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Literature Review

Trisomy screening

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First and second trimester antenatal screening for Down's syndrome: The results of the Serum, Urine and Ultrasound Screening Study (SURUSS)

N. Wald, C. Rodeck, A. Hackshaw, J. Walters, L. Chitty and A. Mackinson

Health Technol Assess 2003 Vol. 7 Issue 11 Pages 1-77

We here report the results of the Serum Urine and Ultrasound Screening Study (SURUSS), a large collaborative study of antenatal screening for Down's syndrome, funded as part of the UK Health Technology Assessment (HTA) Programme, to help determine best screening practice.

Antenatal screening for Down's syndrome has developed rapidly over the last 15 years. In 1988, maternal age screening was improved by the second trimester triple test. Some centres adopted the double test. (A glossary of definitions of the various screening tests and a key to abbreviations used are included at the start of this report.) The triple test was later improved by the addition of maternal serum inhibin-A to form the quadruple test. At the same time, three first trimester markers, serum pregnancy-associated plasma protein A (PAPP-A), free β-human chorionic gonadotrophin (β-hCG) and the ultrasound marker nuchal translucency (NT; see glossary and page 4) were shown to be useful in screening. A systematic review of antenatal screening for Down's syndrome published in 1997 recommended that the second trimester triple or quadruple test should be the test of choice. In 1999 the integrated test was described, which combined markers from the first and second to yield a screening performance better than from either trimester alone. Several urinary markers have been proposed as screening tests, notably β-core fragment and invasive trophoblast antigen (ITA).

The value of SURUSS is that it provides a large dataset on women seen in both the first and second trimester of pregnancy (it is the largest such dataset yet reported), without planned intervention in the first trimester. This allows a direct examination of the screening performance of all individual screening markers – NT and first and second trimester serum and urine markers. The strength of SURUSS is that it can do this in a single large unselected group of pregnant women with data collected in both trimesters, in a collaborative study from 25 centres that together reflect the provision of routine antenatal care.

First-trimester or second-trimester screening, or both, for Down's syndrome

F. Malone, J. Canick, R. Ball, D. Nyberg, C. Comstock, R. Bukowski, et al.

N Engl J Med 2005 Vol. 353 Issue 19 Pages 2001-11

Background

It is uncertain how best to screen pregnant women for the presence of fetal Down's syndrome: to perform first-trimester screening, to perform second-trimester screening, or to use strategies incorporating measurements in both trimesters.

Methods

Women with singleton pregnancies underwent first-trimester combined screening (measurement of nuchal translucency, pregnancy-associated plasma protein A [PAPP-A], and the free beta subunit of human chorionic gonadotropin at 10 weeks 3 days through 13 weeks 6 days of gestation) and second-trimester quadruple screening (measurement of alpha-fetoprotein, total human chorionic gonadotropin, unconjugated estriol, and inhibin A at 15 through 18 weeks of gestation). We compared the results of stepwise sequential screening (risk results provided after each test), fully integrated screening (single risk result provided), and serum integrated screening (identical to fully integrated screening, but without nuchal translucency).

Results

First-trimester screening was performed in 38,167 patients; 117 had a fetus with Down's syndrome. At a 5 percent false positive rate, the rates of detection of Down's syndrome were as follows: with first-trimester combined screening, 87 percent, 85 percent, and 82 percent for measurements performed at 11, 12, and 13 weeks, respectively; with second-trimester quadruple screening, 81 percent; with stepwise sequential screening, 95 percent; with serum integrated screening, 88 percent; and with fully integrated screening with first-trimester measurements performed at 11 weeks, 96 percent. Paired comparisons found significant differences between the tests, except for the comparison between serum integrated screening and combined screening.

Conclusion

First-trimester combined screening at 11 weeks of gestation is better than second-trimester quadruple screening but at 13 weeks has results similar to second-trimester quadruple screening. Both stepwise sequential screening and fully integrated screening have high rates of detection of Down's syndrome, with low false positive rates.

Detection of trisomy 18 and trisomy 13 using first and second trimester Down's syndrome screening markers

J. Bestwick, W. Huttly and N. Wald

J Med Screen 2013 Vol. 20 Issue 2 Pages 57-65

Objective

To estimate the detection rates (DRs) and false-positive rates (FPRs) in the incidental identification of trisomy 18 (T18) and trisomy 13 (T13) as part of antenatal screening for Down's syndrome (DS) using the Combined, Quadruple and Integrated test markers.

Methods

Screening marker levels on 224 T18 and 67 T13 pregnancies screened for DS were evaluated. Estimated means, standard deviations and correlation coefficients were used with published estimates for unaffected pregnancies to derive detection algorithms for the two disorders. DRs and FPRs of the algorithms were estimated using Monte Carlo simulation.

Results

In T18 and T13 pregnancies first trimester nuchal translucency was raised, free β-human chorionic gonadotrophin (hCG) and pregnancy associated plasma protein-A reduced. In T18 pregnancies second trimester alphafetoprotein, unconjugated oestriol and free β-hCG were reduced. In T13 pregnancies second trimester Inhibin-A was raised. These markers specified T18 and T13 algorithms. The DS Combined test algorithm detected 42% of T18 and 59% of T13 (2.00% FPR); 88% and 74% by adding the T18 Combined test algorithm (2.17% FPR) and 89% and 75% by further adding the T13 Combined test algorithm (2.19% FPR). The corresponding detection rates for the Quadruple test were: 5% and 21% (2.00% FPR), 59% and 21% (2.16% FPR) and 59% and 24% (2.28% FPR), and for the Integrated test were: 40% and 60% (2.00% FPR), 92% and 68% (2.12% FPR) and 92% and 74% (2.18% FPR).[Corrected]

Conclusion

Antenatal screening for DS detects about 40% of T18 and about 60% of T13 pregnancies. The addition of a T18 algorithm substantially increases the detection of both trisomies with a small increase in the FPR. The further addition of a T13 algorithm results in a small increase in the detection of T13.

1st trimester trisomy combined screening

A screening program for trisomy 21 at 10-14 weeks using fetal nuchal translucency, maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A

K. Spencer, V. Souter, N. Tul, R. Snijders and K. Nicolaides

Ultrasound Obstet Gynecol 1999 Vol. 13 Issue 4 Pages 231-7

Objective

To examine the potential impact of combining maternal age with fetal nuchal translucency thickness and maternal serum free beta-human chorionic gonadotropin (beta-hCG) and pregnancy-associated plasma protein-A (PAPP-A) in screening for trisomy 21 at 10-14 weeks of gestation.

Methods

Maternal serum free beta-hCG and PAPP-A were measured by KRYPTOR, a random access immunoassay analyzer using time-resolved amplified cryptate emission, in 210 singleton pregnancies with trisomy 21 and 946 chromosomally normal controls, matched for maternal age, gestation and sample storage time. In all cases the fetal crown-rump length and nuchal translucency thickness had been measured by ultrasonography at 10-14 weeks of gestation and maternal blood had been obtained at the time of the scan. The distributions (in multiples of the median; MoM) of free beta-hCG and PAPP-A (corrected for maternal weight) and fetal nuchal translucency (NT) were determined in the trisomy 21 group and the controls. Likelihood ratios for the various marker combinations were calculated and these were used together with the age-related risk for trisomy 21 in the first trimester to calculate the expected detection rate of affected pregnancies, at a fixed false-positive rate, in a population with the maternal age distribution of pregnancies in England and Wales.

Results

In a population with the maternal age distribution of pregnancies in England and Wales, it was estimated that, using the combination of maternal age, fetal nuchal translucency thickness and maternal serum free beta-hCG and PAPP-A, the detection of trisomy 21 pregnancies would be 89% at a fixed false-positive rate of 5%. Alternatively, at a fixed detection rate of 70%, the false-positive rate would be 1%. The inclusion of biochemical parameters added an additional 16% to the detection rate obtained using NT and maternal age alone.

Conclusion

Rapid diagnostic technology like KRYPTOR, which can provide automated reproducible biochemical measurements within 30 min of obtaining a blood sample, will allow the development of interdisciplinary one-stop clinics for early fetal assessment. Such clinics will be able to deliver improved screening sensitivity, rapidly and more efficiently, leading to reduced patient anxiety and stress.

Screening for trisomy 18 by fetal nuchal translucency and maternal serum free beta-hCG and PAPP-A at 10-14 weeks of gestation

N. Tul, K. Spencer, P. Noble, C. Chan and K. Nicolaides

Prenat Diagn 1999 Vol. 19 Issue 11 Pages 1035-42

In a study of 50 cases of trisomy 18 compared with 947 controls we have found the median multiple of the median (MoM) of maternal serum free beta human chorionic gonadotrophin to be significantly decreased (0.281 MoM) in samples collected between the 10th and 14th week of gestation. Similarly, maternal serum pregnancy associated plasma protein A (PAPP-A) levels are also decreased (0.177 MoM), whilst the median nuchal translucency is significantly higher (3.272 MoM). Free beta-hCG MoM was less than the 5th centile of normal in 64 per cent of cases of trisomy 18 and for PAPP-A was less than the 5th centile in 78 per cent of cases. Also, in 78 per cent of cases the nuchal translucency was above the 95th centile. When combined together in a multivariate algorithm with maternal age, we predict that 89 per cent of cases of trisomy 18 could be detected at a 1 per cent false-positive rate. We conclude that specific trisomy 18 risks should be part of developing risk algorithms combining maternal serum biochemistry and nuchal translucency for use in first trimester screening alongside those for trisomy 21.

One-stop clinic for assessment of risk for trisomy 21 at 11-14 weeks: A prospective study of 15 030 pregnancies

R. Bindra, V. Heath, A. Liao, K. Spencer and K. Nicolaides

Ultrasound Obstet Gynecol 2002 Vol. 20 Issue 3 Pages 219-25

Objective

To evaluate the performance of a one-stop clinic for assessment of risk (OSCAR) for trisomy 21 by a combination of maternal age, fetal nuchal translucency (NT) thickness and maternal serum free beta-human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein-A (PAPP-A) at 11-14 weeks of gestation.

Methods

Screening for trisomy 21 was carried out by OSCAR in 15 030 singleton pregnancies with live fetuses at 11-14 weeks. The estimated risk for trisomy 21 was calculated, and the women were counseled regarding this risk and the option of invasive testing or expectant management. Follow-up of the outcome of all pregnancies was carried out. The detection and false-positive rates for different risk cut-offs were calculated.

Results

Fetal NT and maternal serum free beta-hCG and PAPP-A were successfully measured in all cases. Pregnancy outcome, including karyotype results or the birth of a phenotypically normal baby, was obtained from 14 383 cases. The median maternal age of these cases was 34 (range 15-49) years and in 6768 (47.1%) the age was 35 years or greater. The median gestation at screening was 12 (range 11-14) weeks and the median fetal crown-rump length was 64 (range 45-84) mm. The estimated risk for trisomy 21 based on maternal age, fetal NT and maternal serum free beta-hCG and PAPP-A was 1 in 300 or greater in 6.8% (967 of 14 240) normal pregnancies, in 91.5% (75 of 82) of those with trisomy 21 and in 88.5% (54 of 61) of those with other chromosomal defects. For a fixed false-positive rate of 5% the respective detection rates of screening for trisomy 21 by maternal age alone, maternal age and serum free beta-hCG and PAPP-A, maternal age and fetal NT, and by maternal age, fetal NT and maternal serum biochemistry were 30.5%, 59.8%, 79.3% and 90.2%, respectively.

