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Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
[Säkerhet och effektivitet vid heminduktion jämfört med igångsättning av förlossning på sjukhus]

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1. Abstract

Background
In Sweden almost all deliveries take place in a hospital-based obstetric unit. Induction of labour is a common obstetric intervention with 19% of all deliveries being induced during 2018 in Sweden. A significant increase in the number of inductions is expected, due to recently changed guidelines enabling earlier induction of late term pregnancies. To meet the expected increased demand at delivery wards, outpatient induction may be an option, provided that the safety and effectiveness of the procedure is ensured.

Question at issue
Is outpatient induction of labour, compared with inpatient induction, a safe and effective alternative regarding the risk of stillbirth/neonatal mortality and morbidity, maternal mortality and morbidity, and maternal satisfaction with care and birth experience, in women with low-risk pregnancies?

Methods
Two authors performed searches January 2020 in Medline, Embase, the Cochrane Library, Cinahl, PsycInfo and Web of Science, 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
Six randomised controlled trials (RCTs (n=1,273)), four cohort studies (n=3,355), four case series (n=2,121) and two qualitative studies were included. The RCTs had some problems with directness and some major study limitations, mainly due to early randomisation resulting in spontaneous onset of labour before the intervention was given as well as essential differences between the characteristics of study participants in the in- versus outpatient group. Imprecision was an issue for all critical outcomes due to rare events. Analyses and conclusions were based mainly on the RCTs. No intergroup differences were demonstrated for any of the neonatal/paediatric outcomes. Based on very low certainty of evidence (death, hypoxic ischemic encephalopathy, admission to neonatal intensive care, meconium aspiration syndrome, neonatal seizures, disability in childhood, birth trauma, Apgar score <4 at 5 min) it was concluded that it is uncertain how outpatient induction affects these outcomes. Based on low certainty of evidence, there may be no difference in need for respiratory support and neonatal infections, however the 95% CI of the estimate was wide for both outcomes. There were no maternal deaths in the six RCTs. Mode of delivery, including caesarean, instrumental, and unassisted vaginal delivery showed little or no difference between out- and inpatient induction (low certainty of evidence). There may be a reduction or no difference in time from induction to delivery (pooled mean difference approximately 4 hs), and no difference in hospital stay although with a wide confidence interval, comparing outpatient with inpatient induction (low certainty of evidence). Unplanned home delivery occurred at rare occasions. Severe maternal complications were rare, and the effect of outpatient induction was uncertain. Maternal satisfaction was similar or somewhat higher after outpatient compared with inpatient induction, based on low certainty of evidence.
In the qualitative studies, women described that the home environment resulted in physical and emotional comforts, which helped them cope better with their labour and improved their birth experiences.
The estimate of a small average reduction in delivery costs of 2300 SEK after outpatient compared with inpatient induction is based on several uncertain assumptions.

Concluding remarks
This systematic review, including six RCTs, comparing out- with inpatient induction of labour for women with a singleton uncomplicated pregnancy planned for induction, shows that it is uncertain whether severe neonatal and maternal complications are affected (GRADE ⊕◯◯◯). There may be little or no difference in mode of delivery, while time from induction to delivery may be shortened, but total length of stay may be unaffected after out-vs. inpatient induction (GRADE ⊕⊕◯◯). There is a need for high quality trials to assess safety, effectiveness and costs.

2. Populärvetenskaplig sammanfattning – Swedish summary in plain language

I denna HTA-rapport har vi utvärderat frågeställningen:

- Är igångsättning av förlossning, hemma jämfört med på sjukhus, vid låg-risk graviditet säkert och effektivt, avseende risker för barn och mamma (död och allvarliga skador, samt blödning och infektion hos mamman), förlossningssätt, tid från igångsättning till förlossning samt vårdtid?

Slutsats: Genomgång av det vetenskapliga underlaget visar att det är osäkert huruvida risken för svåra komplikationer skiljer sig åt om igångsättning av förlossning, vid en låg-riskgraviditet, sker hemma istället för på sjukhus. Förlossningssättet (kejsarsnitt, vaginal förlossning med eller utan sugklocka) verkar inte påverkas eller gör det möjligen i ringa utsträckning. Tiden från igångsättning till förlossning kan möjligen minska med fyra timmar men vårdtiden verkar vara oförändrad. Påverkan på kostnad går inte att beräkna pga. osäkra data avseende vårdtider.

Bakgrund: I Sverige sker nästan alla förlossningar på sjukhus. Närmare 20% av alla förlossningar sätts igång av olika skäl. I Sverige förväntas en ökning av antalet igångsättningar, efter att riktlinjerna har ändrats så att igångsättning vid 41 veckor istället för 42 fullgångna graviditetsveckor för kvinnor med en okomplicerad graviditet blir valbart för kvinnan. För att möta en förväntat ökad efterfrågan på igångsättning har förlossningskliniker i VGR och i Sverige övervägt möjligheten att erbjuda igångsättning i hemmet istället för på sjukhus. Med igångsättning i det här sammanhanget avses utmognad av livmoderhalsen. Utmognad kan åstadkommas med olika metoder, antigen mekaniskt med en ballongkateter i livmoderhalsen eller med läkemedel (prostaglandiner). Igångsättning i hemmet skulle för kvinnan innebära att hon efter undersökning på sjukhuset kan få behandling med ballongkateter eller läkemedel och därefter avvakta förlossningsstart i hemmet på liknande sätt som vid spontan förlossningsstart. Syftet med den aktuella rapporten är att sammanfatta kunskapsläget för igångsättning av förlossning/utmognad av livmoderhalsen i hemmet jämfört med på sjukhus.

Metod: Med hjälp av etablerade metoder identifierades vetenskapliga studier som kunde bidra till att svara på den aktuella frågeställningen. För att utreda hur tillförlitliga studiernas resultat var, granskades de enskilda studiernas kvalitet, följt av en bedömning av den sammanlagda vetenskapliga kvaliteten på underlaget.

Resultat: Föreliggande rapport baseras huvudsakligen på sex randomiserade studier med 1,273 kvinnor som motsvarade frågeställningen. Dessutom bidrog fyra kohortstudier, fyra fallserier och två kvalitativa studier till rapporten. Studierna hade generellt stora brister i kvaliteten. De allvarliga biverkningar man ville studera var ovanliga och eftersom endast enstaka händelser (av biverkningar) rapporterades i studierna, utgjorde otillräcklig studiestorlek en stark begräsning.

Det vetenskapliga underlaget var otillräckligt för att bedöma följande utfallsmått: *dödföddhet/död i nyföddhetsperioden*, *hjärnskada baserat på syrebrist*, *vård på intensivvårdsavdelning för nyfödda*, *mekonium aspirationssyndrom, kramper i nyföddhetsperioden*, *förlossningsskada hos barnet, Apgar score <4 vid 5 minuter, funktionsnedsättning i barndomen.*
För utfallsmåtten *behov av andningsstöd* och *infektion i nyföddhetsperioden* var det vetenskapliga underlaget något bättre, men skattningarna var osäkra och risken bedömdes kunna variera åt båda håll.
Det fanns inga *dödsfall* hos mödrarna i någon av studierna. Igångsättning verkade inte påverka *förlossningssättet*, dvs andelen kejsarsnitt, vaginala förlossningar med eller utan sugklocka var liknande efter igångsättning hemma jämfört med på sjukhus.
Komplikationer i form av *blödning mer än 1000 ml*, *infektion* samt *överstimulering av livmodern* var ovanliga och effekten av igångsättning i hemmet kunde inte bedömas. Andra allvarliga komplikationer rapporterades inte.
Tiden från igångsättning till förlossning bedömdes variera mellan ingen skillnad till fyra timmar kortare vid igångsättning hemma. *Vårdtiden* bedömdes vara i genomsnitt fyra timmar kortare, men kunde även vara upp till tre timmar längre. Mödrarna redovisade oftast att de var nöjda med igångsättning hemma. Jämfört med igångsättning på sjukhus skattade mödrarna att de var lika eller något nöjdare.

Kostnaden för igångsättning hemma var svårvärderad, då den var beroende av antal besök som krävs på förlossningsavdelningen, olika handläggningar av fortsatt igångsättning efter första dygnet samt osäkerhet i vårdtid. *Etiska aspekter* inkluderade det osäkra kunskapsläget kring igångsättning hemma och därmed en ofullständig information om riskerna för kvinnan.

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 written in plain language.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, May 27th, 2020

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DDS: Doctor of dental surgery
MD: Medical doctor
PhD: Doctor of Philosophy
OD: Odontology doctor
PT: Physiotherapist
RN: Registered Nurse

3. Summary of findings

Outcomes	Study design Number of studies	Relative effect (95% CI)	Absolute effects * Outpatient vs. inpatient	Certainty of evidence GRADE[1]
Critical outcomes for decision making				
Stillbirth/neonatal mortality	2 RCT 1 Cohort		1/658 vs. 0/647 (n.s.) 1/907 vs. 0/85 (n.s.)	GRADE ⊕◯◯◯ Very low [1]
Hypoxic ischemic encephalopathy or need for therapeutic hypothermia	2 RCT 1 Cohort		3/658 vs. 3/647 (n.s.) 1/907 vs. 0/85 (n.s.)	GRADE ⊕◯◯◯ Very low [1]
Admission to the neonatal intensive care unit	4 RCT 2 Cohort	RR: 1.28 (95% CI 0.66 to 2.49) not included in meta-analysis	20/645 vs. 16/643 (n.s.) 83/1,518 vs. 59/653 (n.s.)	GRADE ⊕◯◯◯ Very low [2]
Meconium aspiration syndrome	2 RCT 1 Cohort		1/182 vs. 1/165 (n.s.) 1/811 vs. 0/85 (n.s.)	GRADE ⊕◯◯◯ Very low [1]
Need for respiratory support	3 RCT 1 Cohort	RR: 0.97 (95% CI 0.51 to 1.82)	18/655 vs. 18/266 (n.s.) 5/177 vs. 7/96 (n.s.)	GRADE ⊕⊕◯◯ Low [3]
Neonatal infection	4 RCT 1 Cohort	RR: 0.91 (95% CI 0.53 to 1.55) not included in meta-analysis	49/804 vs. 59/409 (n.s.) 1/177 vs. 0/96 (n.s.)	GRADE ⊕⊕◯◯ Low [4]
Neonatal seizures	4 RCT	RR: 1.47 (95% CI 0.25 to 8.68)	3/852 vs 4/842 (n.s.)	GRADE ⊕◯◯◯ Very low [5]
Disability in childhood	Not reported			
Composite neonatal mortality and morbidity	1 RCT 1 Cohort		40/336 vs. 60/335 (p=0.038) 84/611 vs. 62/568 (n.s.)	GRADE ⊕◯◯◯ Very low [4]
Maternal death	6 RCT 3 Cohort		0/1,056 vs. 0/1,045 (n.s.) 0/1,695 vs. 0/749 (n.s.)	GRADE ⊕◯◯◯ Very low [1]
Cardiorespiratory arrest	Not reported			
Internal organ damage	Not reported			
Hysterectomy	1 RCT		0/150 vs. 2/150 (n.s.) [#]	GRADE ⊕◯◯◯ Very low [1]
Intensive care admission	1 RCT		2/407 vs. 0/416 (n.s) [#]	GRADE ⊕◯◯◯ Very low [1]
Pulmonary embolism	Not reported			
Stroke	Not reported			

Important outcomes for decision making				
Birth trauma	1 RCT		1/64 vs. 2/53 (n.s.)	GRADE ⊕◯◯◯ Very low [1]
Apgar score < 4 at 5 minutes	1 Cohort		0/177 vs. 0/96	GRADE ⊕◯◯◯ Very low [1]
Unplanned home delivery	2 RCT 1 Cohort		2/467 vs.1/480 (n.s.) Cohort: 0/811 vs. 0/85 (n.s.)	GRADE ⊕◯◯◯ Very low [1]
Time from induction of labour to delivery	2 RCT 1 Cohort	Mean diff -4.17 h (95% CI -8.67 to 0.33) not included in meta-analysis	Range of reported times (median): 21.4-24.85h vs. 20.7-29.02h (n.s.) 35.4 h vs. 22.5 h (p<0.001)	GRADE ⊕⊕◯◯ Low [4]
Uterine hyperstimulation	5 RCT 2 Cohort	RR: 0.79 (95% CI: 0.39 to 1.61) not included in meta-analysis	23/854 vs. 31/863 (p-value range: 0.029 to >0.05) 51/1,518 vs. 45/653 (n.s.)	GRADE ⊕◯◯◯ Very low [2]
Caesarean delivery	6 RCT 4 Cohort	RR: 1.04 (95% CI: 0.87 to 1.24) not included in meta-analysis	212/919 vs. 215/608 (n.s.) 586/1,735 vs. 274/789 (n.s.)	GRADE ⊕⊕◯◯ Low [7]
Instrumental vaginal delivery	6 RCT 4 Cohort	RR: 1.00 (95% CI: 0.85 to 1.17) not included in meta-analysis	186/919 vs. 173/927 (n.s.) 482/1,735 vs. 161/786 (p-value range: 0.037 to >0.05)	GRADE ⊕⊕◯◯ Low [7]
Unassisted vaginal birth	6 RCT 4 Cohort	RR: 0.99 (95% CI: 0.99 to 1.08)	513/919 vs. 539/927 (n.s.) 669/1,735 vs. 353/789 (n.s)	GRADE ⊕⊕◯◯ Low [7]
Maternal infection	2 RCT		RCT 1: Suspected infection 26/215 vs. 27/233 (n.s.) Proven infection 0/215 vs. 1/233 (n.s.) RCT 2: Chorioamnionitis 3/65 vs. 3/64 (n.s.) Endometritis 1/65 vs. 1/64 (n.s.)	GRADE ⊕◯◯◯ Very low [5]
Haemorrhage >1000 ml	1 RCT 1 Cohort		0/65 vs. 1/53 (n.s.) 114/907 vs. 8/85 (n.s.)	GRADE ⊕◯◯◯ Very low [1]
Length of hospital stay	3 RCT	Mean diff -3.94 h (95% CI -10.97 to 3.08)	Range of reported times: 14.25-79.2h vs. 21.45-79.2h (n.s.)	GRADE ⊕⊕◯◯ Low [8]
Maternal satisfaction	3 RCT		High satisfaction rating 83/149 vs. 59/150 p=0.008 Satisfied (5 point scale) 3.83 vs. 3.67 (95% CI: -0.33 to 0.02)	GRADE ⊕⊕◯◯ Low [8]

Footnotes:
* Absolute effects for event rates, presented as the sum of all events / the total numbers of participants, across the RCTs or cohort studies, respectively, with range of p-values, or not significant: n.s
[#] p-value calculated with Fisher's exact test
[1] Downgraded because of serious study limitations (one step), very serious imprecision (two steps).
[2] Downgraded because of serious study limitations (one step), indirectness (one step) and imprecision (one step).
[3] Downgraded because of serious study limitations (one step) and imprecision (one step).
[4] Downgraded because of serious study limitations (one step), some inconsistency, indirectness and uncertain precision (one step).
[5] Downgraded because of serious study limitations (one step), some inconsistency and indirectness, very serious imprecision (two steps).
[7] Downgraded because of serious study limitations (one step) and indirectness (one step).
[8] Downgraded because of serious study limitations (one step), some inconsistency and indirectness and uncertain precision (one step).

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 aremoderately 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 substantiallydifferent from the estimate of effect

4. Abbreviations/Acronyms

ACOG: American College of Obstetricians and Gynecologists
ARM: Artificial Rupture of Membranes
BMI: body mass index
CI: Confidence Interval
CTG: Cardiotocography
DSOG: Danish Society of Obstetrics and Gynecology
HIE: Hypoxic Ischaemic Encephalopathy
HTA: Health Technology Assessment
ICU: Intensive Care Unit
Induction: Induction of labour
MAS: Meconium Aspiration Syndrome
NICE: National Institute for Health and Care Excellence
NICU: Neonatal Intensive Care Unit
NNT: Number Needed to Treat
OR: Odds Ratio
PGE2: Prostaglandin E2
PROM: Premature Rupture Of Membranes
RCT: Randomised Controlled Trial
RR: Relative Risk
SBU: Swedish Agency for Health Technology Assessment and Assessment of Social Services
SD: Standard deviation
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

Disease/disorder of interest and its degree of severity

Induction of labour is a common obstetric intervention. According to the Swedish Pregnancy Register, 19% of all deliveries in Sweden were induced in 2018 (any indication). The frequency of induction is expected to rise significantly ahead. This is mainly due to the new data received from the recently published SWEdish Postterm Induction Study (SWEPIS) (Wennerholm *et al*., 2019). SWEPIS was one of three randomised trials included in a Health Technology Assessment (HTA)-report, evaluating induction at 41 or 42 completed gestational weeks (Alkmark *et al*., 2020). This report concluded that a strategy of induction at 41 completed weeks compared with a strategy of expectant management to 42 completed weeks in low risk pregnancies may reduce the rate of stillbirth/neonatal mortality.

The Swedish Society of Obstetrics and Gynecology (SFOG) recently presented new recommendations stating that women should be allowed to choose themselves whether they want to be induced at 41+0 weeks (2020, Nya SFOG-råd om induktion). If most women will elect induction at 41+0 weeks, this might increase the induction rate to about 30% (instead of 19%), challenging the capacity of the obstetric units. Outpatient induction could be a possible solution. Such a strategy could also be preferable for other patients depending on reason for induction and medical background.

