultrasound and biochemistry values. No details were recorded for the remaining four tests.

Primary amniocentesis

Primary amniocentesis due to age indication (maternal age over 35 years) was performed in three cases (3/41; 7.3%).

Primary noninvasive prenatal testing (NIPT)

NIPT was applied as primary screening method in one case (1/41; 2.4%).

Primary triple test

Although triple test is quite outdated nowadays, in one case this screening strategy was required due to the following reasons: First pregnancy consultation took place at week 15 and hence too late for first trimester screening. Further, there was no maternal age indication for invasive diagnostic as the expecting woman was 27 years old, and NIPT was not available at that time. Both triple test as well as ultrasound scan at week 15+1 was inconspicuous. However, at week 28+6 the fetus displayed cardiac insufficiency. A subsequent amniocentesis showed a trisomy 21 karyotype. Hence, the only case for which a triple test was performed, received a false negative test result (sensitivity =0%). As this chromosomal abnormality was first detected by ultrasound, it is counted in the ultrasound group (primary ultrasound, refer above). Table 1 lists all detected aneuploidies arranged by their respective detection method.

Assuming that NIPT test strategy with or without preceding ultrasound examination would have been applied in all pregnancies of our cohort (Table 2), 62.5% (solely NIPT) respectively 71.5% (ultrasound followed by NIPT) of all chromosomal abnormalities would have been detected. The details are listed in Table 2. In the combined group, more aneuploidies were detected by ultrasound than by NIPT (18 *vs.* 11.3).

Discussion

In this study, 18 out of a total of 41 aneuploidies were primarily detected by abnormal ultrasound findings. Nevertheless, it must be noted, that all examinations were performed at a practice which is specialized in prenatal diagnostics and that in a non-specialized setting,

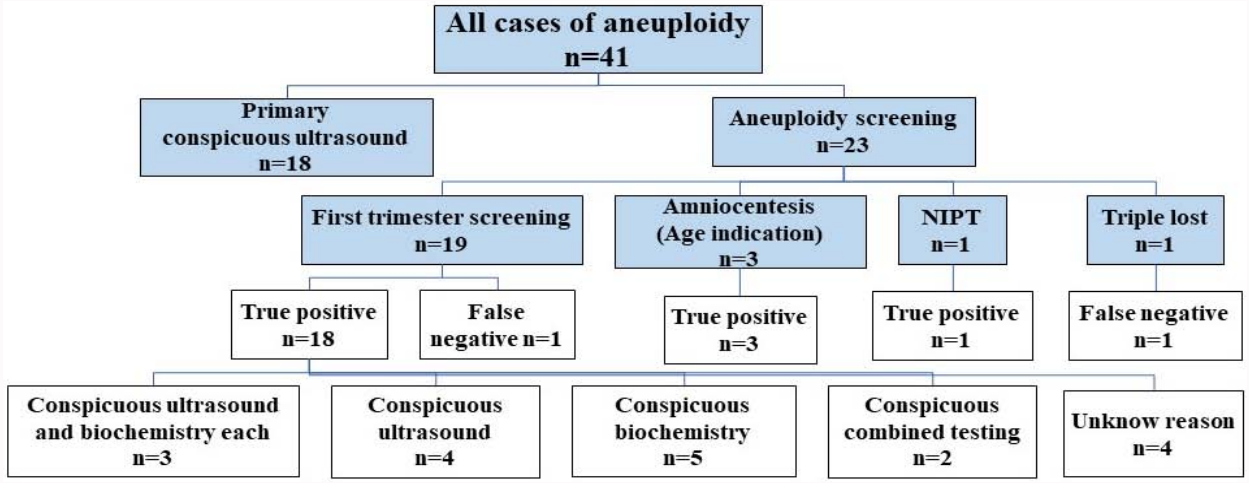

Figure 1: In view of first trimester screening.

Table 1: Number of cases detected by ultrasound and additional detection by subsequent screening methods. Total detection ratio in brackets. 1) Primary conspicuous ultrasound or thickened nuchal translucency; representing the actual purpose of ultrasound screening. 2) Additional number of detected aneuploidies by combined first trimester screening in comparison to the number of detected aneuploidies by primary ultrasound without measurement of NT (first column).

