PREPRED

Preeclampsia Prevention in Denmark

En del af **DO-iT**

Projektgruppe:

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Ann Tabor, Professor emeritus[1]
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3. University of Exeter
4. Fetal Medicine Foundation

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DSOG
Dansk Selskab for Obstetrik og Gynækologi

Forebyggelse af præeklampsi i Danmark

Profylakse til risikogrupper

- Svær præeklampsi i tidligere graviditet (evidensgrad A)
- Kronisk nyresygdom (evidensgrad A)
- Autoimmun sygdom som SLE eller antiphospholipid syndrom (evidensgrad B)
- Prægestationel diabetes type 1 eller 2 (evidensgrad B)
- Behandlingskrævende essentiel hypertension (evidensgrad B)
- Æg doneret (evidensgrad B)
- Flerfoldsgravide
- BMI > 30

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- Behandlingskrævende essentiel hypertension (evidensgrad B)
- Æg doneret (evidensgrad B)
- Flerfoldsgravide
- BMI > 30

Acetylsalicylsyre (Magnyl)

150 mg/dag

Opstartes inden gestationsuge 16

Acetylsalicylsyre-guideline 2021: Inkl. flere risikomarkører

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Forebyggelse af præeklampsi i Danmark

ULTRASOUND in Obstetrics & Gynecology
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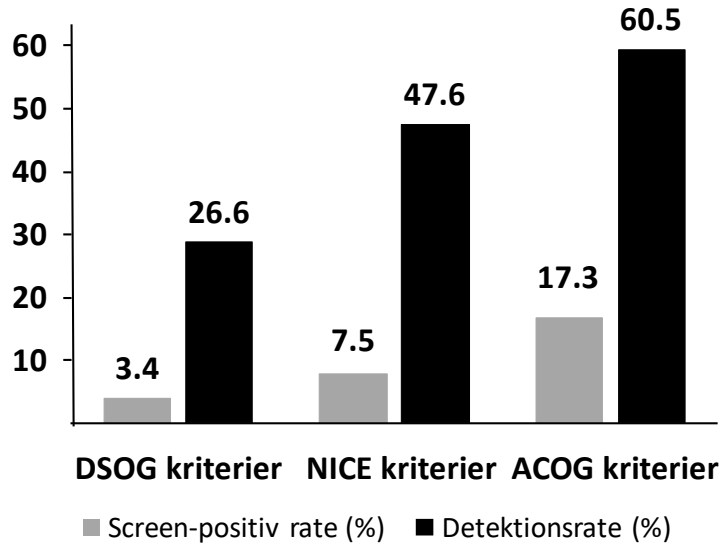
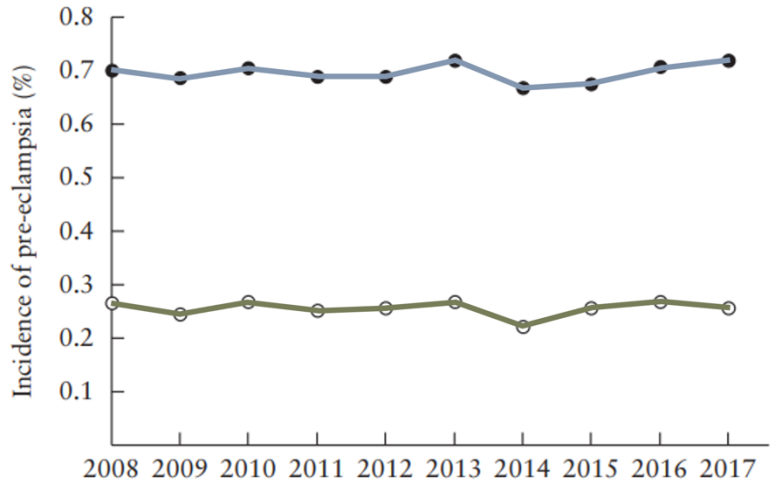
Original Paper

Prediction of preterm pre-eclampsia according to NICE and ACOG criteria: descriptive study of 597 492 Danish births from 2008 to 2017

L Rode, CK Ekelund, I Riishede, S Rasmussen, Ø Lidegaard, A Tabor





Incidence of preterm preeclampsia (●) and early onset preeclampsia (○)

< 1/3 af præeklampsi-tilfælde detekteres

Uændret forekomst af præeklampsi

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The Fetal Medicine Foundation

Prof. Kypros Nicolaides

The FMF preeclampsia screening model

Kombinerer *a priori* risiko fra maternelle markører med **biofysiske** og **biokemiske** mål

Muliggør beregning af *individuel* risiko for præeklampsi

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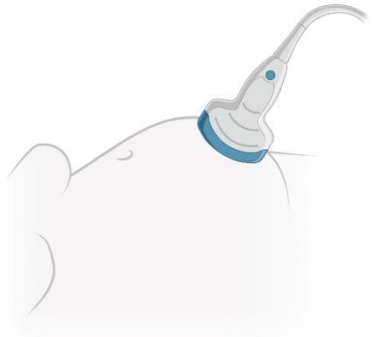
The FMF preeclampsia screening model

Maternelle karakteristika

- Alder
- BMI
- Etnicitet
- Kroniske sygdomme:
  Diabetes
  Nyresygdom
  Hypertension
  Autoimmun sygdom
- Rygning
- Fertilitetsbehandling
- Obstetrisk anamnese

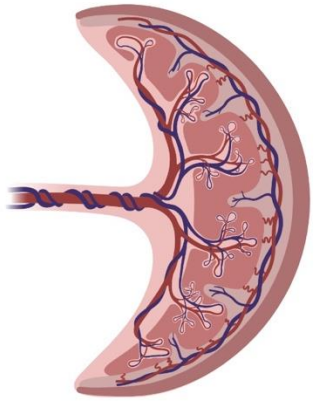
Biofysiske markører



Aa. uterinae flow

Blodtryk (Mean Arterial Pressure)

Biokemiske markører



Pregnancy associated plasma protein-A
(PAPP-A)

Placental growth factor
(PlGF)

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Detektionsrate for en 10 % screen positiv rate	PE < 37 uger
Maternelle karakteristika og PAPP-A	**49%**
Maternelle karakteristika og blodtryk	**51%**
Maternelle karakteristika og flow i arteria uterina	**58%**
Maternelle karakteristika og PlGF	**61%**
Maternelle karakteristika, blodtryk, flow i arteria uterina, PAPP-A og PlGF	**75%**

Tan et al. UOG 2018
Poon et al. Obst. Gyn. Int 2014

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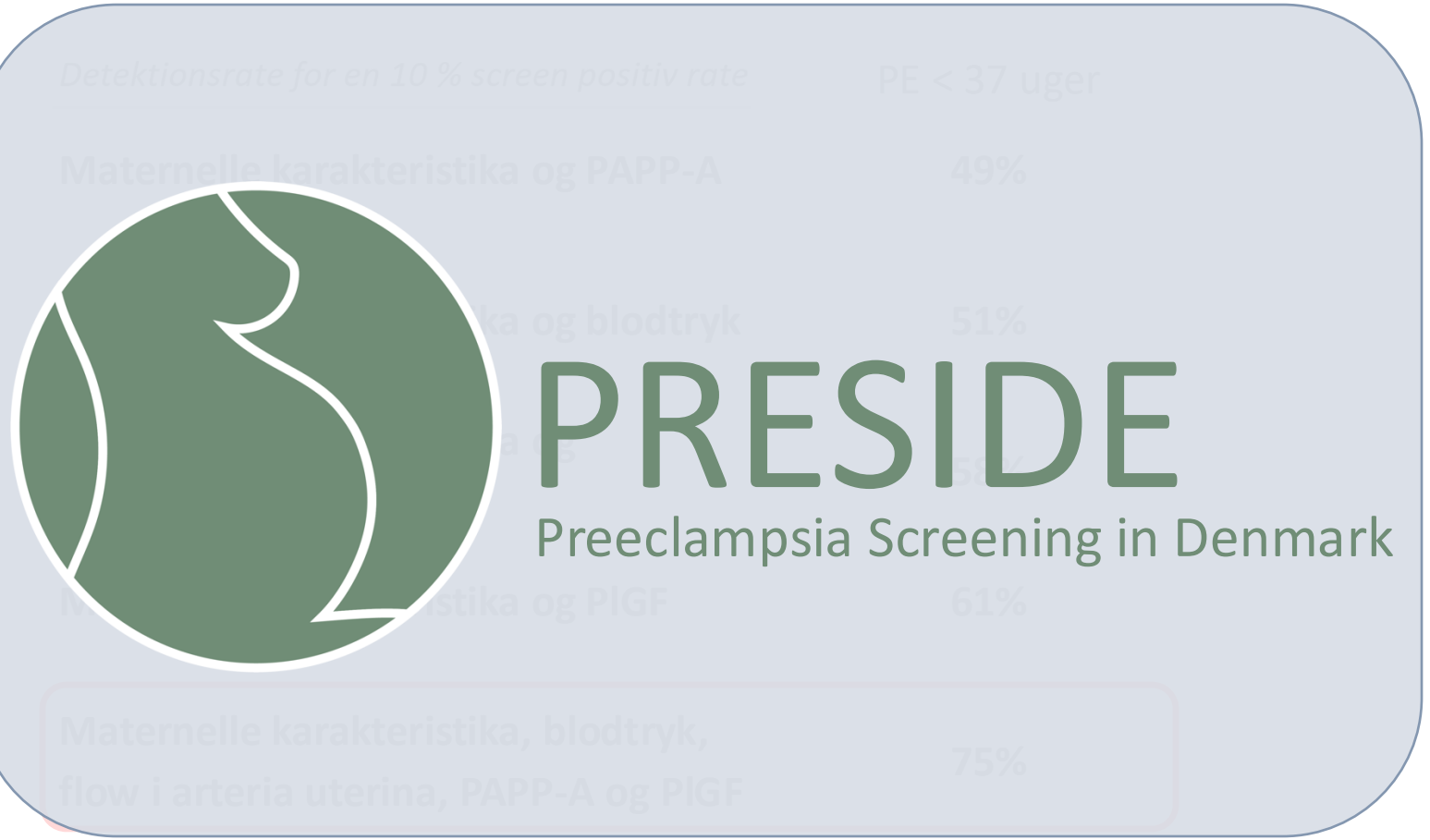