In Sweden, induction has so far been performed in an inpatient (i.e. at a delivery ward in hospital) setting. The method used for induction is determined by e.g. the state of the cervix, whether the indication is premature rupture of membranes (PROM) or if the woman has had a previous caesarean section. Induction in a woman with an unfavourable cervix (Bishop Score <6 in primiparous and <5 in multiparous) is typically initiated by pharmaceutical (prostaglandins) or mechanical (balloon catheter) (Kelly *et al*., 2013, SFOG 2016) ripening of the cervix.

In women with an unfavourable cervix, outpatient induction, where the woman is allowed to return home for the ripening process after satisfactory foetal monitoring, is an alternative to inpatient induction. Women come back to the hospital upon start of active delivery in the same way as women with spontaneous onset of delivery. Outpatient induction is currently practiced in several countries around the world. Also, in the Nordic countries, some hospitals in Finland and Denmark practice outpatient induction either with prostaglandins or balloon method. At these hospitals 42-75% of all inductions are started as outpatient inductions (Kruit *et al*., 2016, personal communication (*Jan 23, 2020, oral, Kristine Sylvan Andersen, Senior Midwife, Rigshospitalet, Copenhagen, Denmark*)).

Another important aspect is the woman´s preference and satisfaction associated with the induction process. Studies on women´s experience of outpatient versus inpatient induction show that women allocated to outpatient induction were more satisfied. They experienced better sleep and a more relaxed situation at home with their family and their anxiety level was not increased compared with the inpatients (Turnbull *et al.*, 2013).

However, only few studies have tested if induction by cervical ripening could be performed in an outpatient setting, and none of them was sufficiently powered to study the rare outcome of severe neonatal or maternal morbidity or death (Kelly *et al*., 2013; Biem *et al*., 2003; Mohamad *et al*., 2018; Policiano *et al*., 2017; Sciscione *et al*., 2001; Wilkinson *et al*., 2015a; Wilkinson *et al*., 2015b). New studies on the subject have been published after the latest Cochrane review (Kelly *et al*., 2013).

Prevalence and incidence

During 2019, 18,999 children were delivered in the Region Västra Götaland (VGR). There were 4,058 inductions (21.4%).
At Sahlgrenska University Hospital, 10,137 children were delivered and 2,371 inductions (23.4%) were undertaken (Swedish pregnancy register). The frequency of induction is expected to be significantly higher in 2020.

Present treatment

When delivery starts spontaneously, women usually stay at home during the phase of cervical ripening and are admitted to the hospital upon entering active labour. The choice of method for induction depends on the state of the cervix. When the cervix is ripe, delivery can be induced by amniotomy. Otherwise induction needs to start with cervical ripening, either by dilatation of the cervix using a balloon catheter or by the use of oral or vaginal prostaglandins. Today this treatment is carried out as an inpatient procedure. After satisfactory foetal monitoring and determined cephalic presentation, the woman receives the appropriate induction treatment and remains in the obstetric unit until delivery.

The normal pathway through the healthcare system and current wait time for medical assessment/treatment

In Sweden almost all babies are delivered at an obstetric unit (secondary care) where midwives, obstetricians, and assistant nurses work in a team. There are no primary care delivery units in Sweden, deliveries only supervised by a midwife outside a hospital. The rate of planned home deliveries is about 1/1,000 deliveries compared with 20/1,000 in Denmark, 10/1,000 in Norway and 170/1,000 in the Netherlands (Lindgren *et al*., 2014; Nederland SPR). Until now there has been little or no wait time for induction in Sweden. Traditionally, there was almost no wait time, occasionally one or two days depending on the indication and the available capacity in the labour ward. However, as more women ask for induction at week 41+0, waiting time has increased and may be up to three days. As there is currently not enough capacity for the increasing demand, inductions are frequently postponed.

Present recommendations from medical societies or health authorities

In Sweden there are no national guidelines for women planned for induction regarding whether the cervical ripening should take place at home or at the hospital. However, hospitals in Sweden currently practice inpatient induction of labour except for small pilot studies at some sites during the last year. In Denmark outpatient induction is practiced and guidelines from the Danish Society of Obstetrics and Gynecology (DSOG) states that outpatient compared with inpatient induction does not seem to be associated with an increased risk in low risk pregnancies. Risks of misoprostol self-medication in an outpatient setting have not been sufficiently studied and should only be used with great caution (DSOG, 2014).
The World Health Organization (WHO) does not recommend outpatient induction for improving birth outcomes (WHO, 2011). This recommendation is in part based on the feasibility of outpatient induction in under-resourced settings. The American College of Obstetricians and Gynecologists (ACOG) states that outpatient cervical ripening, particularly mechanical methods may be appropriate for induction of labour in selected patients (ACOG 2009). The National Institute for Health Care and Excellence (NICE) guidelines states that: “In the outpatient setting, induction of labour should only be carried out if safety and support procedures are in place” and “The practice of induction of labour in an outpatient setting should be audited continuously” (NICE 2008).

6. Health Technology at issue: Outpatient induction of labour in uncomplicated singleton pregnancies with cephalic presentation

When labour needs to be induced, women are usually admitted to the hospital. It often takes half a day or longer before active labour begins, thus diverting valuable resources at the hospital.

Swedish delivery units are currently under enormous pressure to be able to provide for up to 30% inductions among all pregnancies, instead of previous induction rate of approximately 20%, due to new recommendations by SFOG (SFOG 2020). Outpatient induction may have the potential to release resources at the delivery units. However, although outpatient induction has been performed for years in Australia, Great Britain, Denmark and Finland and has already started in some hospitals also in Sweden, the safety for the mother and the unborn child has not been proven and the same applies for effectiveness, acceptability and cost-effectiveness of outpatient induction.

This HTA report is evaluating whether induction in an outpatient setting is a safe alternative compared with inpatient management concerning stillbirth/neonatal mortality, neonatal morbidity and maternal mortality and morbidity. Also, women´s experiences and level of satisfaction with care associated with induction in an outpatient setting as well as putative economic benefits are evaluated.

7. Focused question

Is outpatient induction of labour, compared with inpatient induction, a safe and effective alternative regarding stillbirth/neonatal mortality, neonatal morbidity, maternal mortality and morbidity, and maternal satisfaction with care and birth experience, in healthy women with an uncomplicated singleton pregnancy?

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

P – Women with a low risk* induction in gestational week 37+0 to 41+6 planned for induction of labour (with a live foetus in cephalic presentation, no previous caesarean section and normal cardiotocography).

* Low risk in this report means no intra-uterine growth restriction, no preeclampsia, no diabetes requiring medication, no oligohydramnios, no known foetal malformation comprising induction and/or delivery. This specification is not mandatory for article inclusion.

I – Outpatient induction of labour

C – Inpatient** induction of labour

** Inpatient in this report means management in hospital at a unit led by either obstetricians or midwives.

O – Outcomes are listed next page

Critical for decision-making (GRADE assessment, if data is available)
Perinatal outcomes (according to Core Outcome Set for Induction Of Labour COSIOL (Dos Santos *et al.,* 2018))

Stillbirth/Neonatal mortality
Hypoxic ischemic encephalopathy (HIE) or need for therapeutic hypothermia
Admission to neonatal intensive care unit (NICU)
Meconium aspiration syndrome (MAS)
Respiratory support
Neonatal infection
Neonatal seizures
Disability in childhood
Composite neonatal mortality and morbidity

Maternal outcomes (*according to COSIOL)*
Maternal mortality
Cardiorespiratory arrest
Damage to internal organs (bowel, bladder, or ureters)
Hysterectomy for any complications resulting from birth
Intensive care admission
Pulmonary embolism
Stroke

Important for decision-making
Neonatal outcomes continued
Birth trauma
Apgar score < 4 at 5 minutes

Maternal outcomes continued
Unplanned home delivery
Time from induction of labour to delivery
Uterine hyperstimulation
Mode of delivery including caesarean, instrumental and unassisted vaginal delivery
Haemorrhage > 1000 ml
Maternal infection
Length of hospital stay
Maternal satisfaction
Women's experience/acceptability (no GRADE assessment)

8. Methods

Systematic literature search (appendix 1)

During January 2020 two authors (TS, EKK) performed systematic searches in Medline, Embase, the Cochrane Library, Cinahl, PsycInfo and Web of Science. Reference lists of relevant articles 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, who read the articles independently of one another. 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 and cohort studies have been critically appraised using checklists for assessment of RCTs and observational studies 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 risk ratio (RR) or mean difference with 95% CI, as the primary analysis method. As a secondary analysis method 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). Sensitivity analyses were conducted for outcomes when studies with different induction methods in the randomisation groups were included. 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 (pages 7-9). 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 (March 25, 2020) using the search terms *(outpatient OR outpatients OR out-patient OR out-patients) AND AREA[ConditionSearch] (cervical ripening OR induced labor OR induced labour OR labor induction OR labour induction OR induced labor OR induced labour OR induce labor OR induce labour OR inducing labor OR inducing labour OR cervical priming OR preinduction OR pre-induction)* identified 30 trials. Nine of these were relevant for our PICO.

9. Results

Literature search (Appendix 1)

The literature search identified 595 articles after removal of duplicates. After reading the abstracts 521 articles were excluded. Another 31 articles were excluded by two authors after reading the articles in full text. The remaining 43 articles were sent to all participants of the project group, and 17 articles (six RCTs, five cohort studies, four case series and two qualitative studies) were finally included in the assessment (Appendix 2).

Included studies

Six RCTs with a total of 1,273 patients (Beckmann *et al*., 2019; Biem *et al*., 2003; Henry *et al*., 2013; Kuper *et al*., 2018; Wilkinson *et al*., 2015a; Wilkinson *et al*., 2015b), five cohort studies with 3,355 patients (Chang *et al*., 2005; Clarke *et al*., 2017; Cundiff *et al*., 2017; Stock *et al* 2014; Turnbull *et al*., 2013), as well as four case series with 2,121 patients were included. The case series were originally reported as two RCTs (Agarwal *et al*., 2012; McGee *et al*., 2019) and as two cohort studies (Barnfield *et al*., 2018; Kruit *et al*., 2016) but were handled as case series, since the interventions in those studies were not applicable in this HTA-report or the control group did not fulfil the inclusion criteria. In addition, two qualitative studies with 86 patients matched the PICO (O´Brien *et al*., 2013; Oster *et al*., 2011).

Six of the studies were carried out in Australia (Beckmann *et al*., 2019; Henry *et al*., 2013; Oster *et al*., 2011; Turnbull *et al*., 2013; Wilkinson *et al.,* 2015a; Wilkinson *et al*., 2015b), three in the United Kingdom (Clarke *et al*., 2017; O´Brien *et al*., 2013; Stock *et al*., 2014), two in the United States (Chang *et al*., 2005; Kuper *et al*., 2018) and two in Canada (Biem *et al*., 2003; Cundiff *et al*., 2017).

The case series were carried out in India (Agarwal *et al*., 2012), United Kingdom (Barnfield *et al*., 2018), Finland (Kruit *et al*., 2016) and Australia (McGee *et al*., 2019).

Almost all studies included only “low-risk” pregnancies. The definition of low risk differed somewhat between the studies but generally it included a singleton pregnancy in cephalic presentation with no suspicion of intrauterine growth restriction or malformations, no previous uterine surgery and no maternal morbidity. The inclusion criteria were generally in accordance with our PICO, except for some studies including small for gestational age (SGA) foetuses.

The interventions examined in the RCTs and cohort studies all involved cervical ripening in an outpatient setting compared with inpatient management. The treatment differed between the studies with some studies comparing Prostaglandin E2 (PGE2) (with oral or vaginal administration routes) in out- and inpatient settings (Biem *et al*., 2003; Chang *et al*., 2005; Clarke *et al*., 2017; Cundiff *et al*., 2017; Oster *et al*., 2011; Stock *et al*., 2014; Turnbull *et al*., 2013; Wilkinson *et al*., 2015b). One study used balloon catheter in both groups (Wilkinson *et al*., 2015a). Another study compared Foley catheter in the outpatient group with Foley catheter plus oxytocin infusion in the inpatient group (Kuper *et al*., 2018) while two studies compared balloon catheter in the outpatient group with PGE2 in the inpatient group (Beckmann *et al*., 2019; Henry *et al*., 2013). Sensitivity analyses excluding these three studies were conducted due to the mixed interventions and considered in the conclusions. Since the induction methods in the inpatient groups in these three studies were likely to result in shorter time intervals in relation to delivery than in the outpatient groups, the outcomes measuring time were reported in subgroups of receiving the same or different induction methods.

Directness, study limitations and precision
Generally, the included studies (RCTs as well as cohort studies) had problems with directness, study limitations and precision. Directness was affected by the different treatment standards in the countries studied compared with the Swedish setting, e.g. while Sweden has a comparably low caesarean section rate of 17.3% (Socialstyrelsen 2018), the rate of caesarean section is much higher in most of the studies ranging from 18.2% (outpatient group in Wilkinson *et al*., 2015a) to 42.4% (inpatient group in Stock *et al*., 2014). In two studies the rate was lower. In Chang et al. (2005) the rate was 14.1% in the outpatient group and in the study by Kuper *et al*. (2018) who included parous women only, the rate was 3-5%.

Most of the included studies had some or major study limitations. One recurrent problem was the difference between the number of women being randomised and the number of women actually receiving the allocated treatment. Due to early randomisation, e.g. a day before the planned induction, a considerable part of the study population had entered labour spontaneously. In one study almost half of the randomised women never received the allocated treatment (Wilkinson *et al*., 2015b). In this trial eligibility criteria were also modified halfway through the trial because of an adverse event in the outpatient group, excluding women with diet-controlled diabetes, body mass index >35 or women with suspected small for gestational age (SGA) foetus. Another RCT was stopped in advance after an interim analysis, due to large attrition between obtained consent and randomisation, as well as between randomisation and induction, resulting in too few events for any inference (Beckmann *et al*., 2019). Except for Wilkinson *et al*. (2015b) and selected outcomes in Beckmann *et al*. (2019), studies reported either the per protocol or the intention to treat (ITT) analysis.

The included study populations differed by their inclusion criteria regarding gestational age, indication for induction, cervical status and parity. One RCT had unadjusted differences in baseline data, e.g. modified Bishop score was lower in the inpatient group (Beckmann *et al*., 2019). Other studies also had intergroup differences concerning e.g. morbidity, indication for induction or parity (Chang *et al*., 2005; Cundiff *et al*., 2017; Biem *et al.,* 2003) The method of induction differed between and within studies. The studies were generally underpowered for analysis of the rare events regarding severe maternal or perinatal morbidity or mortality, resulting in imprecise results.

Results per outcome

<u>Outcomes – Critical for decision-making</u>

Stillbirth/neonatal mortality (Appendix 4.1.1)
Stillbirth/neonatal death was reported in two RCTs (Beckmann *et al*., 2019; Wilkinson *et al*., 2015b) and one cohort study (Stock *et al*., 2014), including 2,508 women. Beckmann *et al*. (2019) reported no deaths and the other RCT (Wilkinson *et al*., 2015b) reported one case of perinatal death in a participant allocated to the outpatient group and involved a woman who did not require cervical ripening but laboured spontaneously. The case was part of the intention to treat (ITT) analysis. No deaths were reported in the per protocol group. The cohort study reported one death in the outpatient and none in the inpatient group (Stock *et al*., 2014). The neonatal death followed long labour requiring subsequent doses of dinoprostone and oxytocin augmentation and operative delivery.

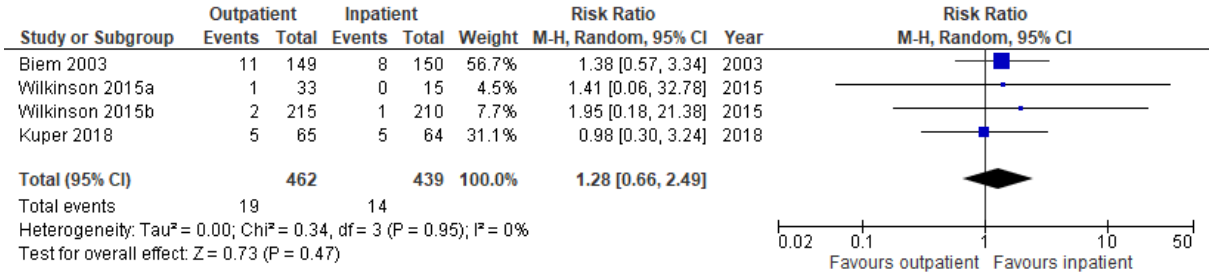
<u>Conclusion</u>: It is uncertain whether outpatient compared with inpatient induction affects the rate of stillbirth/neonatal mortality (GRADE ⊕◯◯◯).

Hypoxic ischemic encephalopathy or need for therapeutic hypothermia (Appendix 4.1.2)
This outcome was reported in two RCTs and one cohort study, including 2,508 women. One RCT reported an ITT analysis with three events in each group (0.7%). In a per protocol analysis of the same study there were three events (1.4%) in the outpatient and two events (0.95%) in the inpatient group. In the cohort study there was one event in the outpatient group.

Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of HIE or need for therapeutic hypothermia (GRADE ⊕◯◯◯).

Admission to the neonatal intensive care unit (NICU) (Appendix 4.1.3)
Admission to NICU was reported in four RCTs, two cohort studies and two case series, including 4,488 women. The length of the NICU stay differed between the included studies. The RCTs reported no significant difference in admission to NICU between the outpatient and the inpatient groups. Meta-analysis showed a RR of 1.28 (95% CI 0.66 to 2.49) (Fig. 1). Peto OR was 1.34 (95% CI 0.66 to 2.72). Omitting the study by Kuper *et al.,* (2018), which added oxytocin to the inpatient group, did not alter the result: RR 1.54 (95% CI 0.66 to 3.56).

Fig. 1. Meta-analysis of randomised controlled trials comparing outpatient induction of labour with inpatient induction of labour. Outcome: Admission to the neonatal intensive care unit (NICU).



The cohort studies reported no significant differences in admission to NICU between the outpatient and the inpatient group and thereby support the data from the RCTs.

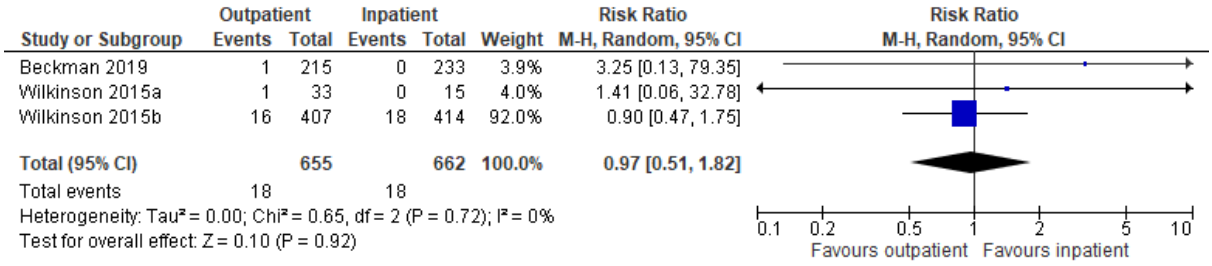
Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of NICU admission (GRADE ⊕◯◯◯).

Meconium aspiration syndrome (Appendix 4.1.4)
Meconium aspiration syndrome was reported in two RCTs and one cohort study, including 1,340 women. All studies reported very few events, three in total and there were no clear differences between the outpatient and inpatient groups.

Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of meconium aspiration syndrome (GRADE ⊕◯◯◯).

Need for respiratory support (Appendix 4.1.5)
Need for respiratory support was reported in three RCTs and one cohort study, including 1,863 women. All RCTs concluded that there was no difference in events between the outpatient and the inpatient group. Meta-analysis showed a RR of 0.97 (95% CI 0.51 to 1.82) (Fig. 2). Peto OR was 1.00 (95% CI 0.51 to 1.94). Omitting the study with different induction methods in the two randomisation groups (Beckmann *et al*., 2019) did not alter the result: RR 0.92 (95% CI 0.48 to 1.76).

Fig. 2. Meta-analysis of randomised controlled trials comparing outpatient induction of labour with inpatient induction of labour. Outcome: Need for respiratory support.



In the cohort study neonatal breathing difficulties were reported in five children (2.8%) in the outpatient and seven (7.1%) children in the inpatient group.

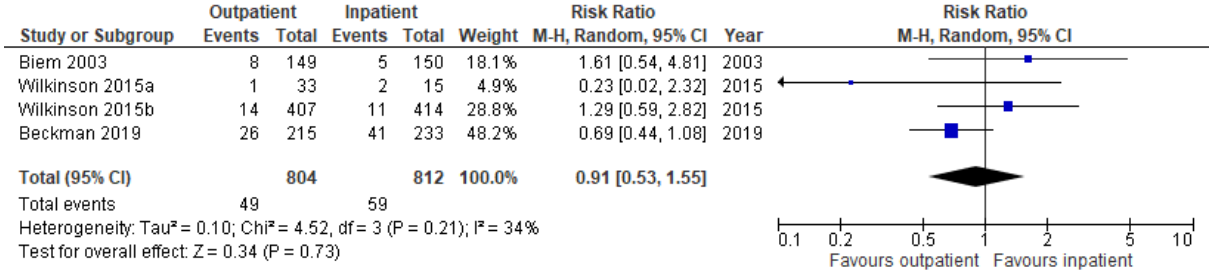
Conclusion: There may be little or no difference in the rate of need for respiratory support comparing outpatient with inpatient induction, although the CI for the estimate is wide (GRADE ⊕⊕◯◯).

Neonatal infection (Appendix 4.1.6)

Neonatal infection was reported in four RCTs and one cohort study, including 2,453 women. The definition of neonatal infection differed somewhat between the studies. The rate of neonatal infections was similar between the outpatient and inpatient groups.

The RCTs did not show a significant difference in neonatal infection between the groups. Meta-analysis showed a RR of 0.91 (95% CI 0.53 to 1.55) (Fig. 3). Omitting the study with different induction methods in the two randomisation groups (Beckmann *et al*., 2019) did not alter the result substantially: RR 1.20 (95% CI 0.61 to 2.39).

Fig. 3. Meta-analysis of randomised controlled trials comparing outpatient induction of labour with inpatient induction of labour. Outcome: Neonatal infection.



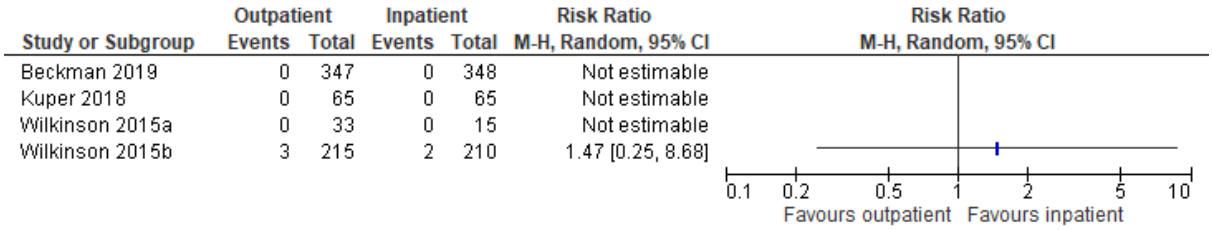
The cohort study supported the data in the RCTs.

Conclusion: There may be little or no difference in the rate of neonatal infection comparing outpatient with inpatient induction, although the CI for the estimate is wide (GRADE ⊕⊕◯◯).

Neonatal seizures (Appendix 4.1.7)

Neonatal seizures were reported in four RCTs, including 1,699 women with few events reported. One RCT performed an ITT analysis and reported three (0.7%) events in each group. In the per protocol analysis of the same study, three (1.4%) and two (0.95%) events were reported in the outpatient and inpatient groups, respectively. The other three RCTs reported no events. The results are displayed in a forest plot (Fig. 4).

Fig. 4. Forest plot of randomised trials comparing outpatient induction of labour with inpatient induction of labour. Outcome: Neonatal seizures.



Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of neonatal seizures (GRADE ⊕○○○).

Composite neonatal mortality and morbidity (Appendix 4.1.8)
A neonatal composite outcome was reported in one RCT and one cohort study, including 1,874 women. The composite outcomes were similar but not identical (App. 4.1.8a+b). The ITT analysis in the RCT showed a significant difference with a more favourable outcome in the outpatient group (11.9% vs 17.9%, p=0.04), while the per protocol analysis showed similar results, although non-significant (18.6% vs 25.8%, p=0.07). The cohort study reported similar rates in the two groups (14% vs 11%).

Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of neonatal composite outcomes (GRADE ⊕○○○).

Disability in childhood
Disability in childhood was reported in one cohort study, including 992 women. However, only children with adverse outcome at birth were followed and no systematic follow-up of the study population was performed.
Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of disability in childhood (GRADE ⊕○○○).

Maternal mortality
The outcome was not reported in any study.

Cardiorespiratory arrest
The outcome was not reported in any study.

Damage to internal organs (bowel, bladder or ureters)
The outcome was not reported in any study.

Hysterectomy for any complications resulting from birth (Appendix 4.2.1)
Hysterectomy was reported in one RCT, including 300 women. There were two events in the inpatient and none in the outpatient group.

Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of hysterectomy (GRADE ⊕○○○).

Intensive care admission (Appendix 4.2.2)
Intensive care admission was reported in one RCT, including 827 women. Two events (0.005%) were reported in the outpatient group and none in the inpatient group.

Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of intensive care admission (GRADE ⊕◯◯◯).

Pulmonary embolism
The outcome was not reported in any study.

Stroke
The outcome was not reported in any study.

Outcomes - Important for decision-making

Birth trauma (Appendix 4.1.9)
Birth trauma was reported in one RCT, including 129 women. The RCT reported one case of birth injury in the outpatient (2%) and two in the inpatient (3%) group, p=0.62. The birth injuries included one brachial plexus injury, one cephalohematoma and one case with both a scalp laceration and a cephalohematoma. It was unclear what injury occurred in what group.

Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of birth trauma (GRADE ⊕◯◯◯).

Apgar score < 4 at 5 minutes (Appendix 4.1.10)
Apgar score < 4 at 5 minutes was reported in one cohort study, including 293 women. No events were reported in either group.

Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of Apgar score < 4 at 5 minutes (GRADE ⊕◯◯◯).

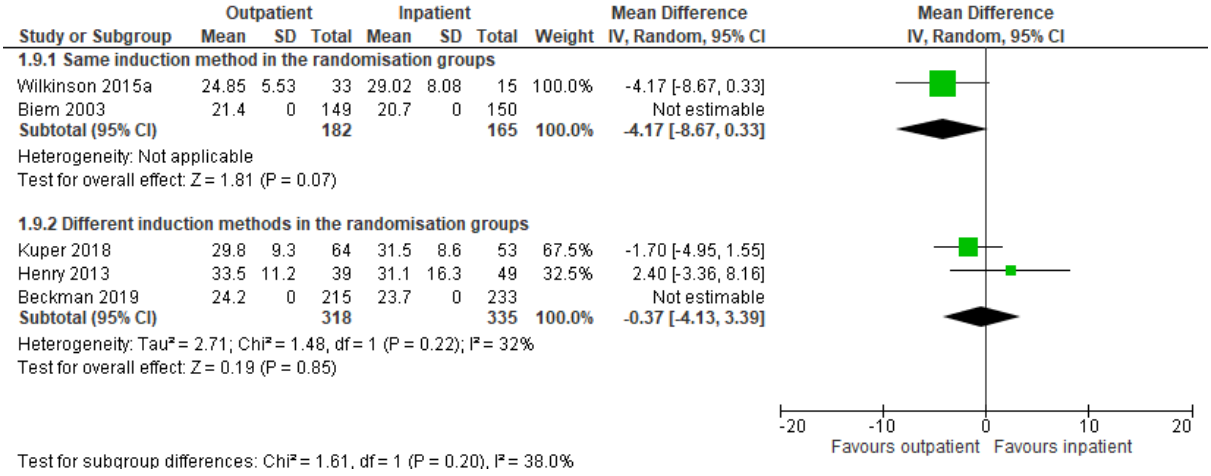
Unplanned home delivery (Appendix 4.2.3)
Unplanned home delivery was a rare event, reported in two RCTs, one cohort study and one case series, including 2,721 women. One RCT reported one event of unplanned home delivery in the outpatient group and no events in the inpatient group. Regarding this outcome, only the women receiving the allocated treatment were analysed. The other RCT performed an ITT analysis and reported one event in each group. Both these events involved women who did not receive allocated treatment. The cohort study reported no events and the case series reported one event (0.25%).

Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of unplanned home delivery (GRADE ⊕◯◯◯).

Time from induction of labour to delivery (Appendix 4.2.4)
Time from induction of labour to delivery was reported in five RCTs and one cohort study including 2,265 women. One study included only the vaginal deliveries in the analysis, while the other studies included all deliveries. No significant difference in time from induction of labour to delivery was reported in the RCTs. This outcome was analysed in subgroups of studies with either the same or with different induction methods in the randomisation groups. This was due to the fact that results of studies with different induction methods are likely to depend more on the induction method itself than on the randomisation groups. Two studies used balloon catheter in the outpatient group and PGE2 in the inpatient group (Beckmann *et al.,* 2019; Henry *et al*., 2013) and a third study used Foley catheter in both groups but added oxytocin to inpatients (Kuper *et al.*, 2018).

Of two studies applying the same induction method, the larger showed no difference and the smaller favoured outpatient induction, demonstrating a mean difference of – 4.17 hours (95% CI -8.67 to 0.33). The results of the three studies with different induction methods implied no significant difference (Fig. 5).

Fig. 5. Meta-analysis of randomised controlled trials comparing outpatient induction of labour with inpatient induction of labour, analysed in subgroups of receiving the same or different induction methods. Outcome: Time from induction of labour to delivery.



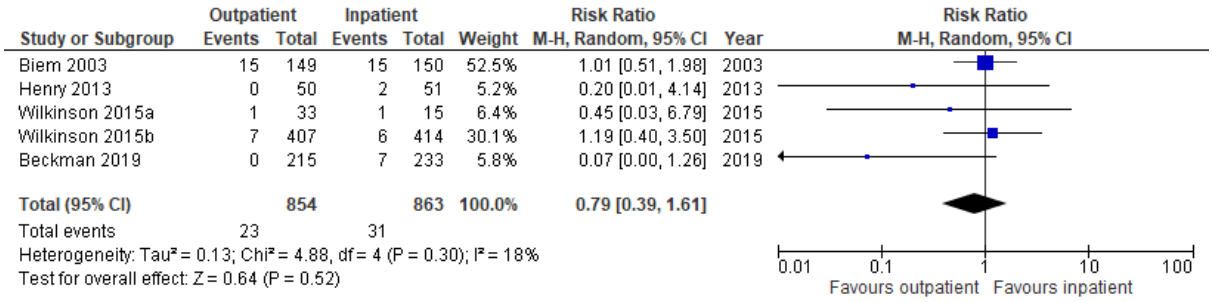
The cohort study did report a significant difference in time from induction to delivery between the outpatient and the inpatient group (35.45 (34.4-36.5) hours versus 22.5 (21.1-23.9) hours, p<0.001). Both groups received PGE2 gel vaginally.

Conclusion: Outpatient compared with inpatient induction, receiving the same induction method, may result in a reduction or no difference in time from induction to delivery (GRADE ⊕⊕◯◯).

Uterine hyperstimulation (Appendix 4.2.5)

Uterine hyperstimulation was reported in five RCTs and two cohort studies, including 4,142 women. The definition of uterine hyperstimulation differed between the included studies, five or more contractions per 10 minutes, six or more contractions per 10 minutes, increased uterine activity and not defined in one trial. One RCT performed an ITT analysis and reported a significant difference in uterine hyperstimulation between the outpatient group (no events) that were treated by balloon and the inpatient group (seven events, 3%) that received prostaglandin intervention (p=0.029). Meta-analysis showed a RR of 0.79 (95% CI 0.39 to 1.61) (Fig. 6). Peto OR was 0.72 (95% CI 0.42 to 1.25). Omitting two studies with different induction methods in the two randomisation groups (Henry *et al*., 2013, Beckmann *et al*., 2019) did not alter the result substantially: RR 1.02 (95% CI 0.58 to 1.78).

Fig. 6. Meta-analysis of randomised controlled trials comparing outpatient induction of labour with inpatient induction of labour. Outcome: Uterine hyperstimulation.



One cohort study reported a difference between the outpatient group, n=19 (2.1%) and no events in the inpatient group. The treatment in this study was dinoprostone (PGE2) in both groups.

Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of uterine hyperstimulation (GRADE ⊕◯◯◯).

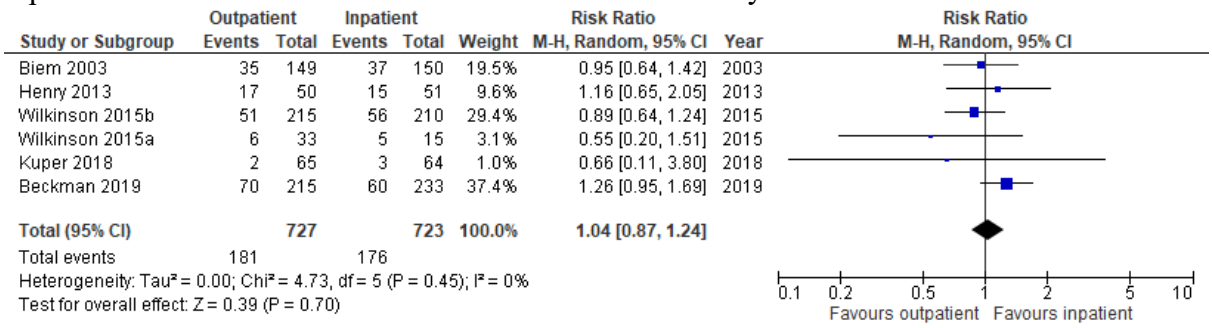
Mode of delivery (Appendix 4.2.6)

Mode of delivery was reported in six RCTs and four cohort studies, including 4,944 women. These studies compared the rate of caesarean section, instrumental vaginal birth and unassisted vaginal birth between the groups. None of the included participants had had previous uterine surgery. There was no significant difference between the outpatient and inpatient groups concerning mode of delivery in the included studies.

