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Induction of labour at 41 or 42 weeks of gestation

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Induction of labour at 41 or 42 weeks of gestation [Igångsättning av förlossning vid 41 eller 42 fullgångna graviditetsveckor]

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1. Abstract

Background
The average length of human gestation is 40 weeks from the first day of the last menstrual period but can vary by several weeks. During 2018, 22% of deliveries in Region Västra Götaland (VGR) in Sweden occurred at 41 gestational weeks and 0 days (41+0) or later (prolonged pregnancy) and 6.1% at week 42+0 or later (post term pregnancy). Observational studies show that post term compared with term deliveries are associated with increased perinatal mortality and morbidity as well as maternal morbidity. Induction of labour (induction) before post term is used to avoid these adverse effects but is controversial since the procedure is associated with adverse effects such as prolonged labour, adverse neonatal outcome, uterine hyperstimulation, and an increased risk of uterine rupture.

A Health Technology Assessment (HTA) report from our HTA unit in 2012 evaluating induction between weeks 41+0 to 42+0 versus expectant management with different upper limits of gestational age (in some studies up to 44 weeks) showed lower perinatal mortality and morbidity and no difference in caesarean delivery rates with early induction. Various guidelines from different countries recommend induction between weeks 41+0 and 42+0. Today, most obstetric units in Sweden offer induction at gestational week 42+0.

Question at issue
Is a strategy of induction at 41 weeks + (0 to 2 days) compared with a strategy of expectant management with various regimes of foetal surveillance and induction at 42 weeks + (0 to 1 day) superior in terms of decreased stillbirth/neonatal mortality and neonatal morbidity without increasing maternal mortality and morbidity, in healthy women with an uncomplicated singleton pregnancy?

Methods
Two authors performed searches during October and November 2019 in PubMed, Embase, the Cochrane Library, Cinahl, PsycInfo and a number of HTA databases, selected studies, independently assessed abstracts and made a first selection of full-text articles. These articles were sent to all authors and inclusion was decided in consensus. The studies were critically appraised, and data were extracted. When possible, data were pooled in meta-analysis using Rev-Man 5.3 and presented as forest plots. The certainty of evidence was assessed using the GRADE approach.

Results
Three randomised controlled trials (RCTs) but no observational study fulfilled our PICO criteria and were included. The RCTs had minor problems with directness, minor or some problems with study limitations, and some or major problems with precision for important outcomes. The rates of stillbirth/neonatal mortality were 0.04% and 0.35% in the induction and expectant management groups, respectively. The corresponding rates of composite outcomes of stillbirth/neonatal mortality and neonatal morbidity were 2.1% and 2.2%. Conclusions: A strategy of induction at 41 completed weeks compared with a strategy of expectant management to 42 completed weeks may reduce the rate of stillbirth/neonatal mortality, while the magnitude of the reduction is uncertain (pooled Peto odds ratio 0.20; 95% CI 0.06 to 0.70, GRADE ⊕⊕◯◯); may result in a moderate increase or decrease or in little or no difference in the rate of composite outcomes of stillbirth/neonatal mortality and neonatal morbidity (pooled RR 0.78; 95% CI 0.40 to 1.52; GRADE ⊕⊕◯◯); will probably reduce the rate of admittance to neonatal intensive care unit (pooled RR 0.79; 95% CI 0.63 to 0.99, GRADE ⊕⊕⊕◯); results in little or no difference in caesarean, operative vaginal delivery and post-partum haemorrhage rates (GRADE⊕⊕⊕⊕); and probably results in little or no difference in the rate of perineal tears grade 3-4 (GRADE ⊕⊕⊕◯).

Concluding remarks
This systematic review, including three RCTs with 5,161 women and comparing the strategies to induce labour at 41 completed weeks with expectant management including various regimes of foetal surveillance and induction at 42 completed weeks, shows that stillbirth/neonatal mortality may be reduced but to an uncertain extent, while any direction of the effect on stillbirth/neonatal mortality and neonatal morbidity combined is uncertain. There were, or were probably, no differences between the groups for important maternal outcomes.

2. Svensk sammanfattning – Swedish summary

Bakgrund
Genomsnittlig graviditetslängd är 40 veckor från sista menstruationens första dag men graviditetslängden kan variera med flera veckor. Under 2018 skedde 22% av förlossningarna i Västra Götalandsregionen (VGR) vid 41 fulla graviditetsveckor eller senare och 6,1% skedde vid 42 fulla graviditetsveckor eller senare (överburenhet). Observationsstudier visar att överburenhet är förknippad med ökad perinatal dödlighet och sjuklighet hos barnet samt ökad sjuklighet hos modern. Igångsättning av förlossning (induktion) används för att undvika dessa negativa effekter men är kontroversiell eftersom induktion kan vara förenad med risker såsom utdragen förlossning, överstimulering av livmodern och ökad risk för livmoderruptur.

I en HTA-rapport från vår HTA-enhet 2012 utvärderades induktion mellan 41veckor och 0 dagar (41+0) och 42+0 jämfört med exspektans. Utvärderingen visade lägre perinatal dödlighet och sjuklighet och ingen skillnad i kejsarsnittsfrekvens med tidig induktion. Riktlinjer från olika länder rekommenderar induktion vid 41 till 42 fulla graviditetsveckor och i Sverige erbjuder de flesta obstetriska enheter idag induktion vid 42 fulla graviditetsveckor.

Fokuserad fråga
Medför induktion vid 41 veckor + (0 till 2 dagar) istället för exspektans med varierande grad av fosterövervakning och induktion vid 42 veckor + (0 till 1 dag) minskad intrauterin fosterdöd/neonatal dödlighet och neonatal sjuklighet, utan ökad risk för maternell dödlighet och sjuklighet, hos friska kvinnor med okomplicerad graviditet?

Metod
Två författare utförde under oktober och november 2019 sökningar i PubMed, Embase, Cochrane Library, Cinahl, PsycInfo och ett antal HTA-databaser, selekterade studier, utvärderade individuellt abstracts och gjorde ett första urval av fulltextartiklar. Dessa artiklar skickades till alla författare och inklusion beslutades vid ett konsensusmöte. Studierna granskades kritiskt och data extraherades. När så var möjligt poolades data i meta-analyser med RevMan 5.3. Resultatens tillförlitlighet bedömdes enligt GRADE.

Resultat
Tre randomiserade kontrollerade studier (RCT), men ingen observationsstudie, uppfyllde PICO och inkluderades. De inkluderade studierna hade små problem med överförbarhet, mindre eller vissa problem med studiebegränsningar, och vissa eller stora problem med precision för viktiga utfallsmått. Frekvensen intrauterin fosterdöd/neonatal död var 0,04% och 0,35% i tidig induktions- respektive exspektansgruppen. Motsvarande siffror för kompositutfall inkluderande intrauterin fosterdöd/neonatal död och neonatal sjuklighet, primärt utfall i de båda största studierna, var 2,1% och 2,2%.

Slutsatser: En strategi med induktion vid 41 fulla veckor jämfört med exspektans och induktion vid 42 fulla veckors graviditetslängd skulle kunna minska frekvensen intrauterin fosterdöd/neonatal död, men storleksordningen på minskningen är osäker (poolad Peto odds ratio 0,20; 95% KI 0,06 till 0,70; GRADE ⊕⊕◯◯), skulle kunna resultera i att frekvensen av ett kompositutfall inkluderande intrauterin fosterdöd/neonatal död och neonatal sjuklighet ökar eller minskar måttligt eller resulterar i liten eller ingen skillnad (poolad RR 0,78; 95% KI 0,40 till 1,52; GRADE ⊕⊕◯◯), minskar troligen frekvensen av inläggningar på neonatal vårdavdelning (poolad RR 0.79; 95% KI 0.63 to 0.99; GRADE ⊕⊕⊕◯), resulterar i liten eller ingen skillnad i frekvensen kejsarsnitt, operativ vaginal förlossning och postpartumblödning (GRADE ⊕⊕⊕⊕), samt resulterar troligen i liten eller ingen skillnad vad gäller bäckenbottenbristningar grad 3-4 (GRADE ⊕⊕⊕◯).

Sammanfattande slutsats

Denna systematiska översikt inkluderande tre RCT'er med 5,161 patienter som jämfört strategier för induktion vid 41 fulla veckor med strategier för exspektans med varierande grad av fosterövervakning och induktion vid 42 fulla veckor visar att intrauterin fosterdöd/neonatal död skulle kunna minska vid tidig induktion men det är oklart hur stor minskningen är, samt skulle kunna resultera i att frekvensen av ett kompositutfall inkluderande intrauterin fosterdöd/neonatal död och neonatal sjuklighet inte påverkas i någon säker riktning. För viktiga maternella utfall fanns, eller fanns troligen, ingen eller liten, skillnad.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is intended for decision makers and is ended with a concluding summary.

Susanna Wallerstedt Chair, Meeting of Regional board for quality assurance of activity-based HTA, HTA-centrum Region Västra Götaland, Sweden, [January 29th, 2020]

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PhD Doctor of Philosophy
OD Odontology doctor
PT Physiotherapist
RN Registered Nurse

3. **Summary of findings** Induction week 41 vs expectancy to week 42

Outcomes	Study design Number of studies	Relative effect (95% CI)	Absolute effect	Certainty of evidence GRADE
Critical outcomes for decision making				
Stillbirth/neonatal mortality	3 RCTs	Peto OR 0.20 (0.06 to 0.70)	0.04% vs 0.35%	⊕⊕◯◯[1]
Hypoxic ischaemic encephalopathy 1-3	1 RCT	RR 0.66 (0.11 to 3.96)	0.1% vs 0.2%%	⊕◯◯◯[2]
Intracranial haemorrhage	2 RCTs	RR 0.50 (0.05 to 5.48)	0.07% vs 0.15%	⊕◯◯◯[3]
Composite stillbirth/neonatal mortality and neonatal morbidity	2 RCTs	RR 0.78 (0.40 to 1.52)	2.1% vs 2.2%	⊕⊕◯◯[4]
Maternal mortality	2 RCTs		0% vs 0%	-
Important outcomes for decision making				
Neonatal:				
Convulsions	1 RCT	RR 0.33 (0.03 to 3.18)	0.07% vs 0.22%	-
Meconium aspiration syndrome	3 RCTs	Peto OR 0.38 (0.17 to 0.86)	0.23% vs 0.66%	⊕⊕◯◯[5]
Mechanical ventilation	1 RCT	RR 0.60 (0.14 to 2.49)	0.22% vs 0.36%	-
Obstetric brachial plexus injury	2 RCTs	RR 3.98 (0.45 to 35.56)	0.30% vs 0.07%	-
Infections: sepsis, pneumonia	2 RCTs	Range RR 0.45 to 1.0	Range 0.6 to 4.1 vs 0.4 to 4.1	-
Admission to NICU	3 RCTs	RR 0.79 (0.63 to 0.99)	5.0% vs 6.4%	⊕⊕⊕◯[6]
Apgar score <4 at 5 min	2 RCTs	Peto OR 0.75 (0.17 to 3.30)	0.13% vs 0.17%	-
Maternal:				
Caesarean delivery	3 RCTs	RR 0.96 (0.82 to 1.11)	11.5% vs 12.0%	⊕⊕⊕⊕[7]
Operative vaginal delivery	2 RCTs	RR 0.91 (0.75 to 1.10)	7.9% vs 8.7%	⊕⊕⊕⊕[7]
Perineal tear grade 3-4	2 RCTs	RR 0.84 (0.61 to 1.15)	3.0% vs 3.6%	⊕⊕⊕◯[8]
Uterine rupture	1 RCTs		0% vs 0%	-
Admittance to ICU	2 RCTs	Peto OR 2.36 (0.54 to 10.40)	0.22% vs 0.09%	-
Postpartum haemorrhage	2 RCTs	RR 1.02 (0.85 to 1.21)	9.7% vs 9.2%	⊕⊕⊕⊕[7]
Infections: endometritis, chorioamnionitis, sepsis	2 RCTs	Range RR 0.33 to 3.0		-
Women's experience	Not reported			

All critical outcomes and some pre-specified important outcomes were assessed according to GRADE

Footnotes:
[1] Downgraded one step due to serious imprecision (only 9 events) and one step due to some study limitations and indirectness in the Swedish context in the INDEX study.
[2] Downgraded three steps due to very serious imprecision (only 5 events) and inability to evaluate consistency (only one study).
[3] Downgraded three steps due to very serious imprecision (only 3 events) and inconsistency.
[4] Downgraded two steps due to serious imprecision, some study limitations, differences in definitions of the composite outcomes, some inconsistency and indirectness in the INDEX study.
[5] Downgraded one step due to serious imprecision and one step due to higher incidence in the Gelisen trial, which does not define Meconium aspiration syndrome.
[6] Downgraded one step due to some uncertainty about directness in the INDEX study and some study limitations.
[7] Some uncertainty about directness in the INDEX study was not enough to downgrade one step.
[8] Downgraded one step due to uncertain precision and some uncertainty about directness in the INDEX study.

Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/Acronyms

AD: Abdominal Diameter
AFI: Amniotic Fluid Index
ARRIVE: A Randomized Trial of Induction Versus Expectant Management
BMI body mass index
CI: Confidence Interval
CTG: Cardiotocography
HIE: Hypoxic Ischaemic Encephalopathy
HTA: Health Technology Assessment
ICU: Intensive Care Unit
INDEX: INDuction of labour at 41 weeks compared with a policy of EXpectant management until 42 weeks
Induction: Induction of labour
KI: Konfidensintervall
MAS: Meconium Aspiration Syndrome
NICU: Neonatal Intensive Care Unit
NNT: Number Needed to Treat
OR: Odds Ratio
RCT: Randomised Controlled Trial
RR: Relative Risk
SBU: Swedish Agency for Health Technology Assessment and Assessment of Social Services
SGA: Small for Gestational Age
SR: Systematic Review
SWEPIS: SWEdish Postterm Induction Study
WHO: World Health Organization
VGR: Region Västra Götaland in Sweden

5. Background

Finding the optimal time to give birth involves balancing risks and benefits (as well as economic costs).