Tan et al. UOG 2018
Poon et al. Obst. Gyn. Int 2014

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Original Paper | Open Access

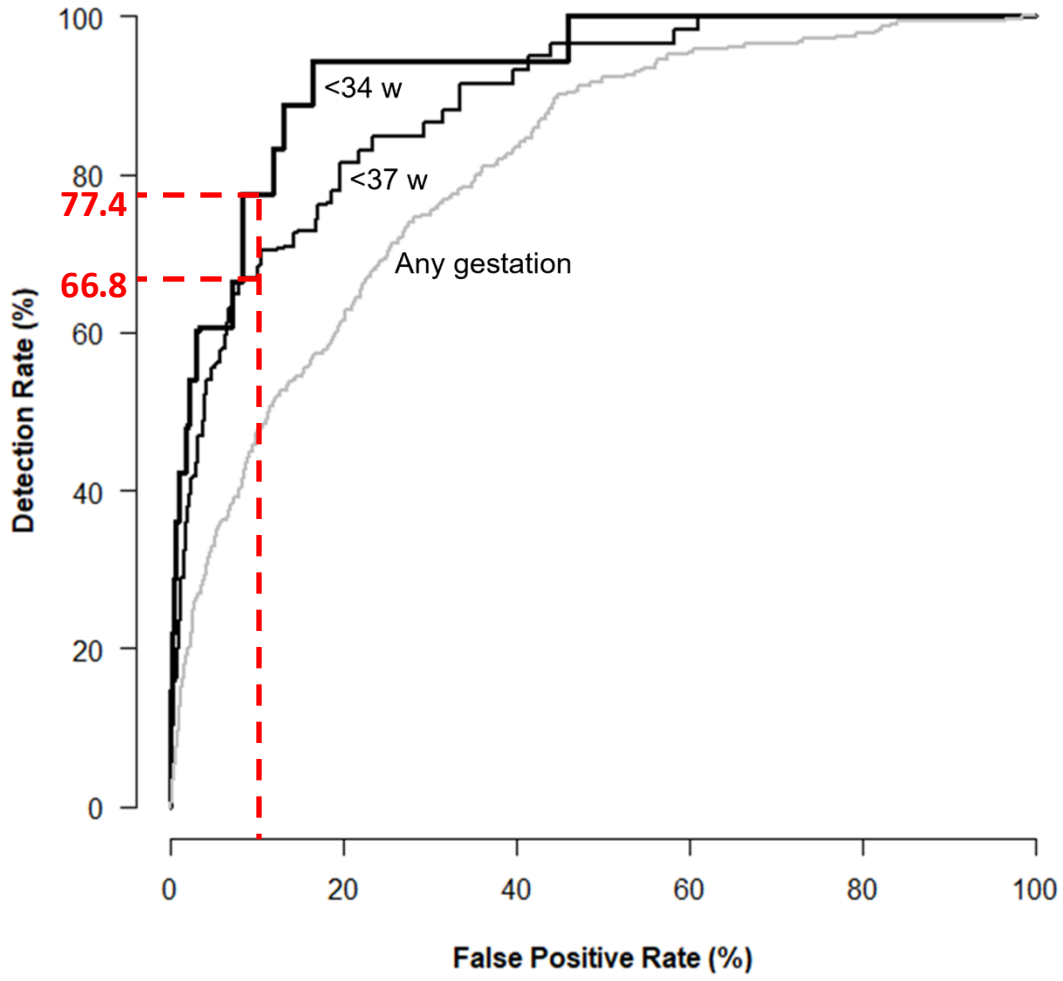
Pre-eclampsia screening in Denmark (PRESIDE): national validation study

I. Riishede, L. Rode, L. Sperling, M. Overgaard, J. D. Ravn, P. Sandager, H. Skov, S. R. Wagner, P. Nørgaard, T. D. Clausen, C. A. Juel Jensen, K. Pihl, F. S. Jørgensen, J. K. Munk, H. J. Zingenberg, N. G. Pedersen, M. R. Andersen, A. Wright, D. Wright, A. Tabor, C. K. Ekelund

Women included (n = 8,783) May 2019 - Dec 2020

Screening by maternal factors + MAP + UtPI + PlGF + PAPP-A

Preeclampsia	Detection rate at 10 % screen pos. rate
< 34 weeks	**77.4%** (95% CI 57.6%;97.2%)
< 37 weeks	**66.8%** (95% CI 54.4%;79.1%)
All PE	**44.1%** (95% CI 38.5%;49.7%)



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AOGS Acta Obstetricia et Gynecologica Scandinavica Open Access

ORIGINAL RESEARCH ARTICLE | Open Access

Motivation towards first trimester screening for preeclampsia among pregnant women in Denmark: A cross-sectional questionnaire study

Sandra Maria Behnke Gerdes, Ch
Julie Midtgaard, Finn Stener Jørge

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Original Paper | Full Access

Screening for pre-eclampsia with competing risks model using placental growth factor measurements in blood samples collected before 11 weeks' gestation

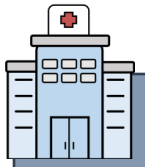
I. Riishede, C. K. Ekelund, L. Sperling, M. Overgaard, C. S. Knudsen, T. D. Clausen, K. Pihl, H. J. Zingenberg, A. Wright, D. Wright, A. Tabor, L. Rode, Collaborators

PRESIDE

Preeclampsia Screening in Denmark

1

2



Myndigheder /SST

Implementerings-studie

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Region Hovedstaden

Rigshospitalet

novo nordisk foundation

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Preeclampsia Prevention in Denmark

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Study protocol

PREPRED (PREeclampsia PREvention in Denmark)

Multiple baseline interrupted time series study

Formål:

At evaluere **effekt**, **deltagelse** og **sikkerhed** af præeklampsi-screening i Denmark

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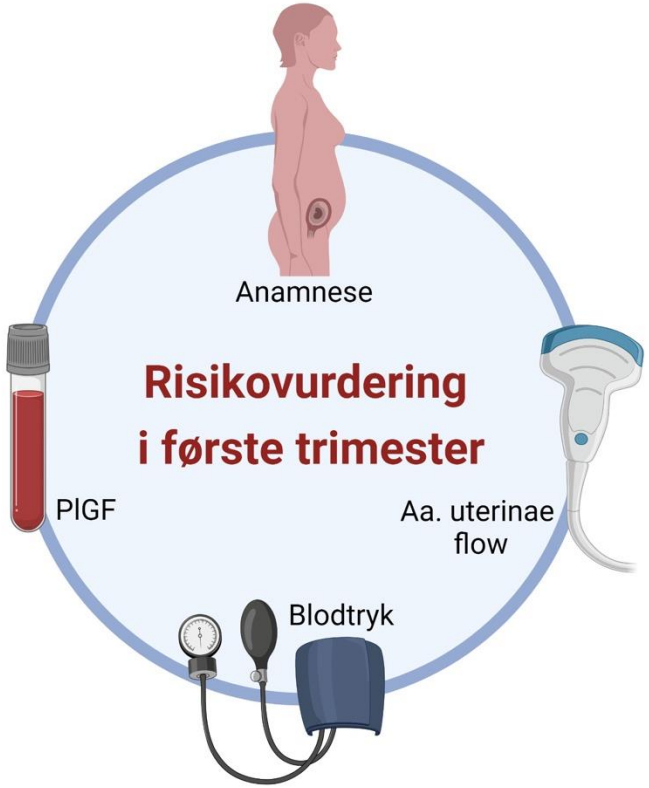
Preeclampsia Prevention in Denmark



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GA 11-14

- Føtalmedicinsk Afdeling (22)

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GA 7-11

- Praktiserende læge (3500)

GA 10-14

- Klinisk Biokemisk Afdeling (12)

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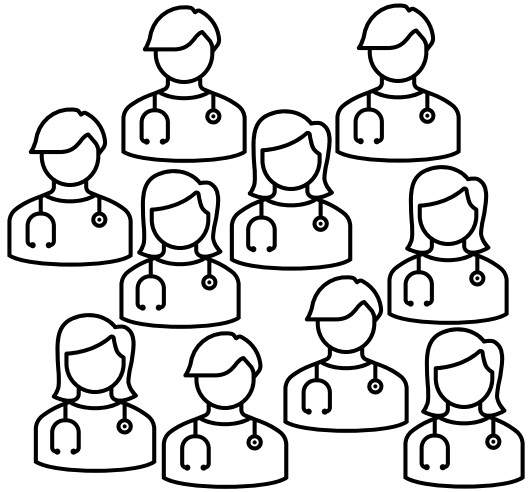

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Danish OBGYN
Multicenter Trials Consortium