Caesarean delivery

The rate of caesarean section was generally high (up to 42.4%) except for one study that had very low rate. This trial included only parous women. Meta-analysis of the six RCTs showed a RR of 1.04 (95% CI 0.87 to 1.24) for caesarean delivery (Fig. 7). Omitting three studies with different induction methods in the two randomisation groups (Henry *et al*., 2013, Beckmann *et al*., 2019, Kuper *et al.,* 2018) did not alter the result substantially: RR 0.89 (95% CI 0.69 to 1.14).

Fig. 7. Meta-analysis of randomised controlled trials comparing outpatient induction of labour with inpatient induction of labour. Outcome: Caesarean delivery.

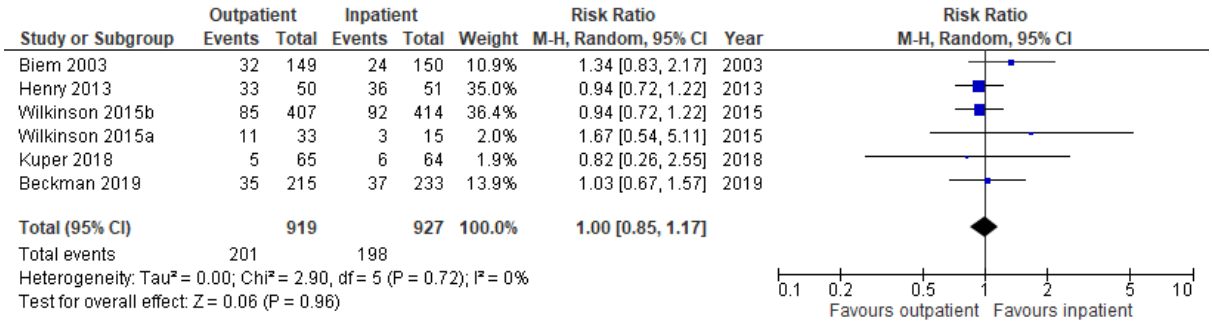


Conclusion: Outpatient instead of inpatient induction may result in little or no difference in the rate of caesarean delivery (GRADE ⊕⊕◯◯).

Instrumental vaginal delivery

A meta-analysis of the six RCTs showed a RR of 1.00 (95% CI 0.85 to 1.17) (Fig. 8). Omitting three studies with different induction methods in the two randomisation groups (Henry *et al*., 2013, Beckmann *et al*., 2019, Kuper *et al.,* 2018) did not alter the result: RR 1.07 (95% CI 0.81 to 1.41).

Fig. 8. Meta-analysis of randomised controlled trials comparing outpatient induction of labour with inpatient induction of labour. Outcome: Instrumental vaginal delivery.

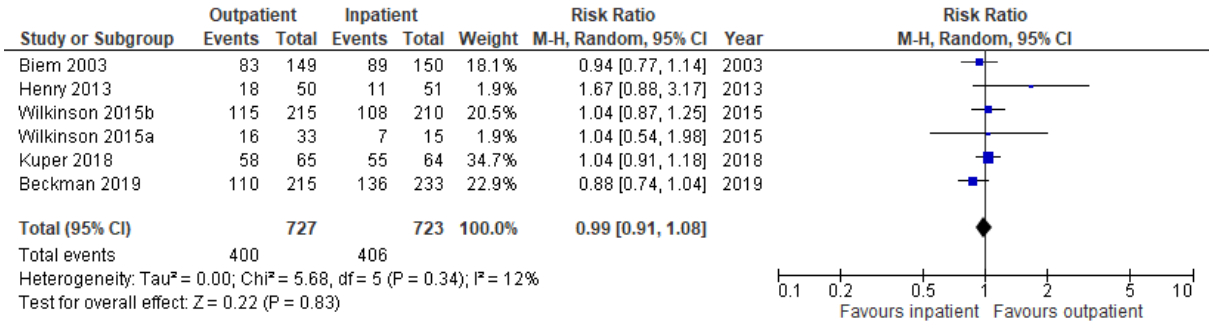


Conclusion: Outpatient instead of inpatient induction may result in little or no difference in the rate of instrumental delivery (GRADE ⊕⊕◯◯).

Unassisted vaginal delivery

The six RCTs also reported unassisted vaginal delivery. None of them demonstrated any difference between out- and inpatient induction. A pooled analysis showed a RR of 0.99 (95% CI 0.99 to 1.08) (Fig 9). Omitting three studies with different induction methods in the two randomisation groups (Henry *et al*., 2013, Beckmann *et al*., 2019, Kuper *et al*., 2018) did not alter the result: RR 1.02 (95% CI 0.93 to 1.11).

Fig. 9. Meta-analysis of randomised controlled trials comparing outpatient induction of labour with inpatient induction of labour. Outcome: Unassisted vaginal delivery.



One cohort study reported a significant difference regarding unassisted vaginal birth with a higher frequency in the outpatient group, n=142 (80.2%) compared with the inpatient group, n=96 (63.5%), RR 1.27 (95% CI 1.04-1.55) p<0.05. This is inconsistent with the data from the RCTs.

Conclusion: Outpatient instead of inpatient induction may result in little or no difference in the rate of unassisted vaginal delivery (GRADE ⊕⊕◯◯).

Haemorrhage >1000 ml (Appendix 4.2.7)
Haemorrhage >1000 ml was reported in one RCT and one cohort study, including 1,121 women. The RCT reported no events (0%) in the outpatient and one event (2%) in the inpatient group, p=0.50. The cohort study reported 114 events (12.6%) in the outpatient group and eight events (9.4%) in the inpatient group, p=0.51.

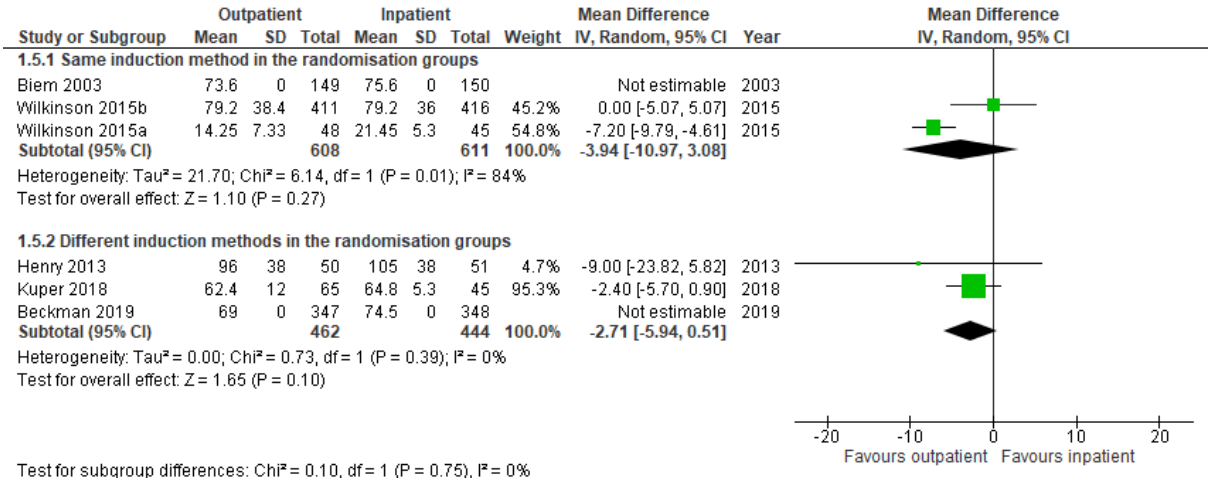
Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of haemorrhage >1000 ml (GRADE ⊕◯◯◯).

Maternal infection (Appendix 4.2.8)
Maternal infection was reported in two RCTs, including 824 women. No significant difference in maternal infection was reported between the outpatient and inpatient groups.

Conclusion: It is uncertain whether outpatient compared with inpatient induction affects the rate of maternal infection (GRADE ⊕◯◯◯).

Length of hospital stay (Appendix 4.2.9)
Length of hospital stay was reported in six RCTs, including 2,100 women. One RCT reported a significant difference of 7 hours shorter stay in the outpatient group. Another RCT did also report a significantly shorter stay in the outpatient group. This trial lacked information on SD and could not be included in the meta-analysis. This outcome was analysed in subgroups of studies with the same or different induction methods in the randomisation groups, to account for a potential dependence on induction methods affecting the length of stay (Fig. 10).

Fig. 10. Meta-analysis of randomised controlled trials comparing outpatient induction of labour with inpatient induction of labour, analysed in subgroups of receiving the same or different induction methods. Outcome: Length of hospital stay (hours)



Conclusion: Outpatient compared with inpatient induction, receiving the same induction method, may result in no difference in length of hospital stay, although the CI for the estimate is wide (GRADE ⊕⊕◯◯).

Maternal satisfaction (Appendix 4.2.10)
Maternal satisfaction was reported in three RCTs and one case series, including 1,707 women. Biem *et al.*, reported high satisfaction ratings in 56% of the women in the outpatient group, compared with 39% in the inpatient group p=0.008, (n=299). In Turnbull *et al*., the main scores regarding the 'satisfied', in a 5-point Likert scale, was 3.83 vs. 3.67, mean difference -0.16 (95% CI: -0.33 to 0.02) in the outpatient group, and the inpatient group, respectively (n=399).
The results from one RCT indicated that women favoured outpatient induction without increasing their anxiety when told they could go home after induction. In the subgroup analysis of women who in fact received the intervention, the magnitude of the effect favouring outpatient induction was even larger. The case series reported that 85.3% of the women returning the questionnaire were satisfied with outpatient induction.
Conclusion: Outpatient compared with inpatient induction, may result in no difference or somewhat higher maternal satisfaction rates (GRADE ⊕⊕◯◯).

Women's experience/acceptability (Appendix 4.2.11)
Women´s experience was reported in one cohort study (Clarke *et al*., 2017), which included 90 low-risk women who received post-date induction and were given the option to receive Propess (PGE2) and return home. Of these, 40 women went home (outpatient), and 50 women stayed at the hospital (inpatient). There was a higher percentage of nulliparous women in the outpatient group (n=31, 78%) compared with the inpatient group (n=32, 64%). There was no description of data collection and no qualitative analysis of the data. The authors concluded that women who experienced the outpatient option, described their experiences positively and presented illustrative quotations (n=3).

Two qualitative interview studies (O´Brien *et al*., 2013; Oster *et al*., 2011) with low to medium quality including 15 and 16 women respectively, described that most of the women expressed a preference for outpatient cervical priming for induction of labour. The women in the outpatient setting described that the home environment resulted in physical and emotional comforts, which helped them cope better with their labour and improved their birth experiences. Women were also found to negotiate between the comfort of home and the perceived safety of the hospital. Feelings of safety within the home environment were perceived by clear written instructions about what to expect after going home, a 24 h ability to call and talk with a midwife for any reason, and assurance that they could come back to the hospital at any time.

10. Ethical aspects

The most serious ethical dilemma associated with introduction of outpatient instead of inpatient induction would be if the strategy is adopted without ensuring sufficient evidence concerning maternal and neonatal safety. This would constitute a potentially increased risk for adverse outcomes, especially if outpatient induction was introduced as a mean to offer induction at 41+0 weeks to all women. In SWEPIS the number needed to treat (NNT) by induction of labour at 41 weeks to prevent one perinatal death was 230, which is lower than previous estimates (Wennerholm *et al*., 2019). A systematic review including 30 trials reported a NNT of 426 (95% CI 338 to 1337) (Middleton *et al*., 2018). Scientific evidence regarding the hard and rare outcomes of severe morbidity or death for mother and child in an outpatient induction setting is lacking and it could be that the NNT by general induction in week 41+0 could be in the same range as the numbers needed to harm by offering outpatient induction.

Ethical dilemmas that might occur are if the woman prefers to stay at the hospital but there is no room for her or on the contrary, she wants to go home but is recommended not to (e.g. because of medical safety aspects). This could result in a conflict between the woman and the clinic where communication with the women are essential to promote informed decisions, safety and maternal satisfaction. There could also be a difference in opinion between the woman and her partner, potentially pressuring the woman into interventions she does not want.

Following the new SFOG guideline, a strategy to offer induction at 41 completed weeks of gestation may result in about 3,200 more women in VGR being induced yearly, and, consequently, prolonged hospital stays for these. 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 the costs and may therefore compete with other health care services. If outpatient induction would be shown to be a safe and effective alternative, these displacement and cost effects of changed routines regarding late term induction might be compensated.

12. Organisational aspects

Time frame for the putative introduction of the new health technology

This new routine could be established within a very short period of time.

Present use of the technology in other hospitals in Region Västra Götaland

Outpatient induction is already in clinical use in highly selected patients in Uppsala and Falun and a small pilot-study has been performed in Lund/Malmö.

Consequences of the new health technology for personnel

The organisation must be changed in such a way that women planned for induction are assessed regarding if their induction is considered low-risk.

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

Some hospitals in other Scandinavian countries have introduced outpatient induction in clinical routine during recent years. At these hospitals 42-75% of all inductions are started as outpatient induction (personal communication, Kruit *et al.,* 2016). In the light of the new SFOG guideline, currently many clinics in Sweden turn to outpatient induction as a solution of the demand for general induction at 41+0 weeks. At our clinic, at Sahlgrenska University Hospital, we expect an induction rate of about 30% (approx. 3,000 women) and that approximately 35% (approx. 1,050) of these would be classified as low-risk induction and could receive cervical ripening in an outpatient setting. Outpatient induction would be feasible if there was an induction of labour ward where clinical examinations and check-ups could be performed and thereby releasing resources and beds in the labouring unit.

13.Economic aspects

Present costs of currently used technologies

Using cost data from the SWEPIS (and the births at the Sahlgrenska University hospital in Gothenburg), the average cost per birth with inpatient induction was estimated to approx. 45,000 SEK. This is based on women being induced at week 42+0.

Expected costs of the new health technology

We have no primary data on cost per birth with outpatient induction. The assumption is that once active labour is started, the average cost per birth is going to be equal to a standard birth (in terms of delivery time, health outcomes, likelihood of NICU, etc.), or perhaps lower, as outpatient inductions is applicable only in low-risk inductions, the cost of which is assessed to be approx. 42,000 SEK. However, compared to the cost of a non-induced birth, outpatient induction will require an additional visit related to administering the induction. Further, for women not entering active labour within 24 hours of induction, additional visits will be necessary, which will further increase costs. From the SWEPIS (Wennerholm *et al*., 2019), it is estimated that around 2% will require such an additional visit. Based on these assumptions, the expected cost per birth with outpatient induction is approx. 42,700 SEK.

Total change in costs

Based on the assumptions above, outpatient compared with inpatient induction would reduce average costs per birth by about 2,300 SEK. This estimate has considerable uncertainty since we lack primary cost data both for inpatient and outpatient induction for the patient group specified in the PICO.

Available economic evaluations or cost advantages/disadvantages

Two studies with relevant health economic consequences were identified in the search. In Adelson *et al.* (2013), a cost comparison was made between outpatient and inpatient induction based on RCT-data from a South Australian study (the OPRA trial). The point estimate showed that outpatient induction reduced health care costs by 319 Australian dollars per birth (approx. 2,000 SEK), but the 95% CI overlapped no difference in mean costs per birth.

In Austin *et al.* (2015), a cost comparison was made between outpatient induction using a Foley catheter and inpatient induction using PGE2 gel based on data from the FOG (RCT) trial in Australia (Henry *et al.,* 2013). The point estimate showed that outpatient induction was 643 Australian dollars (approx. 4,000 SEK) more expensive per birth, but the 95% CI overlapped no difference in mean costs per birth.

In sum, the point estimates from the two studies point in different directions, but in none of them the difference in mean cost per birth was statistically significant.

14.Discussion

Summary of main results

In this HTA-report, including a systematic review and meta-analyses, we found only low or very low certainty of evidence regarding outcomes that are critical or important for decision making when it comes to introducing outpatient induction in clinical practice. Low incidence of adverse maternal and neonatal outcomes, study limitations and underpowered studies limit the ability to make conclusions regarding safety and effectiveness.

The critical outcomes, e.g. stillbirth/neonatal mortality are insufficiently studied. Only two RCTs reported the outcome perinatal death, but both were underpowered for this outcome. The certainty of evidence for the conclusions concerning the other neonatal outcomes were either low or very low, mainly because of few events and study limitations. The certainty of evidence regarding the maternal outcomes was overall low or very low. Outpatient induction may result in little or no difference in mode of delivery, in shorter or no difference in time from induction to delivery, and no difference in hospital stay although with a wide confidence interval (low certainty of evidence). The conclusions for the other maternal outcomes were based on very low certainty of evidence.

Overall completeness and applicability of evidence

The outcomes chosen for the review reflect both effectiveness and safety. They were based on consensus outcomes previously presented (Dos Santos *et al*., 2018). The studies included in the review lacked statistical power to detect intergroup differences for most outcomes.

