ORIGINAL ARTICLE

First-trimester combined screening for trisomy 21 in women with renal disease

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ABSTRACT

Objective To evaluate the results of first-trimester combined screening for Down syndrome in women with chronic renal disease.

Method Fifty-five pregnant women with renal disease were compared with 110 patients matched for maternal age, maternal weight, smoking status, and gestational age. Maternal renal function was assayed at the time of the combined screening, and renal insufficiency was defined by serum creatinine >90 μmol/L and renal clearance <80 mL/min. We defined three groups: kidney disease and normal renal function (group 1), kidney disease and renal insufficiency (group 2), and a control group (group 3). The values of nuchal translucency, pregnancy-associated plasma protein A, human β-chorionic gonadotrophin (hCGβ), and false-positive rates for Down syndrome screening were compared.

Results There were 39 (71%) and 16 (29%) cases in groups 1 and 2, respectively. Nuchal translucency and multiple of the median (MoM) pregnancy-associated plasma protein A were similar in the three groups. However, MoM hCGβ levels were higher in group 2 than in groups 1 and 3 (5.37 vs 1.1 vs 0.98 MoM, $p = 0.0001$). The resulting screen-positive rate was also higher in group 2 than in groups 1 and 3 (43.7% vs 10.2% vs 5.5%, $p = 0.0001$).

Conclusion Trisomy 21 first-trimester screening using hCGβ is not suitable in the case of maternal renal failure. © 2014 John Wiley & Sons, Ltd.

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INTRODUCTION

Down syndrome (DS) screening by means of a first-trimester combined test using maternal age, maternal serum markers, and nuchal translucency (NT) measurement at 11 to 14 weeks has been adopted in most developed countries. It yields an 85% detection rate for a 5% false-positive rate.[1]

Serum markers should be adjusted for several other variables, including maternal weight, diabetes, ethnicity, and maternal smoking status. Maternal diseases may also have an impact on the results of combined testing. Human chorionic gonadotrophin (hCG) values in patients with renal disease have been reported to be high in a few small series[2–6] and one retrospective cohort study suggested that second-trimester DS screening was not suitable because of higher free human β-chorionic gonadotrophin (hCGβ) serum levels in this population.[7]

There are no studies that have evaluated the impact of kidney disease on hCGβ and pregnancy-associated plasma protein A (PAPP-A) at 11 to 14 weeks. The aim of this study was therefore to review the results of first-trimester combined screening in women with kidney disease.

METHODS

All women referred to our center between November 2008 and May 2012 were routinely offered first-trimester combined screening for trisomy 21, and all results were stored in a database. Two markers were assayed, PAPP-A and hCGβ (XPress PerkinElmer, Turku, Finland), and results were expressed in multiple of the median (MoM) corrected for maternal weight, smoking status, and ethnicity. DS risk calculation combining maternal age, NT, and markers was calculated (LifeCycle, PerkinElmer, Turku). A risk >1/250 was considered a screen-positive result.

Patients were informed and gave written consent for these samples to be kept for several years in order to be used

retrospectively for research purposes. All blood samples were kept frozen at −40 °C in the hospital serum bank. NT measurements were performed by Fetal Medicine Foundation-certified sonographers. All measurements were performed using a General Electric Voluson E8 or 730 Expert (GE Medical System, Europe, Buc, France) with a 3.5 to 5 MHz transabdominal or 6 to 8 MHz transvaginal transducer with no time constraint and cine-loop capability, according to the recommended quality criteria.[8] All measurements were performed using a transabdominal approach, unless a technical difficulty indicated transvaginal examination.

We retrospectively identified women with kidney disease in our database. Serum samples from pregnant women without kidney disease were randomly selected and matched with the kidney disease group for maternal age, gestational age, smoking status, and maternal weight in a 1:2 ratio. Twin pregnancies were excluded. Control sera were selected based on the matching criteria and on the date of sampling. Three groups were defined as follows: (1) women with kidney disease and normal renal function (group 1), (2) women with kidney disease and renal failure (group 2) and (3) control group (group 3).