Late term is defined as a pregnancy that reaches between 41+0 (i.e. 41 weeks and 0 days) and 41+6. A pregnancy is usually considered to be "prolonged" after 41+0, but the infant is not considered "post term" until 294 days (42+0) (ACOG 2013, WHO 1977).

Prolonged pregnancy (≥41+0) is associated with increased risks of maternal and foetal/infant complications including stillbirth/neonatal mortality. The prospective risk of stillbirth and neonatal death according to gestational age was evaluated in a recent systematic review (SR) of cohort studies (Muglu et al., 2019). The gestational week specific prospective risk of stillbirth increased from 0.11/1000 at 37 weeks to 3.18/1000 at 42 weeks. According to a report from the Swedish National Board of Health and Welfare the rate of stillbirth at 41weeks was 2/1000 between 2008 and 2016 (Socialstyrelsen, 2018). In the VGR eight and seven stillbirths occurred after 41+0 weeks during 2018 and 2019 respectively.

Observational studies show that post term pregnancy compared with term deliveries also is associated with neonatal morbidity such as asphyxia, meconium aspiration syndrome (MAS), obstetric brachial plexus injuries and sepsis (Olesen et al., 2003). Further, increased risk of maternal complications such as labour dystocia, caesarean delivery, postpartum haemorrhage, and puerperal infection (Olesen et al., 2003) as well as perineal tears grade 3 and 4 and operative vaginal deliveries is reported (Caughey et al., 2004).

Induction of labour (induction) before post term is used in an attempt to avoid these adverse effects. This is a controversial intervention since the medical procedure to induce labour is associated with adverse effects such as prolonged labour, uterine hyperstimulation, maternal and neonatal infectious morbidity and an increased risk of uterine rupture (Gommers et al., 2017, Mozurkewich et al., 2011, Chen et al., 2016). Whether induction increases the risk of caesarean delivery or not varies among studies. Two recent meta-analyses (37 and 157 randomised controlled trials (RCTs), respectively report that induction of labour confers a lower risk of caesarean delivery compared with expectant management (Wood et al., 2014 and Mishanina et al., 2014). It is therefore important to study the benefits and risks of induction, including optimal timing.

A number of RCTs have compared induction with expectant management in pregnancies at and beyond term and several SRs and meta-analyses have been published (Sanchez-Ramos et al., 2003, Gulmezuglo et al., 2012, Wennerholm et al., 2009, Hussain et al., 2011, Middleton et al., 2018). HTA-centrum Region Västra Götaland has previously published two HTA reports, in 2007 and 2012 respectively, evaluating induction vs expectant management in late term and post term pregnancies (Wennerholm et al., 2007, Wennerholm et al., 2012). The first report included 13 RCTs and showed no difference in perinatal mortality but significantly lower rates of MAS and caesarean deliveries in the induction compared with the expectant management group. An update of the HTA report from 2007 in 2012 included 17 RCTs, evaluating induction at 41 to 42 weeks vs expectant management without any defined upper limit, showed a lower rate of perinatal mortality and MAS in the induction group and no difference in caesarean deliveries between the groups (Wennerholm et al., 2012).

A recent Cochrane review (Middleton et al., 2018), comparing a policy of induction at or beyond term with a policy of awaiting spontaneous labour (expectant management), included 30 RCTs. Compared with expectant management, a policy of induction was associated with fewer (all-cause) perinatal deaths (RR 0.33; 95% CI 0.14 to 0.78; 20 trials, 9,960 infants; moderate-quality evidence) and fewer stillbirths (RR 0.33; 95% CI 0.11 to 0.96; 20 trials, 9,960 infants (moderate-quality evidence).

The caesarean delivery rate was lower in the induction group (RR 0.92; 95% CI 0.85 to 0.99; 27 trials, 11,738 women; moderate-quality evidence) and the RR for operative vaginal delivery was 1.07 (95% CI 0.99 to 1.16) (18 trials, 9,281 women, moderate-quality evidence).

It should be noted that the included trials were diverse concerning settings, year of publication (from 1969 to 2018), timing of induction (from 37 to 43 completed weeks), induction methods and gestational age limits for the expectant management group (from 41 weeks to no upper gestational age limit). Only two of the included trials (one of these was available only as an abstract at this time) compared induction at 41weeks with expectant management with various regimes for foetal surveillance and induction at 42+0 (Gelisen et al., 2005, Bruinsma et al., 2017). Hence, the optimal time point for induction after term is unclear.

Since the Cochrane systematic review (Middleton et al., 2018) was conducted, three additional possibly relevant RCTs have been published (Grobman et al., 2018, Keulen et al., 2019, Wennerholm et al., 2019). The ARRIVE (A Randomized Trial of Induction versus Expectant Management) trial, a large trial from the United States, compared induction of labour in low risk nulliparous women (6,106 women) at weeks 39+0 to 39+4 with expectant management until 41+0 (Grobman et al., 2018). No significant intergroup difference was found in the composite adverse perinatal outcome (4.3% vs 5.4%; RR 0.80; 95% CI 0.64 to 1.00), whereas the frequency of caesarean delivery was significantly lower in the induction group (18.6% vs 22.2%; RR 0.84; 95% CI 0.76 to 0.93). The other trials compared induction at 41 weeks versus expectant management and induction at 42 weeks.

The aim of the present HTA report is to evaluate if a strategy of induction at 41weeks + (0 to 2 days) compared with a strategy of expectant management with various regimes of foetal surveillance and induction at 42 weeks + (0 to 1 day) is superior in terms of decreased stillbirth/neonatal mortality and neonatal morbidity without increasing maternal mortality and morbidity, in healthy women with an uncomplicated singleton pregnancy.

Prevalence and incidence

The prevalence and incidence of post term pregnancies may vary depending on the characteristics of the studied population and the method used for determining gestational age. Parity and interventions, e.g. frequency of caesarean delivery and induction, affect the prevalence. Ultrasonographic measurement of foetal biparietal diameter in first or early second trimester is regarded as the most accurate way of estimating gestational age (Selbing and Kjessler, 1985, Saltvedt et al., 2004). An observational study (Grunewald et al., 2011) reported a rate of post term pregnancy (≥42+0) of 6.0% in VGR during 2007-2008. During 2018, 19,311 children were delivered in the VGR (Obstetrix regional database), 4,244 (22.0%) at 41+0 weeks or later and 1,187 (6.1%) at 42+0 weeks or later.

Present management in VGR

In VGR all pregnant women are informed about and offered induction at week 42+0. No routine foetal monitoring (cardiotocography (CTG) or ultrasonic assessment of amniotic fluid and abdominal diameter (AD)) is offered to pregnant women <42 weeks in VGR, nor in most Swedish obstetric units. Most women accept to have induction of labour at week 42+0. Women who prefer expectant management after week 42+0 are referred to an antenatal clinic where outpatient check-ups are offered. These include CTG, cervical examination with membrane sweeping, ultrasonographic examination with assessment of amniotic fluid volume, biophysical profile and measurement of AD. If there is any indication of a non-reassuring foetal status (AD <106 mm, oligohydramniosis (less than expected amniotic fluid volume), absence of foetal movements, non-reassuring CTG), induction is recommended. If the condition of the foetus and mother is normal, outpatient check-ups are offered at weeks 42+3 and 42+5 and induction is recommended at week 43+0.

The normal pathway through the healthcare system and current wait time for induction of labour

In Sweden almost all deliveries occur at an obstetric unit (secondary care) where midwives, obstetricians and assistant nurses work in a team. There are no primary delivery units (deliveries only supervised by a midwife outside a hospital) in Sweden. The rate of planned home deliveries is about 1/1,000 deliveries compared to 20/1,000 in Denmark, 10/1,000 in Norway and 170/1,000 in the Netherlands (Lindgren et al., 2014, Nederland SPR). There is little or no wait time for induction. Wait time may be one or two days depending on the indication for induction and the available capacity in the labour ward.

Number of patients per year who undergo current treatment regimen

In the VGR with 20,000 deliveries per year, approximately 1,200 women go through induction due to post-term pregnancies. If the indication for induction would change from post-term (42+0) to late term (41+0) approximately 3,200 additional women will go through an induction every year, provided that the delivery rate is constant.

Present recommendations from medical societies or health authorities

There are no national guidelines for women at or beyond term regarding when to recommend induction in Sweden. However, most hospitals in Sweden recommend induction at week 42+0. In the Stockholm region a routine ultrasound scan including measurement of abdominal diameter (AD) and assessment of the amniotic fluid volume is offered at week 41+0. In Denmark the guideline recommends foetal surveillance at 41+0 and induction between 41+2 and 41+5 in uncomplicated singleton pregnancies and at 41+0 in women >40 years of age and/or a body mass index (BMI) over 35 kg/m^2 (Wilken-Jensen et al., 2011). WHO has since 2018 a conditional recommendation of induction at 41+0 for women with an uncomplicated pregnancy (WHO 2018). Various guidelines from different countries recommend induction between 41 and 42 weeks (NICE 2014, ACOG Practice Bulletin no. 146, 2014, South Australian Perinatal Practice Guidelines (SAPPG), 2017, Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG), 2007).

6. Health Technology at issue: Induction of labour in uncomplicated singleton pregnancies at 41+0 weeks

This HTA report is evaluating a shift in indication for induction in prolonged pregnancies. The methods used to induce labour are well established. In case of a well engaged foetal head and a ripe cervix (Bishop score ≥6 for primiparas and ≥5 for multiparas) amniotomy is performed, followed by oxytocin infusion after 1-2 hours without spontaneous regular contractions. In case of an unengaged foetal head or a less ripe cervix, any of the following methods is used, according to local routines: mechanical dilation with a Foley-like catheter; oral misoprostol; controlled released vaginal misoprostol insert; prostaglandin E2 vaginally. Induction at 41 completed weeks will imply in mean six hours longer time hospital stay before delivery compared with expectancy and induction at 42 completed weeks (6.5 h; 95% CI 5.5 to 7.5), (Wennerholm et al., 2019).

7. Focused question

Is a strategy of induction at 41 weeks + (0 to 2 days) compared with a strategy of expectant management with various regimes of foetal surveillance and induction at 42 weeks + (0 to 1 day) superior in terms of decreased stillbirth/neonatal mortality and neonatal morbidity without increasing maternal mortality and morbidity, in healthy women with an uncomplicated singleton pregnancy?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P - Women with ultrasonographically verified late term pregnancy (41 weeks) and an uncomplicated (as defined by authors), singleton pregnancy in cephalic presentation

I - Strategy to induce labour at 41 weeks + (0 to 2 days)

C - Strategy of expectant management (with various regimes of foetal surveillance) and induction of labour at 42 weeks + (0 to 1 day)

O

- Critical for decision making (GRADE assessment):

4.1 Neonatal outcomes
4.1.1 Stillbirth/neonatal mortality (intrauterine foetal death; total (<28 days) and early (<7 days) neonatal mortality)
4.1.2 Hypoxic ischemic encephalopathy (HIE) 1-3
4.1.3 Intracranial haemorrhage
4.1.4 Composite stillbirth/neonatal mortality and neonatal morbidity

4.2 Maternal outcome
4.2.1 Mortality (<42 days after delivery)

- Important for decision making (GRADE assessment for some pre-specified important outcomes)

Neonatal outcomes, continued
4.1.5 Convulsions
4.1.6 Meconium aspiration syndrome (MAS) (GRADE assessment)
4.1.7 Mechanical ventilation
4.1.8 Obstetric brachial plexus injury
4.1.9 Neonatal infections; sepsis, pneumonia
4.1.10 Admission to NICU (GRADE assessment)
4.1.11 Apgar score less than 4 at 5 minutes
4.1.12 Macrosomia (birth weight ≥4000 g, or ≥4500 g)/Large for gestational age

Maternal outcomes, continued
4.2.2 Caesarean delivery (GRADE assessment)
4.2.3 Operative vaginal delivery (vacuum extraction/forceps) (GRADE assessment)
4.2.4 Perineal tear grade 3 and 4 (GRADE assessment)
4.2.5 Uterine rupture
4.2.6 Admittance to an intensive care unit (ICU)
4.2.7 Postpartum haemorrhage >1000 ml (GRADE assessment)
4.2.8 Infections: endometritis, chorioamnionitis, sepsis
4.2.9 Women's experience

8. Methods

Systematic literature search (Appendix 1)

During October and November 2019 two authors (TS, EKK) performed systematic searches in PubMed, Embase, the Cochrane Library, Cinahl, PsycInfo and a number of HTA-databases. Reference lists of relevant articles and the previous HTA-report (Wennerholm et al., 2012) were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, selected studies, and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all authors. All authors read the articles independently of one another and it was finally decided in a consensus meeting which articles should be included in the assessment.

Critical appraisal and certainty of evidence

The included studies and their design and patient characteristics are presented in Appendix 2. The excluded studies and the reasons for exclusion are presented in Appendix 3. The included RCTs have been critically appraised using a checklist for assessment of RCTs from Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU). The results of each article have been summarised per outcome in Appendix 4.

Data were extracted by at least two authors per outcome. When possible, data were pooled in meta-analyses, applying a random effect model and presented as forest plots. Point estimates are presented as RR with 95% CI. For outcomes with zero events in any of the arms in any of the trials, Peto odds ratio (OR) was used applying a fixed effect model (Brockhaus et al., 2016). Review Manager 5.3 was used to conduct the meta-analyses. A summary result per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 8). The certainty of evidence was assessed using the GRADE approach (Guyatt, Oxman et al., 2008) for all critical and some pre- specified important outcomes.

Ongoing research

A search in Clinicaltrials.gov (2019-12-12) using the search terms: *AREA[ConditionSearch] (full-term OR fullterm OR postdate OR post-date OR post-term OR postterm OR late term OR beyond term OR prolonged OR 41 weeks OR 42 weeks) AND AREA[InterventionSearch] (induced labour OR induction OR expectant management)* identified 57 trials.

