Peripartum Outcomes After Combined Myo-inositol, Probiotics, Micronutrient Supplementation from Preconception: NiPPeR RCT

Condensation:

A myo-inositol, probiotic and micronutrient supplement starting preconception shortened second stage of labor, reduced operative delivery for delayed second stage and decreased postpartum blood loss.

Short Title: Nutritional supplementation and peripartum outcomes

AJOG at a Glance:

A. Why was the study conducted?

- To assess if a combined myo-inositol, probiotic and micronutrient supplement, starting preconception and continued throughout pregnancy, could improve peripartum outcomes, analyzed as secondary outcomes of a randomized controlled trial.

B. What are the key findings?

- Nutritional intervention reduced the duration of the second stage of labor, clinician intervention for delay in the second stage and postpartum blood loss.

C. What does this study add to what is already known?

- We previously reported that this multi-micronutrient supplementation reduced the risk of preterm delivery, preterm pre-labor rupture of membranes and major postpartum hemorrhage. Now we provide new evidence that nutritional supplementation starting preconception could also shorten the second stage of labor, lower the risk of operative delivery for delayed second stage and decrease postpartum blood loss.

Disclosure of Interests

S.Y.C., P.N.B., Y.S.C., W.S.C., and K.M.G. report grants from Société des Produits Nestlé S.A. during the conduct of the study, and are coinventors on patent filings by Nestlé S.A. related to the NiPPeR intervention or its components. S.Y.C., S.J.B., W.S.C., and K.M.G. are part of an academic consortium that has received grants from Abbott Nutrition, Nestlé S.A., Danone S.A., and BenevolentAI Bio Ltd. outside the submitted work. S.Y.C. has received reimbursement and honoraria into her research funds from Nestlé S.A. for speaking at a conference. K.M.G. has received reimbursement for speaking at conferences sponsored by companies selling nutritional products. All other authors declare no conflict of interest.

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Keywords: assisted delivery, blood loss, cesarean section, delay in second stage of labor, delivery outcomes, instrumental delivery, labor progress, operative delivery, postpartum hemorrhage, pregnancy.

Abstract

Background: Evidence that nutritional supplementation before and during pregnancy improves peripartum outcomes is sparse. In the Nutritional Intervention Preconception and During Pregnancy to Maintain Healthy Glucose Metabolism and Offspring Health (NiPPeR) trial we previously reported that a combined myo-inositol, probiotics and micronutrient supplement starting preconception showed no difference in the primary outcome of gestational glycemia, but did reduce the risk of preterm delivery, preterm pre-labor rupture of membranes and major postpartum hemorrhage.

Objective: To examine the hypothesis that a reduction in major postpartum hemorrhage following a combined nutritional (myo-inositol, probiotics and micronutrient) intervention is linked with promotion of labor progress and reduced operative delivery.

Study Design: This double-blind randomized controlled trial recruited from the community 1729 UK, Singapore and New Zealand women aged 18-38 years planning conception between 2015-2017. Here, the effects of the nutritional intervention compared with a standard micronutrient supplement (control), taken preconception and throughout pregnancy, on the secondary outcomes of peripartum events were examined using multinomial, Poisson and linear regression adjusting for site, ethnicity and important covariates.

Results: Of the women who conceived and progressed beyond 24 weeks' gestation with a singleton pregnancy (n=589), 583 (99%) provided peripartum data. Between women in the intervention (n=293) and control (n=290) groups, there were no differences in rates of labor induction, oxytocin augmentation during labor, instrumental delivery, perineal trauma and intrapartum cesarean section. While duration of the first stage of labor was similar, the second-stage duration was 20% shorter in the intervention group compared with controls [adjusted mean difference -12.0 (95%CI -22.2, -1.2) minutes, p=0.029], accompanied by a reduction in operative delivery for delayed second-stage progress [adjusted risk ratio 0.61 (0.48, 0.95);

p=0.022]. Estimated blood loss was 10% less with intervention compared with control [adjusted mean difference -35.0 (-70.0, -3.5) ml, p=0.047], consistent with previous findings of reduced postpartum hemorrhage.

Conclusion: Supplementation with a specific combination of myo-inositol, probiotics and micronutrients starting preconception and continued in pregnancy reduced both the duration of the second stage of labor and the risk of operative delivery for delay in the second stage, and reduced blood loss at delivery.

Introduction

Poor labor progress is the commonest indication for operative delivery, including instrumental vaginal delivery and cesarean section, which are associated with higher morbidity and mortality for mother and baby.[1-3] One major complication of prolonged labors and operative deliveries is postpartum hemorrhage (PPH),[4] mostly due to tissue trauma from tears and incisions, and uterine atony post-delivery.[5] Despite increased use of uterotonics prophylactically, PPH remains the leading cause of maternal mortality in low resource settings and accounts for almost a quarter of maternal deaths globally.[6]

Effective uterine contractions in conjunction with optimal fetal head positioning and an adequately sized/shaped pelvis, are fundamental to achieving normal labor progress and vaginal birth.[7] With poor labor progress, synthetic oxytocin is commonly administered to augment labor[8] but this is associated with uterine hyperstimulation, uterine rupture and fetal hypoxia, despite close monitoring. Therefore, there is a need to find complementary approaches to improve uterine contractility peripartum to reduce the risk of prolonged labor, operative delivery for poor progress, and PPH.

Micronutrient status has been associated with labor progress and postpartum bleeding. A study found nulliparous women delivered by cesarean section for labor dystocia had lower serum vitamin D concentrations compared with those who delivered vaginally,[9, 10] while there is weak evidence that vitamin D supplementation may reduce severe PPH.[11] Meanwhile, low zinc levels have been associated with prolonged labor[12] and PPH;[13] however, a Cochrane review concluded that zinc supplementation did not improve maternal outcomes.[14] Whether supplementation with a combination of micronutrients could reduce peripartum risks are unclear as few studies collected such data.