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www.prepred.dk

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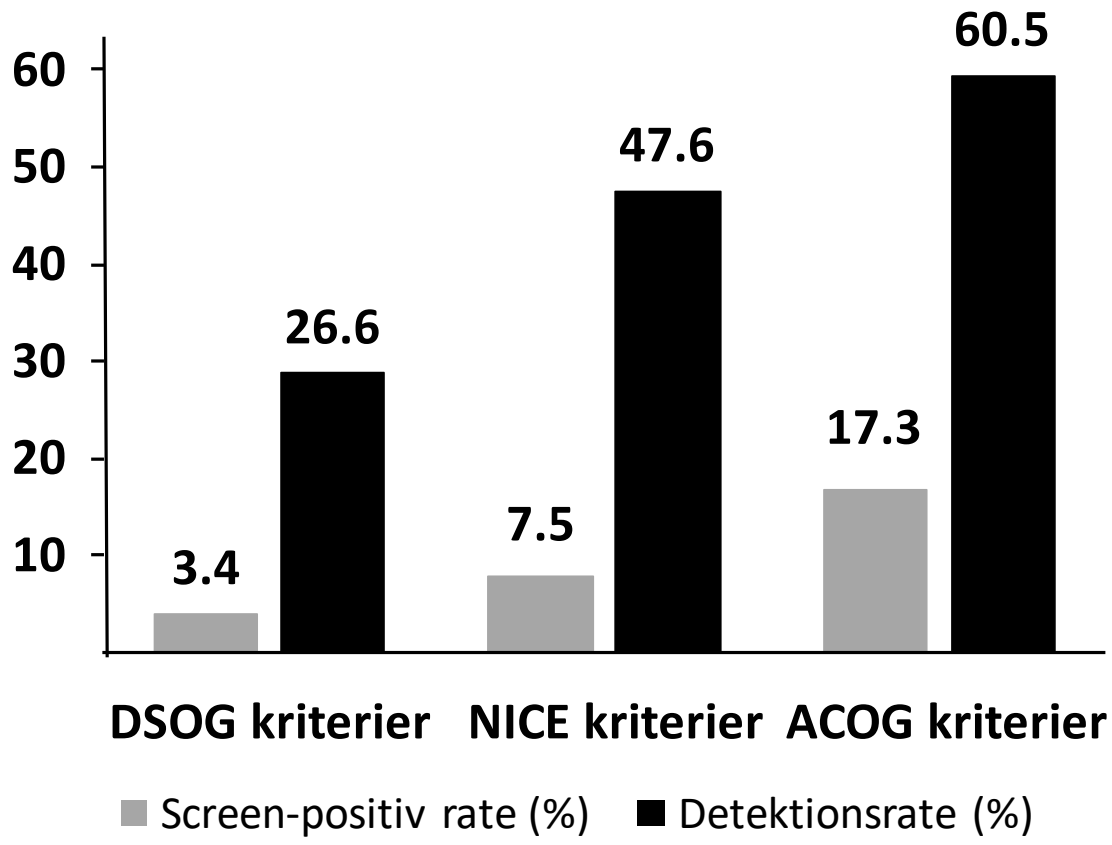
Resultater

- 3.4 % tilbydes magnyl
- Bedre opsporing ved kombination af risikofaktorer



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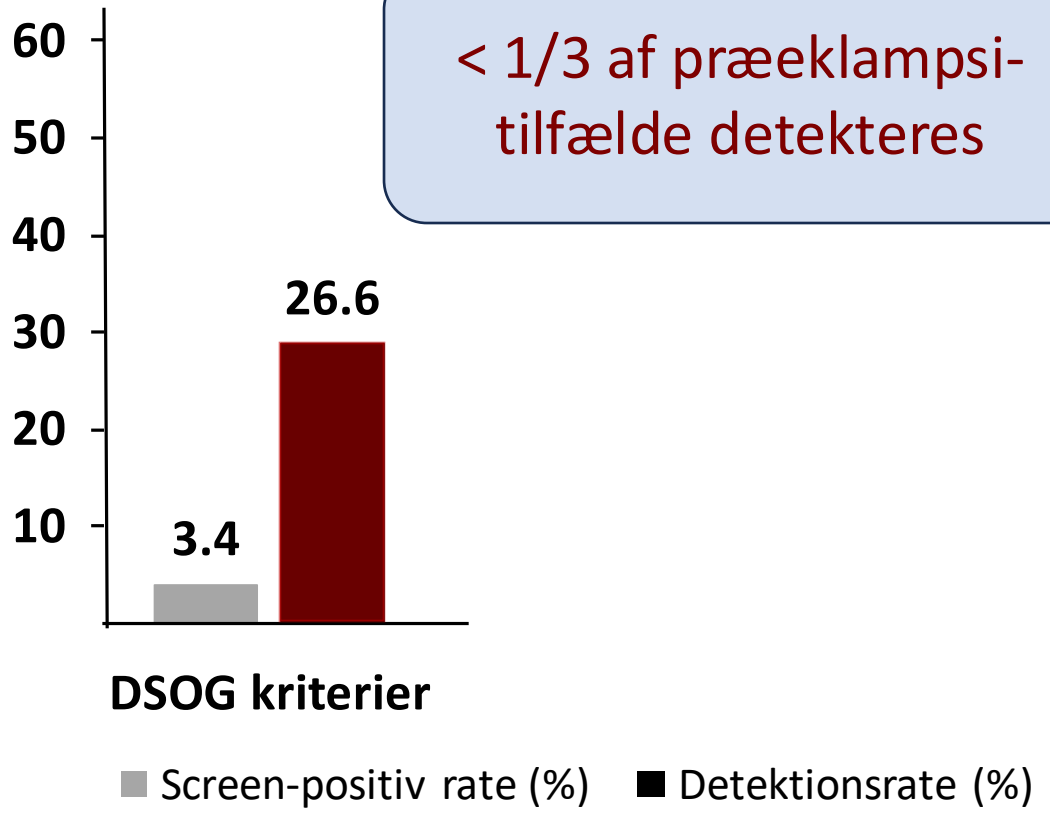

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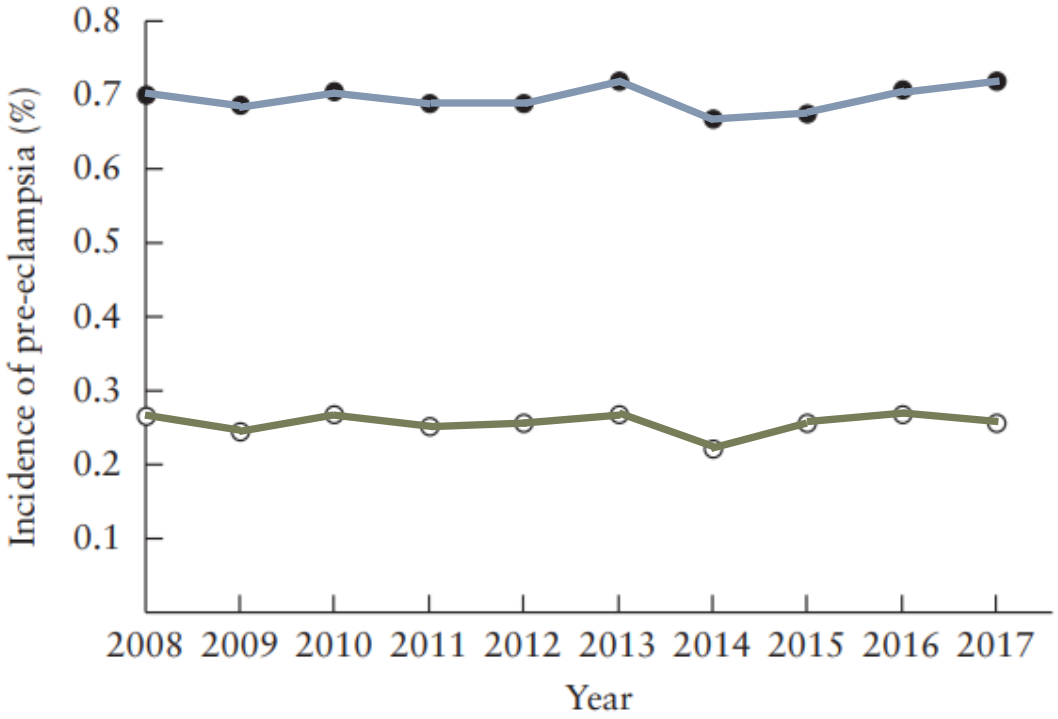
Resultater

- Præeklampsi: 3,2 %
- Præeklampsi < 37 uger: 0,7 %
- Præeklampsi < 34 uger: 0,3 %



Incidence of preterm preeclampsia (●) and early onset preeclampsia (○) among deliveries in Denmark 2008-2017.

Reprinted from Rode et al. Ultrasound Obstet Gynecol Obstet 2021;58(4):561-567.

