Ny veileder for diabetes i svangerskapet – hva er nytt?

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Avdeling for endokrinologi, forebyggende medisin og sykelig overvekt

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Innhold

1. Komiteens arbeid:
   Tilrådning, evidensgrunnlag
2. Bakgrunn for viktigheten av planlagte svangerskap og tidlig intervensjon ved type 1 og 2 diabetes
3. Vektfokus
4. Litt om oppfølging av etablert diabetes hos gravide
5. Postpartum – hva nå?

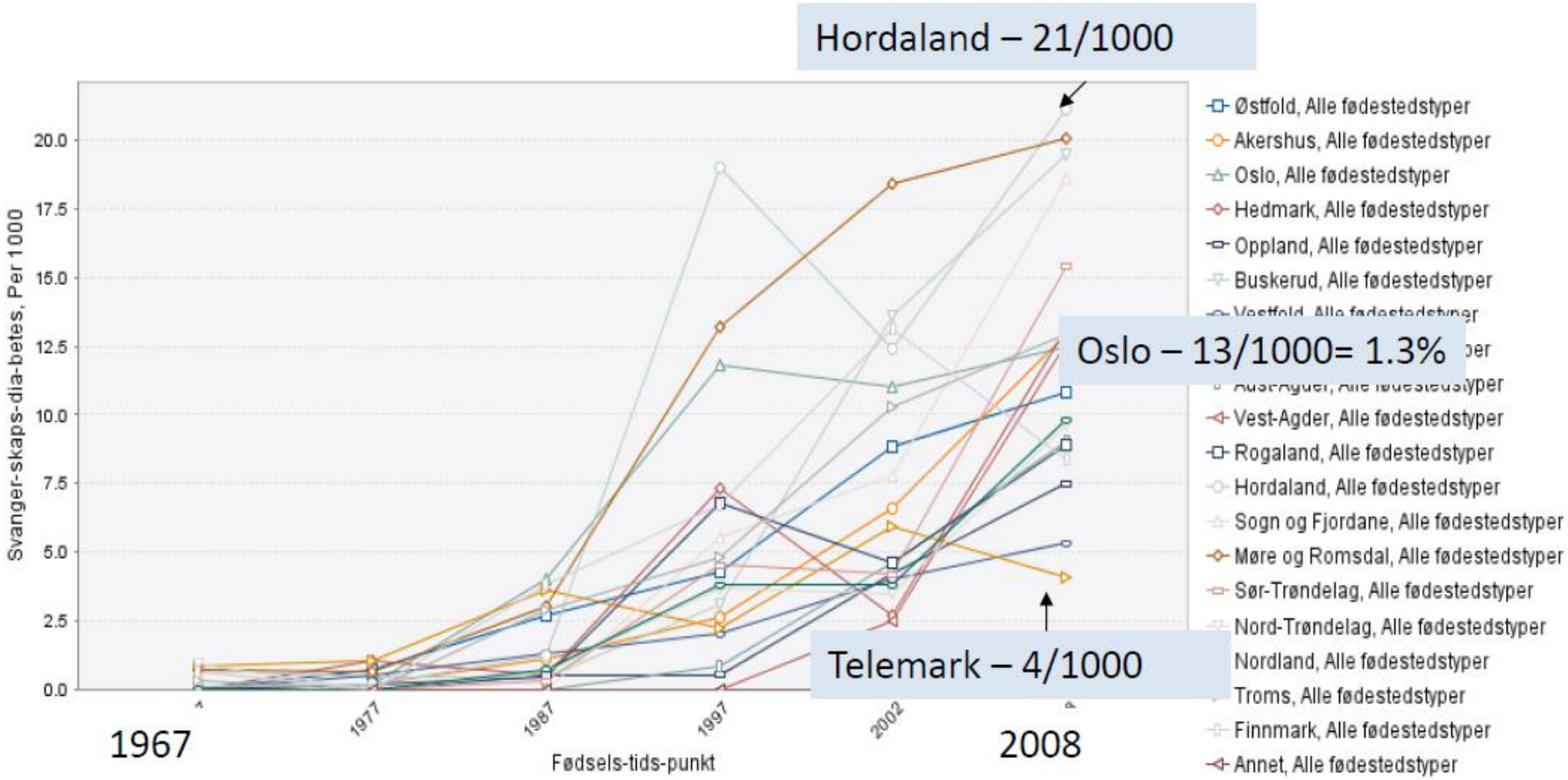
Ny diabetesveileder- på vei ut på høring:

Working group – appointed by The Directorate of Health:
Senior Prof. Kristian F. Hanssen (leader, endocrinologist)
Clinical consultant Hrafnkell Baldur Thordarson (endocrinologist)
Prof Tore Henriksen (obstetrician)
Kirsti Bjerkan (dietitian)
Helene Oeding Holm (midwife)
Hilde Beate Gudim (general practitioner)
Prof Anne Karen Jenum (general practitioner, guideline author)
+++

Status for the GDM guideline: Not yet approved by the The Directorate of Health
New generation of electronical guidelines – based on the Magic app format
Recommendations in multilayered presentation formats

Forekomst av svangerskapsdiabetes, fylkesvis

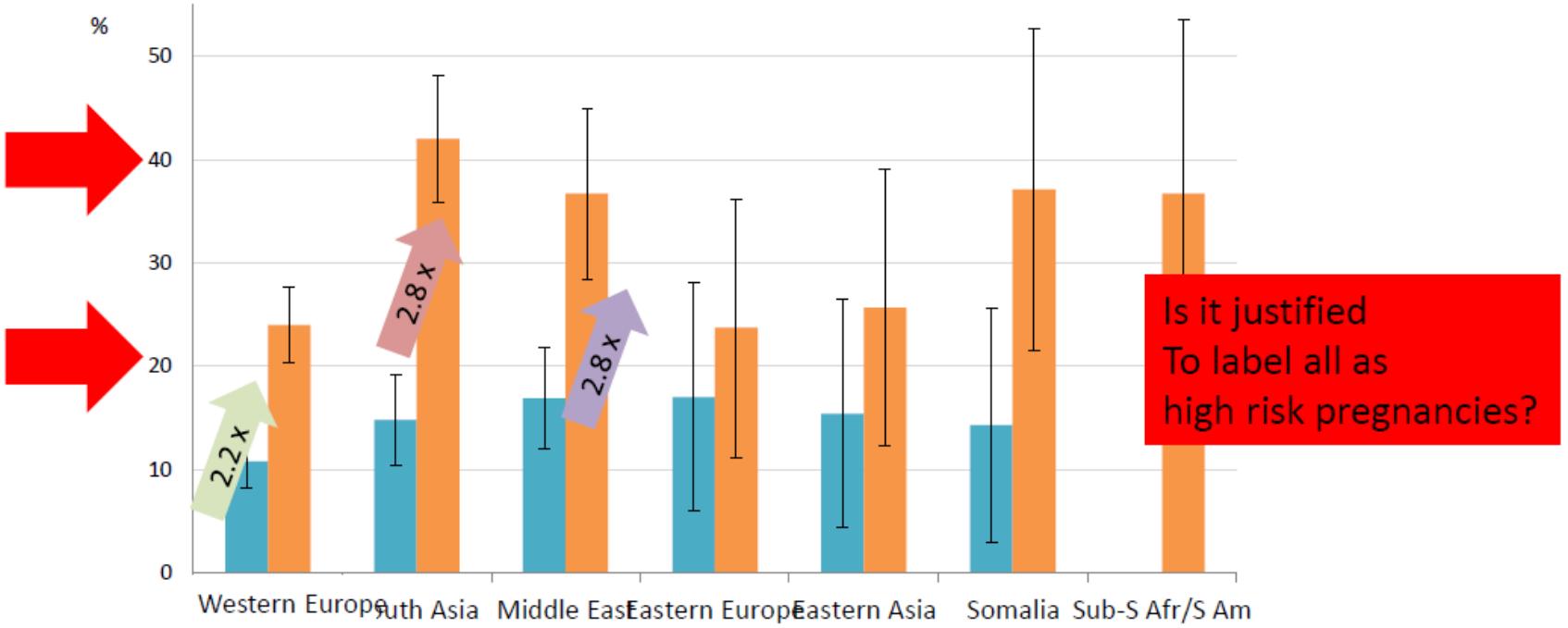
Data from Medical Birth Registry



Regional differences not explained by demografic data,
but probably by differential adherence to risk factor screening

GDM prevalence (95% CI) – universal OGTT GW 28

Criteria	FG	2-h	GDM %
WHO	7.0	7.8	13
IADPSG	5.1	8.5	32



Is it justified
To label all as
high risk pregnancies?

Fasting + 2 h glucose measured at site (HemoCue)
759 women, 2008-2010

Jenum et al, 2012

New criteria for GDM proposed by the guideline g

Criteria	FG mmol/l	1-t	2-t-mmol/l	Abnorm
WHO 1999	7.0		7.8	≥1
IADPSG (WHO 2013)	5.1	10.0	8.5	≥1
Norway 2015	**5.3**		**9.0**	**≥1**

Clinical practice point (Weak evidence)

Criteria proposed by E. Ryan and L. Hartling, based on an OR 2.0 for adverse outcomes.