The NiPPeR randomized controlled trial (RCT)[15] of a nutritional intervention containing myo-inositol, probiotics and enhanced micronutrients, with the primary outcome of maintenance of euglycaemia during pregnancy, found no difference in gestational glycaemia between the intervention arm and the control arm, who received a standard micronutrient supplement.[16] However, there was a significant reduction in preterm delivery, preterm pre-labor rupture of membranes and major PPH (adjusted relative risk 0.44) with the intervention compared with controls. The objective of this further study is to compare in more depth the peripartum outcomes of the two study arms and examine differences that may contribute to the reduction in major PPH. We hypothesized that through the promotion of effective uterine contractility, reflected by improved labor progress and reduced usage of oxytocin augmentation, the intervention could reduce operative delivery rates and decrease postpartum blood loss.

Materials and Methods

The trial was registered on 15th July 2015 (https://www.clinicaltrials.gov/ct2/show/NCT02509988), with first participant enrolment on 3rd August 2015. Our trial was approved by the United Kingdom, Singapore and New Zealand research ethics services at each site. Southampton: Health Research Authority NRES Committee South Central Research Ethics Committee (REC) reference 15/SC/0142, approved 22 April 2015. Singapore: National Healthcare Group Domain Specific Review Board reference 2015/00205, approved 11 June 2015. New Zealand: Health and Disability Ethics Committee (HDEC) reference 15/NTA/21, approved 30 June 2015. All participants provided written informed consent.

Trial study design

Women planning a pregnancy were recruited (n=1729) from the community across 3 sites: New Zealand, UK and Singapore between 2015-2017. The study protocol and details of the

NiPPeR supplements were previously published,[15] in accordance with CONSORT guidelines. Briefly, participants were randomized by an electronic database in a 1:1 ratio to intervention (n=870) or control (n=859) arms, with stratification by site and ethnicity to ensure balanced allocation. Exclusion criteria were pregnancy/lactation at recruitment, assisted conception (apart from taking clomiphene or letrozole alone), serious food allergy, pre-existing diabetes mellitus, use of hormonal contraception or taking metformin, systemic steroids, anticonvulsants or treatment for HIV, Hepatitis B or C in the past month. Supplements from both arms contained folic acid, iron, calcium, iodine and β-carotene; the intervention additionally included myo-inositol, vitamin D, riboflavin, vitamin B6, vitamin B12, zinc and probiotics (*Lactobacillus rhamnosus* and *Bifidobacterium animalis sp. lactis*).[15] Supplements were consumed twice daily from preconception following randomization until delivery. Participants and all study personnel remained blinded to treatment allocation until all pregnancy, delivery and neonatal data had been collected, and analysis of the primary outcome completed. This sub-study of singleton pregnancies delivering beyond 24 weeks' gestation is an analysis of peripartum events pre-specified as secondary outcomes of the trial.

Delivery outcomes

Clinical data, including peripartum events, were abstracted from medical records prospectively. Indications for instrumental vaginal delivery and cesarean section were collected, including documented delay in the first and second stages of labor as defined by the attending obstetric team. For participants with available timings of each stage of labor, a delay in the second stage of labor was also objectively defined according to the American College of Obstetricians and Gynecologists (ACOG)[17]: second stage of >2h without or >3h with epidural in nulliparous women, and >1h without or >2h with epidural in parous women. "Delay in second stage" for this study included cases defined by the attending obstetric team or meeting ACOG definitions. A prolonged third stage of labor was defined as >30 minutes' duration.[18]

Perineal trauma included significant genital tract lacerations, episiotomy with complications, and third/fourth degree tears. Total estimated blood loss at delivery was taken as recorded in routine medical documentation. Major PPH was defined as estimated blood loss >1000ml in the immediate postpartum period, whilst minor PPH as estimated loss of 500-1000ml.[19] Macrosomia was defined as birthweight >4000g.

Statistical analysis

Durations of the first, second and third stages of labor, and total blood loss were $\log_e$ transformed to achieve approximately Normal distributions for analyses. Multinomial (mutually exclusive outcomes), Poisson (categorical outcomes) and linear (continuous outcomes) regression analyses were performed as appropriate, with adjustment for study site and ethnicity (the stratification factors; "basic model"), and for covariates imbalanced between study arms or important factors with prognostic influence on outcomes based on existing literature, specifically maternal age, pre-pregnancy body mass index (BMI), household income (in deciles; marker of socioeconomic status), parity (nulliparous or parous), history of previous cesarean section and smoking ("fully-adjusted model"). For outcomes involving duration of labor and oxytocin-use, additional covariates included epidural analgesia and labor induction, respectively. Log_e-transformed coefficient values are also presented as the anti-log equivalent, calculated based on the median value among controls. No imputation was performed for missing data. With these analyses of secondary outcomes, emphasis was placed on the magnitude of effect and 95% confidence interval (CI), with a p-value <0.05 deemed statistically significant. The interaction-term (study group*parity) was introduced into models to seek potentially different effects by parity. *A priori* sensitivity analyses were conducted excluding preterm deliveries, and those where the actual duration of second stage was not recorded, hence cannot be objectively classed by ACOG definitions for delay in second stage.

Data Sharing

Individual participant data may be shared upon reasonable requests subject to approval by the trial management group and trial consultative panel.

Results

Participant characteristics

Of the women who conceived and fulfilled the study criteria (Figure 1), 588 had a live singleton birth between April 2016 to January 2019, with 583 (99%) providing peripartum data (293 intervention, 290 control). Baseline characteristics were balanced across study groups, except for more nulliparity among controls (Table 1).

