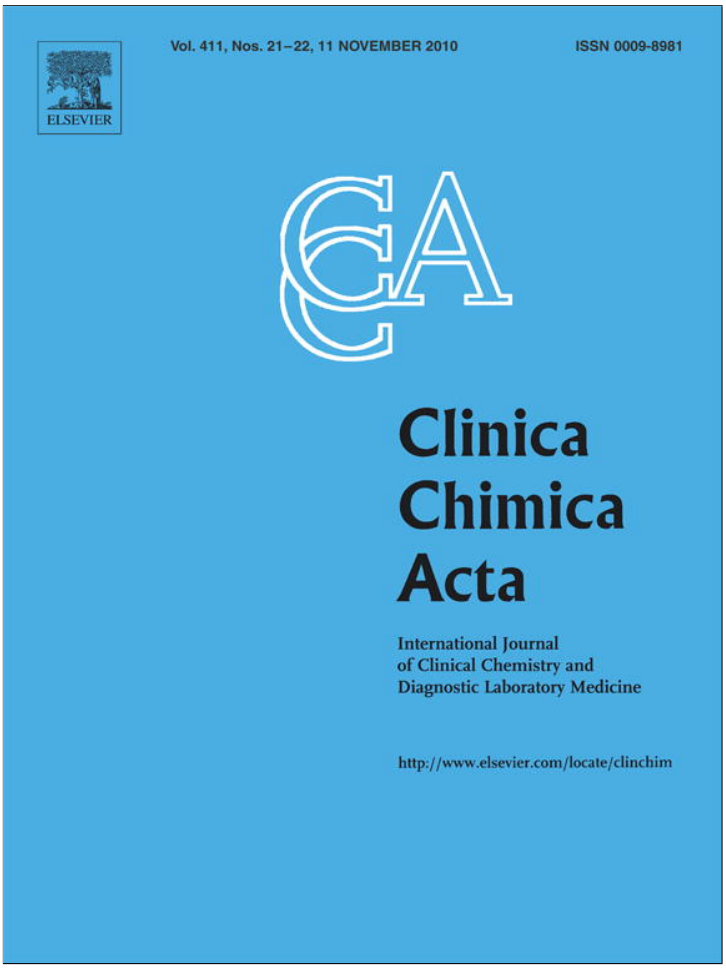

Clinica Chimica Acta 411 (2010) 1547–1552

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Invited critical review

Screening for adverse pregnancy outcome at early gestational age

Sophie Hourrier [a], Laurent J. Salomon [a], Sophie Dreux [b], Françoise Muller [b,c,*]

[a] Gynécologie-Obstétrique, Hôpital Necker Enfants Malades AP-HP, 75015, Paris, France, Université Paris Descartes
[b] Biochimie-Hormonologie, Hôpital Robert Debré AP-HP, 75019, Paris, France
[c] Université Paris Ile de France Ouest, Guyancourt, 78280, France

ARTICLE INFO

Article history:
Received 21 April 2010
Received in revised form 21 June 2010
Accepted 22 June 2010
Available online 27 June 2010

Keywords:
Down syndrome screening
Maternal serum markers
First trimester
Adverse pregnancy outcome
Trisomy 21

ABSTRACT

In the past two decades second-trimester maternal serum screening for Down syndrome has been the most common strategy for prenatal diagnosis of chromosomal aneuploidies. More recently, screening for and diagnosis of chromosomal abnormalities have increasingly been performed in the first trimester. With improvements and technological advances in ultrasound, it is now possible to identify many fetal anomalies at 11–13 weeks of gestation. During the same period biochemical markers in maternal serum (PAPP-A and hCGβ) combined with sonographic measurement of nuchal translucency achieve a Down syndrome detection rate of 85% with a 5% false-positive rate. We describe here the potential of first-trimester markers to screen for Down syndrome as well as other adverse outcomes such as fetal loss, pre-eclampsia, intrauterine growth retardation, and preterm delivery. This early consultation may be the opportunity to help counsel patients and to screen for other adverse complications during pregnancy, such as pre-eclampsia, and to manage potential adverse pregnancy outcomes.

Contents

1. Introduction

The various strategies for prenatal screening have evolved over the last 30 years from a maternal age-based only risk assessment for Down syndrome to the incorporation of multiple serum and ultrasound markers during the first and second trimester for the assessment of a large panel of maternal and fetal risks. Second-trimester screening for Down syndrome using maternal serum markers has long been the generally accepted standard of care [1–4]. In addition, a genetic sonogram can be combined with biochemical screening to further improve screening efficiency [5–12]. At 11–14 weeks of gestation, earlier effective screening for trisomy 21 may now be provided by a

* Corresponding author. Biochimie-Hormonologie, Hôpital Robert Debré, 48, Bd Sérurier, Paris, 75019, France. Tel.: +33 1 40 03 53 82; fax: +33 1 40 03 53 80.
E-mail address: francoise.muller@rdb.aphp.fr (F. Muller).

0009-8981/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.cca.2010.06.024

combination of maternal age, fetal nuchal translucency thickness (NT) and maternal serum markers including free β-human chorionic gonadotropin (hCGβ) and pregnancy-associated plasma protein-A (PAPP-A). This method allowed for early, sensitive and specific screening for Down syndrome, with an overall detection rate of approximately 85% with a false-positive rate of 5% [3,13–18]. It also allowed for earlier information and choice for the women regarding diagnostic testing [19]. This could eventually allow earlier and easier termination of pregnancy [20]. Besides screening for chromosomal anomalies, the 11–14 weeks window became the target for the most pertinent maternal and fetal risk assessment and selection of pregnant women at high medical risk [21]. First-trimester screening offered the possibility to detect adverse pregnancy outcome, including fetal growth disorder, hypertensive disorders, preterm delivery, spontaneous abortion and major fetal abnormalities. It is now clear that the vast majority of major pregnancy abnormalities can be detected and diagnosed during the first trimester of pregnancy and that women prefer first-trimester rather than later diagnosis [22].