Interpretation of the results from the included studies was challenging since the studies were heterogeneous in design, method of intervention, indication for induction, obstetric routines and demographic characteristics. E.g. the difference in risk status and indications for induction were mixed amongst the included trials. The induction methods differed within and across the studies. Two studies compared outpatient induction with balloon catheter with inpatient PGE2 and one study compared outpatient induction with balloon catheter with inpatient induction with balloon catheter and concomitant oxytocin infusion. The risk of uterine hyperstimulation was the reason why outpatient induction with PGE2 was not practiced. The use of pharmalogical induction could affect the efficacy of the intervention, resulting in a faster induction progress (Jozwiak *et al.,* 2011). Demographic characteristics that differed between the studies or were insufficiently demonstrated, were Bishop score, indication for induction, parity and gestational age. Several of the outcomes are affected by these parameters, e.g. length of hospital stay, time from induction to delivery and mode of delivery as well as maternal and neonatal infection. These differences make it challenging or impossible to generalise the findings and to compare the data.

Agreements and disagreements with other studies and reviews

The findings of this HTA-report 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. The latest Cochrane review (Kelly *et al*., 2013) evaluated the effects on outcomes for mothers and babies of induction of labour for women managed as outpatients versus inpatients based on four trials including 1,439 women. The authors concluded that the data available to evaluate the effectiveness or potential hazards of outpatient induction are limited and that it is, therefore, not yet possible to determine whether induction of labour is effective and safe in outpatient settings. Our results share the same dearth.

A meta-analysis by Diederen *et al*. (2019) showed that there were few complications related to the phase of cervical ripening with a balloon catheter regardless of in- or outpatient setting. Sciscione *et al*. (2001) and Sciscione *et al*. (2014) support these data.

A previous systematic review reported that early re-admission differed between women treated with balloon catheter (2.5-8%) and prostaglandins (10-38%) (Weinberg *et al*., 2017).

Regarding women´s experience of outpatient induction Kandola *et al*. (2019) described that the home environment resulted in physical and emotional comfort, which helped women cope better with their labour and improved their birth experiences. Another study not fulfilling our PICO criteria, reported that it was mainly well educated primiparous women that were treated as outpatients and hence a difference between study groups (Howard *et al*., 2014). During the study setting only women willing to try outpatient induction agree to study participation, thus generalizability to an unselected total population is not given.

Implications for research

The strategy of outpatient induction is sparsely studied. The latest Cochrane review (Kelly *et al*., 2013) requests more research into the safety and effectiveness of outpatient induction. For the Swedish obstetric clinics there is an urgent need to offer more women the possibility of induction due to the new guideline from SFOG. Several delivery units have turned to outpatient induction as a possible solution. However, without certainty regarding safety and effectiveness of outpatient induction, the possibility of cervical ripening in an outpatient setting should be explored in an adequately powered, well-designed trial where the safety and effectiveness outcomes should be considered.

15. Future perspectives

Scientific knowledge gaps

We explored a strategy of outpatient cervical ripening versus a strategy of inpatient cervical ripening in low-risk pregnancies in order to evaluate the effect on perinatal and maternal outcomes. We identified several knowledge gaps.

Neonatal and maternal mortality and serious morbidity

It is unclear whether outpatient cervical ripening in low-risk pregnancies is as safe as inpatient induction or is associated with adverse effects.

Induction method

The included trials have used different methods of cervical ripening.
It would be relevant to further compare prostaglandin E2 and Foley catheter (or double balloon catheter) in outpatient cervical ripening with inpatient management in low-risk pregnancies.

Time avoided in hospital by outpatients

Outcome data using time intervals when examining induction of labour are often complicated. There are a variety of start and end points used. The data within the included trials are recorded using a variety of methods, which makes comparing findings from studies difficult. Time avoided in hospital would perhaps be a more informative outcome measure and was reported by Adelson *et al*. (2013), Biem *et al*. (2003) and Stock *et al*. (2014). The average time avoided in hospital ranged between 7.5 and 11.76 hours although the studies by Adelson and Stock were not explicit about how this was calculated. Biem *et al*. (2003) extrapolated the time avoided in hospital from the time of dinoprostone administration to the time of readmission to hospital, correcting for the one-hour initial and mid-point assessments 12 hours later, if done. Further, differences in induction method within the same study and differences regarding characteristics of study participants between in- and outpatient group make interpretation of time variables challenging.

Costs
Results from cost analyses are conflicting. Two economic evaluations alongside trials were identified, and Adelson *et al*. (2013) reported reduced costs with outpatient induction, whereas Austin *et al*. (2015) reported increased costs with outpatient induction. In Ten Eikelder *et al*. (2018), a decision-analytic model (scenario analysis) shows that by assuming reduced hospital time with outpatient induction (as informed by a Dutch RCT in their report), substantial cost-savings could be achieved by using outpatient induction. Further evaluation of this potential benefit would be relevant. This report's estimate of a small average reduction in delivery costs after outpatient induction has considerable uncertainty.

Outpatient induction in a Swedish setting
There are problems with directness in the included trials, of which the majority have been performed in an Anglo-Saxon setting with much higher caesarean section rates. It would be valuable to record data from the Swedish setting to make the applicability as high as possible.

Pregnant women´s experiences of outpatient induction and involvement of planning trials
As previously mentioned, women´s experience of and satisfaction with induction in the outpatient setting is sparsely studied. Further trials on this subject and on partner´s and professional staff´s experience of outpatient induction would contribute to the field.

Ongoing research

The search in Clinicaltrials.gov identified 30 trials. Nine randomised trials were relevant according to the present PICO and are listed below.

Author, Country	Estimated Completion Date	Study Groups; Intervention vs Control	Patients (n) Estimated Enrollment	Gestational Age (weeks)	Outcome Variables
Nichols USA	September 1 2023 Still recruiting	Cervidil (Dinoprostone, Prostaglandin E2 (PGE2), Insert) as Pre-Induction in outpatients vs inpatients.	200	39+0 to 41+6	Patient satisfaction, vaginal delivery rate, operative vaginal delivery rate, caesarean delivery rate, time of admission until discharge, infant 5 minute Apgar score, NICU admission,
Shrivastava USA	December 2019 Not yet published	Cervical ripening with Foley catheter in outpatients vs inpatients.	160	≥ 39	Patient satisfaction scores.
Chan USA	January 2018 Not yet published	Outpatient induction with immediate removal of a transcervical Foley catheter vs inpatient induction with a Foley catheter up to 12 hours.	64	≥ 37	Duration of inpatient hospitalization, duration of labour induction, caesarean section rate, chorioamnionitis, Uterine tachysystole, admission to NICU, Apgar score.
Ausbeck USA	December 13 2019 Not yet published	Cervical ripening with Foley catheter in outpatients vs inpatients.	126	39+0 to 42+0	Time from admission to delivery, patient satisfaction, patient experience, total hospital duration, chorioamnionitis, endometritis, mode of delivery, NICU admission.
Rinne Finland	December 30 2018 Not yet published	Double balloon induction catheter in outpatients vs inpatients.	200	>37 to <41+5	Total hospital stay (days), maternal infection, neonatal infection.
Pierce-Williams USA	December 10 2019 Not yet published	Foley catheter in outpatients vs Foley catheter (and oxytocin) in inpatients.	60	> 37	Patient satisfaction, length of labour induction, mode of delivery, infection rates, Apgar scores, NICU admission,
Esakoff USA	July 2014 Not yet published	Foley catheter in outpatients vs inpatients.	800	Term pregnancy	Caesarean section rate, patient satisfaction, Apgar scores, NICU admissions.
Kohari USA	November 1 2020 Still recruiting	Cervical ripening with Foley catheter in outpatients vs inpatients.	400	> 37	Time from labour induction to delivery, total time in hospital, NICU admission, Apgar scores,
Hedriana USA	June 2021 Still recruiting	Cervical ripening with intracervical balloon in outpatients vs inpatients. All participants are nulliparous.	100	37 to 42	Time from admission to delivery, caesarean delivery, NICU admission.

16.Participants in the project

The question was nominated by

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Participating healthcare professionals

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Administrative support

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Declaration of interests

While working on this HTA report, planning for a Swedish multicenter study “OPTION: Outpatient induction. Labour induction in an outpatient setting - a multicenter randomized controlled trial” started with VS being the principal investigator with shared responsibility together with YC, HS, HE, AH and ÅL also involved in this trial. BB and LB report no conflict of interest.

Project time

The HTA was accomplished during the period of 2019-12-18 to 2020-06-27
Literature searches were made January 20th, 2020.

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

Question(s) at issue:
Is outpatient induction of labour, compared with inpatient induction, a safe and effective alternative regarding stillbirth/neonatal mortality, neonatal morbidity, maternal mortality and morbidity, and maternal satisfaction with care and birth experience, in healthy women with an uncomplicated singleton pregnancy?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P – Women with a low risk* pregnancy in gestational week 37+0 to 41+6 planned for induction of labour (with a live foetus in cephalic presentation, no previous caesarean section and normal cardiotocography).

* Low risk in this report means no intra-uterine growth restriction, no preeclampsia, no diabetes requiring medication, no oligohydramniosis, no known foetal malformation. This specification is not mandatory for article inclusion.

I – Outpatient induction of labour

C – Inpatient** induction of labour

** Inpatient in this report means management in hospital at a unit led by either obstetricians or midwives.

O -

Critical for decision-making (GRADE assessment, if data is available)
Perinatal outcomes (according to Core Outcome Set for Induction Of Labour COSIOL (Dos Santos *et al.,* 2018))

Stillbirth/Neonatal mortality
Hypoxic ischemic encephalopathy (HIE) or need for therapeutic hypothermia
Admission to neonatal intensive care unit (NICU)
Meconium aspiration syndrome (MAS)
Respiratory support
Neonatal infection
Neonatal seizures
Disability in childhood
Composite neonatal mortality and morbidity

Maternal outcomes (*according to COSIOL)*
Maternal mortality
Cardiorespiratory arrest
Damage to internal organs (bowel, bladder, or ureters)
Hysterectomy for any complications resulting from birth
Intensive care admission
Pulmonary embolism
Stroke

Important for decision-making

Neonatal outcomes continued

Birth trauma

Apgar score < 4 at 5 minutes

Maternal outcomes continued

Unplanned home delivery

Time from induction of labour to delivery

Uterine hyperstimulation

Mode of delivery including caesarean, instrumental and unassisted vaginal delivery

Haemorrhage > 1000 ml

Maternal infection

Length of hospital stay

Maternal satisfaction

Women's experience/acceptability (no GRADE assessment)

Eligibility criteria

Study design:

Randomised controlled trials

Non-randomised controlled studies

Case series etc. if >100 patients

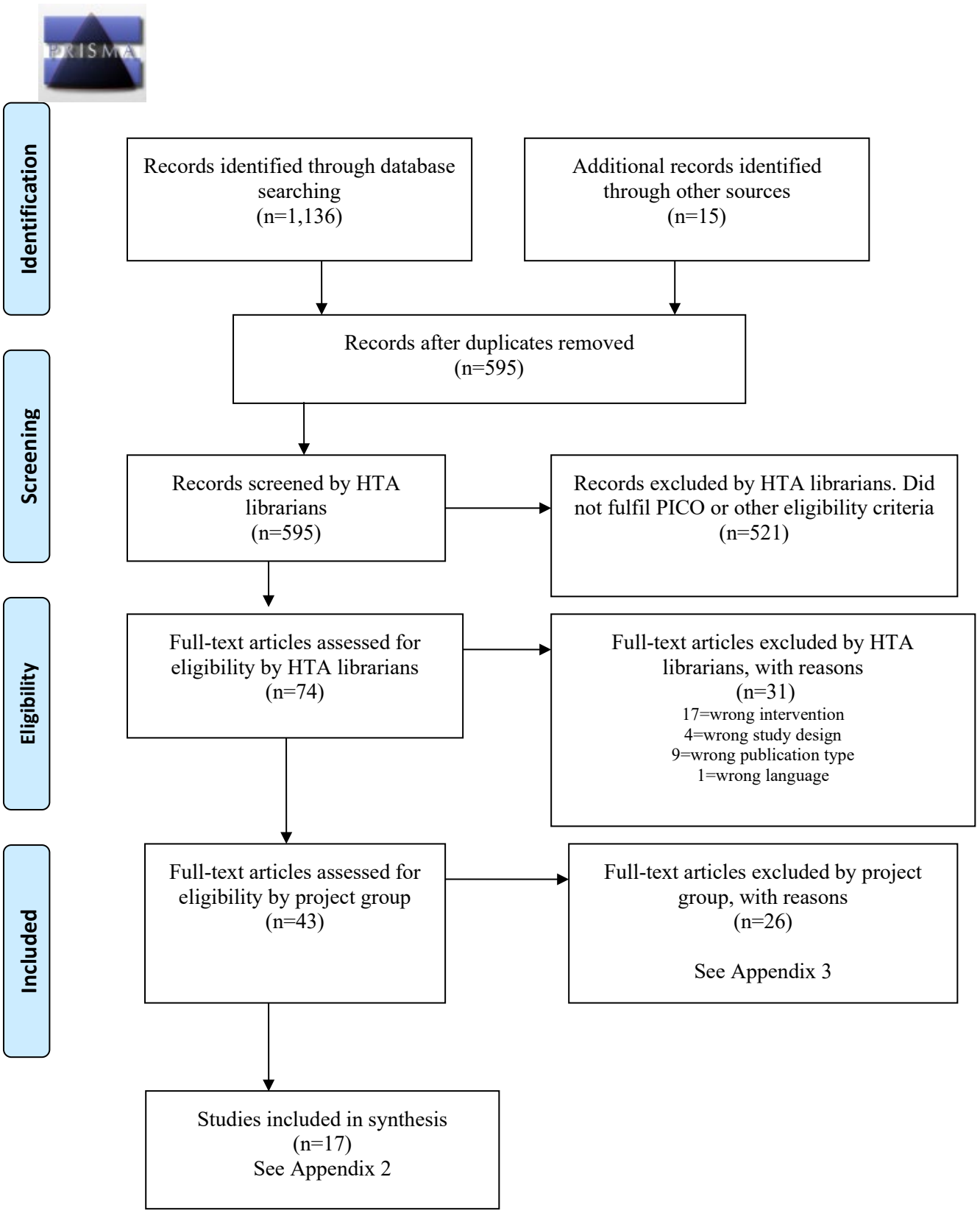
Qualitative studies

Language:

English, German, Swedish, Norwegian, Danish

Publication date: 2003-

Selection process – flow diagram



Modified from Moher et al., 2009

Search strategies

Database: Ovid MEDLINE(R) ALL 1946 to January 09, 2020 (OvidSP)
Date: 10 Jan 2020
No. of results: 226

#	Searches	Results
1	Labor, Induced/ or Cervical Ripening/	9676
2	((labor or labour) and (induction* or induce or induced or inducing)).ab,ti,kf.	13788
3	(cervi* adj1 ripening).ab,ti,kf.	1748
4	cervical priming.ab,ti,kf.	268
5	(preinduction or pre-induction).ab,ti,kf.	1399
6	(outpatient* or out-patient*).ab,ti,kf.	177853
7	Outpatients/	15338
8	ambulatory care/	42272
9	home.ab,ti,kf.	213173
10	1 or 2 or 3 or 4 or 5	19182
11	6 or 7 or 8 or 9	407616
12	10 and 11	384
13	limit 12 to yr="2003 -Current"	241
14	limit 13 to (danish or english or german or norwegian or swedish)	226

Database: Embase 1974 to 2020 January 09 (OvidSP)
Date: 10 Jan 2020
No. of results: 273

#	Searches	Results
1	exp labor induction/ or uterine cervix ripening/	14620
2	((labor or labour) and (induction* or induce or induced or inducing)).ab,ti,kw.	18532
3	(cervi* adj1 ripening).ab,ti,kw.	2491
4	cervical priming.ab,ti,kw.	339
5	(preinduction or pre-induction).ab,ti,kw.	1885
6	(outpatient* or out-patient*).ab,ti,kw.	286304
7	outpatient/ or outpatient care/	150397
8	ambulatory care/	35381
9	home.ab,ti,kw.	298999
10	1 or 2 or 3 or 4 or 5	26886
11	6 or 7 or 8 or 9	612515
12	10 and 11	692
13	limit 12 to (books or chapter or conference abstract or conference paper or editorial or letter or note or tombstone)	284
14	12 not 13	408
15	limit 14 to yr="2003 -Current"	288
16	**limit 15 to (danish or english or german or norwegian or swedish)**	**273**

Database: The Cochrane Library
Date: 10 Jan 2020
No. of results: 140
Cochrane reviews 7
Trials 133

ID	Search	Hits
#1	MeSH descriptor: [Labor, Induced] explode all trees	1163
#2	MeSH descriptor: [Cervical Ripening] explode all trees	352
#3	(labor or labour) NEAR/3 (induction* or induce or induced or inducing):ti,ab,kw	3342
#4	(cervi* NEAR/1 ripening):ti,ab,kw	1373
#5	(cervical priming):ti,ab,kw	269
#6	(preinduction or pre-induction):ti,ab,kw	870
#7	(outpatient* or out-patient*):ti,ab,kw	40108
#8	MeSH descriptor: [Outpatients] explode all trees	1171
#9	MeSH descriptor: [Ambulatory Care] explode all trees	3592
#10	home:ti,ab,kw	38621
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6	4494
#12	#7 OR #8 OR #9 OR #10	77201
#13	#11 AND #12 with Cochrane Library publication date Between Jan 2003 and Jan 2020	198
#14	(clinicaltrials or trialsearch):so	277406
#15	**#13 not #14**	**140**