Rationale for not adhering to the WHO 2013 criteria:

Concerns about labelling 20-40% of pregnancies as GDM **(glucocentric – not total risk appro**

Some identified by WHO 2013 will be at low risk

Effect on total LGA prevalence is unclear

Priorities in health care – suggestions for alternative spending on

- identifying women with GDM
- populationsbased strategies to prevent obesity in young women
- improved care for obese women related their substanially increased risk

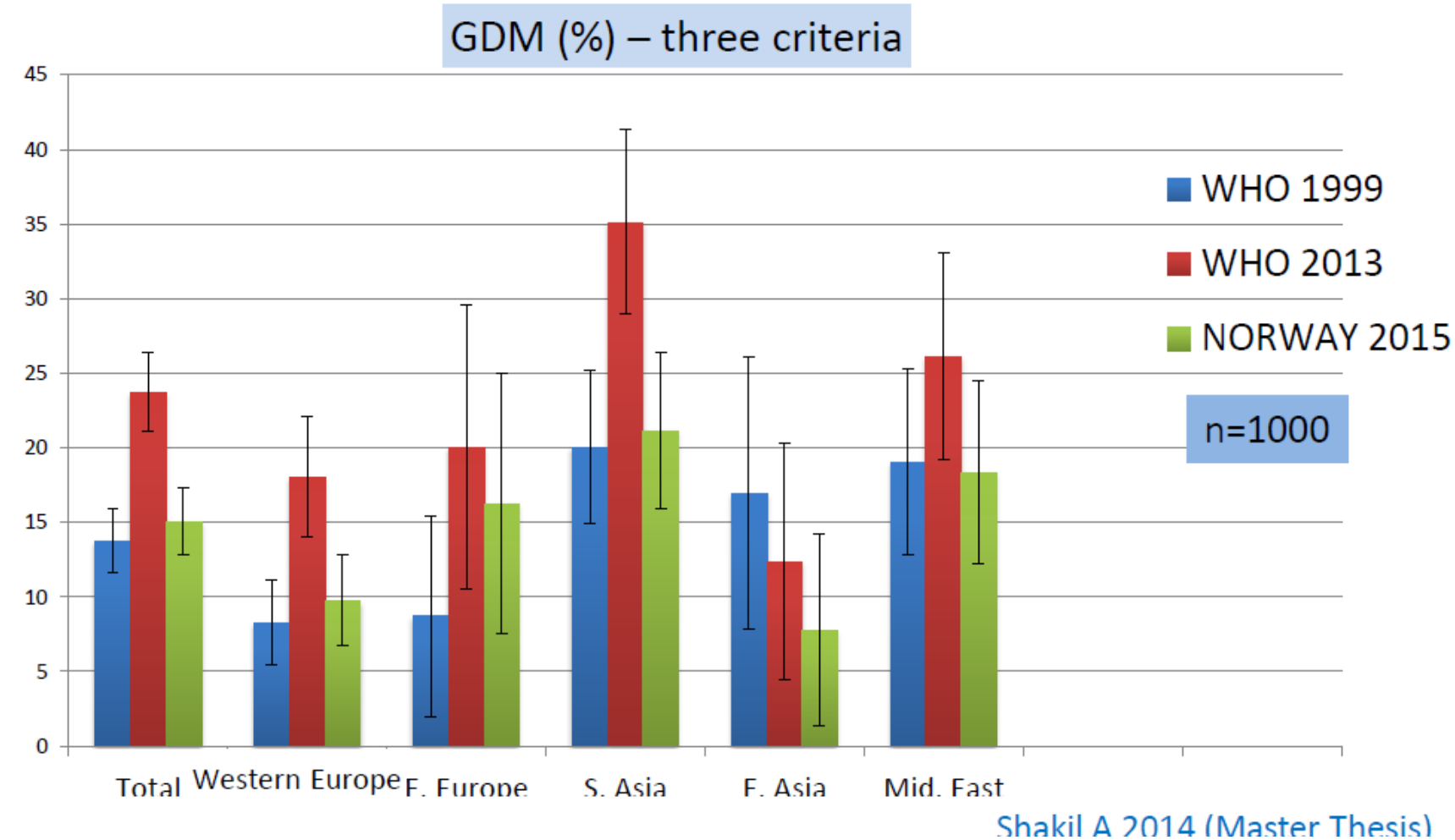
TOO MUCH MEDICINE

Gestational diabetes: new criteria may triple the prevalence but effect on outcomes is unclear

BMJ 2014;348:g1567 doi: 10.1136/bmj.g1567 (Publish

STORK G 2 (2010-2012)
External validation and feasibility study

Universell screening as part of routine antenatal care in the same districts



Shakil A 2014 (Master Thesis)

Screening strategi: svangerskapsdiabetes

STRONG RECOMMENDATION (despite weak direct evidence)
All pregnant women, gestational week 24-28
We recommend OGTT
(unless no risk factors for GDM or already diagnosed with diabtes/GDM)

Rationale:

- Demographic and epidemiologic transition – more women are at risk risk today!
- GDM usually without symptomes in GW 24-28
- Some women with GDM have few classical risk factors
- Few women are without any risk factors (10-15%?)
- With risk factor based screening at least 30% are missed (false negative) and not offered treatment shown to be effective to reduce risk of adverse outcomes. Not only mild cases missed
- More logical, and proven to be feasible that OGTT is routinely offered, than for GPs and midwifes to remember all risk factors

OGTT not necessary if all of these factors are present:
European origin, age < 25 years, BMI < 25 kg/m^2, no previous IGT/GDM or adverse pregnancy outcomes assosiated with GDM, no family history T2D

How to detect undiagnosed diabetes in early pregnancy?

WEAK RECOMMENDATION

All pregnant women, first antenatal booking

We suggest HbA1c to identify women with undiagnosed diabetes

Rationale:

- Demographic and epidemiologic transition – more women with undiagnosed diabetes
- Undiagnosed T2D usually without symptomes, but substantially increase the risk for mother and offspring
- HbA1c > 5.9 % identifies women with high risk of adverse outcomes
- HbA1c >= 6.5 % is diagnostic of diabetes
- Feasible test for women and health care
- Acceptable costs

Diabetes Care Volume 37, November 2014

An Early Pregnancy $HbA_{1c} \geq 5.9\%$ (41 mmol/mol) Is Optimal for Detecting Diabetes and Identifies

Ruth C.E. Hughes,[1] M. Peter Moore,[2] Joanna E. Gullam,[1] Khadeeja Mohamed,[3] and Janet Rowan[4]

Vision: Antenatal care as an instrument to improve maternal and offspring health by addressing the new public health challenges

The fist antenatal booking

- Risk stratification acoording to BMI
- Good dietary councelling to all women to improve short (and long ter outcomes
- Support all women to avoid excessive weight gain
- Support obese women to plan for lower gestational weight gain than IOM recommendations

Postpartum follow-up of women with GDM to

- reduce her risk of T2D
- improve maternal prepregnancy metabolic profile before subsequent pregnancies
- Support a healthy diet and physical activity for the whole family
  - **a life course approach**

Gravide med Type 2 Diabetes fra andr land

Skiller seg fra type 1 Diabetes på mange måter:

- Høyere alder
- Abdominal fedme
- Mange svangerskap
- Økt forekomst av hypertensjon
- lav sosio-økonomisk klasse
- Kulturelle forskjeller (språk,kost os.v.)

Oppsummering

1) Diagnostic criteria for **GDM**:

f. glucose: 5.3 mmol/l

2-h glucose: 9.0 mmol/l

2) OGTT offered to all women in GW 24-28

(except those without any risk factors)

3) HbA1c offered to all at first antenatal booking

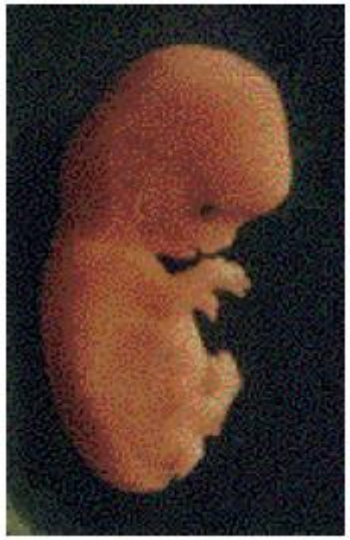
– pregestational diabetes

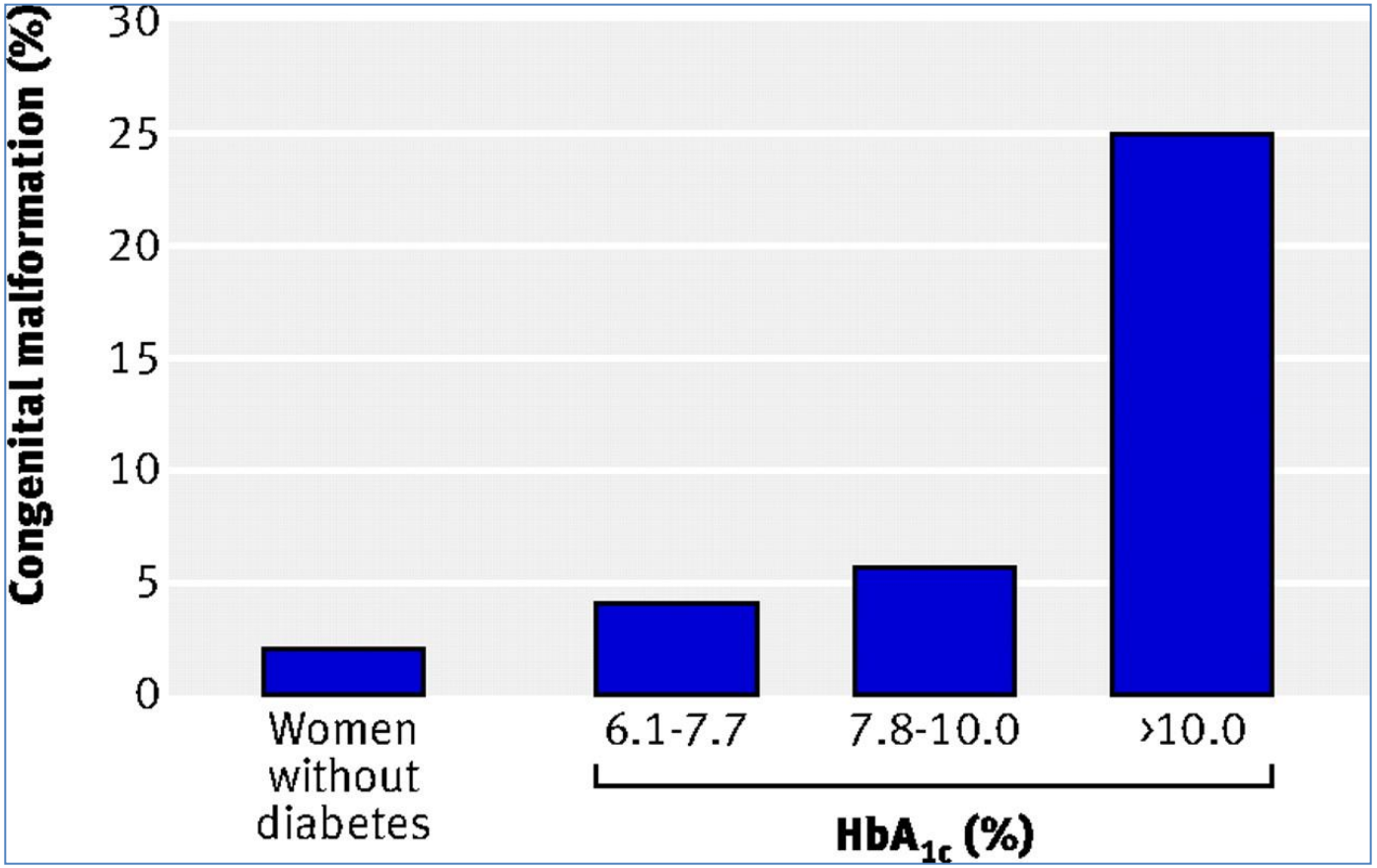
4) HbA1c 3-4 months **postpartum** og yearly thereafter

↓ maternal risk of T2D, ↑ awareness before next pregna

5) Addressing new public health challenges, not only hypergly

Risk for misdannelser i svangerskapet ved type 1 diabetes





Rosenn et al, Obstet Gynecol 1994,Taylor, R. et al. BMJ 2007;334:742-745

BMJ

Type 2 diabetes – er sykdommen "snillere"?