Here we review the methods of early pregnancy screening.

2. Screening for fetal aneuploidy and other fetal abnormalities

2.1. Nuchal translucency thickness (NT)

The technique for NT measurement, the need for appropriate training of sonographers and external quality assurance, as well as the application of NT in effective screening for chromosomal abnormalities are well established [23]. The prevalence of chromosomal defects increases exponentially with NT. NT must be measured at 11–14 weeks (i.e., crown-rump length between 45 and 84 mm) and measurements must be adjusted to crown-rump length, which should also be quality controlled [24]. The relation between fetal NT and chromosomal defects was derived from a screening study involving 96,127 singleton pregnancies. In the chromosomally abnormal group, about 50% had trisomy 21, 25% had trisomy 18 or 13, 10% had Turner syndrome, 5% had triploidy, and 10% had other chromosomal defects [25].

The meta-analysis of 28 studies on a total of 6153 chromosomally normal fetuses with increased NT gave a 7.3% prevalence of major defects [26]. However, due to differences in the definition of abnormal NT (from 2 mm to 5 mm), large differences between the studies in the prevalence of major abnormalities (3% to 50%) were observed.

A wide range of fetal abnormalities have been reported in relation to increased NT, including major cardiac defects, diaphragmatic hernia, exomphalos, skeletal defects, and genetic syndromes, such as congenital adrenal hyperplasia, Noonan syndrome, Smith-Lemli-Opitz syndrome, fetal akinesia and spinal muscular atrophy. In the same review including a total of 67,256 pregnancies, the prevalence of major cardiac defects was 0.24%. NT would have allowed a 37.5% detection rate of cardiac defects for a false-positive rate of 4.9%. Another meta-analysis of screening studies reported that the detection rates were about 37% and 31% for the respective NT cut-offs of the 95th and 99th percentiles [27].

In chromosomally normal fetuses with increase NT and no obvious fetal defects, the prevalence of miscarriage or fetal death increased from 1.3% when NT was between the 95th and 99th percentiles up to 20% for NT over 6.5 mm [28,29]. The majority of fetal deaths occurred before 20 weeks, usually associated with severe hydrops. Another study of 6650 pregnancies reported that in chromosomally normal fetuses the prevalence of miscarriage or fetal death was 1.3% when NT was below the 95th percentile, 1.2% for NT between the 95th and 99th percentiles, and 12.3% for NT above the 99th percentile [30]. Increased NT may also be a consequence of a wide range of overlooked fetal malformations and genetic syndromes which could result in fetal death.

2.2. Maternal serum markers

2.2.1. Trisomy 21 screening

For trisomy 21 screening, two makers are largely used, hCGβ and PAPP-A. Spencer calculated the effectiveness of biochemical markers in discriminating normal and trisomy 21 fetuses in comparison with NT, using the Mahalanobis distance (mean unaffected − mean affected / log SD unaffected)^2. The values were 11.0 for NT, 2.48 for PAPP-A, 1.74 for hCGβ and 0.27 for total hCG. Multiple of median (MoM) can also be used for comparison. In a trisomy 21-affected fetus, the mean pattern of markers showed an increased NT (2.5 MoM), an increased hCGβ (2.2 MoM) and a decreased PAPP-A (0.5 MoM) [31].

However, these biochemical markers are only used in combined strategies, at least combined with maternal age and more frequently combined with maternal age and NT.

The relation between maternal age and trisomy 21 is well established. The spontaneous frequency of chromosomal abnormalities at birth, in the absence of any prenatal diagnosis, is around 6 per 1000 births, with mainly trisomy 21, trisomy 18 and trisomy 13 (1 in 800, 6500, and 12,500 births, respectively) [32]. Moreover, because the incidence of most trisomies varies with maternal age and because the mean age of pregnant women is tending to increase over time, the birth prevalence for trisomy 21 has increased from 1 in 740 in 1974 to 1 in 504 in 1997 [33]. In addition, due to the high intrauterine lethality in aneuploidies, a significantly higher frequency at the time of first-trimester screening is observed and must therefore be taken into account using a correction factor [34].

Therefore, screening for chromosomal abnormalities during the first trimester required maternal age and gestational age adjustments for trisomy 21 frequency. These parameters are used in the risk calculation combining biochemical markers (mainly hCGβ and PAPP-A) and NT measurement (first-trimester combined screening). In addition, serum markers must be adjusted to confounding factors: gestational age, multiple pregnancies, maternal weight, smoking, and ethnicity [35,36]. Those markers, as NT, required appropriate quality control [37].

First-trimester screening combining maternal age, maternal serum markers and NT measurement was first applied by Nicolaides et al. within a One-Stop Clinic for Assessment of Risk (OSCAR) [38] and has now become widely available. Large series have confirmed the high rates of detection using the combined approach. Kagan et al. in a prospective study of 56,771 singleton pregnancies showed that the earlier the blood sample the better the detection rate. For a fixed 5% false-positive rate, the detection rates were 94%, 90% and 83% at 11, 12 and 13 weeks, respectively [39]. However, because the ability to diagnose fetal malformations at ultrasound scan is greater at 12–13 weeks than earlier [40], two strategies may be considered: a one-step screening at 12 weeks or the combination of a blood test at 10 weeks plus NT measurement at 12 weeks. The one-step strategy provided a 90% detection rate for a 5% false-positive rate [39], and the two-step strategy a 96% detection rate for a 5% false-positive rate [39]. However, in a prospective study of 41,782 patients, Wortelboer et al. noted that, in 33% of cases, patients only have biochemical analysis [41].

Large studies including BUN [42], SURUSS [43] and FASTER [44] trials have demonstrated a mean detection rate of 84% for a 5% false-positive rate.

Combined first-trimester screening has the advantages of earlier diagnosis and reassurance over second-trimester screening, as well as a higher detection rate for any given false-positive rate [43–46].

