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A new era in prenatal care: non-invasive prenatal testing in Switzerland

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Summary

QUESTIONS UNDER STUDY: Prenatal care has been significantly influenced by the introduction of non-invasive prenatal testing (NIPT) for aneuploidies in 2012. The aim of this study was to describe the current impact of NIPT on prenatal care.

METHODS: We performed a retrospective data analysis including all women with singleton pregnancies who presented for first trimester screening (FTS) between 1 October 2011 and 30 March 2013 and those seeking NIPT. According to the results of FTS the women were categorised into three risk groups: low risk for aneuploidy (<1:300), intermediate risk (1:300–1:50) and high risk (>1:50). They were counselled about the available options for invasive prenatal testing (IPT) and NIPT available at the time of FTS. The nine months before and after the introduction of NIPT were evaluated regarding further testing after FTS.

RESULTS: In total, 951 women were included: 505 examinations (group 1) were carried out before NIPT became available, 446 (group 2) thereafter. In group 2, 9.0% (40/446) had NIPT. Here, 60.0% (24/40) had a low risk according to FTS. In group 2 there was an increase of 3.6% of additional prenatal tests after FTS. The greatest increase was noted in the intermediate-risk category (10.7%). The number of invasive prenatal tests decreased by 67.4%.

CONCLUSIONS: We observed a notable increase in prenatal testing after the implementation of NIPT. NIPT is an additional test for women who need more reassurance. Since the options for pregnant women become more complex and the costs of NIPT are high, prenatal counselling has become more challenging.

Key words*: NIPT; cell-free foetal DNA in maternal blood; foetal aneuploidies; prenatal counselling; prenatal care*

Introduction

The introduction of non-invasive prenatal testing (NIPT) for foetal aneuploidies, using cell-free foetal DNA extracted from maternal blood, offers a risk-free expansion of the prenatal tests for pregnant women [1]. The currently available cell-free DNA tests are based on the finding that cells of the placenta continuously release large amounts of nucleic acids into the maternal blood. Cell-free foetal DNA comprises about 10% of the total cell-free DNA (maternal and foetal), is only present during pregnancy and is cleared a few hours after birth [2].

With the development of massively parallel genomic sequencing, testing for foetal aneuploidies from maternal blood has now become clinically available [3–5]. Several validation studies from high-risk populations now have reported detection rates for foetal trisomy 21 of >99%, 98% for trisomy 18 and 89% for trisomy 13, with false positive rates of 0.1%, 0.1% and 0.4%, respectively [4–11]. Recently, NIPT has become clinically available for other aneuploidies such as trisomy 16, 22, 45 X0 and 47 XXX, but the published study reports only a small number of each aneuploidy and therefore experience is still very limited [11].

Currently, most pregnant women in industrialised countries have access to a detailed sonographic examination of their foetus's anatomy at 11–14 gestational weeks and are offered a risk assessment for aneuploidies using first trimester screening (FTS). FTS combines the statistical background risk of the mother, foetal anatomy, nuchal translucency measurement and biomarkers in the maternal blood (pregnancy-associated plasma protein A [PAPP-A], free beta human chorionic gonadotropin [HCG]). FTS can achieve a sensitivity of 90% for trisomy 21 with a false positive rate of 3%–5% [12].

In high risk populations, NIPT has been shown to have a higher sensitivity and specificity than FTS with respect to the detection of trisomy 21 [4–10]. It can be started from as early as ten weeks of pregnancy and is not limited to a defined "time window". However, NIPT only offers information on the aneuploidies that are specifically tested, it is not yet implemented in twin pregnancies in Europe and there are only very few studies from low-risk populations [13].

The only diagnostic test today to exclude chromosomal abnormalities with a near 100% accuracy is invasive prenatal testing (IPT) by means of amniocentesis or chorionic villus sampling (CVS). IPT, however, carries a significant risk of miscarriage, estimated to vary around 0.5%–1% [14, 15].

In the light of these facts, the exact role of NIPT in prenatal care remains to be defined. Although the technology is available today and the test can be requested by the patients

at their own expense (approximately 1200 CHF), the indications for NIPT are still debated controversially. Here, we report on the experiences of the implementation of NIPT in clinical practice after its formal introduction in July 2012 in Switzerland. The aim of this study was to describe the current impact of NIPT on prenatal care.

Material and methods

The Praena Test®, the first available NIPT-test, became clinically available at the University Hospital of Basel on 13 July 2012. From July 2012 until February 2013, the Praena Test® (Lifecodexx, Konstanz, Germany) offered the detection of trisomy 21 only. Since February 2013, analysis for trisomies 13 and 18 also became available and the Praena Test® was the only NIPT test used in the study group.