Conclusion

Screening for trisomy 21 by a combination of maternal age, fetal NT and maternal serum biochemistry at 11-14 weeks can be provided in an OSCAR setting and is associated with a detection rate of about 90% for a false-positive rate of 5%.

Accuracy of Down syndrome risks produced in a first-trimester screening programme incorporating fetal nuchal translucency thickness and maternal serum biochemistry

K. Spencer

Prenat Diagn 2002 Vol. 22 Issue 3 Pages 244-6

Over the past three years approximately 12 000 women have been screened in the first trimester through our OSCAR programme, which utilizes fetal NT and maternal serum free beta-hCG and PAPP-A. During this time 30 cases of Down syndrome were identified either prenatally or postnatally. Using an established procedure the accuracy of predicted risk for Down syndrome was assessed in a population of 30 cases of Down syndrome and 11 758 unaffected pregnancies. The correlation between predicted risk and prevalence of Down syndrome was very high (r=0.9995). It is concluded that risks produced by the Fetal Medicine Foundation combined risk algorithm agree very closely with Down syndrome prevalence and can be used with confidence when counselling women of their risk.

Integrated ultrasound and biochemical screening for trisomy 21 using fetal nuchal translucency, absent fetal nasal bone, free beta-hCG and PAPP-A at 11 to 14 weeks

S. Cicero, R. Bindra, G. Rembouskos, K. Spencer and K. Nicolaides

Prenat Diagn 2003 Vol. 23 Issue 4 Pages 306-10

Background

Screening for trisomy 21 by a combination of maternal age, fetal nuchal translucency (NT) thickness and maternal serum free beta-hCG and pregnancy-associated plasma protein-A (PAPP-A) at 11 to 14 weeks of gestation is associated with a detection rate of 90% for a false-positive rate of 5%. Recent evidence suggests that in about 70% of fetuses with trisomy 21, the nasal bone is not visible at the 11th- to 14th-week scan (Cicero et al., 2001). The aim of this study was to examine whether fetal NT thickness and the level of maternal serum biochemical markers is independent of the presence or absence of the nasal bone, and to estimate the performance of a screening test that integrates the two sonographic and the two biochemical markers.

Methods

This was a retrospective case-control study comprising 100 trisomy 21 and 400 chromosomally normal singleton pregnancies at 11 to 14 weeks of gestation. Ultrasound examination was carried out for measurement of fetal NT and assessment of the presence or absence of the fetal nasal bone. Maternal serum free beta-hCG and PAPP-A were measured using the KRYPTOR rapid random-access immunoassay analyser (B·R·A·H·M·S Diagnostica GmbH, Berlin). The distribution of fetal NT, maternal serum free beta-hCG and PAPP-A in trisomy 21 fetuses with absent and present nasal bone was examined.

Results

The nasal bone was absent in 69 and present in 31 of the trisomy 21 fetuses. There were no significant differences in median maternal age, median gestational age, NT delta, free beta-hCG MoM and PAPP-A MoM in trisomy 21 fetuses with and without a visible nasal bone. For a false-positive rate of 5%, it was estimated that screening with the four markers in combination with maternal age would be associated with a detection rate of 97%. For a false-positive rate of 0.5%, the detection rate was 90.5%.

Conclusion

An integrated sonographic and biochemical test at 11 to 14 weeks can potentially identify about 90% of trisomy 21 fetuses for a false-positive rate of 0.5%.

Screening for trisomy 21 in twins using first trimester ultrasound and maternal serum biochemistry in a one-stop clinic: A review of three years experience

K. Spencer and K. Nicolaides

BJOG 2003 Vol. 110 Issue 3 Pages 276-80

Objective
To evaluate the performance of screening for fetal trisomy 21 in the first trimester of twin pregnancies by a combination of maternal serum biochemistry and ultrasonography.

Design
Three year retrospective review of screening performance.

Setting
District General Hospital maternity unit.

Population
All women booked to receive routine antenatal care at Harold Wood Hospital between 1 June 1998 and 30th September 2001. The population included 13,940 women of all ages presenting with pregnancies between 10 weeks 3 days and 13 weeks 6 days gestation. Of these, 230 had a twin pregnancy.

Methods
Women booked into the clinic were offered screening using a combination of maternal serum free beta-hCG and pregnancy-associated plasma protein-A (PAPP-A) and fetal nuchal translucency thickness. Women at increased risk of carrying a fetus with trisomy 21 or trisomy 13/18 (>/=1 in 300 at sampling) were offered counselling and an invasive diagnostic procedure. Follow up of the outcome of all pregnancies was carried out. For women who on examination were at 14 weeks of gestation or greater, or for women presenting as late bookers beyond 14 weeks, screening was performed in the same time frame using only maternal serum free beta-hCG and alpha-fetoprotein.

Main Outcome Measures
The first trimester detection rate for trisomy 21 and all aneuploides, false positive rate, uptake of screening, uptake of invasive testing in women identified at increased risk and fetal loss rates after invasive testing.

Results
Overall, 97.4% of the women with twins (224/230) accepted first trimester screening. The rate of detection of trisomy 21 was 75% (3/4). Fetal death at presentation was found in 3.4% of fetuses (16/460). Of women who accepted screening, 4.3% (10/230) presented too late for fetal nuchal translucency measurement and 10.0% of women (23/230) presented too early. A risk for trisomy 21 was calculated for each fetus based on the individual fetal nuchal translucency thickness and the maternal biochemistry. The false positive rate among those eligible for first trimester screening was 9.0% (19/206) of pregnancies and 6.9% of fetuses (28/412). Uptake of invasive testing was 59% (10/17) with chorionic villus sampling in eight cases and amniocentesis in two. No fetal loss occurred within 28 days of chorionic villus sampling and no loss occurred after amniocentesis. One case of trisomy 21 was identified for every three invasive procedures.

Conclusion
First trimester screening for trisomy 21 in twin pregnancies is both theoretically possible and practically achievable using a combination of nuchal translucency thickness and maternal serum biochemistry. However, dilemmas for the mother and health professionals when both nuchal translucency thickness measurements are normal might suggest that greater reliance be placed on the nuchal translucency thickness risk alone when counselling women about invasive testing.

Impact of a new national screening policy for Down's syndrome in Denmark: Population based cohort study

C. Ekelund, F. Jørgensen, O. Petersen, K. Sundberg and A. Tabor

Bmj 2008 Vol. 337 Pages a2547

Objective
To evaluate the impact of a screening strategy in the first trimester, introduced in Denmark during 2004-6, on the number of infants born with Down's syndrome and the number of chorionic villus samplings and amniocenteses, and to determine detection and false positive rates in the screened population in 2005 and 2006.

Design
Population based cohort study.

Setting
19 Danish departments of gynaecology and obstetrics and a central cytogenetic registry 2000-7.

Participantes
65 000 pregnancies per year.

Main Outcome Measures
The primary outcomes measured were number of fetuses and newborn infants with Down's syndrome diagnosed prenatally and postnatally and number of chorionic villus samplings and amniocenteses carried out. Secondary outcomes measured were number of women screened in 2005 and 2006, screen positive rate, and information on screening in 2005 and 2006 for infants with a postnatal diagnosis of Down's syndrome.

Results
The number of infants born with Down's syndrome decreased from 55-65 per year during 2000-4 to 31 in 2005 and 32 in 2006. The total number of chorionic villus samplings and amniocenteses carried out decreased from 7524 in 2000 to 3510 in 2006. The detection rate in the screened population in 2005 was 86% (95% confidence interval 79% to 92%) and in 2006 was 93% (87% to 97%). The corresponding false positive rates were 3.9% (3.7% to 4.1%) and 3.3% (3.1% to 3.4%).

Conclusion
The introduction of a combined risk assessment during the first trimester at a national level in Denmark halved the number of infants born with Down's syndrome. The strategy also resulted in a sharp decline in the number of chorionic villus samplings and amniocenteses carried out, even before full implementation of the policy.

A mixture model of nuchal translucency thickness in screening for chromosomal defects

D. Wright, K. Kagan, F. Molina, A. Gazzoni and K. Nicolaide

Ultrasound Obstet Gynecol 2008

Objective

Fetal nuchal translucency (NT) thickness increases with crown-rump length (CRL). In screening for chromosomal defects patient-specific risks are derived by multiplying the a priori maternal age-related risk by a likelihood ratio, determined from the deviation of the measured NT from the expected median. To quantify this deviation the measured NT is either subtracted (delta NT) or divided by the expected median (multiple of the median method, MoM). This study examines the validity of these methods.

Methods

NT was prospectively measured at 11 + 0 to 13 + 6 weeks in screening for chromosomal defects. The distribution of NT in euploid and chromosomally abnormal fetuses was examined.

Results

There were 37 078 normal pregnancies and 264 with trisomy 21, 81 with trisomy 18, 38 with trisomy 13 and 27 with Turner syndrome. We found that firstly, contrary to the assumption underlying the delta NT method, the distribution of delta NT changes with CRL and secondly, contrary to the assumption underlying the MoM method the distribution of NT was not Gaussian. Fetal NT followed two distributions, one that was dependent on CRL and one that was independent of CRL. The distribution in which NT increases with CRL was observed in about 95% of euploid fetuses, 5% with trisomy 21, 30% with trisomy 18, 15% with trisomy 13 and 10% with Turner syndrome. The median CRL-independent NT was 2.0 mm for the euploid group and 3.4, 5.5, 4.0 and 7.8 mm for trisomies 21, 18, 13 and Turner syndrome, respectively.

Conclusion

The NT thickness in chromosomally normal and abnormal fetuses follows a mixture of a gestation-dependent and gestation-independent distribution.

First-trimester combined screening for trisomy 21 at 7-14 weeks' gestation

D. Wright, K. Spencer, K. Kagan, N. Tørring, O. Petersen, A. Christou, J. Kallikas and K. Nicolaides

Ultrasound Obstet Gynecol 2010 Vol. 36 Issue 4 Pages 404-11

Objective

To establish an algorithm for first-trimester combined screening for trisomy 21 with biochemical testing from 7 to 14 weeks' gestation and ultrasound testing at 11-13 weeks.

Methods

This was a multicenter study of 886 pregnancies with trisomy 21 and 222 475 unaffected pregnancies with measurements of free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) at 7-14 weeks' gestation. Multiple regression modeling of log-transformed marker values was used to produce log multiples of the median (MoM) values for PAPP-A and free β-hCG. The models included terms for the center attended and the machine used for biochemical analysis, gestational age, maternal racial origin, maternal weight, smoking status and method of conception. Bivariate Gaussian distributions were fitted to log MoM PAPP-A and log MoM free β-hCG in trisomy 21 and in unaffected pregnancies. In each case the patient-specific risk for trisomy 21 was estimated by multiplying the individual maternal age-related risk with the likelihood ratio (LR) for fetal nuchal translucency (NT) according to the mixture model and the combined LR for maternal serum free β-hCG and PAPP-A. Estimates of detection rates for trisomy 21 and false-positive rates were calculated for combined screening with measurements of NT at 12 weeks together with measurements of free β-hCG and PAPP-A from 8 to 13 weeks.