Labor onset and mode of delivery

Overall, analyses found no differences between control and intervention groups in the proportions of women undergoing induction of labor, instrumental vaginal delivery and cesarean section, both in labor and without labor (Supplementary Table 1). Indications for labor induction (Supplementary Table 2) and for operative delivery (Supplementary Table 1) were similar between study groups.

Labor progress

Among those who experienced labor, duration of the first stage (Figure 2A) and the risk of delay in the first stage requiring cesarean section (Figure 2B) were similar between study groups. In contrast, among women who reached the second stage of labor, duration of the second stage was 20% shorter with the intervention compared with controls [fully-adjusted mean difference (aMD) -0.20 (95% CI: -0.37, -0.02) $\log_e$ minutes; equivalent to -12.0 (-22.2, -1.2) minutes, p=0.029; Figure 2A], along with a reduction in the risk of delay in the second stage [fully-adjusted relative risk (aRR) 0.68 (0.48, 0.95), p=0.026, Figure 2B]. Importantly, the risk of requiring operative delivery because of a delayed second stage was also reduced in

the intervention group [aRR 0.61 (0.40, 0.93), p=0.022, Figure 2B]. Epidural take-up was similar between groups and did not account for the difference in labor progression (Figure 2B). The shortened second stage of labor with intervention was also not due to differences in iatrogenic curtailment of labor by operative delivery for indications unrelated to delayed progress that could have occurred earlier during the second stage [aRR 1.3 (0.57, 2.93), p=0.532].

A similar proportion in both study groups received oxytocin, even after accounting for labor induction (Figure 2B). In analyses confined to those who had spontaneous labor-onset where oxytocin use would be limited to the purpose of labor-augmentation, there was a suggestion that the intervention reduced requirement for oxytocin augmentation in the basic model, but this effect was attenuated following additional covariate adjustment, largely due to confounding by parity.

Among women who delivered vaginally, no study group differences were observed in the duration of the third stage of labor (Figure 2A) or in prolonged third stage, with similar proportions choosing physiological management (Figure 2B).

Blood loss at delivery

The previously reported risk reduction in major PPH with the intervention is now further supported by a finding of 10% reduction in estimated blood loss [aMD -0.10 (-0.20, -0.01) $\log_e$ ml; equivalent to -35.0 (-70.0, -3.5) ml; p=0.047], with fewer women requiring a blood transfusion in the intervention group compared with controls (0.3% vs 2.5%) (Table 2). However, there was no significant difference in the overall incidence of any PPH (>500ml) between study groups [aRR 1.09 (0.78, 1.53); p=0.62].

To examine potential pathways underlying the intervention effect of reduced postpartum blood loss, for the purposes of hypothesis generation, we explored other risk factors for PPH

additional to mode of delivery and length of labor. Considering the whole cohort, there were no study group differences in hemorrhage before or during labor, placental/cord anomalies, pre-labor rupture of membranes (combined term and preterm; associated with possible uterine infection/inflammation), and significant perineal trauma (Supplementary Figure 1). However, among the 33 cases of major PPH some of these events had a somewhat lower incidence in the intervention group (Supplementary Table 3).

Interaction and sensitivity analyses confirmed robustness of findings

Non-significant interactions between study group and parity for the outcomes of second stage duration, operative delivery for delayed second stage and estimated blood loss suggest similar intervention effects in nulliparous and parous women. Since the intervention reduced preterm births,[16] which may influence peripartum outcomes, sensitivity analyses were conducted excluding all preterm births (<37 weeks' gestation; n=44); the analyses demonstrated similar results, with the intervention shortening second stage duration by 23% and reducing blood loss by 10% (Supplementary Table 4). With the exclusion of cases where the actual duration of second stage was not recorded (n=19), similar results were obtained for delay in second stage requiring operative delivery (aRR 0.62 (0.41 to 0.95), p=0.026).

Comments

Principal Findings

Supplementation with a specific combination of myo-inositol, probiotics and enhanced micronutrients starting preconception and continued throughout pregnancy reduced both the duration of the second stage of labor and the risk of operative delivery for delay in the second stage, accompanied by decreased postpartum blood loss, consistent with our previous report of a reduction in the incidence of major PPH.

Results in context

With the exception of vitamin D, previous trials of antenatal supplementation separately with myo-inositol, probiotics or the specific micronutrients studied here (vitamins B2, B6, B12, D, zinc) have not reported reductions in duration of labor nor in estimated postpartum blood loss.[16, 20, 21 14, 22-24] A reduction in the incidence of severe PPH from 17% to 12% ($p<0.01$) in a vitamin D trial was considered by the authors to be a spurious finding resulting from potential misclassification.[22] Labor progress was not reported in any previous antenatal supplementation studies, possibly due to the data not being collected as these events were not pre-specified outcomes, rather than there being no effect. It is possible that we observed an effect with the NiPPeR intervention because of the additive or synergistic effects of the various components.

Clinical Implications

Factors associated with increased postpartum blood loss include a raised BMI and higher parity (both adjusted for in our analyses), fetal macrosomia, operative deliveries, intrapartum cesarean section (rather than without labor), a prolonged labor, physiological third stage of labor, genital tract/perineal trauma, placental/cord anomalies (e.g. previa, accreta, velamentous insertion), uterine infections, and retained products of conception. Whilst among those who suffered a major PPH some of these events featured more prominently in the control group, analyses of the whole cohort suggest that the overall reduction in blood loss in the intervention group could not be attributed to a general reduction in any of these except for a reduced risk of a prolonged second stage and operative delivery for delayed second stage. It is likely that there are other factors not recorded in the trial that could have also contributed to decreased postpartum blood loss. Possibilities include changes in blood coagulation and subclinical intrauterine infections or inflammation, which were not measured in our study. Events such as pre-labor rupture of membranes (PROM) may be proxy markers of the latter, but combined term and preterm PROM occurred at similar rates between intervention and control arms

despite a previously reported reduction in exclusively preterm PROM with the NiPPeR intervention (aRR 0.39).[16] Further, the exclusion of preterm cases in sensitivity analyses did not alter results of reduced blood loss. Thus, it is likely that subclinical infection/inflammation is not a major contributor to our findings. No participants had known coagulopathies, and the six participants who took aspirin or clexane as prophylaxis against pre-eclampsia or venous thromboembolism within 7 days prior to delivery did not experience major PPH. Overall, mean birthweights and macrosomia rates were also similar between study groups[16] and cannot explain the reduction in blood loss.

