Effizienz der Fehlbildungsdetektion im 1. Trimenon
Diagnostische Punktionen
Was, wann, wieso …?

Peter Kozlowski

praenatal.de

Pränatal allround

Dortmund 25. November 2017

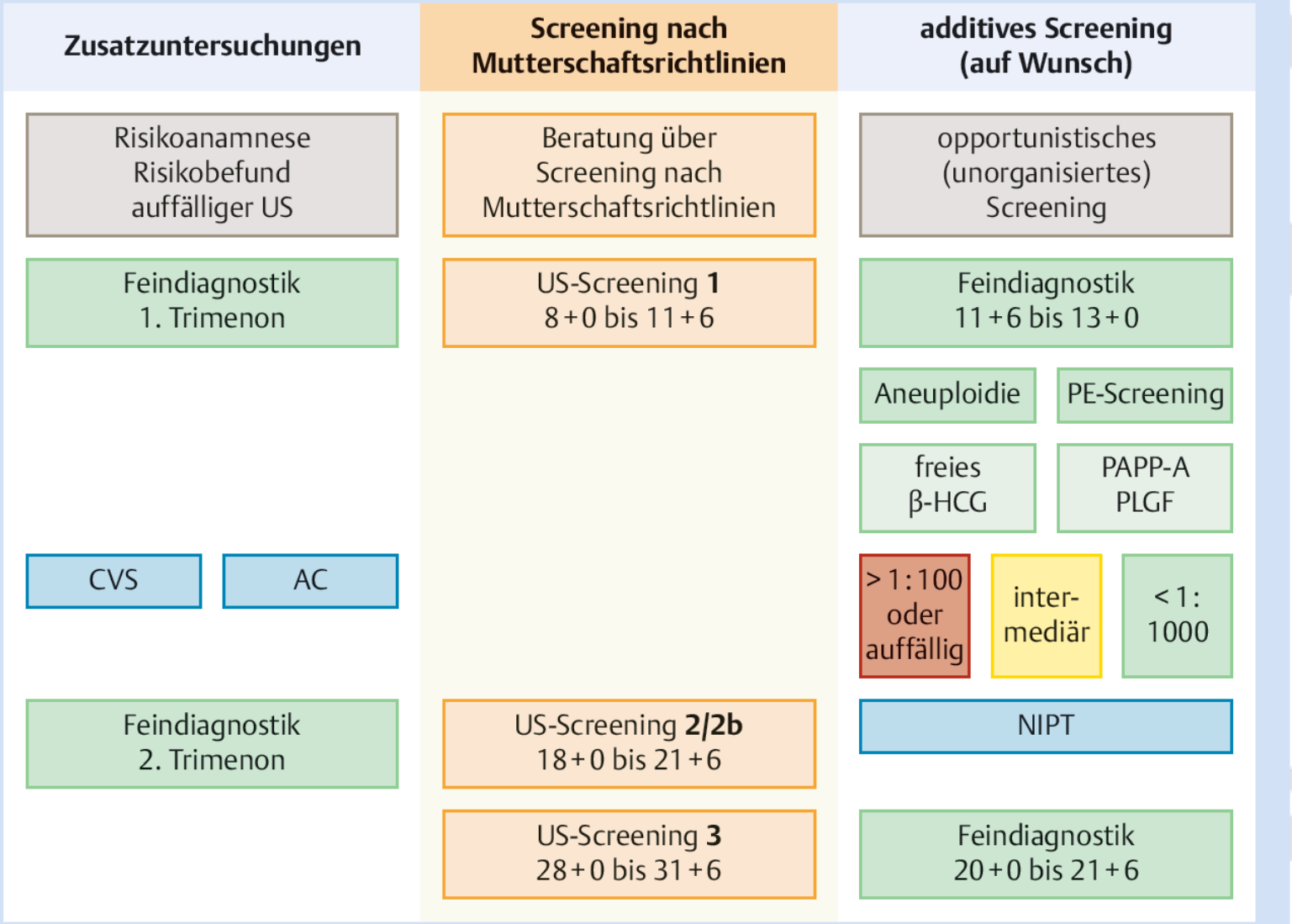

Abb. 1 Übersicht über sonografische Untersuchungen, genetisches Screening und diagnostische Punktionen im 1. und 2./3. Trimenon. AC: Amniozentese, CVS: Chorionzottenbiopsie, NIPT: Nicht invasiver pränataler Test, US: Ultraschall, PE-Screening: Screening auf Praeeklampsie.

Kozlowski 2016 GebFra

Qualitätsanforderungen an die weiterführende differenzierte Ultraschalluntersuchung in der pränatalen Diagnostik (DEGUM-Stufen II und III) im Zeitraum 11–13+6 Schwangerschaftswochen

Quality Requirements for early Fetal Ultrasound Assessment at 11–13+6 Weeks of Gestation (DEGUM Levels II and III)

Authors C. von Kaisenberg[1], R. Chaoui[2], M. Häusler[3], K. O. Kagan[4], P. Kozlowski[5], E. Merz[6], A. Rempen[7], H. Steiner[8], S. Tercanli[9], J. Wisser[10], K. S. Heling[2]

Affiliations Die Institutsangaben sind am Ende des Beitrags gelistet.

v Kaisenberg UiM 2016

Tab. 3 Sonografische Standardbiometrie- und optionale Parameter.

Standardparameter	optionale Parameter
Scheitel-Steiß-Länge (SSL)	
biparietaler Durchmesser (BPD)	Kopf- und Abdomenumfang (KU, AU), Femurlänge (FL)
Nackentransparenz (NT)[1]	Nasenbein (NB)[1]
	intrakranielle Transparenz (IT)/ Hirnstamm
	Herzfrequenz (FHR)
	Trikuspidalklappenfluss (TR)[1]
	Ductus venosus Fluss (DV)[1]
	Aa. uterinae beidseits (Aa. ut.)[1]
	Cervixlänge (Cx)[1]

[1] Nach Aufklärung und Einwilligung (GenDG)/Zertifizierung durch die FMF: NT, NB, T DV, Aa uterinae, Cx.

Tab. 4 Sonografische Standardeinstellungen der fetalen Anatomie- und optionale Parameter [42 – 45].

	Standardparameter	optionale Parameter
Schädel/ Gehirn	Kalotte, Falx cerebri, Plexus chorioidei	Intrakranielle Transparenz IT Hirnstamm
Gesicht	Profil	Augen, Kiefer, Lippen
Nacken	Nackentransparenz (NT)[1]	Nasenbein (NB)[1]
Wirbel-säule		Kontur
Herz/ Thorax	Lage, Kontur Vierkammerblick Lungen	Ausflusstrakte in Farbe Drei-Gefäß-Trachea-Blick Trikuspidalklappenfluss (TR)[1]
Abdo-men	Magen Bauchwand	Zwerchfell Ductus venosus Fluss (DV)[1] NS Arterien bds. der Harnblase
Extremi-täten	Arme und Beine	Hände und Füße (Femur Tibia Fibula Humerus Radius Ulna)
Urogeni-taltrakt	Harnblase	Nieren
Plazenta	Chorionizität, Amnionizi-tät (Mehrlinge), Struktur	Lage, Ansatz der Nabelschnur Aa. uterinae[1]

[1] Nach Aufklärung und Einwilligung (GenDG)/Zertifizierung durch die FMF: NT, NB, TR, DV, Aa uterinae, Cx.

Qualitätsanforderungen an die weiterführende differenzierte Ultraschalluntersuchung in der pränatalen Diagnostik (DEGUM-Stufen II und III) im Zeitraum 11–13+6 Schwangerschaftswochen

Quality Requirements for early Fetal Ultrasound Assessment at 11–13+6 Weeks of Gestation (DEGUM Levels II and III)

Tab. 2 FMF-Protokoll zur Messung der fetalen Nackentransparenz (NT) (© **Abb. 1**).

– 11^{+0} – 13^{+6} Schwangerschaftswochen
– Scheitel-Steiß-Länge 45 – 84 mm
– Vergrößerung: der fetale Kopf und Thorax nehmen den ganzen Bildschirm ein
– Median sagittale Ebene: anterior die Nasenspitze und rechteckige Form des Gaumens, das translucente Diencephalon in der Mitte und die Nackenhaut posterior[1]
– neutrale Position
– unterscheide zwischen der fetalen Haut und dem Amnion
– messe die breiteste Stelle der NT
– Plazierung der Caliper: diese sollten auf den beiden Linien liegen, welche die Nackentransparenz begrenzen, so nah wie möglich zu dem schwarzen Bereich ohne jedoch in de Nackentransparenz zu liegen.
– drehe das Gain herunter wenn das Bild vergrößert wird
– mache mehr als ein Bild, speichere das mit dem größten Messwert in der Datenbank welches alle obigen Kriterien erfüllt
– semiautomatisierte Technik: kann verwendet werden
– nuchal cord: verwende den Mittelwert der NT ober und unterhalb der Nabelschnur

[1] Kleine Abweichungen von der exakten Mittellinie würden bedeuten, dass die Nasenspitze nicht sichtbar ist und der Prozessus Zygomatikus der Maxilla erscheint.

v Kaisenberg UiM 2016

PRENATAL DIAGNOSIS
Prenat Diagn 2011; **31**: 90–102.
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI:** 10.1002/pd.2642

Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11–13 weeks

Argyro Syngelaki[1,2,3], Teodora Chelemen[1,2], Themistoklis Dagklis[1], Lindsey Allan[1] and Kypros H. Nicolaides[1,2,3]*

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[2]*Department of Fetal Medicine, Medway Maritime Hospital, Gillingham, UK*
[3]*Department of Fetal Medicine, University College Hospital, London, UK*

45.191 Schwangerschaften 11-13 Wochen
332 Aneuploidien (ausgeschlossen)
488 Fetale Anomalien
213 (43,6%) entdeckt

100% Exencephalie, Holoprosencephalie, Omphalocele, Megazystis
77% Fehlen von Händen u/o Füßen
50% Zwerchfellhernien
50% Letale Skelettdysplasien
34% Schwere Herzfehler
14% Spina bifida aperta

Syngelaki 2011 Prenat Diagn

Ultrasound Obstet Gynecol 2017; **50**: 429–441
Published online 7 September 2017 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17246

Systematic review of first-trimester ultrasound screening for detection of fetal structural anomalies and factors that affect screening performance

J. N. KARIM[1], N. W. ROBERTS[2], L. J. SALOMON[3] and A. T. PAPAGEORGHIOU[1,4]

[1]*Nuffield Department of Obstetrics & Gynaecology, University of Oxford, Oxford, UK;* [2]*Bodleian Health Care Libraries, University of Oxford, Oxford, UK;* [3]*Maternité Necker-Enfants Malades, AP-HP, Université Paris Descartes, Paris, France;* [4]*Fetal Medicine Unit, Department of Obstetrics and Gynaecology, St. George's University Hospitals NHS Foundation Trust, Molecular and Clinical Sciences Research Institute, London, UK*

