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High risk in the first-trimester combined screening: long-term outcomes of the children

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Abstract

Objective

To bring new accuracy to the prognosis of outcomes of euploid fetuses with an extremely high risk in the first-trimester combined screening when compared to the low-risk group.

Study Design

The data included pregnancies with a trisomy 21 risk ≥ 1:50 in the combined first-trimester screening but normal fetal chromosomes. The control group had a risk value ≤ 1:300. Miscarriage, termination of pregnancy, stillbirth, premature delivery, and delivery of an unhealthy child were considered adverse outcomes. The impact of each component in the combined first-trimester screening was analyzed separately. Statistical comparisons were made by using the chi-square test, Fisher-Freeman-Halton test, Mann-Whitney test or t-test.

Results

The study comprised 483 women (161 cases and 322 controls). The mean follow-up time of children born alive was 61.4 months. An adverse outcome was detected in 11.8 % of the cases and in 5.9 % of the controls. After adjusting the values of mother´s age, parity, and smoking habit the odds ratio for an adverse outcome was 2.1 (95% CI: 1.0 – 4.5, p = 0.05) for cases. When evaluating the effect of 1 SD increase in MOM of PAPP-A or 1 SD decrease in MOM of NT or β-hCG to any adverse outcome, 1 SD increase in PAPP-A MOM decreased the risk of adverse outcome by OR 0.48 (95% CI: 0.3 - 0.8, p = 0.05) while the others were not significant.

Conclusion

Euploid fetuses with a high risk in the combined first-trimester screening have a twofold risk for adverse outcomes when compared to those with a low risk.

Keywords: first-trimester screening; outcome; long-term follow-up; high-risk group

Introduction

Combined first-trimester screening (FTS) for fetal aneuploidies is efficient.[1-4] In FTS fetal nuchal translucency (NT) thickness and maternal serum markers´ pregnancy-associated plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin (fβ-hCG) are measured and transformed to multiples of median (MoM). Maternal age, smoking status, diabetes, and weight are taken into account in the risk assessment. A mathematical model is used to establish an individual risk rate for trisomy 21. Counselling and diagnostic procedures are offered to those with a positive test result. The cut-off level of further procedures is arbitrarily chosen and varies between different countries; in Finland the cut-off level has been set to ≥ 1:250.

After counselling, fetal karyotyping or non-invasive prenatal testing (NIPT) is offered to the parents.

Individual parameters of the FTS associate with different adverse outcomes. Thickness of the NT predicts structural defects and miscarriages among euploid fetuses.[5-8] Low PAPP-A level associates with miscarriage, pregnancy induced hypertension, pre-eclampsia, gestational diabetes, preterm delivery, fetal growth restriction, and stillbirth.[7, 9-17] Elevated PAPP-A has also been associated with placenta accreta[18]. Low β-hCG level predicts fetal growth restriction[10,11] and fetal loss.[7,9,19] Despite these negative implications, the positive predictive values for different adverse outcomes for each individual marker has been relatively low. In the previous literature most studies focus on pregnancy complications and do not have any data about the long-term health of the children born from these pregnancies.

The aim of our study was to find out whether those with a very high risk rate (≥ 1/50) for trisomy 21 in the first-trimester combined screening and normal karyotype have an increased risk for adverse outcomes compared to those with a normal (≤ 1/300) risk rate. The performance of individual markers alone in predicting adverse outcomes has been low. Therefore, we wanted to find out if one or more of the different components of the combined screening can be associated with a specific outcome.

Material and methods

We identified all singleton pregnancies with a high risk (≥ 1:50) in the FTS for trisomy 21 and normal karyotype who visited the Fetal Medicine Center of Helsinki University Hospital during 2009-2012. For each, two control patients were selected; the controls were from the same ultrasound screening day and the ages were matched as closely as possible. The controls had a risk of < 1:300 for trisomy 21 in the FTS. We did not use NIPT at the time of this study.

The FTS was performed according to the guidelines by Finnish Ministry of Social Affairs and Health. Gestational age was corrected according to the crown-rump length measured at the ultrasound examination in cases where the discrepancy was more than four days in the gestational age counted from the last menstrual period. NT was measured by a trained sonographer or a perinatologist according to the Fetal Medicine Foundation protocol. [20]

Serum samples of PAPP-A, and fβ-hCG were collected on the day of the ultrasound examination.

