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Challenges in prenatal screening and diagnosis in the Netherlands

Bakker, Merel

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Dankwoord

Abstracts

OP 18.03 - First trimester screening in the Netherlands: why is the uptake so low?

M. Bakker, E. Pajkrt, R. J. S. Snijders, K. Bouman, C. M. Bilardo Short Oral Presentation at the 21th World Congress on Ultrasound in Obstetrics and Gynecology, September 18-22, 2011, Los Angeles, USA.

Objective:

The combined test (CT) for Down syndrome screening was implemented in the Netherlands in 2007. After introduction of the CT the uptake of screening was much lower than uptakes reported in the UK and Denmark. Purpose of this study was to identify determinants which may explain this relatively low uptake.

Methods:

1140 women were invited to fill out a questionnaire at 20 weeks of gestation. Recruitment took place at 12 ultrasound clinics in the Northeast (NE) and Northwest (NW) of the Netherlands. The questionnaire was derived from a questionnaire developed by Seror et al in France which addressed women's decisions on first trimester screening and invasive testing for Down syndrome.

Results:

837 (73%) women returned the questionnaire; 816 of these were filled out complete and used for analysis. The uptake of the CT in the NE of the Netherlands was significantly lower (N=77; 17%, 12% <36 years and 46% >36 years) than in the NW of the Netherlands (N=194; 52%, 49% <36 years and 75% >36 years).

The majority of participants (95%) appreciated being informed about the CT. Of these women 66% did *not* opt for the CT; however 25% would opt for the test if the aim was to detect major congenital malformations. This would result in a participation rate of 50% instead of 33%.

Conclusion:

The uptake of the CT in the Netherlands is low compared to other European countries. One of the reasons is that the CT is offered exclusively as Down syndrome screening and little or no information is given on the fact that the scan may reveal major congenital malformations. This study shows that counseling should include this information and needs improvement.

Inter-operator reliability of manual and semi-automated measurement (SONO-NT) and Manual and semi-automated measurement of the nuchal translucency – are there any clinical significant differences?

Oral Presentation at the 11th World Congress in Fetal Medicine,
June 24-28, 2012, Kos, Greece.

Objective:

Are the differences between the manual and semi-automated NT measurement clinically relevant?

Patients and methods:

Cross-sectional study on singleton pregnancies between 11+0 - 13+6 weeks of gestation. Two FMF-accredited operators obtained manual and semi-automated NT measurements of 99 NT-images. The maximal acceptable difference in NT measurements within and between operators was 0.15 mm. Intra and inter-operator differences were analyzed by the paired Student's t-test and homogeneity of variances by the Levene's test. Intra and inter-operator agreement were quantified with Bland and Altman's limits of agreement and changes in women's risk status were tested with the binomial test.

Results:

Intra-operator agreement.

■ Table – Differences in measurement

	OPERATOR 1			OPERATOR 2		
	Mean Δ	SD	R ²	Mean Δ	SD	R ²
Manual	.0116*	.07824	0.985	.0581*	.17618	0.928
Inner-inner	.0000*	.08452	0.985	.0162*	.10371	0.976
Inner-middle	-.0162*	.11755	0.973	-.0109*	.12462	0.966

*T-test: $p < .001$

■ Table – Difference in risk calculation (risk <1:200 or ≥1:200)

	OPERATOR 1 N(%)	OPERATOR 2 N(%)
Manual (1) Manual (1)	0	0
Inner-inner (1) Inner-inner (2)	0	0
Inner-middle (1) Inner-middle (2)	2 (2%)	2 (2%)
Manual Inner-inner	3 (3%)	4 (4%)
Manual Inner-middle	5 (5%)*	3 (3%)

*McNemar $p < .05$ and * $p = 0.063$

■ Table – Differences in measurement

	Mean Δ	SD	R ²
Manual (R1) Manual (R2)	-.0285*	.18678	0.919
Inner-inner (R1) Inner-inner (R2)	.0505*	.15477	0.949
Inner-middle (R1) Inner-middle (R2)	.0756*	.16850	0.942

*T-test: $p < .001$

■ Table – Difference in risk calculation

	N (%)
Manual (R1) - Manual (R2)	2 (2%)
Inner-inner (R1) - Inner-inner (R2)	1 (1%)
Inner-middle (R1) - Inner-middle (R2)	2 (2%)

*McNemar significant

Conclusion:

Intra-operator variability: High R² for all 3 measurement-methods. Mean Δ + SD of SONO-NT: = or \uparrow than manual method for operator₁ and \downarrow for operator 2. Difference in Risk Calculation: up to 5% difference in risk calculation.