Besides first-trimester Down syndrome combined screening strategies, other policies have been used, including integrated, sequential independent, combined sequential and contingent strategies [43,44,47,48]. These different approaches have been proposed combining first- and second-trimester markers. Integrated testing consists of measurement of first-trimester PAPP-A and NT associated with a quadruple test (hCG, AFP, estriol and inhibin A) in the second trimester, combined with maternal age in a single test result. Sequential

independent screening consists of first-trimester screening based on maternal age and NT with chorionic villous sampling (CVS) in the case of a positive result, and second-trimester serum marker screening when the first step is negative. Combined sequential screening consists of first-trimester screening based on maternal age and NT combined with second-trimester serum marker screening in a single test result. Contingent screening consists of first-trimester screening with CVS in the case of a positive result, no further investigation in the case of a low risk result and second-trimester screening in the case of intermediate risk [49–51].

Palomaki et al. using the SURUSS cohort parameters and truncation limits, compared these different strategies in a case–control study based on less than 600 patients having both NT and serum markers screening. They calculated with a computer simulation that integrated screening is the most efficient strategy, and needs fewer amniocenteses or CVSs to detect the same rate of Down syndrome (1.2% false-positive rate for 84.3% detection rate for integrated versus 2% for contingent method). This reduction of false-positive tests represents a 40% reduction of amniocentesis. But for all strategies, increasing the false-positive rate from 2% to 5% raises the detection rate from 85% to approximately 90% [52].

Some authors have proposed first-trimester screening in a one-stop clinic: women can receive pre-test counseling, biochemical testing, ultrasound examination and post-test counseling on the same day, with a trisomy 21 detection rate of more than 90% and a false-positive rate of 5.2%. In the case of intermediate risk, it was proposed to define the risk more accurately with an ultrasound examination of the nasal bones, ductus venosus and tricuspid Doppler [16,18,53,54].

2.2.2. Other aneuploidies or genetic syndromes

In fetuses with trisomy 18, the pattern of markers shows increased NT (3.5 MoM), and decreased hCGβ (0.2 MoM) and PAPP-A (0.2 MoM). In the case of trisomy 13, NT increases too (about 2.5 MoM), and blood tests show decreased values of hCGβ (0.5 MoM) and PAPP-A (0.5 MoM). In triploidy I (diandric), NT is generally increased (2.5 MoM), hCGβ is increased (8 MoM), and PAPP-A is decreased (about 0.8 MoM). In triploidy II (digynic), NT is not modified, and hCGβ and PAPP-A are decreased (0.2 and 0.1 MoM, respectively) [13–15,31,39,55]. Turner syndrome (45,X) is characterized by abnormal NT (4.76 MoM), with normal first-trimester maternal serum markers. In Cornelia de Lange syndrome, large NT [56,57] and low PAPP-A (below 0.2 MoM) have been reported [58,59]. It has been suggested that the gene for Cornelia de Lange syndrome may map to the structural gene of PAPP-A.

2.3. Screening for chromosomal abnormalities in twins

In twin pregnancies, biochemical marker levels are globally twice those in singleton pregnancies. Thus Spencer in a review of the literature found a median PAPP-A of 1.83 MoM and a median hCGβ of 2.03 MoM. However, it seems that PAPP-A depends on chorionicity, and is lower in monochorionic than in dichorionic pregnancies [60]. Zygosity is also relevant to prenatal screening: monochorionic twins are monozygotic and therefore the risk of aneuploidies for both fetuses is identical to that of a singleton pregnancy; dichorionic twins are dizygotic in 90% of cases, so diagnostic testing is necessary for both [61]. Moreover, PAPP-A increases in cases of a vanishing twin, and the detection rate for trisomy 21 falls from 85% to 75% [62].

Therefore, interpretation of biochemical markers for first-trimester screening in twins remains hazardous and requires further studies to be achievable. NT measurement alone remains the most widely used screening test for trisomy 21 in twins during the first trimester [63].

2.4. Cost-effectiveness and ethical considerations

A computer simulation study based on the SURUSS population showed that the most appropriate screening test for Down syndrome is the contingent screening strategy. First-trimester screening alone offers the best cost-effectiveness for a lower false-positive rate, fewer procedures and so fewer euploid miscarriages, and the lowest cost per case of trisomy 21 detected [64].

In choosing such a screening strategy for Down syndrome, it is necessary to consider various issues: financial costs, timing and availability of diagnostic test versus adherence to cut-off levels, acceptability of strategies, and holding first-trimester results until the second trimester. First-trimester screening allows most women to be reassured early in gestation or to have an early diagnosis and a first-trimester termination of pregnancy, which seems to be what the patients prefer [65,66]. Moreover, the responsibility of physicians is to give women the most accurate risk assessment to allow them to understand and decide whether or not to undergo invasive testing. Nicolaides et al. proved that pregnant women were able to make rational decision about invasive testing: less than 1% wanted chorionic villous sampling when their risk was below 1 in 10,000, and 95% when the risk was more than 1 in 50 [67]. First-trimester screening must be proposed in specialized center where patients should receive pre-test counseling to give them the keys to understanding this information, the benefits and risks of the screening. With this information, women should be able to choose whether or not they want an early result, an integrated test, and an invasive procedure, depending on their personal values or beliefs.

3. Prediction of adverse pregnancy outcomes

Large studies have shown that markers used in first-trimester screening could also predict pregnancy adverse outcomes such as intrauterine growth retardation, pre-eclampsia, stillbirth, and preterm delivery. A low PAPP-A is strongly associated with intrauterine growth retardation, fetal demise before or after 24 weeks and preterm delivery. This correlation exists also for hCGβ, but it is a less effective marker.

