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Effect of intrapartum hyoscine butylbromide and sodium bicarbonate on spontaneous vaginal birth in nulliparous women after induction of labour (SAINT): multicentre randomised placebo controlled factorial trial

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2026;395:e101069
http://dx.doi.org/10.1136/bmj-2026-101069

Accepted: 07 October 2026

ABSTRACT

OBJECTIVE

To determine whether intrapartum hyoscine butylbromide, sodium bicarbonate, and their combination increase the rate of spontaneous vaginal birth in nulliparous women undergoing induction of labour.

DESIGN

Multicentre, randomised, double blind, placebo controlled, 2×2 factorial phase 3 trial (SAINT).

SETTING

11 Norwegian hospitals providing comprehensive obstetric care.

PARTICIPANTS

Nulliparous women aged 18-50 years with a singleton live fetus in cephalic presentation at term with an indication for induction of labour.

INTERVENTIONS

Participants were randomly assigned (1:1:1:1) to oral sodium bicarbonate (4×1 g per dose) plus intravenous hyoscine butylbromide (20 mg per dose), oral sodium bicarbonate plus intravenous placebo, oral placebo plus intravenous hyoscine butylbromide, or double placebo. The investigational medicinal product was administered at the onset of active labour and repeated every four hours to a maximum of three doses.

MAIN OUTCOME MEASURE

Spontaneous vaginal birth (no instrumental or caesarean delivery).

RESULTS

Between 4 January 2023 and 29 January 2025, 3094 nulliparous women were randomised, and 2963 comprised the full analysis set. Spontaneous vaginal birth occurred in 57% (422/741) in the bicarbonate plus hyoscine butylbromide arm, 61% (445/734) in the bicarbonate arm, 61% (449/741) in the hyoscine butylbromide arm, and 56% (422/747) in the double placebo arm. Marginal risk differences for spontaneous vaginal birth compared with double placebo were -0.2 (95% confidence interval -5.1 to 4.7; P=0.93) percentage points for combined treatment, 3.1 (-1.7 to 8.0; P=0.21) percentage points for bicarbonate, and 4.0 (-0.8 to 8.9; P=0.10) percentage points for hyoscine butylbromide. Serious adverse events were similar between groups, and no treatment related serious morbidity or deaths were observed.

CONCLUSIONS

No clear evidence was found that intrapartum hyoscine butylbromide, sodium bicarbonate, or their combination increased spontaneous vaginal birth compared with placebo. Although small beneficial effects cannot be excluded, the findings do not support routine intrapartum use of either agent to facilitate spontaneous vaginal birth after induction of labour.

TRIAL REGISTRATION

European Clinical Trials Database (EudraCT; 2021-000392-37); EU Clinical Trials Information System (CTIS; EU CT number 2024-511848-55-00); ClinicalTrials.gov (NCT05719467).

WHAT IS ALREADY KNOWN ON THIS TOPIC

Nulliparous women undergoing induction of labour have a relatively high occurrence of instrumental and caesarean delivery

Small trials suggest that hyoscine butylbromide might shorten labour, but evidence for an effect on mode of birth is insufficient

Two small unblinded trials suggested benefits from oral sodium bicarbonate in labour dystocia, but no trial has evaluated both agents after induction of labour

WHAT THIS STUDY ADDS

Neither agent, alone or in combination, clearly increased spontaneous vaginal birth, although small beneficial effects of either agent could not be excluded

The findings do not support routine intrapartum use of hyoscine butylbromide or sodium bicarbonate after induction of labour

Introduction

Induction of labour is common in high income settings and is done for a range of maternal and fetal indications.[1-3] In most cases, the relevant clinical alternative is expectant management with continued pregnancy until spontaneous onset of labour. For selected indications—such as hypertensive disorders of pregnancy, post-term pregnancy, prelabour rupture of membranes at term, and maternal diabetes—randomised trials have shown that induction of labour, compared with expectant management, is associated with favourable effects on maternal and neonatal endpoints, including lower rates of caesarean delivery, maternal morbidity, perinatal mortality, and composite

maternal or neonatal endpoints.[4-7] Despite these benefits in specific clinical scenarios, nulliparous women undergoing induction of labour represent a population with a high occurrence of obstetric intervention, particularly operative delivery, compared with women entering labour spontaneously.[4 8-14] This increased occurrence largely reflects the underlying maternal or fetal conditions leading to induction rather than a causal effect of the induction process itself.[13 15] As rates of induction of labour continue to rise internationally, optimising management during induced labour, especially among nulliparous women, has become a key priority in obstetric care.

Hyoscine butylbromide, an antispasmodic agent with effects on smooth muscle, has been reported in small trials to accelerate cervical dilation and shorten the duration of labour.[16-19] Sodium bicarbonate, a lactate buffer commonly used to enhance muscular performance,[20] has been hypothesised to improve uterine contractility in the context of labour dystocia.[21 22] Despite the absence of guideline endorsement, both agents are used off-label in labour wards, driven largely by physiological rationale and results from small clinical studies rather than high quality evidence of effects on mode of birth.[16 17 19 21 22] However, existing studies have important limitations; they are generally small, often open label, conducted mainly in women with spontaneous rather than induced labour, and not designed to evaluate effects on operative delivery—the outcome most relevant to contemporary obstetric decision making.[16 17 21 23] Because the two interventions act through different biological mechanisms and at different stages of labour, that they could have independent, additive effects on the risk of operative delivery seemed plausible.

We conducted a multicentre, randomised, placebo controlled, 2×2 factorial trial to determine whether intrapartum administration of hyoscine butylbromide, sodium bicarbonate, or their combination increases the rate of spontaneous vaginal birth in nulliparous women after induction of labour. Secondary objectives were to assess progress of labour and maternal and neonatal outcomes.

We hypothesised that treatment with hyoscine butylbromide, sodium bicarbonate, or their combination would increase the rate of spontaneous vaginal birth compared with placebo.

Methods

Study design

The Safe Induction of Labour Trial (SAINT) was a multicentre, randomised, double blind, placebo controlled trial with a 2×2 factorial design, conducted at 11 Norwegian hospitals providing comprehensive obstetric services (supplementary figure S1). Recruitment initially started at 10 study sites as specified in the trial protocol (version 9). An additional site within one of the hospital trusts was added during the recruitment period to enhance enrolment. This site operated under the same protocol, training, monitoring, and governance framework and did not constitute a substantive change to the trial conduct. The trial protocol and statistical analysis plan (version 1.0, dated 3 June 2025) are available as part of the supplementary materials, and the protocol has been published previously.[24] An independent data monitoring committee oversaw interim analyses of efficacy and safety. Although the trial had a 2×2 factorial randomisation structure, the main analyses were prespecified as three pairwise comparisons of each active regimen versus double placebo, consistent with a four arm, parallel group analytical framework.

Participants

Eligible participants were nulliparous pregnant women aged 18-50 years with a singleton live fetus in cephalic presentation at ≥37 weeks of gestation who had an indication for induction of labour according to national and local clinical guidelines. Indications for induction included both medical and non-medical indications accepted in routine obstetric practice. However, elective induction of labour without a recognised indication is not routinely practised in Norway.

Key exclusion criteria were known hypersensitivity to the study drugs, maternal heart disease requiring cardiac telemetry, major electrolyte abnormalities, advanced kidney disease, intestinal obstruction, myasthenia gravis, untreated glaucoma, persistent maternal or fetal tachycardia, and major fetal cardiac or gastrointestinal disease. A complete list of inclusion and exclusion criteria is provided in supplementary table S1.

Eligible women received information about the study when they were allocated a place at the maternity unit and when an indication for induction of labour had been established, in accordance with local clinical pathways. The attending obstetrician or midwife provided written and oral study information. Written informed consent was obtained before the onset of active labour and before randomisation.

Randomisation and masking

At the onset of active labour, defined as a fully effaced cervix dilated to 4 cm with regular contractions, participants were randomly assigned in a 1:1:1:1 ratio to one of the following four treatments: oral bicarbonate plus intravenous hyoscine butylbromide (hereafter referred to as bicarbonate plus hyoscine butylbromide); oral bicarbonate plus intravenous placebo (hereafter referred to as bicarbonate); oral placebo plus intravenous hyoscine butylbromide (hereafter referred to as hyoscine butylbromide); and oral placebo plus intravenous placebo (hereafter referred to as double placebo).

