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Prenatal Screening Software

Study overview on first trimester aneuploidy and pre-eclampsia screening algorithms

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Content

First trimester screening algorithms for aneuploidies and pre-eclampsia

First trimester screening algorithms, either for fetal trisomies 13, 18 and 21 or for pre-eclampsia, are highly technical products designed to compute individual risk from maternal characteristics (e.g. maternal age, weight, height, ethnicity), maternal medical history (e.g. outcome of previous pregnancy, history of hypertensive disorders), ultrasonographic measurements during the first trimester scan (e.g. crown-rump length, nuchal translucency, fetal nasal bone presence or absence) and maternal serum markers measurement (e.g. PAPP-A, PlGF, free βhCG).

Trustworthiness of the individual risk assessment relies not only on the quality of the input data but also on the performance of the algorithms.

In order to provide a reliable risk assessment, the algorithms should be up-to-date, using the latest published medians generators and correction factors.

This booklet presents you with the publications on which Thermo Scientific™ B·R·A·H·M·S™ Fast Screen pre I plus 3.0 algorithms for first trimester aneuploidies and pre-eclampsia screening are based, together with the published performances of these algorithms.

1. First trimester screening for aneuploidies

Screening for fetal aneuploidies at 11 to 13 weeks

Nicolaides KH

Prenat. Diagn., vol. 31, no. 1, pp. 7–15, Jan. 2011

Abstract

Effective screening for major aneuploidies can be provided in the first trimester of pregnancy. Screening by a combination of fetal nuchal translucency and maternal serum free-β-human chorionic gonadotrophin and pregnancy-associated plasma protein-A can identify about 90% of fetuses with trisomy 21 and other major aneuploidies for a false-positive rate of 5%. Improvement in the performance of first-trimester screening can be achieved by firstly, inclusion in the ultrasound examination assessment of the nasal bone and flow in the ductus venosus, hepatic artery and across the tricuspid valve, and secondly, carrying out the biochemical test at 9 to 10 weeks and the ultrasound scan at 12 weeks.

KEY FACTS

- **In the last decade biochemical testing has moved to the first trimester because when this is combined with the ultrasound marker of fetal NT thickness, the performance of screening is superior to second-trimester screening.**
- **The ultrasononographic and biochemical markers can be combined to provide more effective screening than either method individually.**
- **Assessment of each of these ultrasound markers (absence of the nasal bone, increased impedance to flow in the ductus venosus and tricuspid regurgitation) can be incorporated into first-trimester combined screening by maternal age, fetal NT and serum free β-hCG and PAPP-A resulting in improvement of the performance of screening with an increase in detection rate to 93 to 96% and a decrease in false-positive rate to 2.5%**

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

Based on KRYPTOR data

Kagan KO, Wright D, Valencia C, Maiz N, and Nicolaides KH

J Hum. Reprod., vol. 23, no. 9, pp. 1968–1975, 2008

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 β-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.

Conclusions

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.

KEY FACTS

- **Screening for trisomy 21 by maternal age, fetal NT and serum biochemistry increased the detection rate to 89%.**
- **Screening for trisomy 18 by maternal age, fetal NT and serum biochemistry increased the detection rate to 93%.**
- **Screening for trisomy 13 by maternal age, fetal NT and serum biochemistry increased the detection rate to 77% and this was further improved to 87% by the addition of FHR.**

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

Based on KRYPTOR data

Wright D, Spencer K, Kagan K, Tørring N, Petersen OB, Christou A, Kallikas J, and Nicolaides KH

Ultrasound Obstet. Gynecol., vol. 36, no. 4, pp. 404–411, 2010

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.

Conclusions

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.