A search in WHO ICTRP (2019-12-12) using the search terms:
(full-term AND induced labour) OR (fullterm AND induced labour) OR (postdate AND induced labour) OR (post-date AND induced labour) OR (post-term AND induced labour) OR (postterm AND induced labour) OR (late term AND induced labour) OR (beyond term AND induced labour) OR (prolonged AND induced labour) OR (41 weeks AND induced labour) OR (42 weeks AND induced labour)

OR

(full-term AND induction) OR (fullterm AND induction) OR (postdate AND induction) OR (post-date AND induction) OR (post-term AND induction) OR (postterm AND induction) OR (late term AND induction) OR (beyond term AND induction) OR (prolonged AND induction) OR (41 weeks AND induction) OR (42 weeks AND induction)

OR

(full-term AND expectant management) OR (fullterm AND expectant management) OR (postdate AND expectant management) OR (post-date AND expectant management) OR (post-term AND expectant management) OR (postterm AND expectant management) OR (late term AND expectant management) OR (beyond term AND expectant management) OR (prolonged AND expectant management) OR (41 weeks AND expectant management) OR (42 weeks AND expectant management)
identified 150 trials. Eight of these 57+150 trials were potentially relevant for the question at issue and evaluated further.

9. Results

Literature search (Appendix 1)

The literature search identified 983 articles after removal of duplicates. After reading the abstracts 927 articles were excluded. A total of 79 articles were read in full text – this includes the 23 included articles in the previous HTA report (Wennerholm et al., 2012). Only one study from the previous report fulfilled the gestational age criteria applied in the present PICO. Totally 48 articles were excluded by two authors. The remaining 31 articles were sent to all authors, and three RCT articles were finally included in the assessment (Appendix 2). Excluded studies, with reasons, are presented in Appendix 3.

Included studies

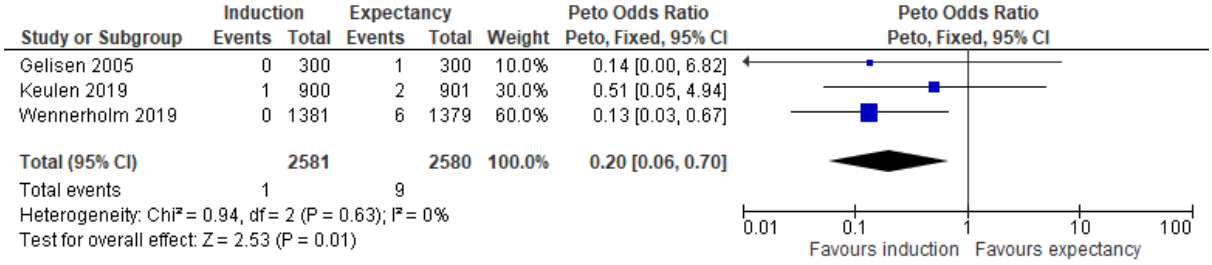
Three RCTs with 5,161 patients were included. A previous caesarean delivery was an exclusion criterion in all three trials. The first RCT (Gelisen et al., 2005) had some or major problems regarding directness, study limitations and precision. The trial was small and had no published study protocol. In the expectant management group routine surveillance with ultrasound was performed twice weekly. The second RCT (Keulen et al., 2019), the INDEX study, had a non-inferiority design and some problems with indirectness in relation to the Swedish setting, since the delivery care in the Netherlands is divided into primary care (delivery supervised by a community midwife at home or at hospital) and secondary care (delivery supervised by clinical midwives and obstetricians). There were some minor problems with study limitations but not with precision for the primary composite outcome. Foetal surveillance during expectant care was according to local protocols and could include consultations, CTG, and ultrasonographic assessment of amniotic fluid volume. The third RCT (Wennerholm et al., 2019), the SWEPIS study, had minor problems with directness, including a lower inclusion rate than expected (22% of eligible women), some problems regarding study limitations for the outcome stillbirth/neonatal mortality but no or minor problems for the other outcomes. Inclusion of women in the Stockholm region, but not in the other centres, was performed after a routine ultrasonographic assessment. Foetal surveillance in the expectant group was according to local protocols. The study included continuous reporting of serious adverse events to a safety monitoring board and was for ethical reasons stopped early after inclusion of 27.5% (2,760/10,038) of the planned sample size when significantly more stillbirth/neonatal deaths were observed in the expectant management group. Regarding precision, the study had major problems for the composite outcome and stillbirth/neonatal mortality due to early cancelation and few events.

Results per outcome

Outcomes – Critical for decision-making

Stillbirth/neonatal mortality (intrauterine foetal death; total (<28 days) and early (<7 days) neonatal mortality (Appendix 4.1.1)
Stillbirth/neonatal mortality was reported in all three RCTs. The first RCT reported no difference in stillbirth/neonatal mortality between the induction (no deaths) and the expectant management group (one death, 0.3%), p=1.0. The second RCT reported no difference in stillbirth/neonatal mortality between the induction (one death, 0.11%) and the expectant management group (two deaths, 0.22%), p=1.0. The third RCT was stopped early when a significant difference in stillbirth/neonatal mortality was observed between the induction (no deaths) and the expectant management group (six deaths, 0.4%), p=0.03. The six deaths were five stillbirths and one neonatal death.

Fig. 1. Meta-analysis of studies comparing induction of labour with expectant management. Outcome: stillbirth/neonatal mortality



Meta-analysis of the three RCTs (5,161 patients) showed a Peto OR of 0.20 (95% CI 0.06 to 0.70), favouring induction (Fig. 1). After exclusion of the only neonatal death, the Peto OR for stillbirth was 0.21 (95% CI 0.06 to 0.78).

Conclusion: A strategy of induction at 41 completed weeks compared with a strategy of expectant management to 42 completed weeks may reduce stillbirth/neonatal mortality (GRADE ⊕⊕◯◯).

Hypoxic ischemic encephalopathy (HIE) 1-3 (Appendix 4.1.2)
Hypoxic ischemic encephalopathy 1-3 was reported in one RCT with no significant difference in HIE between the induction group (0.1%) and the expectant management group (0.2%).

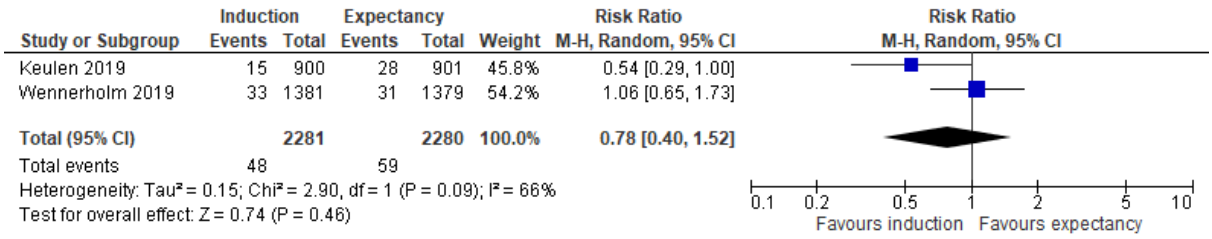
Conclusion: It is uncertain whether a strategy of induction at 41 completed weeks compared with a strategy of expectant management to 42 completed weeks affects the rate of HIE (GRADE ⊕◯◯◯).

Intracranial haemorrhage (Appendix 4.1.3)
Intracranial haemorrhage was reported in two RCTs. There was no intracranial haemorrhage in one of the RCTs and the other RCT reported no significant difference in intracranial haemorrhage between the induction (0.07%) and the expectant management group (0.15%), p=1.0.

Conclusion: It is uncertain whether a strategy of induction at 41 completed weeks compared with a strategy of expectant management to 42 completed weeks affects the rate of intracranial haemorrhage (GRADE ⊕◯◯◯).

Composite stillbirth/neonatal mortality and neonatal morbidity. (Appendix 4.1.4)
A composite stillbirth/neonatal outcome was reported as primary outcome in the two largest RCTs. One of these had a non-inferiority design and a composite outcome including stillbirth/neonatal mortality and neonatal morbidity defined as 5 min Apgar score<7, meconium aspiration syndrome, obstetric brachial plexus injury, intracranial haemorrhage and neonatal intensive care unit admission. This RCT reported a significant difference in the composite outcome between the induction (1.7%) and the expectant management groups (3.1%), p=0.045. The other RCT had a superiority design and a similar composite outcome which did not include neonatal intensive care unit admission but included metabolic acidosis, hypoxic ischemic encephalopathy grades 1-3, neonatal convulsions, and mechanical ventilation within the first 72 hours. This RCT reported no significant difference between the induction (2.4%) and the expectant management group (2.2%). Meta-analysis showed a pooled RR of 0.78 (95% CI 0.40 to 1.52) (Fig. 2).

Fig. 2. Meta-analysis of studies comparing induction of labour with expectant management.
Outcome: Composite stillbirth/neonatal mortality and neonatal morbidity



Conclusion: A strategy of induction at 41 completed weeks compared with a strategy of expectant management to 42 completed weeks may result in a moderate increase or decrease or in little or no difference in the rate of composite outcomes of stillbirth/neonatal mortality and neonatal morbidity (GRADE ⊕⊕◯◯).

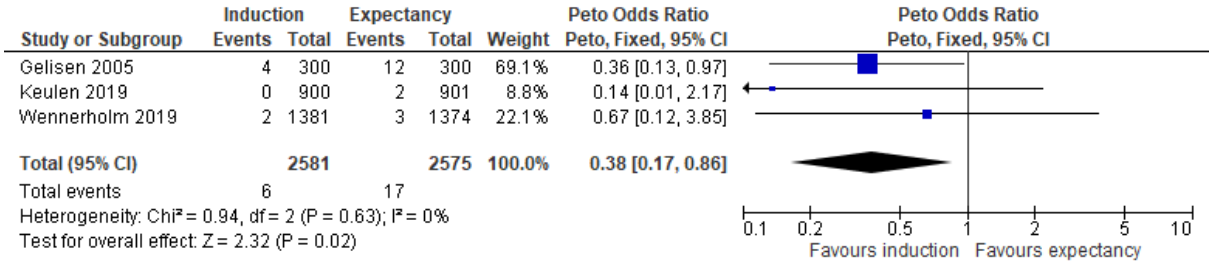
Maternal mortality (Appendix 4.2.1)
Maternal mortality was reported in two RCTs. There was no maternal mortality in either of the RCTs.

Outcomes – Important for decision-making

Neonatal convulsions (Appendix 4.1.5)
Neonatal convulsions were reported in one RCT with one (0.1%) vs three (0.2%) in the induction and the expectant management group respectively, p=0.62.

Meconium aspiration syndrome (MAS) (Appendix 4.1.6)
Meconium aspiration syndrome was reported in all three RCTs (5,156 patients). One RCT with 600 patients reported a significant difference between the induction (1.3%) and the expectant management groups (4%), p=0.03. This RCT did not define meconium aspiration syndrome and had a higher incidence. The second RCT reported no meconium aspiration syndrome in the induction and two cases in the expectant management group (0.2%). Meconium aspiration syndrome was defined as respiratory distress after birth in the presence of meconium stained amniotic fluid. The third RCT reported no significant difference between the induction (0.1%) versus the expectant management group (0.2%), p=1.00. The pooled Peto OR was 0.38 (95% CI 0.17 to 0.86) (Fig. 3).

Fig. 3. Meta-analysis of studies comparing induction of labour with expectant management. Outcome: Meconium aspiration syndrome



A sensitivity analysis omitting the Gelisen trial, due to lack of definition of MAS and a divergent incidence, resulted in a non-significant difference, pooled Peto OR 0.42 (95% CI 0.10 to 1.86).

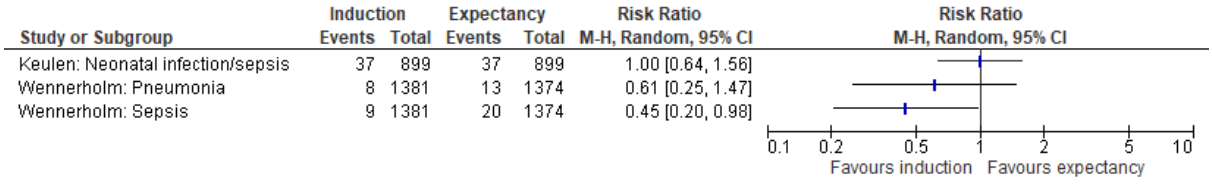
Conclusion: A strategy of induction at 41 completed weeks compared with a strategy of expectant management to 42 completed weeks may reduce the frequency of meconium aspiration syndrome (GRADE ⊕⊕◯◯).

Mechanical ventilation (Appendix 4.1.7)
Mechanical ventilation of the neonate within the first 72 h was reported in one RCT. The RCT reported no significant difference between the induction (0.2%) versus the expectant management group (0.4%), p=0.72.

Obstetric brachial plexus injury (Appendix 4.1.8)
Obstetric brachial plexus injury was reported in two RCTs. The first of these did not report any cases of brachial plexus injury. The second reported no significant difference between the induction (0.3%) and the expectant management group (0.1%), p=0.38.

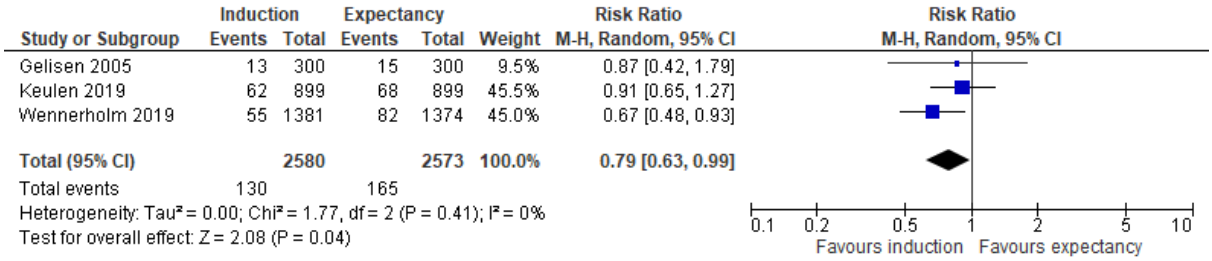
Neonatal infections: Sepsis, Pneumonia (Appendix 4.1.9)
Neonatal infections were reported in two RCTs. The first RCT reported neonatal infections and sepsis as one category. No significant difference was seen between the induction (4.1%) and the expectant management group (4.1%), p=1.00. The other RCT reported sepsis (0.7% versus 1.5%, p=0.06) and pneumonia (0.6% versus 0.9%, p=0.38) separately (Fig. 4).