Art und Kollektiv	Prävalenz (%)	Detektion (%)
schwer low risk	1,0	46
alle Typen low risk	1,8	32
alle Typen high risk	6,6	61

Metaanalyse 30 Studien n > 200.000

Karim 2017 UOG

Organdiagnostik 11^{+0}-13^{+6} Wochen

(fast) immer erkennbar	potentiell erkennbar	selten oder nie erkennbar
Body stalk Anomalie	Fehlende Hände/Füße	Mikrocephalie
Anencephalie	Zwerchfellhernie	Balkenmangel
Alobäre Holoprosencephalie	Letale Skelettdysplasie	Ventrikulomegalie
Omphalocele	Polydaktylie	Teratome
Gastroschisis	Schwere Herzfehler	Ovarialzysten
Megazystis	Spina bifida aperta	Lungensequester
	Gesichtsspalten	C.a. Lungenmalformation

Intracerebral Translucency

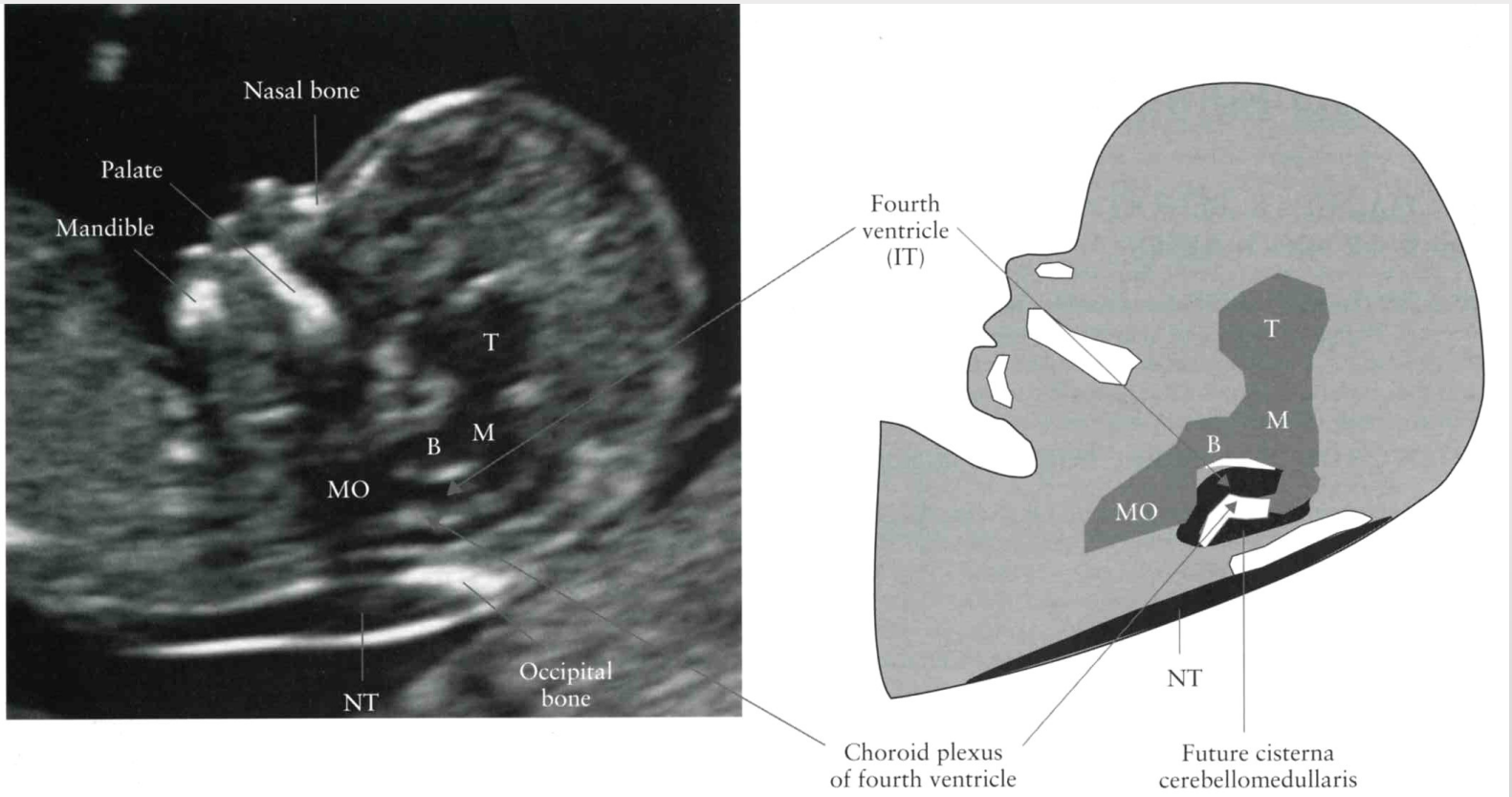


Figure 1 Ultrasound image in the mid-sagittal plane of the fetal face showing the nasal bone, palate, mandible, nuchal translucency (NT), thalamus (T), midbrain (M), brain stem (B) and medulla oblongata (MO). The fourth ventricle presents as an intracranial translucency (IT) between the brain stem and the choroid plexus.

Chaoui 2009

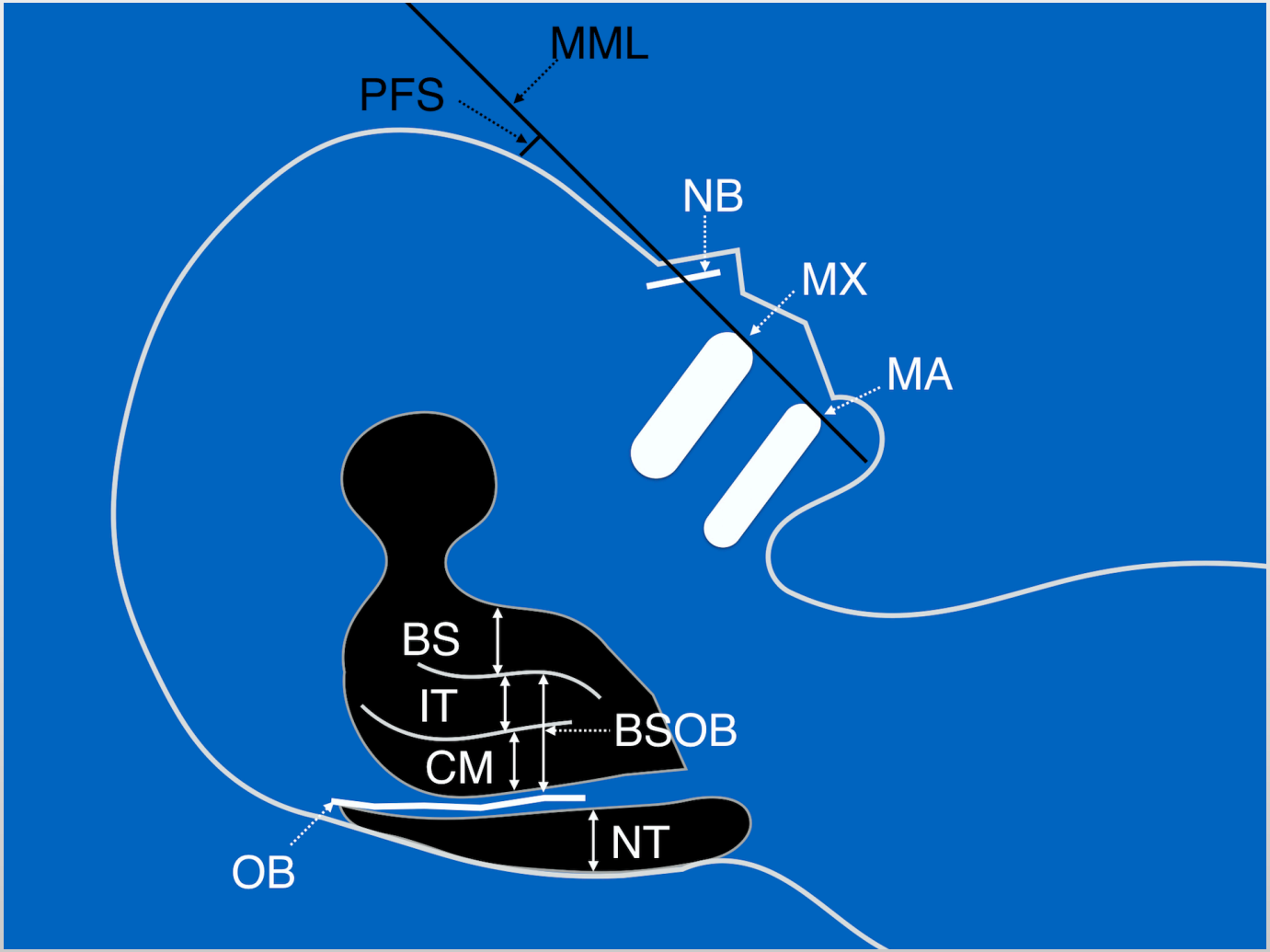
Review

Thieme

Das fetale Profil im ersten Trimenon – mehr als nur NT

The Fetal Profile – More Than Just NT

Autoren
Markus Hoopmann, Karl Oliver Kagan



Hoopmann 2017 UiM

ULTRASOUND
in Obstetrics & Gynecology

isuog

Ultrasound Obstet Gynecol 2017; **50**: 45–48
Published online 23 April 2017 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17286

Impact of holoprosencephaly, exomphalos, megacystis and increased nuchal translucency on first-trimester screening for chromosomal abnormalities

A. SYNGELAKI, L. GUERRA, I. CECCACCI, T. EFETURK and K. H. NICOLAIDES

Harris Birthright Research Centre for Fetal Medicine, Fetal Medicine Research Institute, King's College Hospital, London, UK

Table 1 Prevalence of alobar holoprosencephaly, exomphalos, megacystis and nuchal translucency thickness (NT) ≥ 3.5 mm and incidence of associated chromosomal abnormalities in 108 982 fetuses screened in the first trimester

