SWEdish Post-term Induction Study
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Swedish multicentre register based randomised controlled superiority trial to compare induction of labour at 41 completed gestational weeks versus induction at 42 completed gestational weeks

SFOG veckan,
Örebro, 2016

Background

- Postterm (≥42+0 gestational weeks, GW) and late term (≥ 41+0 GW) pregnancy as compared to term pregnancy (39+0-40+6 GW) is associated with an increased risk for the mother and the baby
- Older women, women with obesity and intrauterine growth restricted babies are at increased risk
- Standard care in many countries, including Sweden, is induction of labour at 42+0 GW
- There is some scientific support that induction of labour at 41+0-42+0 GW as compared with expectant management and induction at ≥42+0 GW will reduce perinatal mortality and morbidity without an increase in caesarean section rates and negative delivery experiences – but these data are based on partly outdated studies executed several decades ago
- Scientific evidence for when intervention should be undertaken in the natural course of pregnancy is important since 15-20% of all pregnancies last more than 41+0 GW
- No study with adequate sample size has compared induction at 41+0 versus 42+0 GW

Systematiska översikter och meta-analyser:
Induktion 41+0-42+0 GV vs expektans och induktion vid 42 GV eller senare

	Myers et al AHQR 17 RCTs	Sanchez-Ramos et al, 2003 Meta-analys 16 RCTs, OR, 95% CI	Gulmezoglu et al, 2012 Meta-analys 19 RCTs, varav 3 med intervention i v 38-40 OR, 95% CI	Wennerholm et al, 2009 Meta-analys 13 RCTs, OR, 95% CI	Hussain et al, 2011 Meta-analys 16 RCTs OR, 95% CI	Wennerholm et al, 2012 Uppdaterad meta-analys, 17 RCTs, OR, 95% CI
Perinatal död	Fördel induktion	0,41 0,14-1,18	0,30 0,09-0,99	0,33 0,10-1,09	0,31 0,11-0,88	0,32 0,11-0,91
Mekoniumaspiration	Ingen skillnad	0,46 0,18-1,21	0,39 0,21-0,75	0,43 0,23-0,79	0,43 0,23-0,79	0,47 0,25-0,90
Kejsarsnitt	Ingen skillnad	0,88 0,78-0,99	41v: 0,92 0,76-1,12 42 v: 0,97 0,72-1,31	0,87 0,80-0,96	NA	0,94 0,80-1,11

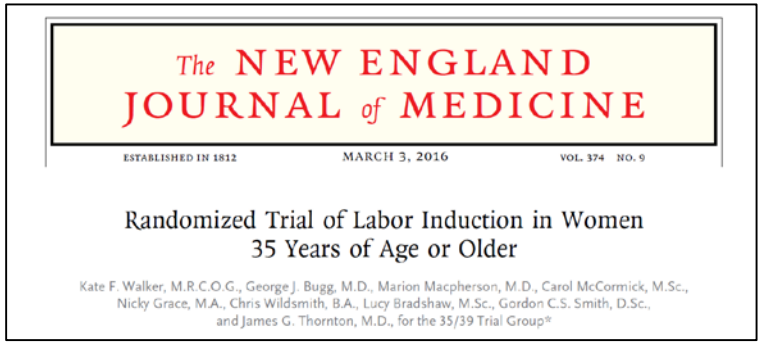
Induktion 41+0-42+0 GV vs expektans:
Lägre eller samma risk för perinatal död, mekoniumaspiration och kejsarsnitt

Problems encountered

- Important outcomes such as perinatal mortality and hypoxic-ischemic encephalopathy (HIE) are rare events
- We expect the outcome to be only moderately affected by management (active *vs.* expectant)

  - **A large multicentre trial is required**

Nyligen publicerad RCT


The NEW ENGLAND JOURNAL of MEDICINE

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Randomized Trial of Labor Induction in Women 35 Years of Age or Older

Kate F. Walker, M.R.C.O.G., George J. Bugg, M.D., Marion Macpherson, M.D., Carol McCormick, M.Sc., Nicky Grace, M.A., Chris Wildsmith, B.A., Lucy Bradshaw, M.Sc., Gordon C.S. Smith, D.Sc., and James G. Thornton, M.D., for the 35/39 Trial Group*

35/39 studien (Storbritannien)

Totalt 630 förstföderskor ≥35 år

1. Induktion i GV 39+0-39+6-7 (n=315)
2. Expektans och induktion i GV 41+0-42+0 (n=315)

Resultat:

Ingen skillnad i frekvens av kejsarsnitt (”primary outcome”) mellan grupperna (32% vs 33%) eller övriga maternella eller neonatala utfall.