Lifecycle® Database (Perkin Elmer, Turku, Finland) was used to calculate the risk assessment for Down syndrome.

Invasive testing was offered to all cases. If the parents opted against invasive testing but the child was born without dysmorphic features and did not present them during the follow-up, the child was considered healthy. Termination of pregnancy, miscarriage, stillbirth, very and extremely preterm delivery (≤ 32+0 gestational weeks) and delivery of an unhealthy child were considered adverse outcomes. The child was considered unhealthy if there were major structural defects, neurodevelopmental impairment, or genetic syndromes. Children with minor structural defects (spontaneously closed ventricular septal defects, inguinal herniation, testicular retention, congenital dislocation of the hip) or inherited diseases (hereditary angioneurotic edema, thalassemia minor) were counted together with the healthy ones. Neurodevelopmental impairment was verified by visits to special healthcare because of problems of cognition, speech, or if the child had not achieved the developmental milestones and was treated in the special healthcare for this reason.

Follow-up was conducted from the hospital charts, and counted in months.

Pregnancy induced hypertension, pre-eclampsia, and fetal growth restriction (≤ 5th centile) were recorded. Pregnancy induced hypertension was defined as two or more blood pressure recordings ≥ 140/90 mmHg after 20 gestational weeks. Pregnancy induced hypertension accompanied by proteinuria was defined as pre-eclampsia.

The impact of individual FTS variables (NT, β-hCG, PAPP-A) on the outcome were assessed both together and separately.

This study was approved by Helsinki University Ethical Committee (Dnro 264/13/03/03/2013 October 30, 2013)

Statistical analysis

The characteristics of the study population are presented as means with standard deviations (SD) or as counts with percentages. The data were presented as means with standard deviations (±SD) or as counts with percentages. Statistical comparisons were made by using the chi-square test, Fisher-Freeman-Halton test, Mann-Whitney test or t-test. Conditional fixed-effects (FE) models were used to estimate odds ratios with 95% confidence intervals. All analyses were performed in the Stata Statistical Software, Release 15.1 (StataCorp LP, College Station, TX, USA).

Results

The test population consisted of 161 cases (FTS risk ≥ 1:50) and 322 controls (FTS risk < 1:300). Invasive testing was declined by 14 (9 %) of the high-risk group. None of these children was diagnosed with aneuploidy during the follow-up.

Characteristics of the cases and the controls are shown in Table 1. The mothers in the high-risk group were older than in the control group and the first-trimester ultrasound screening was performed earlier to them. Otherwise the groups were comparable. The results of the screening tests (NT, PAPP-A, β-hCG) are shown in Table 2.

The follow-up time of children born alive (n = 475) was in mean 61.4 ± 11.2 months (range 25 days – 85 months).

An adverse outcome was detected in 19 / 161 (11.8 %) of the cases and in 19 / 322 (5.9 %) of the controls. Seven (4 cases, 3 controls) children had more than one adverse outcome. Fetal loss occurred in eight pregnancies presented in Table 3. The children with adverse outcomes are presented in Table 4. Two children were born prematurely without any complications in the follow-up period.

The risk for an adverse outcome was increased among cases (OR 2.1, 95% CI 1.2 - 3.5, p = 0.009) even after adjusting for age, parity, and smoking (OR 2.1, 95% CI 1.0 – 4.5, p = 0.05).

When evaluating the effect of 1 SD increase in MOM of PAPP-A or 1 SD decrease in MOM of NT or β-hCG to any adverse outcome, 1 SD increase in PAPP-A MOM decreased the risk of adverse outcome by OR 0.48 (95% CI: 0.3 - 0.8, p = 0.05) while the others were not significant.

Comment

This study showed that adverse outcomes for euploid fetuses with an extremely high (≥ 1/50) FTS risk were approximately twice as likely when compared to the control group with a low risk in the screening. For the individual FTS parameters, the only one to show an effect on the outcome was PAPP-A.

Liu et al. have shown similar result in their study with an OR of 1.7 for obstetric complications when they compared a high-risk FTS group to a low-risk group. [21] The major differences between our study and the study of Liu et al. are in the definition of high risk and adverse outcomes: in our study high risk was ≥ 1:50 compared to ≥ 1:270 in their study. However, their focus was more on pregnancy complications, while our study focused on the health of the children born from the pregnancies with a high FTS risk rate. Although these two studies are not directly comparable, the results show a similar rate of risk increase.