The present retrospective data analysis included all singleton pregnancies between 1 October 2011 and 30 March 2013, who presented for FTS at the University Hospital of Basel between 11–14 weeks of gestation and all women seeking NIPT based on the results of internal and external FTS. FTS was offered as a combined test including nuchal translucency measurement, PAPP-A and free beta-HCG. Biochemical markers were not offered to women who had a HCG injection for induction of ovulation or for other reasons. Some women also declined to take the additional blood test. The risk derived from FTS according to the combined test or according to age risk and nuchal translucency measurement was analysed. The data were analysed anonymously in retrospect from our database and therefore informed consent was not obtained. All internal FTS were conducted according to the guidelines of the Foetal Medicine Foundation (FMF), London with GE Voluson E8 Expert ultrasound machines (GE Medical Systems, Zipf, Austria). Risk calculation was performed with the Viewpoint software (GE, Viewpoint Bildverarbeitung Version 5.6.12.601, Wessling, Germany). Experienced FMF-certified sonographers performed all internal ultrasound examinations and invasive procedures. As a standard of care, all women were counselled about the different methods available at the time of investigation and were presented with the various options of both invasive and non-invasive prenatal diagnostic procedures. The individual risk of aneuploidy was discussed based on the results of FTS.

The women were categorised into three risk groups according to the results of FTS: low risk for aneuploidy <1:300; intermediate risk 1:300–1:50; high risk >1:50. Nuchal translucency >95th percentile or the presence of foetal structural abnormalities were considered as high risk, regardless of the risk calculation. Risk calculation was always performed for trisomy 21, 13 and 18 individually. The women were grouped according to their highest risk for aneuploidy (trisomy 21, 13 or 18).

All statistical analyses were performed using the R system for statistical computation Version 2.15.1. A p-value <0.05 was considered significant. Frequencies in the tables were compared using the chi-square test. If the expected frequency was less than 5, the Fisher test was used.

Results

During the observational period, 951 women presented for a routine 11–14 week ultrasound scan. Five hundred and five sonographic examinations were carried out before NIPT became available, whereas 446 sonographic examinations were conducted after the formal introduction of NIPT. Of the patients, 13.9% (133/951) were pregnant after infertility treatment. The comparison of the baseline characteristics between both groups revealed no statistically significant differences (table 1). In the study population, 13.6% (129/951) were screened positive after FTS according to a cut-off of >1:300.

Experience with NIPT and characteristics of the women who opted for NIPT

Nine percent of all patients (40/446) decided to take advantage of the Praena Test®. The mean interval between the blood collection and the test result was 14 business days (range: 10–40 days). We did not have any samples that could not be analysed because of a low foetal cell-free DNA fraction. The median gestational time at testing was 16 weeks. One test screened positive for trisomy 18 and was confirmed by CVS. In the women who had negative NIPT test results there were no aneuploidies detected at birth. We also did not have any false positive NIPT tests.

Of these 40 women, 62.5% (25/40) were ≥35 years old (table 2). The median age of the women opting for NIPT was 35.4 years; 15.0% (6/40) had previously undergone infertility treatment and 60.0% (24/40) had a low risk for aneuploidy according to FTS (table 2).

Changes in prenatal care after introduction of NIPT

Since the introduction of NIPT, there has been an overall increase of 3.6% of additional prenatal tests including both

Table 1: Baseline characteristics of the patients included in the two respective study groups. Group 1: before the introduction of NIPT; group 2: after the introduction of NIPT. The maternal age is presented as mean value (± standard deviation).

	Group 1 n = 505		Group 2 n = 446		p-overall
Risk group according to FTS					
Low risk (n)	431	(85.3%)	391	(87.7%)	0.180
Intermediate risk (n)	37	(7.3%)	35	(7.9%)	
High risk (n)	37	(7.3%)	20	(4.5%)	
Mode of conception					
Natural conception (n)	437	(86.5%)	382	(85.7%)	0.764
After assisted reproduction (n)	68	(13.5%)	64	(14.3%)	
Maternal age (y)	31.8	(±5.8)	31.4	(±5.6)	0.247

FTS = first trimester screening; NIPT = non-invasive prenatal testing

IPT and NIPT after FTS (8.5% vs 12.1%, p = 0.068). In the low risk category this increase amounted to 4.7% (2.2% vs 6.9%, p <0.149), whereas in the intermediate risk category this increase was 10.7% (35.1% vs 45.8%, p = 0.016). In the high risk category an increase of 1.8% (55.0% vs 56.8%, p = 0.149) was noted (table 3).

In contrast, the overall decrease of IPT was 5.5% (8.8% vs 3.1%, p = 0.001). The decrease was 1.1% in the low-risk group, 29.4% in the intermediate-risk group and 16.8% in the high-risk group (table 3). Since the introduction of NIPT, the total number of invasive prenatal procedures decreased by 67.4% (43 vs 14).

Discussion

Our study summarises the first experience with NIPT in Switzerland. We compared the first nine months since the introduction of NIPT with the nine months after NIPT became available. The baseline characteristics were similar in both groups. The higher number of patients that "screen positive" in FTS in our population is explained by a mixed collective constituted of low risk patients and referred higher risk patients.

As the Swiss guidelines for pregnancy care recommend offering FTS after counselling to all women, NIPT was not used as a first-line prenatal test in the study group [16, 17].