Results

In trisomy 21 pregnancies the mean log MoM free β-hCG increased linearly with gestation between 7 and 14 weeks, whereas the relation between log MoM PAPP-A and gestation was fitted by a quadratic equation such that the maximum separation between trisomy 21 and unaffected pregnancies occurs at 9-10 weeks. At a false-positive rate of 3% the detection rate of combined screening at 12 weeks was 86% and this increased to 90% by biochemical testing at 9 weeks and ultrasound scanning at 12 weeks. The detection rate increased to 92% by measuring PAPP-A at 9 weeks and free β-hCG at the time of the scan at 12 weeks.

Conclusion

The performance of first-trimester biochemical screening for trisomy 21 is best at 9-10 weeks rather than at 7-8 or 11-14 weeks.

A reassessment of biochemical marker distributions in trisomy 21-affected and unaffected twin pregnancies in the first trimester

H. Madsen, S. Ball, D. Wright, N. Tørring, O. Petersen, K. Nicolaides and K. Spencer

Ultrasound Obstet Gynecol 2011 Vol. 37 Issue 1 Pages 38-47

Objective

To estimate the difference between levels of the two biochemical markers pregnancy-associated plasma protein-A (PAPP-A) and maternal serum free β-human chorionic gonadotropin (free β-hCG) in twin pregnancies relative to singleton pregnancies and establish an improved screening procedure for chromosomal abnormalities such as trisomy 21 in twin pregnancies.

Methods

4843 unaffected and 47 trisomy 21-affected twin pregnancies were included in the study. Chorionicity-specific medians were generated for PAPP-A and free β-hCG from gestational ages 8 to 14 weeks. Multiple of the median values for each of the biochemical markers were calculated. Detection rates and false-positive rates were estimated for screening tests incorporating nuchal translucency and maternal age, with and without biochemistry.

Results

Medians for the two biochemical markers for monochorionic and dichorionic twins in unaffected pregnancies show a gestational age-specific increase relative to singleton medians. Allowing for gestation and chorionicity, twin pregnancies affected with trisomy 21 had higher levels of free β-hCG and lower levels of PAPP-A. Adding biochemistry into the risk assessment using a fixed risk cut-off of 1 in 100 increased the detection rate for fetal trisomy 21 in dizygotic twin pregnancies from 78 to 90%, and decreased the false-positive rate from 8.0 to 5.9%.

Conclusion

Generation of chorionicity-specific medians for the biochemical markers and their use in risk assessment can improve the performance of first-trimester screening for chromosomal abnormalities in twins to a level comparable with that in singleton pregnancies.

Prospective study evaluating performance of first-trimester combined screening for trisomy 21 using repeat sampling of maternal serum markers PAPP-A and free β-hCG

C. Ekelund, D. Wright, S. Ball, I. Kirkegaard, P. Nørgaard, S. Sørensen, et al.

Ultrasound Obstet Gynecol 2012 Vol. 40 Issue 3 Pages 276-81

Objective

To prospectively evaluate the performance of first-trimester combined screening for trisomy 21 using the biochemical markers pregnancy-associated plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin (free β-hCG) obtained before and at the time of the nuchal translucency (NT) scan.

Methods

Three fetal medicine departments in Denmark participated in the study. Screening for trisomy 21 was set up as a two-step approach with blood sampling performed before the NT scan (early sample) and again at the time of the NT scan (late sample). PAPP-A and free β-hCG were measured on both the early and late samples. Age-standardized detection and false-positive rates for different screening protocols were calculated.

Results

We collected two blood samples in 27 pregnancies affected by trisomy 21 and in 3891 control pregnancies. The early samples were taken between gestational ages 8 + 0 and 13 + 6 weeks, and the late samples between 11 + 3 and 14 + 6 weeks. The median interval between the samples was 17 (range, 1-40) days. We found a significantly better estimated screening performance when using early sampling vs late sampling ($P < 0.05$). With a risk cut-off of 1 in 100, at the time of the risk assessment the estimated detection and false-positive rates when using the early sample were 91% (95% CI, 81-98%) and 1.6% (95% CI, 1.3-2.0%), respectively. For fixed false-positive rates the highest detection rates were achieved using both blood samples. When comparing early sampling vs double sampling there was no significant difference in screening performance.

Conclusion

In combined first-trimester screening for trisomy 21, use of early sampling with measurement of PAPP-A and free β-hCG before the time of the NT scan can optimize screening performance. Using maternal serum markers obtained both before and at the time of the NT scan has the potential to further improve performance, but larger studies are needed to confirm this potential.

Performance of first trimester screening for Trisomy 21 in twin pregnancies

E. Bergstrand, C. Borregaard Miltoft and A. Tabor

Prenat Diagn 2021 Vol. 41 Issue 2 Pages 210-217

Objective

To assess the performance of the Danish first trimester screening program in twin pregnancies.

Methods

Retrospective, nation-wide, cohort study with data collected from the Danish Fetal Medicine Database (DFMD) and The Danish Central Cytogenetic Registry (DCCR). The cohort included all women with twin pregnancies participating in the national first trimester screening program for Trisomy 21. Risk assessment was based on maternal age, nuchal translucency (NT) thickness and, if available, biochemical markers (β-hCG and PAPP-A).

Results

8812 twin pregnancies including 42 pregnancies with Trisomy 21 had a risk assessment between 2009 and 2017. The detection rate (DR) for pregnancies with a risk assessment based on maternal age and NT only (missing data on biochemical markers, n = 4693) was 69.6% (95% CI: 50.8%-88.4%) for a 6.3% false positive rate (FPR) (95% CI: 5.6%-7.0%), whereas for pregnancies with a risk assessment based on all three parameters (n = 4119) the DR was 89.5% (95% CI: 76.7%-100.0%) for a 7.2% FPR (95% CI: 6.4%-8.0%).

Conclusion

The DR of Trisomy 21 in twin pregnancies, seems as high as for singleton pregnancies, when using optimal screening techniques, but the FPR is nearly twice as high.

Prenatal screening tests and prevalence of fetal aneuploidies in a tertiary hospital in Thailand

P. Wongkrajang, J. Jittikoon, S. Sangroongruangsri, P. Talungchit, P. Ruangvutilert, T. Panchalee, et al.

PLoS One 2023 Vol. 18 Issue 4 Pages e0284829

This study evaluated prenatal screening test performance and the prevalence of common aneuploidies at Siriraj Hospital, Thailand. We collected data from screening tests which are first-trimester test, quadruple test, and noninvasive prenatal tests (NIPT) between January 2016 and December 2020. Thirty percent (7,860/25,736) of pregnancies received prenatal screening tests for aneuploidies disorders, and 17.8% underwent prenatal diagnosis tests without screening. The highest percentage of screening tests was first-trimester test (64.5%). The high-risk results were 4% for first-trimester test, 6.6% for quadruple test, and 1.3% for NIPT. The serum screening tests for trisomy 13 and 18 had no true positives; therefore, we could not calculate sensitivity. For the first-trimester test, the sensitivity for trisomy 21 was 71.4% (95% confidence intervals (CI) 30.3-94.9); specificity for trisomy 13 and 18 was 99.9% (95% CI 99.8-99.9); and for trisomy 21 was 96.1% (95% CI 95.6-96.7). For the quadruple test, the specificity for trisomy 18 was 99.6% (95% CI 98.9-99.8), while the sensitivity and specificity for trisomy 21 were 50% (95% CI 26.7-97.3) and 93.9% (95% CI 92.2-95.3), respectively. NIPT had 100% sensitivity and specificity for trisomy 13, 18 and 21, and there were neither false negatives nor false positives. For pregnant women < 35 years, the prevalence of trisomy 13, 18, and 21 per 1,000 births was 0.28 (95% CI 0.12-0.67), 0.28 (95% CI 0.12-0.67), and 0.89 (95% CI 0.54-1.45), respectively. For pregnant women ≥35 years, the prevalence of trisomy 13, 18, and 21 per 1,000 births was 0.26 (95% CI 0.06-1.03), 2.59 (95% CI 1.67-4.01), and 7.25 (95% CI 5.58-9.41), respectively. For all pregnancies, the prevalence of trisomy 13, 18, and 21 per 1,000 births was 0.27 (95% CI 0.13-0.57), 0.97 (95% CI 0.66-1.44), 2.80 (95% CI 2.22-3.52), respectively.

2nd trimester trisomy combined screening

Prospective assessment of the Hong Kong Hospital Authority universal Down syndrome screening programme

D. Sahota, W. C. Leung, W. Chan, W. To, E. Lau and T. Leung

Hong Kong Med J 2013 Vol. 19 Issue 2 Pages 101-8

Objective
To evaluate the performance of the locally developed universal Down syndrome screening programme.

Design
Population-based cohort study in the period July 2010 to June 2011 inclusive.

Setting
Four Hong Kong Hospital Authority Departments of Obstetrics and Gynaecology and a central university-based laboratory for maternal serum processing and risk determination.

Participants
Women were offered either a first-trimester combined test (nuchal translucency, free beta human chorionic gonadotropin, and pregnancy-associated plasma protein-A) or nuchal-translucency-only test, or a second-trimester double test (alpha-fetoprotein and total human chorionic gonadotropin) for detection of Down syndrome according to their gestational age. Those with a trisomy 21 term risk of 1:250 or higher were offered a diagnostic test.

Results
A total of 16 205 pregnancies were screened of which 13 331 (82.3%) had a first-trimester combined test, 125 (0.8%) had a nuchal-translucency test only, and 2749 (17.0%) had a second-trimester double test. There were 38 pregnancies affected by Down syndrome. The first-trimester screening tests had a 91.2% (31/34) detection rate with a screen-positive rate of 5.1% (690/13 456). The second-trimester test had a 100% (4/4) detection rate with a screen-positive rate of 6.3% (172/2749). There were seven (0.9%) pregnancies that miscarried following an invasive diagnostic test. There were two Down syndrome-affected live births, both with an estimated first-trimester trisomy 21 term risk lower than 1:250.

Conclusion
The universal screening programme offered at the four units was effective and achieved the expected detection rates and low false-positive rates, and to maintain these, the current emphasis on training, quality control, and regular auditing must continue.

Prospective study of the feasibility and effectiveness of a second-trimester quadruple test for Down syndrome in Thailand

P. Kaewsuksai and S. Jitsurong

Int J Gynaecol Obstet 2017 Vol. 139 Issue 2 Pages 217-221

Objective

To evaluate the feasibility and effectiveness of a quadruple test for Down syndrome in the second trimester of pregnancy in clinical settings in Thailand.

Methods

From October 2015 to September 2016, a prospective study was undertaken in 19 hospitals in Songkhla province, Thailand. Women with a singleton pregnancy of 14-18 weeks were enrolled and underwent the quadruple test. The risk cutoff value was set at 1:250. All women with a positive test (risk ≥1:250) were offered amniocentesis. Women were followed up until delivery.

Results

Among 2375 women, 206 (8.7%) had a positive quadruple test; 98 (47.6%) of these women voluntarily underwent amniocentesis. Overall, seven pregnancies were complicated with chromosomal abnormalities (2.9 cases in 1000), including four cases of Down syndrome (1.7 in 1000) and three of other abnormalities. The detection, false-positive, and accuracy rates of the quadruple test for Down syndrome were 75.0%, 8.6%, and 91.4%, respectively.

Conclusion

The quadruple test was found to be a feasible and efficient method for screening for Down syndrome in the second trimester of pregnancy in a Thai clinical setting. The test should be performed for pregnant women before an invasive test for Down syndrome.

