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Effect of intrapartum epidural analgesia on rate of emergency delivery for presumed fetal compromise: nationwide registry-based cohort study

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KEYWORDS: epidural analgesia; fetal compromise; fetal growth restriction; FGR; intrapartum; labor; placental insufficiency; SGA; small-for-gestational age

CONTRIBUTION

What are the novel findings of this work?
Epidural analgesia (EDA) is associated with a higher risk of emergency delivery for presumed fetal compromise compared with no analgesia and alternative forms of analgesia. Relative risks of fetal compromise after EDA *vs* no analgesia were modestly but consistently modified by birth-weight centile, supporting the theory that reduced placental reserves exacerbate the adverse effect on the fetus of maternal hemodynamic changes induced by EDA.

What are the clinical implications of this work?
Use of labor EDA has increased substantially in recent decades, and its value for women requiring pain relief during labor is unquestioned. However, alternative forms of pain management may be preferable in some pregnancies, particularly those with a high background risk of fetal compromise.

ABSTRACT

Objectives *To determine the rate of emergency delivery for presumed fetal compromise after epidural analgesia (EDA) compared with that after alternative analgesia or no analgesia, and to assess whether this rate is increased in pregnancies with reduced placental reserve.*

Methods *This was a nationwide registry-based cohort study of 629 951 singleton pregnancies delivered at 36 + 0 to 42 + 0 weeks of gestation that were recorded in the Dutch national birth registry between 2014 and 2018, including 120 426 cases that received EDA, 86 957 that received alternative analgesia and 422 568 that received no analgesia during labor. Pregnancies with congenital anomaly, chromosomal abnormality, fetal demise, planned Cesarean delivery, non-cephalic presentation at delivery and use of multiple forms of analgesia were excluded. The primary outcome was emergency delivery for presumed fetal compromise. Secondary outcomes included delivery characteristics and neonatal outcome. Negative binomial regression analysis was stratified by parity and results are presented according to birth-weight centile, after adjusting for confounding.*

Results *Among women who received EDA, 13.2% underwent emergency delivery for presumed fetal compromise, compared with 4.1% of women who had no analgesia (relative risk (RR), 3.23 (95% CI, 3.16–3.31)) and 7.0% of women who received alternative analgesia (RR, 1.72 (95% CI, 1.67–1.77)). Independent of birth weight, the RR of presumed fetal compromise after EDA* vs *no analgesia was higher in parous women (adjusted RR (aRR), 2.15 (95% CI, 2.04–2.27)) compared with nulliparous women (RR, 1.88 (95% CI, 1.84–1.94)). Stratified for parity, the effect of EDA was modified significantly by birth-weight centile (interaction* P*-value, < 0.001 for nulliparous and 0.004 for parous women). The emergency delivery rate following EDA was highest in those*

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with a birth weight < 5th centile (25.2% of nulliparous and 16.6% of parous women), falling with each increasing birth-weight centile category up to the 91st–95th centile (11.8% of nulliparous and 7.2% of parous women).

Conclusions *Intrapartum EDA is associated with a higher risk of emergency delivery for presumed fetal compromise compared with no analgesia and alternative analgesia, after adjusting for relevant confounding. The highest rate of emergency delivery for presumed fetal compromise was observed at the lowest birth-weight centiles. RRs of emergency delivery for presumed fetal compromise after EDA were modestly but consistently modified by birth-weight centile, supporting the hypothesis that the adverse effects of EDA are exacerbated by reduced placental function. While EDA provides effective pain relief during labor, alternative strategies for pain management may be preferable in pregnancies with a high background risk of fetal compromise. © 2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

The most effective method for pain relief during labor is epidural analgesia (EDA)[1]. Worldwide use of EDA has increased substantially in recent decades[1–4]. In 2018, 21.5% of all women giving birth in The Netherlands received intrapartum EDA, compared with 11.3% in 2008 and 5.3% in 2003[5–7]. A Cochrane review of randomized controlled trials (RCTs) demonstrated that EDA is associated with a higher rate of instrumental vaginal delivery compared with no analgesia and alternative forms of analgesia[1]. Reasons underlying this association, and whether instrumental deliveries were related to obstructed labor or fetal compromise, were not specified. Due to conflicting study results, it remains unclear whether EDA increases the risk of emergency Cesarean delivery for fetal compromise[1].