The only individual screening parameter that had an effect on the outcomes was PAPP-A. Low PAPP-A level has been associated with miscarriage, stillbirth, preterm delivery, pregnancy induced hypertension, pre-eclampsia, small for gestation age newborns, intra-uterine growth restriction. [7,10,12,13-15] The positive predictive value of low PAPP-

A for these adverse outcomes is relatively low. In many institutions, fetal growth in pregnancies with low PAPP-A requires follow-up. Our result adds further evidence on the significance of PAPP-A, but unfortunately the small number of cases makes an estimation of its effect on different adverse outcomes unreliable.

The strength of this study is the relatively long follow-up time of the children. Since the neurodevelopmental problems are not apparent at the time of birth, studies with no follow-up lack this information. The main limitation of our study is the small number of cases which made it impossible to discriminate different adverse outcomes. Another limitation is that we did not adjust for growth restricted newborns. There were more newborns whose growth was restricted or who were small for gestational age among the cases compared to the controls. However, when checking these cases only one of these children had an adverse outcome and the outcome of the remaining 12 was favorable. Thus, it seems that the lack of adjusting for this parameter had no major effect on the results.

After a high risk result in the screening most parents opt for karyotyping of the fetus or NIPT. Although the karyotype of the fetus is normal, residual anxiety of the wellbeing of the offspring remains, especially with a very high risk rate.[22] Parental counselling is extremely important both in the pre-test and post-test situation. The result of our study is also applicable to parental counselling. Telling the parents that there is a 90% chance of receiving a healthy child in the high-risk FTS group after a normal karyotyping result compared to 95% in the low risk group is comforting to those who raise the question about the prognosis of the pregnancy in this situation. This study shows the importance of pre-test counselling in fetal screening in general. Those attending fetal screening should understand that a positive screening result does not mean an unhealthy offspring nor does a negative screening result guarantee a healthy child.

Conclusion

Euploid fetuses with a high risk in the FTS have a twofold risk for adverse outcomes when compared to those with a low risk. From the individual FTS parameters PAPP-A had the strongest effect on the outcomes.

Acknowledgements

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Legends for tables:

Table 1. Characteristics of cases (FTS risk ≥ 1/50) and controls (FTS risk < 1/300).

Table 1. Characteristics of cases (FTS risk ≥ 1/50) and controls (FTS risk < 1/300)

Variable mean ± SD n (%)	Cases n = 161	Controls n = 322	P-value
Maternal age (years)	34.7 ± 6.0	32.3 ± 5.1	< 0.001
Gestational age at NT measurement (weeks + days)	11+5, ± 3	12+1 ± 5	< 0.001
Nulliparous	66 (41)	141 (44)	0.6
Smokers	16 (10)	27 (8)	0.6
Pregnancy complications			
Gestational diabetes	20 (12)	28 (9)	0.2
Hypertension	7 (4)	12 (4)	0.7
Pre-eclampsia	2 (1.2)	1 (0.3)	0.2
Gestational age at birth (weeks + days)	39.7 ± 1.9	40.0 ± 1.9	0.1
Birth weight (grams)	3421 ± 608	3529 ± 549	0.06
SGA	8	5	0.03
Male	81 (52)	155 (49)	0.5

pH	7.26 ± 0.09	7.26 ± 0.09	0.9
Apgar 5 min < 7,	10 (6)	15 (4.6)	0.5
FTS Combined first-trimester screening; SD standard deviation; SGA small for gestational age			

Table 2. Characteristics of first-trimester combined screening variables among cases. and controls

Table 2. Characteristics of first-trimester combined screening variables among cases and controls		
Varible mean ± SD	Cases n = 161	Controls n = 322
NT (mm)	2.31 ± 0.67	1.10 ± 0.37
PAPP-A	1596 ± 1402	2047 ± 1534
fβ-hCG	81.0 ± 58.0	53.7 ± 42.2
Median of MOMs		
NT	2.07 ± 0.57	0.96 ± 0.31
PAPP-A	1.03 ± 0.72	1.29 ± 0.87
fβ-hCG	1.90 ± 1.23	1.17 ± 0.90
SD standard deviation, NT nuchal translucency, PAPP-A Pregnancy-associated protein-A, fβ-hCG free human-beta chorionic gonadotropin, MOM multiple of median		

