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ORIGINAL RESEARCH ARTICLE

Neonatal outcomes associated with time from a high fetal blood lactate concentration to operative delivery

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Abstract

Introduction: Adjunctive technologies to cardiotocography intend to increase the specificity of the diagnosis of fetal hypoxia. If correctly diagnosed, time to delivery could affect neonatal outcome. In the present study, we aimed to investigate the effect of time from when fetal distress is indicated by a high fetal blood sample (FBS) lactate concentration to operative delivery on the risk of adverse neonatal outcomes.

Material and methods: We conducted a prospective observational study. Deliveries with a singleton fetus in cephalic presentation at 36^{+0} weeks of gestation or later were included. Adverse neonatal outcomes, related to decision-to-delivery interval (DDI), were investigated in operative deliveries indicated by an FBS lactate concentration of at least 4.8 mmol/L. We applied logistic regression to estimate crude and adjusted odds ratios (aOR) of various adverse neonatal outcomes, with associated 95% confidence intervals (CI), for a DDI exceeding 20 minutes, compared with a DDI of 20 minutes or less. ClinicalTrials.gov Identifier: NCT04779294.

Results: The main analysis included 228 women with an operative delivery indicated by an FBS lactate concentration of 4.8 mmol/L or greater. The risk of all adverse neonatal outcomes was significantly increased for both DDI groups compared with the reference group (deliveries with an FBS lactate below 4.2 mmol/L within 60 minutes before delivery). In operative deliveries indicated by an FBS lactate concentration of 4.8 mmol/L or more, there was a significantly increased risk of a 5-minute Apgar score less than 7 if the DDI exceeded 20 minutes, compared with a DDI of 20 minutes or less (aOR 8.1, 95% CI 1.1–60.9). We found no statistically significant effect on other short-term outcomes for deliveries with DDI longer than 20 minutes, compared with those with DDI of 20 minutes or less (pH ≤7.10: aOR 2.0, 95% CI 0.5–8.4; transfer to the neonatal intensive care unit: aOR 1.1, 95% CI 0.4–3.5).

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; CTG, cardiotocography; DDI, decision-to-delivery interval; FBS, fetal blood sample; OR, odds ratio; STAN, ST segment analysis.

Conclusions: After a high FBS lactate measurement, the increased risk of adverse neonatal outcome is further augmented if the DDI exceeds 20 minutes. These findings give support to current Norwegian guidelines for intervention in cases of fetal distress.

KEYWORDS
decision-to-delivery interval, fetal blood sample, fetal distress, fetal monitoring, labor, lactate, operative delivery

1 | INTRODUCTION

The incidence of severe birth asphyxia is low in developed countries, but the risk of perinatal morbidity and mortality remains a concern.[1] The main aim of fetal surveillance is to reduce this risk. Evidence of the effect of cardiotocography (CTG) is scarce.[2] Despite this, it is widely used in high-income countries.[3] One of the main arguments against routine use of CTG is its low specificity to predict clinically significant hypoxia.[2,4] To improve the specificity of CTG, adjunctive surveillance methods have been introduced: fetal blood sampling (FBS) with measurement of scalp pH or lactate and ST analysis (STAN) of the fetal electrocardiogram.[5–8]

There is no strong evidence of when or how fast to intervene in the case of a non-reassuring CTG. The National Institute for Health and Care Excellence recommends a decision-to-delivery interval (DDI) of 75 minutes or less in cases of suspected asphyxia without immediate threat to the life of the mother or fetus (category 2 emergency cesarean section, according to the classification suggested by Lucas et al.[9]), and a DDI of 30 minutes in cases of immediate maternal or fetal threat (category 1 cesarean section).[10] A common guideline for Austria, Germany, and Switzerland endorses a shorter DDI of 20 minutes or less in case of fetal distress.[11] The national guideline in Norway recommends a DDI of 20–30 minutes or less for category 2 cesarean section, and delivery as soon as possible for category 1 cesarean section.[12]

If hypoxia during labor is progressing, time from diagnosis of fetal distress to delivery should affect neonatal outcome. This was shown for use of CTG combined with STAN, where the risk of adverse outcome increased with increasing time from indication of hypoxia to delivery.[13,14] The evidence is conflicting for the use of CTG as a single method or in combination with FBS pH measurement.[15–17]

No previous studies have investigated the effect of DDI limited to deliveries with indication to intervene based on high FBS lactate concentration in the setting of a non-reassuring CTG.

In the present study, we aimed to assess the risk of adverse neonatal outcomes in operative deliveries after a high FBS lactate concentration, and the association between the length of the DDI and the risks of adverse neonatal outcomes. We hypothesized that neonatal morbidity would increase with increasing length of the DDI.