Creatinine was retrospectively assayed in all samples (enzymatic creatinine, ADVIA, Siemens). Maternal renal function was assessed based on serum creatinine levels and clearance. Renal clearance was calculated using the Cockcroft–Gault formula. Renal insufficiency was defined by serum creatinine levels >90 μmol/L and an estimated renal clearance <80 mL/min.[9] The primary criterion of renal insufficiency was the serum creatinine level.

The MoM values of NT, PAPP-A, and hCGβ recorded at the time of first-trimester screening were retrieved and compared between groups. The screen-positive rate (SPR) for DS screening was also calculated and compared between groups.

Statistical analyses were performed using analysis of variance, the Chi2 test, and the Fisher test (Statistica 8.0, Statsoft France).

RESULTS

During the study period, 10 643 women requested combined first-trimester DS screening, and 55 of these (0.05%) had chronic kidney disease. The control group consisted of 110 women. Among the 55 women with kidney disease, 16 presented chronic renal failure, with persistent creatinine >90 μmol/L, and clearance <80 mL/min. The study group was therefore divided into two subgroups: group 1 consisting of 39 (71%) women with kidney disease and normal renal function and group 2 consisting of 16 (29%) women with renal insufficiency.

Table 1 shows the baseline characteristics of our population. The median gestational age at birth was 36 weeks [range 19.1 (*in utero* fetal death); 41.5] in the study group and 39 [14.1 (termination of pregnancy because of trisomy 21); 41.5] in the control group.

Kidney diseases are summarized in Table 2. Among the 55 patients with kidney disease, eight had a kidney transplant, and 11 had only one functional kidney. In addition, five were on dialysis before and during their pregnancy.

An invasive procedure for fetal karyotyping was performed in 18 women, 8/55 cases and 10/110 controls. Eleven fetal karyotypes were determined for an estimated risk of trisomy 21 ≥ 1/250 (four in the kidney disease group and seven in the control group), two for personal history (trisomy 21 and Stickler syndrome), and five ultrasound abnormalities. Fetal karyotype was normal in all cases with maternal kidney disease. There were two cases of trisomy 21 (1.81%) in the control group (calculated risk at 1/10 and 1/11). Maternal age, NT, and MoM PAPP-A were similar in the three groups. However, median serum hCGβ levels were higher in group 2 than in groups 1 and 3 (5.37 vs 1.01 vs 0.98 MoM, $p = 0.0001$). The resulting SPR (Table 3) was also higher in group 2 than in groups 1 and 3 (43.7% vs 10.2% vs 5.45%, $p = 0.0001$). There was a strong correlation between hCGβ in MoM and maternal serum creatinine levels (Figure 1, $r = 0.8678$, $p = 0.001$) and renal clearance ($r = -0.4475$, $p = 0.001$). However, no creatinine cut-off level could be found (Table 3). No correlation was found between the MoM PAPP-A and serum creatinine levels ($r = -0.0336$, $p = 0.6780$) or with renal clearance ($r = 0.0198$, $p = 0.8081$).

DISCUSSION

Our study provides important information for practitioners involved in first-trimester DS screening. Our results suggest that the first-trimester combined screening test may be hampered in women with kidney disease and renal failure as hCGβ is dramatically increased in these women, thus

Table 1 **Baseline population characteristics (median and ranges in brackets)**

Parameter	KD group without RF $n = 39$	KD group with RF $n = 16$	Control group $n = 110$	p
Maternal age	33 (27–41)	33 (25–43)	32 (22–44)	NS
BMI	21.1 (18–30)	22.2 (17–31)	21.3 (17–32)	NS
Gestational age (weeks)	12.4 (11.6–13.6)	12.3 (12–13.5)	12.4 (11.6–13.6)	NS
Creatinine (μmol/L)	56 (41–79)	115 (92–477)	56 (41–80)	<10–5
Clearance (mL/min)	104 (68–171)	45 (11–78.3)	117 (80–243)	<10–5
NT (mm)	1.4 (0.7–3.7)	1.38 (0.8–2.2)	1.6 (0.5–5.2)	NS
PAPP-A (MoM)	0.94 (0.18–1.39)	1.02 (0.2–3.4)	0.98 (0.14–4.09)	NS (0.09)
hCGβ (MoM)	1.1 (0.51–27)	5.37 (1.38–41.7)	0.98 (0.23–4.38)	<10–4
DS risk (1/)	2230 (5–10 000)	378 (5–7981)	4100 (10–10 000)	<10–3

KD, kidney disease; RF, renal failure; BMI, body mass index; NT, nuchal translucency; MoM, multiple of median; DS, Down syndrome; PAPP-A, pregnancy-associated plasma protein A; hCGβ, human β-chorionic gonadotrophin.

