**Pethidine versus nitrous oxide for pain relief during labor in multiparous women. A randomized controlled trial**

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**Summary**

Intravenous pethidine and inhaled nitrous oxide have similar intrapartum analgesic effects in multiparas 20–30 minutes after administration. Maternal and neonatal adverse effects are also comparable.

**Short Title:** Intrapartum pethidine versus nitrous oxide in multiparous women

**AJOG at a Glance**

**Why the study was conducted**

Parous women sometimes decline epidural analgesia, particularly multiparous women who are expected to have a shorter delivery duration than primiparous and parous women who have a contraindication or specific preferences. The present trial was conducted to compare the efficacy and adverse effects of intravenous pethidine and inhaled nitrous oxide for intrapartum analgesia in multiparous women as an alternative to an epidural.

**Key findings**

The results of the present randomized trial indicate that the severity of pain as measured by visual analog scale score is similar after 20–30 minutes of intravenous pethidine or inhaled nitrous oxide administration. The prevalences of maternal and neonatal adverse effects are also comparable. The proportion of women who established breastfeeding immediately at delivery tended to be higher among women who used nitrous oxide.

**What this adds to the literature**

Inhaled nitrous oxide has similar efficacy to intravenous pethidine but tended to be associated with an increased breastfeeding rate immediately after birth. These observations suggest that parous women and providers should avoid intrapartum opioid use when epidural analgesia is not an option, thereby lessening concerns regarding postpartum chronic opioid use.

**Keywords:** intrapartum analgesia; multiparous; nitrous oxide; pethidine

**Abstract**

**Objective**

Multiparous women, who are expected to have a shorter labor than primiparas, sometimes prefer to avoid intrapartum invasive pain relief such as neuraxial analgesia. In addition, neuraxial analgesia may be contraindicated or may not be immediately available upon request in some medical centers. In these cases, the initial drug of choice for multiparous women in labor is unknown. Thus, we compared the efficacy and adverse effects of intravenous pethidine (meperidine) and inhaled nitrous oxide (NO) for intrapartum analgesia in multiparas.

**Methods**

This randomized controlled trial was conducted at Emek Medical Center, Afula, Israel, between August 2016 and May 2019. Term, singleton, multiparous women in labor were randomized in a 1:1 ratio to 50 mg intravenous pethidine or inhaled nitrous oxide. The primary outcome was pain intensity 20–30 minutes after analgesic administration measured by a visual analog scale (VAS) from 0 to 10 cm. Secondary outcomes included need for additional analgesia, labor length, delivery mode, and maternal and neonatal adverse effects. To detect a 1±2.6 difference in the VAS score between the groups, 214 women (107 in each group) were needed to achieve 80% power with an alpha of 0.05.

**Results**

Of the 214 women enrolled, 14 were excluded after randomization. Of the 200 analyzed, 102 received nitrous oxide and 98 received intravenous pethidine. Demographic and obstetric variables were comparable between the two groups. The VAS score 20–30 minutes after analgesic administration did not differ between the groups (7.6±2.7 and 7.7±2.3 in the pethidine and nitrous oxide groups, respectively, p=0.89). There were no significant differences between the groups in the rate of additional analgesic use, labor length, delivery mode, Apgar score, rate of breastfeeding, patient satisfaction, or maternal and neonatal adverse effects.

**Conclusion**

Pain intensity was comparable in multiparas 20–30 minutes after administration of pethidine and nitrous oxide. Adverse effects were also comparable.

**Clinical Trial Registration:** ClinicalTrials.gov identifier NCT02783508

**Introduction**

Pain relief during childbirth is an essential part of good medical care (1). The intensity of pain during childbirth and its management influence the course of the labor, maternal and fetal outcomes, and satisfaction with the entire birth process (1). A good painkiller should be strong enough to reduce pain perception while having as few adverse effects as possible (2). Parous women who are interested in pain relief, particularly multiparas, who are expected to have a shorter delivery duration than primiparas, might prefer to avoid the use of invasive approaches such as neuraxial analgesia. In addition, even in institutions where anesthesia is fully available for the obstetric team, there may be situations where neuraxial analgesia is not immediately available or fails for technical reasons or where the patient has a contraindication, as in the case of thrombocytopenia (1).