The trial was conducted in high-resource settings with deliveries occurring in well-equipped and professionally-staffed units where risk of peripartum adversity is already low. Moreover, the recruited population were generally healthy and well-nourished, so it is notable that a nutritional supplement was still able to improve some peripartum outcomes further. From a women's perspective a 20-minute shortening of the second stage would be welcomed. At an institutional level, with constant pressure to increase resource-efficiency, this would have cumulative significance for labor ward management.

Since peripartum events were not primary outcomes of the trial, the study was not statistically powered to detect differences in labor length or blood loss at delivery, and the relatively modest sample size and number of events increased the possibility of types 1 and 2 statistical errors. Thus, findings should not be used to infer definitive treatment effects until further additional evidence is generated.

Research Implications

The mechanism of effect of the supplement, and which components either individually or in combination could be mediating the shortening of the second stage and reduced blood loss, are topics for further research. Observational and mechanistic studies in pre-clinical models and in

human tissues can provide clues to the potential underlying pathways involved. Zinc is an important co-factor in promoting blood coagulation,[13] and low zinc levels are associated with PPH. Several of the components including myo-inositol,[25] B-vitamers,[26] vitamin D[27, 28] and zinc[29,30], have demonstrated a role in the regulation of myometrial contractility. For example, myo-inositol (a naturally-occurring carbohydrate present ubiquitously in cells and enriched in fruits, grains, and nuts[31, 32]) could stimulate contraction of the myometrium from non-pregnant rats *ex-vivo* by facilitating the use of extracellular calcium;[25] a mechanism similar to one described for oxytocin.[33] Zinc-containing proteins regulate expression of oxytocin-induced contractile-associated factors in human myometrium.[29] Altered regulation of the general uteroplacental environment by inflammation, chemocytokines, eicosanoids and growth factors, which all play key roles in governing labor progress, could also be involved. After all, outside the context of pregnancy, myo-inositol, probiotics and micronutrients are known to impact such factors.[34, 35]

The postulation that the intervention could facilitate myometrial contractility is not inconsistent with our previous finding of reduced preterm delivery. Facilitation of labor progress at term is likely a distinct phenomenon to the triggers of premature onset of labor, thus, it is plausible that various components of the intervention could promote the former yet suppress the latter. Even if myometrial contractility is facilitated, our inability to detect any possible difference in first stage duration may be due to imprecision in estimating the timing of labor onset, which frequently occurs prior to hospital admission. Whereas the start of the second stage of labor, and hence its duration, is generally more precisely determined as women are mostly already admitted onto the labor ward.

Strengths and Limitations

The robust conduct of this double-blind RCT, which included prospectively collected data and

minimization of residual confounding through randomization, with external oversight by an independent data monitoring and trial steering committee, is a strength. Over 96% of women showed good adherence defined *a priori* as supplement intake greater than 60% averaged from recruitment to delivery.[16] However, documented timings of different stages of labor and estimates of blood loss show some subjectivity in routine medical record keeping. Despite these limitations, the mutually supportive findings that the intervention group had a lower incidence of delay in the second stage of labor alongside an overall reduction in the length of the second stage of labor, as well as a lower incidence of major PPH accompanied by an overall reduction in total estimated blood loss, reduces the likelihood that these are spurious findings. Even though recruitment occurred across three different countries with inclusion of multiple ethnicities, generalizability to the global population is limited by the lack of African and Amerindian women, in particular.

Conclusions

A supplement containing myo-inositol, probiotics and micronutrients starting preconception and continued throughout pregnancy reduced the length of the second stage of labor, operative delivery for delayed second stage, and blood loss at delivery. This needs confirmation by specifically designed clinical trials to better understand the underlying mechanisms and how nutritional supplementation may best be incorporated into clinical practice to improve peripartum outcomes.

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Table 1: Baseline characteristics of participants providing peripartum data