Inter-operator: High R² for all 3 measurement-methods. Mean Δ + SD \downarrow using SONO-NT. Difference in Risk Calculation: max. 2% difference in risk calculation.

Manual measurement according to the FMF guidelines is sufficient for reliable NT measurements. Less experienced operators will benefit from the semi-automated SONO-NT (mean Δ and SD \downarrow). However, experience lies not only in number of cases... also in precision of image acquisition!

OP 07.03 - Manual and semi-automated measurement of the nuchal translucency – are there any clinical significant differences?

M. Bakker, P. B. Mulder, E. Birnie, C. M. Bilardo

Short Oral Presentation at the 22th World Congress on Ultrasound in Obstetrics and Gynecology, September 9-12, 2012, Copenhagen, Denmark.

Objectives:

Are the differences between the manual and semi-automated measurement of the nuchal translucency (NT) clinically relevant?

Methods:

Retrospectively 100 NT images from singleton pregnancies were selected, obtained at 11+0 to 13+6 weeks of gestation. All images had been acquired trans-abdominally using a Voluson E8 equipped with a 4-8 Hz probe (GE Medical Systems). Only images without measurements were used. For each image two trained operators obtained the manual measurements (according to FMF guidelines) and the semi-automated NT measurements (SONONT: inner-inner and inner-middle method). The respective NT measurements and the associated risk on trisomy 21, calculated in Astraia, were transformed into a low (<1:200) or high risk (\geq 1:200) category. A change in risk status was considered a clinically relevant difference and tested with the McNemar's test.

Results:

The misclassification rate of operator 1 was 3.3% (CI [0.007 – 0.092], $p=.99$) between the manual and inner-inner method; 5.4% (CI [0.018 – 0.122], $p=.06$) between the manual and inner-middle method; and 4.3% (CI [0.012 – 0.108], $p=.13$) between the inner-inner and inner-middle method. For operator 2, the misclassification rates were 4.3% (CI [0.012 – 0.108], $p=.63$), 3.3% (CI [0.007 – 0.092], $p=.25$) and 5.5% (CI [0.018 – 0.122], $p=.06$) respectively. Between the manual measurements of the two operators, two cases were discordant (2.2%, CI [0.003 – 0.076], $p=.500$).

Conclusions:

There are no significant differences in classification between the manual measurement and SONO-NT measurements. In our opinion manual measurement according to the FMF guidelines is sufficient for a valid risk calculation for Down syndrome.

P 06.07 - Inter-operator reliability of manual and semi-automated measurement (SONO-NT)

M. Bakker, P. B. Mulder, E. Birnie, C. M. Bilardo

Poster at the 22th World Congress on Ultrasound in Obstetrics and Gynecology, September 9-12, 2012, Copenhagen, Denmark.

Objectives:

To compare the inter-operator reliability of: manual and semi-automated nuchal translucency (NT) measurements.

Methods:

Retrospectively 100 NT images of singleton pregnancies were selected, obtained at 11+0 to 13+6 weeks of gestation. All had been acquired trans-abdominally using a Voluson E8 equipped with a 4-8 Hz probe (GE Medical Systems). Only images without measurements were used. For each image, two operators obtained the manual measurements (according to FMF guidelines) and semi-automated NT measurements (SONO-NT: inner-inner and inner-middle method). Inter-measurement reliability within operators for the inner-inner and inner-middle measurement was compared to the operators' manual measurement. Inter-operator reliability of the manual, inner-inner and inner-middle measurements was assessed by comparing the measurement of operator 1 to the same measurement of operator 2. The maximal clinically acceptable difference was considered to be 0.1 mm (using t-tests and R^2).

Results:

Compared to the operators' manual measurement, the R of operator 1 was 0.975 for inner-inner and 0.972 for inner-middle measurements; and 0.951 and 0.955 respectively for operator 2. The inter-operator reliability coefficient R was 0.918 for manual, 0.941 for inner-inner and 0.933 for inner-middle measurements. The mean difference between the operators' manual measurements was -0.02 mm (CI [-0.061 – 0.017]), 0.06 mm between inner-inner (CI [0.027 – 0.099]) and 0.09 mm between inner-middle measurements (CI [0.048 – 0.126]). The manual and inner-inner mean difference did not deviate significantly when the clinically accepted difference of 0.1 mm was taken into account. The inner-middle mean differences did however.