3.1. Pre-eclampsia

Pre-eclampsia occurs in about 2% of pregnancies and is one of the main causes of maternal and perinatal morbidity and mortality [68]. The pathophysiology is incompletely understood, but involves impaired vascular remodeling of the maternal–fetal interface and dysfunctional placental or endothelial response. The ability to identify women at risk of developing pre-eclampsia would not only mean they could be offered closer antenatal surveillance, but would also help to select those who may benefit from specific treatment. Table 1 summarizes various studies of PAPP-A and hCGβ in pre-eclampsia. In a case–control study Spencer et al. found for women with low PAPP-A an odds ratio of 2.1 of developing pre-eclampsia, severe pregnancy-induced hypertension (95% CI 1.3–3.6) [73]. Conversely, there is no evidence of adverse outcomes when PAPP-A is high [76,77], even if some authors found that PAPP-A values were significantly higher in women who delivered large-for-gestational-age infants (odds ratio of 1.38) [78].

Second-trimester uterine artery Doppler velocimetry with increased impedance is a reflection of impaired placentation and is strongly associated with the risk of developing pre-eclampsia [79]. Spencer et al. found that the combination of first-trimester serum PAPP-A and second-trimester uterine artery mean pulsatility index (PI) improves the screening efficacy for the prediction of pre-eclampsia, with a detection rate of 62.1% and a 5% false-positive rate [80]. Poon et al. [81] found a detection rate of early pre-eclampsia (before 34 weeks) of 80%, with a 5% false-positive rate using a combination of maternal factors such as age, body mass index, racial origin, history of pre-eclampsia, chronic hypertension and method of conception, uterine artery low pulsatility index, mean arterial pressure and PAPP-A.

Nicolaides et al. achieved a 90% detection rate of severe pre-eclampsia (i.e., requiring delivery before 34 weeks) with a 9% false-positive rate using a combination of maternal serum placental protein

Table 1
Studies of maternal serum PAPP-A and hCGβ in pre-eclampsia.

References	Study design	Total	*N*	PAPP-A				hCGβ			
				Cut-off	Sen %	OR	95% CI	Cut-off	Sen %	OR	95% CI
[69]	Prosp Multi	5297	135	<5th	11.1			<5th	7.4	NS	NS
[70]	Prosp Uni	1622	27	<0.25 MoM	14.8	6.09	2.2–16.9	<0.2 MoM	NS		
[71]	Prosp Multi	8839	331	<5th	7.6	2.3	1.6–3.3	<5th	4.1	NS	NS
[72]	Prosp Multi	33,395	764	<5th	7.85	1.54	1.16–2.03	<5th	NS		
[73]	Case–Control	281	61	<5th		1.33	0.6–2.98	NS			
[74]	Case–Control	3076	32	0.6 MoM	18	2.56	1.18–5.71	1.16 MoM	NS		
[75]	Case–Control	47,992	222	<5th	14.6	3.7	2.3–4.8	<5th	NS		

Sensitivity (Sen) and odds ratio (OR) of different cut-off levels and 95% confidence interval (CI). MoM = multiple of median. 5th = 5th percentile. Prosp Multi = prospective multicenter study; Prosp Uni = prospective unicenter study. NS = not stated.

13 (PP-13) and first-trimester uterine artery pulsatility index [82]. The aim of screening for pre-eclampsia is to propose an adapted antenatal follow-up without fetal or maternal risk (except maternal anxiety), so the false-positive rate could be increased to maximize the detection rate.

3.2. Fetal growth retardation

Low birth weight remains a major cause of perinatal morbidity and identification of fetuses at risk of growth retardation could allow suitable follow-up to be proposed. A low value of PAPP-A is strongly associated with intrauterine growth retardation with an odds ratio ranging from 2.64 to 3.21 (Table 2).

An association between hCGβ lower than the 1st percentile and intrauterine growth retardation has been observed, with an odds ratio of 2.7 (95% CI 1.3–5.9) [83], whereas in a study of 46,262 women Spencer et al. found no association [75]. Goetzinger et al. found an association between high hCGβ and intrauterine growth retardation, with an odds ratio of 1.6 (95% CI 1.0–2.6), but with a 0.045 *p* value [84]. Ong et al. found that hCGβ was <10th percentile in 20% of women who developed gestational diabetes [69].

3.3. Fetal loss

A low PAPP-A value, as well as a low hCGβ value or an increased NT, is associated with pregnancy loss, especially before 20 weeks, and the BUN study group found that the rate of fetal loss was only 0.36% before 20 weeks and 0.48% after 20 weeks when these three markers were in normal range. Therefore, a low PAPP-A value is a strong marker of fetal loss even at an early stage of pregnancy, with an odds ratio ranging from 1.9 to 3.9 (Table 3) [87]. Moreover, Smith et al. found that a low level of PAPP-A was strongly associated with stillbirth due to placental dysfunction, defined as abruption or association with growth restriction, with a hazard ratio of 46.0 (95% CI 11.9–178.0), but was not associated with other causes of stillbirth [88]. For patients with low PAPP-A and high AFP (alpha-fetoprotein) in the second trimester, Smith et al. reported odds ratios of 8.5 for delivering a small-for-gestational-age infant, 36.7 for delivering stillbirth after 24 weeks, and 9.9 for delivering preterm (before 37 weeks) [71]. Low PAPP-A and high AFP reflect the combined effect of pathophysiological processes in early placental development. Dugoff et al. found a correlation between low PAPP-A and placental abruption ($p<0.02$) [72]. Some studies found an association between low hCGβ and fetal loss before 24 weeks [70,72,76,85] with odds ratio of 3.64 to 6.3, and one study after 24 weeks with an odds ratio of 1.8 [85].

3.4. Premature delivery

Preterm delivery occurs in approximately 5% of pregnancies [89]. Preterm infants are at increased risks of adverse neonatal outcome, including chronic lung disease, brain injuries, and infectious diseases. Early identification of women at risk of preterm delivery would allow them to be offered attentive follow-up, including cervical measurement by ultrasound and antenatal corticosteroid therapy if necessary. A low PAPP-A value is strongly associated with preterm delivery before 32 weeks with an odds ratio ranging from 2 1.87 to 2.99 (Table 4). There is no correlation between preterm delivery and hCGβ value.