Table 2 **Etiologies of 55 cases of maternal kidney disease**

Categories of kidney disease		*n* (%)
Primary glomerular nephropathy		7 (12.7)
	Focal and segmental hyalinosis	1
	Berger's disease	5
	Gitelman syndrome	1
Secondary glomerular nephropathy		10 (18.2)
	Lupus nephritis	4
	Diabetic nephropathy	2
	Henoch–Schönlein purpura	2
	Post-streptococcal glomerulonephritis	2
Tubulointerstitial nephritis		1 (1.8)
Sarcoidosis		1
Renal vascular disease		6 (11)
	Renal damage after severe eclampsia	1
	Vascular renal damage	4
	Hemolytic and uremic syndrome	1
Congenital kidney disease		19 (34.5)
	Autosomal dominant polycystic disease	9
	Alport syndrome	3
	Medullary sponge kidney	1
	Ureteropelvic junction obstruction	1
	Congenital renal malformation	5
Urologic cause		2 (3.6)
	Renal cancer	1
	Orotic aciduria	1
Drug-related kidney damage		2 (3.6)
Unknown		8 (14.6)

Table 3 **Screen-positive rate in first-trimester Down syndrome serum screening using hCGβ and PAPP-A compared with different serum creatinine cut-offs**

Variable		SPR %
Control group		5.45% (6/110)
Total KD group and maternal serum creatinine		19.6% (11/55)
	KD group without RF (creatinine <90 μmol/L)	10.2% (4/39)
	KD group with RF (90< creatinine <120 μmol/L	60% (3/5)
	KD group with RF (120< creatinine <200 μmol/L	33.33% (3/9)
	KD group with RF (creatinine ≥200 μmol/L)	50% (1/2)
Total KD group and maternal creatinine clearance		
	KD and clearance >80 mL/min	3.2% (1/31)
	KD and 61< clearance <80 mL/min	50% (1/2)
	KD and 30< clearance <60 mL/min	41.6% (5/12)
	KD and clearance <30 mL/min	50% (1/2)

SPR, screen-positive rate; hCGβ, human β-chorionic gonadotrophin; PAPP-A, pregnancy-associated plasma protein A; RF, renal failure; KD, kidney disease; Cl, clearance.

artificially increasing the SPR. Such screening should therefore not be routinely offered in such a setting, and the focus should be on achieving quality screening based on ultrasound markers in order to provide the highest standard of care.[10,11]

The SPR was significantly higher (43.75%) in the group with renal failure than in the control group (5.45%) and in the kidney disease group with normal renal function (10.2%; $p < 0.0001$). This was mainly because of a significant difference

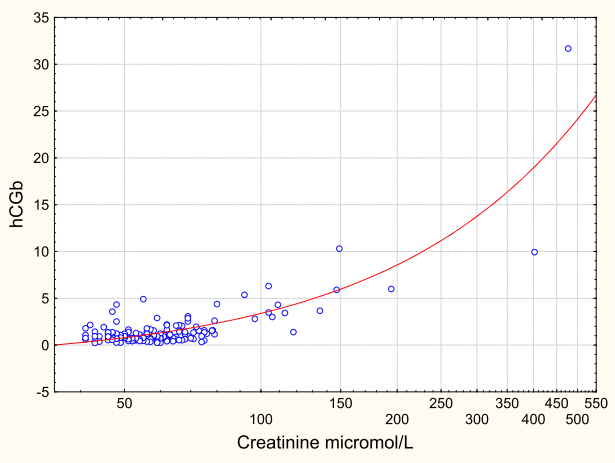

Figure 1 Correlation between MoM hCGβ and maternal serum creatinine levels (μmol/L)

in hCGβ MoM (5.37 MoM vs 0.98 MoM, $p < 0.0001$) because all three groups were comparable for other risk markers, namely maternal age, NT, and PAPP-A. Abnormal hCGβ levels have been reported in a similar population later in pregnancy, in a study on second-trimester DS screening.[7] Recently, Grande *et al.*[12] published similar results based on a smaller series. They suggested three different methods for hCGβ MoM adjustment in order to accurately reduce the SPR in patients with renal failure and obtain results that match better with a control group. By applying their approach to our data base, we reduced the SPR to 11.1% to 13.3% depending on the adjustment method. This interesting approach should be tested in a larger series of patients including DS cases.

