Partikel und Philosophie:
Die Physiker werden selbst zum Forschungsgegenstand **S. 33**

„Die Zeit“
18.8.2011

Früher erkennen

Ein neuer Test weist Krankheiten bei ungeborenen Kindern nach – gefahrlos und schon in der 10. Woche. Diese Möglichkeit wird eine neue Debatte erzwingen VON ULRICH BAHNSEN

Trisomie 21 ist eine schwere Behinderung. Bei Nachweis während der Schwangerschaft entscheiden sich 90 Prozent der Frauen für eine Abtreibung

Sequenom: Patent auf cffDNA

Praenatal plus

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DIAGNOSTICS

Fetal Nucleic Acid Technology

- Fetal Nucleic Acid Technology
- Clinical Studies

Diagnostics > Fetal Nucleic Acid Technology

Fetal Nucleic Acid Technology

SEQureDx™, a Sequenom Technology is a revolutionary approach to genetic screening. Rather than harvesting placental tissue cells (as is required for chorionic villus sampling), or entering the uterus to sample the amniotic fluid surrounding the baby (as is done with amniocentesis), SEQureDx Technology extracts DNA material safely and comfortably from the blood of the mother.

The process is simple: once the mother's blood is extracted in a common blood draw, SEQureDx Technology utilizes circulating fetal nucleic acids in maternal blood to examine the genetic status of the fetus. This breakthrough suggests that effective screening may be accomplished in the future without the risks associated with disturbing the amniotic fluid that surrounds the baby in the uterus.

While a number of genetic defects have the potential to be detected using the Sequenom's SEQureDx Technology, the first application is the analysis of fetal RhD. RhD disease can occur when the blood of an expectant mother is incompatible with her unborn child. RhD incompatibility affects approximately one in one thousand live born infants and can lead to jaundice, anemia, brain damage, heart failure and death.

For more information please email us at SEQureDx@sequenom.com.

Internet | Geschützter Modus: Aktiv

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Dennis Lo, M.D.

Dennis Lo received his BA from the U
degrees from the University of Oxford.
DNA in maternal plasma in 1997. Sin
diagnostic applications of this phenor
applications of this technology for the
monogenic diseases and fetal chromo
in his capacity as a consultant to Se

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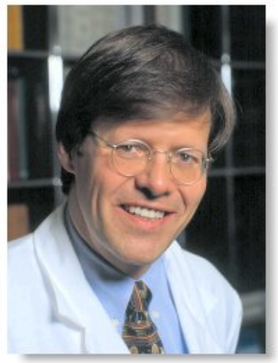
Wolfgang Holzgreve, MD



Dr. Holzgreve graduated from tl
University, Münster, Germany
of Science in Health and Medic
Berkeley. From 1976 to 1978,
Germany, and finished his resi
of Obstetrics and Gynecology,
and 1984, he completed a Fell
Reproductive Genetics, at the
Reproductive Sciences at the U
Holzgreve was Board Certified
Gynecology in 1985.

By 1991, he had risen to the ra
Geschäftsf. Oberarzt, Departm
Münster. In August 1995, he m
appointment as Chairman of th
Department of Obstetrics and Gynecology, University of Basel, from w
Freiburg in 2009.

Köln, 21.06.2017

Praenatal plus

NIPT - how we do it !

Statements der ISUOG und der DEGUM

Rüdiger Stressig

Praenatal plus
DKHZ Sankt Augustin
Stadt. Kliniken Köln

PRENATAL DIAGNOSIS
Prenat Diagn 2011; **31**: 3–6.
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI:** 10.1002/pd.2685

Prenat Diagn
2011

EDITORIAL

A model for a new pyramid of prenatal care based on the 11 to 13 weeks' assessment

Kypros H. Nicolaides[1,2]*

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[2]*Department of Fetal Medicine, University College Hospital, London, UK*

One century ago it was recognized that with the methods and material at our disposal we were not making all the progress possible toward solving many problems of prenatal diagnosis and treatment (Ballantyne, 1901, 1921). In order to achieve these objectives it was urged that a new means of investigation should be undertaken which had not yet been tried, at least not yet attempted on a large scale and in a systematic fashion. This led to the introduction of prenatal care which constituted a major advance in the care of pregnant women and played a pivotal role in the substantial reduction in maternal and perinatal mortality achieved during the last century.

In 1929, the Ministry of Health in the UK issued a Memorandum on Antenatal Clinics recommending

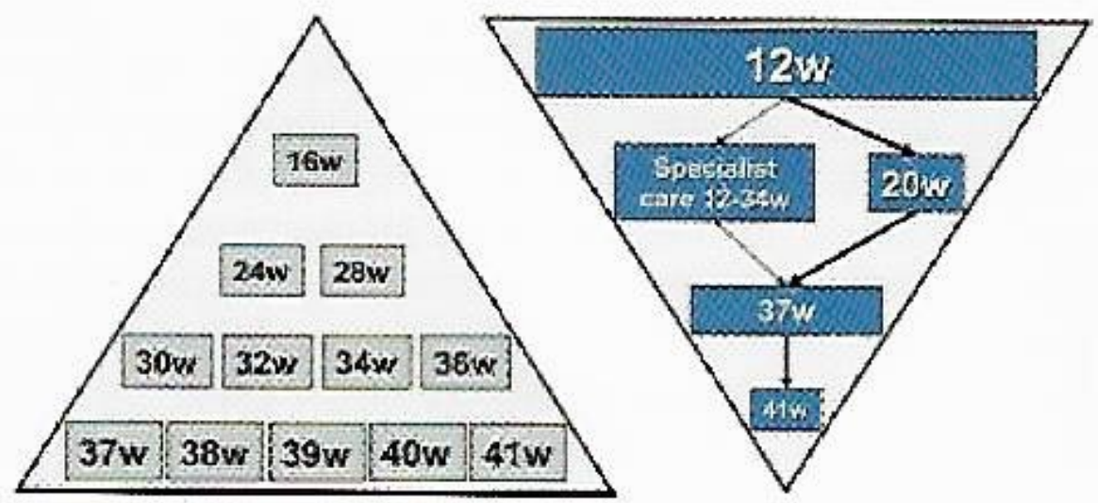

Figure 1—Pyramid of prenatal care: past (left) and future (right)