The randomisation sequence was computer generated in advance by the Clinical Trials Unit at Oslo University Hospital, using block randomisation with randomly varying block sizes of four and eight, stratified by study site. Concealment of allocation was ensured through centrally prepared, sequentially numbered investigational medicinal product

doi: 10.1136/bmj-2026-101069 | *BMJ* 2026;395:e101069 | the bmj

kits, packed, labelled, and sealed by the Hospital Pharmacy at Oslo University Hospital according to the randomisation schedule. At each site, participants were assigned the lowest available randomisation number, and the attending midwife administered the corresponding sealed kit. Block sizes were not disclosed to investigators or clinical staff, and allocation was therefore not predictable. Participants, clinical staff, investigators, and outcome assessors were all masked to treatment allocation.

Interventions

Midwives administered the investigational medicinal product at the onset of active labour and at four hour intervals for up to three doses during the first and second stages of labour. Each dose comprised oral sodium bicarbonate (4 g) or matching oral placebo and intravenous hyoscine butylbromide (20 mg) or matching intravenous placebo.[25 26] The full dosing schedule is provided in the trial protocol (supplementary materials). All other obstetric care followed national and local guidelines. Decisions about operative delivery were made by the clinical team according to routine practice.

Induction of labour was conducted according to Norwegian national guidelines, which define accepted indications for induction and recommended induction methods in nulliparous women. Before the start of the trial, we conducted a national alignment process to harmonise the choice and sequence of induction methods across participating centres.

In women with a Bishop score <6, induction typically started with a Foley balloon catheter for 24-36 hours, followed by oral or vaginal prostaglandins if needed. Inpatient or outpatient induction followed local practice. When the Bishop score was ≥6, amniotomy was performed, followed by oxytocin augmentation after one to three hours if adequate contractions were not established. The investigational medicinal products were administered after completion of the induction phase, on achievement of active labour, and therefore did not influence the choice or sequence of induction methods.

Oral sodium bicarbonate tablets and matching placebo tablets were manufactured by Kratab AS (Kragerø Tablettproduksjon AS, Kragerø, Norway) in accordance with Good Manufacturing Practice. The placebo tablets were formulated to match the active tablets in size, appearance, and taste. Intravenous hyoscine butylbromide was ordered from Sanofi-Aventis, and intravenous placebo (0.9% sodium chloride) was ordered from Dyckerhoff Pharma GmbH & Co KG (Köln, Germany), and both were identical in appearance and volume. Both were commercially available products manufactured in accordance with Good Manufacturing Practice.

All tablets and intravenous solutions were relabelled, blinded, and packed into sealed, sequentially numbered kits by the Hospital Pharmacy at Oslo University Hospital (Rikshospitalet). The trial used a double dummy design, in which all participants received both an oral tablet and an intravenous injection, ensuring effective masking of participants, clinical staff, investigators, and outcome assessors.

Progress of labour was assessed according to routine clinical practice at each participating site, including use of partograms and established national and local action lines. Decisions about oxytocin augmentation, amniotomy, and operative delivery were made by the attending clinical team on the basis of standard obstetric criteria. We had no trial specific definition of failed induction of labour. Indications for caesarean delivery followed routine clinical practice and national guidelines.

Trial endpoints

The primary endpoint was spontaneous vaginal birth versus operative delivery (instrumental or caesarean delivery). Key secondary endpoints included vaginal versus caesarean delivery, mode of birth (spontaneous vaginal birth, instrumental delivery, or caesarean section), time from the onset of active labour to spontaneous vaginal birth, time from the first investigational medicinal product dose to spontaneous vaginal birth, and mean cervical dilation rate from the first investigational medicinal product dose to a cervical dilation of 10 cm or a caesarean delivery. Other maternal secondary endpoints included changes in heart rate and pain score 30 minutes after the first dose of investigational medicinal product, obstetric anal sphincter injury (restricted to vaginal births), and dichotomisations of postpartum haemorrhage and urinary retention. Neonatal secondary endpoints included dichotomisations of arterial and venous cord blood pH, five minute and 10 minute Apgar scores, and admission to the neonatal intensive care unit. A complete list with specific definitions of all secondary endpoints is provided in supplementary table S2. Safety outcomes and adverse events were assessed for 24 hours after the final dose of investigational medicinal product. All secondary endpoints were prespecified in the approved trial protocol and the statistical analysis plan, both finalised before database lock and unmasking.

Endpoint selection

We selected the primary endpoint, spontaneous vaginal birth, a priori as a clinically meaningful and patient relevant endpoint that integrates labour progress and the need for obstetric intervention. The following secondary endpoints are reported as part of this study: vaginal birth, mode of birth, time from onset of active labour to spontaneous vaginal birth, time from the first study drug administration to spontaneous vaginal birth, mean cervical dilation rate, change in maternal heart rate 30 minutes after the first study drug administration, change in pain score 30 minutes after the first study drug administration, obstetric anal sphincter injury, postpartum haemorrhage >500 mL, postpartum haemorrhage >1000 mL, postpartum haemorrhage >1500 mL, urinary retention diagnosed in the delivery ward, urinary retention diagnosed

in the postnatal ward, urinary retention at hospital discharge, venous cord blood pH <7.10, venous cord blood pH <7.20, arterial cord blood pH <7.00, arterial cord blood pH <7.10, arterial cord blood pH <7.20, five minute Apgar score <7, 10 minute Apgar score <7, and admission to the neonatal intensive care unit.

Additional prespecified secondary endpoints included in the trial protocol and statistical analysis plan will be reported separately in subsequent publications. These include time from cervical dilation of 10 cm to spontaneous vaginal birth, time from start of active pushing to spontaneous vaginal birth, time from onset of active labour to cervical dilation of 10 cm, time from the first study drug administration to cervical dilation of 10 cm, total time of oxytocin administration, total amount of oxytocin administered, estimated blood loss, change in fetal heart rate 30 minutes after the first study drug administration, venous cord blood pH, arterial cord blood pH, and birth experience, including the mean overall Childbirth Experience Questionnaire score and the subscores for the dimensions of own capacity, professional support, perceived safety, and participation.

Thus, the primary and secondary endpoints in the study reflect existing core endpoint initiatives.[27] The full list of prespecified endpoints can be found in supplementary table S2.

Adverse events and safety profile

We based evaluations of harm on the incidence, intensity, and type of adverse events in addition to the patient's physical examination findings, vital signs, and potentially abnormal baseline laboratory results. Safety outcome data were registered from the first dose of investigational medicinal product until 24 hours after the last dose. We defined a serious adverse event in accordance with good clinical practice (ICH-GCP E6). Adverse events classified as serious adverse events were reported within 24 hours. Postpartum haemorrhage >1500 mL was predefined as a serious adverse event. Suspected unexpected serious adverse reactions were reported immediately to the medical monitors. All adverse events were coded using the Medical Dictionary for Regulatory Activities, version 27.1.

Statistical analysis

A 15% relative increase in spontaneous vaginal birth in any active treatment arm versus double placebo, corresponding to a risk ratio of 1.15, was prespecified as clinically meaningful. Assuming a spontaneous vaginal birth rate of 56.6% in the double placebo arm—based on contemporary Norwegian data in nulliparous women undergoing induction of labour—this corresponds to an absolute increase of approximately 8.5 percentage points (from 56.6% to 65.1%).[9] The sample size calculation was based on a two sided test of probabilities between each active treatment arm and the double placebo arm, with 80% power and a Bonferroni corrected significance level of 0.05/3 to account for the three prespecified pairwise comparisons. This yielded 710 participants per group and a total sample size of 2840 in the four arm, parallel group trial. We targeted enrolment of 3000 participants to allow for attrition. The sample size calculation and the statistical analysis, including assumption checks and alternative analyses, handling of missing data, and sensitivity analyses, are described in detail in the statistical analysis plan.