Fig. 4. Forest plot of studies comparing induction of labour with expectant management. Outcome: Neonatal infections, sepsis, pneumonia.



Admittance to neonatal intensive care unit (NICU) (Appendix 4.1.10)
Admittance to NICU was reported in all three RCTs. One RCT reported no significant difference between the groups (4.3% versus 5.0%, p=0.4). The second RCT reported admittance to NICU as well as to medium care without any significant difference between the groups regarding admittance to NICU (0.3% versus 0.8%, p=0.23), medium care (6.6% versus 6.7%, p=0.90), or either of them (6.9% versus 7.6%, p=0.59). The third RCT reported a significant reduction in admittance to NICU in the induction (4.0%) compared with the expectant management group (6.0%), p=0.02. The pooled RR was 0.79 (95% CI 0.63 to 0.99) (Fig. 5).

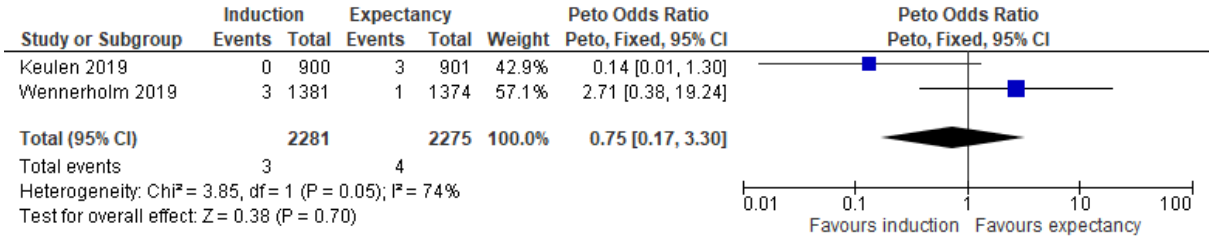
Fig. 5. Meta-analysis of studies comparing induction of labour with expectant management.
Outcome: Admittance to neonatal intensive care unit including medium level care



Conclusion: A strategy of induction at 41 completed weeks compared with a strategy of expectant management to 42 completed weeks probably reduces the frequency of admittance to neonatal intensive care unit (GRADE ⊕⊕⊕◯).

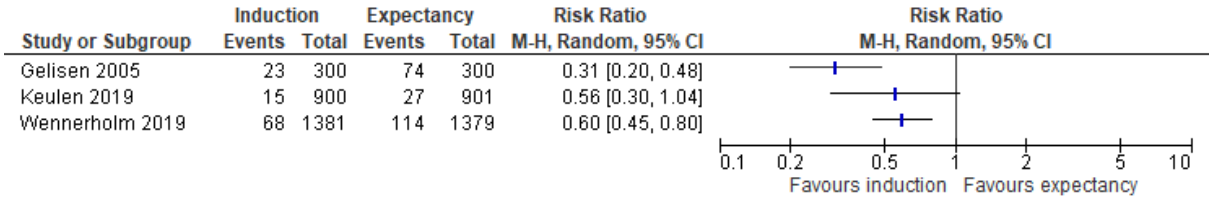
Apgar score less than 4 at 5 minutes (Appendix 4.1.11)
Apgar score <4 at 5 minutes was reported in two RCTs (4,556 patients). The first RCT reported no events in the induction and three events in the expectant management group (1.3%). The other RCT reported no significant difference between the induction (0.22%) and the expectant management group (0.07%), p=0.63. The Peto OR was 0.75 (95% CI 0.17 to 3.30), (Fig. 6).

Fig. 6. Meta-analysis of studies comparing induction of labour with expectant management.
Outcome: Apgar score <4 at 5 minutes



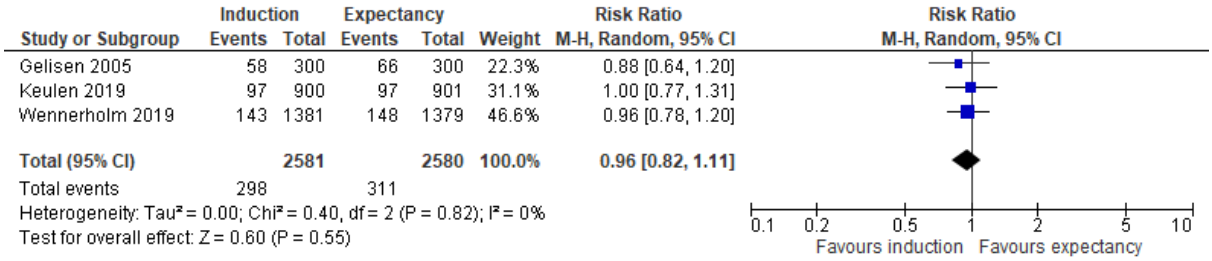
Macrosomia/ large for gestational age (LGA) (Appendix 4.1.12)
Macrosomia was reported in two and large for gestational age in one RCT (5,161 patients). The first RCT reported macrosomia and showed a significant difference (p<0.001). The second RCT reported large for gestational age and showed no significant difference between the induction (1.7%) and the expectant management groups (3.0%), p=0.07. The third RCT reported macrosomia and showed a significant difference between the groups of 4.9% versus 8.3%, p=<0.01. No summary estimate was calculated, due to heterogeneous definitions of the outcome (Fig. 7).

Fig. 7. Forest-plot of studies comparing induction of labour with expectant management.
Outcome: Macrosomia applying different definitions (Gelisen: >4000g, Keulen: large for gestational age, Wennerholm: >4500g)



Caesarean delivery (Appendix 4.2.2)
Caesarean delivery was reported in all three RCTs. None of the RCTs reported any significant difference between the induction (19.3%, 10.8% and 10.4% respectively) and the expectant management groups (22.0%, 10.8% and 10.7% respectively). The pooled RR was 0.96 (95% CI 0.82 to 1.11) (Fig. 8).

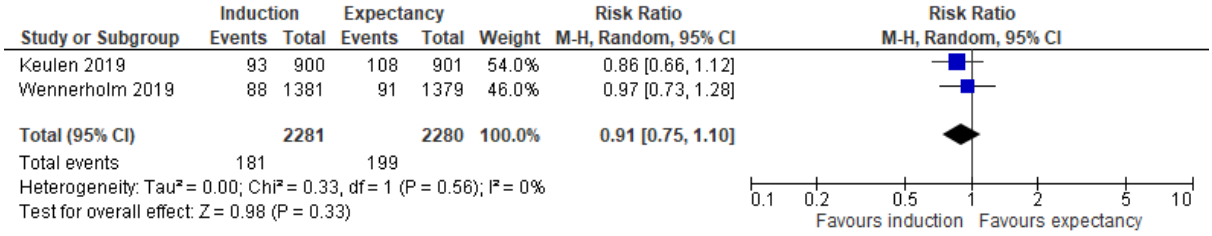
Fig. 8. Meta-analysis of studies comparing induction of labour with expectant management. Outcome: Caesarean delivery



Conclusion: A strategy of induction at 41 completed weeks compared with a strategy of expectant management to 42 completed weeks results in little or no difference in the frequency of caesarean delivery (GRADE ⊕⊕⊕⊕).

Operative vaginal delivery (Appendix 4.2.3)
Operative vaginal delivery was reported in two RCTs (4,561 patients). No significant difference was observed between the induction (10.3% and 6.4%, respectively) and the expectant management (12% and 6.6%, respectively) groups. The pooled RR was 0.91 (95% CI 0.75 to 1.10) (Fig.9).

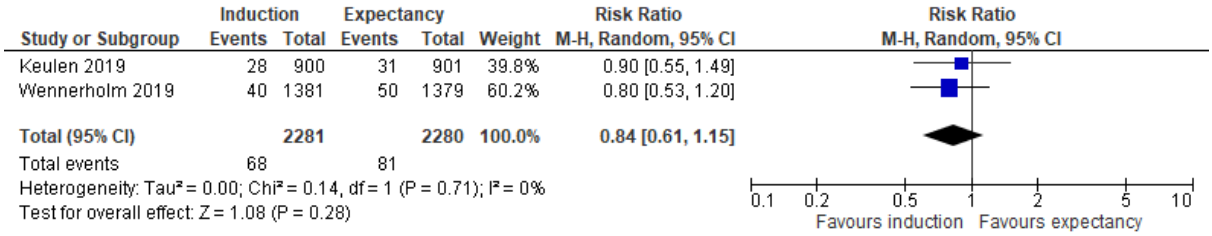
Fig. 9. Meta-analysis of studies comparing induction of labour with expectant management. Outcome: Operative vaginal delivery



Conclusion: A strategy of induction at 41 completed weeks compared with a strategy of expectant management to 42 completed weeks results in little or no difference in operative vaginal delivery rate (GRADE ⊕⊕⊕⊕).

Perineal tears grade 3-4 (Appendix 4.2.4)
Perineal tears grade 3-4 were reported in two RCTs (4,561 patients) with no significant differences between the induction (3.5% and 2.9%, respectively) and the expectant management (3.9% and 3.6%, respectively) groups. The pooled RR was 0.84 (95% CI 0.61 to 1.15) (Fig. 10).

Fig. 10. Meta-analysis of studies comparing induction of labour with expectant management. Outcome: Perineal tear grade 3-4

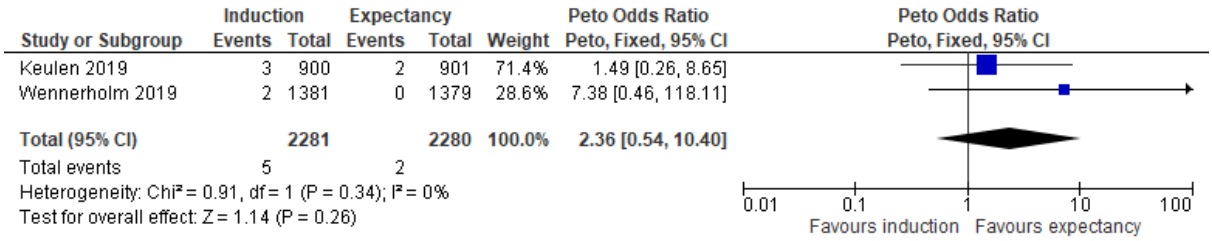


Conclusion: A strategy of induction at 41 completed weeks compared with a strategy of expectant management to 42 completed weeks probably results in little or no difference in perineal tears grade 3 – 4 (GRADE⊕⊕⊕◯).

Uterine rupture (Appendix 4.2.5)
Uterine rupture was reported in one RCT. No cases of uterine rupture were observed in that trial.

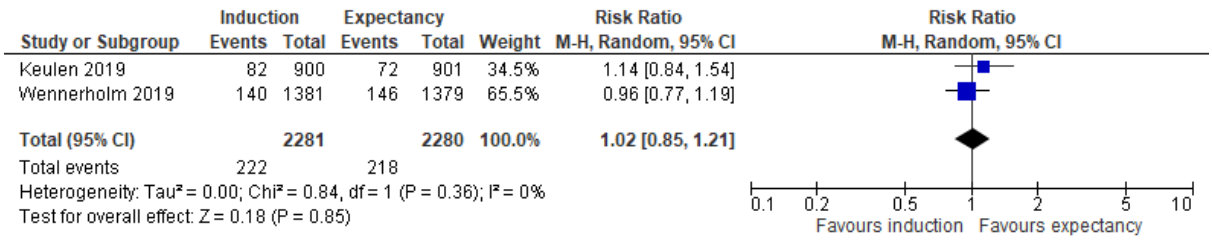
Maternal admittance to an intensive care unit (ICU) (Appendix 4.2.6)
Maternal admittance to ICU was reported in two RCTs (4,561 patients). The first RCT reported no significant difference between the induction (0.33%) and the expectant management groups (0.22%), p=0.66. The second RCT reported no significant difference between the groups (0.14% versus 0.0%), p=0.50. Meta-analysis showed a Peto OR of 2.36 (95% CI 0.54 to 10.40) (Fig. 11).

Fig. 11. Meta-analysis of studies comparing induction of labour with expectant management. Outcome: Maternal admission to an intensive care unit.



Postpartum haemorrhage (Appendix 4.2.7)
Postpartum haemorrhage was reported in two RCTs (4,561 patients). Neither of the RCTs reported any significant difference between the induction (9.1% and 10.1%, respectively) and the expectant management (8.0% and 10.6%, respectively) groups. The pooled RR was 1.02 (95% CI 0.85 to 1.21) (Fig. 12).

Fig. 12. Meta-analysis of studies comparing induction of labour with expectant management. Outcome: Postpartum haemorrhage (Keulen ≥1000mL and Wennerholm >1000mL)



Conclusion: A strategy of induction at 41 completed weeks compared with a strategy of expectant management to 42 completed weeks results in little or no difference in postpartum haemorrhage (GRADE ⊕⊕⊕⊕).

Infections: Endometritis, Chorioamnionitis, Sepsis (Appendix 4.2.8)
Maternal infections were reported in two RCTs. The first RCT only reported fever ≥38°C and use of antibiotics during labour. The second RCT reported five different infection diagnoses; chorioamnionitis, wound infection, urinary tract infection, endometritis and sepsis. Regarding endometritis, there was a significant difference between the induction (1.3%) and the expectant management group (0.4%), p=0.02. There were no significant differences between the groups for any of the other infection diagnoses. No cases of sepsis were reported.

Woman´s experience
Woman´s experience was not reported in any of the included RCTs.

10. Ethical aspects

Changing the indication for induction to include low-risk singleton pregnancies that reach 41+0 may result in fewer stillbirth/neonatal deaths, while the direction of the effect on stillbirth/neonatal mortality and neonatal morbidity combined is uncertain (low certainty of evidence for both outcomes), without increasing complications related to induction (moderate or high certainty of evidence). The latest and largest RCT was stopped early after inclusion of only 28% of the planned number of women for ethical and safety reasons when a significantly higher stillbirth/neonatal mortality rate in the expectant management compared with the induction at 41 completed weeks group was observed. Stopping this study early negatively affects the certainty of evidence (GRADE) for the stillbirth/neonatal mortality as well as for the composite stillbirth/neonatal mortality and neonatal morbidity outcome. Thus, early induction may be in line with the ethical principle of beneficence and non-maleficence.