FETAL ANEUPLOIDIES

Ultrasound Obstet Gynecol 2013; **41**: 102–113
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.12342

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GUIDELINES

Praenatal plus

UOG 2013

ISUOG Practice Guidelines: performance of first-trimester fetal ultrasound scan

Clinical Standards Committee

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) is a scientific organization that encourages safe clinical practice and high-quality teaching and research related to diagnostic imaging in women's healthcare. The ISUOG Clinical Standards Committee (CSC) has a remit to develop Practice Guidelines and Consensus Statements that provide healthcare practitioners with a consensus-based approach for diagnostic imaging. They are intended to reflect what is considered by ISUOG to be the best practice at the time at which they are issued. Although ISUOG has made every effort to ensure that Guidelines are accurate when issued, neither the Society nor any of its employees or members accept any liability for the consequences of any inaccurate or misleading data, opinions or statements issued by the CSC. The ISUOG CSC documents are not intended to establish a legal standard of care because interpretation of the evidence that underpins the Guidelines may be influenced by individual circumstances, local protocol and available resources. Approved Guidelines can be distributed freely with the permission of ISUOG (info@isuog.org).

INTRODUCTION

Routine ultrasound examination is an established part of antenatal care if resources are available and access possible. It is commonly performed in the second trimester[1], although routine scanning is offered increasingly during the first trimester, particularly in high-resource settings. Ongoing technological advancements, including high-frequency transvaginal scanning, have allowed the resolution of ultrasound imaging in the first trimester to evolve to a level at which early fetal development can be assessed and monitored in detail.

The aim of this document is to provide guidance for healthcare practitioners performing, or planning to perform, routine or indicated first-trimester fetal ultrasound scans. 'First trimester' here refers to a stage of pregnancy starting from the time at which viability can be confirmed (i.e. presence of a gestational sac in the uterine cavity with an embryo demonstrating cardiac activity) up to 13 + 6 weeks of gestation. Ultrasound scans performed after this gestational age are not considered in these Guidelines. Throughout these Guidelines we use the term 'embryo' for before 10 weeks and 'fetus' thereafter, to reflect the fact that after 10 weeks of gestation organogenesis is essentially complete and further development involves predominantly fetal growth and organ maturation[2,3].

GENERAL CONSIDERATIONS

What is the purpose of a first-trimester fetal ultrasound scan?

In general, the main goal of a fetal ultrasound scan is to provide accurate information which will facilitate the delivery of optimized antenatal care with the best possible outcomes for mother and fetus. In early pregnancy, it is important to confirm viability, establish gestational age accurately, determine the number of fetuses and, in the presence of a multiple pregnancy, assess chorionicity and amnionicity. Towards the end of the first trimester, the scan also offers an opportunity to detect gross fetal abnormalities and, in health systems that offer first-trimester aneuploidy screening, measure the nuchal translucency thickness (NT). It is acknowledged, however, that many gross malformations may develop later in pregnancy or may not be detected even with appropriate equipment and in the most experienced of hands.

When should a first-trimester fetal ultrasound scan be performed?

There is no reason to offer routine ultrasound simply to confirm an ongoing early pregnancy in the absence of any clinical concerns, pathological symptoms or specific indications. It is advisable to offer the first ultrasound scan when gestational age is thought to be between 11 and 13 + 6 weeks' gestation, as this provides an opportunity to achieve the aims outlined above, i.e. confirm viability, establish gestational age accurately, determine the number of viable fetuses and, if requested, evaluate fetal gross anatomy and risk of aneuploidy[4–20]. Before starting the examination, a healthcare provider should counsel the woman/couple regarding the potential benefits and limitations of the first-trimester ultrasound scan. (**GOOD PRACTICE POINT**)

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CONSENSUS STATEMENT

ISUOG consensus statement on the impact of non-invasive prenatal testing (NIPT) on prenatal ultrasound practice

The emergence of effective cell-free fetal DNA-based techniques to screen for trisomy 21 and other aneuploidies has greatly expanded the range of prenatal tests available over the last few years. Non-invasive prenatal testing (NIPT) is rapidly being incorporated into prenatal care, thus changing the traditional approach to prenatal screening and diagnosis. However, although NIPT techniques are highly efficient, their role and performance must be considered alongside and combined with other screening modalities. The role of prenatal ultrasound in particular needs to be reassessed as NIPT becomes more widely available.

It is important to emphasize that the main goal of prenatal screening is to provide accurate information that will facilitate the delivery of optimized antenatal care, with the best possible outcome for both mother and fetus. Women should be informed about prenatal screening performance by appropriately trained health professionals, allowing them to make an informed decision. It is the parent's choice to undergo such procedures, and their wishes should be determined and respected.

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) has compiled the following Consensus Statement, which will be updated on a regular basis.