We did the main analysis of each endpoint on the full analysis set, defined as all eligible, randomised participants who received at least one investigational medicinal product dose. We also did sensitivity analyses based on the intention-to-treat set (all randomised participants) and the per protocol set (all eligible, randomised participants with no major protocol deviations) for comparison purposes to assess the robustness of the main results and their impact on the overall conclusions. Safety analyses were based on the safety set, defined as all participants who received at least one investigational medicinal product dose, including ineligible and non-randomised participants. Only participants who gave written informed consent before the onset of active labour were included in the analysis sets.

We analysed the primary endpoint by using binary logistic regression, including treatment arm as a four level categorical variable. To account for important prognostic factors, we adjusted for age, body mass index before pregnancy, main indication for induction, and study site, all included as fixed effects. We estimated marginal risk differences for spontaneous vaginal birth from the fitted covariate adjusted binary logistic regression models by averaging individual level, model based predicted comparisons over the observed sample and present them as percentage points, with 95% confidence intervals derived using the delta method. We compared the corresponding P values with the Bonferroni corrected significance level of 0.017 (0.05/3). To explore a possible effect modification between the study drugs, we did an additional analysis in which we replaced the four level categorical variable for treatment arm by the respective indicator variables for bicarbonate and hyoscine butylbromide in addition to an interaction term between the two. We analysed the dichotomous secondary endpoints similarly to the primary endpoint.

We analysed the single categorical secondary endpoint (mode of birth) by using multinomial logistic regression, with spontaneous vaginal birth as the baseline outcome category and the same covariate adjustment as for the primary endpoint. We estimated marginal risk differences for spontaneous vaginal birth, operative vaginal delivery, and caesarean delivery by averaging individual level, model based predicted comparisons from the fitted covariate adjusted regression model over the observed sample.

We analysed the continuous secondary endpoints by using linear regression (changes in maternal heart rate and pain score 30 minutes after the first investigational medicinal product dose) and median regression (mean cervical dilation rate), with the same covariate

doi: 10.1136/bmj-2026-101069 | *BMJ* 2026;395:e101069 | the bmj

adjustment as for the primary endpoint. We estimated marginal mean and median differences by averaging individual level, model based predicted comparisons from the fitted covariate adjusted regression models over the observed sample.

We analysed the time-to-event secondary endpoints by using Fine-Gray regression to account for competing risks (spontaneous vaginal birth and operative delivery), with the same covariate adjustment as for the primary endpoint. We estimated marginal sub-distribution hazard ratios for spontaneous vaginal birth by averaging individual level, model based predicted comparisons from the fitted covariate adjusted regression models over the observed sample. Analyses of time-to-event secondary endpoints used Stata/SE 19.0. We used R version 4.5.2 for analyses of all remaining endpoints.

Good clinical practice monitoring

The trial was conducted in accordance with good clinical practice, with independent monitoring conducted throughout according to a prespecified, risk based monitoring plan. Monitoring included site initiation visits before enrolment and regular on-site monitoring visits during the trial. Key elements monitored included informed consent procedures, eligibility criteria, protocol adherence, investigational medicinal product accountability, and source data verification of predefined efficacy and safety variables, including mode of birth and adverse events.

Trial oversight included an independent data monitoring committee established before enrolment of the first participant. We did an interim analysis of the primary endpoint and safety data after approximately two thirds of participants had been enrolled. We applied conservative statistical thresholds to permit early stopping for overwhelming benefit or harm, while preserving the overall type 1 error rate. We defined no formal stopping rule for futility. After review of the interim efficacy and safety data, the data monitoring committee recommended that the trial continue as planned.

Patient and public involvement

We incorporated patient and public involvement during the planning and preparatory phase of the study, as described in the approved trial protocol and the annual progress reports submitted to the funder. A user group affiliated with Oslo University Hospital contributed input on the study rationale, feasibility, and participant facing information materials, including the timing of provision of information and

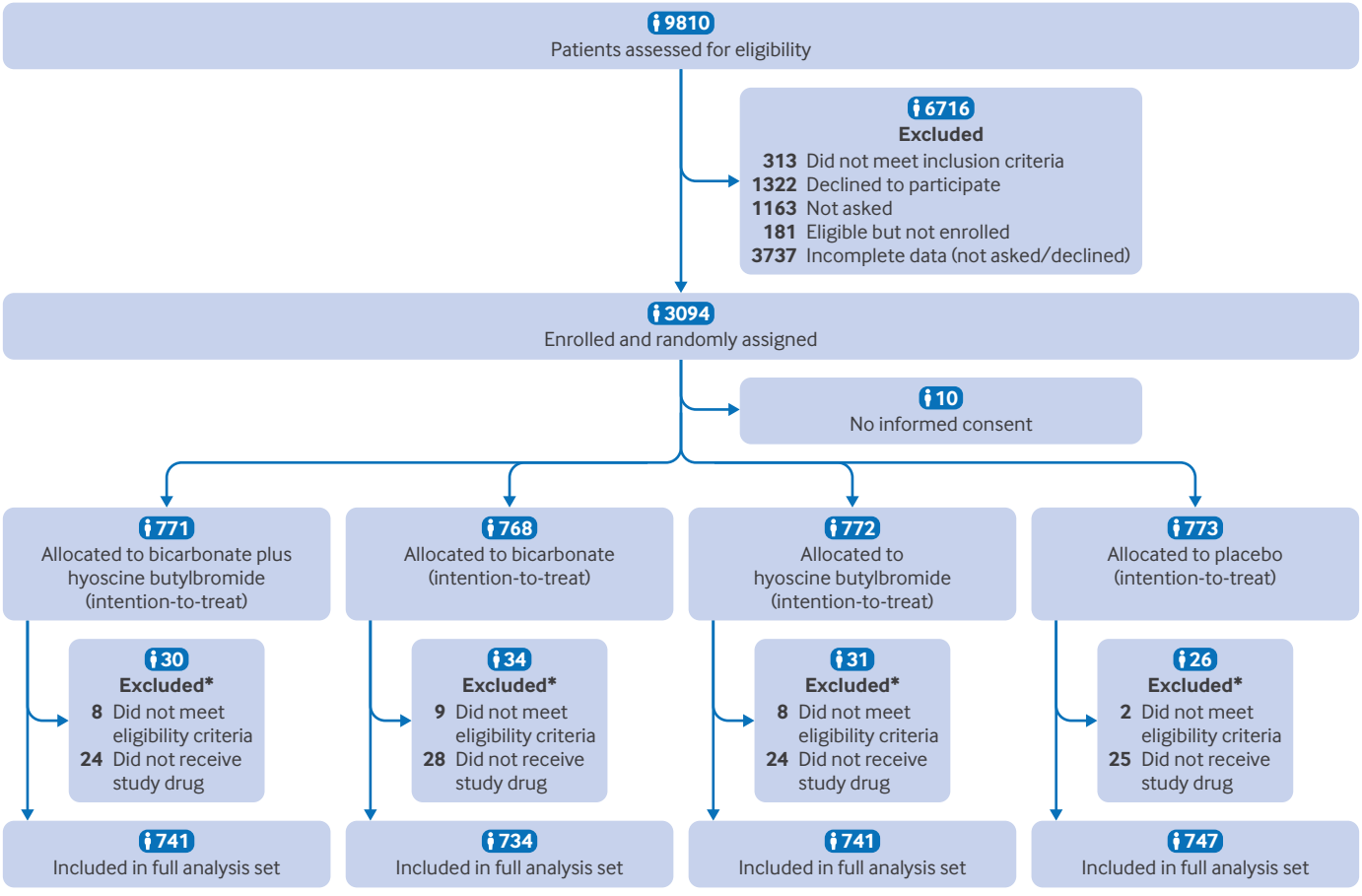

Fig 1 | CONSORT diagram. *More than one exclusion criterion possible

the inclusion of patient reported outcomes. These contributions informed the final study design before trial initiation.