The effectiveness of induction is an issue currently filled with diverse opinions and ideas among caregivers. Therefore, it is critical that the basic ethical principle of autonomy is respected and that proper unbiased written information regarding benefits and risks with induction versus expectant management is given to allow women to make informed decisions.

A strategy of induction at 41 completed weeks of gestation would result in about 3,200 more women in VGR being induced yearly, and, consequently, a prolonged hospital stay for these. Furthermore, the absolute risk for perinatal death is low even at 42 completed weeks (3.18/1,000, including not only low risk pregnancies) (Socialstyrelsen 2018, Muglu et al., 2019), and induction is an intervention in the natural process of pregnancy and childbirth. Some women may want to avoid interventions and might regard the benefits for herself and the unborn child being greater with expectant management.

Other methods for reducing stillbirth/neonatal mortality, e.g. routine surveillance with ultrasound in order to detect foetuses at risk, could be argued for. None of the stillbirth/neonatal deaths in the SWEPIS trial occurred in sites with routine ultrasound scans at week 41+0. The possible benefits of ultrasound at 41 weeks for reduction of stillbirth/neonatal mortality is insufficiently studied.

A putative increase in inductions may create crowding in delivery wards resulting in displacement effects, including, for instance, women receiving substandard care or being referred to other hospitals. Furthermore, such a change would increase costs and may therefore compete with other health care services. If there is a benefit in saved lives, a higher cost would be justified.

11. Organisational aspects

Time frame for the putative introduction of induction of labour at week 41+0

If induction at week 41+0 is recommended to low-risk women, the organisation will need one to two months to prepare for the introduction and implementation of this new indication for induction. In order to preserve patient safety, a new perspective on the organisation for patients undergoing induction will be necessary. According to available research, induction includes longer time in the hospital for cervical ripening, i.e. before active labour, than for those with spontaneous onset of labour. Cervical ripening, before the first stage of labour, requires less nursing and care than the active phases of labour. Today women undergoing induction are cared for at the delivery ward from the start of the induction process through the active phase until delivery. In case of inducing additional women, there is a risk that the delivery ward will be occupied by women being induced thus reducing available capacity for women in active labour. Therefore, in order to improve capacity, additional strategies have to be considered.

Present use of induction of labour at 41 weeks in Sweden

To our knowledge there are no hospitals in the VGR that routinely induce women with uncomplicated pregnancies at week 41+0. However, Falun and Uppsala have recently started to offer induction of labour at week 41+0.

Consequences of induction of labour at 41 weeks for personnel

Induction at 41 completed gestational weeks does not involve a new technique but implies an extension of the indication for a well-known intervention. Therefore, an extensive education effort for staff involved in the induction process is not needed. However, without the creation of a ward for induction (both facilities and staff) or other kind of organisation, an increase in the number of women with induction will affect the work load at the delivery ward for midwives, obstetricians and assistant nurses.

Consequences for other clinics or supporting functions at the hospital or in Region Västra Götaland

There is a risk of having to refer women to nearby hospitals due to lack of available beds at the delivery ward. The nearby hospitals within the VGR may for similar reasons also face problems with available beds due to more inductions. According to current research there might be a slight increase in use of epidural anaesthesia with induction, affecting the anaesthesiology departments (Wennerholm et al., 2019).

12. Economic aspects

Present costs of currently used technologies

Based on 326 births at the Sahlgrenska University Hospital (within the SWEPIS trial), the average cost per birth, including cost for neonatal care, among women randomised to induction at 42+0 was estimated to 41,790 Swedish kronor (SEK) with 95% CI from 38,010 to 45,569 SEK.

Expected costs of induction of labour at 41 weeks

Based on 345 births at the Sahlgrenska University Hospital (within the SWEPIS trial), the average cost per birth, including cost for neonatal care, among women randomised to induction at 41+(0-2) was estimated to 45,048 SEK with 95% CI from 41,716 to 48,380 SEK.

Total change in costs

The mean cost per birth was 3,259 SEK higher with the new technology (induction at 41+(0-2) instead of expectant management and induction at 42+0), but the 95% CI overlaps no difference (95% CI: 1,756 SEK cheaper to 8,274 SEK more expensive).

When analysing the components of the cost per birth, the new technology is significantly more expensive in terms of the actual birth per se, but is less expensive in terms of neonatal care and hospital care costs, which gives a relatively small difference in the mean cost per birth.

Cost-effectiveness of induction at 41 weeks

Based on the point estimate of the increase in mean cost per birth (3,259 SEK) based on the Sahlgrenska University Hospital cohort within the SWEPIS trial and the point estimate of increased life expectancy per birth in our meta-analysis, it is possible to calculate the cost-effectiveness of the new technology in terms of the cost per gained life-year. Based on the difference (low certainty of evidence) in stillbirth/neonatal mortality (see Appendix 4.1.1), the increase in life expectancy per birth with the new technology is about 0.25 life years (0.1 if using a discount rate of 3%, which is generally recommended in Swedish health economic analyses). This gives a cost per gained life year of approximately 13,000 SEK (33,000 SEK if using discounted life-years) with the 95% CI ranging from approx. 33,000 SEK per gained life year to a situation where the new technology is dominant (i.e. both cheaper and better). It should be noted that the cost analyses do not include long-term costs of chronically ill children.

Possibility to adopt and use the new technology within the present budget

Assuming that the difference in mean cost per birth is approx. 3,259 SEK, the health care budget will see cost increases, which will displace some current offered health care services.

Available economic evaluations or cost advantages/disadvantages

One economic study was identified in the systematic searches and reviews. Kaimal et al. analysed induction at 41 weeks compared with expectant management with antenatal testing until 42 weeks using a decision analytic model in a US health care perspective. The results indicated that induction at 41 weeks was on average $360 more expensive (per birth), and the cost per gained (quality-adjusted) life year was $10,945 (Kaimal et al., 2011). It should be noted that the cost analyses neither include long-term costs of chronically ill children nor the economic impact on society and families of stillbirth/neonatal deaths. A recent Australian study showed that large direct health care costs and macroeconomic costs of stillbirth extend beyond the time of pregnancy and birth and up to at least two years postpartum (Callander et al., 2019).

13. Discussion

In this systematic review including meta-analyses we found that a strategy of induction of labour at gestational week 41+(0-2) may reduce stillbirth/neonatal mortality but to an uncertain extent; while the direction of the effect on stillbirth/neonatal mortality and neonatal morbidity combined, primary outcome in the two largest RCTs, is uncertain; and does not or does probably not increase the risk for caesarean delivery, operative vaginal delivery, post-partum haemorrhage or perineal tears 3-4. The certainty of evidence for the effect on stillbirth/neonatal mortality is reduced due to few events (nine deaths in the three RCTs) and the early stop of the SWEPIS trial when a significant difference in stillbirths/neonatal mortality was observed during a statistical analysis which was not prespecified. Trials stopped early tend to overestimate treatment effects.

Stillbirths constituted eight of nine prenatal/neonatal deaths in the three RCTs in the present HTA. In the VGR, eight and seven stillbirths occurred after week 41+0 in 2018 and 2019, respectively. Inducing labour at 41 completed weeks cannot be expected to reduce stillbirths beyond this. Further, it is unknown whether all of these cases could have been prevented by induction at 41 completed weeks. The effect of induction week 41 instead of 42 on neonatal mortality cannot be estimated based on present available data.

The certainty of evidence for a reduction of meconium aspiration syndrome, comparing a strategy of induction of labour at 41 with 42 completed weeks, is low and the certainty of evidence for a reduction of admittance to neonatal intensive care unit is moderate. Critical outcomes like hypoxic ischemic encephalopathy, intracranial haemorrhage are still insufficiently studied.

The findings of this HTA are mainly in line with previously published meta-analyses with other focused questions and PICOs and other RCTs and cohort studies not fulfilling our present PICO criteria. In the latest Cochrane review (Middleton et al., 2018, 30 trials), comparing induction of labour at term or beyond term in uncomplicated pregnancies with expectant management until week 42+0 or later, i.e. with different limits for gestational age than we used, the authors concluded that a policy of induction is associated with a reduction in perinatal mortality and stillbirth (moderate quality of evidence). In the Cochrane review, the rate of caesarean delivery was lower in the induction group whereas the present meta-analysis demonstrated no difference.

The present systematic review included three RCTs. Our PICO allowed inclusion of large cohort studies, but no observational studies applied the exact gestational age limits defined in our PICO. However, our search identified four large Nordic cohort studies and one systematic review that are of interest but did not meet our inclusion criteria (Appendix 5). The two Swedish cohort studies reported that expectant management was associated with an increase in perinatal mortality (Grunewald et al., 2011, Lindgren et al., 2017). The third study, from Finland, concluded that induction did not affect perinatal mortality but increased the caesarean delivery rate (Pyykönen et al., 2018). The Danish cohort study reported a decrease in perinatal mortality and caesarean delivery rates in favour of a more active management after a change in national guidelines (Zizzo et al., 2017). A more recent Danish cohort study, published after the literature search was performed, comparing all births from week 41+3 (>150,000) in Denmark during 16 years, before and after introducing the new guidelines reported no significant differences in stillbirth, perinatal mortality and low Apgar score (Rydahl et al., 2019a). A systematic review and meta-analysis of RCTs and cohort studies concluded that induction before week 42+0 was associated with few favourable outcomes and several adverse outcomes e.g. caesarean delivery (RR 1.11, CI 95% 1.09 to 1.14) (Rydahl et al., 2019b).

Another important aspect is women's experiences of induction versus expectant management but none of the included RCTs in the present HTA reported this outcome. Heimstad et al. (2007) conducted the only RCT that assessed women's experiences of induction versus expectant management at week 41+2 or surveillance and induction at week 42+6 (n=508). According to the results, three of four women would prefer a future induction if they would have the opportunity to choose (p=0.001). Of women who underwent induction, 84% had a positive birth experience.

In summary, a strategy of induction of labour in uncomplicated pregnancies at 41 weeks in comparison with a strategy of expectant management to 42 weeks with various routines of foetal surveillance:

- May reduce the rate of stillbirth/neonatal mortality although the magnitude of the reduction is imprecise (low certainty of evidence).
- May result in a moderate increase or decrease or little or no difference in the rate of a composite outcome of stillbirth/neonatal mortality and neonatal morbidity (low certainty of evidence)
- Results in little or no difference in caesarean and operative vaginal delivery rates and post-partum haemorrhage (high certainty of evidence)
- Probably results in little or no difference in frequency of perineal tears grade 3-4 (moderate certainty of evidence).

14. Future perspectives

Scientific knowledge gaps

We explored a strategy of induction at 41 completed weeks versus a strategy of expectant management until 42 completed weeks in order to evaluate the effect on perinatal outcome. However, this field of research is complex and there are still scientific knowledge gaps.

Stillbirth/neonatal mortality
The magnitude of the reduced stillbirth/neonatal mortality in late term pregnancies is still imprecise although any new RCTs are unlikely to be performed.

Induction according to risk profile
Induction of labour at late term for all might not be the only way to improve perinatal outcome. Another approach might be to induce labour according to a risk profile of the women e.g. primiparous women, older women and women with high BMI (Flenady et al., 2011, Stephansson et al., 2001, Socialstyrelsen, 2018). However, there is no consensus for management of women with these risk factors and prolonged pregnancy. In the SWEPIS trial, all stillbirth/neonatal deaths occurred in primiparous and there were too few events to analyse parity as a risk factor. Further, in the INDEX trial, two out of three stillbirths occurred in multiparous women and in the Gelisen trial (Gelisen et al., 2005), parity was not reported. Consequently, we cannot identify and select women at risk with current knowledge (Lawn et al., 2016; Lawn et al., 2006; Delaney et al., 2008).

Increased surveillance
With a dysfunctional placenta (foetuses with intrauterine growth restriction (IUGR) and/or having oligohydramniosis), foetuses are at a higher risk for stillbirth/neonatal mortality and about 20 percent of stillbirths occurring at late term and post term are believed to be associated with placental dysfunction (Divon et al., 1998). There are conflicting results regarding detection rate of IUGR with ultrasound at term (Nabhan et al., 2008, Sovio et al., 2015). Yet, as many as 75% of stillbirth/neonatal deaths are not associated with any known risk factors (Flenady et al., 2011).
Reducing using routine surveillance with ultrasound in order to detect foetuses at risk could be argued for. None of the stillbirths/neonatal deaths in the SWEPIS trial occurred in sites with routine ultrasound scans at 41 completed weeks. Potential stillbirth/neonatal mortality benefits of an ultrasound in late term pregnancies are insufficiently studied. A Swedish retrospective study demonstrated a reduction in “small for gestational age” (SGA) but no reduction in rates of composite stillbirth/neonatal mortality and morbidity or stillbirth with routine ultrasound at 41 weeks compared with indicated ultrasound (Lindqvist et al., 2014).
A Cochrane review including 13 trials (27,024 women) evaluating routine ultrasound in late pregnancies (after 24 weeks) in low risk or unselected populations reported no antenatal or neonatal benefit (Bricker et al., 2015). However, there were no RCTs on routine ultrasound in late term pregnancies. We currently have no effective diagnostic method to detect foetuses at risk for stillbirth (ACOG Practice Bulletin no. 146, 2014; Delaney et al., 2008; Nabhan et al., 2008; Lindqvist et al., 2014, Henrichs et al., 2019).

Pregnant women’s experiences of induction and involvement in planning trials
As previously discussed, we did not find any trials meeting our PICO criteria that evaluated women’s experiences of induction. Further, none of the included trials had any patient involvement in the planning of the trial. Hence, we have little knowledge from RCTs on what pregnant women consider important regarding induction versus expectant management. However, we know from studies how women being induced perceive their situation and what they prefer. Women want unbiased high quality information about induction, about alternative options and potential outcomes, as well as time to reflect on their personal values and preferences (Lou et al., 2019), which does not differ from women undergoing induction for other reasons than post term pregnancy (Coates et al., 2019).