	Routine ultrasound	Routine ultrasound + thickened nuchal translucency at first trimester screening[1)]	Additional detection by combined first trimester screening[2)]	Amniocentesis or chorionic villus sampling[2)]	NIPT[2)]
Trisomy 21 (n=14)	4 (28.60%)	6 (42.90%)	+6 (→ 10/11) (90.9%)	+2 (6/6) (100.00%)	+1 (5/5) (100.00%)
Trisomy 18 (n=5)	3 (60.0%)	5 (100.0%)	+2 (→ 5/5) (100%)	no case	no case
Trisomy 13 (n=3)	2 (66.6%)	2 (66.6%)	+1 (→ 3/3) (100%)	no case	no case
Sex chromosomal abnormalities (n=6)	0 (0%)	1 (16.6%)	+6 (→ 6/6) (100%)	no case	no case
Others (n=13)	9 (69.2%)	11 (84.6%)	+3 (→ 12/12) (100%)	+1 (→ 10/10) (100%)	no case
Total (n=41)	18/41 (43.9%)	25/41 (61.0%)	36/37 (97.3%)	16/16 (100%)	5/5 (100%)

Table 2: Theoretical number of detected aneuploidies by NIPT with/without preceding ultrasound examination. Total detection rate in brackets. 1) Number of detected cases by ultrasound + number of detected cases by NIPT.

Aneuploidy	Solely NIPT	Ultrasound followed by NIPT[1)]
Trisomy 21 (n=14)	13.43/14 (95.90%)	4+9.59 (13.59/14) (97.10%)
Trisomy 18 (n=5)	4.32/5 (86.50%)	3+1.73 (4.73/5) (94.60%)
Trisomy 13 (n=3)	2.33/3 (77.50%)	2+0.77 (2.77/3) (100%)
Sex chromosomal abnormalities (n=6)	5.54/6 (92.40%)	0+5.54 (5.54/6) (92.40%)
Others (n=13)	0/0	9+0
Total (n=41)	25.6/41 (62.46%)	18+11,32 (29.32/41) (71.50%)

the detection rate would probably have been lower. Moreover, it is possible that further chromosomal abnormalities went undetected in this study, as the fetuses' karyotypes were not systematically analyzed after birth. Especially mosaicisms with low number of aneuploid cells could remain unremarked in this data set [12].

The point in time for the earliest possible detection of chromosomal disorders depends on the management of prenatal health care. According to the German Maternity Guidelines [13], the first ultrasound examination is scheduled around 10 weeks of gestation. Hence, a considerable number of affected pregnancies has already suffered a miscarriage to this point [14] and will not be documented. Furthermore, the latest examination date of a fetus with known aneuploidy is not equivalent to its possible survival time with a certain disease. On the one hand, some pregnancies would have continued longer but were terminated by decision of the mother. On the other hand, some fetuses already died days or even weeks before their diagnosis, depending on the time interval between the last two examinations. And finally, a remarkable number of pregnant women need some time to accept the severity of a given disease. In our patient group, a decision for abortion required up to two weeks with repetitive ultrasound sessions of the affected fetus, which underlines the high psychic stress of the parents [15].

Four women in this study were noticeably often affected by different kinds of aneuploidies (n=4 out of 41) in consecutive pregnancies without having a parental balanced translocation or comparable chromosomal defects. Further, the study found one twin pregnancy with simultaneous presence of trisomy 21 in one sibling and triple-X-syndrome in the other. It has to be assumed that there are other yet unknown reasons for repetitive aneuploidies [16], and it could be reasonable to perform frequent examinations at early gestational age in following pregnancies [17].

In five study cases, amniocentesis and chorionic villus sampling were performed simultaneously. Four out of these five pregnancies were affected by placenta mosaicism (1x trisomy 4, 1x trisomy 8, 2x trisomy 16). The fifth case had a complete trisomy 9. This demonstrates that chromosomal abnormalities, which usually result in early miscarriage, can still be found at later weeks of gestation [18]. In particular, this applies to placental mosaicisms [19]. Especially noticeable is one case with trisomy 16 in the chorionic villus sampling probe, while the corresponding amniocentesis probe revealed no trisomy, but an inversion of chromosome 6 and a 5% fraction of isodisomy, which underlines that both placenta and fetus are targets of chromosomal abnormalities and both are worth to be tested. Likewise, this again shows the higher risk for repetitive disorders, as described above. Generally, placental mosaicisms have a high risk for developing placental insufficiency and can therefore place the fetus at risk, even if it is healthy itself [20,21]. The described four mosaicism cases of this study all developed placental insufficiency between 30+6 and 37+3 weeks of gestation (median 31+4). Without previous genetic diagnostic, these four cases would not have been detected by the following routine ultrasound examination which would have been performed between week 19 and 22, according to the maternity guidelines [13], due to the lack of abnormal ultrasound findings. The subsequent routine ultrasound check-up would then have been scheduled between week 29 and 32 [13], when three out of the four fetuses would have already passed away without diagnosis. The fourth baby was still developing normal at that time and its mosaicism would not have been detected by ultrasound; however, it probably would have died in the further course of pregnancy. These four cases are representing the commonly known causes of unexpected fetal death and they are avoidable, when the expecting mother is offered well-matched diagnostics at early gestation [22].