EDA is known to lead to maternal hemodynamic changes, including hypotension, which is one of the most common side effects[8], and an acute decrease in maternal plasma epinephrine level, resulting in temporary uterine hypertonia[9]. Both mechanisms can result in decreased uteroplacental perfusion[10,11]. Modest suppression of maternal blood pressure is of limited concern in healthy fetuses, but can have serious ramifications for those with reduced placental reserves or impaired placental function. Without timely reversal, reduced uteroplacental perfusion can lead to perinatal hypoxia and birth asphyxia, which are important contributors to stillbirth, hypoxic ischemic encephalopathy and cerebral palsy[12,13].

Once fetal compromise is suspected during labor, emergency delivery (instrumental vaginal delivery or Cesarean section) may be necessary to mitigate the consequences of fetal hypoxia and prevent peripartum demise. This might be particularly true for growth-restricted fetuses that are already challenged by impaired placental function[13,14].

The aim of this nationwide registry-based cohort study was to test the hypothesis that a higher rate of emergency delivery for presumed fetal compromise is observed after EDA compared with alternative analgesia and no analgesia. We further hypothesized that the rate of emergency delivery for presumed fetal compromise is highest in pregnancies complicated by impaired placental function, with birth-weight centile as a proxy for placental function. This effect could be reflected in a dose–response interaction between birth-weight centile and the risk of fetal compromise after EDA.

METHODS

This retrospective population cohort study was conducted using data from Perined, the national perinatal registry in The Netherlands[15]. Submission of data to Perined is obligatory for midwives, obstetricians and neonatologists, and over 96% of all births in The Netherlands are recorded in the registry[16]. The registry contains anonymized information about pregnancy, childbirth and newborn hospital admissions/readmissions. Data are recorded as reported by the caregiver and checked annually for consistency. Ethical approval was obtained from the Perined committee for research and ethics (approval no. 20.04).

From all records between 1 January 2014 and 31 December 2018, we selected singletons delivered between 36 + 0 and 42 + 0 weeks of gestation. We excluded pregnancies with congenital anomaly, chromosomal abnormality, non-cephalic presentation, antenatal demise, planned Cesarean section or unknown mode of delivery, birth weight or gestational age at delivery. Women who received multiple forms of analgesia during delivery were also excluded from analysis, with the exception of those who used (additional) analgesia during emergency Cesarean section.

Analysis was performed according to three predetermined groups: women receiving labor epidural, those receiving alternative analgesia during labor and those not receiving labor analgesia. Labor epidural was defined as EDA administered during the first stage of labor (dilation phase). Alternative analgesia was defined as use of sedatives, opioids and non-opioids starting in the first stage of labor. The no analgesia group included women who did not receive any form of analgesia during labor and those who received analgesia during emergency Cesarean section only.

The primary outcome was emergency delivery, either instrumental vaginal delivery (ventouse or forceps) or emergency Cesarean section, for presumed fetal compromise. Fetal compromise was defined as reported by the caregiver. Obstructed labor as an indication for emergency delivery was included in the primary outcome only if accompanied by fetal compromise. In order to relate the primary outcome to impaired placental function, we calculated birth-weight centiles according to Hoftiezer population reference charts[17] for all infants.

Severe small-for-gestational age (SGA) was defined as a birth weight below the 3rd centile. Mild SGA was defined as a birth weight between the 3rd and 10th centiles.

Secondary outcomes related to delivery were duration of second stage of labor, episiotomy, postpartum hemorrhage and meconium-stained amniotic fluid. Neonatal outcomes included 5-min Apgar score < 7, umbilical artery pH < 7.10, neonatal intensive care unit (NICU) admission and neonatal mortality.