Both inhaled analgesics and intravenous opioids are pharmacological options for analgesia during childbirth (2,3). Inhaled nitrous oxide has been used for pain relief during childbirth since the late 19th century (3). Nitrous oxide in combination with oxygen at a concentration of 50:50 is the most commonly used dose during childbirth. Its onset of effect is rapid (within 30–60 seconds) and so is the clearance (3–4 exhalations) (1). Moreover, it affects the mother’s pain sensation and has anti-anxiety effects (3). Various adverse effects associated with nitrous oxide have been reported, such as nausea, dizziness, and drowsiness (1).

Opioids are also widely used for pain relief during childbirth. Their advantage is that they are inexpensive, easy to use, and have high availability (4). Pethidine (meperidine) is one of the most widely used opioids. Given intravenously (or intramuscularly), its effects begin within a few minutes and last 2–4 hours (3). Opioids have known adverse effects on the mother, including nausea, vomiting, discomfort, and risk of chronic use postpartum. In the newborn, the drug may lead to postpartum respiratory depression, difficult breastfeeding, and restlessness due to transfer across the placenta (5).

Data comparing these two drugs are scarce, and there is currently no first-line painkiller in women who wish to avoid neuraxial analgesia. Accordingly, the aim of the present trial was to compare these two agents to determine the superior painkiller in this setting. Because most primiparous women elect to have neuraxial analgesia (6), the study population selected for this trial included only multiparous women.

**Patients and methods**

This randomized controlled trial was conducted in the delivery ward of Emek Medical Center, Afula, Israel, between August 2016 and May 2018. The study population comprised term singleton pregnant women (37–41 weeks) who were admitted to the delivery ward in labor and expressed their desire for analgesia. The criteria for exclusion included women who expressed their desire for neuraxial analgesia in advance, women who received pethidine 24 hours before entering the delivery room, women with any contraindication to vaginal birth, known susceptibility to pethidine or nitrous oxide, history of drug use, and women who had a previous cesarean section. The recruitment for the trial was conducted in the delivery ward.

Consenting women received upon request one of the study drugs. The use of each of the study drugs was according to the usual delivery room protocols. The pethidine group received intravenous pethidine at a dose of 50 mg diluted in 100 mL of 0.9% sodium chloride solution infused over 10 minutes. Repeated doses of pethidine, if required, were given in the same dose at intervals of at least two hours and up to a maximum of four doses. The nitrous oxide group received inhaled nitrous oxide combined with oxygen at a concentration of 50:50. The mask attached to the device was adapted to adhere to the woman’s face and connected to the device using a tube with a valve for gas emissions. The women were instructed and trained by midwives to press the mask forward and breathe through it once the contraction began. The goal was to achieve at least three deep inhalations through the mask and exhale through it. Between contractions, the woman was instructed not to breathe through the mask.

Prior to analgesic administration, the women were asked about the severity of the pain according to a visual analog scale (VAS) from 0 to 10, where 10 indicates unbearable pain. At the analgesic request, the baseline VAS score was recorded by midwives immediately before the study drugs were administered. About 20–30 minutes after administration of one of the study drugs, the midwives again recorded the pain severity using the VAS. The maximum VAS score during the last contraction was recorded. In cases where the VAS had not decreased at 20–30 minutes, a crossover between the drugs or an epidural was offered.

Data collection was performed using the hospital’s electronic forms. The basic demographic and obstetric characteristics of the women were collected from the admission forms. Data on the course of labor, use of labor induction, time from administration of the painkiller to delivery, use of additional painkillers, and mode of delivery were collected from the electronic forms of the delivery ward. Neonatal outcomes were collected from the electronic admission forms in the nursery. Data on the severity of pain and adverse effects were documented in a dedicated study form. Repeated pethidine use, transition from one group to another, or use of an epidural was documented in the designated form.

Women were monitored in the labor and delivery ward. Vital signs were examined before the analgesic was given and 20–30 minutes after the drug was received and continued hourly until delivery. Assessment of maternal sedation and occurrence of nausea, vomiting, headache, and dry mouth were recorded during the first hour after the administration of the analgesic. Midwives assessed maternal sedation on a 4-point scale where: 0 is alert; 1, mildly drowsy; 2, moderately drowsy; and 3, asleep (7).

Maternal satisfaction and desire to use the same analgesic in a future delivery were assessed by a questionnaire delivered to the mother within 48 hours of birth. Respondents expressed their satisfaction on a 5-point scale, where 1 is very dissatisfied and 5 is very satisfied.

**Randomization**

Women were randomly assigned to the study group or the control group at a 1:1 ratio. A researcher (RS) not otherwise involved in enrolling women into the trial prepared the random allocation in blocks of 10 using computer-generated random allocation. Eligible women were assigned the next available sequence in the randomization list. The list was concealed and investigators and the enrolled participants were unaware of the upcoming group assignments until the moment of assignment. Placebo was not used, and the details of the research drug were unmasked to the midwife and medical staff.