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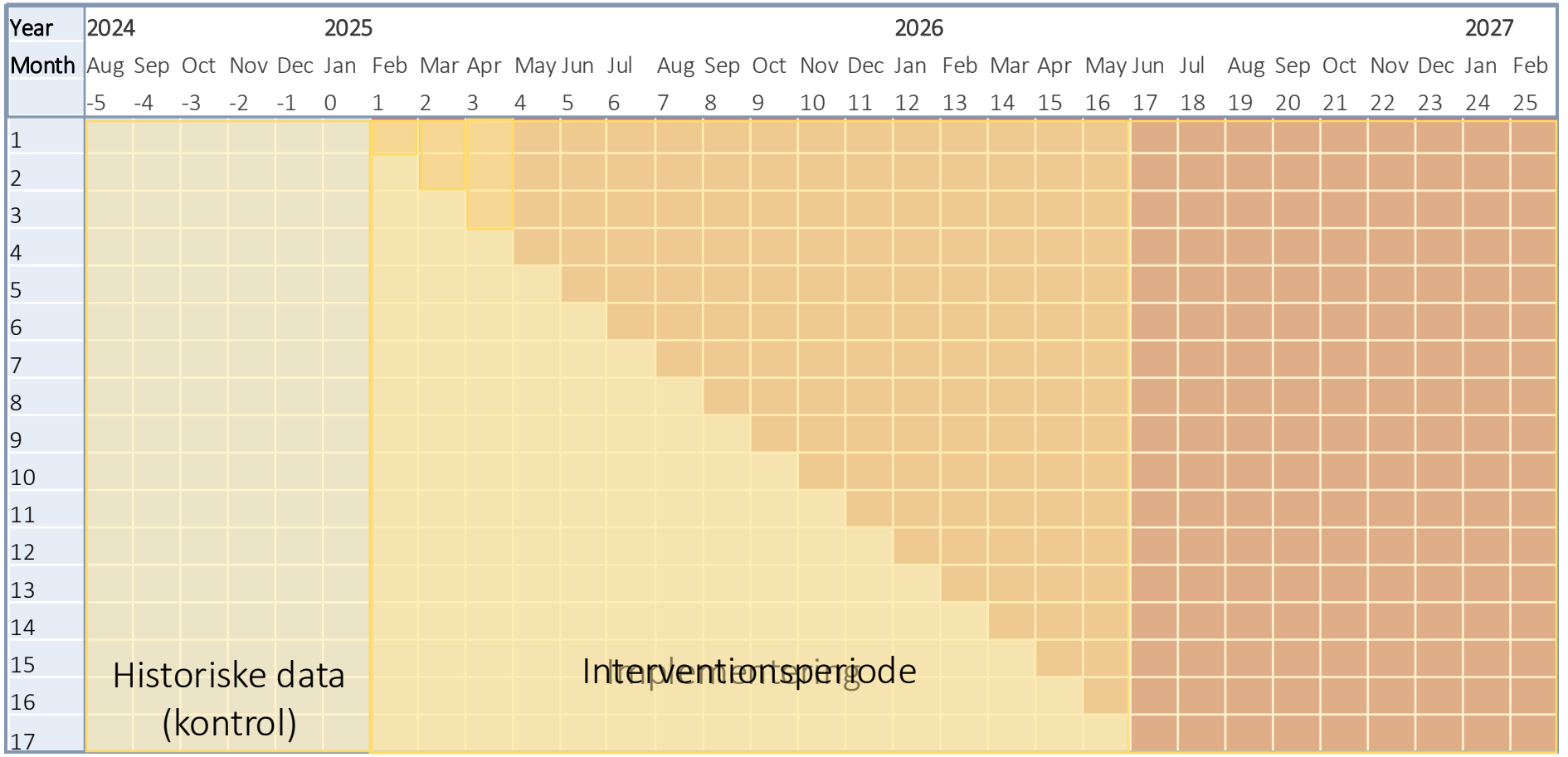
Multiple baseline interrupted time series design

Baseline

Intervention



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Studiedesign

- Præeklampsi-screening tilbydes som add-on til cFTS
- 22 fødesteder (landsdækkende)
- Interrupted time series studie med multiple starttidspunkter
- Hver måned startes screening på et nyt hospital

Baseline-periode:

Nuværende guidelines anvendes frem til opstart af screening

Cluster Randomized Trial

- Randomisering i ”clusters” (n=17)
- Tilfældigt opstartstidspunkt
- Praktisk foranstaltning
- Øger validitet
- Tentativ rækkefølge – kan justeres

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Outcomes

Implementering	• Screeningsoptag (deltagelsesprocent) • Magnyl-compliance • Påvirkning af nuværende 1. trimester screening • Acceptabelt for gravide og sundhedspersonale?
Effekt	• Incidens af præeklampsi • FGR og stillbirth • Præterm fødsel < 32, 34 og 37 uger • Neonatal-indlæggelser
Sikkerhed	• Svær post-partum blødning (>1500 mL) • Maternelle og neonatale interkranielle blødninger • Abruptio placenta

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Styregruppe

Føtalmedicin:
Finn S. Jørgensen, Københavns Universitetshospital - Hvidovre
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Eva Hoseth, Aalborg Universitetshospital - Aalborg
Lene Sperling, Odense Universitetshospital - Odense

Dansk Selskab for Klinisk Biokemi, DSKB:
Martin Overgaard, Odense Universitetshospital

Dansk Selskab for Obestetrik og Gynækologi, DSOG:
Lise Lotte Torvin Andersen, forperson

Dansk Føtalmedicinsk Selskab, DFMS:
Anne-Cathrine Shalmi, forperson

Jordemoderforeningen:
Nina Olsén, forperson

Dansk Præmatur Forening:
Julie Ognes-Olesen, forperson

Praktiserende Lægers Organisation, PLO:
Afventer

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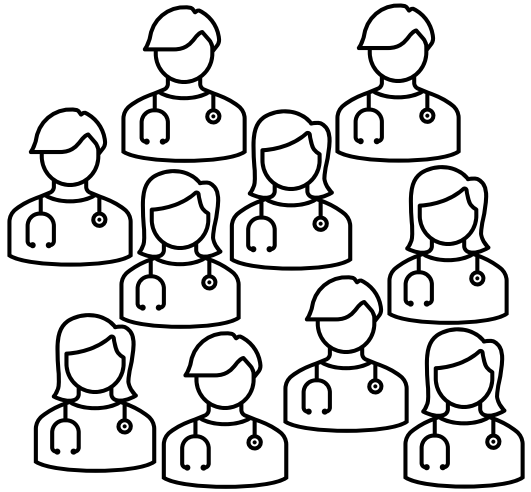

GA 7-11

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Tentativ opstartsrækkefølge

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For gravide | For sundhedspersonale | PREPRED

Herunder kan du se, hvornår tilbuddet om screening for svangerskabsforgiftning bliver tilgængeligt på dit fødested (listen er tentativ, opdateres primo 2025)

- **Februar 2025:** *Nordsjællands Hospital, Hillerød*
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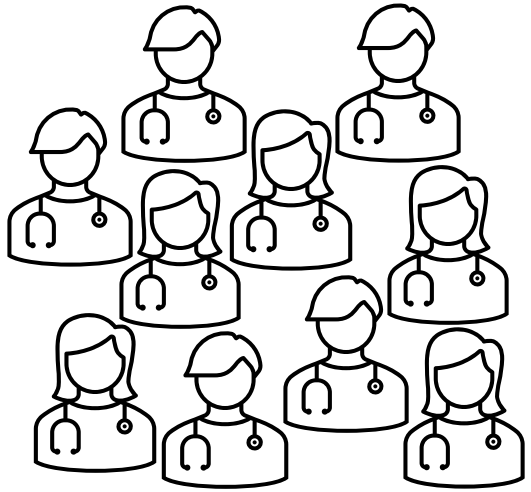

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Original Paper | Full Access

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I. Riishede, C. K. Ekelund, L. Sperling, M. Overgaard, C. S. Knudsen, T. D. Clausen, K. Pihl, H. J. Zingenberg, A. Wright, D. Wright, A. Tabor, L. Rode, Collaborators

First published: 12 September 2023 | https://doi-org.ep.fjernadgang.kb.dk/10.1002/uog.27462

Women with a PlGF measurement (n = 8,386)

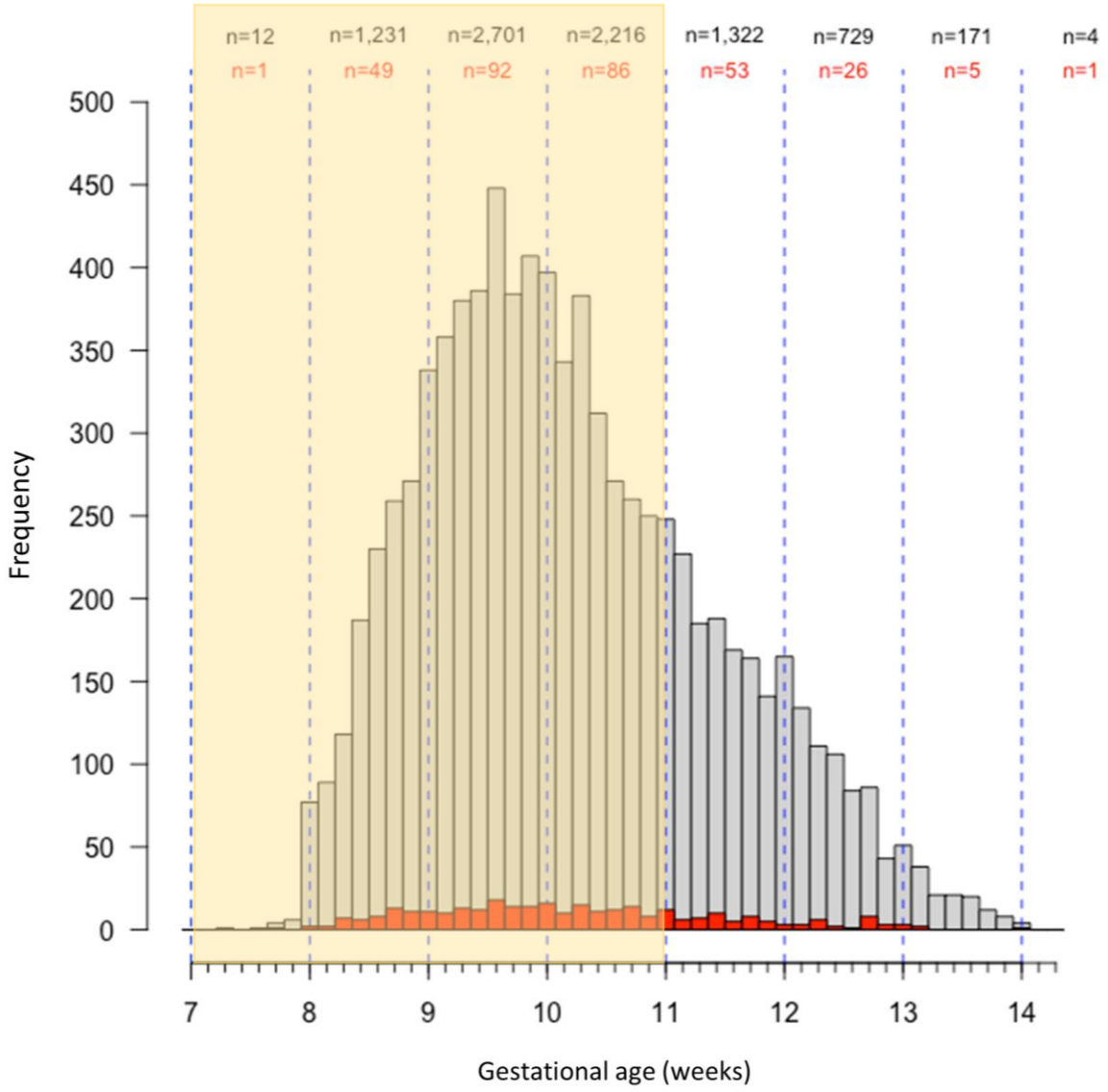
Distribution of routine blood sampling:

Before 11 weeks' gestation: **73%** (6,160)

In week 10: **26%** (2,216)

Before 10 weeks' gestation: **47%** (3,944)

Distribution of gestational ages at the time of routine cFTS



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Red: Preterm preeclampsia (<37 weeks)

Blue: Term preeclampsia (≥37 weeks)

Black: Unaffected pregnancies

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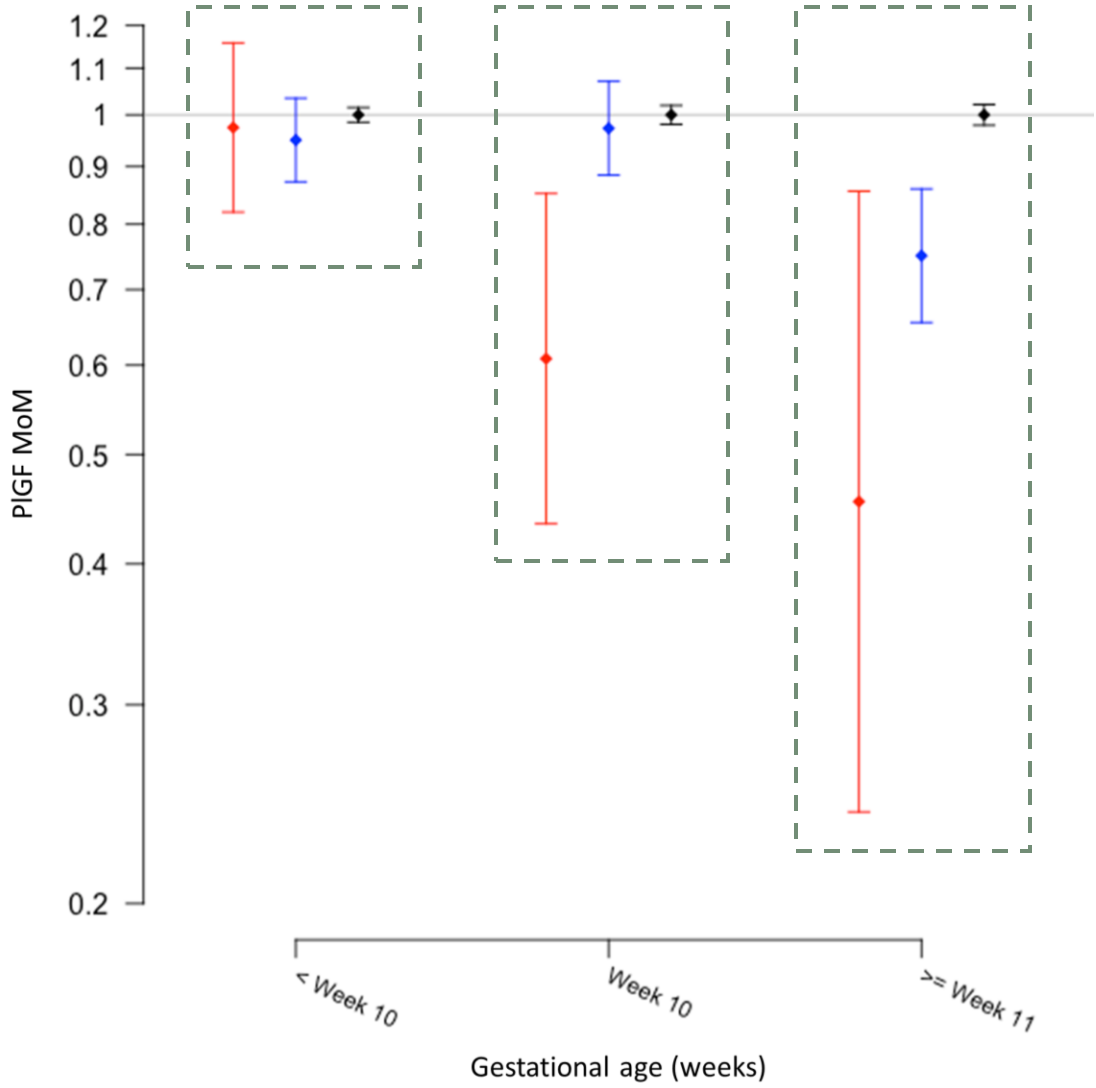
PlGF MoM-values in pregnancies with preeclampsia and unaffected pregnancies by gestational age at time of routine blood sampling



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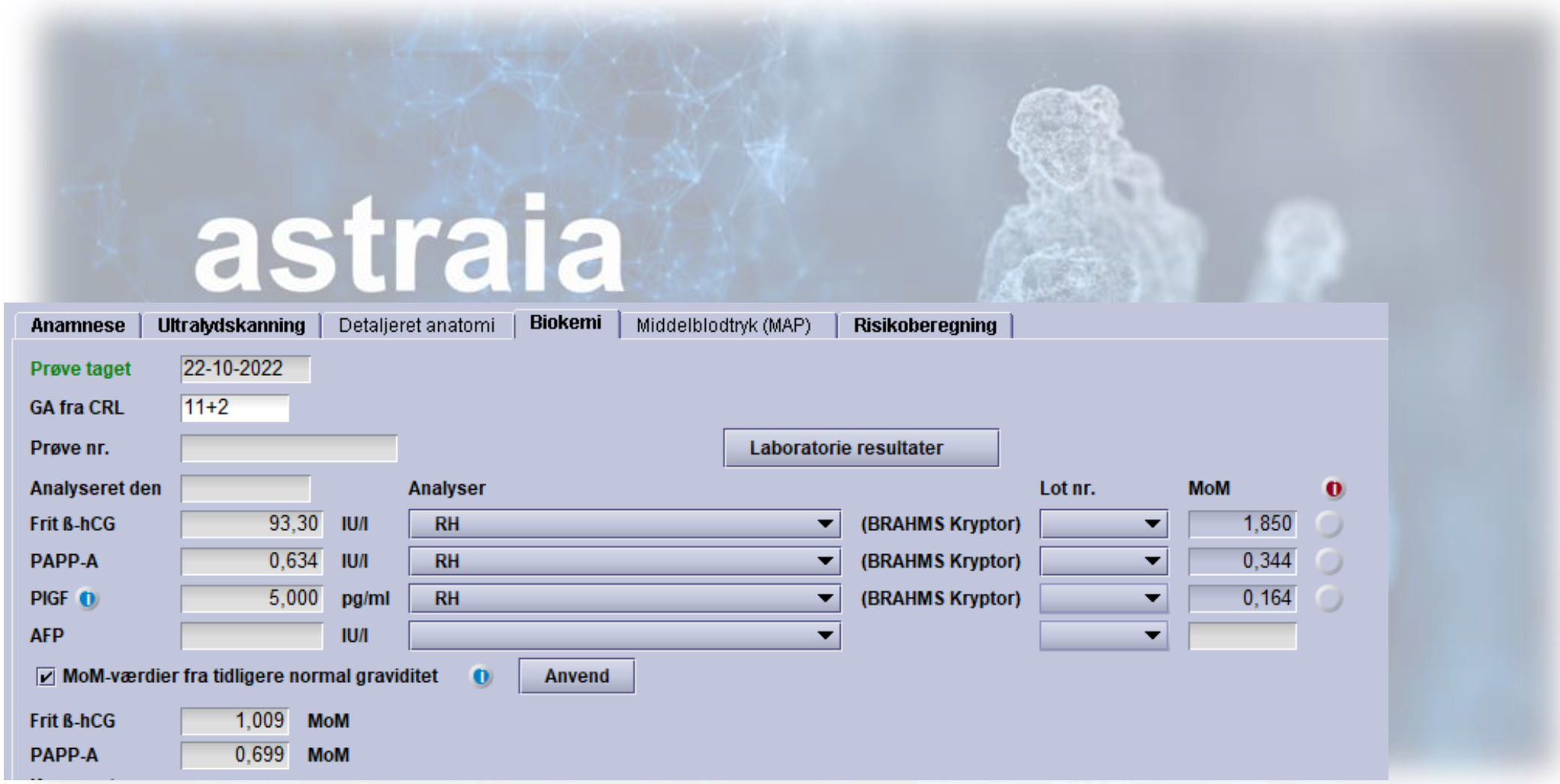