Statistical analysis

Baseline characteristics and outcomes were summarized using descriptive statistics. Categorical variables are presented as *n* (%) and continuous variables as mean ± SD or median (interquartile range). Analysis of the rate of emergency delivery for presumed fetal compromise was performed according to pain-relief category (EDA, alternative or no pain relief) and birth-weight-centile group. For this population-based study, risk ratio was considered to be a more appropriate measure of association compared with odds ratio. Therefore, we used negative binomial regression to identify confounders and analyze the effects of type of analgesia and birth-weight centile on the primary outcome. Negative binomial regression uses the logarithm of counts, making the regression coefficients difficult to interpret, similar to logistic regression. After exponentiation, the coefficient values express incidence-rate ratios, which can be regarded as rate ratios or risk ratios, since our primary outcome was dichotomous, coded as zero or one. Univariable negative binomial regression analysis with emergency delivery for presumed fetal compromise as the outcome was performed to identify potential confounders of the effect of EDA compared with alternative or no analgesia, including maternal age, ethnicity, parity, previous Cesarean section, gestational age at delivery, hypertension, pre-eclampsia/HELLP syndrome, diabetes mellitus (including gestational diabetes), labor induction, severe SGA and mild SGA. Second stage duration > 60 min was assessed, both as a confounder and an outcome. In the univariable regression model, previous Cesarean section was coded as zero in nulliparous women. Confounders with a *P*-value < 0.05 were subsequently examined separately for nulliparous and parous women. Individual variables that changed the relative risk (RR) of the primary outcome following EDA by more than 10% were considered relevant and included in the final adjusted models to calculate RR. RR with 95% CI are presented before and after adjusting for identified confounders. Effect modification was assessed by adding an interaction term for birth-weight-centile group and type of analgesia to the model, and examining the statistical significance and direction of the interaction effect in the successive centile groups. A subanalysis was performed to examine separately the components of the primary outcome i.e. instrumental vaginal delivery for presumed fetal compromise and emergency Cesarean section for presumed fetal compromise.

Because of the large sample size, *P*-values were considered relatively uninformative, except in the analysis of effect modification and identification of confounders. Missing data were declared if the prevalence was above 0.5%. Imputation of missing data was not performed. Records with missing data on variables that were deemed relevant for the primary analysis were excluded from analysis. Data analysis was performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Between 1 January 2014 and 31 December 2018, there were 807 901 singleton pregnancies registered in the Perined database. After exclusion of 177 950 cases for reasons outlined in the Methods, 629 951 pregnancies were included, of which 120 426 underwent labor epidural, 86 957 used alternative analgesia and 422 568 had no form of labor analgesia. Characteristics of the study population are summarized in Table 1. Women were mostly of Caucasian ethnicity. Women receiving EDA were younger, more often nulliparous, had higher rates of comorbidity (hypertension, pre-eclampsia/HELLP) and were less likely to have had spontaneous onset of labor, compared with those who received no analgesia and alternative analgesia. Parous women receiving EDA more often had a history of a Cesarean section. Among nulliparous women, 30.8% received EDA, 15.4% received alternative analgesia and 53.8% received no analgesia. Among parous women, 10.2% received EDA, 12.6% received alternative analgesia and 77.3% received no analgesia.

Emergency delivery for presumed fetal compromise

In the epidural group, 13.2% had an emergency delivery for presumed fetal compromise, compared with 4.1% of women who had no analgesia (RR, 3.23 (95% CI, 3.16–3.31)) and 7.0% of women who received alternative analgesia (RR, 1.72 (95% CI, 1.67–1.77)). The rate of emergency delivery for presumed fetal compromise was highest in women receiving EDA and with severe SGA (27.0% in nulliparous and 17.1% in parous women), falling gradually with increasing birth weight up to the 91st–95th centile, at which the lowest rate was recorded among women receiving EDA (11.8% in nulliparous and 7.2% in parous women) (Figure 1). The absolute difference (in percentage points) in the rate of emergency delivery for presumed fetal compromise between women receiving EDA and those receiving no analgesia was highest in those with a birth weight between the 5th and 10th centiles (8.7% in nulliparous and 9.2% in parous women), decreasing gradually with increasing birth weight until >95th centile (5.1% in nulliparous and 4.4% in parous women) (Figure S1).