**Primary outcome**

The primary outcome was pain severity measured 20–30 minutes after administration of one of the study drugs by VAS score.

**Sample size**

To demonstrate a difference of 1 in a VAS (on a scale from 0 to 10 cm) with a standard deviation of 2.6 (7,8) 20–30 minutes after analgesic administration, 214 women in total were needed to achieve a power of 80% and a two-sided alpha of 0.05.

**Ethics**

The institutional review board at Emek Medical Center, Afula, Israel, approved the trial protocol on June 21, 2016 (#0072-16-EMC). All individual participants provided informed consent. The trial was registered at [Clinical](http://www.clinical)Trials.gov (identifier: NCT02783508). A local data monitoring committee implemented quality control of the screening and verification of protocol compliance.

**Statistical analysis**

Continuous variables are presented using standard distribution indices (mean, standard deviation, median, and range). Categorical variables are presented using frequency and relative frequency. The relationship between the study groups (group 1, pethidine; group 2, nitrous oxide) and categorical variables was examined using a chi-square test (or Fisher’s exact test), and the difference between the different levels of these variables is represented by odds ratio (OR). For continuous variables, the relationship was examined using a Student’s test (or Wilcoxon test). Data processing was performed using SAS 9.4 software. Results were significant at *P*<0.05. An intention-to-treat analysis was used.

**Results**

During the study period, 214 women were recruited to participate in the study, 106 in the pethidine group and 108 in the nitrous oxide group. Of all recruited women, 14 were excluded from the final analysis: eight from the pethidine group (four were excluded from the time of data collection after delivery because it became clear that they had received pethidine 24 hours before recruitment, three whose labor progressed rapidly before they received the study drug, and one whose primary and several secondary outcomes were not collected) and six from the nitrous oxide group (four whose labor progressed rapidly before they received the study drug, one who was at 35 weeks gestation after the dating was repeated, and one whose primary outcome and several secondary outcomes were not collected). Thus, the overall data of 200 women—102 in the nitrous oxide group and 98 in the pethidine group—were analyzed (Figure 1).

The demographic and intrapartum variables of the trial groups are presented in Table 1. There were no significant differences between the two groups in cervical conditions (dilatation and effacement) at analgesic request. Pain severities according to VAS score at the time of analgesic requirement were 7.9±1.9 and 7.8±2.2 in the nitrous oxide and pethidine groups, respectively (*P*=0.69). In addition, 76.5% and 68.4% of women in the nitrous oxide and pethidine groups, respectively, had VAS scores of 7 or more (*P=*0.21) at analgesic request. Mean VAS scores 20–30 minutes from administration of the analgesic (i.e., the primary outcome) were 7.7±2.3 and 7.6±2.7 in the nitrous oxide and pethidine groups, respectively (*P*=0.89) (Table 2). The VAS score at 60 minutes was significantly lower in the pethidine group than in the nitrous oxide group (7.7±2.3 vs. 8.6±1.9, respectively; *P=*0.03), although the difference was less than 1.0. At 120 and 180 minutes, the VAS did not differ significantly between the groups (Table 2). In addition, there was no significant difference between the groups in the need for an additional analgesic, including epidural. There were no significant differences between the groups in terms of the mother’s satisfaction with the pain relief or the willingness to use the same painkiller in future deliveries.

Time from analgesic request to delivery and the mode of delivery were not significantly different between the groups. In the nitrous oxide group, all women had spontaneous vaginal delivery, whereas there were four (4.1%) cases of vacuum deliveries in the pethidine group. There were no cesarean deliveries in either group (Table 3). There were no significant differences between the groups in the incidence of adverse effects that could be attributed to the analgesic used (Table 3).

Neonatal outcomes are presented in Table 4. There were no significant differences between the groups in terms of Apgar score, cord arterial pH, or need for oxygen supplementation immediately after delivery. The percentage of neonates who breastfed immediately after delivery was 95.1% in the nitrous oxide group compared with 87.8% in the pethidine group (*P*=0.06). The rates of breastfeeding at 24 hours postpartum were similar (*P*=0.71). Other neonatal outcomes examined were comparable between the two groups.