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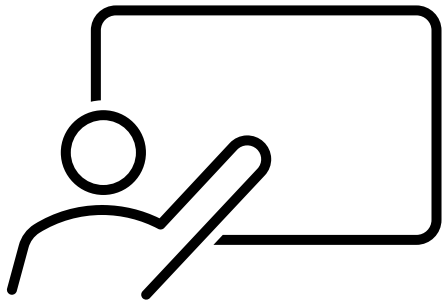
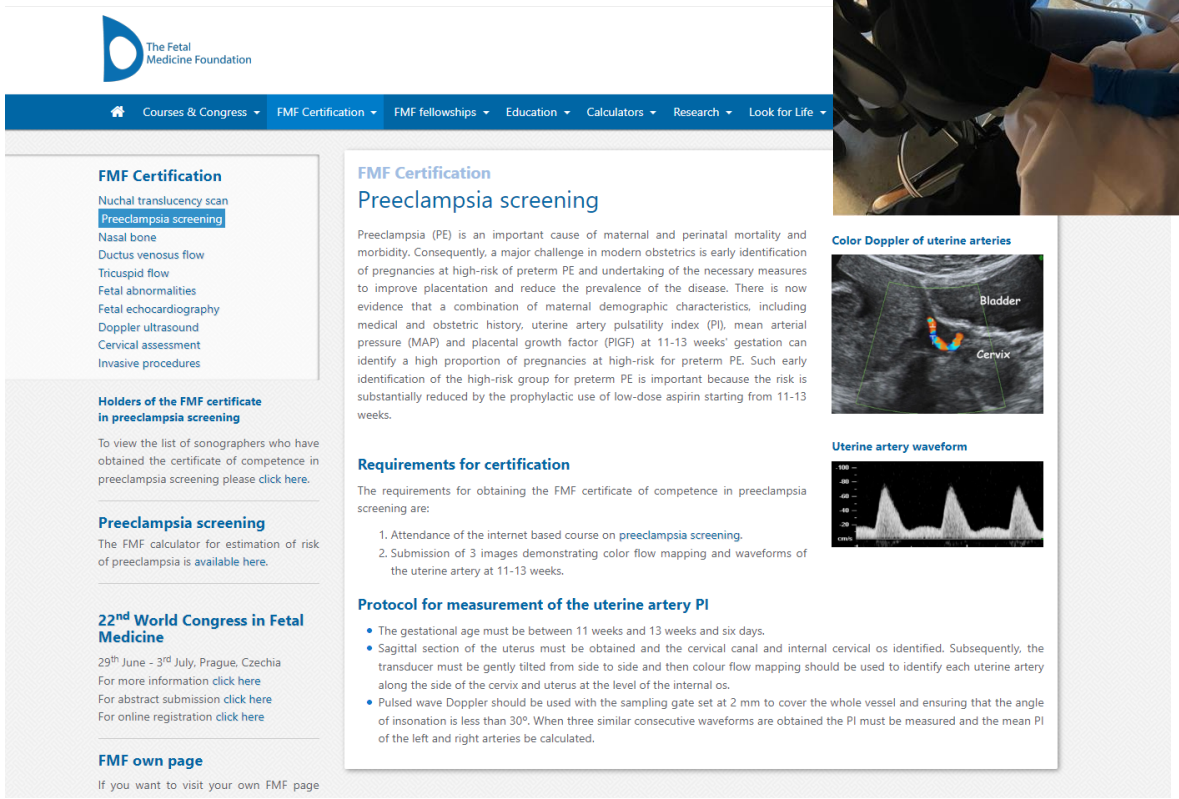
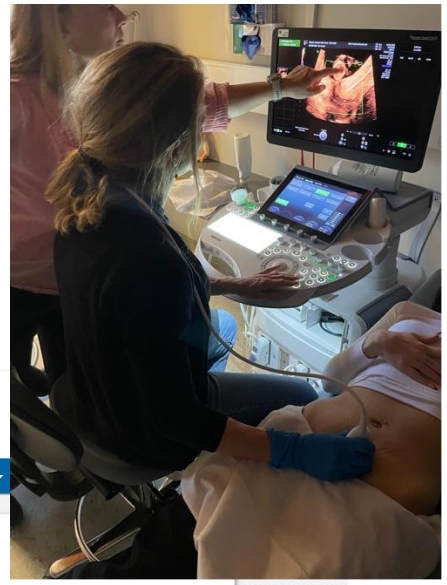
Opstartsmøde og temadag Hillerød



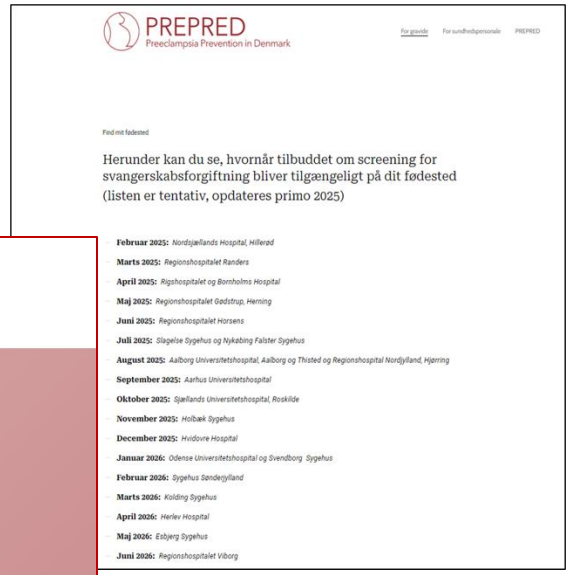




PREPRED

Preeclampsia Prevention in Denmark

www.prepred.dk



dfms

Dansk Føtalmedicinsk Selskab

Kursus juni 2025

Første trimester

Oplæg DFMS Årsmøde 2025

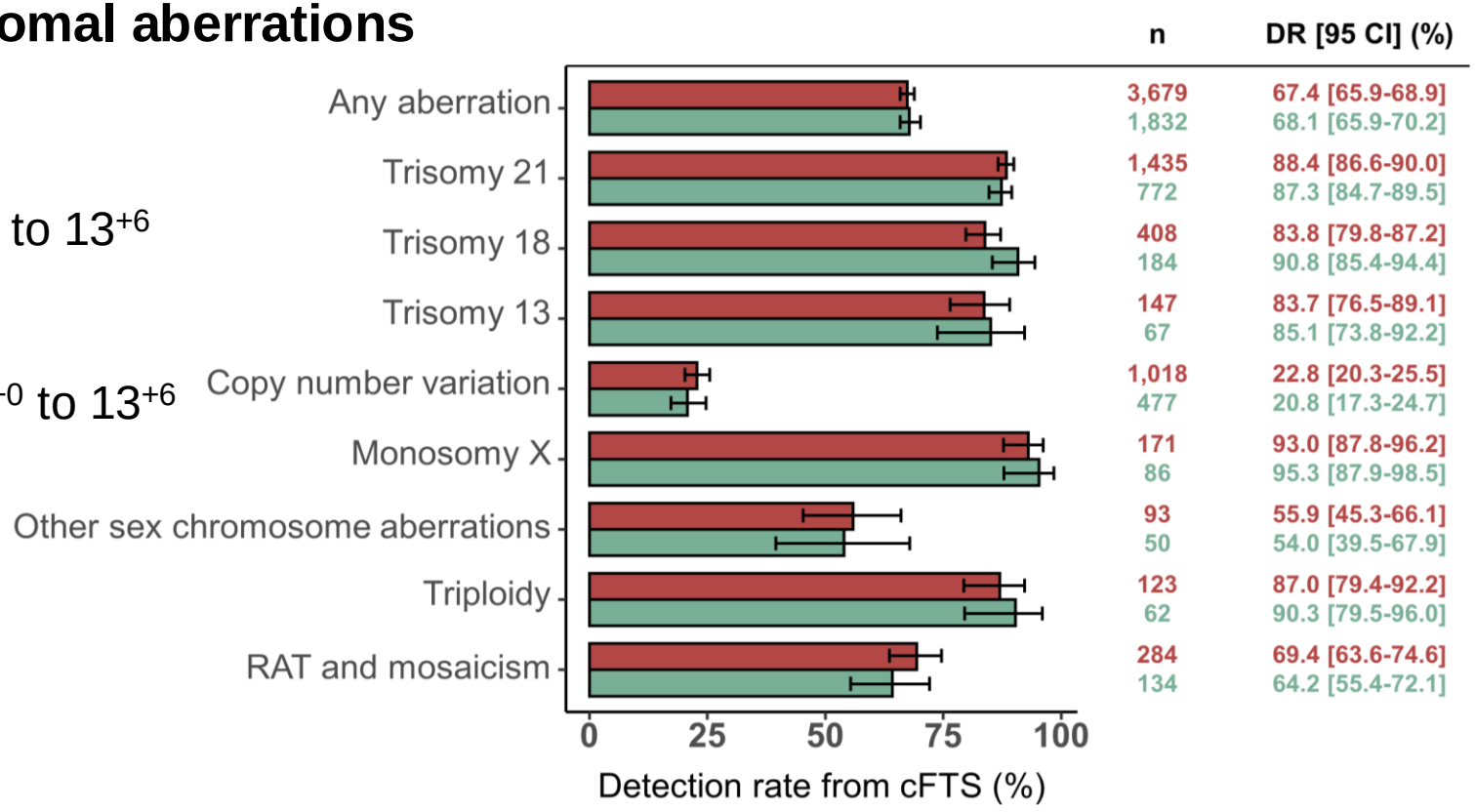
PRESIDE

Preeclampsia Screening in Denmark

Will it affect performance if blood is collected at 10-14 weeks?