Subanalysis of the type of delivery showed a similar pattern, with the highest rate of emergency delivery for presumed fetal compromise occurring in those who received EDA and delivered a severely SGA neonate, both for instrumental vaginal delivery (15.5% in nulliparous

Table 1 Baseline characteristics and delivery and neonatal outcomes of Perined cohort, according to analgesia use during labor

Characteristic	*No analgesia* (n = *422 568*)	*Epidural analgesia* (n = *120 426*)	*Alternative analgesia* (n = *86 957*)
Maternal			
Age (years)	30.9 ± 4.6	29.7 ± 4.9	30.2 ± 4.9
Ethnicity			
Caucasian	89.7	90.8	89.9
Other	9.0	9.0	10.0
Unknown	1.3	0.2	0.1
Nulliparous	34.8	70.0	48.5
Parous	65.2	30.0	51.5
Previous CS*	5.3	22.7	12.0
GA at delivery (weeks)	39+6 ± 1+1	39+6 ± 1+2	39+5 ± 1+2
Hypertension	4.5	9.4	7.6
PE/HELLP syndrome	0.2	0.5	0.4
Diabetes†	2.9	5.3	5.4
Onset of labor			
Spontaneous	84.6	59.2	62.8
Induction	14.6	38.5	35.8
AROM	7.4	15.5	17.2
Medication‡	3.2	7.7	7.8
Foley catheter	4.0	15.3	10.8
Unknown	0.8	2.3	1.4
Delivery			
Second-stage duration (min)	1 (0–13)	26 (9–53)	16 (6–39)
0–30 min	79.8	42.6	61.1
31–60 min	6.8	24.1	18.3
61–180 min	7.6	20.2	13.7
Unknown	5.8	13.1	6.9
Mode of delivery			
Spontaneous	90.7	69.0	82.4
Instrumental VD	5.3	16.5	11.4
Unplanned CS	4.0	14.5	6.2
ED for presumed fetal compromise	4.1	13.2	7.0
Episiotomy	16.1	34.1	27.4
PPH (> 1 L)	5.5	7.5	7.1
Meconium-stained AF	12.8	14.7	14.1
Neonatal			
Female sex	49.4	48.0	47.4
Birth weight (g)	3496 ± 473	3455 ± 480	3483 ± 487
Severe SGA§	1.9	2.6	2.2
Mild SGA¶	7.7	9.5	8.4
5-min Apgar score < 7	0.7	1.9	1.3
UA pH tested	5.8	16.1	11.2
UA pH < 7.10**	8.8	9.6	12.1
Admission to NICU	1.3	3.7	1.4
Death††	0.05	0.05	0.03

Data are given as mean ± SD, % or median (interquartile range). *Percentage calculated only in parous women. †Including diabetes mellitus Type 1, diabetes mellitus Type 2 and gestational diabetes. ‡Oxytocin and/or prostaglandin. §Birth weight below 3rd percentile. ¶Birth weight between 3rd and 10th percentiles. **Percentage calculated only in neonates in whom umbilical artery (UA) pH was tested. ††Intrapartum until 28 days postpartum. AF, amniotic fluid; AROM, artificial rupture of membranes; CS, Cesarean section; ED, emergency delivery; GA, gestational age; NICU, neonatal intensive care unit; PE, pre-eclampsia; PPH, postpartum hemorrhage; SGA, small-for-gestational age; VD, vaginal delivery.

and 7.6% in parous women) and emergency Cesarean section (11.5% in nulliparous and 9.5% in parous women) (Figures S2 and S3).

On univariable analysis, all preidentified maternal, intrapartum and neonatal risk factors were associated significantly with emergency delivery for presumed fetal compromise, with the exception of Caucasian ethnicity (Table S1). After stratification by parity, all factors were significantly associated, with the exception of gestational age at delivery in parous women (Table 2). In nulliparous women, the effect of EDA on the RR of fetal compromise did not change by more than 10% for any of the evaluated variables. In parous women, labor induction, second stage duration > 60 min and previous Cesarean section showed relevant confounding and, therefore, these variables were included in the adjusted analysis (Figures 2 and S4).