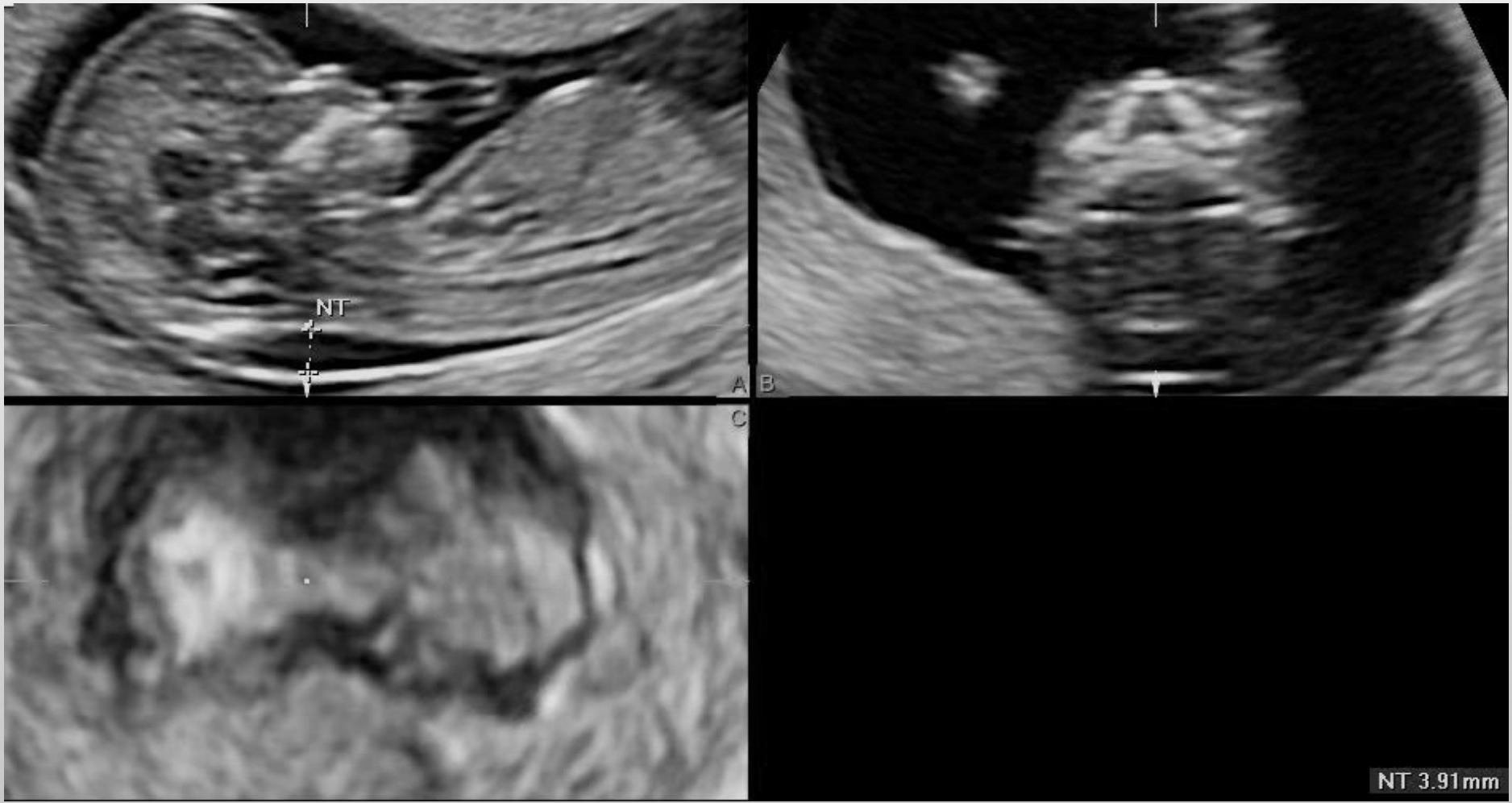
			Abnormal karyotype					
Defect	n	*Total*	*Trisomy 21*	*Trisomy 18*	*Trisomy 13*	*Triploidy*	*Monosomy X*	*Other*
Holoprosencephaly	37	29 (78.4)	0 (0)	5 (17.2)	18 (62.1)	5 (17.2)	0 (0)	1 (3.4)
Exomphalos	260	106 (40.8)	6 (5.7)	58 (54.7)	25 (23.6)	5 (4.7)	7 (6.6)	5 (4.7)
Liver	33	15 (45.5)	0 (0)	9 (60.0)	4 (26.7)	1 (6.7)	1 (6.7)	0 (0)
Bowel only	227	91 (40.1)	6 (6.6)	49 (53.8)	21 (23.1)	4 (4.4)	6 (6.6)	5 (5.5)
CRL 45–54 mm	128	53 (41.4)	2 (3.8)	35 (66.0)	5 (9.4)	3 (5.7)	4 (7.5)	4 (7.5)
CRL 55–84 mm	99	38 (38.4)	4 (10.5)	14 (36.8)	16 (42.1)	1 (2.6)	2 (5.3)	1 (2.6)
Megacystis	81	15 (18.5)	4 (26.7)	5 (33.3)	3 (20.0)	0 (0)	0 (0)	3 (20.0)
Bladder 7–15 mm	63	12 (19.0)	3 (25.0)	3 (25.0)	3 (25.0)	0 (0)	0 (0)	3 (25.0)
Bladder > 15 mm	18	3 (16.7)	1 (33.3)	2 (66.7)	0 (0)	0 (0)	0 (0)	0 (0)
NT ≥ 3.5 mm	919	446 (48.5)	227 (50.9)	101 (22.6)	32 (7.2)	6 (1.3)	59 (13.2)	21 (4.7)
Any of the above	1175	495 (42.1)	230 (46.5)	119 (24.0)	49 (9.9)	12 (2.4)	59 (11.9)	27 (5.5)
Total population	108 982	870	432	166	56	35	63	118
Defects or increased NT	1175 (1.1)	495 (56.9)	230 (53.2)	119 (71.7)	48 (85.7)	12 (34.3)	59 (93.7)	27 (22.9)
CT risk ≥ 1 in 100	924 (0.8)	488 (56.1)	229 (53.0)	118 (71.1)	47 (83.9)	11 (31.4)	59 (93.7)	24 (20.3)

Data are given as *n* or *n* (%). CRL, crown–rump length; CT, combined test.

Syngelaki 2017 UOG

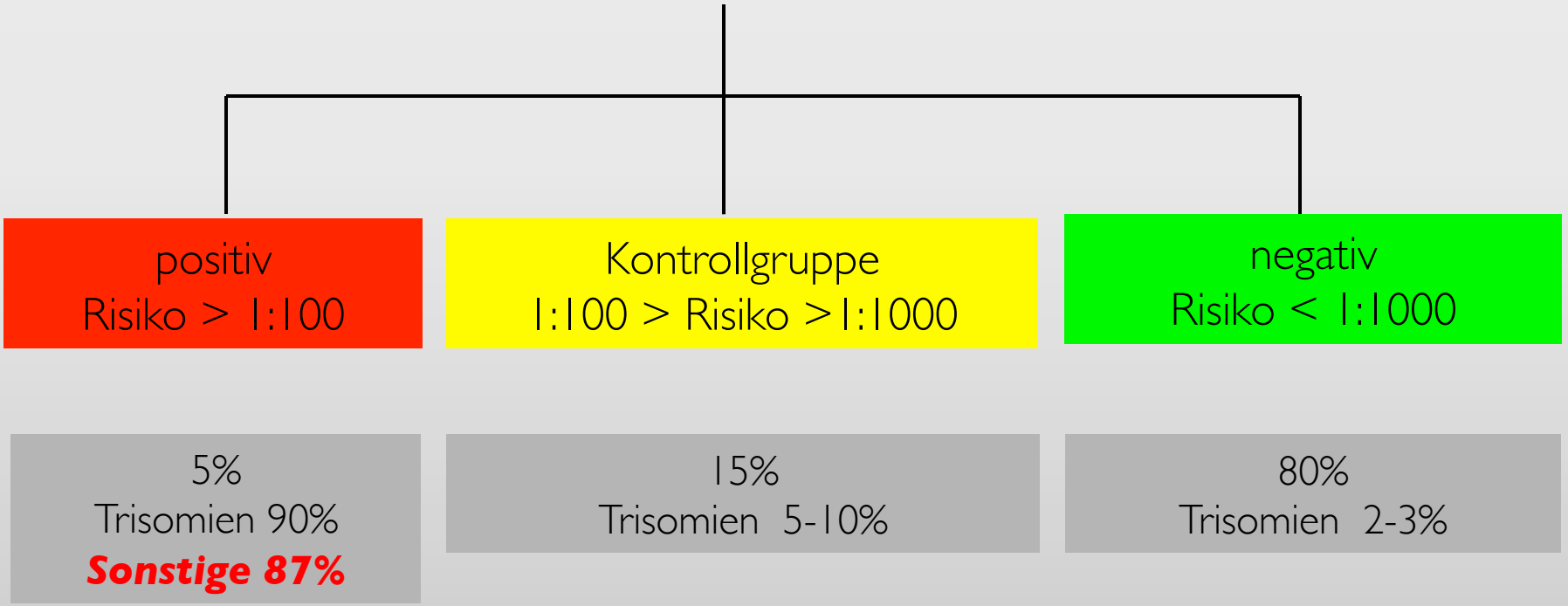
SSL	50 mm	60 mm	70 mm	80 mm
Median (mm)	1,4	1,7	1,9	2,0
95. Perz. (mm)	2,2	2,4	2,6	2,8

NT- Percentilen (gerundet nach Nicolaides 2007)



Basis ETS (Combined Screening)

Alter, NT, ß-HCG, PAPP-A



OBSTETRICS

Cell-free DNA vs sequential screening for the detection of fetal chromosomal abnormalities

Mary E. Norton, MD; Rebecca J. Baer, MPH; Ronald J. Wapner, MD; Miriam Kuppermann, PhD; Laura L. Jelliffe-Pawlowski, PhD; Robert J. Currier, PhD

BACKGROUND: Sequential and cell-free DNA (cfDNA) screening are both tests for the common aneuploidies. Although cfDNA has a greater detection rate (DR) for trisomy 21, sequential screening also can identify risk for other aneuploidies. The comparative DR for all chromosomal abnormalities is unknown.

OBJECTIVE: To compare sequential and cfDNA screening for detection of fetal chromosomal abnormalities in a general prenatal cohort.

STUDY DESIGN: The performance of sequential screening for the detection of chromosome abnormalities in a cohort of patients screened through the California Prenatal Screening Program with estimated due dates between August 2009 and December 2012 was compared with the estimated DRs and false-positive rates (FPRs) of cfDNA screening if used as primary screening in this same cohort. DR and FPR for cfDNA screening were abstracted from the published literature, as were the rates of "no results" in euploid and aneuploid cases. Chromosome abnormalities in the entire cohort were categorized as detectable (trisomies 13, 18, and 21, and sex chromosome aneuploidy), or not detectable (other chromosome abnormalities) by cfDNA screening. DR and FPR were compared for individual and all chromosome abnormalities. DR and FPR for the cohort were compared if "no results" cases were considered "screen negative" or "screen positive" for aneuploidy. DR and FPR rates were compared by use of the Fisher exact test.

RESULTS: Of 452,901 women who underwent sequential screening during the time period of the study, 2575 (0.57%) had a fetal chromosomal abnormality; 2101 were detected for a DR of 81.6%, and 19,929 euploid fetuses had positive sequential screening for an FPR rate of 4.5%. If no results cases were presumed normal, cfDNA screening would have detected 1820 chromosome abnormalities (70.7%) with an FPR of 0.7%. If no results cases were considered screen positive, 1985 (77.1%) cases would be detected at a total screen positive rate of 3.7%. In either case, the detection rate of sequential screening for all aneuploidies in the cohort was greater than cfDNA ($P<.0001$).

CONCLUSION: For primary population screening, cfDNA provides lower DR than sequential screening if considering detection of all chromosomal abnormalities. Assuming that no results cfDNA cases are high-risk improves cfDNA detection but with a greater FPR. cfDNA should not be adopted as primary screening without further evaluation of the implications for detection of all chromosomal abnormalities and how to best evaluate no results cases.