Trisomy 21 screening based on first and second trimester in a Taiwanese population

R. Lan, C. Chou, P. Wang, R. Chen and C. Hsiao

Taiwan J Obstet Gynecol 2018 Vol. 57 Issue 4 Pages 551-554

Objective

This study investigates the performance of first- and second-trimester screening tests for detecting fetal trisomy 21 in a Taiwanese population.

Materials and Methods

This multicenter study 29,137 cases enrolled the chromosomal abnormality screening between 2013 and 2014 two years period from Taipei city. There were 23,990 was done the first trimester screening using a combination of fetal nuchal translucency, maternal serum β-human chorionic gonadotropin, and pregnancy-associated plasma protein-A between 11(+0) and 13(+6) weeks of gestation age. Second-trimester screening was done for 5149 cases using a double test (β-human chorionic gonadotropin and serum alpha fetoprotein) between 15 and 20 weeks of gestation. The cut-off risk for both is 1:270 or higher.

Results

This multicenter study 29,137 cases that completed first- and second-trimester screening, and the outcome was available in 28,726 cases. The mean maternal age of the screen-positive group was 34.6 ± 4.2 years. The first-trimester had 891 cases screening positive with a detection rate of 97.5% for fetal trisomy 21, and false positive rate of 3.5%. In the second-trimester had 334 cases screening positive, the detection rate and false positive rate were 33.3% and 6.4% for trisomy 21, respectively.

Conclusion

The first-trimester screening had higher performance with a lower false positive rate than the second-trimester screening. First-trimester screening could reduce the rate of unnecessary invasive testing for all pregnant women.

A technical and clinical evaluation of the new ThermoFisher B·R·A·H·M·S unconjugated estriol and inhibin-A assays and their use in second trimester Down syndrome screening

D. Sahota, F. Tsang, J. Gu, W. Fung, K. Mok and C. Wong

Scand J Clin Lab Invest 2021 Vol. 81 Issue 5 Pages 371-378

To evaluate second-trimester Down syndrome screening performance of the new ThermoFisher B·R·A·H·M·S GOLD unconjugated estriol (uE3) and inhibin-A assays. Serum samples were analyzed for levels of uE3 and inhibin-A using the ThermoFisher B·R·A·H·M·S GOLD immunoanalyzer and compared to other platforms. Levels were transformed to multiples of the median (MoM) in unaffected pregnancies. Log(10) MoM distributions in unaffected and Down syndrome pregnancies were assessed for central tendency (mean) and dispersion (SD). Empirical and estimated screening performances were determined. Correlation between B·R·A·H·M·S and AutoDELFIA(®) uE3 and inhibin-A were 0.63 and 0.97, respectively, the respective mean difference was 31.3% [95%CI 50.2% to -112.8%] and -23.3% [95%CI -41.9% to -4.7%]. Passing-Bablok indicated significant systematic (-2.78 [95%CI -3.57 to -2.04]) and proportional bias (1.30 [95%CI 1.15 to -1.47]) between uE3 assays and significant proportional bias (0.71[95%CI 0.65-0.78]) between inhibin-A assays. The uE3 and inhibin-A log(10) MoM distribution mean [SD] in unaffected and Down syndrome pregnancies were 0.0024 [SD = 0.2341] and -0.0001 [SD = 0.2078], and -0.2028 [SD = 0.2495] and 0.3645 [SD = 0.2576], respectively. The new B·R·A·H·M·S uE3 and inhibin-A assays had an 81-83% detection rate for Trisomy21 for a 5% false-positive rate. The new B·R·A·H·M·S assays achieved the expected screening performance provided the risk estimation model is adjusted to account for the higher B·R·A·H·M·S uE3 MoM measurement distribution variance.

Analytical publications

Discordant Down syndrome risk calculation with low maternal serum markers: About five cases of digynic triploidies

E. Roland, E. Voirin-Mathieu, S. Verchain, H. Odaert, S. Dreux and G. Renom

Gynecol Obstet Fertil Senol 2023 Vol. 51 Issue 3 Pages 172-175

Objective

We compare the risk of Down syndrome among five patients carrying a foetus with digynic triploidy and suggest a course of action for these particular serological profiles.

Methods

The concentrations of the different markers used are transformed into multiples of the median by using each of the three software types present on the French market which then determine the risk of Down syndrome.

Results

For comparable biochemical and ultrasound profiles, the risk of Down syndrome turns out to be vastly different depending on the type of software employed. The relevance of an immediate diagnostic procedure, of a cell free DNA test or of a basic ultrasound follow-up then arises, leading to a potentially variable care pathway for the patient.

Conclusion

This study confirms that for this type of biochemical profile, the laboratory's advisory service is fundamental, that a control ultrasound is essential and that an invasive procedure must be used almost invariably due to the extremely substantial risk factors.

Analytical publications

Analyte stability

Focus on preanalytics for Down's syndrome screening during first trimester of pregnancy

R. Gebeile, C. Roger, C. Doche and L. Doche

Ann Biol Clin (Paris) 2014 Vol. 72 Issue 2 Pages 207-12

The aim of the study is to specify the pre-analytical conditions required for Down's syndrome screening in first trimester by maternal serum markers. The concentration variation of both markers, hCGβ and PAPP-A, was analyzed at room temperature, at 4°C and during freezing-thawing cycles. Serum can be kept during 72h between 2 and 8°C with an acceptable bias of 5% for each marker. It can also undergo three freezing-thawing cycles without any variation of results. Preservation at room temperature (between 20 and 25°C) requires an analysis within 24h. From this study, writing recommendations enable to give a precise frame to pre-analytical processing and transport of blood samples, in a field where variations can lead to heavy therapeutic decisions.

Stability of placental growth factor, soluble fms-like tyrosine kinase 1, and soluble fms-like tyrosine kinase 1 e15a in human serum and plasma

S. Rowson, M. Reddy, D. L. Rolnik, F. Da Silva Costa and K. Palmer

Placenta 2019 Vol. 86 Pages 1-3

Placental growth factor (PlGF), total soluble fms-like tyrosine-kinase 1 (sFlt-1) and its placental-specific variant, sFlt-1 e15a, show promise as biomarkers for the prediction and diagnosis of preeclampsia. This study describes the degradation of PlGF, sFlt-1 and sFlt-1 e15a within maternal serum and plasma to assist clinical implementation. Whole blood was refrigerated at °C for up to 48 h prior to centrifugation for isolation of plasma and serum. PlGF and sFlt-1 were quantified using the B·R·A·H·M·S KRYPTOR Compact PLUS; sFlt-1 e15a via a custom ELISA. All three analytes are stable for at least 48 h at 4 °C. Serum and plasma performed comparably.

Analytical publications

Interferences

Undetectable pregnancy-associated plasma protein-A in antenatal serum Down's syndrome screening: a case of assay interference

C. Williams, K. Hambridge, M. Petchey, J. Martin and K. Spencer

Ann Clin Biochem 2015 Vol. 52 Issue Pt 5 Pages 615-9

Serum pregnancy-associated plasma protein-A (PAPP-A) is measured in Down's syndrome screening, routinely offered to women in pregnancy. We present the case of an undetectable pregnancy-associated plasma protein-A concentration on the PerkinElmer AutoDELFIA system where immunoassay interference was suspected. Investigations performed, including dilution and recovery studies and antibody-blocking tube incubations, all yielded serum pregnancy-associated plasma protein-A concentrations of <25 mU/L. Pregnancy-associated plasma protein-A was also undetectable on two alternative pregnancy-associated plasma protein-A assays. An experimental manual Delfia procedure suggested the site of interference was between the secondary antibody and the pregnancy-associated plasma protein-A molecule. This case of negative interference in the PerkinElmer pregnancy-associated plasma protein-A assay produced a falsely high Down's syndrome risk that might have led to an unnecessary invasive procedure with the potential for fetal loss. This highlights the need for Down's syndrome screening laboratories to be vigilant to immunoassay interference due to the significant impact of the results on patient decision outcome.

Assay interference leading to erroneous PAPP-A results

S. L. Jones, I. Mills, M. Petchey and C. Williams

Ultrasound Obstet Gynecol 2022

Assay interference is a rare but recognized issue for immunoassays. There have been very few case reports of interference in assays for prenatal screening biomarkers. We report a series of 13 cases in which falsely low pregnancy-associated plasma protein-A (PAPP-A) marker levels were obtained due to assay interference in Roche Elecsys and Perkin Elmer AutoDELFIA immunoassays.

Re: Assay interference leading to erroneous pregnancy-associated plasma protein-A results

A. Matyszkiewicz, M. Wiecheć and A. Nocuń

Ultrasound Obstet Gynecol 2023 Vol. 62 Issue 6 Pages 913

We read with interest the report by Jones et al. of a series of cases with extremely low levels of pregnancy-associated plasma protein-A (PAPP-A), which were determined to have resulted from assay interference. Such interference would, if not recognized, lead to false-positive screening results for trisomy 21 and further unnecessary invasive testing, follow-up and parental stress. In countries in which non-invasive prenatal testing (NIPT) is not covered by the national healthcare system, this method is not applied routinely to discriminate false-positive PAPP-A cases.

High levels of hemolysis do not affect measurement of PAPP-A, β-HCG and TRAb on B·R·A·H·M·S KRYPTOR compact plus

P. Pettersson Pablo, C. Aneskans and M. Vink

Scand J Clin Lab Invest 2023 Vol. 83 Issue 6 Pages 367-370

To assess the impact of high levels of hemolysis on the laboratory results for free β-hCG, PAPP-A, and TRAb performed on the B·R·A·H·M·S KRYPTOR Compact PLUS. Adapted from the CLSI guidelines EP07-A2, paired difference testing was performed on serum samples from the routine laboratory workflow. Three sample pools for each assessed analyte was prepared and subjected to increased levels of added hemolysate. For β-hCG and PAPP-A, the relative difference in the measured analyte concentration between the sample with 0 g/L added Hb and the samples with increasing free Hb concentrations (up to 6 g/L), was well below the pre-set acceptance criterion of 10% at all levels. The TRAb results showed greater variation than the other analytes, likely a consequence of imprecision rather than hemolysis. Hemolysis has a negligible effect on the analysis results of free beta-hCG, PAPP-A and TRAb measured on the B·R·A·H·M·S KRYPTOR Compact PLUS

Analytical publications

Sample type

The influence of different sample collection types on the levels of markers used for Down's syndrome screening as measured by the KRYPTOR Immunosassay system

K. Spencer

Ann Clin Biochem 2003 Vol. 40 Issue Pt 2 Pages 166-8

Background

In a rapid point-of-care screening programme for chromosomal anomalies, analysis of biochemical markers in maternal blood can now be accomplished in a rapid time frame (less than 20 min). The need to leave whole blood samples some 10 min for coagulation and a further 5 min for centrifugation adds additional processing time.

Methods

The possibilities for reducing this processing time were investigated using various anticoagulated blood collection systems and the KRYPTOR analytical platform. Plasma levels of alpha-fetoprotein (AFP), pregnancy-associated plasma protein-A (PAPP-A) and free human chronic gonadotrophin beta-subunit (beta-hCG) were compared with those in maternal serum.

Results

From the mean results from ten patients it was shown that use of heparin plasma resulted in a statistically significant reduction in levels of PAPP-A and that EDTA plasma reduced the levels of PAPP-A dramatically. For AFP, levels in citrated plasma and EDTA plasma were also significantly reduced, whereas levels of free beta-hCG were not affected.