KEY FACTS

- **In the assessment of patient-specific risks for trisomy 21 the a-priori maternal age-related risk is multiplied by likelihood ratios (LR), determined from the deviation of the measured NT, free β-hCG and PAPP-A from the respective expected levels.**
- **One option in screening for trisomy 21 is to perform biochemical testing and the ultrasound scan in the same visit at 12 weeks, with estimated detection rates of 86 and 90% at false positive rates of 3 and 5%, respectively.**
- **An alternative strategy for first-trimester combined screening is for biochemical testing and ultrasound scanning to be carried out in two separate visits, with the first done at 9 weeks and the second at 12 weeks. For false-positive rates of 3 and 5% the estimated detection rates would be 90 and 93%, respectively.**

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

Based on KRYPTOR data

Kagan KO, Wright D, Spencer K, Molina FS, and Nicolaides KH

Ultrasound Obstet. Gynecol., vol. 31, no. 5, pp. 493–502, 2008

Objective

To use multiple regression analysis to define the contribution of maternal variables that influence the measured concentration of free beta-human chorionic gonadotropin (β-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 β-hCG and PAPP-A at 11+0to 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 β-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 96803 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 β-hCG was12%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 β-hCG and PAPP-A the estimated detection rate was 65% for a false-positive rate of 5%.

Conclusions

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

KEY FACTS

Assessment of accurate patient-specific risks necessitates making adjustments in the measured maternal serum concentration of free β-hCG and PAPP-A to correct for gestational age, maternal weight, ethnicity, smoking status, method of conception and parity.

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

Based on KRYPTOR data

Kagan KO, Frisova V, Nicolaides KH, and Spencer K

Prenat. Diagn., vol. 27, no. 9, pp. 849–853, Sep. 2007

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.

Conclusions

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.

KEY FACTS

- **The findings of this study that in chromosomally normal pregnancies at 11–13+6 weeks of gestation cigarette smoking is associated with a reduction of about 20% in the maternal serum concentration for PAPP-A and 3% in free β-hCG.**
- **In the overall performance of screening there would be little impact by correcting for the dose-dependent rather than the all or nil effect of smoking.**

Fetal Size and Dating: Charts Recommended for Clinical Obstetric Practice

Loughna P, Chitty L, Evans T, and Chudleigh T
Ultrasound, vol. 17, no. 3, pp. 160–166, 2009

Introduction

The charts and tables presented here represent those recommended by BMUS for routine use. The application of the recommended charts in clinical practice has not been addressed as dating policies and the identification of growth related problems should form part of locally derived protocols.

KEY FACTS

- **Accurate dating of pregnancy is critical to the quality of the national screening programme for Down's syndrome. Whilst it is recommended practice that all pregnancies are dated by ultrasound using crown-rump length rather than menstrual dates (NICE Antenatal Care Guidelines)**
- **The recommended equation for calculation of gestational age from crown rump length is $GA=8.052x(CRLx1.037)^{1/2} + 23.73$**

A mixture model of ductus venosus pulsatility index in screening for aneuploidies at 11-13 weeks' gestation

Maiz N, Wright D, Ferreira AFA, Syngelaki A, and Nicolaides KH
Fetal Diagn. Ther., vol. 31, no. 4, pp. 221–229, 2012

Objective
To assess the value of ductus venosus pulsatility index for veins (DV PIV) in screening for aneuploidies at 11–13 weeks' gestation.

Methods
Fetal DV PIV was measured in singleton pregnancies undergoing first-trimester screening for aneuploidies. In euploid (n = 44,756) and aneuploid (202 cases of trisomy 21, 72 cases of trisomy 18 and 30 cases of trisomy 13) fetuses, DV PIV was best described by a mixture model of distributions. Performance of screening for aneuploidies by DV PIV alone and in combination with fetal nuchal translucency (NT) thickness and serum free β-hCG and PAPP-A was estimated.

Results
In euploid pregnancies there was a bimodal distribution of DV PIV with a dominant crown-rump length (CRL)-dependent part, accounting for around 97% of cases in Caucasians and around 93% in Afro-Caribbeans, and a smaller CRL-independent distribution. In aneuploidies the dominant part was the CRL-independent distribution, which accounted for around 85% cases of trisomies 21 and 18 and 70% of cases of trisomy 13. In screening for trisomy 21 by maternal age, NT and biochemistry at a risk cutoff of 1 in 100, the detection rate was 89.7% and false positive rate was 2.74%; with addition of DV PIV, the values were 93.5 and 1.63%, respectively.