In addition, professional stakeholder organisations, including the Norwegian Society of Obstetrics and Gynaecology and midwifery representatives, were involved during the preparatory phase through consultation on alignment of induction procedures, staff training, and implementation strategies, as outlined in the protocol and reported annually to the funder. These organisations contributed professional and stakeholder perspectives but did not represent patient or public user groups. Patients were consulted about experiences with the study drugs during the trial but were not involved in recruitment, conduct of the trial, analysis, or interpretation of results. We acknowledge this as a limitation.

Results

Characteristics of participants

Between 4 January 2023 and 29 January 2025, 9810 nulliparous women scheduled for induction were screened; 3094 consented and were randomised, and 2963 formed the full analysis set (fig 1). Of these, 741 were assigned to bicarbonate plus hyoscine butylbromide, 734 to bicarbonate, 741 to hyoscine butylbromide, and 747 to double placebo. Baseline characteristics seemed to be balanced across treatment arms (table 1; supplementary tables S3 and S4), including mean age (31.0 years), mean body mass index (26.5), and indications for induction. The four most common indications were post-term pregnancy (22%), prelabour rupture of membranes (16%), maternal diabetes (13%), and pre-eclampsia (9%). Induction methods and study site distribution were similar across treatment arms (supplementary tables S5 and S6; supplementary figure S2). The distribution of induction methods, including use of balloon catheter, prostaglandins, amniotomy, and oxytocin augmentation, was similar across treatment arms.

Adherence

More than 99% of participants completed the study. In the full analysis set, 1112 (38%) received one dose, 1068 (36%) received two doses, and 783 (26%) received three doses (supplementary tables S7 and S8).

Primary endpoint

Overall, 1738 (59%) participants had a spontaneous vaginal birth, 691 (23%) an instrumental delivery, and 531 (18%) a caesarean delivery (table 2). The proportions of women who had a spontaneous vaginal birth were 57% (422/741) in the bicarbonate plus hyoscine butylbromide arm, 61% (445/734) in the bicarbonate arm, 61% (449/741) in the hyoscine butylbromide arm, and 56% (422/747) in the double placebo arm. Compared with double placebo, the marginal risk differences for spontaneous vaginal birth were -0.2 (95% confidence interval (CI) -5.1 to 4.7; P=0.93) percentage points for bicarbonate plus

Table 1 | Descriptive statistics of key baseline characteristics, overall* and by treatment arm. Values are numbers (percentages) unless stated otherwise

Characteristic	Overall (n=2963)	Bicarbonate plus hyoscine butylbromide (n=741)	Bicarbonate (n=734)	Hyoscine butylbromide (n=741)	Double placebo (n=747)
Mean (SD) maternal age, years	31.0 (4.6)	30.9 (4.6)	30.9 (4.6)	31.0 (4.4)	31.1 (4.7)
Mean (SD) BMI†	26.5 (5.9)	26.7 (6.0)	26.6 (6.1)	26.6 (5.9)	26.2 (5.7)
Indication:‡					
Post-term pregnancy§	650 (22)	155 (21)	161 (22)	171 (23)	163 (22)
PROM	477 (16)	101 (14)	133 (18)	115 (16)	128 (17)
Diabetes	394 (13)	106 (14)	86 (12)	98 (13)	104 (14)
Pre-eclampsia	255 (9)	63 (9)	69 (9)	76 (10)	47 (6)
Hypertension	218 (7)	52 (7)	52 (7)	56 (8)	58 (8)
Other maternal	217 (7)	74 (10)	43 (6)	46 (6)	54 (7)
IUGR	200 (7)	47 (6)	62 (8)	49 (7)	42 (6)
Oligohydramnios	176 (6)	50 (7)	38 (5)	41 (6)	47 (6)
Other fetal	137 (5)	35 (5)	40 (5)	29 (4)	33 (4)
Large fetus	93 (3)	24 (3)	15 (2)	26 (4)	28 (4)
Intrahepatic cholestasis	58 (2)	15 (2)	7 (1)	17 (2)	19 (3)
Maternal request	65 (2)	16 (2)	22 (3)	10 (1)	17 (2)
Polyhydramnios	13 (<1)	3 (<1)	3 (<1)	3 (<1)	4 (1)
Pelvic girdle pain	9 (<1)	0 (0)	3 (<1)	3 (<1)	3 (<1)
Fetal malformations	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Mean (SD) gestational length, days¶	280.4 (10.6)	280.3 (10.5)	280.4 (10.7)	280.5 (10.8)	280.5 (10.4)
Missing	3 (<1)	0 (0)	1 (<1)	2 (<1)	0 (0)
Bishop score:**					
<6	2508 (85)	628 (85)	622 (85)	630 (85)	628 (84)
Missing	222 (7)	55 (7)	49 (7)	61 (8)	57 (8)

BMI=body mass index; IUGR=intrauterine growth restriction; PROM=prelabour rupture of membranes; SD=standard deviation.
*Based on full analysis set.
†BMI before pregnancy or BMI in first trimester if pre-pregnancy BMI is unknown.
‡Main indication for induction of labour.
§Defined as pregnancy duration of ≥294 days. In cases of maternal age ≥38 years, post-term pregnancy was defined as ≥290 days.
¶Gestational length at time of induction, in days.
**Bishop score as recorded at start of induction.

hyoscine butylbromide, 3.1 (-1.7 to 8.0; P=0.21) percentage points for bicarbonate, and 4.0 (-0.8 to 8.9; P=0.10) percentage points for hyoscine butylbromide (table 2; fig 2). None of these comparisons met the prespecified threshold for statistical significance. However, most values within the confidence intervals for bicarbonate and hyoscine butylbromide were compatible with modest increases in spontaneous vaginal birth, indicating that small beneficial effects cannot be excluded. Analysis of the primary endpoint based on the intention-to-treat set yielded estimates that were highly consistent with the main analysis (supplementary table S9). In the sensitivity analysis assessing interaction between the two study drugs, we observed a negative interaction (P=0.04), suggesting attenuation of the individual treatment effects when bicarbonate and hyoscine butylbromide were administered in combination. However, neither of the main effects was statistically significant. The marginal risk differences for bicarbonate were -4.2 (95% CI -9.1 to 0.6) percentage points with hyoscine butylbromide and 3.1 (-1.7 to 8.0) percentage points with intravenous placebo. Conversely, the marginal risk differences for hyoscine butylbromide compared with intravenous placebo were -3.3 percentage points (-8.2 to 1.5) with bicarbonate and 4.0 (-0.8 to 8.9) percentage points with oral placebo. This analysis was exploratory. Results from stratified analyses of spontaneous vaginal birth by study site are shown in supplementary figure S5. Site specific estimates showed some variation in magnitude and direction; however, confidence intervals were wide with substantial overlap, and the analyses did not show major differential treatment effects across sites.

Maternal endpoints

We observed no material differences among treatment arms in vaginal versus caesarean delivery or in the distribution of mode of birth (fig 2). Median times from first dose of study drug to spontaneous vaginal birth, accounting for operative delivery as a competing risk, were 10.8 hours with bicarbonate plus hyoscine butylbromide, 9.9 hours with bicarbonate, 9.2 hours with hyoscine butylbromide, and 11.1 hours with double placebo (table 3; supplementary tables S10 and S11; supplementary figures S3 and S4). Among women with operative delivery, 48% (591/1222) had prolonged labour as the main indication, with a range from 46% (132/290) in the hyoscine butylbromide arm and 46% (132/288) in the bicarbonate arm to 52% (170/325) in the double placebo arm (supplementary table S10). Conversely, 43% (527/1222) had fetal distress as the main indication for operative delivery, with a range from 39% (125/325) in the double placebo arm to 47% (134/288) in the bicarbonate arm.

Maternal heart rate increased modestly 30 minutes after the first dose in the hyoscine butylbromide containing arms (differences in means: 1.3 and 1.8 beats per minute for bicarbonate plus hyoscine butylbromide and hyoscine butylbromide, respectively (fig 3)). Pain scores, obstetric anal sphincter injury, postpartum haemorrhage categories (defined using thresholds of >500 mL, >1000 mL, and >1500 mL blood loss), and urinary retention did not differ between groups (fig 3). Oxytocin augmentation was used in 75% of labours.