Characteristics	n	Type 2 DM	Type 1 DM
Age (yr)	23	33.9	28.8
BMI (kg/m^2)	12	30.2	24.2
DM duration (yr)	15	5.9	11.9
Chronic hypertension (%)	6	11.2	5.5
Retinopathy (%)	13	6.2	25.3
Micro/macroalbuminuria (%)	10	2.9	6.8
Prepregnancy care (%)	11	18.8	34.8
Gestational age at booking (wk)	12	16.2	15.2
HbA1c (%)			
At booking	9	7.20	8.06
Second trimester	4	5.70	6.23
Third trimester	7	5.69	6.00

n, Number of papers contributing to each characteristic.

Balsells Metaanalysis, JCEM 2009

Timing of congenital malformations

Weeks

0.
1.
2.
3.
4.
5.
6.
7.

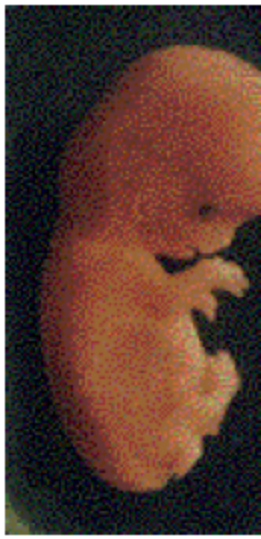
Ovulation

Caudal regression

Spina bifida, anencephalus

Transposition, renal abnormalities

Ventricular septal defect, anal atresia



Nye poenger i retningslinjer type 1 og type 2 diabetes

- Svært viktig med veiledning FØR svangerskapet
- HbA1c < 7.0% før svangerskapet
- Type 2 diabetes:
- Evt Metformin ikke sulfonylurea
- Vektøkning i svangerskapet som anbefalt i IOM retningslinjer

Vektøkning: viktig for makrosomi i diabetiske svangerskap?

- Også ved T1DM ses økt pregravid BMI, og forekomst av makrosomi er fortsatt høy tross streng bls regulering. Føtal veksthemming er sjelden utenom ved DN eller PE.
- Hvilke andre faktorer kan bidra til makrosomi?

BMI-appropriate gestational weight gain:
12.5–18.0 kg for underweight,
11.5–16.0 kg for normal weight,
7.0–11.5 kg for overweight,
and 5.0–9.0 kg for obese women
(IOM 2009)

Gestational weight gain (GWG) in T1 DM	Excessive (*n* = 62)	Appropriate (*n* = 37)	Insufficient (*n* = 16)	*P* value
Total, kg	17.7 (10–30)	13.1 (6–16)	8.5 (−2 to 11)	<0.001
<8 weeks, g/week	257 (−303 to 2,016)	216 (−335 to 515)	87 (−385 to 463)	0.003
8–21 weeks, g/week	405 (42–818)	293 (−177 to 717)	171 (−692 to 338)	<0.001
21–36 weeks, g/week	640 (271–1,173)	444 (27–771)	350 (−100 to 533)	<0.001

Offspring birth weight decreased across the groups 3,681 [2,374–4,500] vs. 3,395 [2,910–4,322] vs. 3,295 [2,766–4,340] g [*P* = 0.02] resp). In regression analysis, GWG (kg) was associated with offspring birth weight (g) (β = 19; *P* = 0.02) when adjusted for prepregnancy BMI, HbA_{1c} at 36 weeks, smoking, parity, and ethnicity.

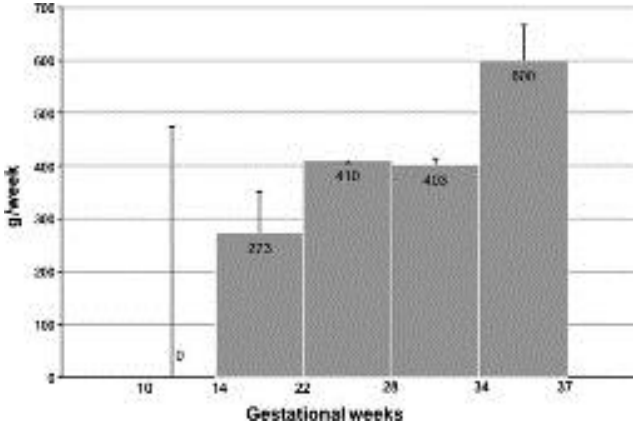
In infants of **T1 diabetes** mothers, severe neonatal morbidity was comparable across the GWG groups.

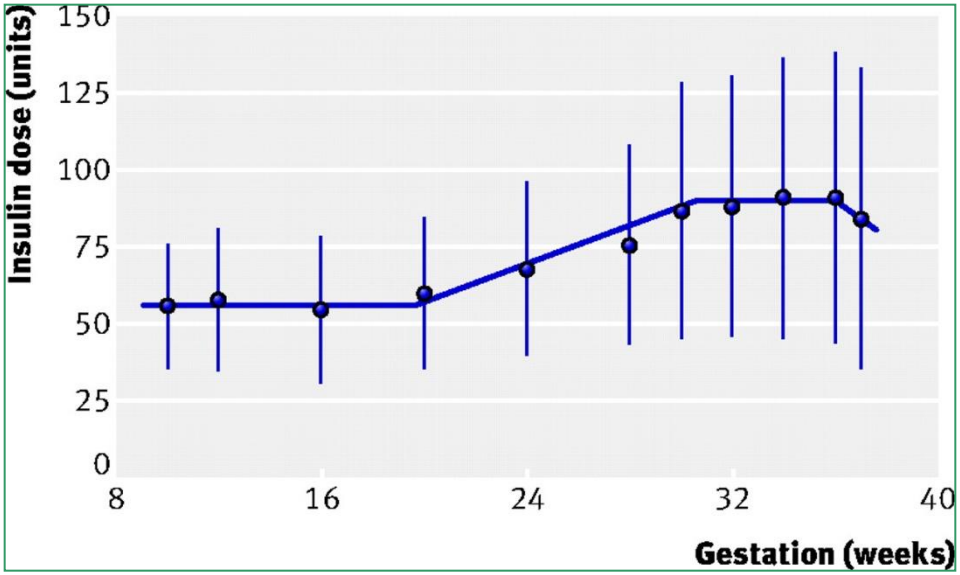
Secher DC 2014

Begrense vektøkning: viktig for perinatal morbiditet i T2DM svangerskap?

17 women (29%) gained ≤5 kg, and 41 gained >5 kg. Median GWG was 3.7 kg (-4.7 - 5 kg) and 12.1 kg (5.5-25.5 kg), resp. Prepregnancy BMI was 33.5 kg/m^{2,} (30-53) vs. 36.8 kg/m^2 (30-48), P = 0.037, and median HbA1c 6.7% at first visit in both groups and 5.7 and 6.0%, P = 0.620, in late pregnancy, resp.
GWG ≤5 kg was associated with lower birth weight z score (P = 0.008), lower rates of LGA infants (12 vs. 39%, P = 0.041), delivery closer to term (268 vs. 262 days, P = 0.039), and less perinatal morbidity (35 vs. 71%, P = 0.024) compared with pregnancies with GWG >5 kg.

Asbjørnsdottir 2008, Parellada 2014





Glargine, detemir, aspart og lispro i svangerskap:

- Non-inferiority for maternelle og føtale outcomes, men gir i noen studier lavere fbls.
- Langsiktige negative utfall for barna er foreløpig ikke publisert.
- Små studier
- Lite data for glulisine (Apidra).

Metaanalyse ShiShi Arch Gyn Obst 2015.

Hypoglykemi
– specific risks in pregnancy

- Økt insulin sensitivitet til uke 10-12
- Kan gi ”impaired awareness”
- Fall i blodsukker kan ses ved svekket placenta funksjon (risk for IUFD)

Diabetes and forløsning

- Vurder induksjon ved uke 38 (T1DM), bør forløses ved termin
- Latensfase: vanlig insulinregine dersom i form og godt næringsinntak.
- Aktiv fødsel: bls hver time, mål : Glucose goal: 4-6 mmol/l.

- **Start glucose infusion: 50mg/ml by body weight:**

Bls <3,5mmol/l	**60kg 180ml/t – 80kg 250 ml/t – 100kg 300ml/t**
Bls 3,5-6,0 mmol/l	60kg 90ml/t – 80kg 125 ml/t – 100kg 150ml/t
Bls 6,1-8,0 mmol/l	2IE HV insulin sc, dersom høy etter 2t, gjenta etter protokoll.
Bls 8,1-10,0 mmol/l	4IE HV insulin sc, dersom høy etter 2t, gjenta etter protokoll.
Bls >10,0mmol/l	6IE HV insulin sc, dersom høy etter 2t, gjenta etter protokoll.
Bevisstløs? 200mg/ml 40 ml iv umiddelbart , gjenta etter 10min dersom fortsatt bevisstløs. Stopp infusjon etter fødsel dersom bls b-glc 5,0-12,0 mmol/l.	

Hypertensjon hos gravide

Insidens

- 8-10 % of pregnancies.

Kronisk hypertensjon 1-2 %, gestasjonell hypertensjon 4-5 %, preeclampsia ca 3 % (Norge).

Definisjoner

Kronisk hypertensjon : pregestasjonell eller BT≥140/90 mmHg før 20. uke.

Dersom proteinuria mulig preeklampsi («superimposed preeclampsia")

Gestasjonell hypertensjon: BT≥140/90 mmHg etter 20. uke uten proteinuri og BT normalt 12 uker postpartum.