Database: CINAHL Complete, PsycINFO (EBSCOhost Research Databases)
Date: 10 Jan 2020
No. of results: 101

S11	**S7 AND S8** Avgränsare - Publiceringsdatum: 20030101-20201231 Utökning - Sök med likvärdiga ämnesord Begränsa genom att Language: - english Sökinställningar - Boolesk/fras	**165**
S10	S7 AND S8 Avgränsare - Publiceringsdatum: 20030101-20201231 Utökning - Sök med likvärdiga ämnesord Sökinställningar - Boolesk/fras	169
S9	S7 AND S8	192
S8	S5 OR S6	438,569
S7	S1 OR S2 OR S3 OR S4	4,950
S6	TI home OR AB home OR SU home	297,369
S5	TI ((outpatient* or out-patient*)) OR AB ((outpatient* or out-patient*)) OR SU ((outpatient* or out-patient*))	150,607
S4	TI ((preinduction or pre-induction)) OR AB ((preinduction or pre-induction)) OR SU ((preinduction or pre-induction))	366
S3	TI cervical priming OR AB cervical priming OR SU cervical priming	56
S2	TI (cervi* N1 ripening) OR AB (cervi* N1 ripening) OR SU (cervi* N1 ripening)	502
S1	TI (((labor or labour) N3 (induction* or induce or induced or inducing))) OR AB (((labor or labour) N3 (induction* or induce or induced or inducing))) OR SU (((labor or labour) N3 (induction* or induce or induced or inducing)))	4,480

Database: Web of Science Core Collection
Date: 10 Jan 2020
No. of results: 344

Set	Save History / Create AlertOpen Saved History
# 9	#6 AND #5 **Refined by: PUBLICATION YEARS:** (2020 OR 2011 OR 2003 OR 2019 OR 2010 OR 2018 OR 2009 OR 2017 OR 2008 OR 2016 OR 2007 OR 2015 OR 2006 OR 2014 OR 2005 OR 2013 OR 2004 OR 2012) AND **LANGUAGES:** (ENGLISH OR GERMAN) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years*
# 8	#6 AND #5 **Refined by: PUBLICATION YEARS:** (2020 OR 2011 OR 2003 OR 2019 OR 2010 OR 2018 OR 2009 OR 2017 OR 2008 OR 2016 OR 2007 OR 2015 OR 2006 OR 2014 OR 2005 OR 2013 OR 2004 OR 2012) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years*
# 7	#6 AND #5 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years*
# 6	**TOPIC:** (outpatient OR out-patient OR home) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years*
# 5	#4 OR #3 OR #2 OR #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years*
# 4	**TOPIC:** (preinduction OR pre-induction) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years*
# 3	**TOPIC:** (cervical priming) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years*
# 2	**TOPIC:** ((cervical OR cervix) AND ripening) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years*
# 1	**TOPIC:** ((labor OR labour) AND (induction* OR induce OR induced OR inducing)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years*

Reference lists
A comprehensive review of reference lists brought 15 new records

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Reference lists

Included studies:

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Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 2. Characteristics of included studies

Author Year Country	Original Study Design	Study Duration (years)	Study Groups; Intervention vs control	Patients (n)	Gestational Age (weeks)	Outcome variables*
Beckmann 2019 Australia	RCT	September 2015-October 2018	Balloon catheter to outpatients PGE2 to inpatients	347 + 348	≥ 37+0 Median gestational age at IOL: 41.0 (40.3-41.4) vs 41.0 (40.4-41.3)	*Composite neonatal measure comprising one or more of: nursery admission, intubation/ cardiac compressions, acidaemia, hypoxic ischaemic encephalopathy, seizure, infection, pulmonary hypertension, stillbirth or death.* Secondary outcomes included clinical outcomes (mode of birth, maternal and/or neonatal infection, meconium liquor, uterine hyperstimulation), process outcomes (duration of labour, length of stay) and healthcare experience.
Biem 2003 Canada	RCT	July 1999-September 2001	Vaginal controlled-release PGE2 to out- and inpatients	150 + 150	≥ 37+0 Gestation (days): 286 + 284	*Satisfaction (proportion with high mean ratings, i.e., ≥ 7, at 4 hourly calls during first 12 hours after insertion).* Ratings of anxiety and pain; overall satisfaction; duration of hospital stay uterine hyperstimulation, neonatal intensive care unit admission, 5-minute Apgar scores; induction to delivery interval. Apshyxia. Meconiun Aspiration
Chang 2005 USA	Cohort study	August 1999-July 2002	Misoprostol 50 μg intravaginally to out-and inpatients Inpatients had coexisting complication (i.e. diabetes)	177 + 96	≥ 38	Occurrence of home deliveries, need for prompt or closer attention to the newborn infant, route of delivery, Apgar <4 at 1 and 5 minutes.
Clarke 2017 United Kingdom	Cohort study	Not clearly specified	Propess to out- and inpatients	40 + 50	40 + 10-12	Describes the development of a home induction of labour framework. No clear outcomes.
Cundiff 2017 Canada	Cohort study	July 1998-March 2012	Dinoprostone vaginal insert to out- and inpatients. (indications for IOL were PROM or post date pregnancies)	611 + 568	> 37	*Composite neonatal safety outcome that included 5-minute Apgar score <7 and NICU admission >12 hours or transfer to level III nursery.* Mode of delivery

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 2. Characteristics of included studies

Author Year Country	Original Study Design	Study Duration (years)	Study Groups; Intervention vs control	Patients (n)	Gestational Age (weeks)	Outcome variables*
Henry 2013 Australia	RCT	June 2009-December 2010	Foley catheter to outpatients Prostaglandin E2 gel to inpatients	50 + 51	≥ 37	*Total inpatient hours from time of randomisation to delivery.* Mode of birth, induction to delivery interval, total inpatient stay. Patient acceptability was assessed through the patient satisfaction questionnaire, and rate of unplanned (not in labour) hospital readmission, Apgar scores, admission to newborn care.
Kuper 2018 USA	RCT	May 2016-October 2017	Foley catheter to outpatients Foley catheter and concomitant oxytocin infusion to inpatients. Only parous women	65 + 64	39+0-42+7	Chorioamnionitis, meconium-stained fluid, Shoulder dystocia, caesarean delivery, operative vaginal delivery, postpartum haemorrhage (>1000 ml), Endometritis Birth injuries, neonatal intensive care unit admission, total hospital duration.
O´Brien 2013 United Kingdom	Qualitative study	January 2009-December 2010	Slow release dinoprostone pessary and remote continuous trans-abdominal fetal ECG monitoring to outpatients	70	≥ 37+0	Women´s experience of induction of labour.
Oster 2011 Australia	Qualitative study	The OPRA trial lasted August 2008-May 2011 The interviews occurred over a 4-week period from March to April 2009.	Vaginal PGE2 gel to out- and inpatients	7 + 9	37 - 42	Part of the OPRA trial. The trial includes a small-scale qualitative study exploring women's experiences of cervical priming for induction of labour in inpatient and outpatient settings.
Stock 2014 United Kingdom	Retrospective cohort study	January 2007-June 2010	Dinoprostone (PGE2) vaginal gel to out- and inpatients	907 + 85	41+3-42+0	*Birth outside of the hospital. uterine; maternal death; antepartum hemorrhage; and postpartum hemorrhage greater than 1,000 mL. meconium stained liquor;admission to neonatal unit within 24 hours of delivery for greater than 48 hours' duration; neonatal encephalopathy defined as seizures within 24 hours of birth or requirement for cooling); and extended perinatal mortality (stillbirth or neonatal death within 28 days of delivery). HIE and meconium aspiration.* Mode of delivery; cesarean delivery for failed induction of labor (as documented by the caregiver); prostaglandin-to-delivery interval.

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 2. Characteristics of included studies

Author Year Country	Original Study Design	Study Duration (years)	Study Groups; Intervention vs control	Patients (n)	Gestational Age (weeks)	Outcome variables*
Turnbull 2013 Australia	RCT (analysed as a cohort study)	August 2008-May 2011	Vaginal PGE2 gel to out- and inpatients	407 + 414		Psychosocial outcomes from the OPRA trial; women´s axiety and satisfaction with care.
Wilkinson 2015a Australia	Pilot RCT	October 2012-July 2013	Double balloon catheter to out- and inpatients	33 + 15	37 - 42	Method of delivery (Spontaneous vaginal, Instrumental, Caesarean section) Mean (SD) time catheter inserted to vaginal delivery. Meconium-stained liquor Postpartum haemorrhage > 1000 ml after caesarean section, Hyperstimulation
Wilkinson 2015b Australia	RCT	August 2008-May 2011	Vaginal PGE2 gel to out- and inpatients	407 + 414	37 - 42	Method of delivery, Meconium–stained liquor Hyperstimulation, Length of stay (mean days). HIE, perinatal death, admission to NICU, infection, respiratory problems
Case series						
Agarwal 2012 India	RCT	February 2010-January 2011	Isosorbide mononitrate (IMN) or placebo to outpatients	100 + 100	> 40	*Apgar scores at 1 and 5 minutes and whether admission to the neonatal nursery was necessary.* Uterine hyperstimulation, meconium-stained liquor, and postpartum haemorrhage.
Barnfield 2018 United Kingdom	Retrospective cohort study	March 2010-December 2015	Prostin (3 mg dinoprostone pessary) to outpatients	ITT: 502 Outpatients: 400	T+14 (42+0)	*Out of hospital delivery, stillbirth or early neonatal death, admission to SCBU (level 1, none was transferred to a level III tertiary unit), seizures,* mode of delivery, maternal death, intensive care unit admission (mother), Postpartum haemorrhage > 1000 ml at caesarean section.
Kruit 2016 Finland	Cohort study	January 2011-January 2012	Foley catheter to out- and inpatients. Nearly 50% of the inpatient group had gestational age > 42 weeks.	204+281	≥ 37 - 42+1	Postpartum haemorrhage ≥ 1000 ml, intrapartum infection, postpartum infection, neonatal infection, admission to neonatal intensive care unit. Fetal death

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 2. Characteristics of included studies

Author Year Country	Original Study Design	Study Duration (years)	Study Groups; Intervention vs control	Patients (n)	Gestational Age (weeks)	Outcome variables*
McGee 2019 Australia	RCT	May 2015-July 2017	Latex vs silicone Foley catheter to outpatients	269 latex foley catheter+ 265 silicone catheter	≥ 36	Intrapartum antibiotics for suspected chorioamnionitis, mode of birth, special care nursery/neonatal intensive care unit admission.

* Outcomes in Italics: Primary outcome.

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 3. Excluded studies

Author, year	Reason for exclusion
Adelson PL, 2013	Cost effectiveness article. Wrong design.
Adeniji AO, 2013	Too few patients.
Attanayake K, 2016	Preinduction. Wrong intervention. Self-administration of isosorbide mononitrate or placebo at home at 39+0, 39+2, 39+4, 39+6 and 40+1 gestational weeks as a preparation for induction of labour.
Austin K, 2015	Cost effectiveness article. Wrong design.
Bendix JM, 2019	Unclear presentation.
Bollapragada SS, 2009	Preinduction. Wrong intervention. Self-administration of isosorbide mononitrate at home at 48 h, 32 h and 16 h before a scheduled induction of labour.
Bullarbo M, 2007	Pregnancies from 42+0. Wrong population.
Diederen M, 2018	Systematic Review.
Eddama O, 2009	Cost effectiveness article. Wrong intervention.
Habib SM, 2008	Preinduction. Wrong intervention. Self-administration of isosorbide mononitrate or placebo at home at 36 h, 24 h and 12 h before a scheduled induction of labour.
Howard K, 2014	Wrong outcome.
Kandola D, 2019	Quality analysis
Kelly AJ, 2013	Systematic Review.
McKenna DS, 2004	Cost effectiveness. Several high-risk pregnancies and unclear gestational age.
Neiji Z, 2019	Too few patients. Preinduction.Wrong intervention.
Policiano C, 2017	40% high risk pregnancies.
PonMalar J, 2017	Preinduction. Wrong intervention. 25 μg misoprostol or placebo was administered in women in gestational week 38+4-40+0. Induction of labour was scheduled at 40+4 -41+0.
Reid M, 2011	Preinduction. Wrong intervention. Self-administration of isosorbide mononitrate or placebo at home every 16th hour maximum three times as a preparation for induction of labour.
Schmitz, 2014	Preinduction. Wrong intervention. Isosorbide mononitrate or placebo was applied at 41+0, 41+2 and 41+4. Intervention was performed in hospital and time in between was spent at home.
Smith LK, 2017	Systematic review
Spallici MD, 2007	Preinduction. Wrong intervention. Lyophylized hyaluronidase or placebo was injected into the cervix once or twice depending on BS. Evaluation continuously until spontaneous onset of labour, gestational age ≥ 42 weeks or if any occurrence happened.
Toohill J, 2004	Unclear presentation.
Turnbull D, 2013	Midwifes experience.
Weinberg D, 2017	Systematic review.
Vetter G, 2016	Wrong intervention. Women with PROM stay at home or at the hospital until start of induction after 24 h.
Vogel JP, 2017	Systematic Review.

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.1.a Randomised trials
Outcome variable: Stillbirth/Neonatal mortality

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention to Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention to Treat (ITT) Per protocol (PP) (as defined by authors)				
Beckman 2019 Australia	RCT	695 (347+348)	44 (11+13)	448 (215 + 233)	PP 0/215 (0%)	PP 0/233 (0%)	Outcome noted in table 2	+/?	?/-	-
Wilkinson 2015b Australia	RCT	827 or 823 (411+416) (408+415) (407+414)	2 (1+1)	425 (215+210) (168+210)	ITT 1/407 (0.003%) PP 0/215 (0%)	ITT 0/414 (0%) PP 0/210 (0%)	Outcome noted in table 3 as perinatal death. Case involved a woman who did not require ripening and laboured spontaneously.	+	?	-

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.1.b Observational studies
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 *
				Outpatient Induction of Labour	Inpatient Induction of Labour				
Stock SJ 2014 United Kingdom	Cohort study	1536 N=907+85 I=811 C=85		1/907 (0.11%) 0.11 (95% CI 0.01-0.54) P=1.00	0/85 (0%)		+	?	-
Barnfield 2018 United Kingdom	Case series	400		0/400 (0%)		Derived from Table 2 live births			
Kruit H 2016 Finland	Case series	204		0/204 (0%)					

C Control, I Intervention

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.2.a Randomised controlled trials
Outcome variable: Hypoxic ischaemic encephalopathy or need for therapeutic hypothermia

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention to Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention to Treat (ITT) Per protocol (PP) (as defined by authors)				
Beckman 2019 Australia	RCT	695 (347+348)	44 (11+13)	448 (215 + 233)	PP 0/215 (0%)	PP 0/233 (0%)		+/?	?/-	-
Wilkinson 2015b Australia	RCT	827 or 823 (411+416) (408+415) (407+414)	2 (1+1)	425 (215+210) (168+210)	ITT 3/407 (0.74%) PP 3/215 (1.4%)	ITT 3/414 (0.72%) PP 2/210 (0.95%)		+	?	-

RCT randomised controlled trial

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.2.b Observational studies
Outcome variable: Hypoxic ischaemic encephalopathy or need for therapeutic hypothermia

* + 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 *
				Outpatient Induction of Labour	Inpatient Induction of Labour				
Stock 2014 United Kingdom	Cohort study	1536 N=907+85 I=811 C=85		1/907 (0.11%)	0/85 (0%)	neonatal encephalopathy defined as seizures within 24 hours of birth or requirement for cooling	+	?	-

C Control, I Intervention

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.3.a Randomised controlled trials
Outcome variable: Neonatal Intensive Care Unit (NICU) Admission

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention to Treat (ITT) Per protocol PP (as defined by authors)	Inpatient Induction of Labour Intention to Treat (ITT) Per protocol PP (as defined by authors)				
Biem 2003 Canada	RCT	300 (150+150)	1 (1+0)	299 (149+150)	PP 11/149 (7.4%)	PP 8/150 (5.3%)		?	+	-
Kuper 2018 USA	RCT	129 (65+64)	12 (1+11)	117 (64+53)	ITT 5/65 (8%) RR 1.0 (95% CI 0.3-3.2) P =>0.99	ITT 5/64 (8%)		?	?	-
Wilkinson 2015a Australia	RCT	48 (33+15)	4 (3+1)	44 (30+14)	ITT 1/33 (3%)	ITT 0/15 (0%)		+	?	-
Wilkinson 2015b Australia	RCT	827 or 823 (411+416) (408+415) (407+414)	2 (1+1)	425 (215+210) (168+210)	ITT 3/407 (0.74%) PP 2/215 (0.93%)	ITT 3/414 (0.72%) PP 1/210 (0.48%)		+	?	-

RCT Randomised controlled trial

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.3.b Observational studies
Outcome variable: Neonatal Intensive Care Unit (NICU) Admission

* + 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 *
Cundiff 2017 Canada	Cohort study	1179 N=1179 I=611 C=568		75/611 (12%) p=0.259	58/568 (10%)	NICU >12 or transfer to level III nursery	?	?	?
Stock 2014 United Kingdom	Cohort study	1536 N=907+85 I=811 C=85		8/907 (0.88%) 0.88 (95% CI 0.45-1.7) p=0.39	1/85 (1,1%) 1.2 (95% CI 0.06-0.57)	Admission to neonatal unit within 24 hours of delivery for greater than 48 hours' duration	+	?	?
Kruit 2016 Finland	Case-series	204		4/185 (2.2%)		NICU admission, table 3+ table 4			
McGee 2019 Australia	Case-series	534		106/534 (19.9%)		SCN/NICU admission – table 4 Reason for NICU/SCN admission: neonatal condition including respiratory distress and high lactate (26 silicone, 20 latex), congenital condition (15 silicone, six latex), maternal gestational diabetes (10 silicone, 14 latex), infection risk (five silicone, four latex), intrauterine growth restriction / small for gestational age (four silicone, two latex).			