Conclusions:

The inter-observer reliability for both the SONO-NT measurements and manual measurements is high. Mean difference between operators is lowest for the manual measurements. Manual measurement according to FMF guidelines is sufficient for reliable NT measurements.

List of Publications

First Author

- Targeted ultrasound examination and DNA testing for Noonan syndrome, in fetuses with increased nuchal translucency and normal karyotype. Bakker M., Pajkrt E., Mathijssen I. B., Bilardo C. M. *Prenat Diagn* 2011 Sep; 31(9): 833-40.
- Low uptake of the combined test in the Netherlands – which factors contribute? Bakker M., Birnie E., Pajkrt E., Bilardo C. M., Snijders R. J. *Prenat Diagn* 2012 Dec; 32(13): 1305-12.
- Intra-operator and inter-operator reliability of manual and semiautomated measurement of fetal nuchal translucency: a cross sectional study. Bakker M., Mulder P., Birnie E., Bilardo C. M., *Prenat Diagn* 2013 Dec; 33(13): 1264-71.
- Increased nuchal translucency with normal karyotype and anomaly scan: what next? Bakker M., Pajkrt E., Bilardo C. M. *Best Pract Res Clin Obstet Gynaecol.* 2013 Dec 3; pii: S1521-6934(13)00157-0.
- Total pregnancy loss after chorionic villus sampling and amniocentesis in the Netherlands: a cohort study. *UOG* 2016 Jun - Accepted.
- Prenasal thickness, prefrontal space ratio and other facial profile markers in first trimester fetuses with aneuploidies, cleft palate and micrognathia. Submitted.
- Nasal bone length, prenasal thickness, prenasal thickness-to-nasal bone length ratio and prefontal space ratio in second and third trimester fetuses with Down syndrome. Vos F. I., De Jong-Pleij E. A. P., Bakker M., Kagan O. K., Ribbert L. S. M., Tromp E., Bilardo C. M. *Fetal Diagnosis and Therapy*, 2015 Jan 30. [Epub ahead of print]
- Trends in serial measurements of five ultrasound markers measured in second and third trimester Downsyndrome fetuses. Vos F. I., De Jong-Pleij E. A. P., Bakker M., Tromp E., Bilardo C. M. *Fetal Diagnosis and Therapy*, 2015; 38(1): 48-54.
- Fetal facial profile markers of Down syndrome in the second and third trimester of pregnancy. Vos F. I., De Jong-Pleij E. A. P., Bakker M., Tromp E., Kagan O. K., Bilardo C. M. *Ultrasound Obstet Gynecol.* 2015 Aug; 46(2): 18-73.
- Fetal profile markers in second and third trimester fetuses with trisomy 18. Vos F. I., De Jong-Pleij E. A. P., Bakker M., Tromp E., Manten G. T., Bilardo C. M. *Ultrasound Obstet Gynecol.* 2015 Jul; 46(1): 66-72.
- Premaxillary protrusion assessment by the maxilla-nasion-mandible angle in fetuses with facial clefts. De Jong-Pleij E. A. P., Pistorius L. R., Ribbert L. S., Breugem C. C., Bakker M., Tromp E., Bilardo C. M. *Prenat Diagn.* 2013 Apr; 33(4): 354-9.

Co-author

- Is 3D technique superior to 2D in Down syndrome screening? A review of six second and third trimester fetal profile markers. Vos F. I., Bakker M., De Jong-Pleij E. A. P., Ribbert L. S. M., Tromp E., Bilardo C. M. *Prenat Diagn.* 2015 Mar; 35(3): 207-13.
- OP 18.03 - First trimester screening in the Netherlands: why is the uptake so low? Bakker M., Pajkrt E., Snijders R. J. S., Bouman K., Bilardo C. M. Short Oral Presentation at the 21th World Congress on Ultrasound in Obstetrics and Gynecology, 18-22 September 2011, Los Angeles, USA.