Table 3. Cases with fetal loss: miscarriage (MC), termination of pregnancy (TOP), or stillbirth (SB)

Table 3. Cases with fetal loss: miscarriage (MC), termination of pregnancy (TOP), or stillbirth (SB)

FTS risk 1/	NT MoM /PAPP-A MoM/β-hCG MoM	Gestational age (weeks)	Reason	Invasive testing result	Pathological examination after fetal loss
20	1.8/0.4/1.9	15	MC	Normal	No explanation found.
40	0.4/0.2/4.3	17	MC	Normal	No pathological examination.
45	1.5/0.2/1.3	16	MC	Normal	Fetal hydrops, club foot.
45	1.7/0.5/1.5	16	MC	No testing	Normal karyotype and anatomy. Chorionamnionitis.
35	1.4/0.4/1.9	23	TOP	Normal	Hypoplastic right ventricle, tricuspic atresia, hydrops.
45	1.8/0.8/2.0	20	TOP	Normal	Hydrocephalus.
3200	1.3/0.3/0.4	12	TOP	Not offered	Normal karyotype, holoprosencephaly.
1800	1.0/1.0/1.0	23	SB	Not offered	Normal karyotype. Anti-D- immunization, hydrops.

FTS first trimester screening, NT nuchal translucency, MoM Multiples of median, PAPP-A pregnancy associated plasma protein A, β-hCG human chorionic gonadotropin β, PROM premature rupture of membranes

Table 4. Children with syndromes, genetic disorders, structural defects, or neurodevelopmental impairment.

Table 4. Children with syndromes, genetic disorders, structural defects, or neurodevelopmental impairment		
Risk 1/	Diagnosis	NT MOM / PAPP-A MOM / β-hCG MOM
Syndromes and submicroscopic genetic changes		
15	Microduplication of chromosome 16. Duplicated thumb, VSD, delayed neurodevelopment. Small for gestational age.	1.8/0.1/1.2
15	WAGR syndrome.	2.3/1.6/1.0
25	Deletion in chromosome 7 (Williams syndrome). VSD, neurodevelopmental impairment.	0.5/0.3/2.1
25	VACTERL syndrome.	2.6/0.8/0.6
35	Cutis laxa –gene mutation. Delayed neurodevelopment.VSD.	1.8/0.4/1.6
610	Beckwith-Wiedeman syndrome.	0.7/1.6/4.0
Structural defects		
25	Diastolic cardiac dysfunction diagnosed at four years of age.	1.5/0.3/2.4
25	Chylothorax.	2.0/1.1/0.5
40	Glandular hypospadia (operated).	1.2/0.2/5.2
50	Hypolasia of cerebellar vermis, neurodevelopmental impairment.	2.2/0.7/0.7
650	Arnold Chiari I.	1.1/1.0/1.3

1000	Gastroschisis, anal atresia, preterm delivery at 29 weeks. Perinatal death at 25 days.	0.7/0.7/1.3
1100	Thoracal lymphangioma .	1.5/1.1/0.8
2400	Synostosis of the sagittal suture, operated.	0.3/1.3/1.2
2800	Pulmonary valve stenosis and insufficiency.	0.6/0.9/1.4
16000	Polysyndactylia in fingers and toes, operated.	1.7/0.6/0.4
21000	Duplicated thumb.	1.1/0.7/0.5
21000	Aortic valve stenosis, bicuspic aortic valve, attention deficit disorder.	1.2/1.1/0.7
Neurodevelopmental impairment		
15	Expressive language disorder, epilepsy.	2.4/1.2/2.9
25	Developmental disorder of language and speech.	1.5/0.3/1.8
45	Attention deficit disorder, childhood emotional disorder.	2.2/2.4/1.4
1400	Expressive language disorder.	0.9/1.3/4.3
3400	Developmental disorder of language and speech.	1.2/1.7/0.7
3800	Developmental disorder of speech and language.	0.7/1.2/0.8
23000	Intellectual disability and autistic disorder.	0.9/0.5/0.5
28000	Autistic disorder and childhood emotional disorder.	0.8/0.9/0.9
34000	Developmental disorder of language and speech.	0.8/1.0/0.5
51000	Expressive language disorder.	0.8/1.1/0.7

NT nuchal translucency, PAPP-A Pregnancy-associated protein-A, fβ-hCG free human-beta chorionic gonadotropin, MOM multiple of median, VSD ventricular septal defect