Neonatal endpoints

Arterial or venous cord blood pH <7.20 was less common in the bicarbonate containing arms (table 3; supplementary figure S6). However, we observed no differences in Apgar scores or neonatal intensive care unit admission.

Sensitivity analyses

Sensitivity analyses based on the intention-to-treat set (primary endpoint only) and per protocol set (all endpoints) yielded findings that were consistent with the main analyses and did not alter the overall interpretation of the results. Results of the sensitivity analyses of the primary endpoint are presented in supplementary table S9.

Safety

Serious adverse events occurred in 10% (313/2992) of participants, with similar rates across treatment arms. Postpartum haemorrhage accounted for most events (range 8-9% across treatment arms). One neonatal death, one case of neonatal seizure, and one case of neonatal asphyxia were reported and judged to be unrelated to study treatment (supplementary tables S12-S16). No emergency unmasking occurred.

Discussion

In this large, randomised, double blind trial including 2963 nulliparous women undergoing induction of

Table 2 | Marginal treatment effects* on spontaneous vaginal birth versus operative delivery, overall and by treatment arm†

Primary endpoint	Overall No (%) (n=2963)	Bicarbonate plus hyoscine butylbromide (n=741)			Bicarbonate (n=734)			Hyoscine butylbromide (n=741)			Double placebo (n=747)
		No (%)	RD‡ (95% CI)	P value	No (%)	RD‡ (95% CI)	P value	No (%)	RD‡ (95% CI)	P value	No (%)
Spontaneous vaginal birth:											
Yes	1738 (59)	422 (57)	0.2 (-5.1 to 4.7)	0.93	445 (61)	3.1 (-1.7 to 8.0)	0.21	449 (61)	4.0 (-0.8 to 8.9)	0.10	422 (56)
Missing	3 (<1)	0 (0)	NE		1 (<1)	NE		2 (<1)	NE		0 (0)

CI=confidence interval; RD=risk difference (in percentage points); NE=not estimated.
*Estimated by averaging individual level, model based predicted comparisons from fitted binary logistic regression models, adjusted for age (continuous), body mass index (continuous), main indication for induction, and study site (all included as fixed effects).
†Based on full analysis set.
‡In percentage points.

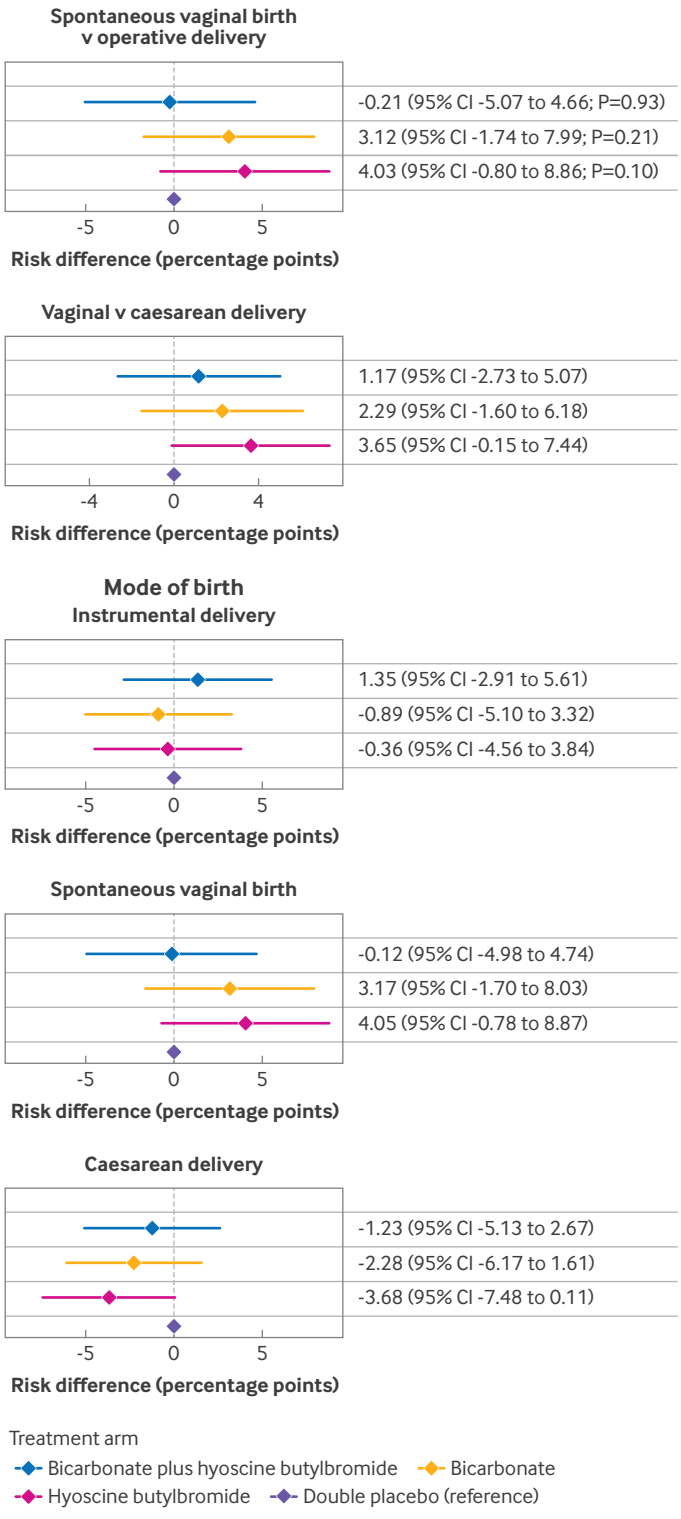

Fig 2 | Marginal treatment effects on spontaneous vaginal birth versus operative delivery and vaginal versus caesarean delivery, and marginal risk differences for mode of birth categories. Spontaneous vaginal birth versus operative birth and vaginal versus caesarean delivery: estimated by averaging individual level, model based predicted comparisons from fitted binary logistic regression models, adjusted for age (continuous), body mass index (BMI) (continuous), main indication for induction, and study site (all included as fixed effects). Mode of birth: estimated by averaging individual level, model based predicted comparisons from fitted multinomial logistic regression model, adjusted for age (continuous), BMI (continuous), main indication for induction, and study site (all included as fixed effects). Based on full analysis set, including 2963 participants. CI=confidence interval

labour, we found no clear evidence that hyoscine butylbromide or sodium bicarbonate increased the rate of spontaneous vaginal birth compared with placebo. Although point estimates favoured higher rates of spontaneous vaginal birth and vaginal versus caesarean delivery, with marginal risk differences of approximately 3-4 percentage points, these effects were modest and did not meet the prespecified target. No significant differences existed between treatment arms in duration of labour or in maternal and neonatal outcomes, and no serious adverse events were considered related to the study treatments.

Comparison with other studies

Our findings are not directly comparable with those of earlier trials suggesting that hyoscine butylbromide may shorten the first stage of labour or that oral bicarbonate may benefit women with labour dystocia.[16 17] These studies were generally small, unblinded, and conducted largely in women with spontaneous onset of labour rather than induction. Moreover, most were underpowered to detect differences in mode of birth, the outcome most relevant to current obstetric practice. By contrast, our trial was powered to detect a clinically meaningful improvement in spontaneous vaginal birth and specifically enrolled nulliparous women undergoing induction of labour, a group with a high occurrence of operative delivery. The absence of clear benefit across the primary and key secondary outcomes therefore does not support routine intrapartum use of these agents to facilitate vaginal birth after induction.

Previous meta-analyses incorporated fewer nulliparous women than were included in this single trial, and the contributing studies were not designed to evaluate operative delivery rates.[18 19 28] Our study is the largest to date evaluating hyoscine butylbromide in labour and the only double blind trial to assess either agent among nulliparous women undergoing induction of labour. For these reasons, our findings are not directly comparable with earlier evidence but instead provide novel and substantially more precise evidence for this population.