Key words: aneuploidy screening, cell-free DNA screening, noninvasive prenatal screening, noninvasive prenatal testing, sequential screening

452.901 ETS
0,6 % Anomalien
davon 71% der cfDNA zugänglich

Norton 2016 AJOG

TABLE 4
Detection rate and false-positive rate of sequential screening and cfDNA screening for all aneuploidies

	Detection rate for all chromosomal abnormalities	False-positive rate
Sequential screening	81.6%	4.5%
cfDNA, "no results" assumed normal	70.7%	0.7%
cfDNA, "no results" assumed high risk	77.1%	3.7%

cfDNA, cell-free DNA.

Norton et al. Cell-free DNA and sequential screening. Am J Obstet Gynecol 2016.

Spektrum genetischer Anomalien

Original Research ajog.org

OBSTETRICS

Chromosomal abnormalities not currently detected by cell-free fetal DNA: a retrospective analysis at a single center

Hagit Shani, MD; Tamar Goldwaser, MD; Jennifer Keating, MS; Susan Klugman, MD

n=3.182 zytogenetische Analysen
n=1.037 plus Microarray
220 (7%) Chromosomenanomalien

57% Tris 21,18,13 und SCA
22% Mosaike, unbalancierte Translokationen
21% pathologische Microarrays

Shani 2016 AJOG

Ultrasound Obstet Gynecol 2017; **49**: 714–720
Published online 26 April 2017 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17283

Accuracy of first-trimester combined test in screening for trisomies 21, 18 and 13

M. SANTORUM[1], D. WRIGHT[2], A. SYNGELAKI[1], N. KARAGIOTI[1] and K. H. NICOLAIDES[1]

[1]*Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK;* [2]*Institute of Health Research, University of Exeter, Exeter, UK*

KEYWORDS: chromosomal abnormalities; first-trimester combined test; screening; trisomy 13; trisomy 18; trisomy 21

ETS-Risiko 21,18,13	n	%	Anomalien in dieser Gruppe	davon Trisomie 21,18,13	Erfasste Chromosomen-anomalien (gesamt)
>1:10	1486	1,4	653 (43,9%)	80,6%	75,1
>1:50	3699	3,4	742 (20,0%)	78,9%	85,3
>1:100	5760	5,3	771 (13,4%)	79,1%	88,6

Santorum 2017 UOG

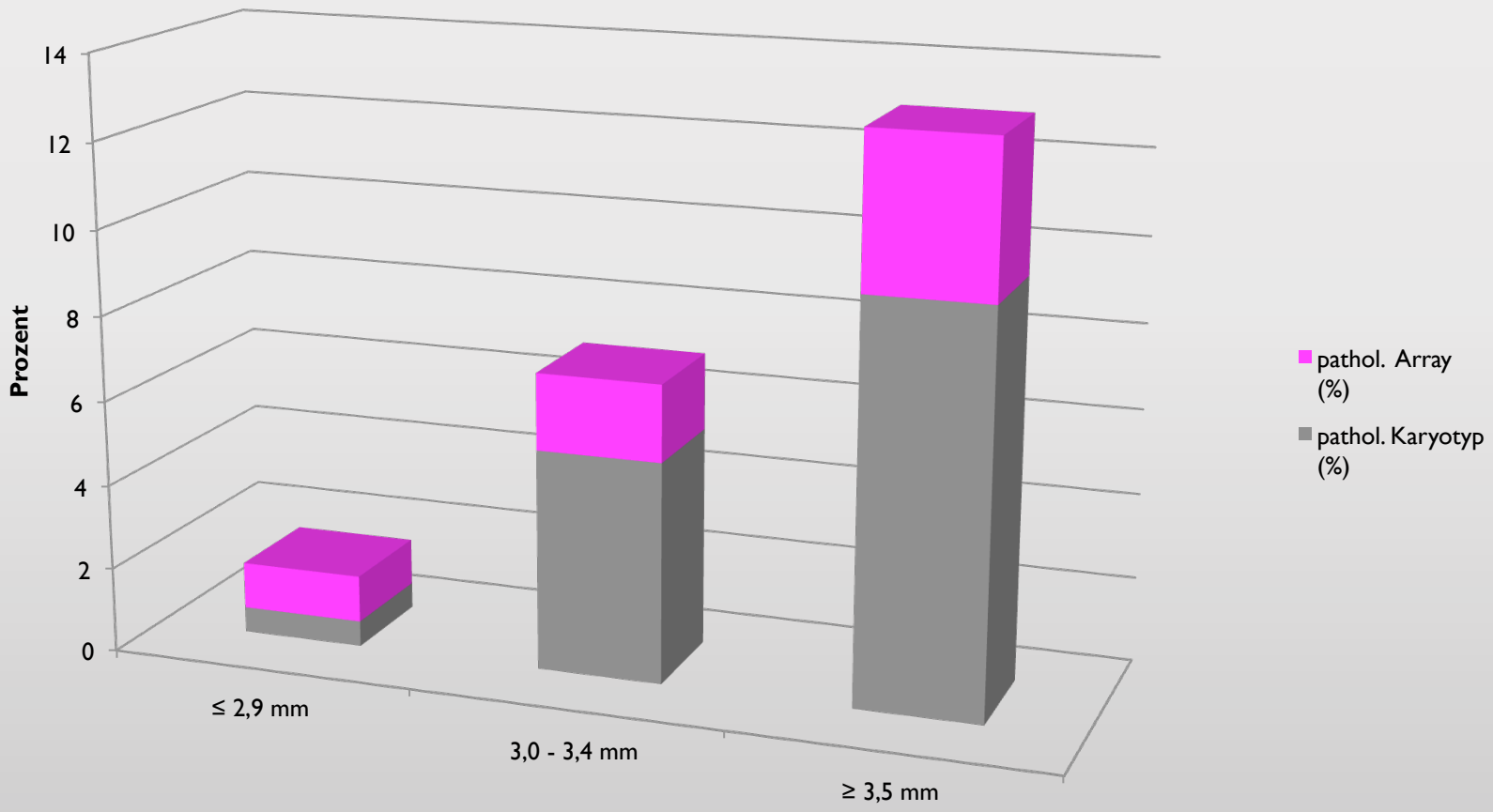
n=108.982
Chromosomenanomalien n=870 (0,8%)
davon Trisomie 21,18,13 n=654 (75,2%)

Schwellenwerte für NT und ETS

Erstautor	n	Kriterium	Karyotyp pathol.	CNV pathol.
Kagan 2006	11.315	NT > 95. Perz. - 3,4mm	7,1%	-
		NT 3,5 - 11,5mm	20-70%	
Äyräs 2013	1.063	NT 95. Perz. - 3,4mm	10%	-
		NT ≥ 3,5mm	42%	
Petersen 2014	11.864	NT 95-99. Perz.	10,4%	kA
		NT ≥ 99. Perz.	34,8%	
	10.205	komb ETS-Risiko > 1:300	11,4%	kA
		komb ETS-Risiko > 1:10	56%	
Maya 2017	1.588	NT ≤ 2,9mm	0,6%	1,1%
		NT 3,0 – 3,4mm	5,2%	1,8%
		NT ≥ 3,5mm	9,4%	3,6%
Vogel 2017	575	komb ETS-Risiko > 1:300	6,3% 22% nicht T13,18,21 oder SCA	2,6%
		komb ETS-Risiko 1:300 - 1:100	2,4% 37,5% nicht T13,18,21 oder SCA	2,7%
		komb ETS-Risiko 1:100 - 1:50	4,4% 50% nicht T13,18,21 oder SCA	4,4%
		komb ETS-Risiko > 1:50	15,8% 9% nicht T13,18,21 oder SCA	0,7%

Kozlowski et al 2017 (under review)

NT-Breite und genetische Anomalien



Daten nach Maya 2017

Schwellenwerte für NT und ETS

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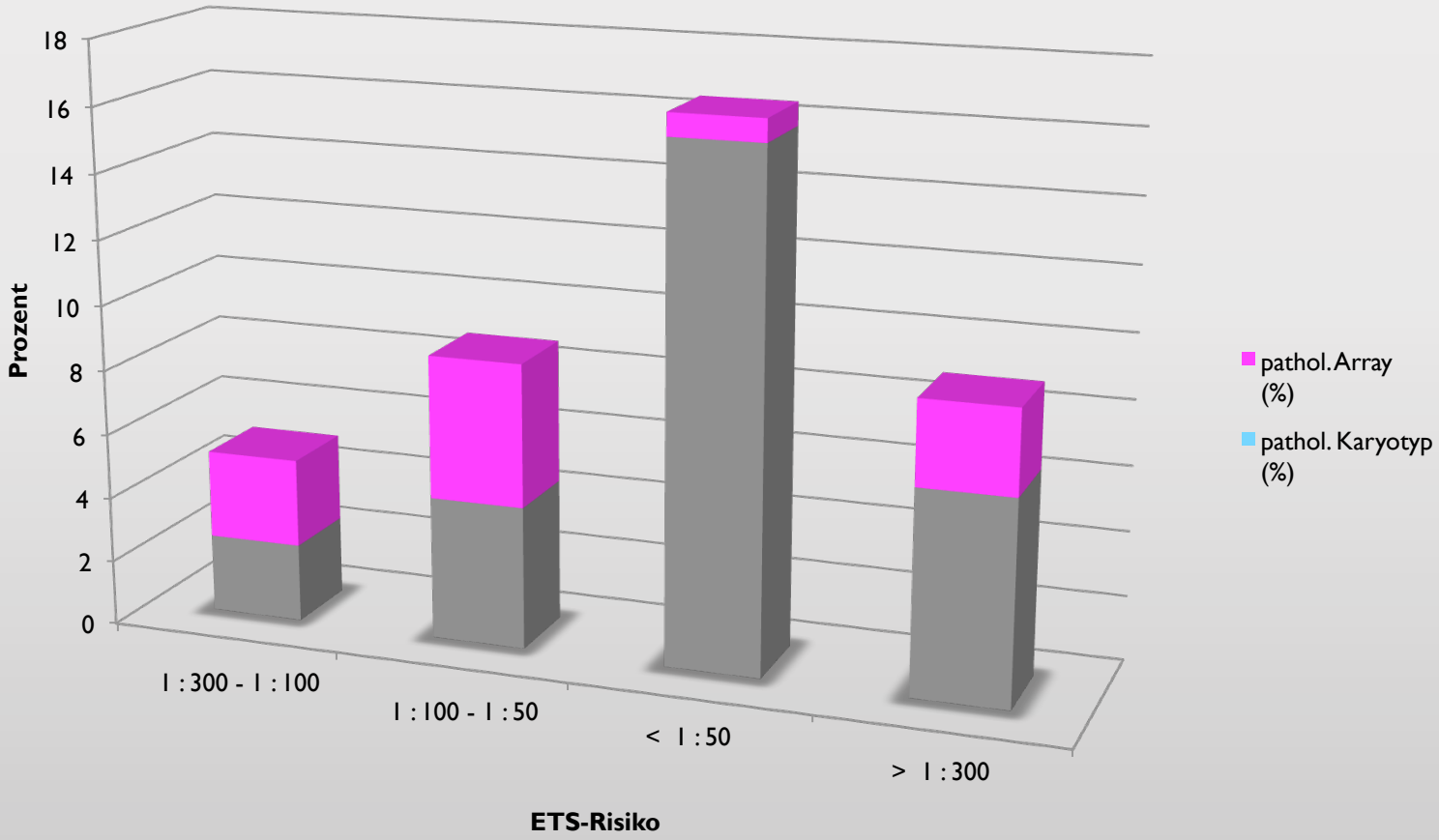
Kozlowski et al 2017 (under review)