Detection rates of chromosomal aberrations

- Doubletest sampling GA 8^{+0} to 13^{+6} (current practice)
- Doubletest sampling GA 10^{+0} to 13^{+6}



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Preeclampsia Prevention in Denmark

Project initiators

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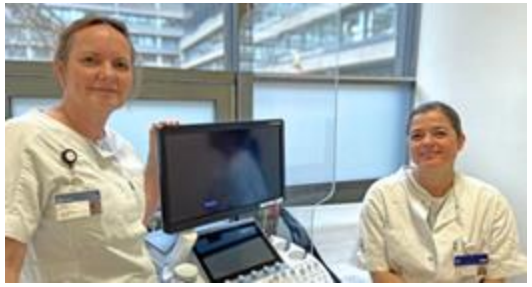

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Detection rate at 10% screen positive rate	PE <34 weeks (n=16)	PE <37 weeks (n=55)	All PE (n=303)
Maternal factors (MF)	36.3 (12.4-60.2)	39.1 (26.1-52.2)	30.0 (24.8-35.3)
MF + MAP + UtPI	66.1 (43.4-88.8)	53.4 (40.2-66.6)	36.9 (31.3-42.4)
MF + MAP + UtPI + **PAPP-A**	66.1 (43.4-88.8)	**55.1 (42.0-68.2)**	38.3 (32.8-43.8)
MF + MAP + UtPI + **PlGF**	77.4 (57.6-97.2)	**68.5 (56.2-80.7)**	43.5 (37.9-49.1)
MF + MAP + UtPI + PlGF + PAPP-A	**77.4 (57.6-97.2)**	**66.8 (54.4-79.1)**	**44.1 (38.5-49.7)**

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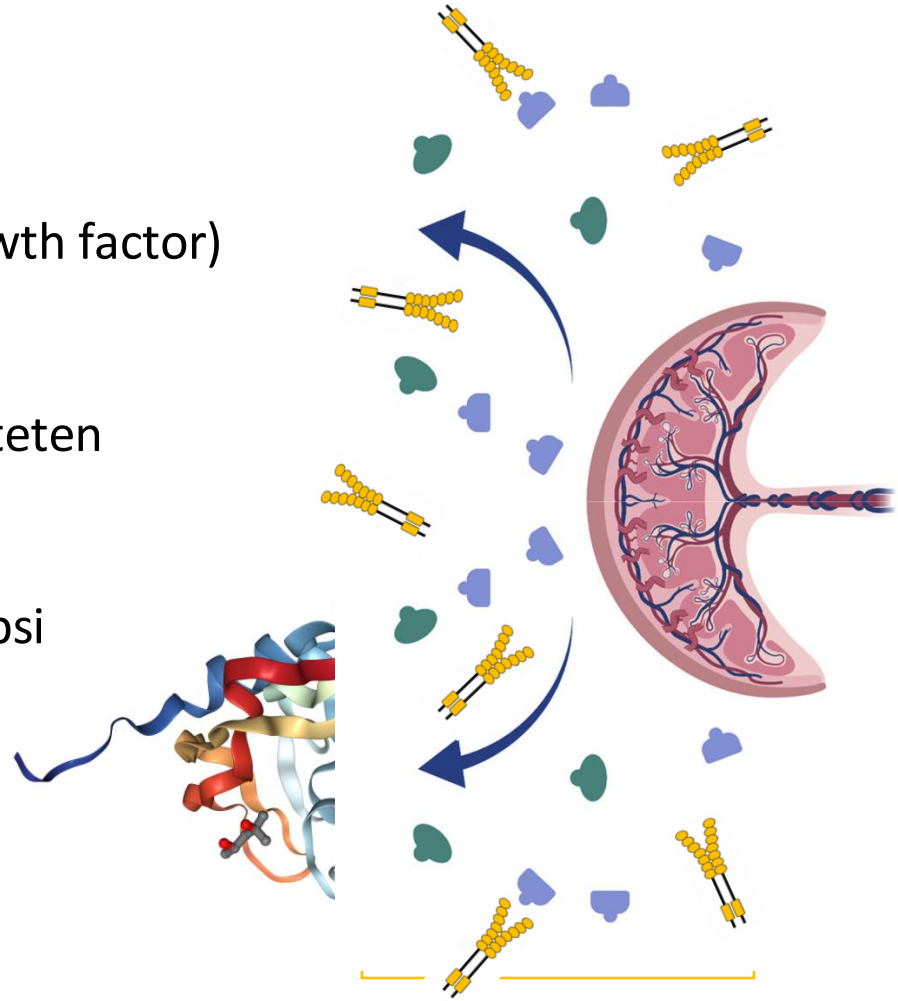
- Placental Growth Factor (PlGF)
  - Medlem af VEGF-familien (vascular endothelial growth factor)
  - Udskilles fra trofoblaster i placenta
  - Spiller en vigtig rolle i kar-nydannelse under graviditeten
  - Optimal placentafunktion afhænger af PlGF
  - PlGF-niveau er nedsat i graviditeter med præeklampsi



PREPRED

Preeclampsia Prevention in Denmark

- Placental Growth Factor (PlGF)
  - Afgørende markør i første trimester screening for præeklampsi

OBSTETRICS

Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation

Neil O'Gorman, MD; David Wright, PhD; Argyro Syngelaki, RM; Ranjit Akolekar, MD; Alan Wright, PhD; Leona C. Poon, MD; Kypros H. Nicolaides, MD

Am J Obstet Gynecol. 2016;214(1):103.e1-103.e12. doi:10.1016/j.ajog.2015.08.034

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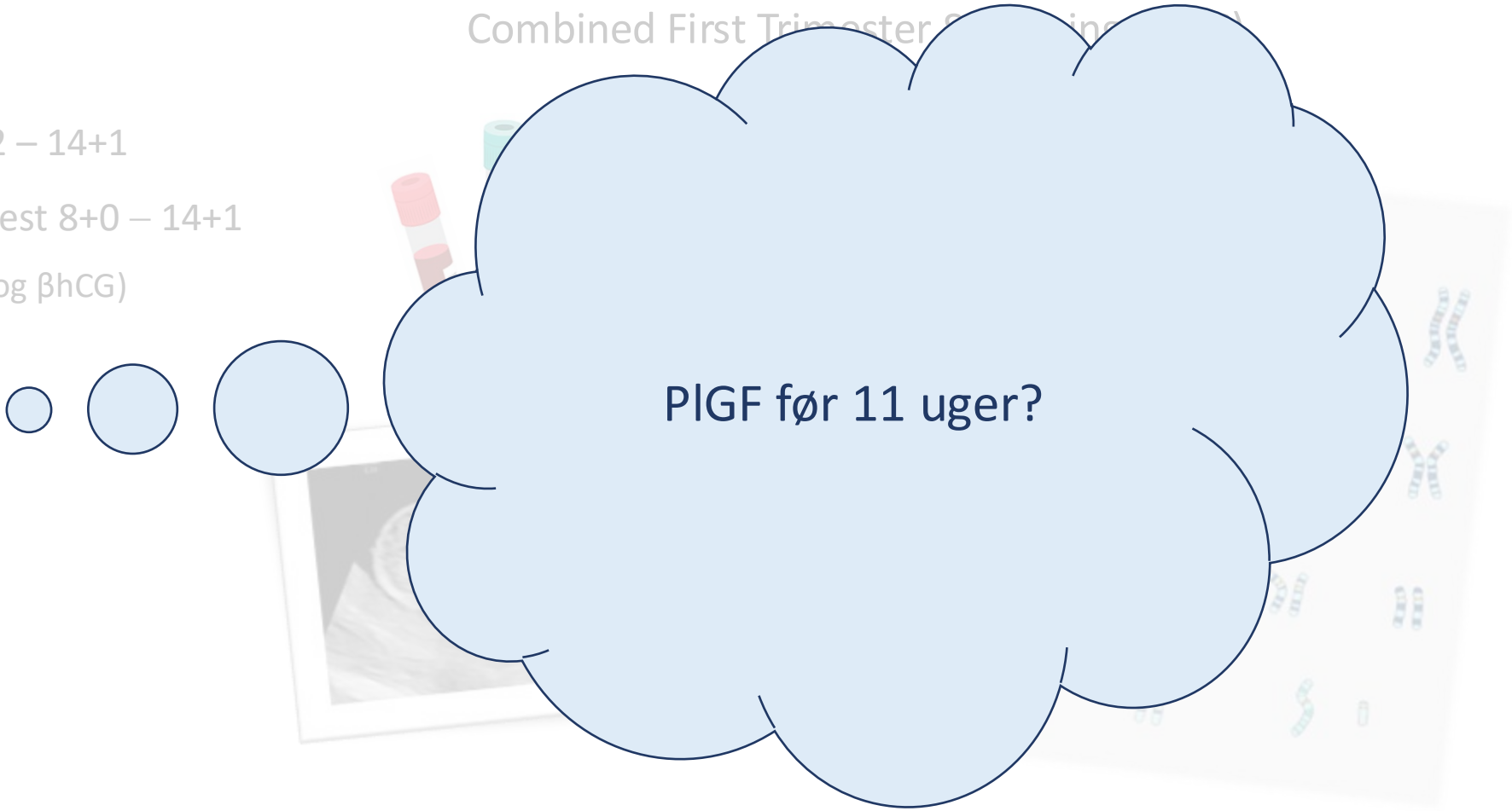
Combined First Trimester Screening (FMF)