Characteristic	Whole cohort		Underwent labor		Reached second stage of labor	
	Control (n=290)	**Intervention (n=293)**	**Control (n=249)**	**Intervention (n=259)**	**Control (n=215)**	**Intervention (n=220)**
Age [years; mean (SD)]	30.1 (3.3)	30.6 (3.3)	29.8 (3.2)	30.4 (3.3)	29.7 (3.2)	30.5 (3.3)
Pre-pregnancy BMI [kg/m^2; median (IQR)]	23.7 (21.3 to 27.5)	23.6 (21.2 to 26.1)	23.6 (21.3 to 27.5)	23.4 (21.0 to 25.7)	23.3 (21.0 to 26.7)	23.4 (21.0 to 25.5)
Study site, n (%)						
UK	93 (32.1)	96 (32.8)	78 (31.3)	83 (32.1)	70 (32.6)	70 (31.8)
SG	81 (27.9)	85 (29.0)	74 (29.7)	76 (29.3)	68 (31.6)	67 (30.5)
NZ	116 (40.0)	112 (38.2)	97 (39.0)	100 (38.6)	77 (35.8)	83 (37.7)
Ethnicity, n (%)						
White Caucasian	168 (58.0)	177 (60.4)	139 (55.8)	156 (60.2)	117 (54.4)	133 (60.5)
Chinese	73 (25.2)	73 (24.9)	66 (26.5)	64 (24.7)	62 (28.8)	56 (25.5)
South Asian	14 (4.8)	16 (5.4)	13 (5.3)	12 (4.6)	11 (5.1)	9 (4.0)
Malay	12 (4.1)	11 (3.8)	11 (4.4)	11 (4.3)	10 (4.7)	11 (5.0)
Other	23 (7.9)	16(5.4)	20 (8.0)	16 (6.2)	15 (7.0)	11 (5.0)
Education, n (%)						
Not degree level	81 (27.9)	83 (28.3)	71 (28.5)	72 (27.8)	60 (27.9)	65 (29.5)
Degree level or higher	209 (72.1)	210 (71.7)	178 (71.5)	187 (72.2)	155 (72.1)	155 (70.5)
Household income, n (%)						
Lowest quintile	5 (1.7)	2 (0.7)	4 (1.6)	2 (0.8)	3 (1.4)	2 (0.9)
Second quintile	21 (7.2)	22 (7.5)	19 (7.6)	21 (8.0)	19 (8.9)	19 (8.6)
Third quintile	69 (23.8)	55 (18.8)	64 (25.7)	44 (17.0)	54 (25.1)	38 (17.3)
Fourth quintile	93 (32.1)	109 (37.2)	76 (30.5)	101 (39.0)	63 (29.3)	85 (38.6)
Highest quintile	92 (31.7)	92 (31.4)	77 (30.9)	81 (31.3)	68 (31.6)	66 (30.0)
Unavailable	10 (3.5)	13 (4.4)	9 (3.6)	10 (3.9)	8 (3.7)	10 (4.6)
Smoking, n (%)						
Never smoked	225 (78.4)	237 (81.4)	195(79.3)	212 (82.1)	174 (82.1)	180 (82.2)
Previous smoker	50 (17.4)	43 (14.8)	40 (16.3)	36 (14.0)	30 (14.1)	30 (13.7)
Active smoker	12 (4.2)	11 (3.8)	11 (4.5)	10 (3.9)	8 (3.8)	9 (4.1)
Nulliparous, n (%)	199 (68.6)	170 (58.0)	177(71.1)	159 (61.4)	148 (68.8)	125 (56.8)
Previous cesarean section (denominator - all parous women), n (%)	29 (31.9)	32 (26.0)	14 (19.4)	15 (15.0)	11 (16.4)	11 (11.6)
Preconception plasma glucose [mmol/L; median (IQR)] in a 75g oral glucose tolerance test						
Fasting	4.9 (4.5 to 5.2)	4.9 (4.6 to 5.2)	4.9 (4.5 to 5.2)	4.9 (4.6 to 5.2)	4.9 (4.5 to 5.2)	4.9 (4.5 to 5.2)
2-hour	5.4 (4.4 to 6.4)	5.5 (4.6 to 6.3)	5.4 (4.4 to 6.4)	5.5 (4.6 to 6.3)	5.3 (4.3 to 6.4)	5.5 (4.6 to 6.3)

Abbreviations: BMI, body mass index; IQR, interquartile range; n, number; SD, standard deviation

Table 2: Effect of the NiPPeR intervention on blood loss, postpartum hemorrhage and blood transfusion

BLOOD LOSS	**Control Median (IQR)**	**Intervention Median (IQR)**	**Effect of Intervention**					
			N	**Adjusted mean difference (95% CI)[a,b]**	**P value**	**N**	**Fully-adjusted mean difference (95% CI)[b,c]**	**P value**
Estimated blood loss at delivery (ml)	350.0 (250.0, 500.0)	300.0 (200.0, 425.0)	561	-42.0 (-77.0 to -10.5)	0.012*	535	-35.0 (-70.0 to -3.5)	0.047*
POSTPARTUM HEMORRHAGE								
Categories of PPH[d]	**Control N cases/total (%)**	**Intervention N cases/total (%)**	**Effect of Intervention**					
			N	**Adjusted RR (95% CI)[a]**	**P value**	**N**	**Fully-adjusted RR (95% CI)[c]**	**P value**
No PPH	226/279 (81.0)	231/282 (81.9)	561	Reference	…	535	Reference	…
Minor PPH (500-1000 ml)	29/279 (10.4)	42/282 (14.9)	561	1.44 (0.85 to 2.45)	0.171	535	1.64 (0.95 to 2.85)	0.078
Major PPH (>1000 ml)	24/279 (8.6)	9/282 (3.2)	561	0.37 (0.16 to 0.82)	0.015*	535	0.43 (0.19 to 0.99)	0.048*
BLOOD TRANSFUSION								
Received blood transfusion	7/286 (2.5)	1/289 (0.3)	Insufficient cases for analysis					…

[a]Basic model: Adjusted for site and ethnicity.
[b]Linear regression, $\log_e$-transformed for analyses, values presented are the calculated equivalent anti-log based on the median value in the control group, and represents estimated mean differences.
[c]Fully-adjusted model: $\log_e$ values adjusted for site, ethnicity, maternal age, pre-pregnancy BMI, household income deciles, parity, previous cesarean section history and smoking.
[d]Multinomial logistic regression analysis.
Statistically significant *p<0.05.
Abbreviations: BMI, body mass index; CI, confidence interval; IQR, interquartile range; N, number; PPH, postpartum hemorrhage; RR, risk ratio.

Figure legends:

Figure 1. Flowchart of study participants from assessment of eligibility, through randomisation, conception and delivery. Abbreviation: cesarean, cesarean section delivery.