**Discussion**

The results of the present study indicate that pain severity as measured by VAS score was similar after 20–30 minutes of intravenous pethidine or nitrous oxide administration among multiparous women in labor. The effect on labor duration and mode of delivery was also comparable. The prevalences of maternal adverse effects, including the degree of drowsiness, were similar in the two groups. There was also no difference in the outcomes of the newborns. The proportion of women who established breastfeeding immediately at delivery tended to be lower among women who used pethidine.

Intravenous opioids and inhaled nitrous oxide are two medications widely used for pain relief during childbirth. Nevertheless, limited data are available on head-to-head comparisons of intravenous pethidine and nitrous oxide in multiparous women only. Chantrasiri et al. reported that the two agents have comparable effectiveness in a small trial, although the women who received nitrous oxide were more satisfied. The trial comprised both primi- and multiparous women (9). Mobaraki et al. randomized 100 mothers to intramuscular pethidine or inhaled nitrous oxide and found, in contrast to the present trial, that nitrous oxide was more effective in relieving pain than pethidine 30 minutes after administration (10). The difference in the results is probably related to the fact that, in the present study, the pethidine was intravenously administered, unlike the intramuscular administration in Mobaraki et al. (10). With intravenous administration, the effect of pethidine is faster and reaches a peak within 5–7 minutes; with intramuscular administration, the peak is 30–50 minutes after administration. Thus, at 30 minutes, the maximal effect may not be achieved with intramuscular administration (11).

Notably, both study drugs had a small effect on decreasing analgesia perception from baseline, as demonstrated at 30, 60, 120, and 180 minutes of administration. The analgesic effects of these agents are reported to be lower than epidural when pain scores are the outcome of interest (12). Nonetheless, the reduction in the VAS score was less than 1 compared with baseline in both groups. On the other hand, more than 30% of the women had some sedative effect related to the study drugs in both groups. This is probably the main effect of these agents during childbirth. Olofsson et al. reported that opioids provide sedation and a sense of euphoria, but that their analgesic effect in labor is limited and that their primary mechanism of action is sedation (13). In the case of nitrous oxide, the minor effect on analgesia perception may have several causes. Women receiving nitrous oxide may start using the mask too late and not once the contraction is felt, despite receiving adequate instruction and training from the midwives. In addition, the method of administration during childbirth, that is, on demand and not in a continuous manner, may also influence the effectiveness. In the field of gastroenterology, Løberg et al. reported that the conflicting finding that nitrous oxide is comparable to intravenous medication in colonoscopy but hardly favorable to placebo in flexible sigmoidoscopy might be explained by the continuous use during colonoscopy and the on-demand use during flexible sigmoidoscopy (14). Furthermore, a concentration other than 50:50 with oxygen may also determine the level of the effect on pain.

According to the results of this study, the incidence of maternal adverse effects was relatively low in the two study groups compared with other reports (7,8). In addition, the incidence of adverse effects was also comparable, versus previous publications that showed higher rates of intravenous opioid use (15,16). In terms of effects on the newborn, there was no difference between the groups in the incidence of the neonatal outcomes examined. The rate of neonatal adverse events was generally low in both study groups and, in accordance with other studies, particularly related to the occurrence of neonatal respiratory depression (9).

The nitrous oxide group tended to have a higher rate of breastfeeding immediately after birth than the pethidine group. This difference could be related to the degree of sleepiness of the mother after birth and her ability to breastfeed. Nevertheless, there was no difference between the groups in sleepiness rate. Intravenously administered pethidine crosses the placenta and can accumulate in the fetal blood system and affect newborn behavior, including suckling ability (17–19). This is in contrast to nitrous oxide, which is rapidly released from the blood system (20). In this study, we did not examine the levels of pethidine and its metabolites in the newborns’ blood, but it is possible that this explanation underlies the difference in the rate of immediate breastfeeding between groups.

Satisfaction is a complex measure associated with various personal and environmental characteristics and is difficult to assess thoroughly. During childbirth, many factors affect the mother’s satisfaction, including her expectations, involvement in the birth process, and relationship with the care team (21,22). In this trial, mothers’ satisfaction and willingness to use the same painkiller in the future were comparable between the groups.

**Strength and limitations**

The different forms of administration of the two study drugs made it difficult to use a placebo and conduct a double-blind trial. The strengths of the study stem from its randomized design that focuses on multiparous women only, that is, a group of parous women that use intrapartum analgesia other than epidural at a higher percentage compared with primiparous women. In addition, the fact that the study was conducted in a single institution, with identical intrapartum management, reinforces the results.