4. Conclusion

In the past two decades, second-trimester maternal serum screening for Down syndrome has been the most common strategy for prenatal diagnosis of chromosomal aneuploidies. More recently, screening for and diagnosis of chromosomal abnormalities have increasingly been performed in the first trimester. With improvements and technological advances in ultrasound, it is now possible to identify many fetal anomalies at 11–13 weeks of gestation. During the same period biochemical markers in maternal serum (PAPP-A and hCGβ) combined with sonographic measurement of nuchal translucency achieve a Down syndrome detection rate of 85%, with a 5% false-positive rate. This early consultation may be the opportunity to help counsel patients and to screen for other adverse complications during

Table 2
Studies of maternal serum PAPP-A and hCGβ in intrauterine growth retardation (<5th percentile).

References	Study design	Total	*n*	PAPP-A				hCGβ			
				Cut-off	Sen %	OR	95% CI	Cut-off	Sen %	OR	95% CI
[69]	Prosp Multi	4297	171	<5th	12.9			Non studied			
[70]	Prosp Uni	1622	49	<0.25 MoM		3.12	1.17–8.29	<0.2 MoM	NS		
[71]	Prosp Multi	8483	353	<5th	12.4	2.8	1.9–4.1	NS	NS	NS	NS
[72]	Prosp Multi	33,395	1300	<5th	12.2	2.81	2.35–3.35	<5th	NS		
[73]	Case/Control	295	84	<5th		2.64	1.28–5.45	NS	NS	NS	NS
[75]	Prosp Multi	46,262	1605	<5th	14.0	3.21		<5th	NS	NS	NS
[83]	Prosp Multi	8012	384	<5th	9.7	2.7	1.9–3.9	<1st	2.0	2.7	1.3–5.9
[84]	Retro Uni	2153	150	<5th	66.7*	2.9	1.6–4.5	>90th	66.7*	1.6	1–2.3

Sensitivity (Sen) and odds ratio (OR) of different cut-off levels and 95% confidence interval (CI). MoM = multiple of median. 5th = 5th percentile. Prosp Multi = prospective multicenter study; Prosp Uni = prospective unicenter study. * sensitivity for both low PAPP-A and high hCGb. NS = not stated.

Table 3
Studies of maternal serum PAPP-A and hCGβ in intrauterine fetal demise.

References	Study design	Total	*n*	Loss period (wks)	PAPP-A				hCGβ			
					Cut-off	Sen %	OR	95% CI	Cut-off	Sen %	OR	95% CI
[69]	Prosp Multi	4297	54	<24	<5th	7.4			<10th	9.3		
[70]	Prosp Uni	1622	30	<24	<0.25 MoM		8.76	3.8–20.4	<0.2 MoM		6.33	
[71]	Prosp Multi	8483	22	>24	<5th	8.75	3.9	1.3–11.7	<5tht	NS		
[72]	Prosp Multi	33,395	1300	<24	<5th	12.9	2.5	1.8–3.3.6	<1st	3.7	3.64	
[72]	Prosp Multi	33,395	1300	>24	<5th	10.5	2.15	1.1–4.1	<1st	NS		
[73]	Case/Control	321	77	Any	<5th		6.84	3.7–12.5	NS	NS	NS	NS
[85]	Prosp Multi	48,225	230	<24	<5th	14.8	3.25		<5th	12	3.1	
[85]	Prosp Multi	48,225	225	>24	<5th	8.4	1.94		<5th	11.7	1.8	
[86]	Prosp Uni	4589	64	<22	<5th	39.1	13.3	7.9–22.4	<5th	37.5	11.7	6.9–19.8

Sensitivity (Sen) and odds ratio (OR) of different cut-off levels and 95% confidence interval (CI). MoM = multiple of median. 5th = 5th percentile. Prosp Multi = prospective multicenter study; Prosp Uni = prospective unicenter study. * sensitivity for both low PAPP-A and high hCGb. NS = not stated. wks = weeks of gestation.

Table 4
Studies of maternal serum PAPP-A and hCGβ in preterm delivery.

References	Study design	Total	*n*	Delivery (wks)	PAPP-A				hCGβ
					Cut-off	Sen %	OR	95% CI	
[71]	Prosp Multi	8839	86	<32	<5th	14	2.9	1.6–1.5	NS
[71]	Prosp Multi	8839	326	33-36	<5th	10.7	2.4	1.7–3.5	NS
[83]	Prosp Multi	8012	87	<34	<5th	9.4	2.3	1.1–4.7	NS
[72]	Prosp Multi	33,395	294	<32	<5th	9.45	1.9	1.2–2.9	NS
[72]	Prosp Multi	33,395	95	32-37	<5th	8.53	1.7	1.5–2	NS
[75]	Prosp Multi	50,902	408	<32	<5th	15	2.99		NS
[75]	Prosp Multi	50,902	1060	<34	<5th	12.4	2.35		NS
[75]	Prosp Multi	50,902	3132	<37	<5th	10.3	1.92		NS

Sensitivity (Sen) and odds ratio (OR) of different cut-off levels and 95% confidence interval (CI). MoM = multiple of median. 5th = 5th percentile. Prosp Multi = prospective multicenter study; Prosp Uni = prospective unicenter study. NS = not stated. wks = weeks of gestation.

pregnancy, such as pre-eclampsia, and to manage potential adverse pregnancy outcomes.