Conclusions
Measurement of DV PIV improves the performance of first-trimester combined test for aneuploidies.

KEY FACTS

- **Increased impedance to flow in the fetal ductus venosus (DV) at 11–13 weeks' gestation is associated with fetal aneuploidies.**
- **Abnormal flow is reported in about 70% of fetuses with trisomy 21 and 18, about 65% of fetuses with trisomy 13 and only 4% of euploid fetuses.**
- **Distribution of the DVPI is corrected for ethnicity.**
- **Including this marker to the algorithm allows improving DR to 93.5% and lowering DR from 2.74% to 1.63%.**

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

Based on KRYPTOR data

Wright D, Kagan KO, Molina FS, Gazzoni A, and Nicolaides KH
Ultrasound Obstet. Gynecol., vol. 31, no. 4, pp. 376–383, Apr. 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 apriori 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 37078 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.

Conclusions

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

KEY FACTS

- **Fetal nuchal translucency (NT) thickness is the single most effective marker of trisomy 21 and all other major chromosomal defects.**
- **In unaffected pregnancies the majority of fetuses demonstrate an increase in NT with CRL and in a minority of cases NT tends to be relatively large and is independent of CRL.**
- **The findings of this study demonstrate that fetal NT follows two distributions, one of which is dependent on CRL while the other is independent of CRL.**
- **The patient-specific risks derived from the new mixture model are accurate and valid for counseling.**

Fetal nasal bone in screening for trisomies 21, 18 and 13 and Turner syndrome at 11-13 weeks of gestation

Kagan KO, Cicero S, Staboulidou I, Wright D, and Nicolaides KH
Ultrasound Obstet. Gynecol., vol. 33, no. 3, pp. 259–64, Mar. 2009

Objective
To investigate the performance of first-trimester screening for aneuploidies by including assessment of the fetal nasal bone in the combined test of maternal age, fetal nuchal translucency (NT) thickness, fetal heart rate (FHR) and serum free beta-human chorionic gonadotropin (beta-hCG) and pregnancy-associated plasma protein-A (PAPP-A).

Methods
Screening by the combined test was performed in singleton pregnancies, including 19,614 with euploid fetuses, 122 with trisomy 21, 36 with trisomy 18, 20 with trisomy 13 and eight with Turner syndrome. In all cases the fetal nasal bone was assessed and classified as present or absent. We examined the performance of two screening strategies: firstly, assessment of the nasal bone in all patients and secondly, first-stage screening using the combined test in all patients followed by second-stage assessment of the nasal bone only in those with an intermediate risk of 1 in 51 to 1 in 1000 after the first stage. To validate the new risk algorithm we used a second independent dataset of 19 651 fetuses, including 139 with trisomy 21.

Results
The nasal bone was absent in 2.6% of the euploid fetuses, 59.8% with trisomy 21, 52.8% with trisomy 18, 45.0% with trisomy 13 and in none of the fetuses with Turner syndrome. Respective figures for an absent nasal bone in the validation population, which contained fewer Black women, were 0.6%, 62.6%, 55.3%, 35.3% and 41.7%. In a screening policy based on maternal age, fetal NT, FHR, serum free beta-hCG and PAPP-A, for a fixed risk cut-off of 1 : 100, the false-positive rate was 3.0%. The standardized detection rates were 91% for trisomy 21 and 100% for trisomy 18, trisomy 13 and Turner syndrome, respectively. Assessment of the nasal bone in all pregnancies reduced the false-positive rate to 2.5% without changing the detection rate. A detection rate of 93% was achieved with the two-stage strategy at a false-positive rate of 2.4% in which it was necessary to assess the nasal bone in only 15% of the total population. In the validation dataset, screening by the combined test and using a risk cut-off of 1 : 100 detected 90% of the cases with trisomy 21 for a false-positive rate of 4%. Inclusion of the nasal bone increased the detection rate to 92% for a false-positive rate of 2.9%. Contingent screening detected 92% of cases for a false-positive rate of 2.9%.

Conclusions
Assessment of the fetal nasal bone improves the performance of first-trimester screening for trisomy 21.