With respect to bicarbonate, earlier trials suggested reduced rates of instrumental delivery, particularly with slow labour progress and elevated lactate.[21 22] These studies, however, were small (142 and 200 participants), were unblinded, and applied different inclusion criteria focused on dystocia rather than induction of labour.[21 22] By contrast, bicarbonate in our protocol was administered at the onset of active labour regardless of labour progression, which may partially explain differences in findings. Methodological limitations and heterogeneous populations in earlier work further reduce comparability. Previous trials evaluating bicarbonate in dysfunctional or prolonged labour have differed in their use of biochemical markers to identify women with impaired uterine contractility. In particular, the trial by Wiberg-Itzel and colleagues measured amniotic fluid lactate as an indicator of myometrial metabolic stress and used this as part of the biological rationale for treatment.[22]

doi: 10.1136/bmj-2026-101069 | *BMJ* 2026;395:e101069 | the bmj

Table 3 | Descriptive statistics of secondary endpoints, overall* and by treatment arm. Values are numbers (percentages) unless stated otherwise

Endpoint	Overall (n=2963)	Bicarbonate plus hyoscine butylbromide (n=741)	Bicarbonate (n=734)	Hyoscine butylbromide (n=741)	Double placebo (n=747)
Vaginal birth:					
Yes	2429 (82)	603 (81)	608 (83)	619 (84)	599 (80)
Missing	3 (<1)	0 (0)	1 (<1)	2 (<1)	0 (0)
Mode of birth:					
Spontaneous vaginal birth	1738 (59)	422 (57)	445 (61)	449 (61)	422 (56)
Instrumental delivery	691 (23)	181 (24)	163 (22)	170 (23)	177 (24)
Caesarean delivery	531 (18)	138 (19)	125 (17)	120 (16)	148 (20)
Missing	3 (<1)	0 (0)	1 (<1)	2 (<1)	0 (0)
Median time from labour to spontaneous vaginal birth†, min	648.0	698.0	631.0	577.0	679.0
Median time from first IMP to spontaneous vaginal birth†, min	617.0	647.0	596.0	552.0	663.0
Cervical dilation rate, cm/h:					
Mean (SD)	1.9 (4.1)	1.9 (4.6)	2.0 (3.6)	2.0 (5.0)	1.7 (3.1)
Median (IQR)	0.9 (0.5-1.8)	0.9 (0.5-1.7)	1.0 (0.5-1.9)	1.0 (0.5-1.8)	0.9 (0.5-1.7)
Missing	25 (1)	7 (1)	8 (1)	4 (1)	6 (1)
Change in maternal heart rate after first IMP, BPM:‡					
Mean (SD)	0.5 (15.0)	-0.7 (18.3)	1.6 (11.1)	0.5 (17.5)	0.8 (11.9)
Median (IQR)	1.0 (-5.0-8.0)	0.0 (-8.0-9.0)	1.0 (-5.0-8.0)	2.0 (-5.0-10.0)	0.0 (-5.0-7.0)
Missing	178 (6)	57 (8)	45 (6)	38 (5)	38 (5)
Change in pain score (VNRS) after first IMP:‡					
Mean (SD)	-0.1 (2.1)	0.0 (2.1)	-0.1 (2.2)	0.0 (2.1)	-0.2 (2.1)
Median (IQR)	0.0 (-0.5-1.0)	0.0 (0.0-1.0)	0.0 (-0.5-1.0)	0.0 (0.0-1.0)	0.0 (-1.0-1.0)
Missing	231 (8)	70 (9)	56 (8)	53 (7)	52 (7)
Obstetric anal sphincter injury:					
Yes	61 (2)	21 (3)	18 (2)	11 (1)	11 (1)
Not applicable	534 (18)	138 (19)	126 (17)	122 (16)	148 (20)
PPH >500 mL:					
Yes	1249 (42)	303 (41)	319 (43)	311 (42)	316 (42)
Missing	7 (<1)	0 (0)	2 (<1)	3 (<1)	2 (<1)
PPH >1000 mL:					
Yes	482 (16)	112 (15)	132 (18)	123 (17)	115 (15)
Missing	7 (<1)	0 (0)	2 (<1)	3 (<1)	2 (<1)
PPH >1500 mL:					
Yes	179 (6)	45 (6)	43 (6)	42 (6)	49 (7)
Missing	7 (<1)	0 (0)	2 (<1)	3 (<1)	2 (<1)
Urinary retention, delivery ward:§					
Yes	626 (21)	152 (21)	149 (20)	162 (22)	163 (22)
Missing	3 (<1)	0 (0)	1 (<1)	2 (<1)	0 (0)
Urinary retention, postnatal ward:¶					
Yes	114 (4)	21 (3)	36 (5)	27 (4)	30 (4)
Missing	3 (<1)	0 (0)	1 (<1)	2 (<1)	0 (0)
Urinary retention at discharge:**					
Yes	21 (1)	7 (1)	7 (1)	3 (<1)	4 (1)
Missing	101 (3)	24 (3)	28 (4)	23 (3)	26 (3)
Umbilical artery pH <7.00:					
Yes	7 (<1)	2 (<1)	3 (<1)	1 (<1)	1 (<1)
Missing	605 (20)	154 (21)	155 (21)	161 (22)	135 (18)
Umbilical artery pH <7.10:					
Yes	109 (4)	34 (5)	22 (3)	28 (4)	25 (3)
Missing	605 (20)	154 (21)	155 (21)	161 (22)	135 (18)
Umbilical artery pH <7.20:					
Yes	778 (26)	181 (24)	172 (23)	203 (27)	222 (30)
Missing	605 (20)	154 (21)	155 (21)	161 (22)	135 (18)
Umbilical vein pH <7.10:					
Yes	8 (<1)	3 (<1)	0 (0)	1 (<1)	4 (1)
Missing	288 (10)	70 (9)	73 (10)	83 (11)	62 (8)
Umbilical vein pH <7.20:					
Yes	105 (4)	21 (3)	20 (3)	27 (4)	37 (5)
Missing	288 (10)	70 (9)	73 (10)	83 (11)	62 (8)
5 minute Apgar score <7:					
Yes	50 (2)	17 (2)	9 (1)	12 (2)	12 (2)
Missing	8 (<1)	2 (<1)	3 (<1)	2 (<1)	1 (<1)
10 minute Apgar score <7:					
Yes	11 (<1)	4 (1)	1 (<1)	3 (<1)	3 (<1)
Missing	9 (<1)	2 (<1)	3 (<1)	3 (<1)	1 (<1)

(Continued)

Table 3 | (Continued)

Endpoint	Overall (n=2963)	Bicarbonate plus hyoscine butylbromide (n=741)	Bicarbonate (n=734)	Hyoscine butylbromide (n=741)	Double placebo (n=747)
NICU admission:					
Yes	228 (8)	65 (9)	56 (8)	55 (7)	52 (7)
Missing	7 (<1)	2 (<1)	2 (<1)	2 (<1)	1 (<1)

BPM=beats per minute; IMP=investigational medicinal product; IQR=interquartile range; NICU=neonatal intensive care unit; PPH=postpartum haemorrhage; SD=standard deviation; VNRS=verbal numeric rating scale.
*Based on full analysis set.
†Defined as time at which cumulative incidence of spontaneous vaginal birth reached 50%, with operative delivery treated as competing risk.
‡Change from before to 30 minutes after first IMP administration.
§Urinary retention diagnosed in delivery ward: need for catheterisation during stay in delivery ward.
¶Urinary retention diagnosed in postnatal ward: need for catheterisation during stay in postnatal ward.
**Urinary retention at discharge: need for permanent urinary retention catheter at time of discharge from postnatal ward.

By contrast, amniotic fluid lactate measurements were not available in Norway during the conduct of our trial, and biochemical selection of women with suspected myometrial fatigue was therefore not feasible. Other trials, including that by Seyedi and colleagues, evaluated bicarbonate in labour dystocia without routine use of amniotic fluid measurements.[21] Future studies may benefit from targeting populations with established labour dystocia and incorporating biochemical markers of uterine fatigue where available, to better define whether bicarbonate has a role in selected subgroups.