- All women should first be offered a first-trimester ultrasound scan according to ISUOG guidelines[1], regardless of their intention to undergo NIPT.
- Pre-test counseling is essential. Various options should be explained clearly to women, discussing the pros and cons of each, including the expected test performance and potential adverse effects.
- Following a normal early pregnancy scan, as defined by ISUOG guidelines[1], three options should be considered for women who wish to have a further risk assessment for trisomy 21 and, to a lesser extent, trisomies 13 and 18:

  (1) Screening strategies based on individual risk calculated from maternal age and nuchal translucency measurement and/or maternal serum markers and/or other ultrasound markers in the first trimester (defined by the conventional crown–rump length range of 45–84 mm).

  At the moment, ISUOG endorses this strategy. Following such screening, women can be offered a choice, according to their calculated individual risk, of having no further testing, undergoing NIPT, or undergoing invasive testing. Cut-offs should be defined on a local/national basis and will be affected by public health priorities and available resources.

  (2) Invasive testing based on background risk (including, for example, maternal age and history of aneuploidy), with no other individual risk calculation.

  (3) NIPT as a first-line screening test.

  Most current guidelines endorse NIPT only for high-risk populations for which adequate data exist. Using NIPT on intermediate- or low-risk patients might be endorsed as a widely available option only when new data emerge and NIPT costs decrease.

- NIPT is not a diagnostic test and confirmatory invasive testing is required in the presence of any abnormal results.
- NIPT has not been evaluated extensively in low-risk populations, in which its positive predictive value is lower than in high-risk populations.
- First-trimester risk estimates for trisomies 21, 18 and 13 based on nuchal translucency measurements and maternal biochemistry should not be computed in a woman who has already received a normal NIPT result for these trisomies.
- NIPT may be discussed as an alternative to invasive testing following an abnormal result on combined screening or offered to patients who are not sufficiently reassured by an 'intermediate risk' result.
- The role of NIPT as an alternative to standard invasive testing in women considered to be at very high risk (>1:10) after combined screening but with no ultrasound anomaly should be evaluated in prospective studies. Expert opinion currently suggests that NIPT should not replace invasive testing in this group. This is based on the fact that only 70% of chromosomal abnormalities in this population are trisomy 21, 18 or 13. Furthermore, emerging microarray techniques may provide additional, clinically relevant information in some cases.
- In the presence of a fetal structural anomaly, the indications for fetal karyotyping and/or microarray testing should not be modified by a normal NIPT result obtained previously.
- Accuracy of NIPT in twin pregnancies should be investigated further.
- Variations in NIPT performance by different providers should be investigated further.
- The so-called 'genetic sonogram', which includes looking for soft markers of trisomy 21, should not be performed in women with a normal NIPT result due to its high false-positive rate and poor positive predictive value.
- It is becoming technically feasible to test non-invasively, not only for trisomies but also for other genetic syndromes. Both healthcare providers and women should therefore be clearly aware of the tests being performed and of their performance, as having multiple tests may increase the false-positive rate.
- Prospective, publicly-funded studies assessing the cost-effectiveness of various screening strategies should be performed as a matter of urgency.

Writing group

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Reference

1. Salomon LJ, Alfirevic Z, Bilardo CM, Chalouhi GE, Ghi T, Kagan KO, Lau TK, Papageorghiou AT, Raine-Fenning NJ, Stirnemann J, Suresh S, Tabor A, Timor-Tritsch IE, Toi A, Yeo G. ISUOG practice guidelines: performance of first-trimester fetal ultrasound scan. *Ultrasound Obstet Gynecol* 2013; 41: 102–113.

UOG
2014

UOG 2014

Praenatal plus

ethisches Ziel aller pränatalen Diagnostik

akkurate frühe pränatale Informationen,
welche Geburt und postnatale Versorgung
verbessern und bestes Outcome für Mutter
und Kind ermöglichen
(„Search and heal“)

Problem: Trisomie 21 ist nicht zu heilen …

Praenatal plus

Vor Ultraschall und NIPT:

fachgebundene genetische Beratung (s.GenDG)
bestmöglicher früher Ultraschall !!
Nichts tun - ETS - NIPT - invasive Diagnostik
Recht auf „Nicht-wissen“

Genetische Beratung

NIPT ist keine Risikoberechnung, sondern eine
genetische Analyse (n. §3, Abs.1a GenDG)
Aufklärungsbroschüren der Ärztekammer
Fixieren individueller Beratungsinhalte
(auch über Alternativen zu NIPT)
fachgebundene genetische Beratung (VÄP)
Zeitbedarf: mindstens 15 Minuten

MERKE:
Prozesse werden *ausschließlich* über
insuffiziente Beratung und Dokumentation geführt
- und verloren !!

Praenatal plus

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F 0221 977 60-33

Deutsches Kinderherzzentrum
Arnold Janssen Straße 29
53757 Sankt Augustin
T 02241 249 651
F 02241 249 652

Informationen über den nicht-invasiven molekulargenetischen Praenatal-Test (NIPT)

Nicht invasive molekulargenetische Praenatal-Tests werden von verschiedenen Firmen und Laboren angeboten. Die folgenden Angaben gelten für alle zur Zeit verfügbaren Tests.

Was kann der Test erkennen und was nicht?

Dieser Test untersucht ausschließlich die Trisomien 21 (Down-Syndrom), 13 (Pätau-Syndrom) und 18 (Edwards-Syndrom) und das Geschlecht des Feten. strukturelle Veränderungen oder zahlenmäßige Abweichungen von anderen Chromosomen werden nicht erfasst.

Das bedeutet, dass nur etwa 70 % der Erbträgerveränderungen, die durch eine Fruchtwasserentnahme oder eine Plazentapunktion erkannt werden können, durch den neuen Test erfasst werden.

Der Test kann bei ehemaligen Zwillingsanlagen (vanishing twin) nicht durchgeführt werden.