Ongoing research

The search in Clinicaltrials.gov and the WHO ICTRP databases identified eight trials. One ongoing trial was relevant for our PICO, the others were published or were outside the question of issue. The relevant trial is a Finnish RCT with the aim to investigate the optimal timing and method of induction of labour in nulliparous late term women with an unfavourable cervix (ISRCTN 83219789, "FIOTIL"). In this trial low risk nulliparous women with an unfavourable cervix will be randomised to induction at 41weeks (intervention group) or to expectant management and induction by 42 weeks (control group). A second randomisation (method of labour induction) is performed for both the intervention and control group with allocation to induction by Foley catheter, oral misoprostol, or combined use of Foley catheter and oral misoprostol. The primary outcome is the rate of caesarean delivery. The target number of women is 600. The trial started in September 2016 and is expected to run until September 2022.

15. Participants in the project

The question was nominated by

Nils Crona, MD, Senior consultant, Head of the Obstetrical department, East hospital, Sahlgrenska University hospital, Gothenburg, Sweden.

Participating healthcare professionals

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Declaration of interests

Among the health care professionals, UBW, HH, HE and AW were authors of one of the included RCTs (SWEPIS) and UBW, HH and HE were also members of the SWEPIS steering group. Christina Bergh, head of HTA-centrum, was also a member of the SWEPIS steering group and she has not taken part in the quality assurance process of the report.

Project time

The HTA was accomplished during the period of October 2nd, 2019 to January 29th, 2020.
Literature searches were made November 26th, 2019.

Appendix 1: PICO, study selection, search strategies, and references

Focused question:
Is a strategy of induction at 41 weeks + (0 to 2 days) compared with a strategy of expectant management with various regimes of foetal surveillance and induction at 42 weeks + (0 to 1 day) superior in terms of decreased stillbirth/neonatal mortality and neonatal morbidity without increasing maternal mortality and morbidity, in healthy women with an uncomplicated singleton pregnancy?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P - Women with ultrasonographically verified late term pregnancy (41 weeks) and an uncomplicated (as defined by authors), singleton pregnancy in cephalic presentation

I - Strategy to induce labour at 41 weeks+ (0-2 days)

C - Strategy of expectant management (with various regimes of foetal surveillance) and induction of labour at 42 weeks+ (0-1 day)

O –

<u>Critical for decision making</u> (GRADE assessment):

4.1 Neonatal outcomes
4.1.1 Stillbirth/neonatal mortality (intrauterine foetal death; total (<28 days) and early (<7 days) neonatal mortality)
4.1.2 Hypoxic ischemic encephalopathy (HIE) 1-3
4.1.3 Intracranial haemorrhage
4.1.4 Composite stillbirth/neonatal mortality and neonatal morbidity

4.2 Maternal outcome
4.2.1 Mortality (<42 days after delivery)

<u>Important for decision making</u>

Neonatal outcomes, continued
4.1.5 Convulsions
4.1.6 Meconium aspiration syndrome (MAS) (GRADE assessment)
4.1.7 Mechanical ventilation
4.1.8 Obstetric brachial plexus injury
4.1.9 Neonatal infections: sepsis, pneumonia
4.1.10 Admission to NICU (GRADE assessment)
4.1.11 Apgar score less than 4 at 5 minutes
4.1.12 Macrosomia (birth weight ≥4000 g, or ≥4500 g)/Large for gestational age

Maternal outcomes, continued
4.2.2 Caesarean delivery (GRADE assessment)
4.2.3 Operative vaginal delivery (vacuum extraction/forceps) (GRADE assessment)
4.2.4 Perineal tear grade 3 and 4 (GRADE assessment)
4.2.5 Uterine rupture
4.2.6 Admittance to an intensive care unit (ICU)
4.2.7 Postpartum haemorrhage >1000 ml (GRADE assessment)
4.2.8 Infections: endometritis, chorioamnionitis, sepsis
4.2.9 Women's experience

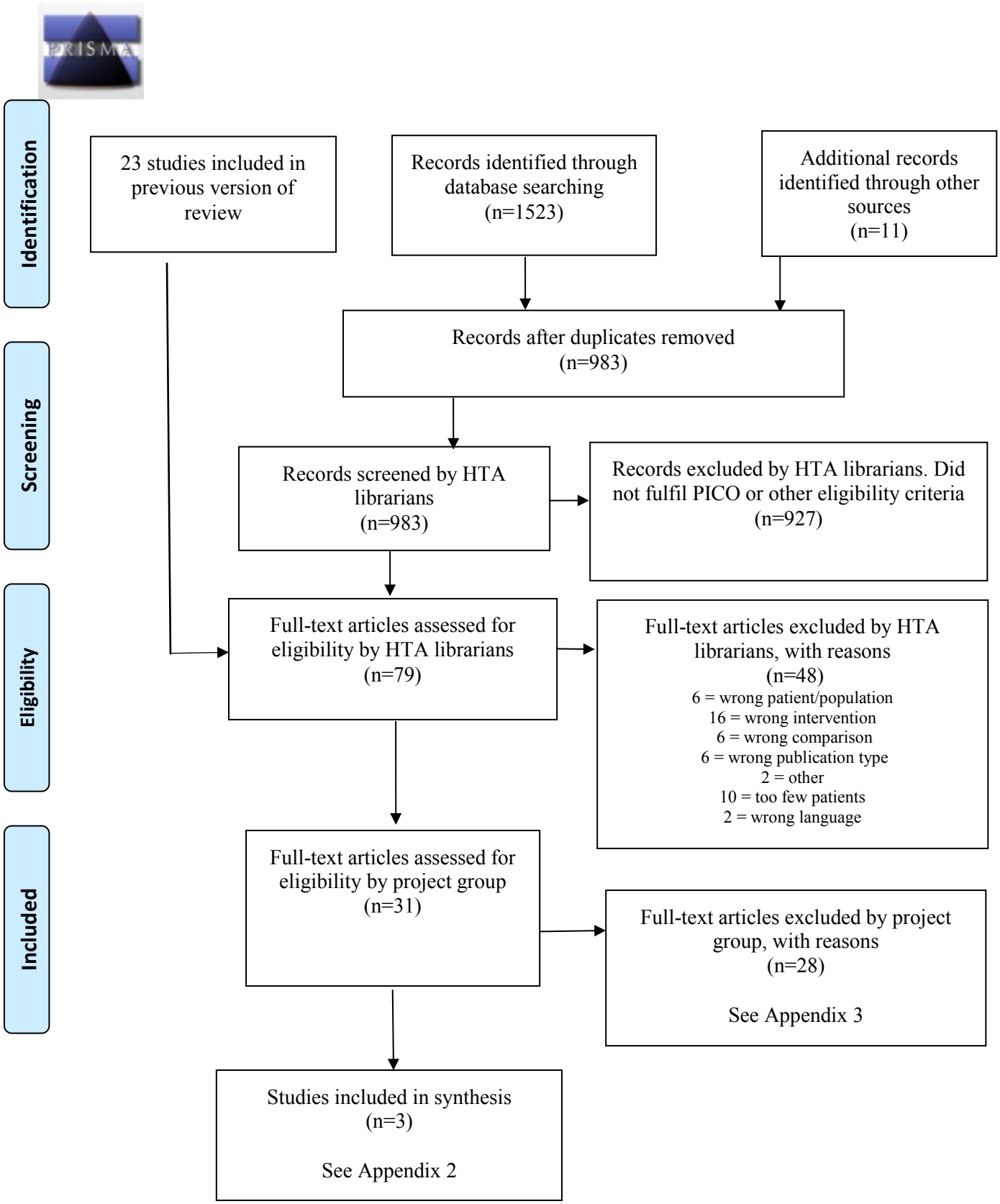
Eligibility criteria

Study design:
Randomised controlled trials
Non-randomised controlled studies if ≥10,000 patients
Qualitative studies

Language:
English, Swedish, Norwegian, Danish

Publication date: 2011-
As this HTA is an update of a previous HTA-report (Wennerholm et al., 2012), literature searches were made with publication date from when the previous searches were made. Relevant articles from the previous report have also been included now.

Selection process – flow diagram



Modified from Moher et al., 2009

Search strategies

Database: PubMed
Date: 18 Oct 2019
No. of results: 697
Search updated Nov 26: 16 results

Search	Query	Items found
#19	**Search #11 NOT #12 Filters: Publication date from 2011/10/01; Swedish; Norwegian; English; Danish**	**697**
#18	Search #11 NOT #12 Filters: Swedish; Norwegian; English; Danish	1883
#13	Search #11 NOT #12	2302
#12	Search Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp]	1771553
#11	Search #7 NOT #10	2349
#10	Search #8 OR #9	4951717
#9	Search animal[ti] OR animals[ti] OR rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR rodent[ti] OR rodents[ti] OR dog[ti] OR dogs[ti] OR cat[ti] OR cats[ti] OR hamster[ti] OR hamsters[ti] OR rabbit[ti] OR rabbits[ti] OR swine[ti] OR murine[ti]	1837515
#8	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	4629995
#7	Search #3 AND #6	2742
#6	Search #4 OR #5	35211
#5	Search "pregnancy, prolonged"[MeSH Terms]	2634
#4	Search (full-term OR fullterm OR post-date OR postdate OR post-term OR postterm OR late term[tiab] OR beyond term[tiab] OR 41 weeks[tiab] OR 42 weeks[tiab] OR prolonged) AND (pregnancy OR pregnancies OR delivery OR deliveries)	35211
#3	Search #1 OR #2	494253
#2	Search "Labor, Induced"[Mesh]	9180
#1	Search (induced[tiab] AND (labor[tiab] OR labour[tiab])) OR induction[tiab] OR (expectant[tiab] AND management[tiab])	491089

Database: Embase 1974 to 2019 October 17
Date: 18 Oct 2019
No. of results: 425
Search updated Nov 26: 10 results

#	Searches	Results
1	((induced and (labor or labour)) or induction or (expectant and management)).ab,kw,ti.	635995
2	exp labor induction/	13438
3	1 or 2	641204
4	((full-term or fullterm or post-date or postdate or post-term or postterm or late term or beyond term or 41 weeks or 42 weeks or prolonged) adj4 (pregnancy or pregnancies or delivery or deliveries)).ab,kw,ti.	9099
5	prolonged pregnancy/	2150
6	4 or 5	10061
7	3 and 6	1721
8	(animal not (animal and human)).sh.	1051340
9	(animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or hamster or hamsters or rabbit or rabbits or swine or murine).ti.	1956744
10	8 or 9	2772236
11	7 not 10	1689
12	**limit 11 to ((danish or english or norwegian or swedish) and yr="2011 -Current" and (article or article in press or conference paper or "review"))**	**425**

Database: CINAHL;PsycINFO (EBSCOhost Research Databases)
Date: 18 Oct 2019
No. of results: 195
Search updated Nov 26: 2 results

#	Undran	Resultat
S5	**S1 AND S2** **Language: - english** **Publiceringsdatum:** **20110101-20191231**	**195**
S4	S1 AND S2	204
S3	S1 AND S2	304
S2	TI ((full-term OR fullterm OR post-date OR postdate OR post-term OR postterm OR "late term" OR "beyond term" OR "41 weeks" OR "42 weeks" OR prolonged) N4 (pregnancy OR pregnancies OR delivery OR deliveries)) OR AB ((full-term OR fullterm OR post-date OR postdate OR post-term OR postterm OR "late term" OR "beyond term" OR "41 weeks" OR "42 weeks" OR prolonged) N4 (pregnancy OR pregnancies OR delivery OR deliveries))	1,975
S1	TI ((induced AND (labor OR labour)) OR induction OR (expectant AND management)) OR AB ((induced AND (labor OR labour)) OR induction OR (expectant AND management))	58,116

Database: The Cochrane Library
Date: 18 Oct 2019
No. of results: 176
Cochrane reviews 8
Trials 168
Search updated Nov 26: 2 results

ID	Search	Hits
#1	(((induced and (labor or labour)) or induction or (expectant and management))):ti,ab,kw (Word variations have been searched)	51993
#2	((full-term or fullterm or post-date or postdate or post-term or postterm or "late term" or "beyond term" or "41 weeks" or "42 weeks" or prolonged) NEAR/4 (pregnancy or pregnancies or delivery or deliveries)):ti,ab,kw (Word variations have been searched)	1259
#3	#1 AND #2	463
#4	(clinicaltrials or trialsearch):so	273412
#5	#3 NOT #4 with Cochrane Library publication date Between Jul 2011 and Oct 2019	176

The web-sites of SBU and Folkehelseinstituttet were visited
18 Oct 2019
Nothing relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 11 new records

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Reference lists

Included studies:

Gelisen O, Caliskan E, Dilbaz S, Ozdas E, Dilbaz B, Ozdas E, et al. Induction of labor with three different techniques at 41 weeks of gestation or spontaneous follow-up until 42 weeks in women with definitely unfavorable cervical scores. Eur J Obstet Gynecol Reprod Biol. 2005;120(2):164-9.