KEY FACTS

- **The nasal bone was absent in 2.6% of the euploid fetuses, in 59.8% with trisomy 21, 52.8% with trisomy 18, 45.0% with trisomy 13.**
- **By assessing the nasal bone in all pregnancies the false-positive rate can be reduced by 17% to 2.5% without affecting the detection rate.**
- **The prevalence of absent nasal bone is affected not only by the fetal karyotype but also by maternal ethnicity.**

Tricuspid regurgitation in screening for trisomies 21, 18 and 13 and Turner syndrome at 11 + 0 to 13 + 6 weeks of gestation

Kagan KO, Valencia C, Livanos P, Wright D, and Nicolaides KH

Ultrasound Obstet. Gynecol., vol. 33, no. 1, pp. 18–22, 2009

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 apriori 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 37078 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.

Conclusions

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

KEY FACTS

- **Tricuspid regurgitation at 11+0to 13+6 weeks is found in about 1% of euploid fetuses, in 56% of fetuses with trisomy 21 and in about one third of fetuses with trisomy 18 and trisomy 13.**
- **Incorporating measurement of DV PIV in first-trimester combined screening can improve the detection rate to about 95% and reduce the false positive rate to about 2.5%.**

Choroid plexus cyst, intracardiac echogenic focus, hyperechogenic bowel and hydronephrosis in screening for trisomy 21 at 11 + 0 to 13 + 6 weeks

Dagklis T, Plasencia W, Maiz N, Duarte L, and Nicolaides KH
Ultrasound Obstet. Gynecol., vol. 31, no. 2, pp. 132–135, 2008

Objective
To investigate the potential value of choroid plexus cyst, intracardiac echogenic focus, hydronephrosis and hyperechogenic bowel as markers of trisomy 21 at 11 + 0 to 13 + 6 weeks.

Methods
We examined three-dimensional volumes from 228 fetuses with trisomy 21 and 797 chromosomally normal fetuses at 11 + 0 to 13 + 6 weeks of gestation. We looked for choroid plexus cysts with a minimum diameter of 1.5 mm, intracardiac echogenic focus, hydronephrosis with a minimum anteroposterior diameter of the pelvis of 1.5 mm and hyperechogenic bowel.

Results
The prevalence of intracardiac echogenic focus, hydronephrosis and hyperechogenic bowel was significantly higher in trisomy 21 than in normal fetuses (9.6% vs. 1.5%, 17.1% vs. 5.3% and 11.4% vs. 2.4%, respectively). There was no significant difference between the two groups in the prevalence of choroid plexus cysts (7.5% vs. 5.0%). There were no significant differences in crown-rump length or nuchal translucency thickness in either chromosomally normal or trisomy 21 fetuses between those with and those without any one of the markers.

Conclusions
At 11 + 0 to 13 + 6 weeks the prevalence of intracardiac echogenic focus, hydronephrosis and hyperechogenic bowel is higher in trisomy 21 than in chromosomally normal fetuses. As there is no significant association between the presence of these markers and nuchal translucency thickness, they could be included in the assessment of risk to improve accuracy of screening.

KEY FACTS

In the first trimester the prevalence of intracardiac echogenic focus, hydronephrosis and hyperechogenic bowel was higher in trisomy 21 than in chromosomally normal fetuses, and this was unrelated to CRL or NT thickness.

Maternal serum placental growth factor in prospective screening for aneuploidies at 8-13 weeks' gestation

Pandya P, Wright D, Syngelaki A, Akolekar R, and Nicolaides KH
Fetal Diagn. Ther., vol. 31, no. 2, pp. 87–93, 2012

Objective
To investigate whether measurement of maternal serum placental growth factor (PLGF) can improve the performance of first-trimester combined screening for trisomy-21 by fetal nuchal translucency (NT) thickness and serum free β-human chorionic gonadotropin (β-hCG) and PAPP-A.