Stratified by parity and adjusted for confounding, the interaction of birth-weight centile (according to centile

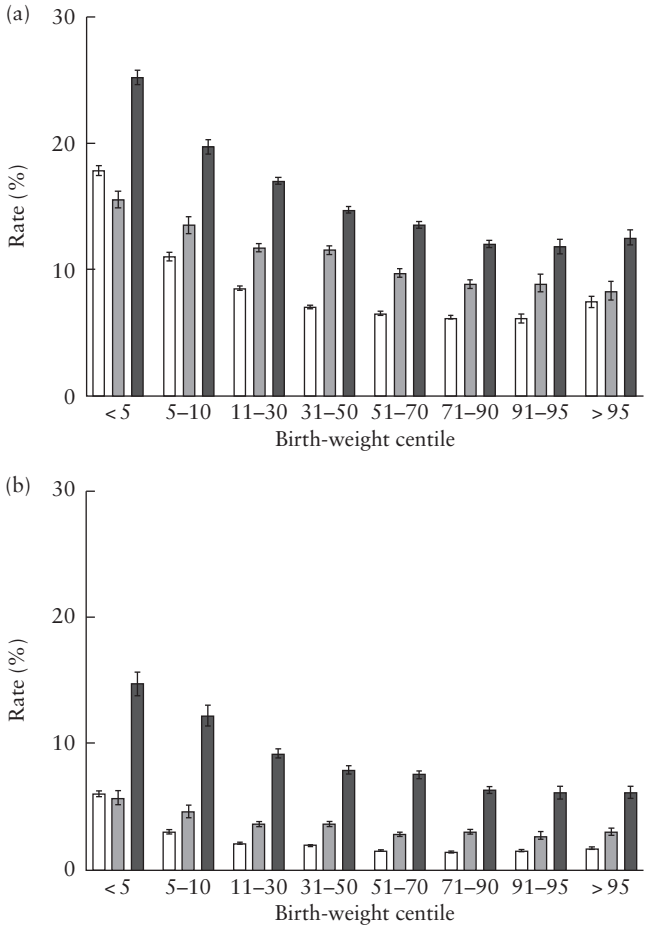

Figure 1 Rate of emergency delivery for presumed fetal compromise in nulliparous (a) and parous (b) women, according to birth-weight centile, for neonates born between 36 + 0 and 42 + 0 weeks' gestation in The Netherlands from 2014 to 2018. Error bars indicate standard error of the mean (SEM). Below 3rd percentile, nulliparous: no analgesia, 23.2% (SEM, 0.63%); alternative analgesia, 18.1% (SEM, 1.12%); labor epidural, 27.0% (SEM, 0.87%). Below 3rd percentile, parous: no analgesia, 8.4% (SEM, 0.46%); alternative analgesia, 6.0% (SEM, 0.90%); labor epidural: 17.1% (SEM, 0.16%). □, no analgesia; ▨, alternative analgesia; ■, labor epidural.

Table 2 Univariable regression analysis of factors associated potentially with need for emergency delivery for presumed fetal compromise, according to parity

	RR (95% CI)	
Risk factor	*Nulliparous (n = 273 451)*	*Parous (n = 356 285)*
Maternal age (in years)	1.04 (1.03–1.04)	1.04 (1.03–1.04)
Caucasian ethnicity	0.952 (0.913–0.994)	0.819 (0.769–0.872)
History of Cesarean section	—	7.40 (7.09–7.73)§
GA at delivery (in weeks)	1.12 (1.11–1.13)	1.01 (0.995–1.03)
Hypertension	1.23 (1.21–1.31)	1.51 (1.38–1.65)
PE/HELLP syndrome	1.37 (1.18–1.58)	2.17 (1.53–3.07)
Diabetes*	1.19 (1.12–1.26)	1.38 (1.26–1.51)
Induction of labor	1.57 (1.53–1.62)	2.09 (2.00–2.18)§
Second-stage duration > 60 min	1.62 (1.58–1.67)	9.26 (8.65–9.91)§
Second-stage duration ≤ 60 min	Ref	Ref
Severe SGA†	2.40 (2.28–2.52)	3.70 (3.35–4.09)
Mild SGA‡	1.54 (1.48–1.59)	1.94 (1.82–2.07)
No SGA	Ref	Ref