Veileder i fødselshjelp 2014

Hypertensjon:
Behandling

- Hvile, saltfattig diett
- KI: ACE-I / ATBR2

- **Hyppigst brukt:**
  Labetalol tabl. 100 mg x 2, opp til 200 mg x 2-3.
  Max plasmakonsentrasjon etter 1-2 t.
- Nifedipin tabl 10 mg x 2, opp til max 40 mg x 2/24t. Effekt etter 45-60 min. Retard preparat: 30 mg x 1 evt. 30 mg x 2
- Metyldopa tabl. 250 mg x 2-3. Opp til 500 mg x 3.
  Effekt etter 3-8 t, full effekt 12 t.
- Vurder kombinasjon for å redusere BV

Veileder i fødselshjelp 2014

Svangerskap og nefropati

- **5-10%** av gravide med diabetes
- **Risk for preeklampsi ved MA** : 42%,
  ved proteinuria 64%.
- **Skal ha intensiv antihypertensiv behandling**:
  men det er ikke vist langtidsskade på nyrefunksjon eller påvirket overlevelse av svangerskap (follow up 16 years)

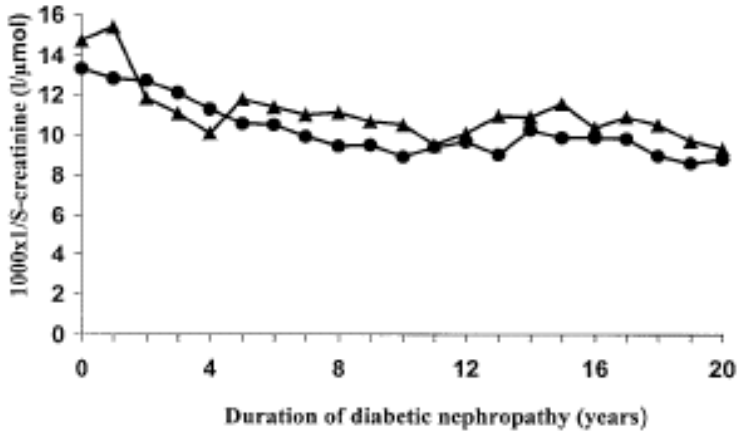
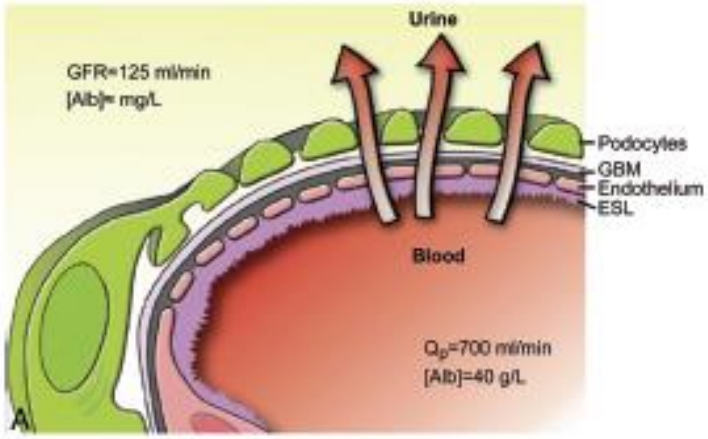


Fig. 1. Mean values of 1/s-creatinine according to duration of diabetic nephropathy in women with Type I diabetes. Pregnant group (▲) and non-pregnant group (●)

Diabetes og proteinuri:

Grad av nyreskade mest viktig for svangerskapsutfall

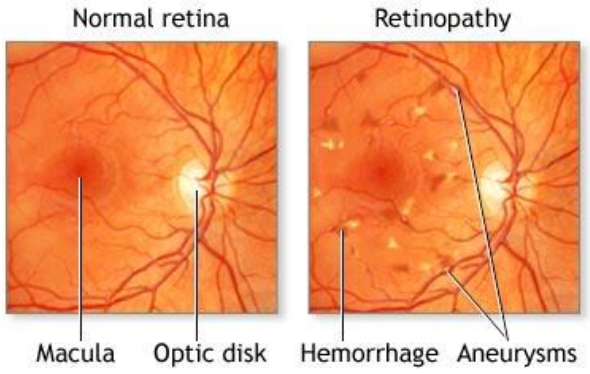


- **mild** nefropati, normalt BT , ingen/lite proteinuri:
  bra outcomes, lav risk for ESRD eller prematur fødsel
- **Moderat/uttalt nyresvikt gir økt :**
  >70% med kreatinin 220 mcmol/l føder prematurt og >40% får preeklampsi.
- Disse har også antakelig økt risk for nedsatt nyrefunksjon: *GFR <40 and proteinuri>1g/d pregestasjonelt)*
  Imbisciati AmJ Kidn Dis 07

Maynard JASN 2009 Lindheimer Obstet Gynecol 2010

Type 1 og 2 diabetes: øyekontroller

- Alle: uke 10-12
- Normale funn: neste us ved uke 32-34
- Retinopati eller diabetes > 10 år:
  kontroll i uke 24 og 32-34
- Proliferativ retinopati
  - individualisere kontroller
  - laser?



Progresjon av retinopati hos gravide

- Oftest forbigående, varer inn i post partum året
- Uvanlig<5%, behov for laser terapi 2%
- Hyppigere ved diabetes >10 år og moderat/ alvorlig RT

Table 4 Patient characteristics and progression of retinopathy

	Progression	No progression	*P*
Number	9	170	
HbA_{1c} at booking (%)	7.5 (1.2)	6.6 (1.5)	0.08
Fall in HbA_{1c} (booking to 24 weeks)	1.6 (1.0)	1.2 (0.9)	0.2
Smokers (%)	55	25	0.06
Prepregnancy care (%)	22	39	0.7

Temple et al. Diab Med 2002, Kaaja Thromb Res 2011

Gjennomført glukosebelastning etter fødsel?

Diagnose	Asia/Afrika N=188 %	Norge N=136 %
Ingen diabetes	40	72
Glukoseintoleranse	34	16
Manifest diabetes	**26**	**12**
Ikke møtt	44	35

Holan S et al. Tidskr Nor Legeforen, 2008

UK: Post partum oppfølging

Post partum	6-13 u	>13 uker	Risk	Årlig HbA1c	
F-bls <6mmol/l	x		Moderat	x	
F-bls 6,0-6,9mmol/l	x		Høy	x	
F-bls >7,0 mmol/l	x		T2 DM sannsynlig		Bekreft diagnose
HbA1c <5,7%		x	Moderat	x	
HbA1c 5,7-6,4%		x	Høy	x	
HbA1c ≥ 6,5%		x	T2 DM sannsynlig		Bekreft diagnose

NICE 2015

Rådgiving før svangerskap:

ved T1-diabetes, T2-diabetes og tidligere svangerskapsdiabetes

- ♀ alder 15-45: Ta opp prevensjon og barneønske med jevne intervaller
- Informer om diabetes risk for barnet.
- **Bør ha HbA1c <7.0% ved unnfangelse:** grunnet risk ved hyperglykemi for organmisdannelser og spontane aborter. Ved kunstig befruktning: god regulering gir økt sannsynlighet for vellykket feste av egget.
- **Skal møte til tidlig kontroll** (uke 7-8 ved påvist graviditet).

Hindre for prekonsepsjonell veiledning

- Ble gravid fortere enn ventet
- Bekymret for mulig infertilitet
- Negativ erfaring med helsepersonell
- Ønske om et ”normalt” svangerskap
- Vansker med å komme til kontroll

Murphy HR et al: Diabetic Medicine 2010;27:92-100

Fraråde/vente med svangerskap?

- Nesten ingen !
- Ved alvorlig og ubehandlet øyesykdom

  (meget få)
- Alvorlig nyresykdom med klart påvirket nyrefunksjon (meget få)
- **For alle med diabetes: viktig å planlegge graviditet** (HbA1c< 7.0 %)

Effectiveness of a Regional Prepregnancy Care Program in Women With Type 1 and Type 2 Diabetes

Benefits beyond glycemic control

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NICHOLAS J. MORRISH, MD[9]
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Strukturert oppfølging har effekt!

OBJECTIVE — To implement and evaluate a regional prepregnancy care program in women with type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS — Prepregnancy care was promoted among patients and health professionals and delivered across 10 regional maternity units. A prospective cohort study of 680 pregnancies in women with type 1 and type 2 diabetes was performed. Primary outcomes were adverse pregnancy outcome (congenital malformation, stillbirth, or neonatal death), congenital malformation, and indicators of pregnancy preparation (5 mg folic acid, gestational age, and A1C). Comparisons were made with a historical cohort (n = 613 pregnancies) from the same units during 1999–2004.

RESULTS — A total of 181 (27%) women attended, and 499 women (73%) did not attend prepregnancy care. Women with prepregnancy care presented earlier (6.7 vs. 7.7 weeks; $P < 0.001$), were more likely to take 5 mg preconception folic acid (88.2 vs. 26.7%; $P < 0.0001$) and had lower A1C levels (A1C 6.9 vs. 7.6%; $P < 0.0001$). They had fewer adverse pregnancy outcomes (1.3 vs. 7.8%; $P = 0.009$). Multivariate logistic regression confirmed that in addition to glycemic control, lack of prepregnancy care was independently associated with adverse outcome (odds ratio 0.2 [95% CI 0.05–0.89]; $P = 0.03$). Compared with 1999–2004, folic acid supplementation increased (40.7 vs. 32.5%; $P = 0.006$) and congenital malformations decreased (4.3 vs. 7.3%; $P = 0.04$).

CONCLUSIONS — Regional prepregnancy care was associated with improved pregnancy preparation and reduced risk of adverse pregnancy outcome in type 1 and type 2 diabetes. Prepregnancy care had benefits beyond improved glycemic control and was a stronger predictor of pregnancy outcome than maternal obesity, ethnicity, or social disadvantage.

Diabetes Care 33:2514–2520, 2010

Rates of adverse pregnancy outcome (congenital malformation, stillbirth, or neonatal death) in women with diabetes are three to five times greater than those of the background maternity population (1,2). It is therefore recommended that all women of reproductive age with diabetes are offered annual preconception counseling and advised to avoid unplanned pregnancy (3). Prepregnancy care is the targeted support and additional clinical care offered to women planning pregnancy.