References

[1] Cuckle H. Established markers in second trimester maternal serum. Early Hum Dev 1996;47 Suppl:S27–9.
[2] Muller F, Bussieres L. Maternal serum markers for fetal trisomy 21 screening. Eur J Obstet Gynecol Reprod Biol 1996;65:3–6.
[3] Spencer K, Souter V, Tul N, Snijders R, Nicolaides K. A screening program for trisomy 21 at 10–14 weeks using fetal nuchal translucency, maternal serum free β-human chorionic gonadotropin and pregnancy associated plasma protein-A. Ultrasound Obstet Gynecol 1999;13:231–7.
[4] Cuckle H. Biochemical screening for Down syndrome. Eur J Obstet Gynecol Reprod Biol 2000;92:97–101.
[5] Benacerraf BR, Barss VA, Laboda LA. A sonographic sign for the detection in the second trimester of the fetus with Down's syndrome. Am J Obstet Gynecol 1985;151:1078–9.
[6] Vintzileos AM, Egan JF. Adjusting the risk for trisomy 21 on the basis of second-trimester ultrasonography. Am J Obstet Gynecol 1995;172:837–44.
[7] Nyberg DA, Luthy DA, Resta RG, Nyberg BC, Williams MA. Age-adjusted ultrasound risk assessment for fetal Down's syndrome during the second trimester: description of the method and analysis of 142 cases. Ultrasound Obstet Gynecol 1998;12:8–14.
[8] Winter TC, Uhrich SB, Souter VL, Nyberg DA. The "genetic sonogram": comparison of the index scoring system with the age-adjusted US risk assessment. Radiology 2000;215:775–82.
[9] Nyberg DA, Souter VL. Sonographic markers of fetal trisomies: second trimester. J Ultrasound Med 2001;20:655–74.
[10] Bromley B, Lieberman E, Shipp TD, Benacerraf BR. The genetic sonogram: a method of risk assessment for Down syndrome in the second trimester. J Ultrasound Med 2002;21:1087–96.
[11] Bahado-Singh R, Shahabi S, Karaca M, Mahoney MJ, Cole L, Oz UA. The comprehensive midtrimester test: high-sensitivity Down syndrome test. Am J Obstet Gynecol 2002;186:803–8.
[12] Schluter PJ, Pritchard G. Mid trimester sonographic findings for the prediction of Down syndrome in a sonographically screened population. Am J Obstet Gynecol 2005;192:10–6.
[13] Tul N, Spencer K, Noble P, Chan C, Nicolaides KH. Screening for trisomy 18 by fetal nuchal translucency and maternal serum free β-hCG and pregnancy associated plasma protein-A at 10–14 weeks of gestation. Prenat Diagn 1999;19:1035–42.
[14] Spencer K, Ong C, Skentou H, Liao AW, Nicolaides KH. Screening for trisomy 13 by fetal nuchal translucency and maternal serum free beta hCG and pregnancy associated plasma protein A at 10–14 weeks of gestation. Prenat Diagn 2000;20:411–6.
[15] Spencer K, Liao AW, Skentou H, Cicero S, Nicolaides KH. Screening for triploidy by fetal nuchal translucency and maternal serum free β Human chorionic gonadotropin and pregnancy associated plasma protein-A at 10–14 weeks of gestation. Prenat Diagn 2000;20:495–9.
[16] Spencer K, Spencer CE, Power M, Dawson C, Nicolaides KH. Screening for chromosomal abnormalities in the first trimester using ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years prospective experience. BJOG 2003;110:281–6.
[17] Avgidou K, Papageorghiou A, Bindra R, Spencer K, Nicolaides KH. Prospective first-trimester screening for trisomy 21 in 30, 564 pregnancies. Am J Obstet Gynecol 2005;192:1761–7.
[18] Nicolaides KH, Spencer K, Avgidou K, Faiola S, Falcon O. Multitcenter study of first-trimester screening for trisomy 21 in 75, 821 pregnancies: results and estimation of the potential impact of individual risk-orientated two-stage first-trimester screening. Ultrasound Obstet Gynecol 2005;25:221–6.
[19] Heckerling PS, Verp MS, Hadro TA. Preferences of pregnant women for amniocentesis or chorionic villus sampling for prenatal testing: comparison of patients' choices and those of a decision-analytic model. J Clin Epidemiol 1994;47: 1215–28.
[20] Kandel I, Merrick J. Late termination of pregnancy. Professional dilemmas. Sci World J 2003;3:903–12.
[21] Ville Y. Prima facie. Ultrasound Obstet Gynecol 2010;35:1–3.
[22] Chaoui R, Nicolaides KH. From nuchal translucency to intracranial translucency: towards the early detection of spina bifida. Ultrasound Obstet Gynecol 2010;35:133–8.
[23] Nicolaides KH. Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. Am J Obstet Gynecol 2004;191:45–67.
[24] Salomon LJ, Bernard M, Amarsy R, Bernard JP, Ville Y. The impact of crown rump length measurement error on combined Down syndrome screening: a simulation study. Ultrasound Obstet Gynecol 2009;33:506–11.
[25] Snijders RJM, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation. Lancet 1998;352:343–6.
[26] Souka AP, von Kaisenberg CS, Hyett JA, Sonek JD, Nicolaides KH. Increased nuchal translucency with normal karyotype. Am J Obstet Gynecol 2005;192:1005–21.
[27] Makrydimas G, Sotiriadis A, Ioannidis JP. Screening performance of first-trimester nuchal translucency for major cardiac defects: a meta-analysis. Am J Obstet Gynecol 2003;189:1330–5.
[28] Souka AP, Snidjers RJM, Novakov A, Soares W, Nicolaides KH. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency at 10–14 weeks of gestation. Ultrasound Obstet Gynecol 1998;11:391–400.