ETS-Risiko und genetische Anomalien



Daten nach Vogel 2017

„Neues“ Ersttrimester-Screening

Trisomie 21-Risiko kann durch cfDNA abgedeckt werden

Neuorientierung des ETS:

- „Nicht cfDNA-erfassbare“ Chromosomenanomalien (30-50%)
- Neuralrohrdefekte
- ZNS-Fehlbildungen
- Spaltbildungen
- Ventrale Spalten
- LUTO
- Schwere Herzfehler
- Screening auf maternofetale Erkrankungen

Diagnostische Punktionen

	Punktion	Kontrolle	Datenpool
Amniozentese	0,81	0,67	0,11
CVS	2,18	1,79	0,22

21 Studien von1.506 Akolekar 2015 UOG
42.716 Amniozentesen
8.89 9 Chorionzottenbiopsien
Indikationen zur Punktionsdiagnostik sind u.U. auch Ursache einer erhöhten Fehlgeburtsgefährdung
Verlustrate muss individualisiert beurteilt werden

Diagnostische Punktionen

Ultrasound Obstet Gynecol 2016; **47**: 38–44
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.15820

Risk of fetal loss associated with invasive testing following combined first-trimester screening for Down syndrome: a national cohort of 147 987 singleton pregnancies

C. B. WULFF*†, T. A. GERDS‡, L. RODE*§, C. K. EKELUND*, O. B. PETERSEN¶, A. TABOR*† and the Danish Fetal Medicine Study Group

**Center of Fetal Medicine, Department of Obstetrics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; †Faculty of Medicine and Health Sciences, University of Copenhagen, Copenhagen, Denmark; ‡Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; §Department of Clinical Biochemistry, Copenhagen University Hospital, Herlev and Gentofte Hospital, Copenhagen, Denmark; ¶Fetal Medicine Unit, Department of Obstetrics and Gynecology, Aarhus University Hospital, Skejby, Denmark*

KEYWORDS: amniocentesis; chorionic villus sampling; combined first-trimester screening; fetal loss; invasive prenatal testing; miscarriage; procedure-related risk; stillbirth

Conclusion *Neither CVS nor AC was associated with increased risk of miscarriage or stillbirth. These findings indicate that the procedure-related risk of CVS and AC is very low.*

Diagnostische Punktionen

Verlustrisiko korreliert mit

- Alter
- BMI
- hohem ß-HCG
- niedrigem PAPP-A
- Blutung
- Erfahrung der Punkteure

Risikofaktoren für PE

- Alter > 40
- BMI > 30 kg/m^2
- IVF
- PE in Anamnese
- Chronische Hypertonie
- Diabetes
- Thrombophilie
- Autoimmunerkrankungen

Empfehlungen aufgrund maternaler Anamnese und Status:

ACOG

DR 90% FPR 64%

NICE

DR 41% FPR 10%

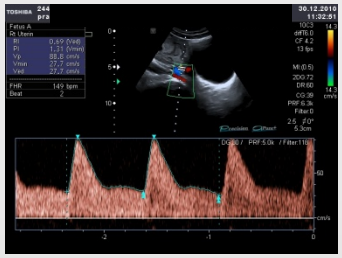
Ultrasound Obstet Gynecol 2007; **30**: 742–749
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.5157

Uterine artery Doppler at 11 + 0 to 13 + 6 weeks in the prediction of pre-eclampsia

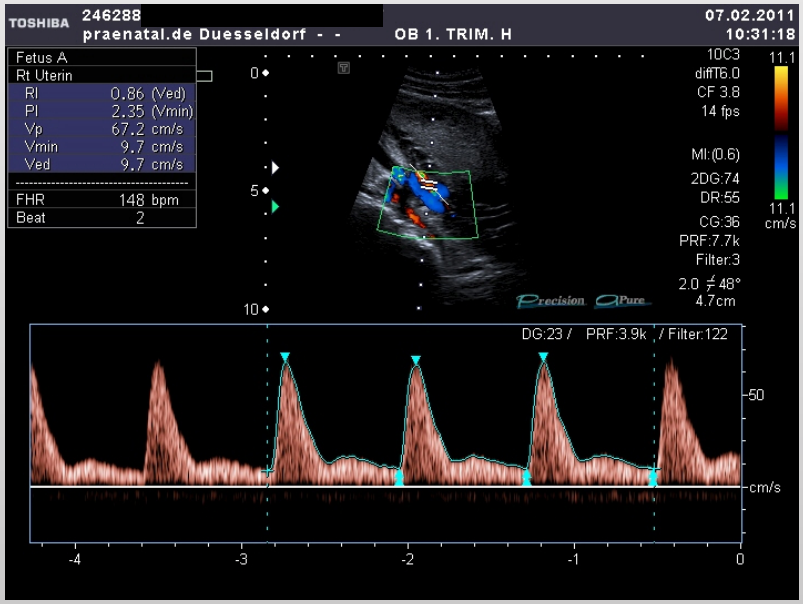
W. PLASENCIA, N. MAIZ, S. BONINO, C. KAIHURA and K. H. NICOLAIDES

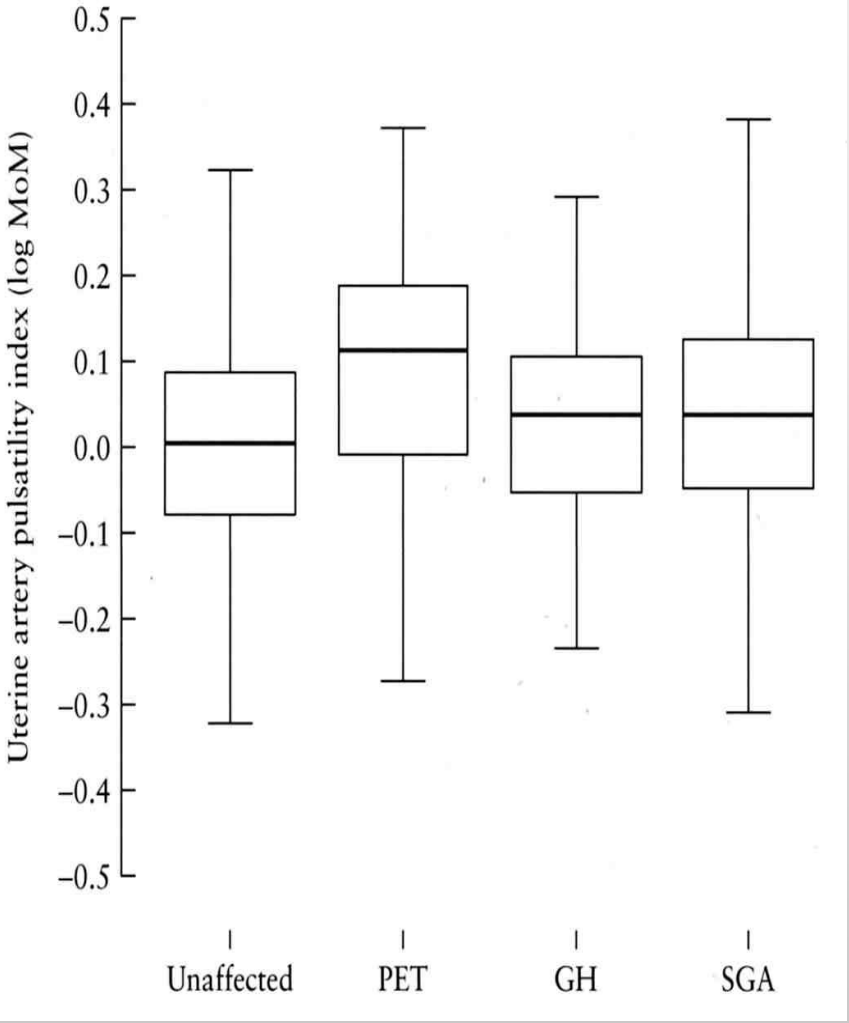
Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK

KEYWORDS: Doppler; first trimester; high-risk pregnancy prediction; pre-eclampsi



PI=(V_{max}-V_{min}) / V_{mean}





Ut A

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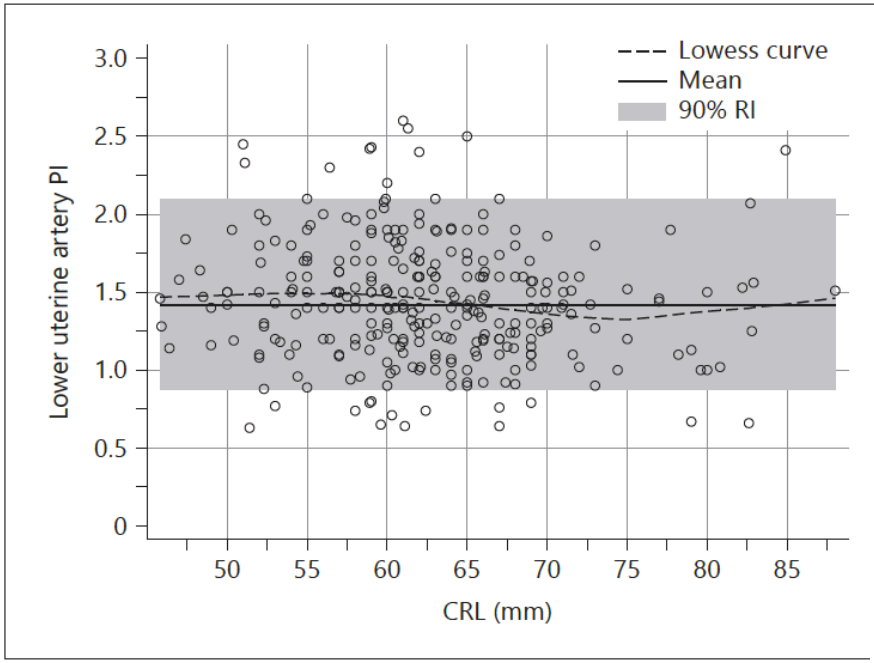