It is well established that for women with type 1 diabetes, specialist prepregnancy care improves glycemic control and reduces adverse pregnancy outcomes (4–11). Yet, despite documented benefits in selected centers of excellence, only two regional programs have been described, both almost 20 years ago (4,11). Failure to improve prepregnancy care provision leaves a majority of women at increased risk of potentially preventable poor pregnancy outcomes. This was confirmed by the Confidential Enquiry for Maternal and Child Health, revealing that only 17% of U.K. maternity units offer prepregnancy care and that only 10% of women, mostly

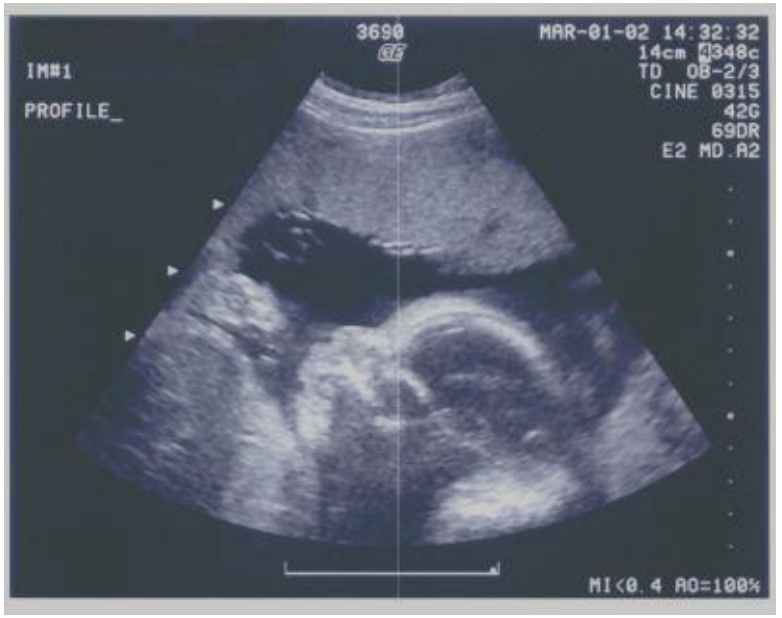
Sammendrag

- Nye retningslinjer for svangerskapsdiabetes omfatter også råd ved overvekt
- Glucosebelastning 24-28 uke hos de aller fleste gravide
- Kriterier for svangerskapsdiabetes :

  fastende > 5.3 mmol/ eller 2 t >9.0 mmol/l
- Tidlig screening HbA1c>5.9 %
- **Ved etablert diabetes**: Organisert veiledning for svangerskapet ved alle sentra HbA1c<7.0

Spørsmål?

Oppfølging av gravide med svangerskapsdiabetes:
Et samarbeid mellom obstetriker og diabeteslege



Elisabeth Qvigstad

overlege, dr.med

Avdeling for endokrinologi, forebyggende medisin og sykelig overvekt

Oslo universitetssykehus

Innhold

- Hvorfor oppfølging i svangerskapet?

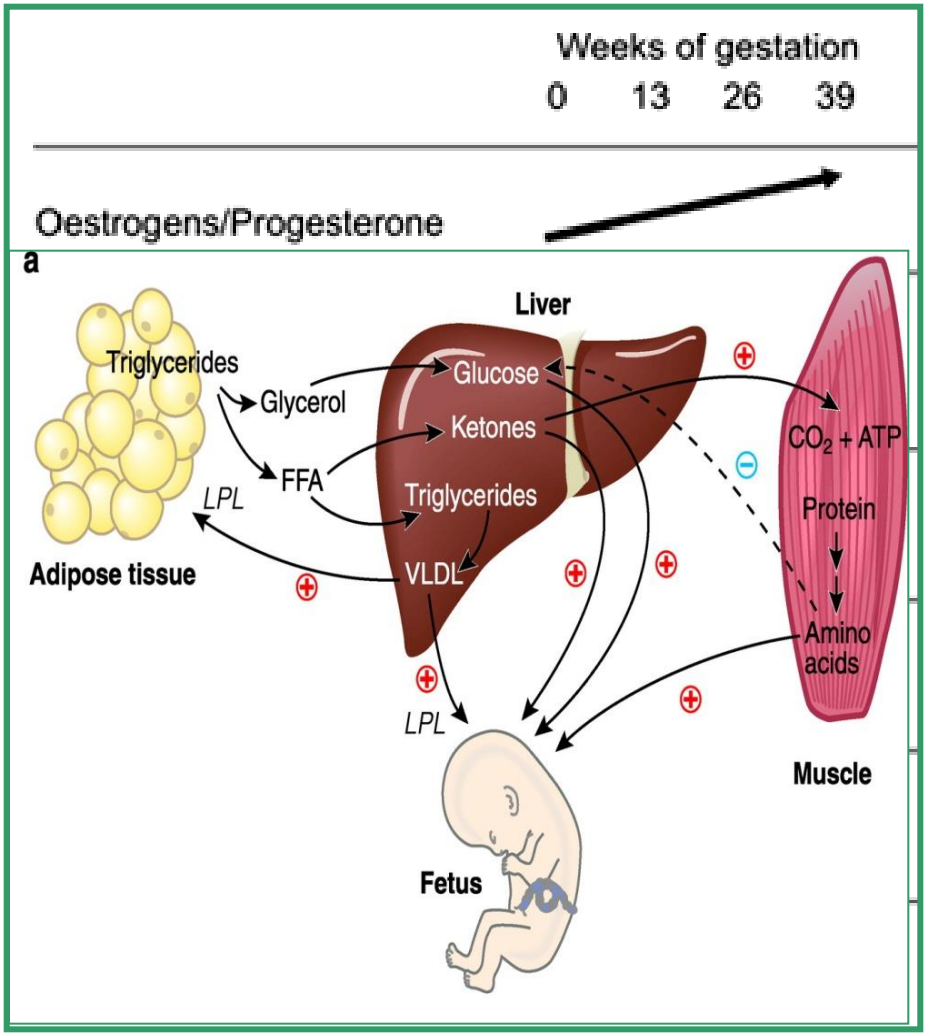
- Behandlingsmål,
  hva slags kontroller?
- Hva slags behandling?
  Insulin, metformin?
- Post partum:
  Livsløpshelse, bedømme
  risk for ny svangerskapsdiabetes
  og familieplanlegging….

Svangerskapsfysiologi

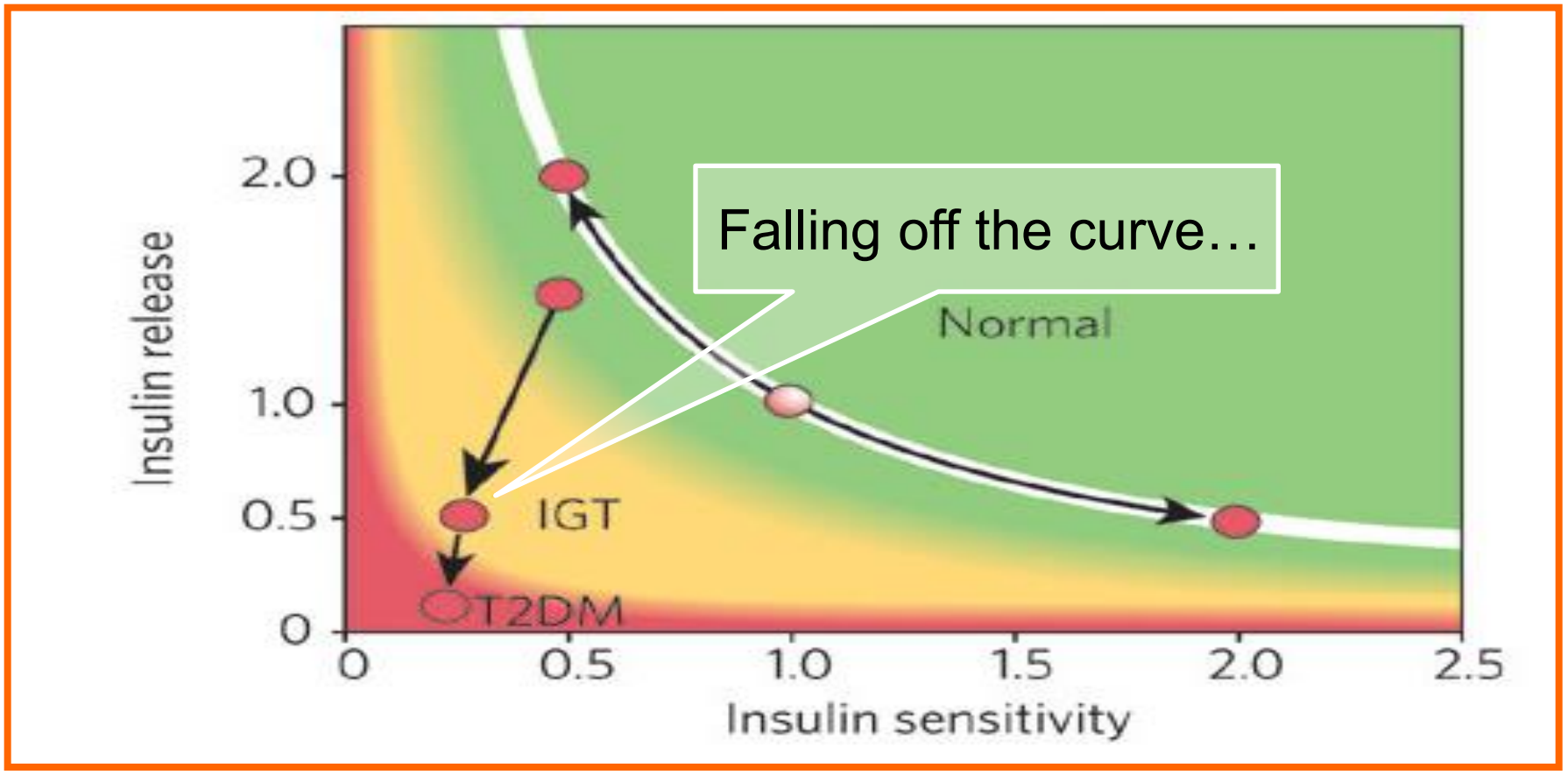
Tidlig: østrogen og progesteron stiger

2. trimester: stigning av hPL, kortisol, prolaktin, nedsatt insulinreseptor-funksjon og økende insulinresistens

"**reprogrammerer**" morens fysiologi : muliggjør stabil tilgang av næring for fosteret tross døgnvariasjon i næringsinntak