Ab welchem Zeitraum ist der Test möglich?

Der Test kann ab der 10. Schwangerschaftswoche durchgeführt werden. Wir empfehlen den Test erst ab der 12. Schwangerschaftswoche, da der Test nur bei unauffälligen Ultraschallbefunden erfolgen sollte. Vor der 12. Schwangerschaftswoche ist die notwendige Ultraschalldiagnostik nicht aussagekräftig genug.

Der Test dauert meist zwischen 3 und 7 Tagen. Bei einem auffälligen Befund des Tests muss eine Amniozentese zur Absicherung angeschlossen werden. Auch diese Untersuchung dauert etwa 2 Wochen. Damit der endgültige Befund nicht zu einem sehr späten Zeitpunkt in der Schwangerschaft vorliegt, werden die Tests von uns bevorzugt zwischen der 12. und 16. Woche angeboten.

Wie sicher ist der NIPT?

Es ist schon länger bekannt, dass im Blut von Schwangeren DNA-Fragmente (Bruchstücke der Erbsubstanz) sind, die aus abgeschilferten Zellen des Trophoblasten (Plazenta, Mutterkuchen) stammen. In den meisten Fällen sind Plazenta und Kind genetisch identisch. Es ist jedoch bekannt, dass es in etwa 1 % der Fälle Chromosomenveränderungen gibt, die nur in der Plazenta oder nur im Feten vorliegen. Diese diskrepanten Fälle würden vom NIPT als falsch-positiv oder falsch-negativ nicht entdeckt.

Der erste Test dieser Art wurde im August 2012 in Deutschland eingeführt. Dementsprechend sind die Fallzahlen im Vergleich zur klassischen Praenatal-Diagnostik gering. Die untersuchenden Labore geben eine Entdeckungsrate für die Trisomien von 98-99 % an, bei einer falsch positiv Rate von 0,2 %. Dies bedeutet, dass in 2 von 1.000 auffälligen Befunden die beschriebene Auffälligkeit nicht beim Kind vorliegt.

Kann der Bluttest das Ersttrimester-Screening ersetzen?

Der neue Bluttest kann das Ersttrimester-Screening (ETS) in der 12. bis 14. Schwangerschaftswoche nicht ersetzen. Eine genaue Ultraschalluntersuchung kann den meisten werdenden Eltern frühzeitig zeigen, dass die Entwicklung ihres Kindes gut und zeitgerecht verläuft. Die Ultraschalluntersuchung kann bei gesundheitlichen Problemen oder Entwicklungsstörungen des Feten sehr oft schon frühzeitige Hinweise geben, z. B. auf einen Herzfehler, eine Skelettdysplasie oder eine Zwerchfellhernie.

Darüber hinaus kann auch überprüft werden, ob ein höheres Risiko für mütterlichen Bluthochdruck und Einschränkungen der Plazentafunktion (Praeeklampsie) oder ein erhöhtes Frühgeburtsrisiko bestehen.

Für wen kann der Bluttest nützlich sein?

In einigen Schwangerschaften ist der Fet im Ultraschall normal entwickelt, die beim Ersttrimesterscreening bestimmten mütterlichen Blutwerte (ein Schwangerschaftshormon und ein Protein) weisen jedoch auf ein höheres Risiko für das Vorliegen einer Trisomie 21 oder Trisomie 13/18 hin. Der Test kann diesen Schwangeren nützen, wenn sie eine der o. g. Trisomien ihres Kindes weitgehend ausschließen möchten, ohne das Fehlgeburtsrisiko einer Fruchtwasserentnahme oder Plazentabiopsie eingehen zu wollen.

Ist der Bluttest bei Auffälligkeiten im Ultraschall sinnvoll?

Auffälligkeiten des Feten im Ultraschallbild, wie z. B. eine verbreiterte Nackentransparenz, können eine Vielzahl möglicher Ursachen genetischer und auch nicht genetisch bedingter Ursachen haben. Für eine umfassende Abklärung ist der Bluttest daher nicht geeignet.

Wer trägt die Kosten des Tests ?

Mittlerweile werden die Kosten für einen Nicht-invasiven pränatalen Test von vielen Krankenkassen zum Teil oder auch ganz übernommen. Da wir hierauf keinen Einfluss haben, bitten wir Sie, dies mit Ihrer Krankenkasse zu klären.

Wer ist für die Mitteilung des Befundes ärztlich verantwortlich?

Für die Aufklärung über die Aussagekraft, Sicherheit und Grenzen des Tests sind ausschließlich die betreuenden und einsendenden Ärztinnen und Ärzte verantwortlich.

Wie bietet Praenatalplus den Bluttest an?

Im Fokus unserer Arbeit stehen die Begleitung und Betreuung des ungeborenen Kindes und der Mutter. Vor jeder Untersuchung steht daher die Beratung über die Möglichkeiten und Grenzen einer vorgeburtlichen Diagnostik. Unser Ziel ist es, mit jeder Schwangeren und jedem Elternpaar den für sie jeweils individuell passenden Umfang der Diagnostik zu erarbeiten.

In der Beratung weisen wir auch darauf hin, dass der Bluttest derzeit nur 3 der zahlreichen Veränderungen der Chromosomen erfasst – und auch diese nicht mit 100-prozentiger Sicherheit erkennen oder ausschließen kann.

Neben der Beratung ist die genaue Untersuchung des ungeborenen Kindes der zweite zentrale Bestandteil der pränatalen Diagnostik.

Der Bluttest wird daher von uns, wie alle anderen vorgeburtlichen genetischen Untersuchungen auch, nur im Zusammenhang mit einer individuellen genetischen Beratung und einer genauen Ultraschalldiagnostik des Feten veranlasst.