Little is known about the reasons for increased maternal serum hCGβ in patients with impaired renal function. Two main pathophysiological mechanisms have been suggested.[7] Hypoxia can stimulate the development of the trophoblast and therefore increase the production of hCG that enters the maternal circulation.[13] In addition, chronic hypertension is commonly associated with renal failure and vasculopathy. This may cause placental hypoxia and therefore increase hCG release into the maternal circulation. Another mechanism is related to decreased renal clearance of hCG due to impaired renal function. This is supported by the correlation found between hCGβ and creatinine levels as well as with other markers of renal function such as β2-microglobulin and α1-microglobulin.[7] The similarity in MoM and in molecular weight for hCGβ, α1-microglobulin, and β2-microglobulin (34, 27, and 11.7 kDa, respectively) favors the hypothesis of a lower hCGβ clearance in women with renal disease.[7] Our data showing both a positive correlation between hCGβ and creatinine levels as well as an increased false-positive rate with decreasing creatinine clearance also support the latter hypothesis. However, an appropriate marker of renal clearance is still lacking in early pregnancy. The Cockcroft–Gault formula is widely used as an indirect estimate of renal clearance capacity. To estimate renal function, guidelines[14] specifically exclude the use of the modification of diet in renal disease formula and the Cockcroft–Gault formula in pregnant women. Therefore, the principal indicator of renal function in this study was serum creatinine. However, physiological changes in early pregnancy are characterized by a substantial and early increase in glomerular filtration rate from around 10 weeks of pregnancy onwards, and this limits the use and meaning of creatinine clearance during pregnancy.[15] Similarly, one may suppose that hypoxia could also impact on placental PAPP-A production. Elevated values of PAPP-A in patients with chronic renal failure could occur because of very low renal clearance as well as increased production related to vascular damage and dialysis.[16,17] However, our study did not pick up any significant variation in PAPP-A values with renal function. PAPP-A being a much bigger molecule than hCGβ, one might have expected an altered clearance of PAPP-A as well.

We should acknowledge several limitations in our study. It was based on a retrospective cohort. Among 55 patients in the kidney disease group, only 16 had renal failure at the time of DS screening, which is likely to limit the power of our findings. Because of the overall low incidence of DS, demonstrating a lower detection rate in patients with renal failure as compared with controls would require an unrealistic number of patients. However, our conclusions are consistent with the available literature. Our data also suggest that in women with kidney disease and normal renal function at the time of the combined test, hCGβ is only marginally increased, and fail to demonstrate a significant increase in the SPR for DS. However, it is likely that our study was also underpowered for such comparisons. Last, five women on dialysis were included. One could hypothesize that their serum creatinine levels did not truly reflect their renal function. We considered they were too few to be excluded or analyzed separately.

In conclusion, first-trimester combined screening may be hampered in women with kidney disease and especially so if there is renal insufficiency because hCGβ levels are significantly increased in these women, and this results in an increased DS SPR. Screening including hCGβ should therefore not be offered in such a setting, and the focus should be on achieving quality screening based on ultrasound risk markers or on the combination of maternal age, first-trimester PAPP-A, and NT with or without second-trimester markers other than hCG or hCGβ. Another approach would be to adjust maternal serum hCGβ, but the adjustment formula must be confirmed in a large series before prospective use. The emergence of noninvasive prenatal testing based on the analysis of free fetal DNA[18] could offer a promising alternative in these patients, although the performance of these techniques in these specific patients should also be evaluated.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- It has been demonstrated that Down syndrome second-trimester maternal serum screening is not suitable for mothers with renal failure. The impact on first-trimester screening has not been evaluated.

WHAT DOES THIS STUDY ADD?

- Based on a series of 55 cases, we demonstrated that Down syndrome first-trimester maternal serum screening is not suitable for mothers with renal failure.

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