**Conclusion**

The best painkiller is one that will have a beneficial effect on the pain with minimal adverse effects for the mother and newborn. Many years of experience have been accumulated in the delivery ward for both nitrous oxide and pethidine. Both are easy to use and associated with low costs. The results of the present trial show that nitrous oxide has similar efficacy to pethidine and might be associated with an increased breastfeeding rate immediately after birth. The use of nitrous oxide to reduce peripartum opioid use is a considerable goal due to the major concern of chronic postpartum opioid use. These observations enable clinicians to provide informed and reliable counsel to mothers, particularly multiparas, regarding the various options for pain relief during childbirth.

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Table 1. Maternal demographic and intrapartum variables of the trial groups

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Nitrous oxide**  **N=102** | **Pethidine**  **N=98** | ***P*-value\*** |
| Maternal age, years | 29.7±4.7  [29.5; 26.0–33.0] | 29.5±5.4  [28; 25.0–33.0] | 0.50 |
| Ethnicity  Jewish  Arabic | 35 (34.3)  67 (65.7) | 23 (23.5)  75 (76.5) | 0.09 |
| Pre-gestational body mass index, kg/m2 | 25±4.7  [24.4; 21.9–28.2] | 25±4.5  [24.9; 21.4–28.0] | 0.81 |
| Parity | 3±1.2  [3; 2–4] | 3.1±1.2  [3; 2–4] | 0.68 |
| Gestational age at delivery | 39.4±1.1  [39.3; 38.6–40.2] | 39.1±1.1  [39.2; 38.2–40.1] | 0.07 |
| Induction of labor | 15 (14.7) | 16 (16.3) | 0.75 |
| Oxytocin augmentation | 45 (44.1) | 34 (34.7) | 0.17 |
| Cervical dilatation at analgesic request | 3.5±1.2  [3.5; 2.5–4.5] | 3.3±1.2  [3; 2.5–4] | 0.24 |
| Cervical effacement at analgesic request | 83±8.3  [80; 80–90] | 82.9±9.0  [80; 80–90] | 0.96 |
| VAS at analgesic request | 7.9±1.9  [8.0; 7.0–10.0] | 7.8±2.2  [8.0; 6.0–10.0] | 0.69 |
| VAS ≥ 7 at analgesic request | 78 (76.5) | 67 (68.4) | 0.21 |

Data are mean±standard deviation, [median, interquartile range], or n (%).

VAS: visual analog scale from 0 cm (no pain) to 10 cm (worst pain).

Table 2. Response to pain after nitrous oxide versus pethidine administration

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Response** | **Nitrous oxide**  **N=102** | **Pethidine**  **N=98** | ***P*-value\*** | **OR (95%CI)** |
| VAS 20–30 min after analgesic request | 7.7±2.3  [8.0; 6.0–10.0] | 7.6±2.7  [8.0; 6.0–10.0] | 0.89 | -- |
| VAS at 60 min | 8.6±1.9  [9.3; 8.0–10.0] | 7.7±2.3  [8.0; 7.0–10.0] | 0.03 | -- |
| VAS at 120 min | 8.5±2.1  [9.5; 8.0–10.0] | 9.0±1.4  [10.0; 8.0–10.0] | 0.63 | -- |
| VAS at 180 min | 8.5±2.0  [9.0; 8.0–10.0] | 8.5±1.9  [9.0; 8.0–10.0] | 0.94 | -- |
| Analgesic crossover | 34 (33.3) | 24 (24.5) | 0.17 | 1.54 (0.83–2.86) |
| Epidural use | 7 (6.9) | 9 (9.2) | 0.54 | 0.73 (0.26–2.04) |
| VAS before second-line use | 9.0±1.6  [10.0; 9.0–10.0] | 8.8±1.7  [10.0; 8.0–10.0] | 0.85 | -- |
| VAS at complete dilatation | 9.4±1.9  [10.0; 10.0–10.0] | 9.4±1.8  [10.0; 10.0–10.0] | 0.76 | -- |
| Efficacy of analgesia from 1 to 5 (most efficient) | 3.4±1.4  [3; 2–5] | 3.1±1.3  [3; 2–4] | 0.1 | -- |
| Maternal satisfaction from 1 to 5 (most satisfied) | 4.0±1.0  [4; 4–5] | 4.1±0.9  [4; 4–5] | 0.98 | -- |
| Future use of the same analgesic | 66 (64.7) | 65 (66.3) | 0.81 | 0.93 (0.52–1.67) |

Data are mean±standard deviation, [median, interquartile range], or n (%).