Conclusion

Use of alternative sample types for PAPP-A is not possible. The sample of choice for first trimester screening using the KRYPTOR platform is maternal serum.

Factors adjusting the risk

Maternal weight correction of maternal serum PAPP-A and free beta-hCG MoM when screening for trisomy 21 in the first trimester of pregnancy

K. Spencer, R. Bindra and K. Nicolaides

Prenat Diagn 2003 Vol. 23 Issue 10 Pages 851-5

Objective

To assess the suitability of either the log-linear or reciprocal-linear regression procedure for maternal weight correction of biochemical marker MoMs in the first trimester.

Methods

Data from two prospective first-trimester OSCAR screening programmes including 32,010 women with first-trimester maternal serum-free beta-hCG and PAPP-A measured by the KRYPTOR analyser was analysed by regression analysis to provide parameters for the log-linear and reciprocal-linear MoM correction procedures. Assessment was made by goodness of fit to the data. The impact on detection rate and false-positive rate of the different correction procedures was assessed using statistical modelling with biochemical markers alone.

Results

Both log-linear and reciprocal-linear correction were shown to fit the data well. For free beta-hCG, the log-linear procedure was marginally superior to the reciprocal-linear procedure (r2=0.986 v 0.980), whilst for PAPP-A the reciprocal-linear procedure was marginally better (r2=0.991 v 0.985). Log-linear correction reduced the variance for both markers more than did the reciprocal-linear procedure. For free beta-hCG, the sd was reduced from 0.2675 to 0.2605 and for PAPP-A, it was reduced from 0.2545 to 0.2336. Correcting for maternal weight was shown to reduce the population false-positive rate from 7.0 to 6.5%, whilst maintaining the same detection rate at a risk cut-off of 1 in a 100. At individual levels, a two-fold variation in risk was demonstrated depending upon the individual's weight.

Conclusion

To provide accurate individual patient-specific risks for trisomy 21, maternal weight must be taken into account and should be a mandatory data item for screening programmes. Maternal weight correction in the first trimester using free beta-hCG and PAPP-A can be best achieved using the log-linear procedure.

Dose dependency between cigarette consumption and reduced maternal serum PAPP-A levels at 11-13+6 weeks of gestation

K. Kagan, V. Frisova, K. Nicolaides and K. Spencer

Prenat Diagn 2007 Vol. 27 Issue 9 Pages 849-53

Objective

To examine whether in smokers there is a significant dose dependency between the number of cigarettes per day and levels of free ss-hCG and pregnancy-associated plasma protein A (PAPP-A) at 11-13(+6) weeks of gestation.

Methods

This was a retrospective analysis of the maternal serum free ss-hCG and PAPP-A levels in relation to the maternal smoking status in 109 263 chromosomally normal singleton pregnancies that had undergone first-trimester screening for Down syndrome by a combination of fetal nuchal translucency thickness and maternal serum biochemistry.

Results

There were 95 287 nonsmokers and 13 976 cigarette smokers. The overall median PAPP-A MoM among cigarette smokers was 0.827, which was 19.6% lower than the value of 1.029 in nonsmokers ($p < 0.0001$ for log(10) MoM). The respective values for beta-hCG MoM were 1.003 for smokers and 1.035 for nonsmokers ($p < 0.0001$ for log(10) MoM) which corresponds to a reduction of 3.1%. There was a significant inverse relationship between the number of cigarettes per day and the level of PAPP-A MoM ($r = 0.989$, $p < 0.0001$) but not the level of free beta-hCG MoM ($r = 0.733$; $p = 0.098$). Using a statistical modeling approach we found that the screen-positive rate when correcting the PAPP-A MoM by an all or nil smoking factor was reduced by only 0.1% (3.75 vs 3.85%) when compared to correcting with a factor related to the smoking dose per day.

Conclusion

In first-trimester screening for Down syndrome by maternal serum PAPP-A and free beta-hCG the impact of correcting for the dose dependant rather than the all or nil effect of smoking is marginal. However, a dose dependent correction improves the accuracy of the individual patient-specific risk.

First-trimester screening for trisomy 21 by free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A: impact of maternal and pregnancy characteristics

K. Kagan, D. Wright, K. Spencer, F. Molina and K. Nicolaides

Ultrasound Obstet Gynecol 2008 Vol. 31 Issue 5 Pages 493-502

Objective

To use multiple regression analysis to define the contribution of maternal variables that influence the measured concentration of free beta-human chorionic gonadotropin (beta-hCG) and pregnancy-associated plasma protein-A (PAPP-A), and the interaction between these covariates, in first-trimester biochemical screening for trisomy 21.

Methods

This was a multicenter study of prospective screening for trisomy 21 by a combination of fetal nuchal translucency thickness, and maternal serum free beta-hCG and PAPP-A at 11 + 0 to 13 + 6 weeks of gestation. In the pregnancies subsequently found to have trisomy 21 and in those with no obvious chromosomal abnormality, we used multiple regression analysis to account for pregnancy characteristics that influence the measured concentrations of free beta-hCG and PAPP-A. We fitted Gaussian distributions to the distribution of log multiples of the median (MoM) values in trisomy 21 and in unaffected pregnancies.

Results

There were 491 cases of trisomy 21 and 96 803 chromosomally normal pregnancies. Compared with values in Caucasian women, those who were parous, non-smokers and those who conceived spontaneously, PAPP-A was 57% higher in women of Afro-Caribbean origin, 3% higher in South Asians, 9% higher in East Asians, 2% higher in nulliparous women, 17% lower in smokers and 10% lower in those conceiving by in-vitro fertilization (IVF). Free beta-hCG was 12% higher in women of Afro-Caribbean origin, 9% lower in South Asians, 8% higher in East Asians, 2% higher in nulliparous women, 4% lower in smokers and 9% higher in those conceiving by IVF. In screening for trisomy 21 by maternal age and serum free beta-hCG and PAPP-A the estimated detection rate was 65% for a false-positive rate of 5%.

Conclusion

In first-trimester biochemical screening for trisomy 21 it is essential to adjust the measured values of free beta-hCG and PAPP-A for maternal and pregnancy characteristics.

Screening for trisomies 21, 18 and 13 by maternal age, fetal nuchal translucency, fetal heart rate, free beta-hCG and pregnancy-associated plasma protein-A

K. Kagan, D. Wright, C. Valencia, N. Maiz and K. Nicolaides

Hum Reprod 2008 Vol. 23 Issue 9 Pages 1968-75

Background

A beneficial consequence of screening for trisomy 21 is the early diagnosis of trisomies 18 and 13. Our objective was to examine the performance of first-trimester screening for trisomies 21, 18 and 13 by maternal age, fetal nuchal translucency (NT) thickness, fetal heart rate (FHR) and maternal serum-free beta-hCG and pregnancy-associated plasma protein-A (PAPP-A).

Methods

Prospective screening for trisomy 21 by maternal age, fetal NT, free beta-hCG and PAPP-A at 11(+0)-13(+6) weeks in singleton pregnancies, including 56 376 normal cases, 395 with trisomy 21, 122 with trisomy 18 and 61 with trisomy 13. Risk algorithms were developed for the calculation of patient-specific risks for each of the three trisomies based on maternal age, NT, FHR, free beta-hCG and PAPP-A. Detection (DR) and false positive rates (FPR) were calculated and adjusted according to the maternal age distribution of pregnancies in England and Wales in 2000-2002.

Results

The DR and FPR were 90% and 3%, respectively, for trisomy 21, 91% and 0.2% for trisomy 18 and 87% and 0.2% for trisomy 13. When screen positivity was defined by an FPR of 3% on the risk for trisomy 21 in conjunction with an FPR of 0.2% on the maximum of the risks for trisomies 13 and 18, the overall FPR was 3.1% and the DRs of trisomies 21, 18 and 13 were 91%, 97% and 94%, respectively.

Conclusion

As a side effect of first-trimester screening for trisomy 21, approximately 95% of trisomy 13 and 18 fetuses can be detected with an 0.1% increase in the FPR.

First-trimester screening markers are altered in pregnancies conceived after IVF/ICSI

A. Gjerris, A. Loft, A. Pinborg, M. Christiansen and A. Tabor

Ultrasound Obstet Gynecol 2009 Vol. 33 Issue 1 Pages 8-17

Objective

To determine the levels of first-trimester screening markers and to assess the false-positive rate for first-trimester combined screening for Down syndrome in a large national population of women pregnant after assisted reproductive technology (ART), in order to decide whether or not to correct risk calculation for mode of conception.

Methods

A national prospective cohort study of 1000 pregnancies achieved after ART was compared with a control group of 2543 pregnancies conceived spontaneously. All women completed a first-trimester combined screening program. Risk calculation was performed retrospectively based on the screening parameters to avoid bias due to the use of different algorithms of risk calculation.

Results

In chromosomally normal pregnancies conceived after in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), the pregnancy-associated plasma protein-A multiples of the median value was significantly decreased when compared with that of pregnancies conceived spontaneously (0.78 and 0.79 vs. 0.98), while there was no difference in the group treated by frozen embryo replacement. There was no difference in the level of free beta-human chorionic gonadotropin between groups. The median nuchal translucency thickness was smaller in the overall ART group compared with controls. The false-positive rate of first-trimester combined screening in the overall ART group, adjusted for maternal age, was significantly higher when compared with controls (9.0% vs. 6.0%).

Conclusion

It seems advisable to use a population of IVF/ICSI pregnancies to establish median curves for the first-trimester serum screening parameters and perhaps also for nuchal translucency thickness. However, care must be taken, as different ART treatment methods and aspects of medical history seem to alter the screening parameters in different ways.

Medians and correction factors for biochemical and ultrasound markers in Chinese women undergoing first-trimester screening for trisomy 21

D. Sahota, T. Leung, T. Fung, L. Chan, L. Law and T. Lau

Ultrasound Obstet Gynecol 2009 Vol. 33 Issue 4 Pages 387-93

Objective

To establish normative values and distribution parameters of first-trimester maternal serum free beta-human chorionic gonadotropin (beta-hCG), pregnancy-associated plasma protein-A (PAPP-A) and fetal nuchal translucency (NT) thickness in Chinese women and to examine the effects of covariates on their levels.

Methods

Maternal serum free beta-hCG, PAPP-A and fetal NT were measured in 9762 women presenting for first-trimester combined screening for Down syndrome at 11 to 14 weeks of gestation. Individuals' markers were converted to multiples of the median (MoM) using expected medians estimated by performing a weighted regression analysis. Multivariate regression analysis was performed to assess the influence of maternal weight, parity, ethnicity, chorionicity in twin pregnancies, smoking, insulin-dependent diabetes and mode of conception on individual marker MoM levels.

Results

Both free beta-hCG and PAPP-A median values demonstrated an exponential relationship with gestational age in days. Multivariate regression analysis indicated that free beta-hCG MoM was statistically significantly dependent on maternal weight ($P < 0.0001$) and chorionicity in twin pregnancy (both monochorionic and dichorionic $P < 0.0001$), that PAPP-A MoM was dependent on maternal weight ($P < 0.0001$), parity ($P < 0.0001$), chorionicity in twin pregnancy (both monochorionic and dichorionic $P < 0.0001$) and mode of conception ($P = 0.002$), and that fetal NT-MoM was dependent on maternal weight ($P = 0.0006$) and mode of conception ($P = 0.012$).