Freemark Horm Res 2006

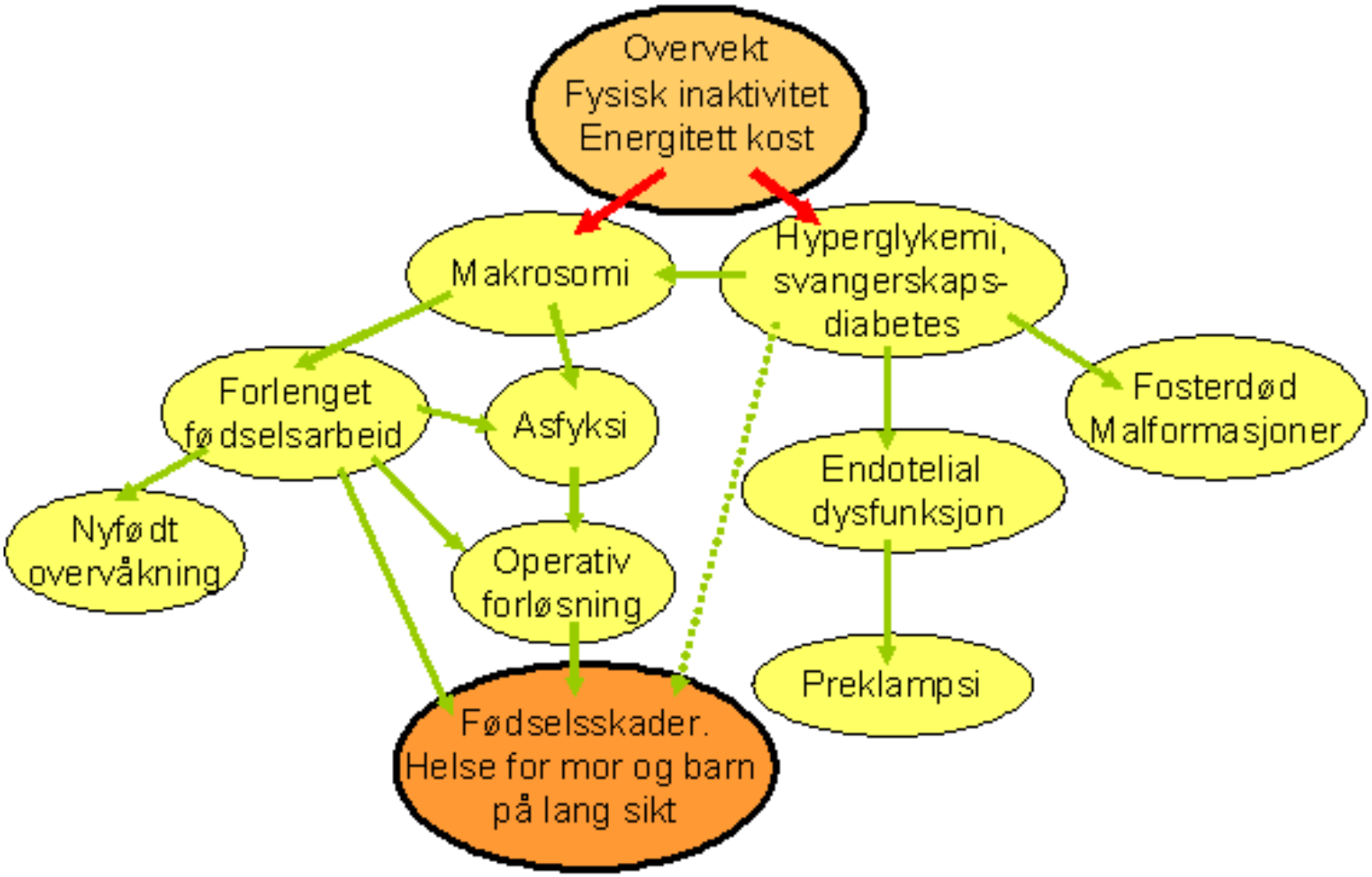


- GDM results when:
  lack of compensation for increased insulin resistance by increased insulin secretion
- Probably heritable defect, associated with type 2 diabetes

Hvorfor er oppfølging av diabetes i svangerskapet viktig?

Etablert diabetes medfører økt risiko for misdannelser og komplikasjoner i svangerskapet. Men også ved svangerskapsdiabetes: økt risiko for komplikasjoner i svangerskapet.

Samspillet mellom økt blodsukker og overvekt, fysisk inaktivitet og energitett kost, for helse hos mor og barn.



Svangerskapskomplikasjoner

Diabetes sammenliknet med ikke diabetes (OR)

	Immigrants	Ethnic Norwegians
Preeclampsia	3.6	4.7
Low birth weight	2.6	2.1
Macrosomia	5.5	3.8
Preterm birth	3.0	3.8
Shoulder dystocia	2.5	3.4
Cesarean section	3.0	4.6

Vangen S et al Diabetes care, 2003

Outcomes (%)	Quartiles (mmol/L) <4.1	4.1-4.3	4.4-4.5	≥4.6	Odds ratio	95% Confidence interval
PIH and preeclampsia	5.8	6.6	7.1	7.9	1.12	0.99-1.26
Induction of labor*	13.1	15.6	16.2	18.8	1.14	1.04-1.25
Assisted delivery	24.9	24.0	25.5	27.5	1.04	0.97-1.13
Emergency cesarean	11.7	12.6	11.9	14.7	1.08	0.98-1.19
Shoulder dystocia	1.4	0.8	1.7	2.2	1.21	0.92-1.62
Preterm delivery	5.2	5.3	3.7	4.6	0.93	0.80-1.09
Birth weight ≥4000 g†	23.4	27.9	28.5	31.7	1.14	1.06-1.22
Birth weight ≥4500 g‡	4.3	6.3	6.8	8.1	1.23	1.08-1.40
LGA†	17.2	18.9	22.7	25.6	1.19	1.10-1.29
Low Apgar score	1.4	1.7	1.4	0.5	0.79	0.61-1.03
Jaundice	2.8	3.2	2.8	2.4	0.95	0.80-1.12
Hypoglycemia	1.5	3.2	2.8	2.4	1.11	0.92-1.35
Respiratory distress	7.9	7.4	8.7	6.4	0.95	0.83-1.07

The material was divided into quartiles according to fasting glucose values. Odds ratio and 95% confidence intervals represent the relative risk for each quartile rise in blood glucose.

n milligrams per deciliter (25%, 50%, and 75% percentiles): 74 mg/dL, 79 mg/dL, and 83 mg/dL.

hypertension; *LGH*, large for gestational age.

Glukose og svangerskapsutfall hos 2904 danske kvinner uten GDM

ur glucose levels during OGTT (quartiles) on the frequency of various outcomes in 2904

nivariate logistic regression analysis

	Quartiles (mmol/L) <5.7	5.7-6.3	6.4-7.1	≥7.2	Odds ratio	95% Confidence interval
	4.8	6.9	8.4	7.2	1.16	1.02-1.31
	13.9	15.1	16.2	18.4	1.11	1.02-1.22
Assisted delivery†	21.8	25.4	27.2	27.6	1.11	1.03-1.20
Emergency cesarean†	10.6	11.0	13.9	15.1	1.16	1.05-1.28
Shoulder dystocia‡	0.4	1.2	1.8	2.9	1.78	1.32-2.40
Preterm delivery	4.2	4.4	5.1	4.9	1.07	0.92-1.25
Birth weight ≥4000 g‡	22.9	27.4	28.8	32.3	1.16	1.08-1.25
Birth weight ≥4500 g*	5.2	5.3	5.6	8.6	1.16	1.01-1.34
LGA‡	16.0	20.7	21.1	27.2	1.23	1.134-1.33
Low Apgar score	1.4	1.0	1.0	1.5	1.00	0.73-1.37
Jaundice	2.4	3.5	3.0	3.7	1.13	0.93-1.36
Hypoglycemia	2.1	2.2	2.9	2.5	1.08	0.88-1.34
Respiratory distress	5.4	8.7	8.1	7.2	1.04	0.92-1.17

The material was divided into quartiles according to 2-hour glucose values. Odds ratio and 95% confidence intervals represent the relative risk for each quartile rise in blood glucose.

Cut points for quartiles in milligrams per deciliter (25%, 50%, and 75% percentiles): 103 mg/dL, 115 mg/dL, and 130 mg/dL.

PIH, Pregnancy-induced hypertension; *LGA*, large for gestational age.

Svangerskapsdiabetes: Hvorfor er risken økt tross bra blodsukker?

- **Fetal and placental weights were increased** in GDM compared to normal (N) pregnancies, despite similar gestational age. Placental histology was consistent with **altered villous morphology**.
- GDM fetuses were significantly **more hypoxic** (O_2 saturation: N 63.2 ± 13.9; GDM 53.8 ± 14.6%, $P < 0.01$; O_2 content: N 5.5 ± 1.4; GDM 4.8 ± 1.2 mmol/l, $P < 0.05$).
- **Glucose** (N 3.4 ± 0.5, GDM 3.9 ± 1.2 mmol/l, $P < 0.05$) and **lactate** (N 1.32 ± 0.49; GDM 1.64 ± 0.75 mmol/l, $P < 0.05$) **concentrations were significantly increased** in the umbilical vein in GDM compared to N fetuses.
- Thus, fetuses from gestational diabetic mothers have increased umbilical glucose concentrations <u>despite normal maternal glucose levels</u> and a reduction in oxygen saturation and O_2 content together with increased lactate concentration, reflecting altered fetal metabolism.
  Suggesting that **'good maternal metabolic control' achieved by currently used methods of monitoring glucose control is not sufficient to ensure a normal oxygenation status and metabolic milieu** for the fetus in GDM pregnancies.

Taricco BJOG 2009

Effekt av maternell diabetes og overvekt hos barn med påvist type 2 diabetes

Variables	Type 2 diabetes	Control	*P* value
n	79	79	
Age (years)	15.7 ± 2.8	14.4 ± 2.8	0.003
Sex (% male)	29.1	38.9	0.1
Race/Ethnicity (%)			<0.0001
Non-Hispanic white	27.9	55.8	
African-American	54.4	27.9	
Hispanic	17.7	16.3	
BMI (kg/m^2)	34.7 ± 7.5	24.0 ± 6.8	<0.0001
BMI *Z* score	2.1 ± 0.7	0.8 ± 1.1	<0.0001
Exposure to maternal diabetes in utero (% yes)	30.4	6.3	<0.0001
Exposure to maternal obesity (BMI ≥25 kg/m^2) in utero (% yes)	57.0	27.4	<0.0001
Maternal education (%)			0.009
Less than high school	13.9	4.7	
High school and more	86.1	94.2	
Household income (%)			<0.0001
<$25,000	49.4	21.6	
>$25,000	50.6	77.9	
Maternal smoking during pregnancy (% yes)	11.4	11.1	0.9
Maternal alcohol consumption during pregnancy (% yes)	1.27	14.7	0.001
Birth weight (g)	3,218 ± 654	3,288 ± 620	0.4
Breast-feeding (% yes)	30.4	65.8	<0.0001
Paternal history of diabetes (% yes)	29.1	6.3	<0.0001

Data are means ± SD unless indicated otherwise.