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Project: Induction of labour at 41 or 42 weeks of gestation

Appendix 2. Characteristics of included studies

Author Year Country	**Study Design**	**Length of Follow-Up**	**Study Groups; Intervention vs control**	**Patients (n)**	**Mean Age (years)** mean (SD)	**Outcome variables**
Gelisen 2005 Turkey	RCT	Until discharge after delivery/neonatal intensive care unit	Induction at 41+1 gw (3 methods: misoprostol vaginally (n=100), oxytocin induction (n=100), Foley balloon, (n=100) vs expectant management and induction at 42 gw (n=300)	600	Misoprostol: 25.9 (5.9) Oxytocin: 26 (4.9) Foley balloon: 24.4 (4.1) EM: 25.6 (5)	perinatal mortality meconium aspiration syndrome admission to neonatal ICU macrosomia caesarean delivery
Keulen 2019 The Netherlands "INDEX"	RCT	Until discharge after delivery/neonatal intensive care unit	Induction at 41+0 to 41+1 gw (n=900) vs expectant management and induction at 42+0 gw (n=901)	1801	41 gw: 30.6 (4.8) 42 gw: 30.7 (4.6)	Composite of perinatal mortality (foetal death, intrapartum death, early neonatal death up to 28 days) and neonatal morbidity (intracranial hemorrhage, meconium aspiration syndrome, obstetric brachial plexus injury, admission to neonata ICU). sepsis (neonatal infection/sepsis), pneumonia, Apgar score <4 at 5 min. caesarean delivery, instrumental delivery, perineal tear grade 3-4, admission to ICU, postpartum haemorrhage (≥1000 ml), maternal intrapartum infection
Wennerholm 2019 Sweden "SWEPIS"	RCT	Until discharge after delivery/neonatal intensive care unit	Induction at 41+0 gw to 41+2 gw (n=1381) vs expectant management and induction at 42+0 to 42+1 gw (n=1379)	2760	41 gw: 31.2 (4.7) 42 gw: 31.1 (4.5)	Composite of perinatal mortality (stillbirth and neonatal death 0-27 days) and neonatal morbidity (hypoxic ischaemic encephalopathy grades 1-3, intracranial haemorrhage, convulsions, meconium aspiration syndrome, mechanical ventilation within 72 h, obstetric brachial plexus injury), sepsis, pneumonia, admission to neonatal ICU, Apgar score <4 at 5 minutes, maternal mortality within 42 days, caesarean delivery, operative vaginal delivery, perineal tear grade 3 and 4, uterine rupture, maternal admission to ICU, postpartum haemorrhage (>1000ml) endometritis/chorioamnionitis/ sepsis.

Gw; gestational weeks, ICU; intensive care unit, RCT; randomised controlled trial

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 3. Excluded articles

Author, year	Reason for exclusion
Akuamoah-Boateng, Midwifery, 2018	Systematic review of women's experiences and perceptions of labour. Wrong gestational age.
Cheng, AJOG, 2012a, USA	Wrong gestational age in intervention and comparison group.
Cheng, BJOG, 2012b, USA	Wrong gestational age in intervention and comparison group.
Danilack, BJOG, 2016a, USA	Wrong gestational age in intervention and comparison group.
Danilack, Ann Epidemiol, 2016b, USA	Wrong gestational age in intervention and comparison group.
Grivell, 2012, AOGS, Australia	Wrong gestational age in intervention and comparison group
Grunewald, 2010, AOGS, Sweden	Wrong gestational age in intervention and comparison groups
Hedegaard, 2014, BMJ Open, Denmark	Wrong population/comparison. Includes multiple pregnancies. Wrong strategy.
Hutcheon, 2015, Canada	Wrong comparison.
Kaimal, 2011, USA	Data on cost effectiveness, included in cost effectiveness analysis, included as "other references."
Keulen, Midwifery, 2018	Systematic review, 22 RCTs. Overlap with HTA report from 2012 (Wennerholm et al., 2012) and the Cochrane reviews Gulmezoglu et al., 2012 and Middleton et al., 2018 with focus on 41-42 gestational week time frame. No further trials identified with gestational age according to PICO.
Knight, PLOS Medicine, 2017, UK	Wrong intervention and comparison groups.
Lindegren, AOGS 2017, Sweden	Wrong intervention and comparison groups.
Liu, AJOG, 2013, Canada	Wrong intervention and comparison groups. No data on pregnancy dating.
Lou, Birth, 2019	Systematic review, wrong research question, wrong gestational age
Marquette, J Obstet Gyn Canada, 2014	Wrong outcome.
Middleton, 2018, Cochrane	Systematic review (30 RCTs). Overlap with HTA report from 2012 (Wennerholm et al., 2012) and the Cochrane review Gulmezoglu et al., 2012. No further trials identified with gestational age according to PICO.
Mya, Reprod Health, 2017	Wrong intervention and comparison groups. No data on pregnancy dating.
Nippita, AOGS, 2016, Australia	Wrong intervention and comparison groups. No data on pregnancy dating.
Pyykönen, AOGS 2018, Finland	Wrong intervention and comparison groups.
Raviraj, ISRN Obstet Gynecol, 2013, Australia	Wrong intervention and comparison groups. No data on pregnancy dating.
Rosenstein, Obstet Gyn 2012, USA	Wrong intervention and comparison groups.
Rydahl, JBI Database System Rev Implement Rep, 2019	Systematic review. Wrong intervention and comparison groups.
Schwartz, Arch Gynecol Obstet, 2016, Germany	Wrong intervention and comparison groups. No data on pregnancy dating.
Stock, BMJ, 2012, Scotland	Wrong intervention and comparison groups. No data on pregnancy dating.
Wolff, Sex Reprod Healthc, 2016, Denmark	Wrong intervention and comparison groups.
Zenzmaier, Arch Gynecol Obstet, 2017, Austria	Wrong intervention and comparison groups.
Zizzo, AOGS 2017, Denmark	Wrong intervention and comparison groups.

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.1.1
Outcome variable: Stillbirth/neonatal mortality

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	**Expectancy to gestational week 42+(0-1)**				
Gelisen 2005 Turkey	RCT	600	NR	**Stillbirth** 0/300 p=1.0	1/300 (0.3%)	No neonatal death	?	?/-	-
Keulen 2019 The Netherlands	RCT	1801	0	**Stillbirth** 1/900 (0.1%) RR 0.50 (95% CI 0.05 to 5.51) p=1.00	2/901 (0.2%)	No neonatal death	?	+/?	-
Wennerholm 2019 Sweden	RCT	2760	2	**Perinatal mortality** 0/1380 p=0.03	6/1379 (0.4%)	One early neonatal death	+	?	-
				Stillbirth 0/1380 P=0.06	5/1379 (0.4%)				
				Neonatal death 0/1380 P=1.0	1/1374 (0.1%)				

CI; confidence interval, NR; not reported, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.1.2
Outcome variable: Hypoxic ischaemic encephalopathy grades 1-3

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Wennerholm 2019 Sweden	RCT	2760	2	2/1381 (0.14%) RR 0.66 (95% CI 0.11 to 3.96) p=1.0	3/1374 (0.22%)	5 stillbirths excluded from expectant group	+	+	-

CI; confidence interval, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.1.3
Outcome variable: Intracranial haemorrhage

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Keulen 2019 The Netherlands	RCT	1801	0	0/900	0/901		?	+/?	-
Wennerholm 2019 Sweden	RCT	2760	2	1/1381 (0.07%) RR 0.50 (95% CI 0.05-5.48) p=1.0	2/1374 (0.15%)	5 stillbirths excluded from expectant group	+	+	-

CI; confidence interval, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.1.4
Outcome variable: Composite stillbirth/neonatal mortality and neonatal morbidity

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Keulen 2019 The Netherlands	RCT	1801	0	15/900 (1.7%) RR 0.54 (95% CI 0.29-1.0) p=0.045	28/901 (3.1%)	Composite variables: -Stillbirth -Neonatal death -5 min Apgar score <7 -meconium aspiration syndrome -obstetric brachial plexus injury -intracranial haemorrhage -NICU admission	?	+/?	+
Wennerholm 2019 Sweden	RCT	2760	2	33/1381 (2.4%) RR 1.06 (95% CI 0.65-1.73) p=0.9	31/1379 (2.2%)	Composite variables: -Stillbirth -Neonatal death -5 min Apgar score <7 -metabolic acidosis -hypoxic ischaemic encephalopathy grades 1-3 -intracranial haemorrhage -neonatal convulsions -meconium aspiration syndrome -mechanical ventilation within first 72 hours -obstetric brachial plexus injury	+	+	-

CI confidence interval, NICU neonatal intensive care unit, RCT randomised controlled trial, RR relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.1.5
Outcome variable: Neonatal convulsions

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Wennerholm 2019 Sweden	RCT	2760	2	1/1381 (0.07%) RR 0.33 (95% CI 0.03-3.18) p=0.62	3/1374 (0.22%)	5 stillbirths excluded from expectant group	+	+	-

CI; confidence interval, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.1.6
Outcome variable: Meconium aspiration syndrome

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Gelisen 2005 Turkey	RCT	600	NR	4/300 (1.3%) p=0.03	12/300 (4%)	No definition of meconium aspiration syndrome	?	?	-
Keulen 2019 The Netherlands	RCT	1801	0	0 /900	2/ 901 (0.22%)	Defined as respiratory distress after birth in the presence of meconium stained amniotic fluid.	?	+/?	-
Wennerholm 2019 Sweden	RCT	2760	2	2/1381 (0.14%) RR 0.66 (95% CI 0.11-3.96) p=1.00	3/1374 (0.22%)	Defined according to ICD10 (P24.0)	+	+	-

CI confidence interval, NR not reported, RCT randomised controlled trial, RR relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.1.7
Outcome variable: Mechanical ventilation of the neonate within the first 72 h

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Wennerholm 2019 Sweden	RCT	2760	2	3/1381 (0.22%) RR 0.60 (0.14-2.49) p=0.72	5/1374 (0.36%)	5 stillbirths excluded from expectant group	+	+	-

CI; confidence interval, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.1.8
Outcome variable: Obstetric brachial plexus injury

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Keulen 2019 The Netherlands	RCT	1801	0	0/900	0/901		?	+/?	-
Wennerholm 2019 Sweden	RCT	2760	2	4/1381 (0.30%) RR 3.98 (95% CI 0.45-35.56) p=0.38	1/1374 (0.07%)	5 stillbirths excluded from expectant group	+	+	-

CI; confidence interval, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.1.9
Outcome variable: Neonatal infections; Sepsis and Pneumonia

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Keulen 2019 The Netherlands	RCT	1801	0	Neonatal infection/sepsis: 37/900 (4.1%) RR 1.00 (95% CI 0.64-1.56) p=1.00	Neonatal infection/sepsis: 37/901 (4.1%)		?	+/?	?
Wennerholm 2019 Sweden	RCT	2760	2	Sepsis: 9/1381(0.7%) RR 0.45 (95% CI 0.20-0.98) p=0.06 Pneumonia: 8/1381 (0.6%) RR 0.61 (95% CI 0.25-1.47) p=0.38	Sepsis: 20/1374 (1.5%) Pneumonia: 13/1374 (0.9%)	5 stillbirths excluded from expectant group	+	+	?

CI; confidence interval, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.1.10
Outcome variable: Admittance to neonatal intensive care unit (NICU)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Gelisen 2005 Turkey	RCT	600	0	13/300 (4.3%) RR 0.87 (95% CI 0.42-1.79) p=0.4	15/300 (5.0%)		?	?/-	-
Keulen 2019 The Netherlands	RCT	1801	0	NICU 3/899 (0.3%) RR 0.38 (95% CI 0.10-1.41) p=0.23 Medium care 59/899 (6.6%) RR 0.98 95% CI (0.69-1.39) p=0.90 NICU or medium care 62/899 (6.9%) RR 0.91 (95% CI 0.65-1.27) p=0.59	NICU 8/899 (0.9%) Medium care 60/899 (6.7%) NICU or medium care 68/899 (7.6%)		?	+/?	?
Wennerholm 2019 Sweden	RCT	2760	2	55/1381 (4.0%) RR 0.67 (95% CI 0.48-0.93) p=0.02	82/1374 (6.0%)	5 stillbirths excluded from expectant group	+	+	+/?

CI; confidence interval, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.1.11
Outcome variable: Apgar score < 4 at 5 minutes

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Keulen 2019 The Netherlands	RCT	1801	0	0/900	3/901 (0.33%)		?	+/?	-
Wennerholm 2019 Sweden	RCT	2760	2	3/1381 (0.22%) RR 2.98 (95% CI 0.31-28.66) p=0.63	1/1374 (0.07%)	5 stillbirths excluded from expectant group	+	+	-

CI; confidence interval, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.1.12
Outcome variable: Macrosomia/large for gestational age

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Gelisen 2005 Turkey	RCT	600	0	23/300 (7.7 %) p<0.001	74/300 (24.7%)	Macrosomia (>4000 g)	?	?/-	?
Keulen 2019 The Netherlands	RCT	1801	0	15/900 (1.7%) RR 0.56 (95% CI 0.30-1.04) p=0.07	27/901 (3.0%)	Large for gestational age >97 centile	?	+/?	?
Wennerholm 2019 Sweden	RCT	2760	2	68/1381 (4.9%) RR 0.60 (95% CI 0.45-0.80) p<0.01	114/1379 (8.3%)	Macrosomia (>4500 g)	+	+	+

CI; confidence interval, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.2.1
Outcome variable: Maternal mortality

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Keulen 2019 The Netherlands	RCT	1801	0	0/900	0/901	Follow-up not defined	?	+/?	-
Wennerholm 2019 Sweden	RCT	2760	2	0/1381	0/1379	<42 days after delivery	+	+	-

RCT; randomised controlled trial

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.2.2
Outcome variable: Caesarean delivery

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Gelisen 2005 Turkey	RCT	600	NR	58 /300 (19.3%) p=0.4	66/300 (22.0%)	Non-elective	?	?/-	?
Keulen 2019 The Netherlands	RCT	1801	0	97/900 (10.8%) RR 1.00 (95% CI 0.77-1.31) p=0.99	97/901 (10.8%)	Indication for caesarean delivery did not differ between groups	?	+/?	+
Wennerholm 2019 Sweden	RCT	2760	2	143/1381 (10.4%) RR 0.96 (95% CI 0.78-1.20) p=0.79	148/1379 (10.7%)	Indication for caesarean delivery did not differ between groups	+	+	+

CI; confidence interval, NR; not reported, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.2.3
Outcome variable: Operative vaginal delivery

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Keulen 2019 The Netherlands	RCT	1801	0	93/900 (10.3%) RR 0.86 (95% CI 0.66 to 1.12) p=0.27	108/901 (12.0%)	Indication for operative vaginal delivery did not differ between groups	?	+/?	+
Wennerholm 2019 Sweden	RCT	2760	2	88/1381 (6.4%) RR 0.97 (95% CI 0.73 to 1.28) p=0.87	91/1379 (6.6%)	Indication for operative vaginal delivery did not differ between groups	+	+	+

CI; confidence interval, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.2.4
Outcome variable: Perineal tear grades 3-4

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Keulen 2019 The Netherlands	RCT	1801	0	28/803 (3.5%) RR 0.90 (95% CI 0.55 to 1.49) p=0.69	31/806 (3.9%)	CD excluded in denominator	?	+/?	?
Wennerholm 2019 Sweden	RCT	2760	2	40/1381 (2.9%) RR 0.80 (95% CI 0.53 to 1.20) p=0.33	50/1379 (3.6%)	All births included in denominator	+	+	?