- GA 11+2 – 14+1
- Doubletest 8+0 – 14+1

  (PAPP-A og βhCG)



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- Study population:
  - Participants from the PRESIDE study who had a PlGF measurement from the **routine** combined first trimester screening (cFTS) blood sample (n = 8,386)

PREPRED
Preeclampsia Prevention in Denmark

Main findings

- Screening for præeklampsi er muligt og gavnligt i Danmark
- FMFs screening for præeklampsi < 37 uger i Denmark (67%) er signifikant bedre en de nuværende guidelines (~30 %)
- PlGF kan tages fra uge 10
- Danske gravide er positivt indstillet overfor præeklampsi-screening

PREPRED

Preeclampsia Prevention in Denmark

Tak for i dag

Projektgruppe:

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Olav Petersen, Professor, PhD[1]
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Arbejdsgange i 1. trimester

Før scanning

Information

Booking

Doubletest

Scanning

Praktisk setup

Personale

Ressourcer

Efter scanning

Risikoestimat

Hjertemagnyl

Opfølgning

Før scanning

Information

- Hvem informerer om screeningstilbuddet?
- Muligheder for at fravælge biokemi aktuelt – hvordan?

Booking

- Hvem booker tid til blodprøvetagning?
- Samarbejde med almen praksis og praksiskoordinatorer?

Doubletest

- Hvornår tages blodprøven typisk (GA)?
- Hvor tages blodprøven? Regionale forskelle?

Scanning

Praktik

- Lokale til blodtryksmøbel
- Måling af a. uterina flow. Udvidet scanningstid?

Personale

- Blodtryksmåling
  Gravide/pårørende
  Personale
- Oplæring i flowmåling
  Certificering
  Audit

Ressourcer

- Lokal prioritering af PREPRED-midler
- Bemanding og rekruttering

Efter scanning

Risikovurdering

- Hvem informerer om resultatet af screening?
- Nuværende arbejdsgang ved høj risiko

Hjertemagnyl

- Information om behandlingen
- Effektuering
  Recept

Opfølgning

- Sikkerhedsnet for gravide med høj risiko
- Samtale
  Oplysning
  For alle gravide?

Arbejdsgange i 1. trimester

Eventuelt

PRESIDE
Preeclampsia Screening in Denmark

FØTO DATABASEN
The Danish Fetal Medicine Database

Future Danish setup for blood samples

Screening for Trisomy 21:

Detection rate ~ 90%

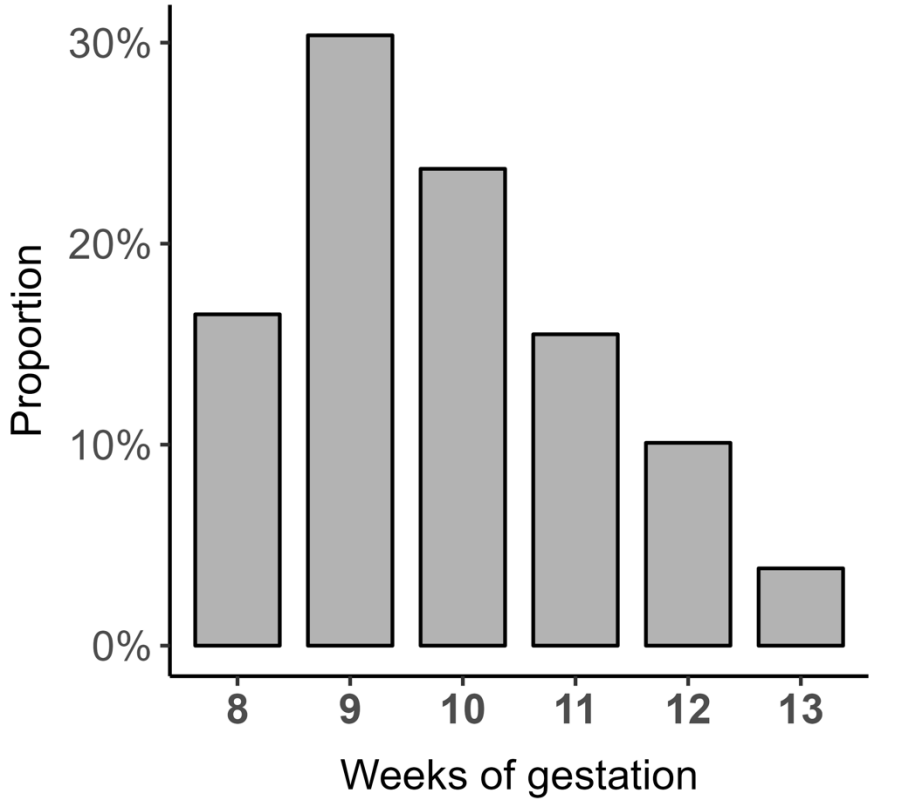
Screen-positive rate ~ 5%

First-trimester combined screening for trisomy 21 at 7–14 weeks' gestation

D. WRIGHT*, K. SPENCER†, K. KAGAN K‡, N. TØRRING§, O. B. PETERSEN¶, A. CHRISTOU**, J. KALLIKAS†† and K. H. NICOLAIDES‡‡

Prospective study evaluating performance of first-trimester combined screening for trisomy 21 using repeat sampling of maternal serum markers PAPP-A and free β-hCG

C. EKELUND*, D. WRIGHT†, S. BALL†, I. KIRKEGAARD‡, P. NØRGAARD§, S. SØRENSEN¶, L. FRIIS-HANSEN**, F. S. JØRGENSEN§, N. TØRRING††, B. H. BECH‡‡, O. B. PETERSEN‡ and A. TABOR*



Histogram of gestational age at doubletest

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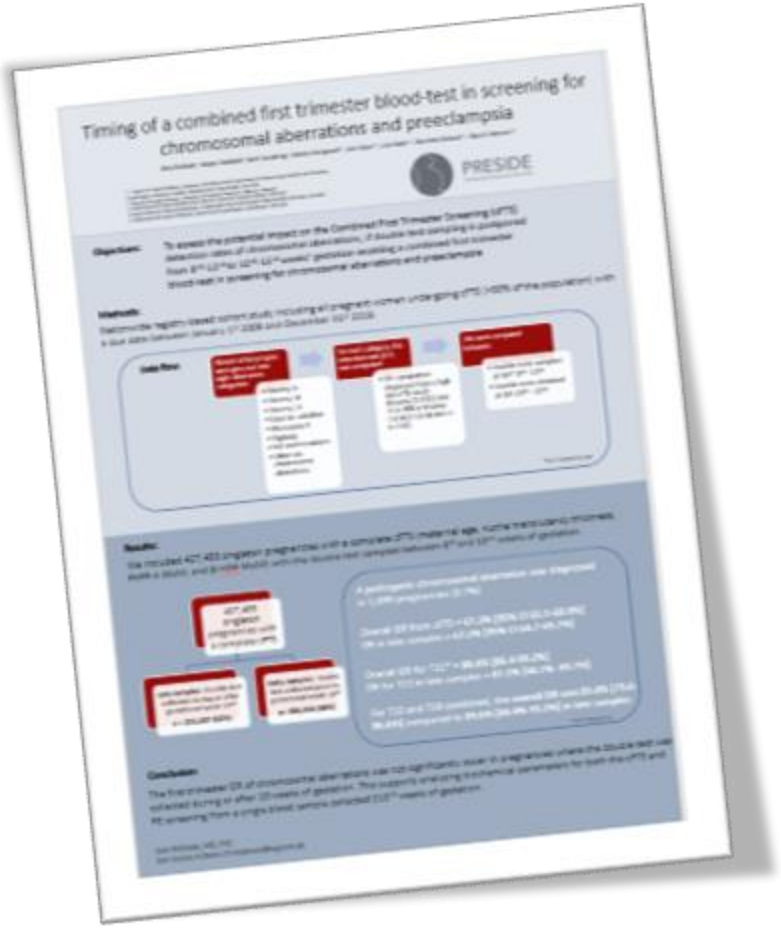
Will it affect performance if blood is collected at 10-14 weeks?



PRESIDE

Preeclampsia Screening in Denmark

Will it affect performance if blood is collected at 10-14 weeks?

Timing of a combined first trimester blood-test in screening for chromosomal aberrations and preeclampsia

Iben Riishede[1], Kasper Gadsbøll[1], Karin Sundberg[1], Martin Overgaard[2,3], Ann Tabor[1,5], Line Rode[1,4], Charlotte Ekelund[1,5], Olav B. Petersen[1,5]

1. Center for Fetal Medicine, Pregnancy and Ultrasound, Department of Gynaecology, Fertility and Obstetrics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
2. Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
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5. Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

427,493 singleton pregnancies with a complete cFTS

Late samples: Double test collected during or after gestational week 10^{+0}

n = 221,037 (52%)

Early samples: Double test collected prior to gestational week 10^{+0}

n= 206,456 (48%)