Power saknas för att visa effekt på ovanliga komplikationer!

Walker KF et al. NEJM 374; (9), 813-22, 2016

Pågående RCTs

INDEX studien (Holland)

Totalt 1800 kvinnor randomiseras till

1. Induktion i GV 41+0 (n=900)
2. Expektans och induktion i GV 42+0 (n=900).

Power saknas för att visa effekt på ovanliga komplikationer!
Hemförlossning vanligt vid spontan förlossningsstart!

ARRIVE studien (USA)

Totalt 6000 förstföderskor randomiseras till

1. Induktion i GV 39+0-39+4 (n=3000)
2. Expektans och induktion i GV 40+5 (n=3000)

Slutsats

Otillräckligt bevis föreligger för att induktion av förlossning i GV 41+0 i jämförelse med avvaktande handläggning och induktion i GV 42+0 GV minskar perinatal mortalitet och morbiditet utan att medföra ökning av operativa förlossningar, negativa förlossningsupplevelser och kostnader

Innan nuvarande rutin att inducera förlossning i GV 42 ändras i Sverige är det viktigt att undersöka om induktion av förlossning i GV 41+0 medför positiva effekter då en betydande del (15-20%) av alla graviditeter varar längre än 41 GV.

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Aim

- To investigate if a policy of induction of labour at 41+0 GW (early induction) is superior, in terms of neonatal and maternal outcomes, as compared to expectant management and induction at 42+0 GW (late induction) in healthy women with a low risk singleton pregnancy

Study design

- A Swedish multicentre register based randomised controlled trial (RCT)

- Randomisation (1:1) will be performed using a computerised module developed by MedSciNet AB, Stockholm, linked to the Swedish Pregnancy Register

➢ **The first RCT using the Swedish Pregnancy Register and the Swedish Neonatal Quality Register (SNQ)!**

Study design

Population:

Healthy women ≥18 years with a normal singleton pregnancy in cephalic presentation at 41 GW

Intervention:

Early induction (41 GW)

Comparison:

Late induction (42 GW)

Outcomes:

Primary: Composite of stillbirth, neonatal mortality and severe neonatal morbidity

Secondary: other adverse neonatal and maternal outcomes, mode of delivery, women's experience, cost effectiveness (and long term child morbidity)

Exclusion criteria

- Women with previous caesarean section or other uterine surgery
- Pregestational and insulindependent gestational diabetes
- Hypertensive disorders in pregnancy
- Multiple pregnancy
- Foetus in breech or transverse position
- SGA (<-22% according to Marsal reference)
- Oligohydramniosis (AFI <50 mm or DVP <20 mm)
- Antenatally detected foetal malformations
- Contraindications to vaginal delivery such as placenta praevia
- PROM
- Language problems

Sample size calculation

We anticipate that induction of labour at 41 GW as compared to induction at 42 GW will reduce the primary outcome (peri/neonatal mortality and morbidity) with 33% from 2.74% to 1.84% (level of significance 0.05, power 80%, drop out rate 10%).

We need a sample size of 10 038 women to be randomised, 5019 to induction of labour at 41+0 GW and 5019 to expectant management and induction at 42+0 GW unless labour start spontaneously or if any pregnancy complication occurs indicating earlier delivery.

In 2014 the number of participating clinics (n=13) had 59 350 deliveries. Given a rate of 18% at 41+0 GW, there will be 32 049 during 3 years. We estimate that 40% (12 820) of these women can be included.

Statistical analysis

Primary statistical analysis:
Intention to treat (ITT) on primary composite outcome

Women with spontaneous labour or PROM after randomisation but before planned induction will be included in the statistical analysis according to ITT

Women with pregnancy complications after randomisation indicating delivery will be included in the statistical analysis according to ITT

Foetuses/newborns with lethal birth defects will be excluded in the analysis of stillbirth, neonatal mortality and morbidity

The statistician will be blinded to group and intervention

Primary outcomes

Composite of perinatal/neonatal mortality and neonatal morbidity, which is defined as at least one of the following variables:

- Perinatal/neonatal mortality (intrauterine fetal death of a fetus that was alive at randomisation or neonatal death with death day 0-27)
- Apgar score <7 at 5 minutes
- Metabolic acidosis defined as pH <7.05 and base excess >12 mmol/l in umbilical artery or pH <7.00 in umbilical artery
- HIE I-III
- Intracranial haemorrhage
- Neonatal convulsions
- Meconium aspiration syndrome
- Mechanical ventilation
- Obstetric brachial plexus injury