Beneath sonographic examination, Pregnancy Associated Plasma Protein-A (PAPP-A) values in maternal blood are suitable to predict placental insufficiency in advanced gestation [23]. In this subgroup, a higher number of isolated placental mosaicisms are found [24-26].

As described above, abnormal placentas can be accompanied by

a similar or a fully different fetal aneuploidy. Hence, it is reasonable to gain amniotic fluid simultaneously to chorionic villus sampling in order to avoid a second puncture and loss of time. However, in Germany this proceeding is not financially covered by public health insurances. In contrast, an amniocentesis without simultaneous chorionic villus sampling will miss potential placental mosaicisms, including the risks of placental insufficiency and intrauterine death.

This study shows that PAPP-A, which is included in the combined first trimester screening, has great importance to identify pregnancies at risk [23-26], as 7 out of 14 first trimester screenings attained positive results solely or only in combination with PAPP-A. While this finding one more time underlines the benefit of this screening method, it also shows that measuring the nuchal translucency without simultaneously assessing the biochemical values is not a qualified proceeding [27].

One cases with trisomy 21 attained a false negative result during first trimester screening. The fetus did not show any malformation nor growth restriction during the entire pregnancy. Therewith, the sensitivity of first trimester screening is 94.7% regarding all cases [28], which were not already conspicuous during prior routine ultrasound screening around week 10. The test positive rate in our study is 10.3% at a high-risk collective with an aneuploidy incidence of 1:110, which is about 6-fold higher than in the normal population (about 1:600 [29]).

It is possible that cases, which were detected by ultrasound at a late gestational age, would have been detected earlier if a first trimester screening had been performed. In contrast, some cases would have been detected anyway by ultrasound examination during the further course of pregnancy if first trimester screening would not have been performed. This applies in particular to 7 out of 15 (46.6%) first trimester screening examinations that attained a positive test result based solely or as well on an increased nuchal translucency. The importance of ultrasound examinations is further underlined by the fact, that all trisomy 13 cases were primarily detected by ultrasound.

The presented detection rates are strongly dependent on the respective test strategy. It must be assumed that several cases would have also been detected by one or several other test methods, depending on which one had been applied as first screening method [30]. For example, a NIPT instead of a first trimester screening could have also led to aneuploidy detection [10]. Nevertheless, even when taking this methodic aspect into account, the limitations of NIPT still persist, namely because it is not suitable to detect a wide number of chromosomal abnormalities. At the same time, about 60% of all aneuploidies are detectable by qualified ultrasound examination without any further testing [31]. Thus, there is only little reason for NIPT without accompanying ultrasound examination, which is in line with current recommendations by ISUOG [32]. According to the presented data, primarily performed amniocentesis has no value in a screening setting. Therewith the age indicated invasive diagnostic is obsolete from a scientific point of view and should be replaced by first trimester screening [33].

Conclusion

Regarding aneuploidy screening, NIPT entails just a little advantage in comparison to unqualified ultrasound examination and is even less precise than qualified ultrasound screening. Any tests sensitivity will improve when combined with a qualified ultrasound examination. This is especially true for first trimester screening when the ultrasound examination not only focuses on the nuchal translucency but rather scans the whole fetus [34].

According to the results on hand, detection rates for chromosomal abnormalities do reach 97.3%. This is markedly more than ultrasound followed by NIPT, which showed a detection rate of 71.5%. NIPT without an accompanied ultrasound examination will miss an even wider number of aneuploidies.

The results from this study demonstrate that the most important examination is ultrasound, especially when also the nuchal translucency thickness is examined. However, ultrasound should be performed by trained specialists. Otherwise, the false-negative-rate would unnecessarily increase [35]. The next most reliable test is the combined first trimester screening, followed by NIPT. Performing amniocentesis is not recommended as a primary screening strategy due to its little additional benefit in contrast to its procedural health risk and costs.

Placental mosaicisms are a main cause for intrauterine growth restriction and fetal death. First trimester screening is generally suitable to detect those chromosomal disorders when performed as combined screening including biochemical analysis of PAPP-A and free β-hCG. NIPT is mainly suitable for trisomy 21 detection and shows wide deficits for other aneuploidies. Furthermore, early placental insufficiency due to mosaicisms offer a remarkable higher rate of NIPT without valid result (no-call). Following this, any uncertain NIPT result would have to be considered as test positive and would dramatically increase the false-positive-rate much above the value communicated by the manufacturers.

The most advantageous test strategy seems to be early ultrasound examination followed by first trimester screening. This offers the highest overall-detection rate for chromosomal diseases and additionally gives information for placental insufficiency and pre-eclampsia when taking the biochemical values into account.

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