SEARCH Dabalea Diab Care 2008

Diabetes i svangerskapet: behandlingsmål

- Fastende/før måltid 4.5-7 mmol/l

  (1.trimester)

  4.5-5.5 mmol/l

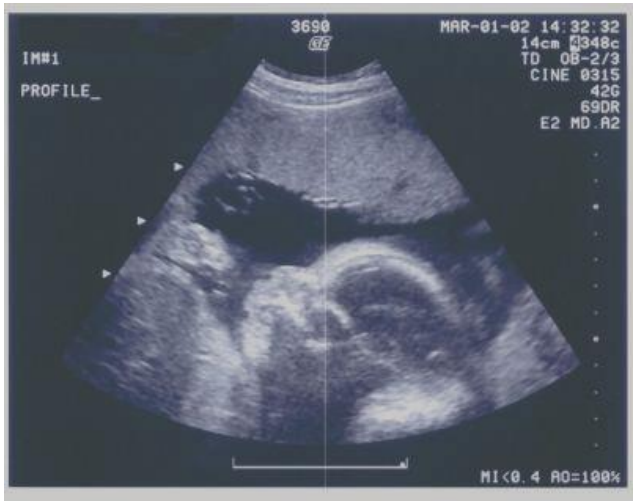
  (3. trimester)

- 1,5 time etter mat (4,5-7 mmol/l)

Kontrollskjema

fyll inn:

- øyelegesvar
- planlagte post partum insulin doser
- insulinpumpe doser
- sykmelding
- yrke/arb.giver



ULLEVÅL universitetssykehus

Diabetes
Undersøkelser og dosering i svangerskapet.

Avdelingsnr. 23000	Avdelingsnavn. **Avdeling for obstetrikk**			
Dokument-ID: 13209, 13467, 13349	Første gang opprettet: 10. Jan-08	Gyldig fra: se prosedyre	Gyldig til: se prosedyre	Versjon 0,1

Barkode

Familieanamnese: _____

Termin:	Glucosebelastning	0 minutter	120 minutter	Høyde:	Vekt:
Para:	Dato:				

Diabetes fra:	Insulin/tbl fra:	Type diabetes:	c-peptid:	AntiGAD:	Anti-TPO:	TSH:	Fritt T4:

Dato:	Glucose mmol/l	HbA1c %	Morgenurin:			BT:	Medikamenter:	Kommentarer:
			Glucose mmol/l,stix	Alb. stix	Alb. microgr/min.			

Øyelege: _____

_____

Forslag til insulindosering etter fødsel: _____

_____

Hvor skal barseloppholdet være: _____

☐ **SE BAKSIDE** 5m

Kontroller: pol. for gravide, OUS

Svangerskaps-uke	Diabetes type 1 og 2	Diabetes - kostregulert
1.konsultasjon	UL	UL
18	Rutine UL	Rutine UL
24	UL	
28	UL	UL
32	UL	
34	CTG	UL
36	CTG	CTG
38	UL	UL
39	CTG	
40	Vurdere induksjon	CTG

Blodsukkermålinger ved svangerskapsdiabetes

- For de fleste som følges på sykehus med svangerskapsdiabetes påvist før uke 32-36.
- Bevisstgjør kostholdsvalg
- Viktig for valg av insulinregime når dette er nødvendig

- Nyttig senere: ved nye konsepsjoner eller mistanke om hyperglykemi

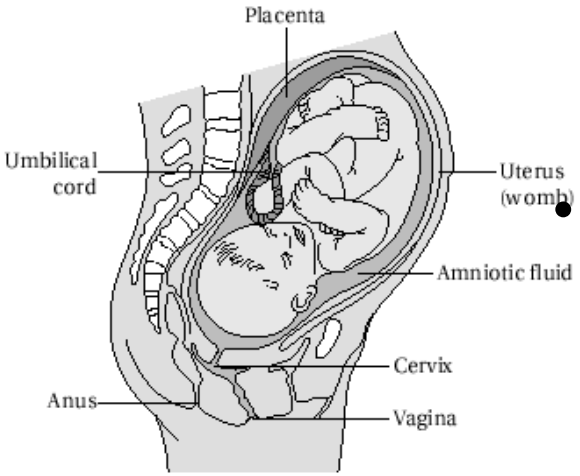
Bedre effekt av intervensjon i høy risk grupper?

- **293** women (previous GDM and/or prepregnancy BMI ≥30 kg/m^2), at <20 weeks of gestation. Randomized to intervention (*n* = 155) or controls (*n* = 138). Intervention: 3 individualized counselings on diet, physical activity, and weight control, and one group meeting with dietitian. Controls had standard care.
- **RESULTS** GDM rate 13.9% in the intervention group and 21.6% in controls, *P* = 0.044, after adjustment for age, prepregnancy BMI, previous GDM status, and GA. Gestational weight gain was lower in the intervention group (−0.58 kg [95% CI −1.12 to −0.04 kg] adjusted *P* = 0.037). The intervention group increased physical activity more and improved their diet, compared to controls.

A moderate individualized lifestyle intervention reduced the GDM rate by 39% in high-risk pregnant women.

Koivusala DC 2015

Behov for insulinbehandling?



The anatomical structures of pregnancy

- Ved: blodglukose **> 8 mmol/l** målt flere ganger uansett tidspunkt
- Behandling i svangerskapet krever **aktiv** justering av insulindosen!
  Vanligvis økes med 2 enheter (evt flere ganger daglig). Ofte økes insulindosen **for lite** og **for langsomt**.
- **Ved høye fastende verdier**: oppstart med langsomt virkende insulin om kvelden.
  Ved høye verdier etter mat; hurtigvirkende insulin
- **Vær oppmerksom på** etnisk gruppe, vekt og tidspunkt i graviditet (grad av insulinresistens).

Metformin vs insulin ved GDM

- 751 kvinner i 20-33 uke randomisert til åpen behandling med metformin eller insulin. 363 fikk metformin, 92.6% fortsatte med metformin frem til forløsning, 46.3% trengte et tillegg av insulin.
- **Forekomst av sammensatt endepunkt :** 32.0% i metformingruppen og 32.2% i insulingruppen (RR, 0.99 [justert]; 95% CI, 0.80;1.23).
- Flere i metformin gruppen ville velge denne behandlingen på nytt (76.6% vs. insulin, 27.2%, P<0.001).
- Hyppigheten av sekundære endepunkt var lik.
- Ikke påvist alvorlige AE ved metforminbruk.

MIG, Rowan et al. NEJM 2008

Metformin, sikkert?

- Bruk av metformin ved type-2 diabetes og ved PCOS har vist at behandlingen er billig og effektiv, og det er ikke vist misdannelser eller teratogenisitet ved bruk av metformin. Randomiserte studier med metformin ved GDM finnes nå, bruken er økende (UK; USA; Australia) og det ventes nye resultater fra oppfølging av metforminbehandlede barn ved 2 års alder.

Best Practice 2013.

Balsells BMJ 2015.

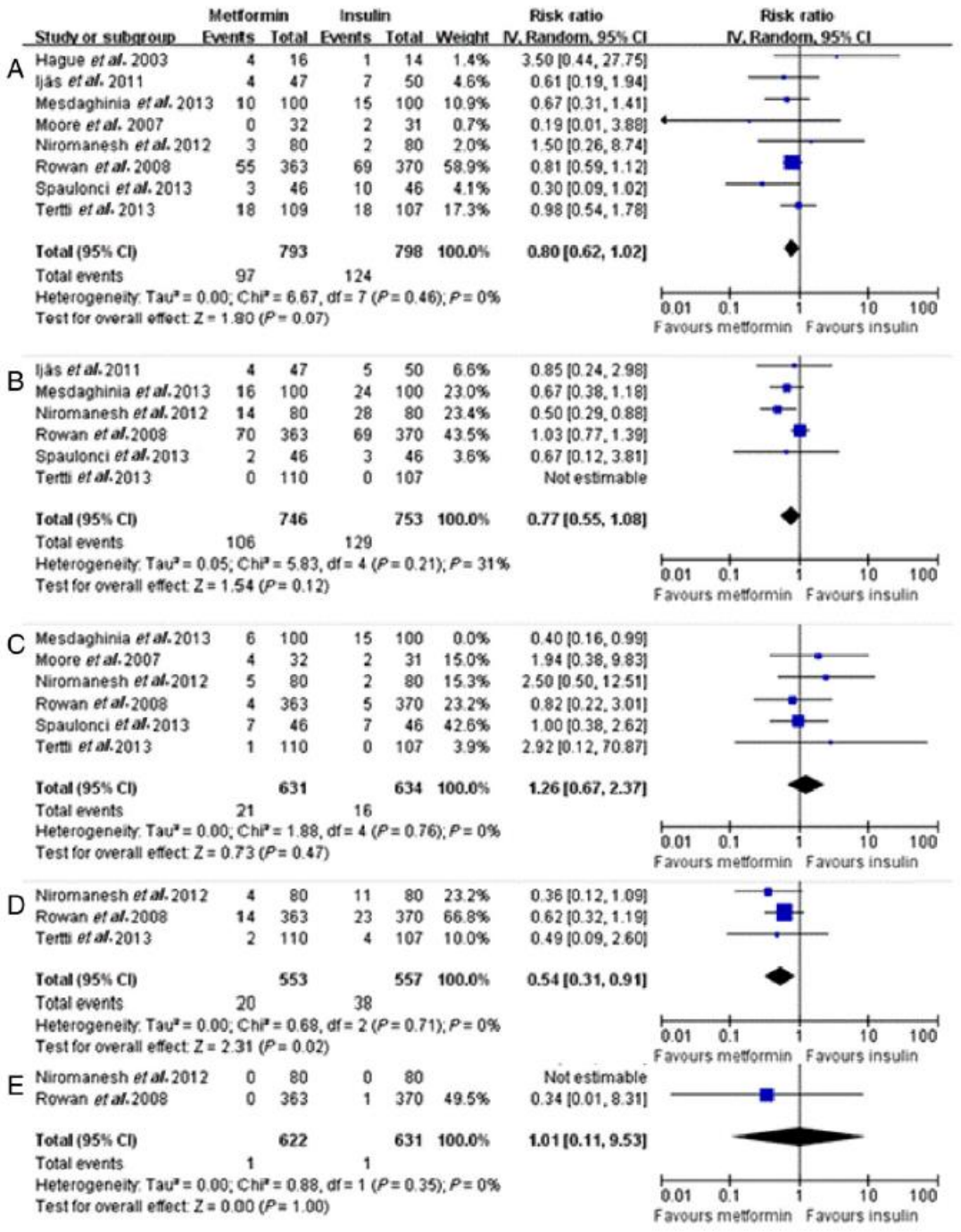
Neonatal hypoglykemi

LGA

RDS

PIH

PD



Zhao et al 2015, Br J Cl Pharm

Uavklarte metformineffekter

- I in vitro studier: metformin asssiert med økt neoangiogenese i brystkreft modeller. I gentoksisitetsstudie vist økt antall strukturelle kromosomale abnormaliteter ved høyere metforminkonsentrasjoner (hamster cellelinje), benmargssuppresjon ved langvarig behandling (mus).
- **Reduksjonen av placental insulin resistens** ved metforminbruk og sviktende placenta funksjon eller føtal vekstretardasjon: kan svekke barnets tilgang på næring når moren faster; og demed svekke fosterveksten.
- Oppfølgingsdata fra MIG-studien indikerer at behandlingen kan påvirke barnets fettfordeling, så langt er det kun vist økt fettmasse på ekstremiteter og ikke visceralt, imidlertid må funnene bekreftes.