Die Informationen über den NIPT habe ich gelesen, verstanden und eine Kopie davon erhalten.

_____ _____

Ort, Datum Ihre Unterschrift

Patientin: Verantwortliche ärztliche Person: _____

Einverständniserklärung: pränatales nicht-invasives genetisches Screening

Ich wünsche, dass die nachfolgende Untersuchung durchgeführt wird:

- ☐ Ersttrimesterscreening (einschl. pränatale Risikoberechnung Trisomie 21, 18, 13)
- ☐ Ultraschall-Organdiagnostik (ggf. Markerscreening)
- ☐ Untersuchung: _____

Ich wurde in dem pränatalmedizinischen Aufklärungsgespräch ausführlich über die geplanten Untersuchungen von o.g. Arzt / Ärztin informiert. Alle nach meiner Ansicht wichtigen Fragen über die Art und die Bedeutung der Untersuchung wurden besprochen und mir verständlich beantwortet. Ich fühle mich gut informiert, habe keine weiteren Fragen mehr und willige in die Untersuchung ein. Ich benötige keine weitere Bedenkzeit.

Ich stimme der Übermittlung der Ergebnisse der Untersuchung zu, an meine(n)

Frauenärztin/arzt: _____

Weitere Ärzte _____

Persönliche Fragen _____

_____

Ärztliche Anmerkungen _____

_____

Ich bin einverstanden, dass Daten zum Schwangerschaftsausgang bei mitbehandelnden Kollegen / Kolleginnen für die Qualitätssicherung erfragt werden dürfen. ☐ ja ☐ nein

Ich bin einverstanden, dass erhobene Daten/Ergebnisse für Fortbildungen und wissenschaftliche Veröffentlichungen anonymisiert genutzt werden können. ☐ ja ☐ nein

Ich bin einverstanden, dass die Untersuchungsergebnisse über die vorgeschriebene Frist von 10 Jahren hinaus aufbewahrt werden. ☐ ja ☐ nein

Widerruf: Ich kann sämtliche oder Teile meiner Einwilligung jederzeit mit Wirkung für die Zukunft widerrufen. Ich habe das Recht, das Ergebnis der Untersuchung oder Teile davon nicht zur Kenntnis zu nehmen und vernichten zu lassen.

_____

Ort / Datum Unterschrift der Schwangeren

_____

Ort / Datum Unterschrift der Ärztin / des Arztes

Praenatal plus

Früher Ultraschall

Praenatal plus

These:
je besser der US, umso seltener müssen pränatale Tests durchgeführt werden

ISUOG-Guideline von 2013
Optimal ab 11+0 Wochen
transabdominal / transvaginal
Erfahrung mit früher US-Diagnostik
Zeitbedarf: mindestens 20 Min

Warum US und nicht Blut ab 9+0 Wochen ?

Kontraindikation von ETS und NIPT bei fetalen Auffälligkeiten (frühe IUGR, NT >3,5mm …)

Entscheidung **nach** US

Nichts tun (DR ?)

ETS +/- Serumbiochemie (1.Wahl)
NIPT (primär, Sekundärtest)

invasive Diagnostik (primär, Sekundärtest)

Weitere Stellungnahmen

NIPT ist kein Diagnostiktest
NIPT derzeit für high-risk-Population
(keine ausreichende Validieren von Daten
bei low- und intermediate Risk)
NIPT ist Second-line-Test nach ETS
ETS >1:10 -> invasive Diagnostik
kein NIPT bei fetaler Anomalie / NT >3,5mm
(unauff. NIPT + auffälliger US: Punktion)
Unklare Genauigkeit bei dizygoten Gemini
Vergleichbarkeit unterschiedlicher Anbieter ?
Kein Softmarker-US bei unauffälligem NIPT !
Monogene Erkrankungen: FPR hoch

Ultrasound Obstet Gynecol 2017; 49: 815–816
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.17483

CONSENSUS STATEMENT

ISUOG updated consensus statement on the impact of cfDNA aneuploidy testing on screening policies and prenatal ultrasound practice

The widespread use of fetal cell-free DNA (cfDNA)-based techniques to screen for trisomy 21 and other aneuploidies has expanded greatly the range of prenatal tests available over the last few years. cfDNA tests are being incorporated rapidly into prenatal care, thus changing the traditional approach to prenatal screening and diagnosis. However, although cfDNA techniques are highly efficient, their role and performance must be considered alongside and combined with other screening modalities. The role of prenatal ultrasound, in particular, needs to be reaffirmed as cfDNA testing becomes more widely available.

It is important to emphasize that the main goal of prenatal screening is to provide accurate information that will facilitate the delivery of optimized antenatal care, with the best possible outcome for both mother and fetus. Women should be informed about the prevalence and the clinical manifestation of the disease of interest and about prenatal screening performance (detection rate, false-positive rate, positive predictive value in the general population, failure rate) by appropriately trained health professionals, allowing them to make an informed decision. It is the parent's choice to undergo such procedures, and their wishes should be determined and respected.

This consensus statement constitutes a revised and updated version of the previously published ISUOG consensus statement on the impact of non-invasive prenatal testing (NIPT) on prenatal ultrasound practice[1]; updates will be produced on a regular basis.

- All women should be offered a first-trimester ultrasound scan according to ISUOG guidelines[2], regardless of their intention to undergo cfDNA testing.