*Including diabetes mellitus Type 1, diabetes mellitus Type 2 and gestational diabetes. †Birth weight below 3rd percentile. ‡Birth weight between 3rd and 10th percentiles. §Relative risk (RR) of epidural analgesia on primary outcome changed by > 10%. GA, gestational age; PE, pre-eclampsia; Ref, reference; SGA, small-for-gestational age.

group) on the effect of EDA on the risk of emergency delivery for presumed fetal compromise was statistically significant (interaction *P*-value, < 0.001 for nulliparous women and 0.004 for parous women). The results indicated a modestly stronger effect of EDA at lower birth-weight centiles. Pooled across birth-weight groups, the RR of fetal compromise following EDA compared with no analgesia was higher in parous women (adjusted RR (aRR), 2.15 (95% CI, 2.04–2.27)) than in nulliparous women (RR, 1.88 (95% CI, 1.84–1.94)). A similar relationship was observed for EDA *vs* alternative analgesia (parous: aRR, 1.94 (95% CI, 1.81–2.07); nulliparous: RR, 1.41 (95% CI, 1.36–1.46)).

Delivery and neonatal outcomes

Compared with women who received no analgesia, women receiving labor epidural were more likely to have a prolonged (> 60 min) second stage of labor (20.2% *vs* 7.6%) and an episiotomy (34.1% *vs* 16.1%) (Table 1). Neonates born after maternal intrapartum epidural use, compared with those born to mothers who received no analgesia, more often had a 5-min Apgar score below 7 (1.9% *vs* 0.7%) and were more often admitted to the NICU (3.7% *vs* 1.3%).