Conclusion

Normative values have been generated to allow conversion of NT, free beta-hCG and PAPP-A to their MoM equivalents and correction factors have been determined to adjust for maternal and pregnancy characteristics for use in ethnic Chinese women undergoing first-trimester screening for aneuploidy.

First-trimester screening for trisomy 21 with adjustment for biochemical results of previous pregnancies

D. Wright, A. Syngelaki, C. Birdir, I. Bedei and K. Nicolaides

Fetal Diagn Ther 2011 Vol. 30 Issue 3 Pages 194-202

Objective

To investigate the effect of associations in serum free β-hCG and PAPP-A between successive pregnancies on the performance of screening for trisomy 21 at 11-13 weeks' gestation.

Methods

In 8,499 women with two consecutive pregnancies, including 49 women with fetal trisomy 21 in the second pregnancy, the correlation in serum free β-hCG multiples of the median (MoM) and PAPP-A MoM between pregnancies was determined, and the effects of correcting for the correlation on the performance of screening was estimated.

Results

There were significant associations between pregnancies in free β-hCG MoM (r = 0.4435) and PAPP-A MoM (r = 0.4796). In screening by maternal age and biochemistry at a risk cutoff of 1 in 100, in the second pregnancies the false-positive rate was 35.5% for those with screen-positive results in the first pregnancy, and this was reduced to 17.1% after adjustment for the results of the first pregnancy. Similarly, in women with screen-negative results in the first pregnancy, adjustment for the results improved the detection rate in the second pregnancy from 66.7 to 81.2%.

Conclusion

In screening for trisomy 21, adjustment for the biochemical findings in a previous pregnancy has major effects on individual patient-specific risks, increases the detection rate and reduces the false-positive rate.

Ethnic-specific reference range affects the efficacy of quadruple test as a universal screening for Down syndrome in a developing country

S. Pranpanus, O. Kor-Anantakul, T. Suntharasaj, C. Suwanrath, T. Hanprasertpong, N. Pruksanusak, et al.

PLoS One 2021 Vol. 16 Issue 5 Pages e0251381

Objective

To evaluate the efficacy of the quadruple test for potential use as a Thai national policy for Down syndrome (DS) screening and establish an accurate equation for risk estimation of Down syndrome based on gestational age, weight and the ethnic-specific reference range of our population.

Methods

A prospective study was conducted on singleton pregnancies at 14 to 21 weeks of gestation to evaluate the efficacy of quadruple DS screening using the automatically calculated Western European descent factor (WF) in our population and the impact of screening using a specific Thai ethnic factor as well as to establish an equation for the risk estimation of DS based on gestational age, weight and a local Thai ethnic factor to correct for the impact of ethnic factor on the screening efficacy.

Results

Of a total of 5,515 women, 12 cases of DS and 8 cases of other aneuploidies were found. The detection rate, false positive rate and specificity were 75.0%, 9.1% and 90.9%, respectively, by automatic calculation with the widely used WF; the screening efficacy was lower when used in Asian populations than in other studies. The best-fitted regression equation of serum quadruple screening of AFP, free β-hCG, uE3 and inhibin A was established by adjustment for gestational age (GA) in days, maternal weight and our Thai-specific ethnic reference range which was created for this study. Calculations with our Thai-specific ethnic model gave a better detection rate of 83.3%, a false positive rate of 9.6% and specificity of 90.4%.

Conclusion

The serum quadruple test had a lower detection rate than expected when the risk estimation was based on the WF reference range. The serum quadruple test using WF had significantly different levels when corrected with our ethnic-specific factor. Using our local ethnic specific model could increase the detection rate of DS screening in Thailand with a minimal increase in false positive rates. Our findings indicate that DS screening should be adjusted with an appropriate individual ethnic factor when used for national screening.

Clinical consequences of maternal serum PAPP-A and free beta hCG levels above 2.0 multiple of median in the first trimester screening

P. Kosinski, A. Frühauf, M. Lipa, A. Szczepkowska, K. Luterek, M. Falis, et al.

Eur J Obstet Gynecol Reprod Biol 2023 Vol. 282 Pages 101-104

Introduction

Extreme levels of either PAPP-A or free β-hCG may be a serious clinical concern. A multicentre study was carried out to determine the frequency and clinical consequences of high (minimum 2,0 MoM) maternal (PAPP)-A and free beta hCG.

Methods

A total number of 8591 patients with singleton pregnancies between 11 + 0-13 + 6 weeks of gestation were enrolled. A total number of 612 cases with first trimester serum level of PAPP-A corresponding to ≥ 2,0 MoM and/or free β-hCG to ≥ 2,0 MoM were included in the statistical analysis. All serum samples were analysed with Roche (Cobas) or KRYPTOR (B·R·A·H·M·S) devices. A retrospective analysis of perinatal outcomes was conducted.

Results

Values of PAPP-A ≥ 2,0 MoM and free β-hCG < 2.0 MoM were detected in 48,5% of patients (n = 297), free β-hCG ≥ 2,0 MoM and PAPP-A concentration < 2,0 MoM in 38,1% of patients (n = 233) and both PAPP-A and free β-hCG ≥ 2,0 multiple of median in 13,4% of patients (n = 82). The highest PAPP-A and free β-hCG concentrations were 19,2 MoM and 16,3 MoM respectively. Patients with both PAPP-A and free β-hCG above 2,0 MoM had a slightly higher (but statistically not significant) prevalence of history of low birthweight (8,3%).

Discussion

Pregnancy outcomes in women with normal ultrasound findings and high PAPP-A /free β-hCG concentration are good. Higher prevalence of pregnancy complications was not detected in either extremely high PAPP-A and free β-hCG concentration groups. In cases of normal ultrasound and isolated high (even extreme) biochemical markers levels the counselling should be comforting.

Neural tube defects

Maternal Prenatal Screening for Fetal Defects

A. MacRae & J. Canick

Maternal Prenatal Screening for Fetal Defects
IN: Current Clinical Pathology: Handbook of Clinical Laboratory Testing During Pregnancy Humana Press, Totowa, NJ, 2003

Even before a woman becomes pregnant, the parents-to-be wonder about the health of their future child. This natural concern is why prenatal screening for fetal disorders has attracted considerable attention over the past two decades or more. The interest is both professional and personal. The promise of foretelling the health of the developing baby puts new demands on laboratorians, clinicians, and patients alike. Laboratorians must be fully cognizant of the clinical implications of their screening service, clinicians must liaise with laboratories to provide accurate clinical information, and patients face new choices in the information that they can now receive about their pregnancy. In the “diagnostic laboratory,” true diagnostic tests are relati vely rare. Most test results are used in subjective combination with clinical evidence to indicate the possibility of a disease or disorder. However, the practice of prenatal screening takes that informal and subjective association of information to a more structured, rational, and evidence-based level. Clinical information and laboratory test results are assembled and combined based on scientific evidence to yield a computed risk of the presence of a targeted disorder. The service is complex, and the results are at times counterintuitive.

Second trimester serum markers

J. Canick & A. MacRae

Semin Perinatol 2005 Vol. 29 Issue 4 Pages 203-8

Prenatal screening for Down syndrome in the early second trimester with multiple maternal serum markers has been available for more than 15 years. The multiple marker combination with the highest screening performance currently available is alpha-fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and inhibin A, together with maternal age (so-called quad marker test). With this combination, a detection rate of 80% at a 5% false positive rate is achieved. Inhibin A, the newest addition to second trimester serum screening, is an alpha-beta subunit hormone of placental origin, and is measured using a monoclonal two-site ELISA validated for use in prenatal screening. Quality control parameters for inhibin A measurement are acceptable and are monitored through the proficiency testing program administered by the College of American Pathologists. Research into other possible second trimester screening markers has included studies on the maternal urine and serum levels of an hCG variant, hyperglosylated hCG (h-hCG; invasive trophoblast antigen). Recent data indicate that h-hCG is similar to hCG itself, although its measurement in maternal urine may improve the performance of the established serum marker combinations. With the introduction of first trimester screening markers and their use in an integrated first and second trimester marker approach to screening, and with the fact that many women do not seek prenatal care until the early second trimester, prenatal screening for Down syndrome using second trimester serum markers remains a major resource in obstetrical care.

Screening for fetal aneuploidy and neural tube defects

D. Driscoll and S. Gross

Genet Med 2009 Vol. 11 Issue 11 Pages 818-21

Maternal serum screening for neural tube defects and fetal aneuploidy in the second trimester has been incorporated into obstetrical practice over the past two decades. Now, as a result of several multicenter trials, first trimester screening between 11 and 14 weeks has been shown to be an effective and reliable screening test for Down syndrome and trisomy 18. This policy updates the American College of Medical Genetics policy statement entitled Second Trimester Maternal Serum Screening for Fetal Open Neural Tube Defects and Aneuploidy (2004), incorporates First trimester diagnosis and screening for fetal aneuploidy (2008) and complements the sections of American College of Medical Genetic's Standards and Guidelines for Clinical Genetics Laboratories entitled Prenatal Screening for Down syndrome (2005) and Prenatal Screening for Open Neural Tube Defects (2005).

Pregnancy outcomes regarding maternal serum AFP value in second trimester screening

K. Bartkute, D. Balsyte, J. Wisser and J. Kurmanavicius

J Perinat Med 2017 Vol. 45 Issue 7 Pages 817-820

AIM

The aim of this study was to evaluate the predictive value of α-fetoprotein in maternal serum (MS-AFP) as a marker for diverse pregnancy outcomes.

Methods

The study was based on pregnancy and delivery data from 5520 women between 1999 and 2014 at University Hospital of Zurich (UHZ).