Methods
In singleton pregnancies attending for routine care, serum PLGF, free β-hCG and PAPP-A were measured at 8(+0)-13(+6) weeks' gestation, and fetal NT was measured at 11(+0)-13(+6) weeks. The population included 12,154 normal and 44 trisomy-21 pregnancies. We examined the effect of adding PLGF on the performance of screening by the combined test.

Results
In the trisomy-21 pregnancies the median multiple of the normal median PLGF, adjusted for gestational age, maternal weight, racial origin, smoking status and method of conception, was significantly reduced (0.6070, 95% CI 0.5543-0.6648), and this did not change significantly with gestational age. Adding PLGF to combined testing with a risk cut-off of 1 in 100 reduced the false positive rate from 2.7% (95% CI 2.5-3.0) to 2.6% (95% CI 2.4-2.8) and increased the detection rate from 85% (95% CI 75-93) to 88% (95% CI 78-95).

Conclusions
Inclusion of serum PLGF improves the performance of the first-trimester combined test in screening for trisomy-21.

KEY FACTS

- **In trisomy-21 pregnancies maternal serum PLGF at 8–13 weeks' gestation is reduced and measurement of this placental product improves the performance of first-trimester combined screening for this aneuploidy.**
- **In normal pregnancy, serum PLGF concentration is affected by maternal age, gestational age, maternal weight, racial origin, cigarette smoking and method of conception.**
- **It is therefore anticipated that a beneficial consequence of incorporating PLGF in first-trimester combined screening for trisomy-21 would be the detection of a high proportion of the other major aneuploidies.**

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

Based on KRYPTOR data

Wright D, Syngelaki A, Birdir C, Bedei I, and Nicolaides KH
Fetal Diagn. Ther., vol. 30, no. 3, pp. 194–202, 2011

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%.

Conclusions
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.

KEY FACTS

- **In women with high free β-hCG and/or low PAPP-A, adjustment of the biochemical profile in the second pregnancy by taking into account the results of their previous pregnancy will improve the performance of screening by reducing the false-positive rate.**
- **In women with low free β-hCG and/or high PAPP-A, adjustment of their results in a subsequent pregnancy improves the performance of screening by increasing the detection rate.**

2. First trimester screening for pre-eclampsia

Competing risks model in screening for preeclampsia by maternal characteristics and medical history

Wright D, Syngelaki A, Akolekar R, Poon LC, and Nicolaides KH
Am. J. Obstet. Gynecol., vol. 213, no. 1, p. 62.e1-62.e10, 2015

Objective

The purpose of this study was to develop a model for preeclampsia based on maternal demographic characteristics and medical history.

Study design

This was a screening study of 120,492 singleton pregnancies at 11-13 weeks' gestation, including 2704 pregnancies (2.2%) that experienced preeclampsia. A survival-time model for the gestational age at delivery with preeclampsia was developed from variables of maternal characteristics and history. This approach assumes that, if the pregnancy was to continue indefinitely, all women would experience preeclampsia and that whether they do so or not before a specified gestational age depends on competition between delivery before or after development of preeclampsia. A 5-fold cross validation study was conducted to compare the performance of the new model with the National Institute for Health and Clinical Excellence (NICE) guidelines.

Results

In the new model, increased risk for preeclampsia, with a consequent shift in the Gaussian distribution of the gestational age at delivery with preeclampsia to the left, is provided by advancing maternal age, increasing weight, Afro-Caribbean and South Asian racial origin, medical history of chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome, family history and personal history of preeclampsia, and conception by in vitro fertilization. The risk for preeclampsia decreases with increasing maternal height and in parous women with no previous preeclampsia; in the latter, the protective effect, which is related inversely to the interpregnancy interval, persists beyond 15 years. At a screen-positive rate of 11%, as defined by NICE, the new model predicted 40%, 48%, and 54% of cases of total preeclampsia and preeclampsia requiring delivery at <37 and <34 weeks' gestation, respectively, which were significantly higher than the respective values of 35%, 40%, and 44% achieved by application of NICE guidelines.

KEY FACTS

A new model that is based on maternal characteristics and medical history has been developed for the estimation of patient- specific risks for preeclampsia. Such estimation of the a priori risk for preeclampsia is an essential first step in the use of Bayes theorem to combine maternal factors with biomarkers for the continuing development of more effective methods of screening for the disease.