CD; caesarean delivery, CI; confidence interval, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.2.5
Outcome variable: Uterine rupture

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Wennerholm 2019 Sweden	RCT	2760	2	0/1381	0/1379		+	+	-

RCT; randomised controlled trial

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.2.6
Outcome variable: Maternal admission intensive care unit (ICU)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Keulen 2019 The Netherlands	RCT	1801	0	3/900 (0.33%) RR 1.50 (95% CI 0.25 to 8.97) p=0.66	2/901 (0.22%)		?	+/?	-
Wennerholm 2019 Sweden	RCT	2760	2	2/1381 (0.14%) p=0.50	0/1379		+	+	-

CI; confidence interval, RCT; randomised controlled trial, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.2.7
Outcome variable: Postpartum haemorrhage >1000 ml

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Keulen 2019 The Netherlands	RCT	1801	0	82/900 (9.1%) RR 1.14 (95% CI 0.84 to 1.54) p=0.40	72/901 (8.0%)	PPH ≥ 1000 ml	?	+/?	+
Wennerholm 2019 Sweden	RCT	2760	2	140/1381 (10.1%) RR 0.96 (95% CI 0.77 to 1.19) p=0.75	146/1379 (10.6%)	PPH > 1000 ml	+	+	+

CI; confidence interval, RCT; randomised controlled trial, PPH; postpartum haemorrhage, RR; relative risk

Project: Induction of labour at 41 or 42 weeks of gestation
Appendix 4.2.8
Outcome variable: Maternal peri- and postpartum infection

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Induction gestational week 41+(0-2)	Expectancy to gestational week 42+(0-1)				
Keulen 2019 The Netherlands	RCT	1801	0	Fever during labour ≥ 38°C 50/900 (5.6%) RR 1.09 (95% CI 0.74 to 1.61) p=0.67	Fever during labour ≥ 38°C 46/901 (5.1%)		?	+/?	?
				Use of antibiotics during labour 48/900 (5.3%) RR 1.37 (95% CI 0.90 to 2.10) p=0.14	Use of antibiotics during labour 35/901 (3.9%)				
Wennerholm 2019 Sweden	RCT	2760	2	Chorioamnionitis 2/1381 (0.1%) RR 0.33 (95% CI 0.07 to 1.65) p=0.29	Chorioamnionitis 6/1379 (0.4%)		+	+	?/-
				Wound infection 4/1381 (0.3%) RR 1.33 (95% CI 0.30 to 5.94) p=1.00	Wound infection 3/1379 (0.2%)				
				Urinary tract infection 5/1381 (0.4%) RR 0.71 (95% CI 0.23 to 2.24) p=0.77	Urinary tract infection 7/1379 (0.5%)	Pyelonephritis included			
				Endometritis 18/1381(1.3%) RR 3.00 (95% CI 1.19 to 7.52) p=0.02	Endometritis 6 /1379 (0.4%)				
				Sepsis 0/1381	Sepsis 0/1379				

CI; confidence interval, RCT, randomised controlled trial, RR; relative risk

Appendix 5

Nordic observational studies analysing the effect of induction of labour in late term and post term pregnancies, excluded from assessment
(references in Appendix 3 or in the section "Other references")

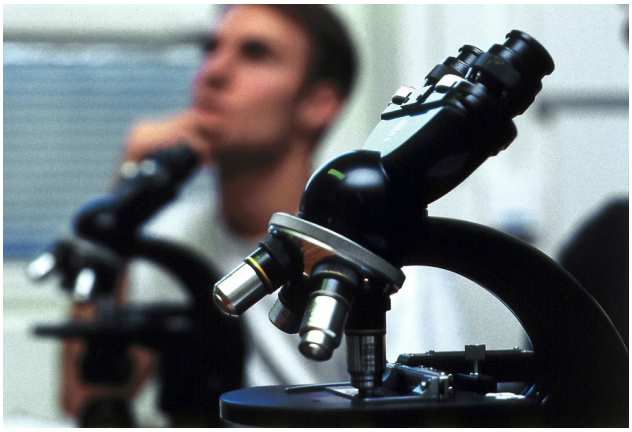
Author Country Year of publication	Study design Source	Study period	Number of included women	Gestational age, weeks	Perinatal mortality	Apgar score <7 at 5 min	Meconium aspiration syndrome	Cesarean delivery/operative vaginal delivery	Comment
Grunewald Sweden 2011	Cohort MBR	2000-2007	119,198	Study population: ≥41+3. Three study groups (≥41+3) according to rate of deliveries ≥42+3 w Year of birth 2000-2004: n=27 311, n=13 160, n=33 206 Year of birth 2005-2007: n=16 865, n=7822, n=20 834 Stockholm formed a separate group	No difference in PNM, yet a reduction in Stockholm for year of birth 2005-2007 (5.9% ≥42+3) vs 2000-2004 (21.0% ≥42+3) PNM: AOR 0.52: 95% CI 0.31-0.83)	No difference in AS between groups 2000-2004. 2005-2007: for the group with the highest rate of post term pregnancies increased rate of low AS (AOR 1.26; 95% CI 1.06 -1.51). Reduction in low AS in Stockholm for year of birth 2005-2007 vs 2000-2004 (AOR 0.69: 95% CI 0.55-0.87)	No difference in MAS between groups 2000-2004 2005-2007: for the group with the highest rate of post term pregnancies increased rate of MAS (AOR 1.55; 95% CI 1.03 -2.33) Reduction in Stockholm for year of birth 2005-2007 vs 2000-2004 AOR 0.49: 95% CI 0.30-0.81	Rates of CD and operative vaginal deliveries (OVD) did not change in Stockholm during the two time periods	No national guidelines Routines differed: IOL at 42 +0 or 43+0 w Stockholm changed routines in 2005 from IOL at 43+0 w to IOL at 42+0 w
Lindegren Sweden 2017	Cohort MBR	2001-2013	199,770	Study population: ≥41+3. Three groups according to rate of deliveries ≥42+3 w and parity Primiparous: n=35 133, n=33 177, n=35 465 Multiparous: n=31 230, 31 621, n=33146	Expectant management vs most active management: AOR not significant different for primiparous or multiparous women	Expectant management vs most active management: AOR (95% CI) Primiparous: 1.27 (1.12-1.46) Multiparous: 0.97 (0.82-1.16)	Expectant management vs most active management: AOR (95% CI) Primiparous: 1.43 (1.16-1.76) Multiparous: 1.23 (0.76-1.97)	Expectant management vs most active management: AOR (95% CI) Primip: 0.82 (0.78-0.86) Multip: 0.85 (0.79-0.91)	No national guidelines during study period. Routines differed: IOL at 42 +0 or 43+0 w

Pyykönen Finland 2018	Cohort MBR	2006-2012	212,716	IOL: Group 1 40+0-40+2 w n=6882 Group 2 40+3-40+5 w n=5543 Group 3 40+6-41+1 w n=5115 Group 4 41+2-41+4 w n=5581 Group 5 41+5-42+0 n=10 167	RR (95% CI) Group 3: 1.00 (0.06-15.98) Group 4: 2.00 (0.18-22.05) Group 5: 2.50 (0.78-7.97)	RR (95% CI) Group 3: 0.39 (0.20-0.79) Group 4: 0.46 (0.24-0.90) Group 5: 0.93 (0.61-1.43)	RR (95% CI) Group 3: 1.09 (0.82-1.44) Group 4: 1.21 (0.94-1.57) Group 5: 1.02 (0.85-1.23)	RR (95% CI) Group 3: CD 1.17 (1.06-1.28) OVD 1.06 (0.99-1.13) Group 4: 1.19 (1.09-1.29) OVD 1.13 (1.07-1.20) Group 5: 1.01 (0.94-1.07) OVD 1.01 (0.97-1.06)	Policy of IOL at 42+0 to 42+2. Propensity score (PS) matched control groups of equal size. Each group compared to all births beyond the studied GA period and the spontaneous births during the studied GA period
Zizzo Denmark 2017	Cohort MBR	2012-2014 2008-2010	2012-14: 42,075 2008-10: 45,430	2012-2014 IOL 41+2-41+6 w (n=42 075) vs 2008-2010 IOL ≥42+0 w (n=45 430)	2012-2014 vs 2008-2010: AOR (95% CI) PNM: 0.62 (0.39-0.96) Stillbirths: 0.50 (0.29-0.89)	AS did not change (AOR 0.96; 95% CI 0.81-1.14)	NA	AOR (95% CI) CD: 0.98 (0.94-1.02) OVD: 0.86 (0.82-0.90)	National guidelines in Denmark changed in 2011 from IOL at ≥42+0 to IOL at 41+2-41+6 w

AOR; adjusted odds ratio, AS; Apgar score, CI; confidence interval, GA; gestational age, IOL; induction of labour, MAS; meconium aspiration syndrome, MBR; Medical Birth Registry, PNM; perinatal mortality, OVD; operative vaginal delivery, PS; propensity score, RR; relative risk, w; weeks of gestation

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

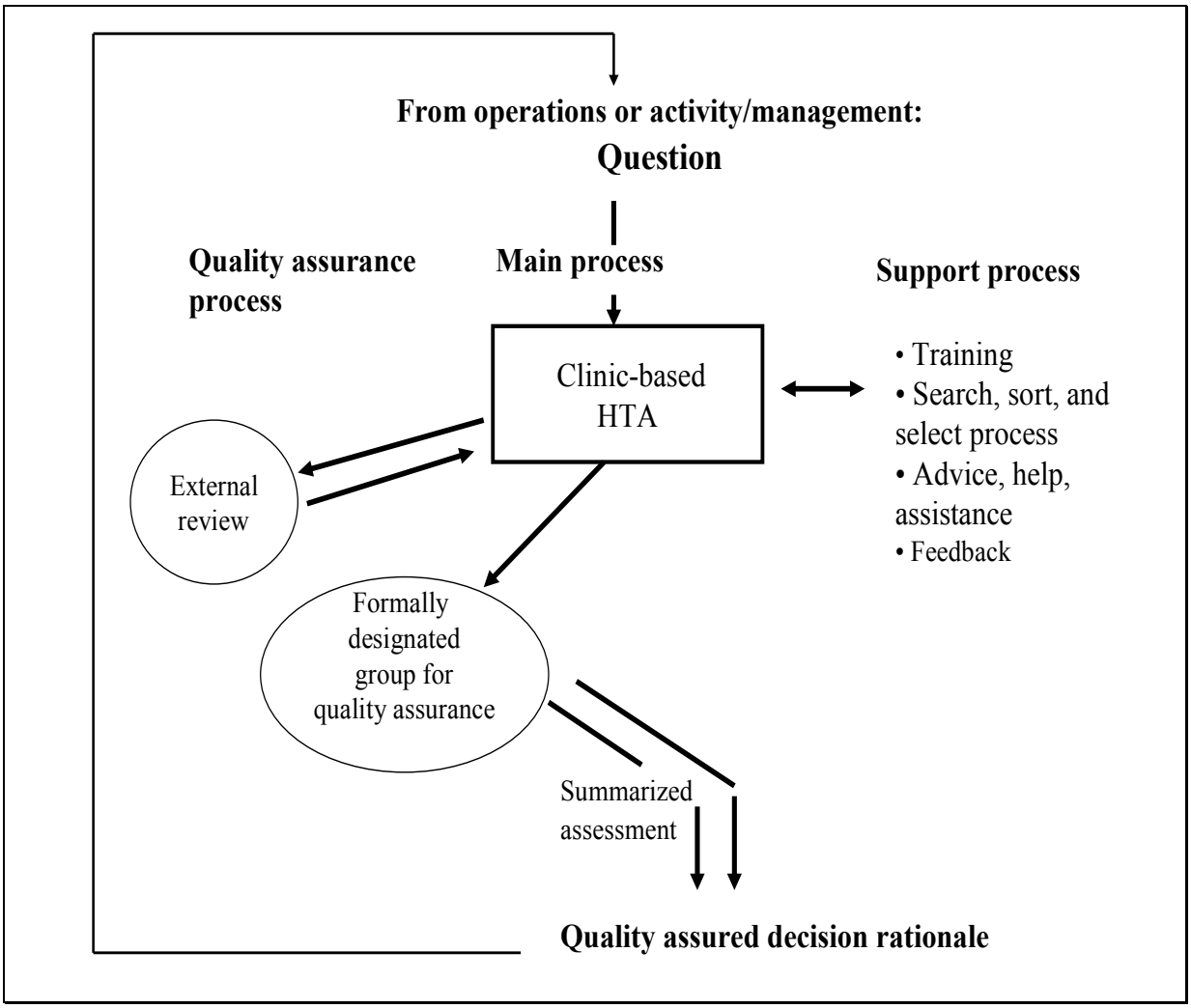
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the certainty of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High certainty of evidence	= (GRADE⊕⊕⊕⊕)
Moderate certainty of evidence	= (GRADE ⊕⊕⊕O)
Low certainty of evidence	= (GRADE ⊕⊕OO)
Very low certainty of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh
Professor, MD
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

Innehållsdeklaration

Denna HTA-rapport är baserad på följande moment:

- [x] Metodbeskrivning
- [x] PICO
- [x] Uttömmande litteratursökning
- [x] Flödesschema
- [x] Urval relevans
- [x] Kvalitetsgranskning
- [x] Tabelldata
- [x] Sammanvägning av resultat
- [x] Metaanalys
- [x] Evidensgradering enligt GRADE
- [x] Sammanfattning
- [x] Ekonomi
- [x] Organisation
- [x] Etik
- [x] Pågående studier
- [x] Exkluderade artiklar
- [x] Expertgrupp deltar
- [x] Extern granskning
- [x] Kunskapsluckor identifierade
- [x] Jävsdeklaration inhämtad från projektdeltagarna

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