Inclusion Criteria

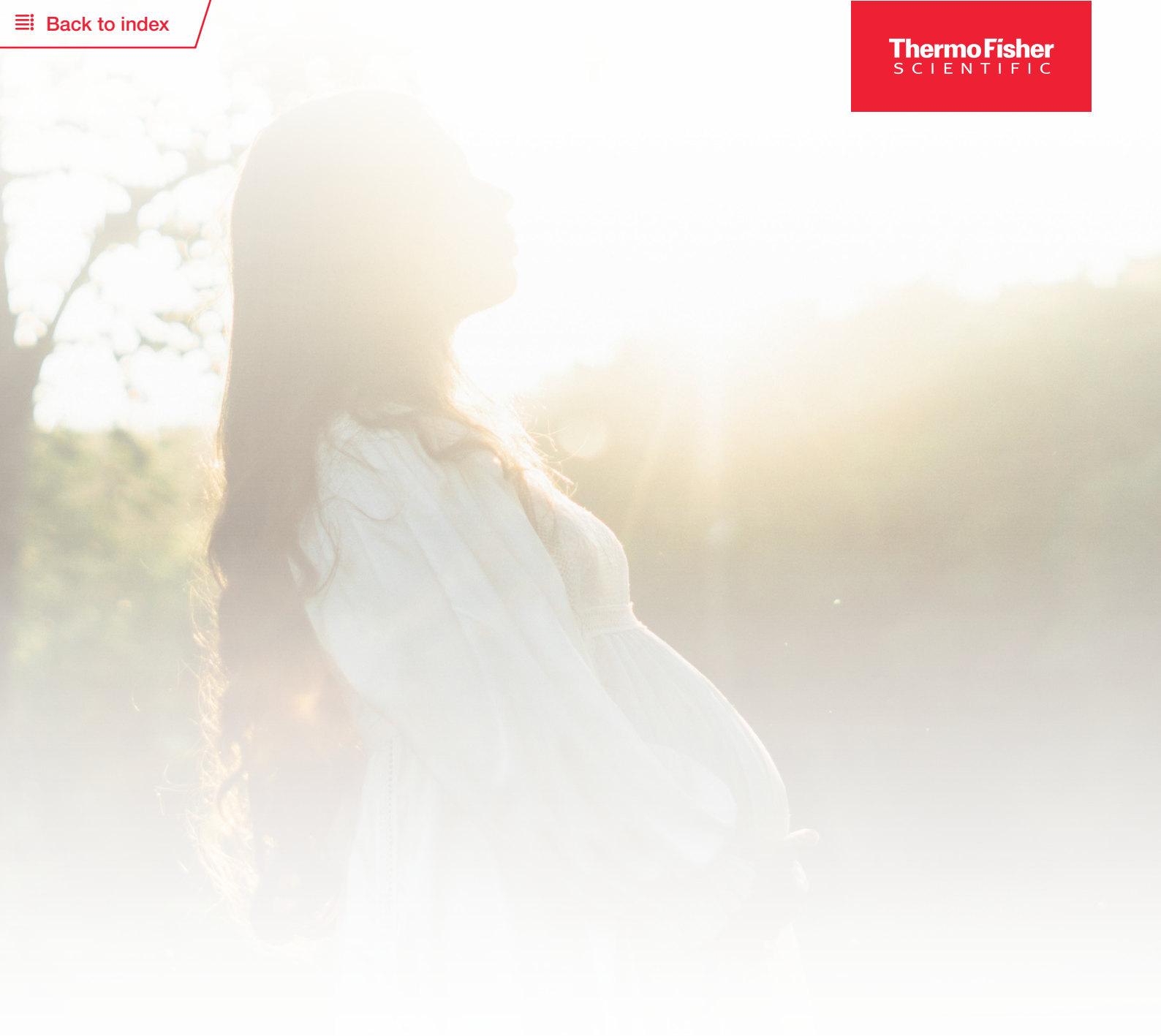
Both MS-AFP and pregnancy outcome were known for the same pregnancy. Pregnancy outcomes and characteristics such as fetal malformation, intrauterine fetal death (IUFD) and intrauterine growth retardation as well as maternal age, weight before pregnancy, gestational age (GA) at delivery, newborn weight, length and head circumference were analyzed with respect to the MS-AFP value. MS-AFP value was categorized into three groups: elevated MS-AFP>2.5 multiples of the median (MoM), normal 0.5-2.49 MoM and decreased <0.5 MoM.

Results

Newborn weight (g) and length (cm) were significantly lower in the elevated MS-AFP ($P<0.001$) group, and infants had 1 week lower GA at delivery ($P<0.05$). In the group of elevated MS-AFP (n=46), 26.1% of pregnancies were significantly related to adverse pregnancy outcomes, such as fetal malformations, fetuses small for gestational age (SGA) and IUFD. Adverse pregnancy outcomes of 5.6% were registered in the group of normal MS-AFP and 7.3% in the group of low MS-AFP ($P<0.05$).

Conclusions

MS-AFP level in the second trimester is still an important indicator of fetal surface malformations; however, ultrasound still outweighs as a screening method. Nevertheless, pregnant women with elevated MS-AFP values and with no sonographically detected fetal malformations should additionally receive the third trimester ultrasound examination to exclude other possible complications of pregnancy.



Screening with PlGF

Maternal serum placental growth factor (PlGF) isoforms 1 and 2 at 11-13 weeks' gestation in normal and pathological pregnancies

M. Nucci, L. Poon, G. Demirdjian, B. Darbouret and K. Nicolaides

Fetal Diagn Ther 2014 Vol. 36 Issue 2 Pages 106-16

Objective

To compare the maternal serum concentration of placental growth factor-1 (PlGF-1) and PlGF-2 at 11-13 weeks' gestation in normal pregnancies and in those complicated by preeclampsia (PE), delivery of small for gestational age (SGA) neonates and fetal trisomies 21, 18 and 13.

Methods

Serum PlGF-1 and PlGF-2 were measured in 270 pathological pregnancies (PE, n = 80; SGA, n = 80; trisomy 21, n = 44; trisomy 18, n = 38; trisomy 13, n = 28) and 590 normal controls. The values were expressed as multiple of the median (MoM) after adjustment for maternal characteristics and corrected for adverse pregnancy outcomes and the median MoM values in each pathological pregnancy were compared to the normal group.

Results

There were significant contributions to PlGF-1 and PlGF-2 from gestational age, smoking and racial origin. In addition, there were significant contributions to PlGF-1 from parity and method of conception. The median MoM of PlGF-1 and PlGF-2 was significantly decreased in PE (0.783 and 0.916 MoM), SGA (0.891 and 0.851 MoM), trisomy 21 (0.609 and 0.749 MoM), trisomy 18 (0.529 and 0.730 MoM) and trisomy 13 (0.373 and 0.699 MoM).

Conclusions

In pathological pregnancies, except SGA, the decrease in serum PlGF-1 at 11-13 weeks' gestation is more marked than the decrease in PlGF-2.

First Trimester Screening for Fetal Aneuploidies Using Placental Growth Factor: The Great Obstetrical Syndrome (GOS) Study

A. Boutin, S. Demers, C. Gasse, Y. Giguère, A. Tétu, G. Laforest, et al.

J Obstet Gynaecol Can 2018 Vol. 40 Issue 8 Pages 1044-1049

Objective

This study sought to estimate the ability of first trimester maternal serum placental growth factor (PlGF) to identify fetal aneuploidies.

Methods

A prospective cohort study of singleton pregnancy at 11 to 13 weeks was conducted. Maternal serum PlGF concentration was measured using B·R·A·H·M·S PlGF plus KRYPTOR automated assays (Thermo Scientific B·R·A·H·M·S, Hennigsdorf, Germany). PlGF and nuchal translucency were log-transformed and reported as multiples of the median (MoM) adjusted for crown-rump length. Detection rates were calculated using receiver-operator characteristic curves.

Results

The study observed 21 cases of fetal aneuploidies (0.4%) out of 4765 participants. Trisomy 21 (13 cases; 0.85 MoM; interquartile range [IQR] 0.80-0.93), trisomy 18 (two cases; 0.77 MoM; IQR 0.66-0.87) and trisomy 13 (two cases; 0.68 MoM; IQR 0.61-0.75) were associated with low PlGF concentrations. The low PlGF values observed in the cases of monosomy X (two cases; 0.85 MoM; IQR 0.82-0.88, P = 0.05), triploidy (0.78 MoM, P = 0.11), and 47,XX,i(22)(p10) (0.18 MoM, P = 0.08) were not statistically different from the controls. A model including maternal age, nuchal translucency, and PlGF could have identified all (95% CI 83%-100%) cases of trisomy 21 and six of the other fetal aneuploidies (75%) at a false-positive rate of 9%.

Conclusions

Low first trimester PlGF is associated with an increased risk of fetal aneuploidy. PlGF combined with first trimester ultrasound (nuchal translucency, uterine artery Doppler, and early fetal anatomy) could identify not only women at high risk for preeclampsia, but also fetuses at high risk of aneuploidy for optimal further testing (non-invasive testing for common aneuploidy screening or chorionic villus sampling for full screening and diagnosis).

First-trimester screening for Down syndrome using quadruple maternal biochemical markers

L. Caron, A. Fillion, Y. Giguère, F. Audibert, J. Forest, C. Gasse, et al.

Clin Chem Lab Med 2023

Objective

Placental growth factor (PlGF) is used for first-trimester preeclampsia screening and could be combined with other biochemical markers for Down syndrome screening. We aim to estimate the predictive value of the combination of pregnancy-associated plasma protein (PAPP-A), free β-human chorionic gonadotropin (free β-hCG), placental growth factor (PlGF) and α-fetoprotein (AFP) with and without nuchal translucency.

Methods

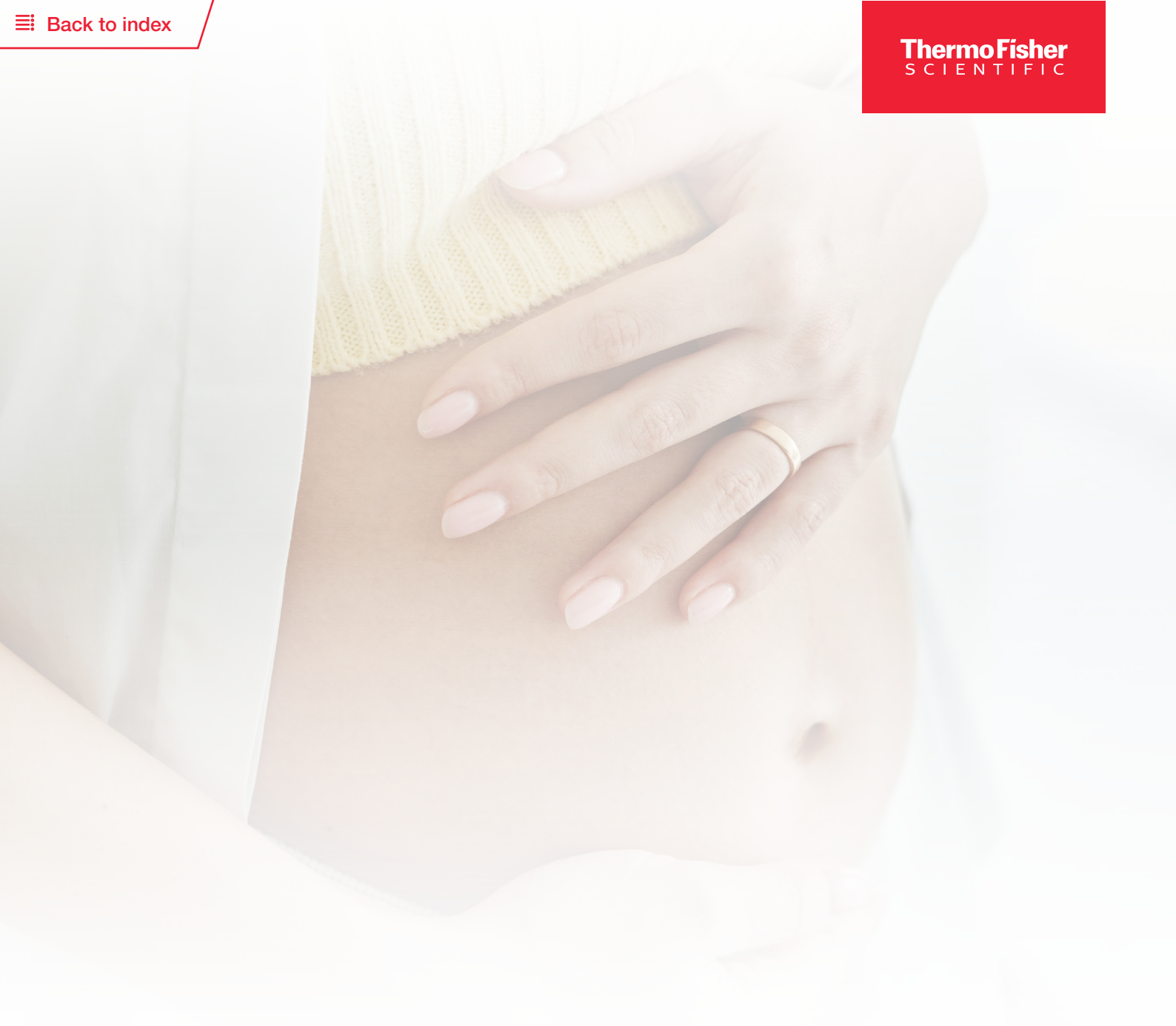
Singleton pregnancies recruited at 11-14 weeks and followed until delivery. The four maternal markers were measured using KRYPTOR (ThermoFisher-B·R·A·H·M·S) and adjusted for gestational age and maternal characteristics. The risk of Down syndrome was calculated using the Fetal Medicine Foundation algorithm and multivariate linear regression analyses in all cases and in 2,200 controls. Receiver-operator characteristic (ROC) curves were used to calculate the detection and false-positive rates.