Figure 1

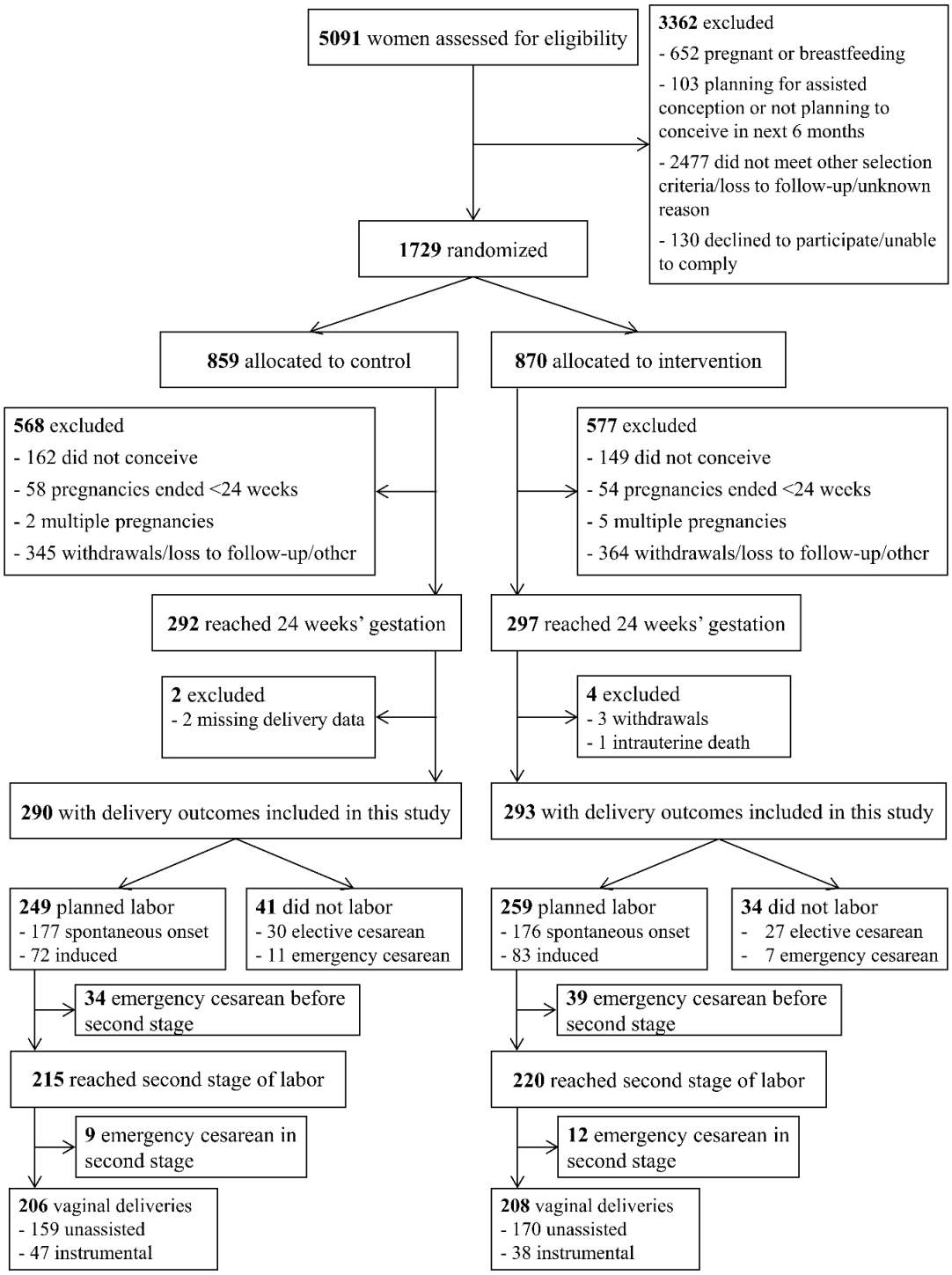
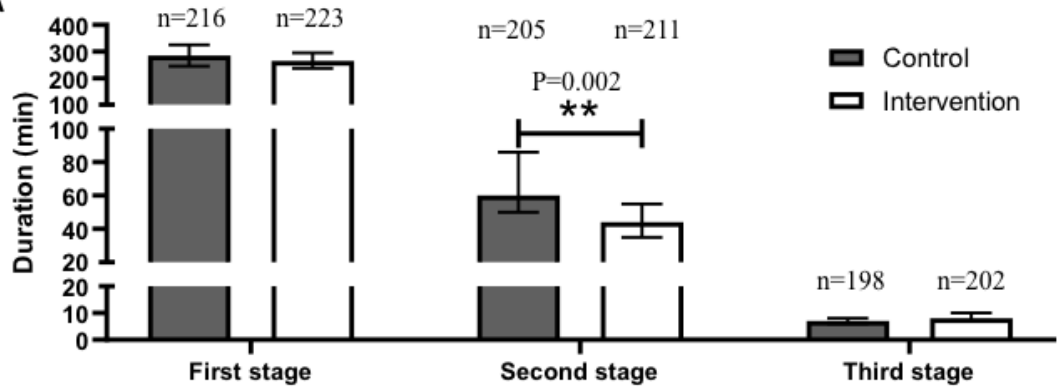


Figure 2. Effect of the NiPPeR intervention on labor progress and oxytocin augmentation among those who labored. (A) Unadjusted comparison of the duration of the three stages of labor between control and intervention groups by Mann-Whitney *U* test. Error bars denote the 95% CI of the mean. (B) Forest plot comparing the risk ratio (RR) between control and intervention groups for factors influencing labor progress. [a]Basic model: adjusted for site and ethnicity. [b]Fully-adjusted model: adjusted for site, ethnicity, maternal age, pre-pregnancy BMI, household income deciles, parity, previous cesarean section history and smoking. [c]Additionally adjusted for epidural use. [d]Not adjusted for parity as already taken into account by ACOG definition and treating clinician. [e]Additionally adjusted for induction of labor; operative delivery includes cesarean section and instrumental vaginal deliveries . Statistically significant *p<0.05, **p<0.01. Only women with available data were included. Abbreviations: BMI, body mass index; CI, confidence interval; IQR, interquartile range; min, minutes; N, number; RR, risk ratio.