Original Paper

Fetal Diagnosis and Therapy

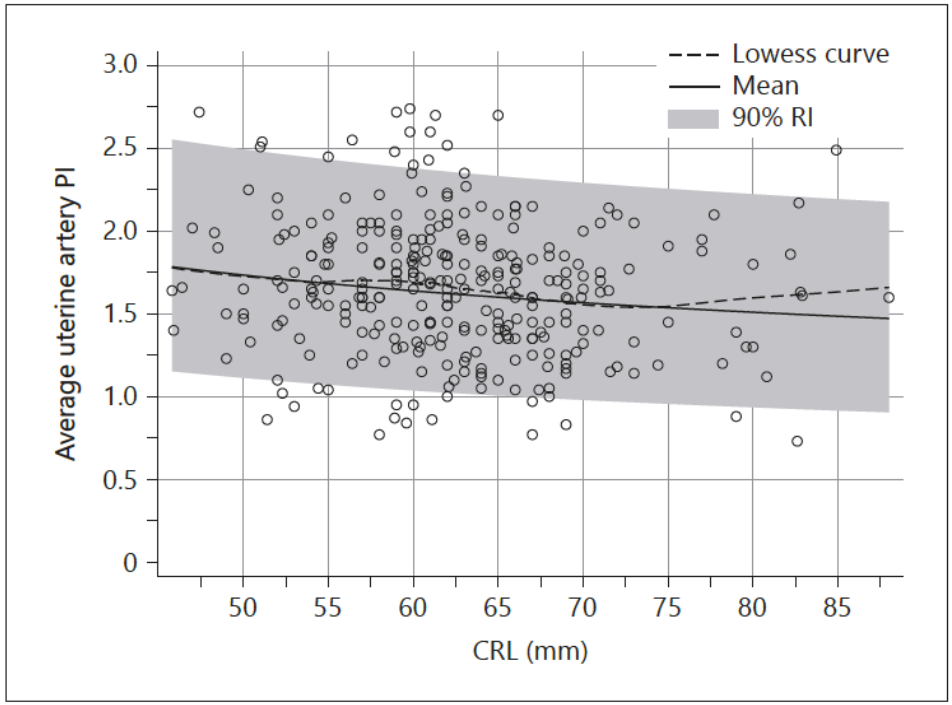
Fetal Diagn Ther 2014;36:299–304
DOI: 10.1159/000361021

Received: December 30, 2013
Accepted after revision: February 28, 2014
Published online: August 1, 2014

Uterine Artery Pulsatility Index Assessment at 11–13+6 Weeks' Gestation

Gus Ridding[a, b] Philip J. Schluter[f, g] Jon A. Hyett[c, d] Andrew C. McLennan[a, c, e]

[a]Maternal Fetal Medicine Unit, Royal North Shore Hospital, [b]Northern Clinical School and [c]Faculty of Medicine, University of Sydney, [d]Maternal Fetal Medicine Unit, Royal Prince Alfred Hospital, [e]Sydney Ultrasound for Women, Sydney, N.S.W., and [f]School of Nursing and Midwifery, The University of Queensland, Brisbane, Qld., Australia; [g]School of Health Sciences, University of Canterbury, Christchurch, New Zealand



Ridding 2014 Fetal Diagn Ther

GebFra Science | Original Article

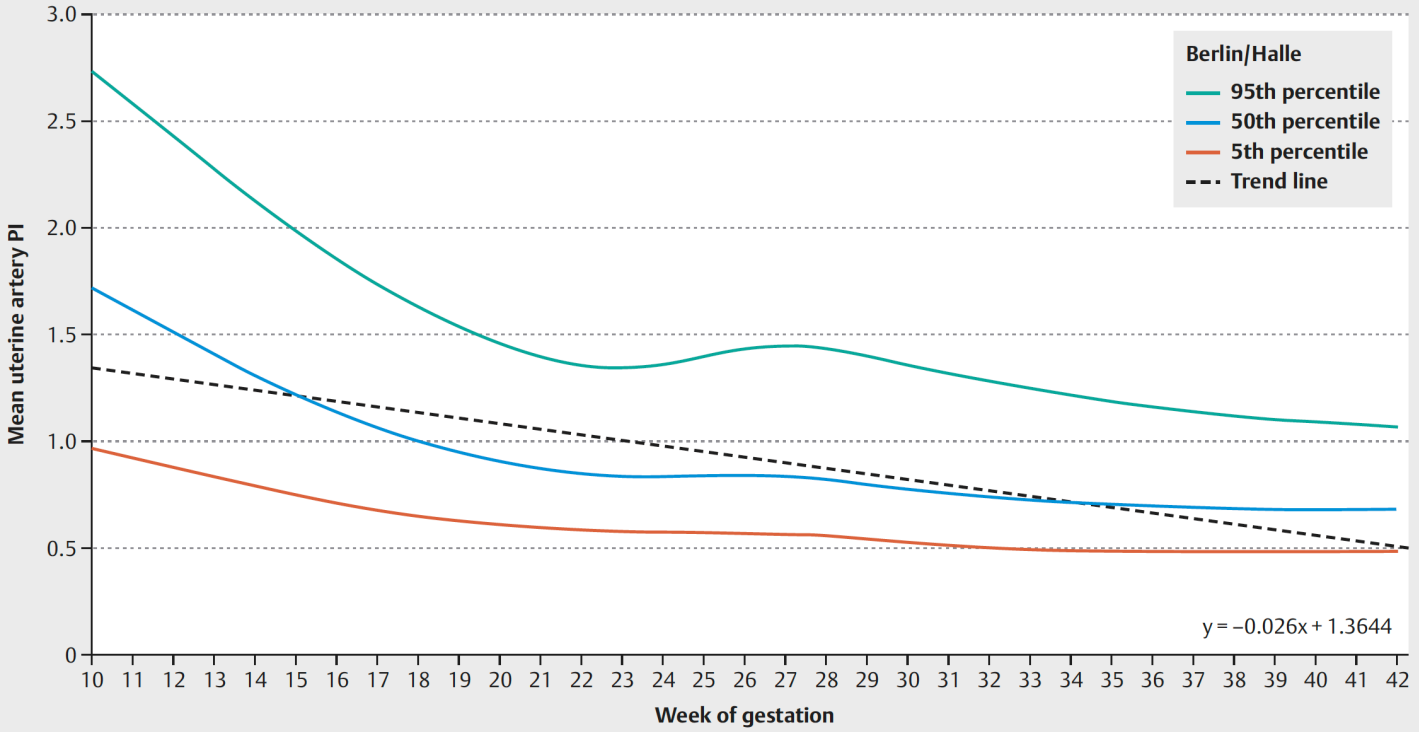
Thieme

Reference Curve for the Mean Uterine Artery Pulsatility Index in Singleton Pregnancies

Referenzkurve des mittleren Pulsatilitätsindex der Arteria uterina in Einlingsschwangerschaften

Authors
Alexander Weichert[1], Andreas Hagen[2], Michael Tchirikov[3], Ilka B. Fuchs[2], Wolfgang Henrich[1], Michael Entezami[2]

ders of trophoblast invasion. Increased resistance in the UA is associated with an increased risk of preeclampsia and/or intrauterine growth restriction (IUGR) and perinatal mortality. In the absence of standardized figures, the normal ranges of



▶ **Fig. 3** 5th, 50th and 95th percentiles of the mean pulsatility index of the uterine arteries (Mean PI, mean of the right and left uterine arteries) together with the formula for the linear trend which corresponds to a weekly decrease in the Mean PI of about 0.026.

▶ **Table 1** 5th, 50th and 95th percentiles according to the week of gestation (GW).

GW	5th percentile	50th percentile	95th percentile
10	0.96	1.71	2.72
11	0.92	1.60	2.57
12	0.88	1.50	2.41
13	0.83	1.40	2.26
14	0.79	1.30	2.11
15	0.74	1.21	1.97
16	0.71	1.13	1.84
17	0.67	1.06	1.72
18	0.64	0.99	1.62
19	0.62	0.94	1.53
20	0.60	0.90	1.45
21	0.59	0.87	1.39
22	0.58	0.85	1.35
23	0.57	0.83	1.34
24	0.57	0.83	1.36
25	0.57	0.84	1.40
26	0.57	0.84	1.43
27	0.56	0.83	1.44
28	0.55	0.82	1.43
29	0.54	0.79	1.40
30	0.52	0.77	1.35
31	0.51	0.75	1.31
32	0.50	0.74	1.28
33	0.49	0.72	1.25
34	0.49	0.71	1.21
35	0.48	0.70	1.18
36	0.48	0.69	1.16
37	0.48	0.69	1.14
38	0.48	0.68	1.12
39	0.48	0.68	1.10
40	0.48	0.68	1.09
41	0.48	0.68	1.08
42	0.49	0.68	1.06

Weichert 2017 GebFra

Ultrasound Obstet Gynecol 2017; **49**: 751–755
Published online 14 May 2017 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.17399

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

N. O'GORMAN[1], D. WRIGHT[2], L. C. POON[1,3#], D. L. ROLNIK[1], A. SYNGELAKI[1], A. WRIGHT[2], R. AKOLEKAR[1,4], S. CICERO[5], D. JANGA[6], J. JANI[7], F. S. MOLINA[8], C. DE PACO MATALLANA[9], N. PAPANTONIOU[10], N. PERSICO[11], W. PLASENCIA[12], M. SINGH[13] and K. H. NICOLAIDES[1#]

[1]*Harris Birthright Centre for Fetal Medicine, King's College Hospital, London, UK;* [2]*Institute of Health Research, University of Exeter, Exeter, UK;* [3]*Chinese University of Hong Kong, Hong Kong, China;* [4]*Medway Maritime Hospital, Gillingham, UK;* [5]*Homerton University Hospital, London, UK;* [6]*North Middlesex University Hospital, London, UK;* [7]*Centre Hospitalier Universitaire Brugmann, Université Libre de Bruxelles, Brussels, Belgium;* [8]*Hospital Universitario San Cecilio, Granada, Spain;* [9]*Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain;* [10]*Attikon University Hospital, Athens, Greece;* [11]*Ospedale Maggiore Policlinico, Milan, Italy;* [12]*Hospiten Group, Tenerife, Canary Islands, Spain;* [13]*Southend University Hospital, Essex, UK*

Table 2 Performance of screening for delivery with pre-eclampsia (PE) < 32, < 37 or ≥ 37 weeks' gestation in validation dataset of 8775 singleton pregnancies using previously developed algorithm based on maternal factors and combinations of biomarkers