Accuracy of competing risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation

O'Gorman N et al.

Ultrasound Obstet. Gynecol., vol. 208, no. 2, pp. 109–112, Jan. 2017

Objective

To examine the diagnostic accuracy of a previously developed model for prediction of preeclampsia (PE) by a combination of maternal factors and biomarkers at 11-13 weeks' gestation.

Methods

This was a prospective first-trimester multicenter study of screening for PE in 8,775 singleton pregnancies. A previously published algorithm was used for the calculation of patient-specific risk of PE in each patient. The detection rates (DR) and false positive rates (FPR) for delivery with PE at <32, <37 and ≥37 weeks were estimated and compared to those in the dataset used for development of the algorithm.

Results

In the study population there were 239 (2.7%) cases that developed PE, including 17 (0.2%), 59 (0.7%) and 180 (2.0%) at <32, <37 and ≥37 weeks, respectively. In combined screening by maternal factors, mean arterial pressure, uterine artery pulsatility index and serum placental growth factor the DR was 100% (95% CI 80-100) for PE at <32 weeks, 75% (95% CI 62-85) for PE at <37 weeks and 43% (95% CI 35-50) for PE at ≥37 weeks, at 10% FPR. These DRs were similar to the estimated rates in the dataset used for development of the model: 89% (95% CI 79-96) for PE at <32 weeks, 75% (95% CI 70-80) for PE at <37 weeks and 47% (95% CI 44-51) for PE at ≥37 weeks.

Conclusions

Combination of maternal factors and biomarkers provides effective first-trimester screening for preterm-PE.

KEY FACTS

- **The best performance of screening was achieved by a combination of maternal factors, MAP, UTPI and PLGF and this was not improved by addition of PAPP-A.**
- **The DR of screening by maternal factors, MAP, UTPI and PLGF, at 10% FPR, was 100% (95% CI 80-100) for PE at <32 weeks, 75% (95% CI 62-85) for PE at <37 weeks and 43% (95% CI 35-50) for PE at >37 weeks.**

Uterine artery pulsatility index in the three trimesters of pregnancy: Effects of maternal characteristics and medical history

Tayyar A, Guerra L, Wright A, Wright D, and Nicolaides KH

Ultrasound Obstet. Gynecol., vol. 45, no. 6, pp. 689–97, Jun. 2015

Objective

To define the contribution of maternal variables that influence the measured uterine artery pulsatility index (UtA-PI) in screening for pregnancy complications.

Methods

Maternal characteristics and medical history were recorded, and UtA-PI was measured, in women with a singleton pregnancy attending for three routine hospital visits at 11 + 0 to 13 + 6 weeks, 19 + 0 to 24 + 6 weeks and 30 + 0 to 34 + 6 weeks or 35 + 0 to 37 + 6 weeks' gestation. For pregnancies delivering phenotypically normal live births or stillbirths at ≥ 24 weeks' gestation, variables from maternal demographic characteristics and medical history that are important in the prediction of UtA-PI were determined from linear mixed-effects multiple regression.

Results

UtA-PI was measured in 90 484 cases in the first trimester, 66 862 cases in the second trimester and 33 470 cases in the third trimester of pregnancy. Significant independent contributions to UtA-PI were provided by gestational age, maternal age, weight, racial origin and a history of pre-eclampsia (PE) in the previous pregnancy. Random-effects multiple regression analysis was used to define the contribution of maternal variables that influence the measured UtA-PI and express the values as multiples of the median (MoM). The model was shown to provide an adequate fit of MoM values for all covariates both in pregnancies that developed PE and in those that did not.

Conclusions

A model was fitted to express the measured UtA-PI as MoMs after adjustment for variables from maternal characteristics and medical history that affect this measurement.