CI confidence interval, C Control, I Intervention

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.4.a Randomised controlled trials
Outcome variable: Meconium aspiration syndrome

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention to Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention to Treat (ITT) Per protocol (PP) (as defined by authors)				
Biem 2003 Canada	RCT	300 (150+150)	1 (1+0)	299 (149+150)	PP 0/149 (0%)	PP 1/150 (0.7%)	Table 4	+/?	?/-	-
Wilkinson 2015a Australia	RCT	48 (33+15)	4 (3+1)	44 (30+14)	ITT 1/33 (3%)	ITT 0/15 (0%)		+	?	-

RCT randomised controlled trial

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.4.b Observational studies
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 *
				Outpatient Induction of Labour	Inpatient Induction of Labour				
Stock 2014 United Kingdom	Cohort study	1536 N=907+85 I=811 C=85		1/811 (0.12%)	0/85 (0%)		+	?	-

C Control, I Intervention

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.5.a Randomised controlled trials
Outcome variable: Need for respiratory support

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Beckman 2019 Australia	RCT	695 (347+348)	44 (11+13)	448 (215 + 233)	PP 1/215 (0.5%) p=0.297	PP 0/233 (0%)	Outcome specified "Intubation/ cardiac compressions".	+/?	?/-	-
Wilkinson 2015a Australia	RCT	48 (33+15)	4 (3+1)	44 (30+14)	ITT 1/33	ITT 0/15	Outcome specified "Respiratory problems".	+	?	-
Wilkinson 2015b Australia	RCT	827 or 823 (411+416) (408+415) (407+414)	2 (1+1)	425 (215+210) (168+210)	ITT 16/407 PP 10/215	ITT 18/414 PP 9/210	Outcome specified "Respiratory problems".	+	?	-

RCT randomised controlled trial

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.5.b Observational studies
Outcome variable: Need for respiratory support

* + 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 *
				Outpatient Induction of Labour	Inpatient Induction of Labour				
Chang 2005 USA	Cohort study	583 N=293 I=177 C=96	20	5/177 (2.8%)	7/96 (7.1%)	"neonatal breathing difficulties"	?	-	-

C Control, I Intervention

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.6.a Randomised controlled trials
Outcome variable: Neonatal infection

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Beckman 2019 Australia	RCT	695 (347+348)	44 (11+13)	448 (215 + 233)	PP 26/215 (12.1%) RR 0.69 (95% CI 0.44-1.08) p=0.103 PP Table S1 "fetal infection" Suspected 24 (11.2%) p=0.041 Proven 2 (0.9%) p=0.140	PP 41/233 (17.6%) PP Table S1 "fetal infection" 42 (18.0%) 0 (0%)	Defined as "neonatal antibiotic use".	+/?	?/-	-
Biem 2003 Canada	RCT	300 (150+150)	1 (1+0) According to footnote table 2	299 (149+150)	PP 8/149 (5%)	PP 5/150 (3%)	Defined as "antibiotics pending septic workup", "pneumonia and VSD" or "pneumonia from GBS".	?	+	-
Wilkinson 2015a Australia	RCT	48 (33+15)	4 (3+1)	44 (30+14)	ITT 1/33	ITT 2/15	Defined as "febrile or given antibiotics". ("These were individually reviewed and complete blood count and blood cultures showed no lymphocytosis or definitive evidence of infection.")	+	?	-
Wilkinson 2015b Australia	RCT	827 or 823 (411+416) (408+415) (407+414)	2 (1+1)	425 (215+210) (168+210)	ITT 14/407 PP 7/215	ITT 11/414 PP 5/210	Defined as "Infection".	+	?	-

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

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.6.b Observational studies
Outcome variable: Neonatal 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 *
				Outpatient Induction of Labour	Inpatient Induction of Labour				
Chang 2005 USA	Cohort	583 N=293 I=177 C=96	20	1/177 (0.4%)	0/96 (0%)	Outcome given ”neonatal suspected sepsis”.	?	-	-
Kruit 2016 Finland	Case series	204		Primiparous 12/115 (10.4%) p=0.48 Multiparous 0/70 p=0.07					
McGee 2019 Australia	Case series	534		9/534		Derived from table 4. In tabel 4 the sum of participants is 540 although the authors in all other tables and figures state 534 as total number of participants.			

C Control, I Intervention

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.7.a Randomised controlled trials
Outcome variable: Neonatal seizures

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Beckman 2019 Australia	RCT	695 (347+348)	44 (11+13)	448 (215 + 233)	0/347	0/348		+/?	?/-	-
Kuper 2018 USA	RTC	129 (65+64)	12 (1+11)	117 (64+53)	0/65	0/65		?	?	-
Wilkinson 2015a Australia	RCT	48 (33+15)	4 (3+1)	44 (30+14)	0/33	0/15		+	?	-
Wilkinson 2015b Australia	RCT	827 or 823 (411+416) (408+415) (407+414)	2 (1+1)	378 (168+210)	3/407 (0.74 %) PP: 3/215 (1.4%)	3/414 (0.72%) PP: 2/210 (0.95%)	Normal development at 2 years	+	?	-

RCT randomised controlled trial

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.8.a Randomised controlled trials
Outcome variable: Composite neonatal mortality and morbidity

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Injtention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Beckmann 2019 Australia	RCT	695 (347+348)	44 (11+13)	448 (215+233)	ITT: 40 (11.9%) RR 0.66 (95% CI 0.46-0.96) p= 0.029 Per protocol: 40 (18.6%) RR 0.77 (95% CI 0.51 to 1.02) p= 0.07	ITT: 60 (17.9%) Per protocol: 60 (25.8%)	Composite outcome included any of the following: nursery admission, intubation/ cardiac compressions, acidaemia, hypoxic ischaemic encephalopathy, seizure, infection, pulmonary hypertension, stillbirth or death	+/?	?/-	?

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

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.8.b Observational studies
Outcome variable: Composite neonatal; morbidity and 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 *
				Outpatient Induction of Labour	Inpatient Induction of Labour				
Cundiff 2017 Canada	Cohort study	1179 N=1179 I=611 C=568		Composite neonatal safety 84/611 (14%) p= 0.137	62/568 (11%)	Composite neonatal safety outcome that included 5-minute Apgar score <7 and NICU admission >12 hours or transfer to level III nursery.	?	?	?

C Control, I Intervention

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.9.a Randomised controlled trials
Outcome variable: Birth trauma

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Kuper 2018 USA	RCT	129 (65+64)	12 (1+11)	117 (64+53)	1 (2%) RR 0.5 95% CI 0.05–5.3 p= 0.62	2 (3%)	Brachial plexus injury (n=1) Cephalohematoma (n=1) Both scalp laceration and a cephalohematoma (n=1)	?	?	-

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

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.1.10.b Observational studies
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=	With-drawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Outpatient Induction of Labour	Inpatient Induction of Labour				
Chang 2005 USA	Cohort study	583 N=293 I=177 C=96	20	0 (0%)	0 (0%)		-	-	-

C control, I Intervention

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.1.a Randomised controlled trials
Outcome variable: Hysterectomy from any complication resulting from childbirth

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Biem 2003 Canada	RCT	300 (150+150)	1 (1+0)	299 (149+150)	ITT: 0/150	2/150	Mentioned in discussion, not an outcome	?	+	-

RCT randomised controlled trial

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.2.a Randomised controlled trials
Outcome variable: Intensive care admission

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

Author year country	Study design	Number of patients randomied n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Wilkinson 2015b Australia	RCT	827 or 823 (411+416) (408+415) (407+414)	449 (243+206)	378 (168+210)	2/407 (0.005%)	0/416	Not deemed due to induction PP haemorrhage Eclampsia	+	?	-

RCT randomised controlled trial

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.3.a Randomised controlled trials
Outcome variable: Unplanned home delivery

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) "Per protocol" (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) "Per protocol" (PP) (as defined by authors)				
Beckman 2019 Australia	RCT	695 (347+348)	44 (11+13)	448 (215+233)	ITT: Returned to birth suite earlier than scheduled: 60/215 (27.9%) p= 0.921 Baby born before arrival: 1/60 (1.6 %)	ITT: 66 (28.2%) 0 (0%)		+/?	?/-	-
Wilkinson 2015b Australia	RCT	827 411+416	2 (1+1)	425 (215+210)	ITT: 1/407 Did not receive PGE2 gel	ITT: 1/414 Did not receive PGE2 gel		+	?	-

RCT randomised controlled trial

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.3.b Observational studies
Outcome variable: Unplanned home 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 *
				Outpatient Induction of Labour n (%)	Inpatient Induction of Labour n (%)				
Stock 2014 United Kingdom	Cohort study	1536 N= 907+85 I=811 C=85		0 (0%)	0 (0%)		+	?	-
Barnfield 2018 United Kingdom	Case series	502		1/400 (0.25%)		400 patients went home following Prostin administration.			

C control, I Intervention

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.4.a Randomised controlled trials
Outcome variable: Time from induction of labour to delivery

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Beckmann 2019 Australia	RCT	695 (347+348)	44 (11+13)	448 (215 + 233)	PP median (inter-quartile range) 24.2 h (19.9-28.2) p= 0.722	PP 23.7 h (16.2-31.9)	Data in suppl table 2 Outpatient: Balloon Inpatient: prostaglandin	+/?	?/-	
Biem 2003 Canada	RCT	300 (150+150)	1 (1+0) According to footnote table 2	299 (149+150)	PP median (95% CI) 21.4 hr (19.2-23.5) p= 0.54	PP 20.7 hr (18.4-23.0)		?	+	
Henry 2013 Australia	RCT	101 (50+51)	13 (11+2)	88 (39+49)	ITT mean (SD) 33.5 hr (11.2) p= 0.402	ITT 31.1 hr (16.3)	Outpatient: Balloon Inpatient: prostaglandin	?	?	
Kuper 2018 USA	RCT	129 (65+64)	12 (1+11)	117 (64+53)	ITT mean (SD) 29.8 hr (9.3) p= 0.28	ITT 31.5 hr (8.6)	Outcome specified "total duration from the study visit to delivery" Outpatient: Balloon only Inpatient: Balloon and concomitant oxytocin infusion	?	?	
Wilkinson 2015a Australia	RCT	48 (33+15)	4 (3+1)	44 (30+14)	ITT mean (SD) 24 h 51 min (5hr 32 min)	ITT 29 h 01 min (8 h 5 min)	Time given for vaginal deliveries only: Mean (SD) time catheter inserted to vaginal delivery (Excludes n = 1 outpatient case whose management changed & delivered spont 5 days after catheter removal)	+	?	

CI confidence interval, RCT randomised controlled trial, SD standard deviation

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.5.a Randomised controlled trials
Outcome variable: Uterine hyperstimulation

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Beckman 2019 Australia	RCT	695 (347+348)	44 (11+13)	448 (215 + 233)	PP: 0/215	PP: 7/233 (3%) p=0.029	Balloon in outpatients and PEG in inpatients Hyperstimulations not defined.	+/?	?/-	+
Biem 2003 Canada	RCT	300 (150+150)	1 (1+0)	299 (149+150)	15/149 (10%) p=0.99	15/150 (10%) p=0.99	Hyperstimulation and non-reassuring F hr (4 resp 1) Defined as 5 or more contractions/10 min	?	+	+
Henry 2013 Australia	RCT	101 (50+51)	13 (11+2)	88 (39+49)	0/50 (0%)	2/51 (2%) p=0.157	5 or more contractions/10 min	?	?	+
Wilkinson 2015a Australia	Pilot RCT	48 (33+15)	4 (3+1)	44 (30+14)	1/33 (3%)	1/15 (7%)	6 or more contractions/10 min	+	?	+
Wilkinson 2015b Australia	RCT	827 or 823 (411+416) (408+415) (407+414)	2 (1+1)	378 (168+210)	7/407 (1.7%) RR=1.19 (0.40-3,50) 0.91	6/414 (1.4%)	6 or more contractions/10 min	+	?	+

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

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.5.b Observational studies
Outcome variable: Uterine hyperstimulation

* + 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 *
				Outpatient Induction of Labour	Inpatient Induction of Labour				
Cundiff 2017 Canada	Cohort study	1179 N=1179 I=611 C=568		32/611(5%)	45/568 (8%) p= 0.290	Increased uterine activity	?	?	+
Stock 2014 United Kingdom	Cohort study	1536 N= 907+85 I=811 C=85		19/907 (2.1%) (95% CI 1.3 to 3.2)	0/85	6 more cases that were related to second dose or oxytocin	+	?	+

CI confidence interval, C control, I Intervention

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.6.a Randomised controlled trials
Outcome variable: Mode of delivery

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Beckman 2019 Australia	RCT	695 (347+348)	44 (11+13)	448 (215 + 233)	PP CS 70 (32.6%) p=0.138 Instrumental VB 35 (16.3%) p=0.989 Unassisted VB 110 (51.2%) p=0.151	PP 60 (25.8%) 37 (15.9%) 136 (58.4%)		+/?	?/-	?
Biem 2003 Canada	RCT	300 (150+150)	1 (1+0) According to footnote table 2	299 (149+150)	PP CS 35/149 (23%) p=0.918 Instrumental VB 32/149 (21%) p=0.287 Unassisted VB 83/149 (56%) p=0.605	PP 37/150 (25%) 24/150 (16%) 89/150 (59%)		?	+	?
Henry 2013 Australia	RCT	101 (50+51)	13 (11+2)	88 (39+49)	ITT CS 17/50 (34%) p=0.620 VB 33/50 (66%) OR 0.85 (95% CI 0.35-1.87) p=0.620 Instrumental VB 18/50 (36%) OR 2.00 (95% CI 0.85-4.9) p=0.109 Unassisted VB 15/50 (30%) p=0.051	ITT 15/51 (29%) 36/51 (71%) 11/51 (22%) 25/51 (49%)		?	?	?

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.6.a Randomised controlled trials
Outcome variable: Mode of delivery

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Kuper 2018 USA	RCT	129 (65+64)	12 (1+11)	117 (64+53)	ITT CS 2/65 (3%) RR 0.7 (95% CI 0.1-3.8) p=0.68 Instrumental VB 5/65 (8%) RR 0.8 (95% CI 0.3-2.6) p=0.73 Unassisted VB 58/65 (89%) p=0.764	ITT 3/64 (5%) 6/64 (9%) 55/64 (86%)	Only parous women included.	?	?	?
Wilkinson 2015a Australia	RCT	48 (33+15)	4 (3+1)	44 (30+14)	ITT CS 6/33 (18.2%) risk difference of −15.1% (95% CI −42.4 – 12.1) p=0.431 Instrumental VB 11/33 (33.3%) p=0.549 Unassisted VB 16/33 (48.5%) p=0.846	ITT 5/15 (33.3%) 3/15 (20%) 7/15 (46.7%)		+	?	?
Wilkinson 2015b Australia	RCT	827 or 823 (411+416) (408+415) (407+414)	2 (1+1)	425 (215+210) (168+210)	ITT CS 91/407 (22.3%) p=0.906 Instrumental VB 85/407 (20.9%) p=0.703 Unassisted VB 231/407 (56.8%) p=0.627	ITT 95/414 (22.9%) 92/414 (22.2%) 227/414 (54.8%)		+	?	?

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.6.a Randomised controlled trials
Outcome variable: Mode of delivery

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
					Inpatient vs outpatient: risk difference -0.59% (-0.3 to 5.1) RR 0.97 (95% CI 0.76 - 1.25) PP CS 51/215 (23.7%) p=0.557 Instrumental VB 49/215 (22.8%) p=0.293 Unassisted VB 115/215 (53.5%) p=0.743 Inpatient vs outpatient: risk difference -2.9% (-11.2 to 5.3) RR 0.89 (95% CI 0.64 - 1.24)	PP 56/210 (26.6%) 46/210 (21.9%) 108/210 (51.4%)				

CI confidence interval, RCT randomised controlled trial, RR relative risk, CS Cesarian section, VB Vaginal birth

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.6.b Observational studies
Outcome variable: Mode of 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 *
				Outpatient Induction of Labour	Inpatient Induction of Labour				
Chang 2005 USA	Cohort study	583 N=293 I=177 C=96	20	CS 25/177 (14.1%) p=0.408 Instrumental VB 12/177 (6.8%) p= 0.018 Unassisted VB 142/177 (80.2%) RR 1.27 (95% CI 1.04-1.55) p=0.004	18/96 (18.8%) 16/96 (16.7%) 61/96 (63.5%)		?	-	?
Clarke 2017 United Kingdom	Cohort study	90 I=40 C=50 (10 excluded who did not receive propess)		CS 13/40 (32.5%) p=0.621 Instrumental VB 10/40 (25%) p=0.802 Unassisted VB 17/40 (42.5%) p=1.00	10/40 (25%) 12/40 (30%) 18/40 (45%)		?	-	?
Cundiff 2017 Canada	Cohort study	1179 N=1179 I=611 C=568		CS 229/611 (38%) p= 0.857 Instrumental VB 135/611 (22%) p= 0.249 Unassisted VB 247/611 (40%) p= 0.261	210/568 (37%) 110/568 (19%) 248/568 (44%)		?	?	?