  - If the woman has had a negative cfDNA test result, nuchal translucency (NT) thickness should still be measured and reported as a raw value and centile. The management of increased NT with a normal cfDNA test result is currently based on local guidelines. However, it is not necessary to compute first-trimester risk estimates for trisomies 21, 18 and 13 based on NT measurements and maternal biochemistry in a woman known to have a normal cfDNA result. Accordingly, soft markers for trisomy 21 should not be assessed in women with a normal cfDNA test result due to their high false-positive rate and poor positive predictive value.
  - If the woman has not had a cfDNA test, pretest counseling is essential. Various options regarding screening or testing for trisomy 21 and, to a lesser extent, trisomies 18 and 13 should be explained clearly, including information on the expected test performance, potential adverse effects, and pros and cons of each option. Following a normal first-trimester scan, as defined by ISUOG guidelines[2], three options might be considered for women who wish to have further risk assessment:

(1) Screening strategies based on individual risk calculated from maternal age and NT measurement and/or maternal serum markers and/or other ultrasound markers in the first trimester (defined by the conventional crown–rump length range of 45–84 mm).
Following such screening, women can be offered a choice, according to their calculated individual risk, of having no further testing, cfDNA testing or invasive testing. Cut-offs, defining two (low/high risk) or three (low/intermediate/high risk) groups, should be defined on a local/national basis and will be affected by public health priorities and available resources. Offering cfDNA testing should always be balanced with the potential and risk of conventional karyotyping, with or without microarray analysis, following invasive sampling. More importantly, the role of cfDNA testing as an alternative to standard invasive testing in women considered to be at very high risk after combined screening (> 1:10) but with no ultrasound anomaly should be evaluated in prospective studies. Expert opinion currently suggests that cfDNA testing should not replace routinely invasive testing in this group, based on the fact that, in this population, only 70% of the chromosomal abnormalities are trisomy 21, 18 or 13, and that chromosomal microarray analysis, if offered, is able to detect a large number of additional anomalies.

(2) cfDNA testing as a first-line screening test.
Most current guidelines endorse cfDNA testing only for high- or intermediate-risk populations, for which comprehensive data exist. Experience in low-risk populations is increasing, apparently confirming the high detection rates published for high-risk populations. However, testing in low-risk women may impact on the quality of both pretest counseling and subsequent ultrasound screening. In particular, cfDNA testing should not replace first-trimester ultrasound and should not be offered when an ultrasound anomaly or markedly increased NT is detected. Using cfDNA in low-risk patients might be endorsed as a widely available option only when more data emerge and cfDNA costs decrease.

(3) Invasive testing based on a woman's preference or background risk (maternal age, previous history, fetal ultrasound anomaly) with no further individual risk calculation.
An invasive test might be discussed in light of the recently reported reduction in the risk of invasive procedures[3,4], as well as the increase in cytogenetic resolution provided by microarray techniques. However, the cost of this option is not usually covered by most national insurance policies and it should not be recommended beyond the context of clinical trials and until sufficient peer-reviewed data and validation studies have been published.

- cfDNA test results should always be interpreted and explained individually in relation to the *a-priori* risk and the fetal fraction.
- In the presence of a fetal structural anomaly, the indications for fetal karyotyping and/or microarray testing should not be modified by a previously normal cfDNA test result.
- In the case of a failed cfDNA test, the patient should be informed about the increased risk of anomalies as well as alternative screening and testing strategies.
- cfDNA testing is not diagnostic, and confirmatory invasive testing is required in the presence of an abnormal result. Whenever there is discordance between an abnormal cfDNA test result and a normal ultrasound examination, amniocentesis rather than chorionic villus sampling should be performed.
- Accuracy of cfDNA testing in twin pregnancies should be investigated further.
- Variations in cfDNA test performance by different providers should be investigated further.
- It is becoming technically feasible to test non-invasively, not only for trisomies but also for other genetic syndromes. Both healthcare providers and women should be clearly aware of the tests being performed and of their performance, as having multiple tests increases the overall false-positive rate and failure rate. The detection rate for microdeletions has yet to be established and most national guidelines currently do not support testing for microdeletions on cfDNA. Screening for microdeletions also raises complex issues regarding pretest and post-test counseling.
- Prospective, publicly funded studies assessing the cost-effectiveness of various screening strategies should be performed as a matter of urgency.

Writing group

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UOG
2017

Ergänzungen gegenüber 2014

Praenatal plus

Bei unauff. NIPT: ETS-Marker speichern,
TR, auff.DV -> Echokardiographie
mglw. auch gute Daten bei low-/ intermediate-Risk
(je niedriger die Prävalenz, je höher PVR / NVR…)
Bedeutung der fetalen Fraktion !!
Testversager: Aneuploidie und strukturelle Defekte
Diskordanz von NIPT und US: invasive Diagnostik
Weiterhin: kein Empfehlung bei Gemini, monogenen Erkrankungen und Mikrodeletionen
Inv. Diagnostik: keine Empfehlung für Array-CGH

UiM
2015

Praenatal
plus

Recommendation

Cell-Free DNA Testing for Fetal Chromosomal Anomalies in clinical practice: Austrian-German-Swiss Recommendations for non-invasive prenatal tests (NIPT)

Drei Länder – Empfehlung zum Einsatz von Nicht-invasiven pränatalen Tests (NIPT) zur Analyse der zellfreien DNA (cfDNA) im mütterlichen Blut zum Screening auf fetale Chromosomenstörungen in der klinischen Praxis

Authors M. Schmid[1], P. Klaritsch[2], W. Arzt[3], T. Burkhardt[4], H. C. Duba[5], M. Häusler[2], E. Hafner[7], U. Lang[2], B. Pertl[6], M. Speicher[8], H. Steiner[9], S. Tercanli[10], E. Merz[11], K. S. Heling[12], B. Eiben[13]