KEY FACTS

- **Several uterine artery Doppler studies have reported that in pregnancies that develop PE, especially in those requiring early delivery, the pulsatility index (PI) is increased**
- **In combined screening for PE, it is essential to standardize the measured values of biomarkers for any variables included in the prior model.**
- **Significant independent contributions to the measured uterine artery PI are provided by maternal characteristics and variables from medical history.**

Mean arterial pressure in the three trimesters of pregnancy: effects of maternal characteristics and medical history

Wright A, Wright D, Ispas CA, Poon LC, and Nicolaides KH
Ultrasound Obstet. Gynecol., vol. 45, no. 6, pp. 698–706, Jun. 2015

Objective
To define the contribution of maternal variables that influences the measured mean arterial pressure (MAP) in screening for pregnancy complications.

Methods
Maternal characteristics and medical history were recorded, and MAP was measured, in women with a singleton pregnancy attending for three routine hospital visits at 11 + 0 to 13 + 6 weeks, 19 + 0 to 24 + 6 weeks and 30 + 0 to 34 + 6 weeks or 35 + 0 to 37 + 6 weeks' gestation. For pregnancies delivering phenotypically normal live births or stillbirths at ≥ 24 weeks' gestation, variables from maternal demographic characteristics and medical history that are important in the prediction of MAP were determined from linear mixed-effects multiple regression analysis.

Results
MAP was measured in 75 841 cases in the first trimester, 30 447 in the second trimester and 31 673 in the third trimester. Significant independent contributions to MAP were provided by gestational age, maternal age, weight, height, Afro-Caribbean racial origin, cigarette smoking, family history of pre-eclampsia (PE), history of PE in the previous pregnancy, interpregnancy interval, chronic hypertension and diabetes mellitus. The effects of some variables were similar, and for others differed, in the three different trimesters. Random-effects multiple regression analysis was used to define the contribution of maternal variables that influence the measured MAP and express the values as multiples of the median (MoMs). The model was shown to provide an adequate fit of MoM values for all covariates, both in pregnancies that developed PE and in those without this complication.

Conclusions
A model was fitted to express the measured MAP as MoMs after adjustment for variables from maternal characteristics and medical history that affect this measurement.

KEY FACTS

- **A useful biophysical marker in screening for PE is mean arterial pressure.**
- **However, MAP is dependent on other characteristics, most importantly maternal weight and chronic hypertension, and for its effective use in risk assessment and screening, these covariates need to be taken into account.**

Serum pregnancy-associated plasma protein-A in the three trimesters of pregnancy: effects of maternal characteristics and medical history

Wright D, Silva M, Papadopoulos S, Wright A, and Nicolaides KH

Ultrasound Obstet. Gynecol., vol. 46, no. 1, pp. 42–50, Jul. 2015

Objective

To define the contribution of maternal variables which influence the measured level of maternal serum pregnancy-associated plasma protein-A (PAPP-A) in screening for pregnancy complications.

Methods

Maternal characteristics and medical history were recorded and serum PAPP-A was measured in women with a singleton pregnancy attending for three routine hospital visits at 11 + 0 to 13 + 6, 19 + 0 to 24 + 6 and 30 + 0 to 34 + 6 weeks' gestation. For pregnancies delivering phenotypically normal live births or stillbirths ≥ 24 weeks' gestation, variables from maternal demographic characteristics and medical history that are important in the prediction of PAPP-A were determined from a linear mixed-effects multiple regression.

Results

Serum PAPP-A was measured in 94,966 cases in the first trimester, 7785 in the second trimester and 8286 in the third trimester. Significant independent contributions to serum PAPP-A were provided by gestational age, maternal weight, height, racial origin, cigarette smoking, diabetes mellitus, method of conception, previous pregnancy with or without pre-eclampsia (PE) and birth-weight Z-score of the neonate in the previous pregnancy. The effects of some variables were similar and those for others differed in the three different trimesters. Random-effects multiple regression analysis was used to define the contribution of maternal variables that influence the measured level of serum PAPP-A and express the values as multiples of the median (MoMs). The model was shown to provide an adequate fit of MoM values for all covariates, both in pregnancies that developed PE and in those without this pregnancy complication.

Conclusions

A model was fitted to express the measured serum PAPP-A across the three trimesters of pregnancy as MoMs, after adjusting for variables from maternal characteristics and medical history that affect this measurement.