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.6.b Observational studies
Outcome variable: Mode of 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 *
				Outpatient Induction of Labour	Inpatient Induction of Labour				
Stock 2014 United Kingdom	Cohort study	1536 N=907+85 I=811 C=85		CS 319/907 (35.2% (95% CI 32.1–38.3)) p= 0.19 Instrumental VB 325/907 (35.8% (95% CI 32.8–39.0) p= 0.12 Unassisted VB 263/907 (29.0% (95% CI 26.1–32.0)) p= 0.80	36/85 (42.4% (95% CI 32.2–53.0)) 23/85 (27.0% (95% CI 18.4–37.2)) 26/85 (30.6% (95% CI 21.5–41.0))		+	?	?
Kruit 2016 Finland	Case series	204 I=204		Nulliparous CS 44/115 (38.3%) Multiparous CS 15/70 (21.4%)		Induction with balloon only			
McGee 2019 Australia	Case series	534 I=534		CS 211/534 (40%) Instrumental VB 77/534 (14%) Unassisted VB 246/534 (46%)					

CI confidence interval, CS Caesarean section, C control, I Intervention, RR relative risk, VB Vaginal birth

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.7.a Randomised controlled trials
Outcome variable: Haemorrhage > 1000 ml

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) "Per protocol" (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Kuper 2018 USA	RCT	129 (65+64)	12 (1+11)	118 (65+53)	ITT: Postpartum haemorrhage 0 (0%) p= 0.50	1 (2%)		?	?	-

RCT randomised controlled trial

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.7.b Observational studies
Outcome variable: 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 *
				Outpatient Induction of Labour n (%)	Inpatient Induction of Labour n (%)				
Stock 2014 United Kingdom	Cohort study	1536 N=907+85 I=811 C=85		114/907 (12.6%) 95% CI 10.6-14.9 p= 0.51	8/85 (9.4%) 95% CI 4.6-17.7		+	?	?
Barnfield 2018 United Kingdom	Case series	502		16.9%		Postpartum haemorrhage > 1000 ml was measured after caesarean section.			
Kruit 2016 Finland	Case series	204		Nulliparous (115+163) Vaginal delivery: 8 (11.3%) p=0.47 Caesarean delivery: 17 (38.6%) p=0.65 Multiparous (70+94) Vaginal delivery: 7 (12.7%) p=0.38 Caesarean delivery: 3 (20.0%) p=1.00					

CI confidence interval, C control, I Intervention

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.8.a Randomised controlled trials
Outcome variable: Maternal infection

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Beckman 2019 Australia	RCT	695 (347+348)	44 (11+13)	448 (215+233)	PP: Suspected: 26/215 (12.1%) p=0.889 Proven: 0 (0%) p=0.336	PP: 27/233 (12.0%) 1 (0.4%)		+/?	?/-	-
Kuper 2018 USA	RCT	129 (65+64)	12 (1+11)	118 (65+53)	ITT: Chorioamnionitis 3/65 (5%) RR 1.0, 95% CI 0.2–4.7 p=> 0.99 Endometritis 1/65 (2%) RR 1.0, 95% CI 0.1–15.4 p=>0.99	 3/64 (5%) 1/64 (2%)		?	?	-

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

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.8.b Observational studies
Outcome variable: Maternal 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 *
				Outpatient Induction of Labour n (%)	Inpatient Induction of Labour n (%)				
Kruit 2016 Finland	Case series	485 (204+281)		Nulliparous n=115 Intrapartum infection: 8 (7.0%) p=0.62 Postpartum infection: 7 (6.1%) p=0.21 Endometritis: 4 (57.1%) Urinary tract infection: 0 (0%) Wound infection: 2 (28.6%) Multiparous n=70 Intrapartum infection: 4 (5.7%) p=0.40 Postpartum infection: 2 (2.9%) p=1.00 Endometritis: 1 (50%) Urinary tract infection: 1 (50%) Wound infection: 0 (0%)					

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.9.a Randomised controlled trials
Outcome variable: Length of hospital stay

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Beckman 2019 Australia	RCT	695 (347+348)	44 (11+13)	448 (215+233)	ITT: (Hours) median (inter-quartile range) 69.0 (44.2-85.3) p= 0.039	ITT: 74.5(53.5-94.5)	Induction methods: Double balloon catheter to outpatients and vaginal PGE2 to inpatients.	+/?	?/-	?
Biem 2003 Canada	RCT	300 (150+150)	1 (1+0)	299 (149+150)	ITT: (Hours) median 73.6 p=0.11	ITT: 75.6		?	+	?
Henry 2013 Australia	RCT	101 (50+51)	13 (11+2)	88 (39+49)	ITT (Hours) mean (SD) 96 (38) RR (95% CI) −9 (−24 to 7) p=0.267	ITT 105 (38)	Induction methods: Foley catheter to outpatients and vaginal PGE2 to inpatients.	?	?	?
Kuper 2018 USA	RCT	129 (65+64)	12 (1+11)	118 (65+53)	ITT (Days): mean (SD) 2.6 (0.5) p=0.29 (Hours) mean (SD) 62.4 (12)	ITT 2.7 (0.6) 64.8 (14.4)	Induction methods: Foley catheter to outpatients and Foley catheter and concomitant oxytocin infusion to inpatients.	?	?	?
Wilkinson 2015a Australia	Pilot RCT	48 (33+15)	4 (3+1)	44 (30+14)	ITT (Hours, minutes) mean (SD) 14 h 15 min (7 h 20 min)	ITT 21 h 27 mins (5 h 18 min)		+/?	?	?/-

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.9.a Randomised controlled trials
Outcome variable: Length of hospital stay

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results				Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)		Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)					
Wilkinson 2015b Australia	RCT	827 or 823 (411+416) (408+415) (407+414)	2 (1+1)	425 (215+210) (168+210)	ITT (Days) mean (SD) 3.3 (1.6) RR (95% CI) 1.64 (1.19-2.28) (Hours) mean (SD) 79.2 (38.4) RR (95% CI) 39.36 (28.56-54.72)	Women recieving Pge mean (SD) 3.3 (1.7) RR (95% CI) 1.64 (1.19-2.28) mean (SD) 79.2 (40.8) RR (95% CI) 39.36 (28.56-54.72)	ITT 3.3 (1.5) (Hours) 79.2 (36)	Women recieving Pge 3.3 (1.5) 79.2 (36)		+	?/-	?/-

CI confidence interval, RCT randomised controlled trial, RR relative risk, SD standard deviation

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.10.a Randomised controlled trials
Outcome variable: Maternal satisfaction

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Biem 2003 Canada	RCT	300	1 (1+0)	299 (149+150)	High satisfaction (rating ≥ 7): 83 (56%); p= 0.008 Satisfaction initial 12 hours: Mean (SD): 6.6 ±2.4 Median: 7.0 p= 0.27 Overall satisfaction: Mean (SD): 7.6 ± 2.1 Median: 9 p= 0.33	High satisfaction (rating ≥ 7): 59 (39%) Satisfaction initial 12 hours: Mean (SD): 5.7 ± 2.5 Median: 5.7 Overall satisfaction: Mean (SD): 7.4 ± 2.4 Median: 8		?	+	-
Turnbull 2012 Australia	RCT substudy 7-week postpartum questionnaire	827 (411+416)	2 (1+1)	425 (215+210) Filled in 7-week postpartum questionnaire 620 (306+314)	**Per Protocol** **Social support** (n =305) 4.17 (0.66) Mean diff-0.25, 95% CI 0.13 to 0.37) **Environment** (n =304) 4.24 (0.75) -0.06 (0.18 to 0.06) **Self-efficacy** (n=305) 3.60 (0.84) -0.17 (0.03 to 0.30)	(n =313) 3.92 (0.80) (n=312) 4.18 (0.73) (n=312) 3.77 (0.85)	5-point lickert scale Excluded: two women with poor pregnancy outcome Approximately 20% of women who received outpatient priming gel did not go home because of non-reassuring electronic fetal monitoring or because they changed their mind after receiving the gel.	-	-	-

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.10.a Randomised controlled trials
Outcome variable: Maternal satisfaction

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
					Readiness (n =304) 3.18 (0.97) -0.22 (0.07 to 0.37) **Stress** (n=304) 3.37 (0.93) -0.22 (-0.07 to -0.36) **Control** (n=304) 3.63 (0.81) -0.13 (-0.003 to -0.26) **Information** (n=304) 3.80 (0.76) -0.18 (-0.06 to -0.29) **Safety** (n=305) 3.72 (0.83) -0.16 (-0.03 to -0.29) **Satisfied** (n=197) 3.83 (0.94) -0.16 (-0.33 to 0.02)	(n=310) 3.00 (0.89) (n=310) 3.16 (0.92) (n=311) 3.50 (0.80) (n=311) 3.63 (0.74) (n=311) 3.67 (0.88) (n=202) 3.67 (0.88)				

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.10.a Randomised controlled trials
Outcome variable: Maternal satisfaction

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
Henry 2013 Australia	RCT	101 (50+51)		88 (48+45)	**Felt a lot of discomfort** ***At insertion*** 26 (55%) OR or mean diff (95% CI) OR 2.9 (1.2-6.9) p= 0.14 ***4-6 h later*** 11 (23%) p=0.18 ***Overall cervical ripening*** 10 (26%), n=39 OR 0.25 (0.10-0.64) p=0.003 **Able to cope with discomfort** ***At insertion*** 43 (92%) p=0.914 ***4-6 h later*** 37 (77%) p=0.862 ***Overall cervical ripening*** 37 (95%), n=39 p= 0.002 **Would choose this method again** 31 (65%) OR 2.5 (1.1-5.8) p=0.31	13 (29%) 16 (36%) 25 (58%), n=43 39 (87%) 34 (76%) 29 (67%), n=43 19 (42%)	Outpatient group recieved Foley catheter Inpatient group recieved PGE2	?	?	-

Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.10.a Randomised controlled trials
Outcome variable: Maternal satisfaction

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

Author year country	Study design	Number of patients randomised n= (outpatient+ inpatient)	With-drawals n= (outpatient+ inpatient)	Received allocated treatment n= (outpatient+ inpatient)	Results		Comments	Directness *	Study limitations *	Precision *
					Outpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)	Inpatient Induction of Labour Intention To Treat (ITT) Per protocol (PP) (as defined by authors)				
					Took prescribed sleeping tablets 31 (65%) p=0.648 **Hours of sleep (before and/or after tablets** 5.8 (+/- 2.0) p= 0.01 **Able to relax** 39 (100%) OR 1.5 (1.2-1.9) p=0.001 **Able to rest** 39 (100%) OR 1.7 (1.3-2.1) p=0.001 **Worried the IOL not safe** 2 (5%) OR 0.14 (0.03-0.67) p=0.006 **Embarrassed by catheter/gel** 2 (5%) p=0.920	27 (61%) 3.4 (+/- 2.9) 28 (65%) 26 (61%) 12 (28%) 2 (5%)	Questions to women who received Foley (n=39) and PGE2 (n=43)			

CI confidence interval, RCT randomised controlled trial, OR odds ratio

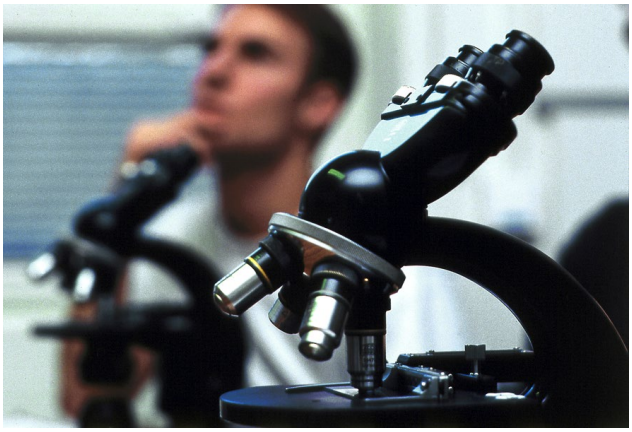
Project: Safety and effectiveness of outpatient compared with inpatient induction of labour in singleton uncomplicated pregnancies
Appendix 4.2.11.b Observational studies
Outcome variable: Maternal experience

* + 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 *
				Outpatient Induction of Labour	Inpatient Induction of Labour				
Clarke 2017 United Kingdom	Cohort Study	90 (40+50)		Having experienced the home option, women reported their experiences positively Women who went home with Propess were asked whether they had appreciated the opportunity to return home. Some of the comments received: I had only been back home for a few hours when I started to get intense tightening's, but it was nice to be in the comfort of my own home with my partner. I don't think that you should extend the time of living 30 minutes from the hospital as I would have struggled with the distance whilst contracting. In my case, the pessary wasn't effective so it was great to be at home for the first 24 hours.		No description of data collection Free-text answers? No qualitative analysis	-	-	

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

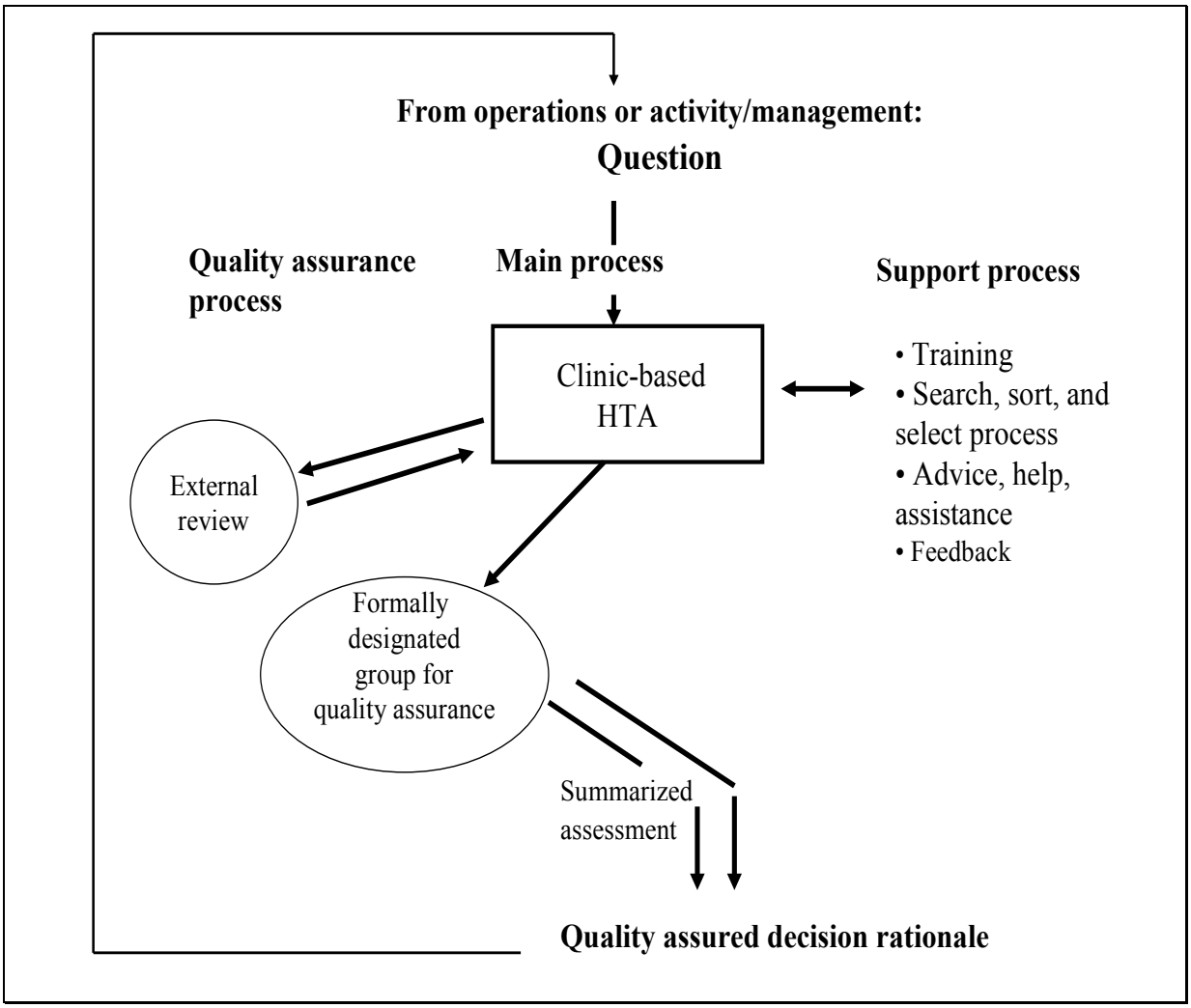
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended 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

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