Secondary outcomes

Secondary infant outcomes:

- Admittance to neonatal intensive care units
- Birth weight
- Macrosomia (>4500 g)
- Apgar score <4 at 5 min
- Therapeutic hypothermia
- Neonatal jaundice
- Pneumonia
- Sepsis
- (Child morbidity and development up to 4 years of age)

Secondary maternal outcomes:

- Use of epidural anaesthesia
- Caesarean section
- Duration of labour
- Assisted vaginal delivery
- Perineal lacerations III-IV
- Postpartum hemorrhage
- Chorioamnionitis
- Wound infection
- Urinary tract infection
- Endometritis
- Sepsis
- Depression/anxiety
- “Self-efficacy”
- Women’s experience of childbirth
- Breastfeeding

- **Cost effectiveness**

Hälsoekonomi

- Total vårdtid/antal besök mor och barn före och efter förlossning
- Läkemedel etc
- Morbiditet mor och barn upp till 3 mån postpartum
- Livskvalitet (QUALYs, EuroQol EQ-5D)
- Uppföljning av barnet upp till 4 års ålder

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Långtidsuppföljning av barnen

Uppföljning av barnen via Patientregistret, CP registret, Obesitas registret och BHV registret

- Psykomotorisk utveckling vid 4 års ålder
- CP
- Död före 4 års ålder

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Patient information and recruitment

- Pregnant women are given oral and written information at the antenatal clinics at around 40 GW
- Potentially eligible women will be consecutively contacted
- Women who are interested in participating are booked for a visit at the antenatal clinic at the hospital at 41+0 to 41+1 GW
- Consenting eligible women will be enrolled and randomised at 41+0 to 41+1 GW
- Women allocated to early induction will be induced within 24 hours
- Women allocated to late induction will be followed according to clinical routine for GW 41+0-42+0.

Methods of labour induction

Early or late induction:
Methods will be according to the clinics' routine:

- If the foetal head is well engaged and the cervix is ripe (Bishop score ≥6 for primiparous and ≥5 for multiparous) amniotomy is performed. Oxytocin infusion will be started after 2 hours if no or not regular contractions.

- If the cervix is unripe (Bishop score <6 for primiparous or <5 for multiparous) or the fetal head is not engaged any of the following methods are used (according to the routine at the clinic):
  - mechanical dilation using a Foley like catheter (BARD or Cook)
  - misoprostol (Cytotec®) orally
  - misoprostol (Misodel®) controlled-released vaginal insert
  - prostaglandin E2 (Minprostin®) gel vaginally
  - prostaglandin E2 (Propess®) vaginal insert

- Mechanical dilation may be followed by prostaglandins and vice versa. If the woman is not in active labour or cervix is still unripe after 48 hours, the clinician together with the woman will decide whether to perform a caesarean section or to continue expectant management until GW 42^{+0}. All inductions will be performed with the patient staying at the hospital until delivery. The clinic's protocol and guidelines for induction and surveillance during induction will be followed. During the active phase of labour fetal surveillance with continuous CTG with or without ST segment analysis (STAN) in combination with foetal scalp blood sampling is recommended.

Data collection

- Data on background variables, obstetric and neonatal outcomes will be obtained from the Pregnancy Register and SNQ
- Complimentary data will be entered in electronic case record form (eCRF) developed by MedSciNet AB
- Data om women's experience will be collected in the Region VG and Örebro/Falun subpopulation by questionnaires (web based or postal) after randomisation and 3 months after delivery: Big Five, Euro-Qol, The Childbirth Experience Questionnaire, the General Self-Efficacy Scale
- Data will be collected on randomised women and on eligible women declining participation but accepting to participate with data

Additional….