Hvordan jeg bruker metformin

- Ved tidlig påvist GDM og fedme må insulinbehov forventes, og vi velger da ofte insulin.

- Ved senere påvist GDM, god tilvekst og normal nyrefunksjon er metformin aktuelt. I tillegg kan metformin kontinueres ved graviditet hos velregulerte type-2 diabetikere, kontinueres ofte også ved PCOS og habituelle aborter.
- I Norge har vi muligheten til å vurdere kvinnens totalsituasjon, preferanser, evne til egenomsorg og compliance. I andre land vil kostnadene ved insulinbruk utelukke insulinbehandling for de fleste.
- Mitt ståsted*: Metformin er et nyttig behandlingsalternativ ved GDM, men bruken er en spesialist-oppgave, blant annet fordi kontraindikasjoner må utelukkes.*

Tidlig påvist svangerskapsdiabetes - flere komplikasjoner?

80% with late GDM had only dietary intervention, 20% received medication.

50% with early GDM had dietary intervention, 45% needed medication (P<0.001).

45% with early GDM had cesareans, 24% with late GDM.

Rate of **macrosomia** (13% vs. 6%) and **LGA** (18% vs. 6%) was significantly more frequent in women with early onset of GDM.

1. trim. U 24-28

Characteristic	Early GTT n=98	Standard GTT n=242	P-value
Perineal laceration, n (%)			
None	60 (61.2%)	98 (40.5%)	
1–2 degree	38 (38.8%)	131 (54.1)	
3–4 degree	0 (0%)	13 (5.4%)	<0.0001
SHD, n (%)			
No	93 (94.9%)	234 (96.7%)	
Yes	5 (5.1%)	8 (3.3%)	0.45
Apgar score at 5 min, n (%)			
0–6	0 (0%)	1 (0.4%)	
7–9	98 (100%)	241 (99.6%)	0.41
Gender of baby, n (%)			
Female	43 (43.9%)	128 (52.9%)	
Male	55 (56.1%)	114 (47.1%)	0.13
Preterm delivery, n (%)			
No	92 (93.9%)	229 (94.6%)	
Yes	6 (6.1%)	13 (5.4%)	0.79
Birth weight, all babies, n (%)			
≤2500 g	10 (10.2%)	13 (5.3%)	
2501–3999 g	75 (76.5%)	215 (88.8%)	
≥4000 g	13 (13.3%)	14 (5.8%)	<0.02
Birth weight, term babies, n (%)			
≤2500 g	4 (4.4%)	7 (3.1%)	
2501–3999 g	74 (81.3%)	208 (90.8%)	
≥4000 g	13 (14.3%)	14 (6.1%)	0.001
Birth weight, percentile, n (%)			
≤10%	9 (9.2%)	11 (4.6%)	
11–89%	71 (72.4%)	215 (88.8%)	
≥90%	18 (18.4%)	16 (6.6%)	0.001
Mode of delivery, n (%)			
NSVD/VBAC	50 (51.0%)	169 (70.1%)	
Cesarean	44 (44.9%)	57 (23.7%)	
LFD	2 (2.0%)	6 (2.5%)	
VAD	2 (2.0%)	9 (3.7%)	0.002
Treatment, n (%)			
Diet	54 (55.1%)	196 (81.0%)	
Insulin	25 (25.5%)	21 (8.7%)	
Glyburide	19 (19.4%)	25 (10.3%)	<0.000
HTN, n (%)			
No	79 (80.6%)	212 (87.6%)	
Yes	19 (19.4%)	30 (12.4%)	0.10

SHD=shoulder dystocia, NSVD=normal spontaneous vaginal delivery, VBAC=vaginal birth after cesarean, LFD=low flap cesarean delivery, VAD=vacuum assisted delivery, HTN=hypertension.

Most et al. J Perinat. Med. 2009

Svangerskapsdiabetes i nytt svangerskap

Race/ethnicity*	GDM criteria†	GDM (*n*)	Age at index pregnancy (years)	Time between pregnancies‡	Rate of GDM recurrence (%)
NHW					
NHW (Dutch)	Center specific	58	27§	12–48 months	30
NHW (Nova Scotia)	1979 NDDG	651	?	?	33
93% NHW (Australia)	ADIPS	100	28	2.4 years	35
NHW (?) (Australia)	Center specific	865	29	?	37
NHW (?) (Australia)	1979 NDDG	19	?	<12 months	84
NHW and minority					
64% NHW, 36% nonwhite (Cleveland)	1979 NDDG	36	28	?	56
80% NHW, 20% non–English speaking, country of birth, including Mediterranean countries (Australia)	ADIPS	117	27	<6 years	62
84% NHW (Washington)	Birth certificate	1,322	?	?	OR 23
Predominantly minority, including Latinas					
81% African American	1979 NDDG	90	24	?	52
93% Latina	1979 NDDG	164	28	<48 months	68
85% Latina	1979 NDDG	78	30	<48 months	69
Japanese	JDS	32	27	26–33 months	66
Asian (Chinese, Filipina, Sri Lankan, Vietnamese)	Center specific	258	?	?	OR 15

Kim 2007 metaanal

Gjennomføring av glukosebelastning post partum

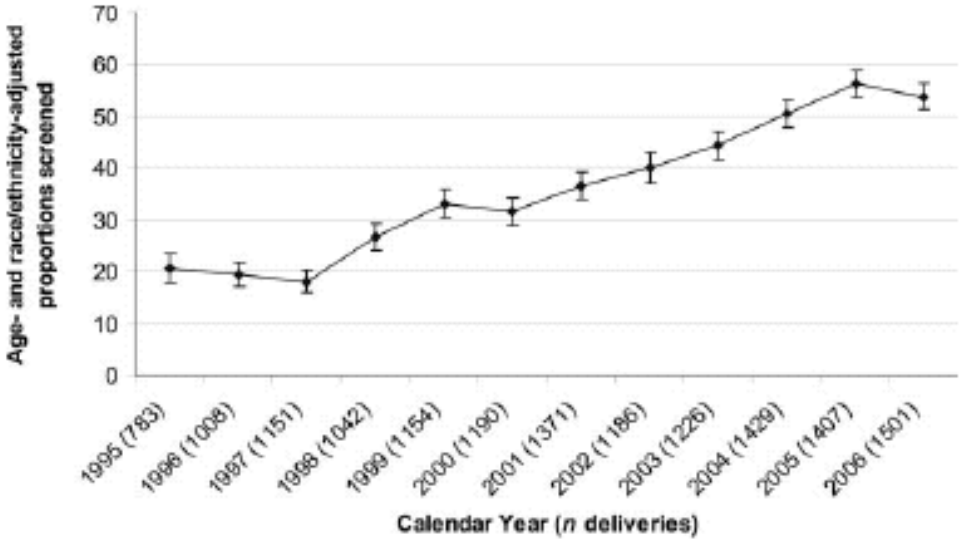


Figure 1—*Age- and race/ethnicity-adjusted proportions of postpartum screening for diabetes among women with histories of GDM by year of delivery. The KPNC GDM registry: 1995–2006.*

- Predictors for screening: older age, asians/hispanics, higher education, early GDM diagnosis, diabetes medications in pregnancy, more health care contacts after delivery
- Less screening in obese and higher parity

TRIAD Diabetes care 2009

Post partum oppfølging

Post partum	6-13 u	>13 uker	Risk	Årlig HbA1c	
F-bls <6mmol/l	x		Moderat	x	
F-bls 6,0-6,9mmol/l	x		Høy	x	
F-bls >7,0 mmol/l	x		T2 DM sannsynlig		Bekreft diagnose
HbA1c <5,7%		x	Moderat	x	
HbA1c 5,7-6,4%		x	Høy	x	
HbA1c ≥ 6,5%		x	T2 DM sannsynlig		Bekreft diagnose

NICE 2015

Post GDM risiko profil

TABLE 2. Phenotypic characteristics of the prior diet-treated GDM group at follow-up 4–23 yr after index pregnancy with GDM as compared with the control group

	Prior GDM group (n = 481)	Control group (n = 1000)	*P*
Age (yr)	42.9 (37.7–47.8)	45.0 (39.9–50.2)	<0.0005
BMI (kg/m^2)	27.9 (24.1–32.9)	24.6 (22.2–27.9)	<0.0005
Waist circumference (cm)	91 (80–100)	78 (71–86)	<0.0005
Waist to hip ratio	0.83 (0.78–0.87)	0.79 (0.76–0.83)	<0.0005
Glucose intolerance	67.6% (325/481)	19.2% (175/910)	<0.0005
IFG	11.0% (53/481)	4.3% (39/910)	<0.0005
IGT	10.6% (51/481)	9.5% (86/910)	0.493
IGT and IFG	6.0% (29/481)	2.2% (20/910)	<0.0005
Diabetes	39.9% (192/481)	3.3% (30/910)	<0.0005
Fasting serum insulin (pmol/liter)	53.8 (34.9–78.3)	31.0 (23.0–48.0)	<0.0005
Systolic BP (mm Hg)[a]	119 (111–126)	120 (110–125)	0.206
Diastolic BP (mm Hg)[a]	73 (66–78)	75 (70–80)	<0.0005
Hypertension (%)	27.8	30.1	0.363
Fasting serum triglyceride (mmol/liter)	1.3 (0.9–1.9)	1.0 (0.7–1.3)	<0.0005
Fasting serum HDL (mmol/liter)	1.4 (1.2–1.7)	1.5 (1.3–1.8)	<0.0005
Urine albumin to creatinine ratio (mg/g)	7.6 (4.6–17.7)	3.0 (3.0–5.0)	<0.0005

Data are presented as median (interquartile range) or proportions (number). BP, Blood pressure.
[a] Nonhypertensive women not taking antihypertensive treatment.

Risiko faktorer i graviditet:

- tidlig diagnose, høyt fbls, overvekt, uten bedring av bls etter fødsel.

Sammendrag

- Årsakene til komplikasjoner ved svangerskapsdiabetes er mer enn forhøyet blodsukker
- Den store utfordringen fremover blir å påvise type 2 diabetes før/tidlig i svangerskapet
- Vi må ha flere planlagte svangerskap hos mødre med økt risiko

Takk for oppmerksomheten!

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