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Neues Konsensuspapier **DEGUM**

Praenatal plus

ist in Vorbereitung …
und wird Beiträge enthalten über:

frühe Feindiagnostik im I. Trimenon
Genetische Beratung
Aufklärung über DR, FPR, PPV und NPV
NIPT als primäres Screening für jede Risikogruppe ?
NIPT und Mehrlinge
Diagnostische Punktionen
Sekundärer Test bei primärem T 21-Risiko < 1:1000 ?
Vorgehen bei Risiko >1:10 / NT > 3,5mm / Fehlbildung
NIPT ausser Trisomien

Praenatal plus

US-Diagnostik im I. Trimenon

Je besser der US, je höher die DR für ETS / NIPT

US *immer* vor ETS / NIPT

DR, FPR, PPV und NPV

Praenatal plus

Metaanalyse von 37 Studien (Gil 2015: Hochrisiko)

DR Tris 21: 99,2%, FPR 0.09%
Tris 18: 96,3% FPR 0,13%
Tris 13: 91% FPR 0,23%

41 Studien (Taylor-Philipps 2016)

Diff. von Hoch- und Niedrigrisiko nach Prävalenzen

DR Tris 21: 95,9% (1:230)
Tris 18: 86,5% (1:1000)
Tris 13: 97,5% (1:2000)

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Testversager

Testversagen in 0,5-3%

Ursachen: niedrige fetale Fraktion (<5%)
Adipositas
frühe SSW
niedrige Prävalenz (Tris 18 und 13)
fetale Pathologie

Prävalenz < FPR: hohe Fehlerquote !

Praenatal plus

Primäres Screening für jedes Alter und jede Risikogruppe ?

Häufig von jungen Schwangeren angefragt,
aber:
Je schlechter US und Beratung, umso häufiger NIPT (Sorgenlösung)

Cenata: 66% aller Teste zw. 11+0 und 13+6 Wochen
weil:
DEGUM 0/I: DR im ETS << 90% !

Frage: ETS / NIPT nur von der Stufe II ?
sinnvoll ? machbar ? bezahlbar ?

NIPT bei Zwillingen

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These: gleiche DR und FPR wie bei Eingingen
höhere Versagerquote (>3%)

mediane fetale Fraktion >8%

1 Studie (!): T21: 31; normal 39
DR 93,7%, FPR 0,23%

Monozygote Gemini: ok
Dizygote Gemini: komplex
(Versagerquote, Zuordnung)

Private Meinung: kein NIPT bei Gemini

Diagnostische Punktionen

Praenatal plus

80% aller Aneuploidien werden im NIPT nicht erfasst

auff.Fet, unauf.NIPT: CVS/AZ
unauf. Fet, auff. NIPT: AZ

US-Auffälligkeit
ETS-Risiko > 1:10
NT >3,5mm (95%-Perzentile, 22-38%)
frühe gesicherte IUGR (14-30%)
auffälliger NIPT
PAPP-A<0,2MoM, ß-HCG<0,2/>5 MoM
Wunsch der Schwangeren (??)

Array-CGH
Euploidie und auff. Fetus: CNV 6-10%)
NT>3,5%: CNV 4%
auff. Fetus und NT>3,5mm: CNV 7%

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Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis

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KEYWORDS: amniocentesis; chorionic villus sampling; CVS; fetal loss; invasive diagnostic procedure; miscarriage; pregnancy loss; prenatal diagnosis; procedure-related loss

ABSTRACT

Objectives *To estimate procedure-related risks of miscarriage following amniocentesis and chorionic villus sampling (CVS) based on a systematic review of the literature and a meta-analysis.*

Methods *A search of MEDLINE, EMBASE, CINHAL and The Cochrane Library (2000–2014) was performed to review relevant citations reporting procedure-related complications of amniocentesis and CVS. Only studies reporting data on more than 1000 procedures were included in this review to minimize the effect of bias from smaller studies. Heterogeneity between studies was estimated using Cochran's Q, the* I^2 *statistic and Egger bias. Meta-analysis of proportions was used to derive weighted pooled estimates for the risk of miscarriage before 24 weeks' gestation. Incidence–rate difference meta-analysis was used to estimate pooled procedure-related risks.*

Results *The weighted pooled risks of miscarriage following invasive procedures were estimated from analysis of controlled studies including 324 losses in 42 716 women who underwent amniocentesis and 207 losses in 8899 women who underwent CVS. The risk of miscarriage prior to 24 weeks in women who underwent amniocentesis and CVS was 0.81% (95% CI, 0.58–1.08%) and 2.18% (95% CI, 1.61–2.82%), respectively. The background rates of miscarriage in women from the control group that did not undergo any procedures were 0.67% (95% CI, 0.46–0.91%) for amniocentesis and 1.79% (95% CI, 0.61–3.58%) for CVS. The weighted pooled procedure-related risks of miscarriage for amniocentesis and CVS were 0.11% (95% CI, −0.04 to 0.26%) and 0.22% (95% CI, −0.71 to 1.16%), respectively.*

Conclusion *The procedure-related risks of miscarriage following amniocentesis and CVS are much lower than are currently quoted.*