Oral and Poster Presentations

- Inter-operator reliability of manual and semi-automated measurement (SONO-NT) and Manual and semi-automated measurement of the nuchal translucency – are there any clinical significant differences? Oral Presentation at the 11th World Congress in Fetal Medicine, 24-28 June 2012, Kos, Greece.
- OP 07.03 - Manual and semi-automated measurement of the nuchal translucency – are there any clinical significant differences? Bakker M., Mulder P. B., Birnie E., Bilardo C. M. Short Oral Presentation at the 22th World Congress on Ultrasound in Obstetrics and Gynecology, 9-12 September 2012, Copenhagen, Denmark.
- P 06.07 - Inter-operator reliability of manual and semi-automated measurement (SONO-NT). Bakker M., Mulder P. B., Birnie E., Bilardo C. M. Poster at the 22th World Congress on Ultrasound in Obstetrics and Gynecology, 9-12 September 2012, Copenhagen, Denmark.
- OP 28.11 - Premaxillary protrusion in fetuses with facial clefts. De Jong-Pleij E., Ribbert L. S., Pistorius L. R., Bakker M., Breugem C., Tromp E., Bilardo C. M. Oral Presentation at the 22th World Congress on Ultrasound in Obstetrics and Gynecology, 9-12 September 2012, Copenhagen, Denmark.
- OP 18.06 - First things first: preconditions to reliably estimate the risk of fetal trisomy. Snijders R., Bakker M., Pajkrt E., Muller-Kobolt A., Sturk G., Bilardo C. Oral Presentation at the 21th World Congress on Ultrasound in Obstetrics and Gynecology, 18-22 September 2011, Los Angeles, USA.
- OP 18.07 - Pre- and postnatal diagnosis of fetal trisomy in the north-east of the Netherlands. Bouman K., Snijders R., De Walle H., Bakker M., Bilardo C. Oral Presentation at the 21th World Congress on Ultrasound in Obstetrics and Gynecology, 18-22 September 2011, Los Angeles, USA.
- OP 12.10 - Diagnosing fetal long QT syndrome (LQTS) using tissue Doppler imaging (TDI), preliminary report. Clur S. B., Bakker M., Ottenkamp J., Bilardo C., Kuipers I., De Bruin-Bon R. Oral Presentation at the 20th World Congress on Ultrasound in Obstetrics and Gynecology, 10-14 October 2010, Prague, Czech Republic.



This thesis is published within the Research Institute SHARE (Science in Healthy Ageing and healthcaRE) of the University Medical Center Groningen / University of Groningen. Further information regarding the institute and its research can be obtained from our website: <http://www.share.umcg.nl/>.

More recent theses can be found in the list below ((co-)supervisors are between brackets).

2016

- * Bonvanie I. J. - *Functional somatic symptoms in adolescence and young adults; personal vulnerabilities and external stressors* (prof. J. G. M. Rosmalen, prof. A. J. Oldehinkel, dr. K. A. M. Janssens)
- * Kamstra J. I. - *Trismus secondary to head and neck cancer; risk factors and exercise therapy* (prof. P. U. Dijkstra, prof. J. L. N. Roodenburg, dr. H. Reintsema)
- * De Greeff J. W. - *Physically active academic lessons: effects on physical fitness and executive functions in primary school children* (prof. C. Visscher, prof. R. L. Bosker, dr. E. Hartman, dr. S. Doolaard)
- * Bruins J. - *Metabolic risk in people with psychotic disorders; no mental health without physical health* (prof. G. H. M. Pijnenborg, prof. E. R. van den Heuvel, dr. F. Jorg, dr. R. Bruggeman)
- * Van Dijk L. - *The reality of practice; an action systems approach to serious gaming* (prof. C. K. van der Sluis, dr. R. M. Bongers)
- * Holtman G. A. - *Diagnostic strategies in children with chronic gastrointestinal symptoms in primary care* (prof. M. Y. Berger, dr. Y. Lisman-van Leeuwen, dr. P. F. van Theenen)
- * Smit R. - *Health economics of tick-borne diseases* (prof. M. J. Postma, prof. K. Poelstra)
- * Lopez Angarita A. - *Self-compassion; a closer look at its assessment, correlates and role in psychological wellbeing* (prof. R. Sanderman, dr. M. J. Schroevers)
- * Norder-Kuper L. - *Common mental disorders; prediction of sickness absence durations and recurrences* (prof. U. Bültmann, prof. J. J. L. van der Klink, dr. C. A. M. Roelen)
- * Zandstra A. R. E. - *Psychosocial adversity and adolescents' mental health problems; moderating influences of basal cortisol, resting heart rate and Dopamine Receptor D4* (prof. J. Ormel, dr. C. A. Hartman)