	PE with delivery < 32 weeks (n = 17)			*PE with delivery < 37 weeks (n = 59)*			*PE with delivery ≥ 37 weeks (n = 180)*		
		DR (%) at:			*DR (%) at:*			*DR (%) at:*	
Screening method	*AUC*	*FPR = 5%*	*FPR = 10%*	*AUC*	*FPR = 5%*	*FPR = 10%*	*AUC*	*FPR = 5%*	*FPR = 10%*
Maternal factors	0.8045	41 (18–67)	53 (28–77)	0.7583	29 (18–42)	41 (28–54)	0.7449	18 (13–25)	37 (30–45)
Maternal factors plus:									
MAP	0.9071	59 (33–82)	71 (44–90)	0.8243	36 (24–49)	47 (34–61)	0.7789	26 (20–33)	37 (30–45)
UtA-PI	0.9309	71 (44–90)	82 (57–96)	0.8537	47 (34–61)	61 (47–73)	0.7539	22 (16–29)	39 (32–47)
PAPP-A	0.8546	47 (23–72)	59 (33–82)	0.7825	37 (25–51)	47 (34–61)	0.7504	21 (15–28)	37 (30–44)
PlGF	0.9506	65 (38–86)	88 (64–99)	0.8722	49 (36–63)	63 (49–75)	0.7578	20 (14–27)	39 (32–46)
MAP, UtA-PI	0.9667	82 (57–96)	94 (71–100)	0.8958	53 (39–66)	71 (58–82)	0.7875	27 (20–34)	41 (34–49)
MAP, PAPP-A	0.9133	65 (38–86)	76 (50–93)	0.8342	41 (28–54)	49 (36–63)	0.7827	28 (21–35)	40 (33–48)
MAP, PlGF	0.9674	76 (50–93)	88 (64–99)	0.8985	53 (39–66)	69 (56–81)	0.7870	29 (22–36)	43 (36–51)
UtA-PI, PAPP-A	0.9339	71 (44–90)	82 (57–96)	0.8583	49 (36–63)	66 (53–78)	0.7571	24 (18–31)	40 (33–48)
UtA-PI, PlGF	0.9772	82 (57–96)	100 (80–100)	0.9000	61 (47–73)	75 (62–85)	0.7619	22 (16–29)	39 (32–47)
PlGF, PAPP-A	0.9510	65 (38–86)	88 (64–99)	0.8741	51 (37–64)	66 (53–78)	0.7589	20 (14–27)	39 (32–47)
MAP, UtA-PI, PAPP-A	0.9644	88 (64–99)	94 (71–100)	0.8956	61 (47–73)	69 (56–81)	0.7892	29 (22–36)	42 (35–50)
MAP, PAPP-A, PlGF	0.9672	76 (50–93)	88 (64–99)	0.8998	54 (41–67)	69 (56–81)	0.7882	29 (22–36)	43 (36–51)
MAP, UtA-PI, PlGF	0.9870	94 (71–100)	100 (80–100)	0.9242	66 (53–78)	75 (62–85)	0.7916	32 (25–39)	43 (35–50)
UtA-PI, PAPP-A, PlGF	0.9769	82 (57–96)	100 (80–100)	0.9004	61 (47–73)	75 (62–85)	0.7626	23 (17–30)	38 (31–46)
MAP, UtA-PI, PAPP-A, PlGF	0.9865	94 (71–100)	100 (80–100)	0.9241	66 (53–78)	80 (67–89)	0.7923	31 (24–38)	43 (35–50)

O´Gorman 2017 UOG

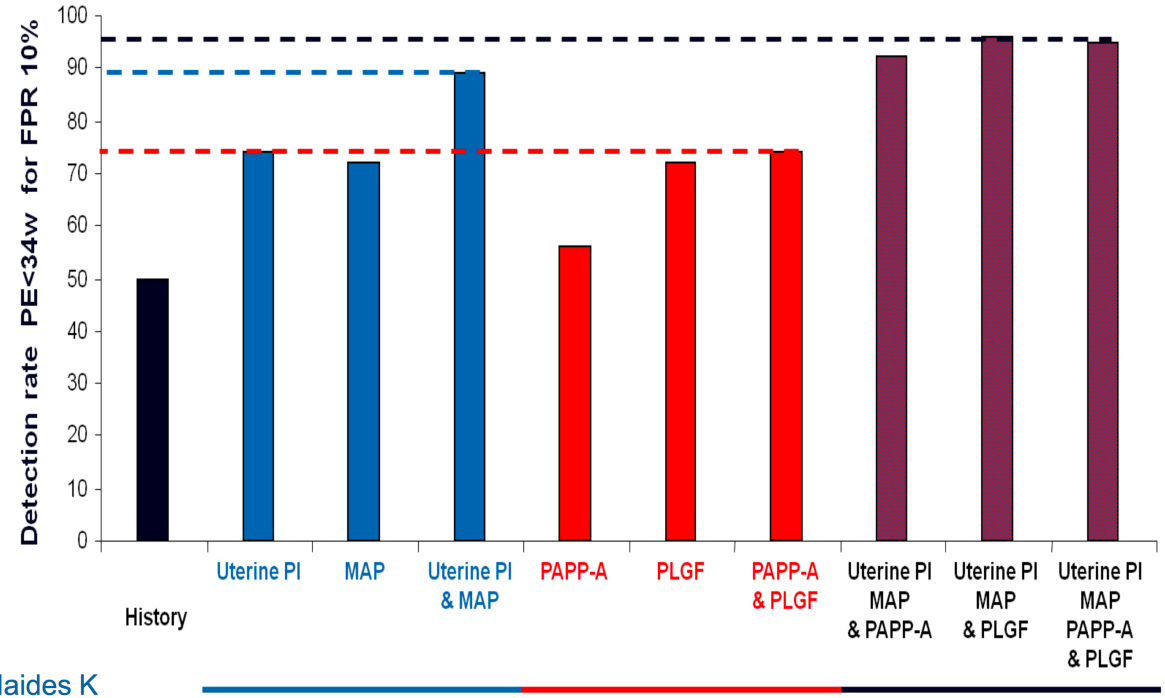
AWMF-Leitlinie

Diagnostik und Therapie hypertensiver Schwangerschaftserkrankungen

DGGG Leitlinienprogramm

AG GESTOSE

Screening – I. Trimenon



AWMF Nr.: 015/018

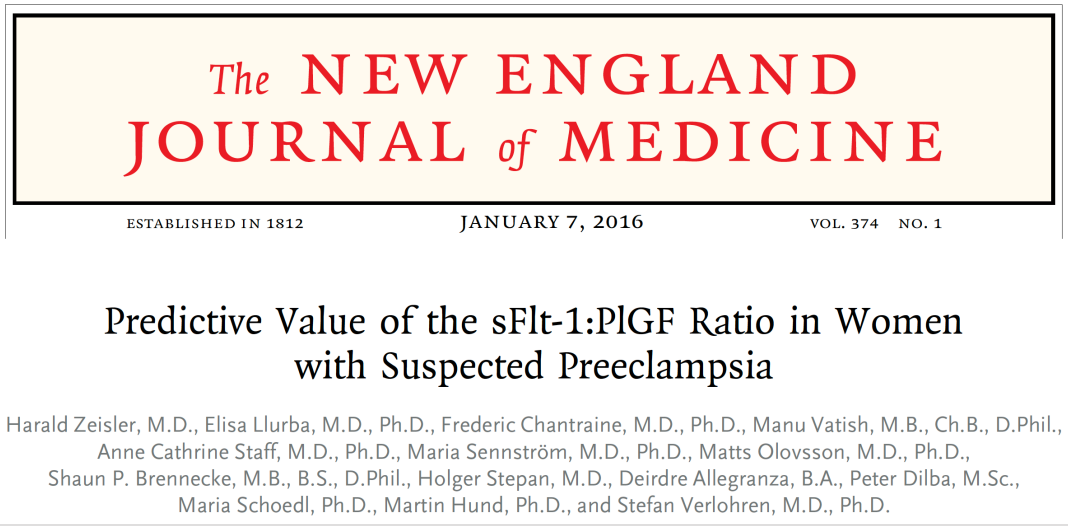
http://www.dggg.de/leitlinien

Detektionsrate PE < 32 SSW (5% FPR)

Matern. Faktor	MAP	Art. uterina			**82%**
Matern. Faktor	MAP	Art. uterina	PAPP-A		**88%**
Matern. Faktor	MAP	Art. uterina	Pl GF		**94%**
Matern. Faktor	MAP	Art. uterina	PAPP-A	Pl GF	**94%**

O´Gorman 2017 UOG

Prädiktion der PE: sFlt-1/PlGF ratio



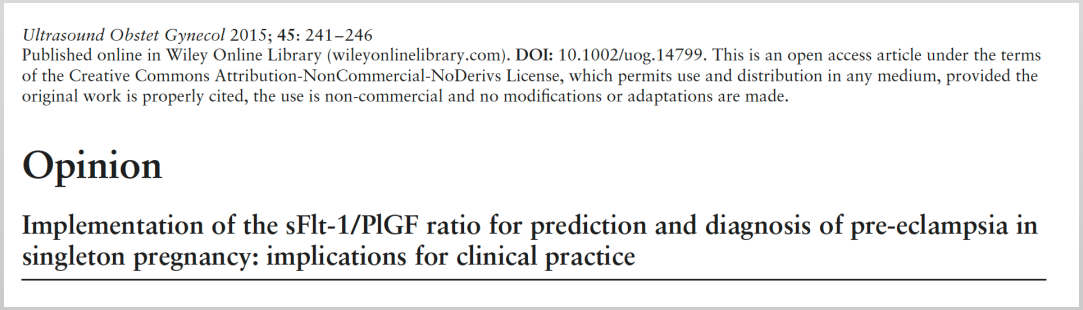
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 7, 2016 VOL. 374 NO. 1

Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia

Harald Zeisler, M.D., Elisa Llurba, M.D., Ph.D., Frederic Chantraine, M.D., Ph.D., Manu Vatish, M.B., Ch.B., D.Phil., Anne Cathrine Staff, M.D., Ph.D., Maria Sennström, M.D., Ph.D., Matts Olovsson, M.D., Ph.D., Shaun P. Brennecke, M.B., B.S., D.Phil., Holger Stepan, M.D., Deirdre Allegranza, B.A., Peter Dilba, M.Sc., Maria Schoedl, Ph.D., Martin Hund, Ph.D., and Stefan Verlohren, M.D., Ph.D.

Zeisler 2016 NEJM



Ultrasound Obstet Gynecol 2015; **45**: 241–246
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.14799.

Opinion

Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice

Stepan 2015 UOG

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 17, 2017 VOL. 377 NO. 7

Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia

Daniel L. Rolnik, M.D., David Wright, Ph.D., Liona C. Poon, M.D., Neil O'Gorman, M.D., Argyro Syngelaki, Ph.D., Catalina de Paco Matallana, M.D., Ranjit Akolekar, M.D., Simona Cicero, M.D., Deepa Janga, M.D., Mandeep Singh, M.D., Francisca S. Molina, M.D., Nicola Persico, M.D., Jacques C. Jani, M.D., Walter Plasencia, M.D., George Papaioannou, M.D., Kinneret Tenenbaum-Gavish, M.D., Hamutal Meiri, Ph.D., Sveinbjorn Gizurarson, Ph.D., Kate Maclagan, Ph.D., and Kypros H. Nicolaides, M.D.

Table 2. Outcomes According to Trial Group.