Experience with NIPT

Conclusive test results with NIPT were obtained in all cases. This is probably due to the low number of patients in the study group and the late median gestational age for testing, since it has been reported that about 2.2% of all tests do not reach the minimal requirement for quality or amount of foetal cell-free DNA in the sample [13]. More than half of the patients who opted for NIPT were over 35 years of age. This might be in part due to a higher statistical risk of aneuploidy at this age, but may also reflect the financial situation of this age group. One could speculate that women after infertility treatment would choose NIPT more frequently than others, mainly because of a higher maternal age and a more attentive position towards pregnancy, but this was not confirmed here. Surprisingly, most of the women that decided to take advantage of NIPT did not have an increased risk in FTS. Here NIPT seems to be a risk-free reassurance test for women who can afford to take the test and who want to take advantage of the higher test sensitivity compared with FTS.

Table 2: Baseline characteristics of the women who opted for NIPT. The maternal age is presented as mean value (± standard deviation).

	NIPT n = 40	
Risk groups according to FTS		
Low risk (n)	24	(60.0%)
Intermediate risk (n)	14	(35.0%)
High risk (n)	2	(5.0%)
Mode of conception		
Natural conception (n)	34	(85.0%)
After assisted reproduction (n)	6	(15.0%)
Maternal age (y)	35.4	(±4.91)

FTS = first trimester screening; NIPT = non-invasive prenatal testing

Changes in prenatal care

In low risk pregnancies, the proportion of women taking IPT was 2.1% before the advent of NIPT. After the introduction of NIPT, almost 6% chose NIPT despite outcome data in low risk populations being scarce [16, 17]. Although false positive rates of around 0.5% for trisomy 21 are reported [18], the consequences and associated risks of a false positive test in a low risk population, which will finally lead to unnecessary IPT and possible miscarriage should not be underestimated.

For the women with an intermediate risk, the increase of additional testing with NIPT was most significant (10.7%) resulting in a drop of IPT of 29.4%. It is not surprising that these women, who had an intermediate risk after FTS before NIPT became available, decided not to undergo IPT (64.9%) because of the risk of miscarriage. It can easily be explained that, on the other hand, the number of women willing to gain more assurance in this group is high. We hypothesise that the number of test takers in this group will continue to rise as the awareness of NIPT grows. It is likely that the intermediate-risk group will benefit most from risk-free testing. As such, coverage of the costs of NIPT testing by health insurance would seem most appropriate in this risk group.

In high risk cases after FTS, an invasive procedure is still recommended [18, 19], especially in those cases with increased nuchal translucency over the 95th percentile, where we know that the risk of structural or genetic anomalies is about 20% [20]. Here the risk for other aneuploidies and genetic syndromes as a result of deletions or duplications that cannot be detected by NIPT should not be underestimated and counselling in this situation should be performed

Table 3: Differences in prenatal testing according to risk category before and after the introduction of NIPT. Group 1: before the introduction of NIPT; group 2: after the introduction of NIPT.

Risk group according to FTS		**n**	**No further tests**		**IPT**		**NIPT**		**IPT special indication / termination**	
Low risk	Group 1	431	411	95.36%	9	2.09%	0	0%	11	2.55%
	Group 2	391	362	92.58%	4	1.02%	23	5.88%	2	0.51%
	p-value		0.997		0.372		<0.001			
Intermediate risk	Group 1	37	24	64.86%	13	35.14%	0	0%	0	0%
	Group 2	35	19	54.29%	2	5.71%	14	40.00%	0	0%
	p-value		0.835		0.018		<0.001			
High risk	group 1	37	15	40.54%	21	56.75%	0	0%	1	2.71%
	Group 2	20	8	40.00%	8	40.00%	3	15.00%	1	5.00%
	p-value		0.333		0.054		0.103			

FTS = first trimester screening; IPT = invasive pregnancy testing; NIPT = non-invasive prenatal testing

by a specialist. Another benefit is that IPT provides accurate information on the karyotype within 24–48 hours. However, even in this group some women opted to have NIPT despite having been informed about its limitations. This confirms prior studies, in which women had a high preference for those tests that help to avoid any risk of miscarriage [21].

Decrease in IPT

Overall, the total number of invasive preterm tests decreased by almost 70%. This was a goal of prenatal research for many years and there certainly will be a further expansion of the screening opportunities given by NIPT in the near future. However, IPT will still be necessary for testing in special indications (inherited risks, infections, etc.) and for positive findings by NIPT. As a result of this trend, we must be aware that expertise in this field will dramatically decline.

Although a long desired goal in prenatal diagnostics, the ability to analyse the foetus with a simple maternal blood sample, has finally become reality [22], prenatal counselling is becoming even more complex. This study shows first experiences in Switzerland with NIPT. It shows the important impact of these tests and their rapid uptake in our society. It also illustrates new challenges in our counselling process and clearly demonstrates the decrease in invasive prenatal tests already. The limitations of this study certainly are the small number of patients with NIPT, which allows only a description of the experiences without the ability to make any statements on the reliability and quality of the NIPT test used.

The challenge now is to develop a new algorithm for prenatal care and to integrate NIPT into national guidelines to allow general access covered by health insurance for all women who, from a public health perspective, could really benefit from NIPT.

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