Göteborg, 2021

Management of late term pregnancy

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, fredagen den 12 mars 2021, klockan 13.00

av Mårten Alkmark

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Avhandlingen baseras på följande delarbeten

I. Wennerholm UB, Saltvedt S, Wessberg A, Alkmark M, Bergh C, Brismar Wendel S, Fadl H, Jonsson M, Ladfors L, Sengpiel V, Wesström J, Wennergren G, Wikström AK, Elden H, Stephansson O, Hagberg H. Induction of labour at 41 weeks versus expectant management and induction of labour at 42 weeks (SWEdish Postterm Induction Study, SWEPIS): multicentre, open label, randomised superiority trial. *BMJ* (Clinical research ed). 2019;367:l6131.

II. Alkmark M, Keulen J.K.J, Kortekaas J.C, Bergh C, van Dillen J, Duijnhoven R.G, Hagberg H, Mol B.W, Molin M, van der Post J.A.M, Saltvedt S, Wikström AK, Wennerholm UB, de Miranda E. Induction of labour at 41 weeks or expectant management until 42 weeks: a systematic review and an individual participant data meta-analysis of randomised trials. *PLoS Medicine* 2020;17(12):e1003436.

III. Alkmark M, Wennerholm UB, Saltvedt S, Bergh C, Carlsson Y, Elden H, Fadl H, Jonsson M, Ladfors L, Sengpiel V, Wesström J, Hagberg H, Svensson M. Induction of labour at 41 weeks of gestation versus expectant management and induction of labour at 42 weeks of gestation: A cost-effectiveness analysis. *Submitted, pending decision.*

IV. Alkmark M, Carlsson Y, Brismar Wendel S, Elden E, Fadl H, Jonsson J, Ladfors L, Saltvedt S, Sengpiel V, Wessberg A, Wikström AK, Hagberg H, Wennerholm UB. Efficacy and safety of oral misoprostol versus transvaginal balloon catheter for labor induction: An observational study within the SWEdish Postterm Induction Study (SWEPIS). *Under revision.*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

Göteborg, 2021

Management of late term pregnancy

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Background: The optimal time point to intervene and induce labour in women with a low-risk pregnancy, in order to decrease the perinatal adverse outcome, is up for debate. Some advocate for induction of labour (IOL) at 41 gestational weeks (GW) and others for expectant management (EM) until 42 GW.

Aim: To clarify, in women with a low-risk singleton pregnancy, if a policy of IOL at 41 GW (late term) compared with EM until 42 GW (postterm) was superior, in terms of neonatal and maternal outcomes, as well as health economic aspects. Furthermore, different methods of IOL in late term/postterm pregnancies were assessed.

Material and methods: *Paper I* was a Swedish multicentre register-based randomised controlled trial in women with a low-risk late term/postterm singleton pregnancy (n=2 760) comparing IOL at 41 GW with EM until 42 GW. The trial was conducted between May 2016 and October 2018. Primary outcome was a composite of perinatal mortality and morbidity. *Paper II* was a one-step individual participant data (IPD) meta-analysis (n=5 161 for aggregate data and 4 561 for IPD) and included trials comparing IOL in women with a low-risk singleton pregnancy at 41 GW with EM until 42 GW. Primary outcome was a composite of perinatal morbidity and mortality. Subgroup analysis was performed on maternal age, body mass index and parity. *Paper III* was a cost-effectiveness analysis alongside Paper I (n=2 746). Primary outcomes were costs per gained life year (LY) and quality adjusted life year (QALY). *Paper IV* was a prospective cohort study on efficacy, safety and women's childbirth experience of IOL with oral misoprostol (OM) (n=744) compared with transvaginal balloon catheter (TVBC) (n=469). Women included in Paper I, who needed cervical ripening for IOL, were assessed. Primary efficacy outcome was vaginal delivery within 24 hours, primary safety outcomes were a composite of neonatal mortality and morbidity and a composite of maternal mortality and morbidity. Women's childbirth experience was measured with the Childbirth Experience Questionnaire (CEQ 2.0).

Results: *Paper I:* The primary outcome did not differ between the groups. However, the trial was truncated early due to safety reasons because a significant decreased perinatal mortality was seen in the IOL group (p=0.03). Similar results in both groups were reported regarding mode of delivery and maternal adverse outcomes, except endometritis. *Paper II:* Three trials were eligible and two contributed with IPD. The primary outcome was significantly lower in the IOL group, relative risk (RR) 0.43 (95 % confidence interval [CI] 0.21 to 0.91), as were perinatal mortality, Peto odds ratio 0.21 (95 % CI 0.06 to 0.78) and admission to neonatal care ≥4 days, RR 0.52 (95 % CI 0.32 to 0.85). Similar results in both groups were reported regarding mode of delivery and maternal adverse outcomes. The primary outcome was significantly lower in the IOL group in nulliparous, but not in parous women. *Paper III*: The incremental cost-effectiveness ratio for IOL compared with EM was €545 per LY (95 % CI ranging from lower costs and better health outcomes [dominant] to €4 002) and €623 per QALY (95 % CI dominant to €4 586). *Paper IV:* Vaginal delivery within 24 hours was significantly lower in the OM group compared with the TVBC group, adjusted RR 0.76 (95 % CI 0.64; 0.89). Primary neonatal and maternal safety outcomes did not differ between groups. Women's childbirth experience was positive overall and similar in the groups.

Conclusion: There are medical benefits of IOL at 41 GW compared with EM until 42 GW and it is cost-effective. TVBC was slightly more effective regarding efficacy. Women approaching 41+0 GW should receive unbiased information regarding benefits and risks with IOL at 41+0 GW compared with EM in order to make an informed decision for herself and her unborn infant.

Keywords: Induction of labour, late term pregnancy, postterm pregnancy, stillbirth, perinatal mortality, cost-effectivenes.

ISBN: 978-91-8009-192-3 (TRYCK) http://hdl.handle.net/2077/67129
ISBN: 978-91-8009-193-0 (PDF)