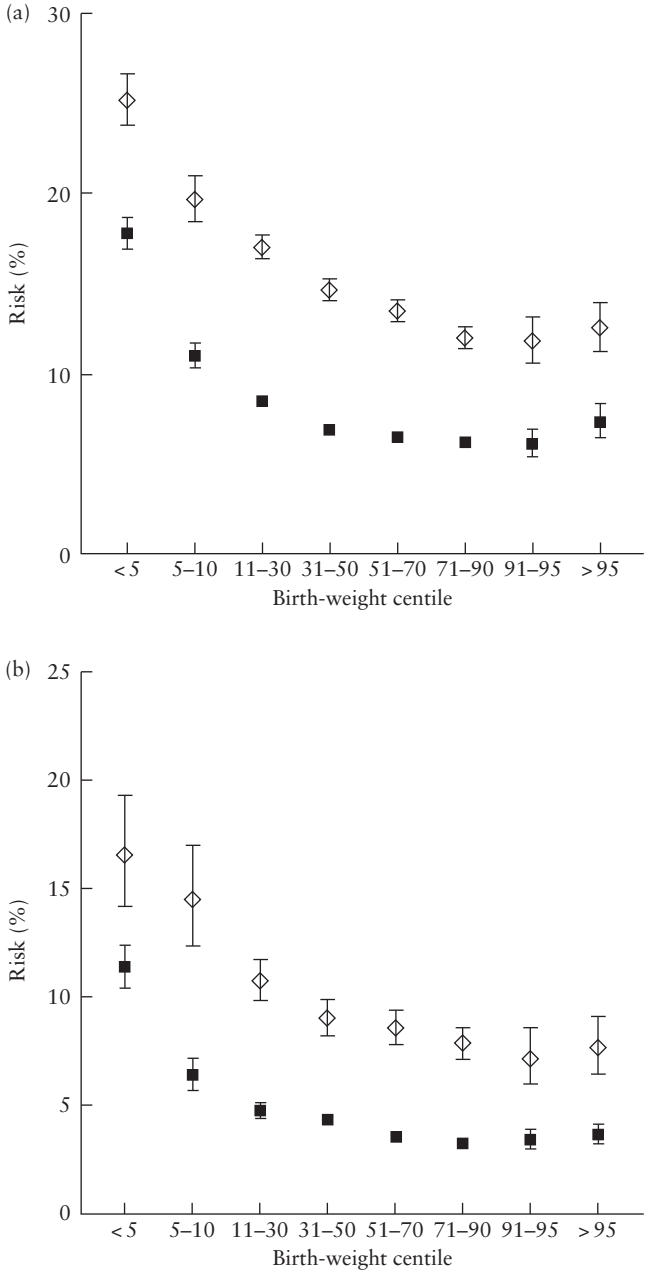

Figure 2 Absolute risk of emergency delivery for presumed fetal compromise in nulliparous (a) and parous (b) women receiving epidural analgesia (◇) or no intrapartum analgesia (■), according to birth-weight centile. Values are estimated marginal means derived from negative binomial regression analysis. Error bars indicate 95% CI. Analysis in (b) was adjusted for relevant confounding variables in parous women: labor induction and previous Cesarean section. Second-stage duration > 60 min was omitted as confounding variable in main analysis because epidural for pain relief is administered before second stage of labor in The Netherlands; secondary analysis including this variable as a confounder is provided in Figure S4.

DISCUSSION

Intrapartum EDA between 36 + 0 and 42 + 0 weeks of gestation was associated with a higher risk of emergency delivery for presumed fetal compromise compared with no intrapartum analgesia and alternative intrapartum analgesia, after adjusting for relevant

confounding variables. The RRs of fetal compromise after EDA compared with alternative or no analgesia were significantly and consistently modified by birth-weight centile in nulliparous and parous women, suggesting that the adverse effects of EDA are exacerbated by reduced placental function. We hypothesize that EDA-induced maternal hemodynamic changes result in decreased uteroplacental perfusion and acute fetal hypoxia.

The RRs of emergency delivery for presumed fetal compromise following EDA *vs* no or alternative analgesia observed in this study are substantial and have not been described hitherto in RCTs[1]. We also found that neonatal outcomes differed between pain-management groups, with the exception of umbilical artery pH < 7.10, which is generally determined only in cases of (presumed) fetal compromise in The Netherlands. Apart from inclusion bias in RCTs, the incongruity is most likely due to the intention-to-treat approach, in which the effects of crossover and pooling strategies obscure causal effects. Moreover, none of the RCTs included in the Cochrane review specified the reason for instrumental delivery[1], whereas this study focused only on fetal compromise.

The findings from this study suggest that the effects of EDA on the risk of emergency delivery for presumed fetal compromise are mediated by reduced placental function. In this population, we observed the highest rate of emergency delivery for presumed fetal compromise in those with a birth weight below the 5th centile, falling gradually in a dose–response manner with increasing birth-weight centile up to the 91st–95th centile. Of note, this pattern was observed in all pain-management groups, which corresponds with previous reports of perinatal mortality distribution according to birth-weight centile[18,13]. Use of alternative analgesia and EDA increase the background risk of emergency delivery for presumed fetal compromise, and EDA consistently more so than alternative analgesia.

In the subanalysis of instrumental vaginal delivery and emergency Cesarean section for presumed fetal compromise, similar patterns were observed, with one exception: among nulliparous women who delivered a neonate with birth weight below the 5th centile, those who received EDA and those who did not use analgesia had a similar emergency Cesarean section rate. We hypothesize that the most vulnerable fetuses, with severely impaired placental function, may not be able to withstand (early) uterine contractions and an emergency Cesarean is performed prior to pain relief request.

The primary outcome was analyzed according to parity since nulliparity was associated with a significantly increased risk of emergency delivery for presumed fetal compromise. However, the RR of emergency delivery following EDA *vs* no labor analgesia was higher in parous compared with nulliparous women. One explanation is that parous women who receive EDA have experienced a more complex labor course and bear a higher intrinsic risk of fetal hypoxia-related outcomes. Another explanation could be that clinicians have a lower threshold for an emergency Cesarean section in women with a history of a Cesarean section, for fear of the potential consequences of uterine rupture.

As studies have shown that the risk of neonatal acidemia is directly proportional to the duration of the second stage of labor, irrespective of cardiotocographic abnormalities[19], and that EDA is associated with a prolonged second stage[20], a secondary analysis with second-stage duration as a confounding variable instead of outcome was performed (Figure S4).