[29] Souka AP, Krampl E, Bakalis S, Heath V, Nicolaides KH. Outcome of pregnancy in chromosomally normal fetuses with increased nuchal translucency in the first trimester. Ultrasound Obstet Gynecol 2001;18:9–17.
[30] Michailidis GD, Economides DL. Nuchal translucency measurement and pregnancy outcome in karyotypically normal fetuses. Ultrasound Obstet Gynecol 2001;17:102–5.
[31] Spencer K. Aneuploidy screening in the first trimester. Am J Med Genet C Semin Med Genet 2007;145c:18–32.
[32] Hook EB. Prevalence, risks and recurrence. In: Brock DHJ, Rodeck CH, Ferguson-Smith MA, editors. Prenatal diagnosis and screening. Edinburg: Churchill Livingstone; 1992. p. 351–92.
[33] Egan JF, Benn P, Borgida AF, Rodis JF, Campbell WA, Vintzileos AM. Efficacy of screening for fetal Down syndrome in the United States from 1974 to 1997. Obstet Gynecol 2000;96:979–85.
[34] Snijders RJM, Sebire NJ, Nicolaides KH. Maternal age and gestational age specific risks for chromosomal defects. Fetal Diag Ther 1995;10:356–7.
[35] Aitken DA, Crossley JA, Spencer K. Prenatal screening for neural tube defects and aneuploidy. In: Rimoin DL, et al, editor. Principles and practice of medical genetics. London: Churchill Livingstone; 2002. p. 763–801.
[36] Spencer K, Staboulidou I, De Jesus Cruz J, Karagiannis G, Nicolaides KH. Maternal serum screening marker levels in women with a previous aneuploidy pregnancy. Prenat Diagn 2009;29:1242–3.
[37] Muller F, Forestier F, Dingeon B, et al. Second trimester trisomy 21 maternal serum marker screening. Results of a countrywide study of 854, 902 patients. Prenat Diagn 2002;22:925–9.
[38] Bindra R, Heath V, Liao A, Spencer K, Nicolaides KH. One-stop clinic for assessment of risk for trisomy 21 at 11–14 weeks: a prospective study of 15 030 pregnancies. Ultrasound Obstet Gynecol 2002;20:219–25.
[39] Kagan KO, Wright D, Baker A, Sahota D, Nicolaides KH. Screening for trisomy 21 by maternal age, fetal nuchal translucency thickness, free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 2008;31:618–24.
[40] Souka AP, Pilalis A, Kavalakis Y, Kosmas Y, Antsaklis P, Antsaklis A. Assessment of fetal anatomy at the 11–14-week ultrasound examination. Ultrasound Obstet Gynecol 2004;24:730–4.
[41] Wortelboer EJ, Koster MP, Stoutenbeek P, et al. First-trimester Down syndrome screening performance in the Dutch population; how to achieve further improvement? Prenat Diagn 2009;29:588–92.
[42] Wapner R, Thom E, Simpson JL, et al. First-trimester screening for trisomies 21 and 18. N Engl J Med 2003;349:1405–13.
[43] Wald NJ, Huttly WJ, Hackshaw AK. Antenatal screening for Down's syndrome with the quadruple test. Lancet 2003;361:835–6.
[44] Malone FD, Canick JA, Ball RH, et al. First-trimester or second-trimester screening, or both, for Down's syndrome. N Engl J Med 2005;353:2001–11.
[45] Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). J Med Screen 2003;10:56–104.
[46] Breathnach FM, Malone FD. Screening for aneuploidy in first- and second-trimester: is there an optimal paradigm? Curr Opin Obstet Gynecol 2007;19:176–82 (review).
[47] Wright D, Bradbury I, Benn P, Cuckle H, Ritchie K. Contingent screening for Down syndrome is an efficient alternative to non-disclosure sequential screening. Prenat Diagn 2004;24:762–6.
[48] Cuckle H, Benn P, Wright D. Down syndrome screening in the first and/or second trimester: model predicted performance using meta-analysis parameters. Semin Perinatol 2005;29:252–7.
[49] Ball RH, Caughey AB, Malone FD, et al. First- and second-trimester evaluation of risk for Down syndrome. Obstet Gynecol 2007;110:10–7.
[50] Reddy UM, Wapner RJ. Comparison of first and second trimester aneuploidy risk assessment. Clin Obstet Gynecol 2007;50:442–53.
[51] Wald NJ, Rudnicka AR, Bestwick JP. Sequential and contingent prenatal screening for Down syndrome. Prenat Diagn 2006;26:769–77.
[52] Palomaki GE, Steinort K, Knight GJ, Haddow JE. Comparing three screening strategies for combining first- and second-trimester Down syndrome markers. Obstet Gynecol 2006;107:367–75.
[53] Maiz N, Valencia C, Kagan FO, Wright D, Nicolaides KH. Ductus venosus Doppler in screening for trisomies 21, 18 and 13 and Turner syndrome at 11–13 weeks of gestation. Ultrasound Obstet Gynecol 2009;33:512–7.
[54] Kagan KO, Valencia C, Livanos P, Wright D, Nicolaides KH. Tricuspid regurgitation in screening for trisomies 21, 18 and 13 and Turner syndrome at 11+0 to 13+6 weeks of gestation. Ultrasound Obstet Gynecol 2009;33:18–22.
[55] Spencer K, Tul N, Nicolaides KH. Maternal serum free beta-hCG and PAPP-A in fetal sex chromosome defects in the first trimester. Prenat Diagn 2000;20:390–4.
[56] Urban M, Hartung J. Ultrasonographic and clinical appearance of a 22-week-old fetus with Brachmann-de Lange syndrome. Am J Med Genet 2001;102:73–5.
[57] Huang WH, Porto M. Abnormal first-trimester fetal nuchal translucency and Cornelia De Lange syndrome. Obstet Gynecol 2002;99:956–8.
[58] Aitken DA, Ireland M, Berry E, et al. Second-trimester pregnancy associated plasma protein-A levels are reduced in Cornelia de Lange syndrome pregnancies. Prenat Diagn 1999;19:706–10.
[59] Arbuzova S, Nikolenko M, Krantz D, Hallahan T, Macri J. Low first-trimester pregnancy-associated plasma protein-A and Cornelia de Lange syndrome. Prenat Diagn 2003;23:864.
[60] Spencer K, Kagan KO, Nicolaides KH. Screening for trisomy 21 in twin pregnancies in the first trimester: an update of the impact of chorionicity on maternal serum markers. Prenat Diagn 2008;28:49–52.