Figure 2

A



B

	N cases/total (%) Control	N cases/total (%) Intervention	Adjusted RR (95% CI)[a]	Fully-adjusted RR (95% CI)[b]
Labor progress				
Delay in first stage[c] (denominator – all who underwent labor)	22/249 (8.8)	23/259 (8.9)		
Delay in second stage[d] (denominator – all reaching second stage)	55/215 (25.6)	42/220 (19.1)		* p=0.026
Delay in second stage requiring operative delivery[d] (denominator – all reaching second stage)	41/215 (19.1)	29/220 (13.2)		* p=0.022
Prolonged third stage (denominator – all vaginal births)	13/198 (6.6)	13/202 (6.4)		
Oxytocin augmentation				
Oxytocin use in labor[c] (denominator – all who underwent labor)	105/249 (42.2)	94/259 (36.3)		
Oxytocin use in labor for augmentation only (denominator – all who had spontaneous labor-onset)	65/177 (36.7)	45/176 (25.6)	* p=0.029	
Maternal choices that can influence duration of labor				
Epidural (denominator – all who labored)	144/249 (57.8)	137/259 (52.9)		
Epidural (denominator – all reaching second stage of labor)	111/215 (51.6)	100/220 (45.5)		
Physiological third stage (denominator – all vaginal births)	14/203 (6.9)	20/206 (9.7)		

Supplementary Table 1: Effect of the NiPPeR intervention on labor-onset, mode of delivery and indications/complications leading to operative delivery

	Control N cases/ 290 (%)	Intervention N cases/ 293 (%)	Effect of Intervention					
			N	Adjusted RR (95% CI)[a]	P value	N	Fully-adjusted RR (95% CI)[b]	P value
Labor-onset (n=583)[c]								
Spontaneous onset	177 (61.0)	176 (60.1)	353	Reference	…	339	Reference	…
Induced	74 (25.5)	86 (29.3)	160	1.18 (0.81 to 1.72)	0.397	152	1.47 (0.97 to 2.20)	0.067
No labour	39 (13.5)	31 (10.6)	70	0.79 (0.47 to 1.32)	0.361	66	0.63 (0.34 to 1.16)	0.137
Mode of delivery (n=583)[c]								
Unassisted vaginal delivery	159 (54.8)	170 (58.0)	329	Reference	…	313	Reference	…
Instrumental delivery	47 (16.2)	38 (13.0)	85	0.73 (0.45 to 1.19)	0.211	81	0.81 (0.48 to 1.38)	0.435
Cesarean section in labour	43 (14.8)	51 (17.4)	94	1.13 (0.71 to 1.80)	0.617	92	1.51 (0.90 to 2.53)	0.120
Cesarean section without labour	41 (14.2)	34 (11.6)	75	0.76 (0.46 to 1.26)	0.287	71	0.65 (0.35 to 1.19)	0.160
Indications/Complications leading to operative deliveries (instrumental and caesarean)[d,e]								
Delay in first or second stage of labour	63 (21.7)	53 (18.1)	583	0.84 (0.61 to 1.16)	0.281	557	0.98 (0.71 to 1.34)	0.883
Suspected fetal hypoxia/abnormal CTG	37 (12.8)	48 (16.4)	583	1.31 (0.88 to 1.94)	0.183	557	1.37 (0.93 to 2.03)	0.114
Placental-related complications (hypertensive disorders of pregnancy, suspected IUGR/SGA, oligohydramnios, abnormal Doppler, placenta/vasa previa, placental abruption)	12 (4.1)	7 (2.4)	583	0.56 (0.23 to 1.37)	0.203	557	0.50 (0.17 to 1.45)	0.199
Other fetal issues (macrosomia, malpresentation, congenital anomaly)	23 (7.9)	20 (6.8)	583	0.85 (0.48 to 1.52)	0.583	557	0.84 (0.46 to 1.53)	0.569
Maternal medical problems (GDM, bladder prolapse etc.)	3 (1.0)	5 (1.7)	583	1.68 (0.40 to 7.00)	0.478	557	1.60 (0.40 to 6.40)	0.507
Failed induction of labour, pre-labor rupture of membranes, chorioamnionitis	3 (1.0)	4 (1.4)	583	1.27 (0.29 to 5.58)	0.755	557	1.15 (0.23 to 5.67)	0.866
Maternal request / psychosocial	15 (5.2)	11 (3.8)	583	0.70 (0.33 to 1.49)	0.354	557	0.72 (0.36 to 1.44)	0.351
Previous cesarean section	15 (5.2)	18 (6.1)	583	1.18 (0.61 to 2.31)	0.621	557	1.09 (0.54 to 2.20)	0.800

[a] Adjusted for site and ethnicity.

[b] Adjusted for site, ethnicity, maternal age, pre-pregnancy BMI, household income, parity, previous cesarean history and smoking (N=557 with full dataset for analyses).

[c] Multinomial logistic regression analysis

[d] Some cases had more than one indication.