KEY FACTS

- **Maternal serum levels of pregnancy-associated plasma protein-A in the first trimester of pregnancy are decreased in pregnancies with impaired placentation resulting in pre-eclampsia (PE).**
- **In normal pregnancy, serum PAPP-A concentration is affected by gestational age and maternal characteristics, including weight, racial origin, cigarette smoking, diabetes mellitus and method of conception**
- **For the effective use of serum PAPP-A measurements in risk assessment, these variables need to be taken into account**

Serum placental growth factor in the three trimesters of pregnancy: effects of maternal characteristics and medical history

Tsiakkas A, Duvdevani N, Wright A, Wright D, and Nicolaides KH

Ultrasound Obstet. Gynecol., vol. 45, no. 5, pp. 591–8, May 2015

Objective

To define the contribution of maternal variables which influence the measured level of maternal serum placental growth factor (PlGF) in screening for pregnancy complications.

Study design

Maternal characteristics and medical history were recorded and serum levels of PlGF were measured in women with a singleton pregnancy attending for three routine hospital visits at 11 + 0 to 13 + 6, 19 + 0 to 24 + 6 and 30 + 0 to 34 + 6 or 35 + 0 to 37 + 6 weeks' gestation. For women delivering phenotypically normal live births or stillbirths ≥ 24 weeks' gestation, variables from maternal demographic characteristics and medical history important in the prediction of PlGF were determined from a linear mixed-effects multiple regression.

Results

Serum levels of PlGF were measured in 38,002 cases in the first trimester, 10,281 in the second trimester and 12,392 in the third trimester. Significant independent contributions to serum PlGF were provided by gestational age, maternal age, weight and racial origin, cigarette smoking, diabetes mellitus, and gestational age at delivery and birth-weight Z-score of the neonate in the previous pregnancy. The machine used to measure serum PlGF was also found to have a significant effect. Allowing for other factors, the effect of maternal age on PlGF changed over the three trimesters, whereas other variables had constant effects over the three trimesters. Random-effects multiple regression analysis was used to define the contribution of maternal variables that influence the measured serum PlGF and express the values as multiples of the median (MoMs). The model was shown to provide an adequate fit of MoM values for all covariates, both in pregnancies that developed pre-eclampsia and in those without this complication.

Conclusions

A model was fitted to express the measured level of maternal serum PlGF across the three trimesters of pregnancy as MoMs, after adjusting for variables of maternal characteristics and medical history that affect this measurement.

KEY FACTS

- **Maternal serum levels of PlGF at 11–13 weeks' gestation are decreased in pregnancies with impaired placentation resulting in pre-eclampsia (PE)**
- **In normal pregnancies, serum PlGF concentration is affected by gestational age and maternal characteristics, including age, weight, racial origin and cigarette smoking**
- **For the effective use of serum PlGF in risk assessment, these variables need to be taken into account.**

Glossary

AFP	Alpha Feto Protein
CRL	Crown-Rump Length
DR	Detection rate
DVPI	Ductus Venosus Pulsatility Index
FHR	Fetal Heart Rate
FPR	False-positive rate
Free βhCG	Free Beta-Subunit of Human Chorionic Gonadotropin
GA	Gestational age
MAP	Mean arterial pressure
MoM	Multiple of the median
MSM	Maternal Serum Markers
NB	Nasal Bone
NHS	National Health Service (public health services of England, Scotland and Wales)
NICE	National Institute for Health and Clinical Excellence (public body of the Department of Health in the United Kingdom)
NT	Nuchal Translucency
PAPP-A	Pregnancy-associated plasma protein A
PE	Pre-eclampsia
PlGF	Placental growth factor
Quadruple test	Second trimester aneuploidy screening using AFP, free βhCG, uE3 and Inhibin A concentrations
sFlt-1	Soluble fms-like tyrosine kinase
TR	Tricuspid Regurgitation
UAPI/UADPI/UtAPI	Uterine artery (Doppler) pulsatility index
uE3	Unconjugated Estriol

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