We also explored whether coadministration of hyoscine butylbromide and bicarbonate might offer additive benefit. This interpretation is consistent with the known pharmacological mechanisms of the two agents, which act on different and potentially opposing components of labour physiology. Outcomes in the combined arm were similar to those with double placebo, and effect estimates suggested attenuation rather than enhancement when the agents were used together. This finding is consistent with the exploratory interaction analysis, which suggested attenuation of the individual treatment effects when sodium bicarbonate and hyoscine butylbromide were coadministered, and provides a potential explanation for the lack of effect observed in the combined treatment arm. Although mechanisms cannot be established from our data, one potential explanation is that the antispasmodic effect of hyoscine butylbromide on uterine smooth muscle could counterbalance any bicarbonate mediated improvement in uterine contractile efficiency. Hyoscine butylbromide is a peripherally acting antimuscarinic agent with well described smooth muscle relaxant effects on the uterus and cervix, which form the basis for its hypothesised role in facilitating cervical dilation.[16-19] By contrast, bicarbonate has been hypothesised to improve uterine contractile efficiency by buffering lactate accumulation in the myometrium during prolonged labour.[21 22] The lower proportion of neonates with umbilical blood pH <7.20 in bicarbonate containing arms suggests maternal drug absorption and placental transfer, consistent with previous studies showing biochemical effects of oral bicarbonate during labour.[21 22] Similarly, the modest increase in maternal heart rate following administration of hyoscine butylbromide is consistent with its known peripheral antimuscarinic effects and has been reported in randomised trials evaluating hyoscine butylbromide in labour.[16 28] Together, these findings suggest that the lack of clinical benefit is unlikely to reflect inadequate drug delivery but rather limited therapeutic value of these mechanisms during induced labour.

Clinical implications

The overall findings across the primary and secondary endpoints did not show clear benefit from pharmacological modulation of cervical relaxation or uterine contractility when using hyoscine butylbromide or bicarbonate in the context of induced labour. Although bicarbonate containing arms had fewer neonates with cord blood pH <7.20, this did not translate into meaningful maternal or neonatal advantages. The small increase in maternal heart rate following hyoscine administration indicates drug activity but no corresponding clinical benefit. Given that neither drug seemed to affect mode of birth, we do not recommend their inclusion in future guidelines to facilitate spontaneous vaginal delivery. If they are used, clinicians should exercise caution when using both agents together, as our findings suggest potential attenuation rather than augmentation of effect. The relatively high risks of postpartum haemorrhage and urinary retention likely reflect the underlying obstetric risk profile of women with induced labour rather than treatment effects.

Strengths and limitations of study

This trial has limitations. Study drugs were administered at the onset of active labour irrespective of early labour progression. Different timing or use in selected subgroups with established labour dystocia might yield different effects. Participants who were not proficient in Norwegian or English were excluded, which may limit generalisability. Hyoscine butylbromide was associated with a small increase in maternal heart rate, which could theoretically have contributed to partial unmasking, although the magnitude was modest and unlikely to have influenced decisions about mode of birth. The trial was powered to detect a moderate-to-large treatment effect, corresponding to a 15% relative increase in spontaneous vaginal birth (approximately 8.5 percentage points). Although the

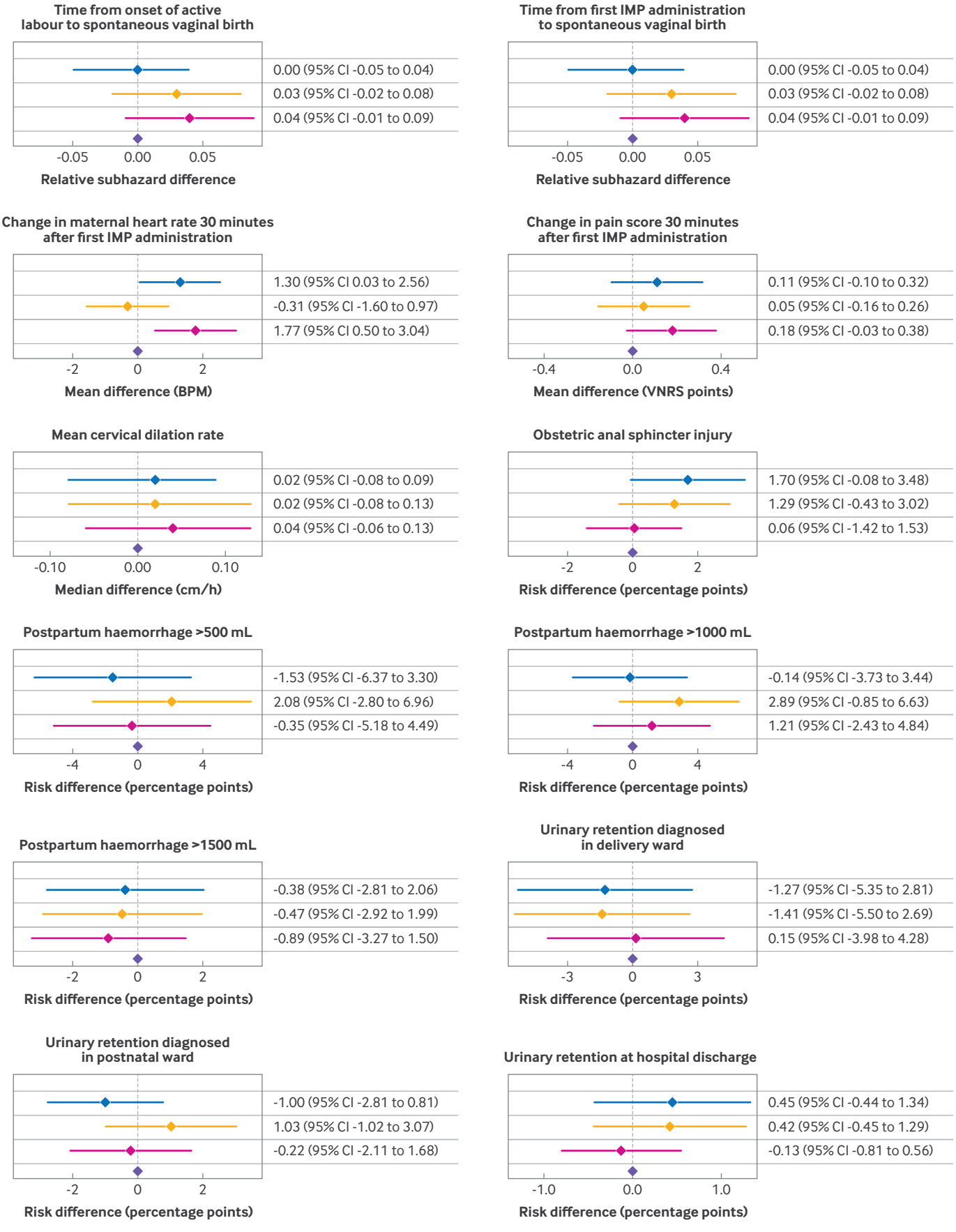
Time from onset of active labour to spontaneous vaginal birth
0.00 (95% CI -0.05 to 0.04)
0.03 (95% CI -0.02 to 0.08)
0.04 (95% CI -0.01 to 0.09)
-0.05
0.00
0.05
Relative subhazard difference
Time from first IMP administration to spontaneous vaginal birth
0.00 (95% CI -0.05 to 0.04)
0.03 (95% CI -0.02 to 0.08)
0.04 (95% CI -0.01 to 0.09)
-0.05
0.00
0.05
Relative subhazard difference
Change in maternal heart rate 30 minutes after first IMP administration
1.30 (95% CI 0.03 to 2.56)
-0.31 (95% CI -1.60 to 0.97)
1.77 (95% CI 0.50 to 3.04)
-2
0
2
Mean difference (BPM)
Change in pain score 30 minutes after first IMP administration
0.11 (95% CI -0.10 to 0.32)
0.05 (95% CI -0.16 to 0.26)
0.18 (95% CI -0.03 to 0.38)
-0.4
0.0
0.4
Mean difference (VNRS points)
Mean cervical dilation rate
0.02 (95% CI -0.08 to 0.09)
0.02 (95% CI -0.08 to 0.13)
0.04 (95% CI -0.06 to 0.13)
-0.10
0.00
0.10
Median difference (cm/h)
Obstetric anal sphincter injury
1.70 (95% CI -0.08 to 3.48)
1.29 (95% CI -0.43 to 3.02)
0.06 (95% CI -1.42 to 1.53)
-2
0
2
Risk difference (percentage points)
Postpartum haemorrhage >500 mL
-1.53 (95% CI -6.37 to 3.30)
2.08 (95% CI -2.80 to 6.96)
-0.35 (95% CI -5.18 to 4.49)
-4
0
4
Risk difference (percentage points)
Postpartum haemorrhage >1000 mL
-0.14 (95% CI -3.73 to 3.44)
2.89 (95% CI -0.85 to 6.63)
1.21 (95% CI -2.43 to 4.84)
-4
0
4
Risk difference (percentage points)
Postpartum haemorrhage >1500 mL
-0.38 (95% CI -2.81 to 2.06)
-0.47 (95% CI -2.92 to 1.99)
-0.89 (95% CI -3.27 to 1.50)
-2
0
2
Risk difference (percentage points)
Urinary retention diagnosed in delivery ward
-1.27 (95% CI -5.35 to 2.81)
-1.41 (95% CI -5.50 to 2.69)
0.15 (95% CI -3.98 to 4.28)
-3
0
3
Risk difference (percentage points)
Urinary retention diagnosed in postnatal ward
-1.00 (95% CI -2.81 to 0.81)
1.03 (95% CI -1.02 to 3.07)
-0.22 (95% CI -2.11 to 1.68)
-2
0
2
Risk difference (percentage points)
Urinary retention at hospital discharge
0.45 (95% CI -0.44 to 1.34)
0.42 (95% CI -0.45 to 1.29)
-0.13 (95% CI -0.81 to 0.56)
-1.0
0.0
1.0
Risk difference (percentage points)
Treatment arm
Bicarbonate plus hyoscine butylbromide
Bicarbonate
Hyoscine butylbromide
Double placebo (reference)