[61] Fisk NM, Bennett PR. Prenatal determination of chorionicity and zygosity. In: Ward RH, Whittle M, editors. Multiple pregnancy; 1995. p. 56–67. (London).
[62] Spencer K, Staboulidou I, Nicolaides KH. First trimester aneuploidy screening in the presence of a vanishing twin: implications for maternal serum markers. Prenat Diagn 2010;30:235–40.
[63] Spencer K, Nicolaides KH. 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. BJOG 2003;110:276–80.
[64] Gekas J, Gagné G, Bujold E, et al. Comparison of different strategies in prenatal screening for Down's syndrome: cost effectiveness analysis of computer simulation. BMJ 2009;338:b138.
[65] Mulvey S, Zachariah R, McIlwaine K, Wallace EM. Do women prefer to have screening tests for Down syndrome that have the lowest screen-positive rate or the highest detection rate? Prenat Diagn 2003;23:828–32.
[66] Spencer K, Aitken D. Factors affecting women's preference for type of prenatal screening test for chromosomal anomalies. Ultrasound Obstet Gynecol 2004;24.
[67] Nicolaides KH, Chervenak FA, McCullough LB, Avgidou K, Papageorghiou A. Evidence-based obstetric ethics and informed decision-making by pregnant women about invasive diagnosis after first-trimester assessment of risk for trisomy 21. Am J Obstet Gynecol 2005;193:322–6.
[68] Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 2005;365:785–99.
[69] Ong CYT, Liao AW, Spencer K, Munim S, Nicolaides KH. First trimester maternal serum free human chorionic gonadotropin and pregnancy associated plasma protein A as predictors of pregnancy complications. BJOG 2000;107:1265–7.
[70] Yaron Y, Ochshorn Y, Heifetz S, Lehavi O, Sapir Y, Orr-Urtreger A. First trimester maternal serum free human chorionic gonadotropin as a predictor of adverse pregnancy outcome. Fetal Diagn Ther 2002;17:352–6.
[71] Smith GC, Shah I, Crossley JA, et al. Pregnancy-associated plasma protein A and alpha-fetoprotein and prediction of adverse perinatal outcome. Obstet Gynecol 2006;107:161–6.
[72] Dugoff L, Hobbins JC, Malone FD, et al. First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (the FASTER Trial). Am J Obstet Gynecol 2004;191:1446–51.
[73] Spencer CA, Allen VM, Flowerdew G, Dooley K, Dodds L. Low levels of maternal serum PAPP-A in early pregnancy and the risk of adverse outcomes. Prenat Diagn 2008;28:1029–36.
[74] Kang JH, Farina A, Park J, et al. Down syndrome biochemical markers and screening for pre-eclampsia at first and second trimester: correlation with the week of onset and the severity. Prenat Diagn 2008;28:704–9.
[75] Spencer K, Cowans N, Avigdou K, Molina F, Nicolaides KH. First-trimester biochemical markers of aneuploidy and the prediction of small-for-gestational age fetuses. Ultrasound Obstet Gynecol 2008;31:15–9.
[76] Goetzl L, Krantz D, Simpson JL, et al. Pregnancy-associated plasma protein A, free beta-hCG, nuchal translucency, and risk of pregnancy loss. Obstet Gynecol 2004;104:30–6.
[77] Cuckle HS, Arbuzova S, Spencer K, et al. Frequency and clinical consequences of extremely high maternal serum PAPP-A levels. Prenat Diagn 2003;23:385–8.
[78] Tul N, Pusenjak S, Osredkar J, Spencer K, Novak-Antolic Z. Predicting complications of pregnancy with first-trimester maternal serum free-betahCG, PAPP-A and inhibin-A. Prenat Diagn 2003;23:990–6.
[79] Papageorghiou AT, Yu CT, Nicolaides KH. The role of uterine artery Doppler in predicting adverse pregnancy outcome. Best Pract Res Clin Obstet Gynaecol 2004;18:383–96.
[80] Spencer K, Yu CK, Cowans NJ, Otigbah C, Nicolaides KH. Prediction of pregnancy complications by first-trimester maternal serum PAPP-A and free beta-hCG and with second-trimester uterine artery Doppler. Prenat Diagn 2005;25:949–53.
[81] Poon LC, Stratieva V, Piras S, Piri S, Nicolaides KH. Hypertensive disorders in pregnancy: combined screening by uterine artery Doppler, blood pressure and serum PAPP-A at 11–13 weeks. Prenat Diagn 2010;30:216–23.
[82] Nicolaides KH, Bindra R, Turan OM, et al. A novel approach to first-trimester screening for early pre-eclampsia combining serum PP-13 and Doppler ultrasound. Ultrasound Obstet Gynecol 2006;27:13–7.
[83] Krantz D, Goetzl L, Simpson JL, et al. Association of extreme first-trimester free human chorionic gonadotropin-b, pregnancy-associated plasma protein A, and nuchal translucency with intrauterine growth restriction and other adverse pregnancy outcomes. Am J Obstet Gynecol 2004;191:1452–8.
[84] Goetzinger KR, Singla A, Gerkowicz S, Dicke JM, Gray DL, Odibo AO. The efficiency of first-trimester serum analytes and maternal characteristics in predicting fetal growth disorders. Am J Obstet Gynecol 2009;201:412.e1-6.
[85] Spencer K, Cowans NJ, Avigdou K, Nicolaides K. First-trimester ultrasound and biochemical markers of aneuploidy and the prediction of impending fetal death. Ultrasound Obstet Gynecol 2006;28:637–43.
[86] Rissanen A, Niemimaa M, Suonpää M, Ryynänen M, Heinonen S. First trimester Down's syndrome screening shows high detection rate for trisomy 21, but poor performance in structural abnormalities—regional outcome results. Fetal Diagn Ther 2007;22:45–50.
[87] Cuckle HS, Sehmi IK, Jones RG, Mason G. Low maternal serum PAPP-A and fetal viability. Prenat Diagn 1999;19:788–90.
[88] Smith GC, Crossley JA, Aitken DA, et al. First-trimester placentation and the risk of antepartum stillbirth. JAMA 2004;292:2249–54.
[89] Steer P. The epidemiology of preterm labour. BJOG 2005;112:1–3.