Results

Twenty-six (0.2%) cases of Down syndrome were diagnosed among 13,386 participants. The combination of the four biomarkers could have detected 88% (95% CI: 72-97%) of the cases at a false-positive rate of 13% (95% CI: 12-15%). The addition of nuchal translucency would have increased the detection rate to 96% (95% CI: 82-99%) at a false-positive rate of 4% (95% CI: 4-5%) using a 1:300 cut-off and to 100% (95% CI: 89-100%) at a false-positive rate of 6% (95% CI: 5-8%) using a 1:500 cut-off.

Conclusions

First-trimester screening using biochemical markers allows the identification of approximately 88% of Down syndrome cases for a false-positive rate of 13%. The addition of nuchal translucency raises the detection rate above 95% with a false-positive rate below 5%.



Other biomarker applications

Use of the combined first-trimester screen result and low PAPP-A to predict risk of adverse fetal outcomes

S. Barrett, C. Bower and N. Hadlow

Prenat Diagn 2008 Vol. 28 Issue 1 Pages 28-35

Objective

To investigate associations between combined first-trimester screen result, pregnancy associated plasma protein-A (PAPP-A) level and adverse fetal outcomes in women.

Methods

Pregnancy outcomes for 10,273 women participating in a community based first-trimester screening (FTS) programme in Western Australia were ascertained by record linkage to birth and birth defect databases. A first-trimester risk cut-off of > or = 1 in 300 defined screen positive women.

Results

Screen positive pregnancies were more likely to have Down syndrome and birth defects (chromosomal or nonchromosomal) than screen negative pregnancies. When birth defects were excluded, screen positive pregnancies were at increased risk of pregnancy loss, low birth weight and preterm birth. Pregnancies with low PAPP-A (< or =0.3 multiples of the median (MoM)) had higher risk of chromosomal abnormality, birth defect, preterm birth, low birth weight, or pregnancy loss, compared to those with PAPP-A > 0.3 MoM. In pregnancies without birth defects, low PAPP-A was a stronger predictor of preterm birth, low birth weight or pregnancy loss than a screen positive result.

Conclusions

Women with positive screen or low PAPP-A were at increased risk for some adverse fetal outcomes. The sensitivity of these parameters was insufficient to support primary screening, but increased surveillance during pregnancy may be appropriate.

First-trimester biochemical markers of aneuploidy and the prediction of small-for-gestational age fetuses

K. Spencer, N. Cowans, K. Avgidou, F. Molina and K. Nicolaides

Ultrasound Obstet Gynecol 2008 Vol. 31 Issue 1 Pages 15-9

Objective

To examine the clinical utility of the first-trimester biochemical markers of aneuploidy in their ability to predict subsequent delivery of a small-for-gestational age (SGA) infant.

Methods

We examined singleton pregnancies with no chromosomal abnormality and with complete outcome data that had undergone screening for trisomy 21 by a combination of fetal nuchal translucency (NT) thickness and maternal serum free beta-human chorionic gonadotropin (beta-hCG) and pregnancy-associated plasma protein-A (PAPP-A) at 11 + 0 and 13 + 6 weeks' gestation. The biochemical markers were converted to multiples of the expected normal median (MoM) for a pregnancy of the same gestation. The association between free beta-hCG and PAPP-A and the incidence of SGA were assessed by comparing the relative incidence at MoM cut-offs and birth-weight centile cut-offs. At various marker levels the likelihood ratios (LR) for SGA were also calculated after excluding other adverse pregnancy complications.

Results

There were 46,262 pregnancies resulting in live births with birth weight at or above the 10(th) centile, and 3,539 below the 10(th) centile for gestation (SGA). There was a significant inverse association between the risk for SGA and maternal serum PAPP-A MoM but not free beta-hCG MoM. At the 5(th) centile of the normal outcome group for PAPP-A (0.415 MoM) the odds ratios for SGA below the 10(th), 5(th) and 3(rd) centiles of normal were 2.70, 3.21 and 3.66 and the respective detection rates for SGA were 12.0%, 14.0% and 16.0%.

Conclusions

Low levels of maternal serum PAPP-A are associated, in the absence of an abnormal karyotype, with an increased risk for subsequent delivery of an SGA infant.

First-trimester ultrasound and biochemical markers of aneuploidy and the prediction of preterm or early preterm delivery

K. Spencer, N. Cowans, F. Molina, K. Kagan and K. Nicolaides

Ultrasound Obstet Gynecol 2008 Vol. 31 Issue 2 Pages 147-52

Objective

To examine the clinical utility of the first-trimester markers of aneuploidy in their ability to predict preterm delivery.

Methods

We examined 54 722 singleton pregnancies with no chromosomal abnormality and with complete outcome data that had undergone screening for trisomy 21 by a combination of fetal nuchal translucency (NT) thickness and maternal serum free beta-human chorionic gonadotropin (beta-hCG) and pregnancy-associated plasma protein-A (PAPP-A) at 11 + 0 and 13 + 6 weeks' gestation. The biochemical markers were converted to multiples of the median (MoM) of the expected normal median for a pregnancy of the same gestation and the measurements of fetal NT were expressed as the difference (delta) from the normal median NT for crown-rump length. The association between free beta-hCG, PAPP-A and delta NT and the incidence of preterm delivery before 37 weeks or early preterm delivery before 34 weeks was assessed by comparing the relative incidence at a number of MoM or delta NT cut-offs and at various centile cut-offs. At various marker levels the likelihood ratios (LR) for preterm delivery and early preterm delivery were also calculated after excluding other adverse pregnancy complications.

Results

The risk of preterm delivery increased with decreasing maternal serum PAPP-A. In the 3132 cases delivering before 37 weeks the PAPP-A MoM was 0.91 and in the 1060 cases delivering before 34 weeks the PAPP-A MoM was 0.90. At the 5th centile of the normal outcome group for PAPP-A (0.415 MoM) the odds ratios for delivery before 37 weeks and before 34 weeks were 1.92 and 2.35, respectively. The respective values for the 5th centile of free beta-hCG (0.41 MoM) were 1.18 and 1.08 and for the 95th centile of delta NT they were 0.91 and 0.77, respectively.

Conclusions

Low levels of maternal serum PAPP-A are associated, in the absence of an abnormal karyotype, with an increased risk of preterm or early preterm delivery. The LR profiles provided at various levels of PAPP-A may be of some help in counseling women with such results and may raise awareness among healthcare professionals for increased surveillance in such cases.

Early fetal growth, PAPP-A and free β-hCG in relation to risk of delivering a small-for-gestational age infant

I. Kirkegaard, T. Henriksen and N. Uldbjerg

Ultrasound Obstet Gynecol 2011 Vol. 37 Issue 3 Pages 341-7

Objective

To examine early fetal growth, pregnancy-associated plasma protein-A (PAPP-A) and free β-human chorionic gonadotropin (β-hCG) in relation to the risk of delivering a small-for-gestational age (SGA) infant.

Methods

Included in the study were 9450 singleton pregnant women who attended the prenatal screening program at Aarhus University Hospital, Denmark, between January 2005 and December 2007. Maternal serum levels of PAPP-A and free β-hCG were measured between gestational weeks 8 and 13. Two ultrasound examinations were performed, the first at 11-13 weeks and the second at 18-22 weeks, from which gestational age was estimated based on crown-rump length and biparietal diameter, respectively. Early fetal growth was expressed as an index: the ratio between the estimated number of days from the first to the second scan and the actual calendar time elapsed in days. SGA was defined as birth weight < 5(th) centile for gestational age, and the risk of SGA was evaluated according to different cut-offs of the early fetal growth index and the serum markers.

Results

PAPP-A < 0.4 MoM combined with an early fetal growth index < 10(th) centile resulted in an increased risk of SGA (odds ratio (OR), 5.8; 95% CI, 2.7-12.7). Low PAPP-A, low free β-hCG and slow early fetal growth were statistically, independently associated with SGA, and the association between free β-hCG < 0.3 MoM and SGA was as strong as that between PAPP-A < 0.3 MoM and SGA (OR, 3.1 and 3.0, respectively).

Conclusions

The combination of slow early fetal growth and low PAPP-A resulted in a nearly six-fold increased risk of delivery of an SGA infant. These findings might improve our chances of early identification of fetuses at increased risk of growth restriction.

Ease of handling[1,2,3,4,5,6,7]

	PAPP-A	Free βhCG	PlGF	AFP	uE3	Inhibin A*	hCG+β
Sample volume	50 µl	26 µl	70 µl	14 µl	50 µl	70 µl	26 µl
Incubation time	19 min	19 min	29 min	9 min	19 min	39 min (preincubation step 30 min, incubation step 9 min)	14 min
Linear direct measuring range	0.010-6 IU/L	0.74-150 IU/L	7.7-7000 pg/ml	1.91-700 ng/mL	0.52-17 nmol/L	53.3-5000 pg/mL	5.0-2000 IU/L
Limit of Detection	0.0054 IU/L	0.09 IU/L	4.91 pg/ml	0.21 ng/mL	0.20 nmol/L	20.9 pg/mL	2.0 IU/L
Limit of Quantitation	0.01 IU/L	0.74 IU/L	7.7 pg/ml	1.91 ng/mL	0.52 nmol/L	53.3 pg/mL	5.0 IU/L
Kit stability on board	29 days	29 days	29 days	15 days	15 days	15 days	29 days
Calibrator	1 point	1 point	1 point	1 point	2 points	1 point	1 point
Calibration stability	15 days	15 days	15 days	15 days	7 days	7 days	15 days

Free βhCG = Free beta Chorionic Gonadotropin Hormone
Total HCG = Total Chorionic Gonadotropin Hormone
PAPP-A = Pregnancy Associated Plasma Protein A
PlGF = Placental Growth Factor
uE3 = unconjugated estriol
AFP = Alphafetoprotein
* Inhibin A is available on B·R·A·H·M·S KRYPTOR GOLD only.

References

1. IFU B·R·A·H·M·S PAPP-A KRYPTOR
2. IFU B·R·A·H·M·S Free βhCG KRYPTOR
3. IFU B·R·A·H·M·S PlGF KRYPTOR
4. IFU B·R·A·H·M·S AFP KRYPTOR
5. IFU B·R·A·H·M·S uE3 KRYPTOR
6. IFU B·R·A·H·M·S Inhibin A KRYPTOR
7. IFU B·R·A·H·M·S hCG+β KRYPTOR

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