- Ethical approval obtained
- eCRF developed by MedSciNet AB
- http://www.medscinet.com/InductionTest/
  > Username and password: user/user
- Funding: FOU (VG,HH), ALF/LUA VG, UBW) and HTA (UBW) about 1.1 miljoner SEK
- Accepted for step 2 but failed, Swedish Research Council (”Klinisk behandlingsforskning”).
- Application sent to Swedish Research Council ”Projektbidrag”
- Study protocol published in BMC Pregnancy and Childbirth:
- Elden H, Hagberg H, Wessberg A, Sengpiel V, Herbst A, Bullarbo M, Bergh C,Bolin K, Malbasic S, Saltvedt S, Stephansson O, Wikström AK, Ladfors L,Wennerholm UB. Study protocol of SWEPIS a Swedish multicentre register based randomised controlled trial to compare induction of labour at 41 completed gestational weeks versus expectant management and induction at 42 completed gestational weeks. BMC Pregnancy Childbirth. 2016 Mar 7;16:49
- Registered in Current Controlled Trials (ISRCT26113652)
- Pilot study in Gothenburg May/June 2016

Deltagande kliniker i SWEPIS:

- SU
- SUS, Malmö/Lund
- Uppsala
- Umeå
- Sunderbyn
- Danderyd
- KS, Solna /Huddinge
- Södersjukhuset
- Södertälje
- Örebro
- Falun
- Visby
- Helsingborg

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Organization

Steering committe

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- Verens Sengpiel
- Lars Ladfors
- Christina Bergh
- Helen Elden
- Andreas Herbst
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- Sissel Saltvedt
- Sopia Brismar Wendel
- Olof Stephansson
- Anna-Karin Wikström
- Marie Bixo
- Helena Fadl
- Jan Weström

Data Safety Monitoring Board

Hans Wedel, professor

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Elisabeth Jangsten, midwife, PhD

Statistician

Nils Gunnar Pehrsson

Pediatrician

Göran Wennergren, professor

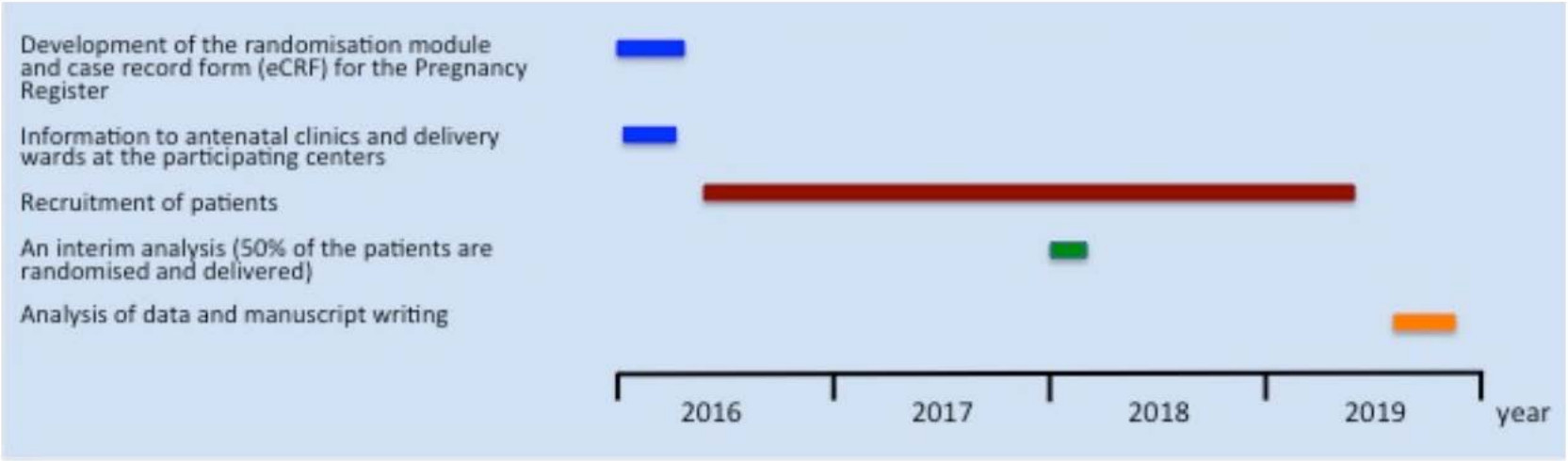
Health economist

Kristian Boli, professor

Advisor

Ben W. Mol, professor, Adelaide

Tidplan



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GÖTEBORGS UNIVERSITET

Sahlgrenska Universitetssjukhuset KVINNOSJUKVÅRD

Har du kommit till 40 fulla graviditetsveckor?

Är du intresserad av att delta i en studie där effekter och upplevelser av igångsättning av förlossning i graviditetsvecka 41 jämförs med igångsättning i graviditetsvecka 42?

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Ansvariga för studien:
Anna Wessberg, barnmorska, studiekoordinator, doktorand
Ulla-Britt Wennerholm, överläkare, docent
Henrik Hagberg, överläkare, professor
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Information delas ut på MVC i GV 40+0 tillsammans med sedvanlig information om induktion vid ÖB