VAS: visual analog scale from 0 cm (no pain) to 10 cm (worst pain).

CI, confidence interval.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **OR (95%CI)** | ***P*-value** | **Pethidine**  **N=98** | **Nitrous oxide**  **N=102** | **Outcome** |
| -- | 0.8 | 2.3±2.19  [1.58; 0.74–3.14] | 2.1±2.14  [1.67; 0.83–2.50] | Time from analgesic use to complete dilatation, h |
| -- | 0.83 | 0.007±0.007  [0.005; 0.003–0.009] | 0.009±0.01  [0.005; 0.003–0.01] | Length of second stage, h |
| -- | 0.77 | 2.50±2.28  [1.77; 0.85–3.31] | 2.22±1.86  [1.76; 1.02–2.75] | Time from analgesic use to delivery, h |
| -- | 0.13 | 0.01±0.005  [0.009; 0.006–0.01] | 0.009±0.006  [0.007; 0.006–0.01] | Length of third stage, h |
| Ref.  --  -- | 0.13 | 94 (95.9)  4 (4.1)  0 (0.0) | 102 (100)  0 (0.0)  0 (0.0) | Mode of delivery  Spontaneous vaginal  Vacuum extraction  Cesarean |
| 0.63 (0.10–3.87) | 0.67 | 3 (3.1) | 2 (2.0) | Postpartum hemorrhage |
| 0.48 (0.04–5.33) | 0.61 | 2 (2.0) | 1 (1.0) | Blood transfusion |
| -- | --- | 0 (0.0) | 0 0.0) | Saturation < 95% |
| 0.96 (0.06–15.57) | >0.99 | 1 (1.0) | 1 (1.0) | Pulse rate > 110 |
| 0.84 (0.31–2.28) | 0.80 | 9 (9.2) | 8 (7.8) | Nausea |
| 1.29 (0.28–5.92) | >0.99 | 3 (3.1) | 4 (3.9) | Vomiting |
| -- |  | 0 (0.0) | 0 (0.0) | Itching |
| 0.96 (0.30–3.01) | 0.92 | 6 (6.1) | 6 (5.9) | Headache |
| 1.26 (0.54–2.92) | 0.59 | 11 (11.2) | 14 (13.7) | Dry mouth |
| 1.16 (0.62–2.17) | 0.64 | 25 (25.5) | 29 (28.4) | Any adverse effect |
| 1.13 (0.62–2.05) | 0.68 | 30 (30.6) | 34 (33.3) | Any sedative effect |

Table 3. Intrapartum outcomes and maternal adverse effects according to trial group

Data are mean±standard deviation, [median, interquartile range], or n (%).

CI, confidence interval.

Table 4. Neonatal outcomes according to trial group

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **OR (95%CI)** | ***P*-value\*** | **Pethidine**  **N=98** | **Nitrous oxide**  **N=102** | **Outcome** |
| -- | 0.16 | 3669.7±332.6  [2802; 3071.5–3581] | 3401.4±373.6  [3399; 3128–3695] | Neonatal birth weight, g |
| Ref.  1.51 (0.86–2.65) | 0.14 | 59 (60.2)  39 (39.8) | 51 (50.0)  51 (50.0) | Neonatal sex  Male  Female |
| 1.44 (0.59–3.55) | 0.42 | 9 (9.2) | 13 (12.7) | Meconium |
| 0.96 (0.06–15.57) | >0.99 | 1 (1.0) | 1 (1.0) | Apgar score < 7 at 1 min |
| -- | 0.49 | 1 (1.0) | 0 (0.0) | Apgar score < 7 at 5 min |
| 0.31 (0.03–3.07) | 0.36 | 3 (3.1) | 1 (1.0) | Cord arterial pH < 7.1 |
| 0.96 (0.06–15.57) | >0.99 | 1 (1.0) | 1 (1.0) | Oxygen use |
| -- | 0.49 | 1 (1.0) | 0 (0.0) | Artificial ventilation |
| -- | 0.11 | 3 (3.1) | 0 (0.0) | NICU admission |
| 2.71 (0.92–7.99) | 0.06 | 86 (87.8) | 97 (95.1) | Breastfed immediately after birth |
| 1.23 (0.40–3.8) | 0.71 | 91 (92.9) | 96 (94.1) | Breastfed 24 h after birth |
| 1.00 (0.54–1.87) | 0.99 | 71 (72.4) | 74 (72.5) | Formula use |

Data are mean±standard deviation, [median, interquartile range], or n (%).

CI, confidence interval.