INTRODUCTION

Amniocentesis and chorionic villus sampling (CVS) are commonly performed invasive procedures for prenatal diagnosis. It is vital that pregnant women are given accurate information about procedure-related risks of miscarriage to enable them to make informed choices about invasive prenatal testing. The UK National Health Service Fetal Anomaly Screening Programme states in its information leaflet for parents that the overall risk of miscarriage after an amniocentesis is about 1% and that after CVS it is about 1–2%[1]. There is inconsistency in the recommendations from various national bodies regarding the procedure-related risks of miscarriage, with the guidelines and information leaflets from the Royal College of Obstetricians and Gynaecologists (RCOG) stating that the additional risk of miscarriage from an amniocentesis is about 1% and that the additional risk from CVS may be slightly higher than that of amniocentesis, and could be in the region of 1–2%[2,3]. The American College of Obstetricians & Gynecologists mentions that the procedure-related loss rate after mid-trimester amniocentesis is less than 1 in 300–500 and that the loss rate for CVS may be the same as that for amniocentesis[4]. The committee opinion from the Society

Praenatal plus

Spezialfrage:
Wo ist die Grenze: NT 3,0 oder 3,5mm ?

auff. CNV

bei NT <2,9 mm: 1,7%
bei NT 3,0-3,5 mm: 7,1%
bei NT > 3,5 mm: 13%

Wofür ist ein NIPT sonst noch gut ?

Praenatal plus

fetale Blutgruppenmerkmale

DR von fet. Rh+im mütterl. Blut: 99,7%
C,c,E,e,Kell

fetales Geschlecht

AGS, X-chromos. Leiden, SMA use.

Mikrodeletionen

22q11: DR 98%, FPR 0,8% (Studienlage!)

Monogene Erkrankungen

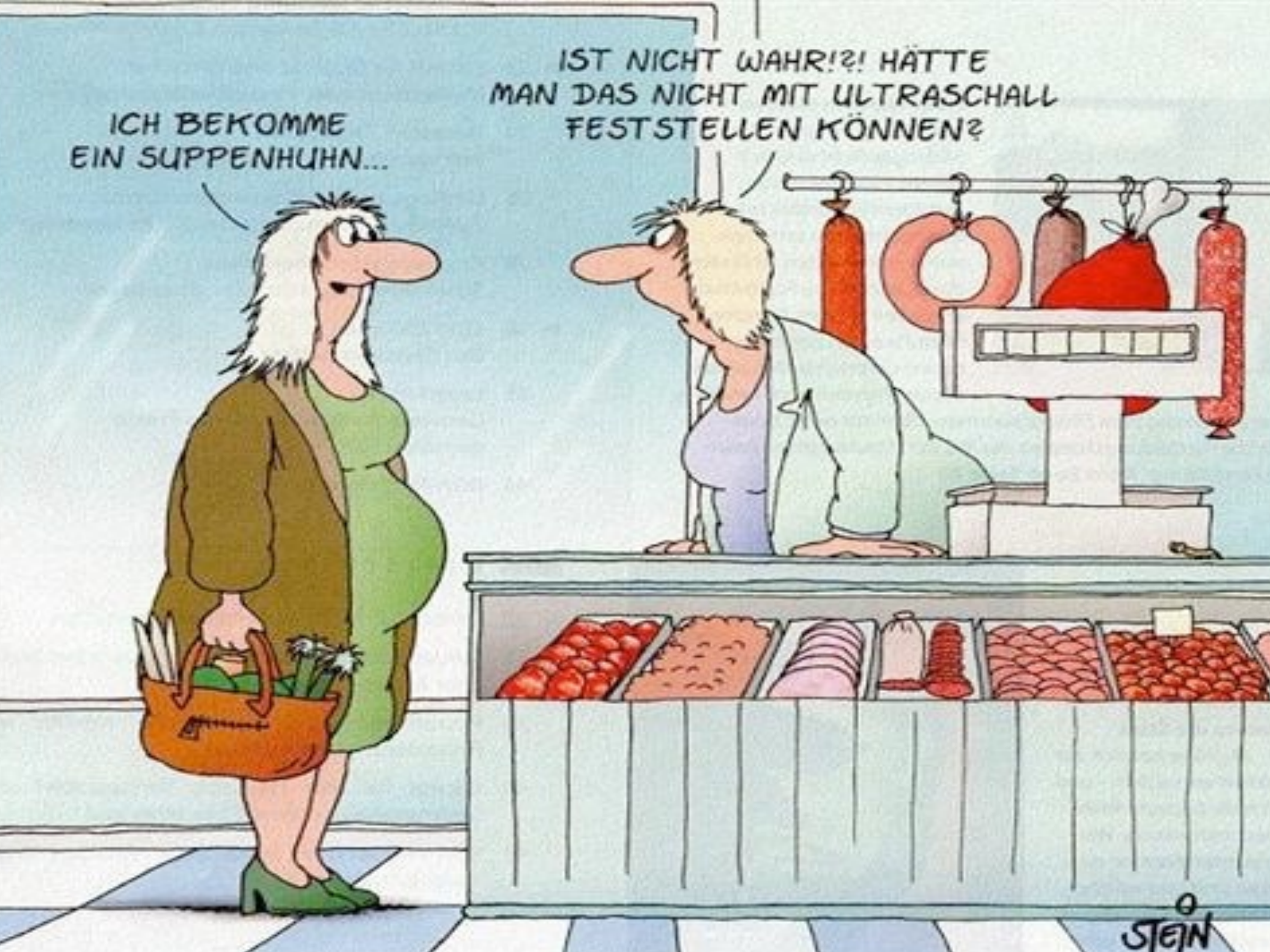
GB: Achondroplasie, TD (Studienlage!)

seltene chromosomale Störungen

möglich, aber mengenmäßig nicht relevant

Praenatal plus

Sag’ zum Abschied leise: Servus


ICH BEKOMME EIN SUPPENHUHN...
IST NICHT WAHR!?! HÄTTE MAN DAS NICHT MIT ULTRASCHALL FESTSTELLEN KÖNNEN?
STEIN