- * Armbrust W. - *The impact of juvenile idiopathic arthritis; moving beyond the joint*
(prof. P. J. J. Sauer, prof. J. H. B. Geertzen, prof. N. M. Wulffraat)
- * Roy A. - *The development of depression in children and adolescents with ADHD*
(prof. A. J. Oldehinkel, dr. C. A. Hartman)
- * Holubcikova J. - *Eating habits, body image and health and behavioural problems of adolescents; the role of school and family context*
(prof. S. A. Reijneveld, dr. J. P. van Dijk, dr. A. Madarasova-Geckova, dr. P. Kolarcik)
- * Nguyen T. P. L. - *Health economics of screening for hypertension in Vietnam*
(prof. M. J. Postma, dr. C. C. M. Schuilinga-Veninga, dr. T. B. Y. Nguyen, dr. E. P. Wright)
- * Mihajlovic J. - *Health economics of targeted cancer therapies; a comparative analysis for Serbia and the Netherlands*
(prof. M. J. Postma, dr. P. Pechlivanoglou)
- * Darvishian M. - *Real-world influenza vaccine effectiveness; new designs and methods to adjust for confounding and bias*
(prof. E. Hak, prof. E. R. van den Heuvel)
- * Berm E. J. J. - *Optimizing treatment with psychotropic agents through precision drug therapy; it is not about the mean*
(prof. B. Wilffert, prof. E. Hak, dr. J. G. Maring)

For more theses from 2016 and earlier please visit our website.

Curriculum Vitæ

Merel Bakker werd op 10 augustus 1981 geboren te Purmerend waar zij in 1999 haar diploma behaalde aan het atheneum “het Da Vinci College”. In datzelfde jaar begon zij aan de studie Medische Biologie nadat zij was uitgeloot voor de studie Geneeskunde. In 2000, nadat zij haar propedeuse had behaald, werd zij alsnog ingeloot voor de studie Geneeskunde aan de Universiteit van Amsterdam. Tijdens deze periode heeft zij onder andere onderzoek gedaan naar Lepra, in Makassar, te Indonesië.

Na het afronden van de studie Geneeskunde is zij als AGNIO in het Kennemer Gasthuis in Haarlem gaan werken. Aansluitend is zij begonnen als arts prenatale diagnostiek in het AMC waar de basis voor haar proefschrift is gelegd. Dit traject heeft zij voortgezet in het UMCG toen zij meeging met prof. dr. Bilardo naar Groningen. Hier werkte zij als arts prenatale diagnostiek en in deeltijd aan haar promotie. Tevens gaf zij trainingen en onderwijs in het verrichten van echoscopisch onderzoek in het eerste en tweede trimester van de zwangerschap en heeft zij gedurende 3 maanden gewerkt aan de Fetal Medicine Unit van de Stellenbosch Universiteit in Kaapstad, Zuid-Afrika. In 2014 is zij met veel plezier gestart met de opleiding tot gynaecoloog in het Deventer Ziekenhuis en heden werkzaam in het UMCG te Groningen.

Dankwoord

Katia, cara *Katia*, wat is het een turbulente maar zeer waardevolle rit geweest! Door alles wat we samen in de afgelopen jaren hebben meegemaakt ben je veel meer voor mij dan 'alleen' mijn promotor. Bedankt voor je blinde vertrouwen in mij, voor de vrije hand die ik heb gekregen, voor je stimulatie om alles eruit te halen wat er in zit, om naar congressen en symposia te gaan en steeds nieuwe dingen aan te blijven pakken. Ik ben door dit alles ver gekomen.

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De promotiecommissie, Prof. dr. S. A. Scherjon, Prof. dr. A. Ranchor, Prof. dr. I. M. van Langen en Prof. dr. O. B. Petersen wil ik graag bedanken voor hun aandacht aan het manuscript.

Mijn paranimfen, *Martine* en *Eline*, vanzelfsprekend.

Lieve *Martine*, wat hebben wij een hoop meegemaakt in 15 jaar tijd! Leuke en minder leuke dingen, maar ik had het voor geen goud willen missen. Waar zou ik soms zijn zonder jou?! Dank je voor luisterend oor, je gevatheid, je humor en warme persoonlijkheid. We moeten dat boek maar eens gaan schrijven.

Lieve *Eline*, lief *Lientje*, promoveren gaat niet over rozen, daar weten wij alles van. Dank je voor alle steun, gezelligheid, humor en inzichten tijdens deze periode. Dat we daar nog maar vele jaren aan vast mogen plakken! Met wijn!

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Merel