[e] Poisson regression analysis

Abbreviations: BMI, body mass index; CI, confidence interval; CTG, cardiotocography; GDM, gestational diabetes; IUGR, intrauterine growth restriction; N, number; RR, risk ratio; SGA, small for gestational age

Supplementary Table 2: Indications for labour induction comparing control and intervention groups

Indications for labor induction	Control N cases/ total (%)	Intervention N cases/ total (%)	N	Adjusted RR (95% CI)[a]	P value	N	Fully-adjusted RR (95% CI)[b]	P value
Placental-related complications (hypertensive disorders of pregnancy, suspected IUGR/SGA, oligohydramnios, abnormal Doppler) or suspected fetal compromise (decreased fetal movements, suspicious CTG)	24/74 (32.4)	28/86 (32.6)	160	0.99 (0.63 to 1.54)	0.959	152	1.05 (0.66 to 1.66)	0.843
Pre-labor rupture of membranes	15/74 (20.3)	19/86 (22.1)	160	1.11 (0.61 to 2.02)	0.732	152	1.30 (0.67 to 2.51)	0.439
Post-term/prolonged pregnancy	16/74 (21.6)	14/86 (16.3)	160	0.74 (0.40 to 1.38)	0.345	152	0.70 (0.36 to 1.33)	0.274
Fetal indications (macrosomia, polyhydramnios, unstable lie, congenital anomaly)	6/74 (8.1)	11/86 (12.8)	160	1.61 (0.65 to 3.97)	0.304	152	1.21 (0.52 to 2.81)	0.656
Gestational diabetes	17/74 (23.0)	19/86 (22.1)	160	0.97 (0.55 to 1.72)	0.928	152	1.02 (0.54 to 1.91)	0.952
Maternal request/psychosocial	6/74 (8.1)	6/86 (7.0)	160	0.82 (0.28 to 2.42)	0.718	152	0.49 (0.16 to 1.48)	0.206
Other maternal health concerns	4/74 (5.4)	4/86 (4.7)	160	0.92 (0.24 to 3.56)	0.903	152	1.23 (0.28 to 5.48)	0.782

[a] Adjusted for site and ethnicity.
[b] Adjusted for site, ethnicity, maternal age, pre-pregnancy BMI, household income deciles, parity, previous cesarean section history and smoking.
Abbreviations: BMI, body mass index; CI, confidence interval; CTG, cardiotocography; IUGR, intrauterine growth restriction; N, number; RR, risk ratio; SGA, small for gestational age.

Supplementary Table 3: Comparison of the incidences of risk factors for postpartum hemorrhage between control and intervention groups among those who experienced major postpartum hemorrhage (>1000 ml).

Risk factors for postpartum hemorrhage	Control (n=24) N (%)	Intervention (n=9) N (%)
Delay in first stage	4 (16.7)	2 (22.2)
Delay in second stage	11 (45.8)	1 (11.1)
Cesarean section delivery	10 (41.7)	6 (66.7)
Instrumental vaginal delivery	7 (29.2)	0 (0.0)
Unusual placental/cord structure[a]	2 (8.3)	0 (0.0)
Physiological or prolonged third stage (>30min)	5 (20.8)	0 (0.0)
Retained placenta and/or manual removal	5 (20.8)	1 (11.1)
Pre-labor rupture of membranes (term and preterm)	5 (20.8)	2 (22.2)
Significant perineal trauma	7 (29.2)	0 (0.0)
Macrosomia	4 (16.7)	2 (22.2)

[a]Succenturiate lobe, battledore/marginal or velamentous cord insertion.

Supplementary Table 4: Sensitivity analyses for the effect of the NiPPeR intervention on second stage of labour and postpartum blood loss excluding preterm deliveries (n=44)

Outcome	Control Median (IQR) or N cases/ total (%)	Intervention Median (IQR) or N cases/ total (%)	N	Adjusted model mean difference or RR (95% CI)[a]	P value	N	Fully-adjusted model mean difference or RR (95% CI)[b]	P value
SECOND STAGE OF LABOR								
Duration of second stage (min)[c]	60.5 (29.0 to 132.8)	44.5 (16.0 to 103.8)	416	-21.2 (-34.5 to -7.3)	0.002*	395	-13.9 (-24.8 to -3.6)[d]	0.009*
Delay in second stage	50/198 (25.3)	39/207 (18.8)	405	0.72 (0.50 to 1.03)	0.071	388	0.66 (0.46 to 0.94)	0.022*
Delay in second stage requiring operative delivery	38/198 (19.2)	29/207 (14.0)	405	0.69 (0.45 to 1.06)	0.090	388	0.62 (0.41 to 0.95)	0.026*
POSTPARTUM BLOOD LOSS								
Estimated blood loss (ml)[c]	350.0 (250.0 to 500.0)	300.0 (225.0 to 490.0)	561	-42.0 (-77.0 to -7.0)	0.016*	535	-35.0 (-70.0 to 3.5)	0.055
Major PPH[e]	24/253 (9.5)	8/265 (3.0)	561	0.30 (0.13 to 0.70)	0.005*	535	0.35 (0.15 to 0.84)	0.019*

[a] Adjusted for site and ethnicity (basic model)
[b] Adjusted for site, ethnicity, maternal age, pre-pregnancy BMI, household income deciles, parity, previous cesarean section history and smoking
[c] Log-transformed for analyses, values presented are the calculated equivalent anti-log based on the median value in the control group, and represents estimated mean differences
[d] Additionally adjusted for epidural use
[e] Poisson regression analysis
* $p<0.05$
Abbreviations: IQR, interquartile range; PPH, postpartum hemorrhage

Supplementary Figure 1. Examining risk factors for postpartum hemorrhage (PPH) that can potentially explain the effect of the NiPPeR intervention in reducing postpartum blood loss. (A) Comparison of the incidences of risk factors for PPH between control and intervention groups among all participants with peripartum data (n=583). [a]Basic model: adjusted for site and ethnicity. [b]Fully-adjusted model: adjusted for site, ethnicity, maternal age, pre-pregnancy BMI, household income deciles, parity, previous cesarean section history and smoking. [c]Succenturiate lobe, battledore/marginal or velamentous cord insertion. Abbreviations: BMI, body mass index; CI, confidence interval; N, number; PPH, postpartum hemorrhage; RR, risk ratio.