Outcome	Aspirin Group (N=798)	Placebo Group (N=822)	Odds Ratio (95% or 99% CI)*
Primary outcome: preterm preeclampsia at <37 wk of gestation — no. (%)	13 (1.6)	35 (4.3)	0.38 (0.20–0.74)
Secondary outcomes according to gestational age			
Adverse outcomes at <34 wk of gestation			
Any — no. (%)	32 (4.0)	53 (6.4)	0.62 (0.34–1.14)
Preeclampsia — no. (%)	3 (0.4)	15 (1.8)	0.18 (0.03–1.03)
Gestational hypertension — no. (%)	2 (0.3)	2 (0.2)	1.02 (0.08–13.49)
Small-for-gestational-age status without preeclampsia — no./total no. (%)†	7/785 (0.9)	14/807 (1.7)	0.53 (0.16–1.77)
Miscarriage or stillbirth without preeclampsia — no. (%)	14 (1.8)	19 (2.3)	0.78 (0.31–1.95)
Abruption without preeclampsia — no. (%)	1 (0.1)	3 (0.4)	0.36 (0.02–7.14)
Spontaneous delivery without preeclampsia — no. (%)	12 (1.5)	12 (1.5)	1.07 (0.37–3.10)

Wem nützt ASS (nicht)?

Am J Obstet Gynecol. 2017 Aug 4. pii: S0002-9378(17)30929-8. doi: 10.1016/j.ajog.2017.07.038. [Epub ahead of print]

ASPRE trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history.

Poon LC[1], Wright D[2], Rolnik DL[3], Syngelaki A[4], Delgado JL[3], Tsokaki T[5], Leipold G[6], Akolekar R[7], Shearing S[8], De Stefani L[9], Jani JC[10], Plasencia W[11], Evangelinakis N[12], Gonzalez-Vanegas O[13], Persico N[14], Nicolaides KH[15].

Author information

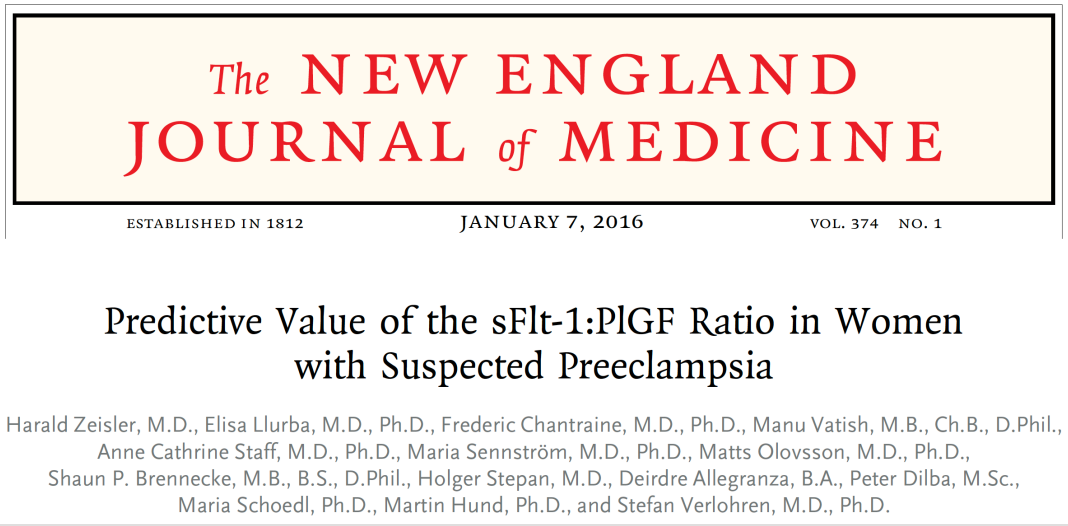
Abstract

OBJECTIVE: We sought to examine whether there are differences in the effect of aspirin on the incidence of preterm preeclampsia in the ASPRE trial in subgroups defined according to maternal characteristics and medical and obstetrical history.

STUDY DESIGN: This was a secondary analysis of data from the ASPRE trial. In ASPRE, women with singleton pregnancies were screened by means of an algorithm that combines maternal factors and biomarkers at 11-13 weeks' gestation. Those with an estimated risk for preterm preeclampsia of >1 in 100 were invited to participate in a double-blind trial of aspirin (150 mg/d) vs placebo from 11-14 weeks' until 36 weeks' gestation. Aspirin was associated with a significant reduction in the incidence of preterm preeclampsia with delivery at <37 weeks' gestation, which was the primary outcome (odds ratio, 0.38; 95% confidence interval, 0.20-0.74; P = .004).

CONCLUSION: The beneficial effect of aspirin in the prevention of preterm preeclampsia may not apply in pregnancies with chronic hypertension. There was no evidence of heterogeneity in the aspirin effect in subgroups defined according to maternal characteristics and obstetrical history.

Prädiktion der PE: sFlt-1/PlGF ratio



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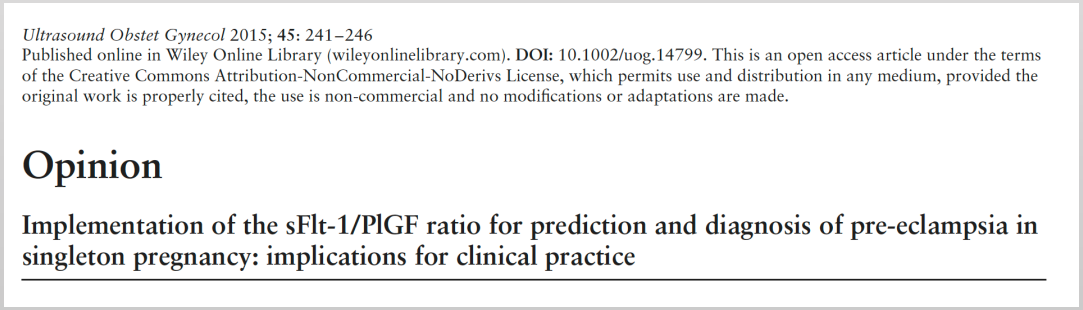
Zeisler 2016 NEJM



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Stepan 2015 UOG

AWMF-Leitlinie

Diagnostik und Therapie hypertensiver Schwangerschaftserkrankungen

DGGG Leitlinienprogramm

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Screening – II. Trimenon

Dopplersonographie Aa. uterinae

- mittlerer PI – alleine oder in Kombination mit einem notching – bester Marker für die Prädiktion einer Präeklampsie (Sensitivität bis zu 93%)
- im low-risk-Kollektiv beträgt die Erkennungsrate eines PI > 1,6 (95. Perz.) für eine early-onset-Präeklampsie bei einer 5% FPR 78% und für Präeklampsie insgesamt 42,8%. Erkennungsraten für späte Präeklampsien sind deutlich niedriger
- klinische Relevanz haben hohe Spezifität und der negative Vorhersagewert von bis zu 99%

Angiogenese-/Antiangiogenesefaktoren

- bei pathol. uterinem Doppler im II. Trimenon kann eine weitere Risikoevaluation und prognostische Abschätzung für die Entwicklung einer Präeklampsie durch die Bestimmung des sFlt-1/PlGF-Quotienten erfolgen

Prädiktion der PE und sFlt-1/PlGF ratio

sFlt-1/PlGF <38
keine PE innerhalb von

- einer Woche (99,3%)
- vier Wochen (94,3%)

sFlt-1/PlGF 38-85 (early onset) 38-110 (late onset)
hohe Wahrscheinlichkeit PE zu entwickeln
Kontrolle in einer Woche (PPV 66% für vier Wochen)

sFlt-1/PlGF >38 (early onset) 38-110 (late onset)
bestehende PE/IUGR (Spezifität 99%)

AWMF-Leitlinie

Diagnostik und Therapie hypertensiver Schwangerschaftserkrankungen

DGGG Leitlinienprogramm

AGSG AG GESTOSE

Vorstellung in der Klinik

- $RR_{systol.}$ ≥ 150 mm Hg bzw. $RR_{diastol.}$ ≥ 100 mm Hg (auch ohne Proteinurie)
- manifeste Präeklampsie
- Hypertonie/Proteinurie und starke Gewichtszunahme im III. Trim. (≥ 1kg/Woche)
- drohende Eklampsie (Prodromalsymptome!)
- klin. V.a. HELLP-Syndrom (v.a. persistierende Oberbauchschmerzen)
- Hinweis für fetale Bedrohung (CTG / Doppler, IUGR)
- milde Hypertonie oder Proteinurie und Risikofaktoren
  - vorbestehende mat. Erkrankung
  - Mehrlingsgravidität
  - frühes Gestationsalter (< 34 SSW)
  - An-/Oligohydramnion
  - pathol. sFlt-1/PlGF - Quotient

fetalmedicine.org - Kalkulator

Risk assessment

Preeclampsia risk

Date: 17-11-2017
Gestational age: 13^{+1} weeks (Measu

Preeclampsia risk from history only

< 32 weeks: 1 in 3333
< 37 weeks: 1 in 263
≥ 37 weeks: 2.3 %

Preeclampsia risk from history plus MAP, UTPI, PLGF, PAPP-A

< 32 weeks: 1 in 10000
< 37 weeks: 1 in 714
≥ 37 weeks: 2.2 %

Recommendation

On the basis of this assessment the patient has been classified as being at low risk for developing PE before 37 weeks. The risk needs to be reassessed at 20 weeks.

Maternal factors

Maternal characteristics

Date of birth: 1987-11-18
Height: 170 cm
Weight: 65 kg
Racial origin: White
Method of conception: Spontanec
Smoking during pregnancy: No
Family history of PE: No

Obstetric history

Nulliparous (no previous pregnancies at ≥24 weeks)

Biophysical measurements

Date of measurement	Weight	MAP	Mean UTPI
17-11-2017	65 kg	90 mmHg (1.05 MoM)	1.2 (0.76 MoM)

Biochemical measurements

Date of measurement	Weight	PLGF	PAPP-A
17-11-2017	65 kg	1 MoM	1 MoM

fetalmedicine.org - Kalkulator

Risk assessment

Preeclampsia risk

Date: 17-11-2017
Gestational age: 13^{+1} weeks (Measu

Maternal factors

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Family history of PE: No

Preeclampsia risk from history only

< 32 weeks: 1 in 3333
< 37 weeks: 1 in 263
≥ 37 weeks: 2.3 %

Preeclampsia risk from history plus MAP, UTPI, PLGF, PAPP-A

< 32 weeks: 1 %
< 37 weeks: 6.8 %
≥ 37 weeks: 13 %

Recommendation

On the basis of this assessment the patient has been classified as being at increased risk for developing PE before 37 weeks. The ASPRE trial has shown that in such women use of low dose aspirin (150mg/night) from now until 36 weeks reduces the incidence of PE before 34 weeks by >80% and PE before 37 weeks by >60%. For more information click here.

Biophysical measurements

Date of measurement	Weight	MAP	Mean UTPI
17-11-2017	65 kg	110 mmHg (1.28 MoM)	1.9 (1.21 MoM)

Biochemical measurements

Date of measurement	Weight	PLGF	PAPP-A
17-11-2017	65 kg	0.5 MoM	0.5 MoM

ASPRE Trial: Compliance

Eingenommene Menge 150 mg ASS / Placebo	Anteil der Schwangeren
< 50%	5 %
50-84,9 %	15 %
≥ 85%	80 %