Clinical implications

EDA use has increased steeply in recent years, with 33.8% of nulliparous and 11.0% of parous women receiving EDA in 2019 in The Netherlands[16]. Therefore, the consequences of epidural analgesia have considerable impact. Based on the numbers in this study, if, within the group of nulliparous women delivering a neonate below the 10th birth-weight centile who express a request for pain relief, the administration of EDA was reduced by 50% and alternative analgesia was given, this would result in an absolute overall reduction in emergency delivery for presumed fetal compromise of 2.7% (from 20.0% to 17.3%), and a 1.7% (from 7.3% to 5.6%) reduction in emergency Cesarean section for presumed fetal compromise. These potential effects are likely to be even more pronounced in contexts with higher background EDA use, such as the UK (44% in 2020) and USA (76% in 2019)[21,22].

It is important to acknowledge that EDA is the most effective method of labor pain management[1]. Maternal pain and stress can also result in decreased uteroplacental blood flow via catecholamine release[23]. However, pain is also a subjective symptom[24]. If pregnant and birthing women and their obstetric caregivers consider the potential increased risk of emergency delivery for fetal compromise associated with EDA, they may be motivated to explore other pain relief methods.

Strengths and limitations

A strength of this study is that the national registry from which the data were obtained covers nearly all births in The Netherlands (over 96%), meaning that our findings are population-based and are not subject to inclusion bias.

A limitation of this study is that, due to the nature of registry data, we cannot exclude bias from residual confounding. For example, maternal smoking status and body mass index were missing from the dataset. Also, data are recorded in the registry as reported by the caregiver and detailed information about the nature of emergency delivery and presumed fetal compromise is lacking. There was some evidence of indication bias, such as the rate of induction and emergency delivery rate in parous women with a history of Cesarean section. However, baseline characteristics between groups were similar and important copredictors were accounted for in the multivariable analysis.

Furthermore, detailed information on the type of epidural and mode of administration (patient-controlled intermittent *vs* continuous infusion) is lacking. It is likely that significant variation in clinical practice existed between Dutch hospitals during the study period. Another

limitation is that alternative pain relief options, including pethidine, morphine, remifentanil and nitrous oxide, were not classified further in our database. Finally, we did not have information on local protocols for dealing with maternal hypotension in the presence of an abnormal fetal heart-rate pattern and indications for emergency delivery. Among others, infusion of fluids, infusion of vasopressor agents and interruption of oxytocin infusion are standard methods in The Netherlands.

Conclusions

Intrapartum EDA is associated with a higher risk of emergency delivery for presumed fetal compromise compared with no analgesia and with alternative forms of analgesia, after adjusting for relevant confounding variables. The RRs of emergency delivery for presumed fetal compromise after EDA *vs* no or alternative analgesia were consistently and significantly modified by birth-weight centile, suggesting that the adverse effects of EDA are exacerbated by reduced placental function. The merits of EDA during labor in women requiring pain management are unquestioned. However, alternative forms of pain relief may be preferable in some cases, particularly those with a high background risk of fetal compromise. These findings should be further evaluated and corroborated in *post-hoc* per-protocol analyses of individual and aggregated data from RCTs on labor pain relief.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Univariable regression analysis of factors potentially associated with need for emergency delivery for presumed fetal compromise in whole cohort

Figure S1 Difference in rate of emergency delivery for presumed fetal compromise between women who received epidural analgesia, alternative analgesia or no analgesia during labor, according to birth-weight centile.

Figures S2 and S3 Rate of emergency instrumental vaginal delivery (Figure S2) and emergency Cesarean delivery (Figure S3) for presumed fetal compromise in nulliparous (a) and parous (b) women, according to birth-weight centile, for neonates born between 36 + 0 and 42 + 0 weeks' gestation in The Netherlands from 2014 to 2018. Error bars indicate standard error of the mean. Green, no analgesia; blue, alternative analgesia; orange, labor epidural.

Figure S4 Absolute risk of emergency delivery for presumed fetal compromise in parous women receiving epidural analgesia (◇) or no intrapartum analgesia (■), according to birth-weight centile. Values are estimated marginal means derived from negative binomial regression analysis. Error bars indicate 95% CI. Adjusted for relevant confounding variables: labor induction, previous Cesarean section and second-stage duration > 60 min.