Fig 3 | Marginal treatment effects on maternal endpoints during labour and after birth. Time from onset of active labour to spontaneous vaginal birth (min) and time from administration of first dose of investigational medicinal product (IMP) to spontaneous vaginal birth (min): estimated by averaging individual level, model based predicted comparisons from fitted Fine-Gray competing risks regression models, adjusted for age (continuous), body mass index (BMI) (continuous), main indication for induction, and study site (all included as fixed effects). Change in maternal heart rate 30 minutes after first IMP dose (beats per minute (BPM)) and change in pain score 30 minutes after first IMP dose (verbal numeric rating scale (VNRS)): estimated by averaging individual level, model based predicted comparisons from fitted linear regression models, adjusted for age (continuous), BMI (continuous), main indication for induction, and study site (all included as fixed effects). Mean cervical dilation rate (cm/h): estimated by averaging individual level, model based predicted comparisons from fitted median regression model, adjusted for age (continuous), BMI (continuous), main indication for induction, and study site (all included as fixed effects). Obstetric anal sphincter injury; postpartum haemorrhage >500 mL, >1000 mL, and >1500 mL; and urinary retention diagnosed in delivery ward, diagnosed in postnatal ward, and at hospital discharge: estimated by averaging individual level, model based predicted comparisons from fitted binary logistic regression models, adjusted for age (continuous), BMI (continuous), main indication for induction, and study site (all included as fixed effects)

point estimates did not show statistically significant benefits, the confidence intervals remained compatible with small beneficial effects on spontaneous vaginal birth. Slow progress as an indication for operative delivery was 6 percentage points lower in both single treatment arms compared with double placebo, but these comparisons were not prespecified, and the study was not designed to detect such differences. Strengths of the trial include its large sample size, nationwide design, rigorous masking and allocation concealment, and high protocol adherence. Although not all prespecified secondary endpoints are reported in the main manuscript, all were defined a priori in the trial protocol and statistical analysis plan.

Conclusions

In conclusion, we found no clear evidence that hyoscine butylbromide or sodium bicarbonate increased spontaneous vaginal birth among nulliparous women undergoing labour induction. Although small beneficial effects cannot be excluded, these findings do not support routine intrapartum use of either agent to reduce operative delivery in this population.

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We express our deepest gratitude to everyone who contributed to the SAINT study, particularly the trial participants and healthcare professionals who made this study possible. We thank the members of the data monitoring committee: Torbjørn Moe Eggbø, Stine Bernitz, Erica Ponzi, and Céline Marie Løken Cunen. We are particularly indebted to national study coordinator Anne-Cathrine Bjørnstad (Oslo University Hospital) and study midwives/nurses Astrid Junker Andvik and Mary Eide Hauge (Haukeland University Hospital), Marit Berger (Akershus University Hospital), Charlotte Dahl (Oslo University Hospital, Ullevål), Kristina Haugen (St Olavs Hospital), Berit Skaatun (Sørlandet Hospital Kristiansand), Linda Matere and Nina Trollvik (University Hospital of North Norway), Farinaz Mosavatchi (Oslo University Hospital, Rikshospitalet), Hege Steen Paulsen and Anniken Aasgaard (Drammen Hospital, Vestre Viken Hospital Trust), Marianne Håland Pedersen (Stavanger University Hospital), Britt H S Udnæs (Østfold Hospital Trust), and Ellen Marie Uv (Bærum Hospital, Vestre Viken Hospital Trust).

Contributors: TMM and IKS were responsible for the grant application and the subsequent research project. TMM was the national coordinating investigator and the chief investigator. Members of the SAINT Consortium provided advice to the chief investigator during the planning and conduct of the trial. IKS was the co-chief investigator, the responsible medical monitor, and senior supervising author. TMM and IKS were responsible for conceptualisation, project administration, supervision, and funding acquisition. TMM, LTL, AVS, NGN, and IKS contributed to methodology and preparation of the original draft. TMM, LTL, AVS, AMK, ÅTRP, EM, RKS, JK, TL, MWV, KS, CH, AFJ, and IKS contributed to the investigation. TMM and IKS curated the data, with input from NGN, and had access to and verified the underlying data. All living authors contributed to review and editing of the manuscript. AMK contributed to the investigation and conduct of the study and reviewed an earlier version of the manuscript. She died before completion of the final revision and was therefore unable to review or approve the version to be published. All living authors reviewed and approved the final manuscript. TMM is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Microsoft 365 Copilot was used solely for copyediting. All changes were reviewed and approved by the authors.

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Funding: This study was funded by the Norwegian National Programme for Clinical Treatment Research in the Specialist Health Services (KLINBEFORSK), through grant 2021205 awarded to TMM. The funder had no role in considering the study design; in the collection, management, analysis, or interpretation of the data; in writing the report; or in the decision to submit the article for publication.

Competing interests: All living authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: funding for the submitted work from the Norwegian National Programme for Clinical Treatment Research in the Specialist Health Services; no financial relationships with any organisations that might

have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. After consultation with her next of kin and to the best of the remaining authors' knowledge, AMK had no competing interests relevant to this work.

Ethical approval: Approved by the Regional Committee for Medical and Health Research Ethics South-East Norway B (235247), the EU Clinical Trials authority (2024-511848-55-00; previous EudraCT number 2021-000392-37), and the Norwegian Medical Products Agency (21/06793-3). All participants gave written informed consent.

Data sharing: The code used to analyse the data in the paper can be found in the supplemental files and is also available on GitHub at https://github.com/trondmic/Safe-induction-of-labor-trial/blob/main/Final%20Report.RMD. The data underlying the findings in this paper are openly and publicly available and can be found at https://doi.org/10.18710/MG91J3. If you encounter problems accessing the data, please contact the corresponding author.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The results of this study will be disseminated to participants and the public through a lay summary made available via participating hospitals and institutional websites and through communication with relevant professional and patient organisations. The findings will also be shared with clinical stakeholders and policy makers through scientific publications and conference presentations.

Provenance and peer review: Externally peer reviewed and not commissioned.

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Supplementary tables and figures
Trial protocol
Statistical analysis plan