Key message

Delivery should be expedited in cases of high fetal blood sample lactate measurement, as a decision-to-delivery interval exceeding 20 minutes increases the risk of adverse neonatal outcome.

2 | MATERIAL AND METHODS

2.1 | Study design and participants

This was a single-center, prospective observational study conducted at Oslo University Hospital, Ullevål, which is a tertiary care hospital with 7000 annual deliveries. The study period was from September 1, 2018, to December 31, 2019. A total of 10 000 pregnant women were invited to the study by written information and passive consent during the first trimester. The study is registered in ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT04779294).

The women received written information about the study together with the invitation to the second-trimester routine ultrasound scan. Information was also available in nine different languages on the hospital web page (https://oslo-universitetssykehus.no/seksjon-klinisk/Sider/Sammenlikning-av-metoder-for-fosterovervakning.aspx). Participation in the study was approved with a passive patient consent. Patients were included in the study unless they actively opted out.

Analyses were restricted to deliveries in gestational week 36^{+0} or later with a singleton fetus in cephalic presentation.

2.2 | Clinical intrapartum routine

Continuous intrapartum CTG was used according to local guidelines.[18] It is indicated in the presence of maternal or fetal risk factors, abnormal findings during intermittent auscultation, or intrapartum risk factors (meconium, fever, or vaginal bleeding), preferably with a fetal internal electrode. In the case of a non-reassuring CTG pattern, FBS lactate was measured using the StatStrip Xpress® Lactate Hospital Meter (Nova Biomedical).

In accordance with local and national guidelines, an FBS lactate concentration of 4.8 mmol/L or greater was considered an indication for expedited delivery. An FBS lactate concentration between 4.2 and 4.8 mmol/L was defined as pre-acidotic and an indication for either delivery or intensified monitoring, with a new sample within 15–30 minutes.[12,18] These limits are based on previous studies, using the Arkray Lactate Pro lactate meter.[19,20] At the time of our study, there was no available recommended cut-off value specified for the StatStrip Xpress Lactate Hospital Meter. An immediate control sample was taken if deemed necessary by the obstetrician on call. Norwegian national guidelines recommend to deliver the fetus within 20 minutes in cases of fetal compromise that is not deemed as immediately life-threatening, and as soon as possible in cases of immediate threat to the life of the mother and/or the fetus (eg suspected uterine rupture, placental abruption, or umbilical cord prolapse). We did not apply STAN or other ancillary methods in addition to CTG with FBS lactate.

The FBS sampling time and lactate concentration were registered in the partogram. Paired (artery and vein) umbilical cord blood samples were obtained after all deliveries and analyzed with Radiometer ABL90 Flex (Radiometer America Inc.).

Clinical data on the mother, the delivery, and the newborn were gathered from the hospital electronic medical records (DIPS [DIPS AS], Partus [CSAM Health AS], and STAN Viewer [Neoventa Medical]) and additionally from the Norwegian Neonatal Network database. Most of the study information was obtained by digital data retrieval, and the remaining information was obtained manually from electronic medical records. The data were registered in EpiData (The EpiData Association, Odense, Denmark).

Time of the first FBS lactate concentration of 4.8 mmol/L or more that was not followed by a normal FBS lactate concentration was recorded and the sampling-to-delivery interval was calculated. This interval was used as the DDI in the study analyses.

2.3 | Outcome measurements

The neonatal outcomes examined in the present study included cord metabolic acidosis (pH <7.00 and base deficit in the extracellular fluid ≥12 mmol/L),[21] cord acidemia (arterial pH ≤7.10), 5-minute Apgar score <7, transfer to the neonatal intensive care unit, neonatal encephalopathy (grade 2 or 3 according to Sarnat & Sarnat[22]), and combined neonatal morbidity (5-minute Apgar score <7, umbilical cord pH ≤7.10, and/or transfer to the neonatal intensive care unit).

Deliveries with cord blood gas data from a single vessel were included if they fulfilled the criteria for cord acidemia or metabolic acidosis, otherwise they were excluded from the analysis. The same applied if the difference between two vessels was insufficient (difference in pH less than 0.02, difference in pCO_2 <0.7 kPa, or cord vessel value of pCO_2 <2.9 kPa[23]). All cases of metabolic acidosis were validated according to the criteria suggested by Kro et al.[23]

2.4 | Statistical analyses

Neonatal outcomes in operative deliveries following an FBS lactate concentration of 4.8 mmol/L or greater were recorded and divided into two groups, based on the time elapsed to delivery: DDI 20 minutes or less and DDI longer than 20 minutes.

Deliveries with a normal FBS lactate concentration (<4.2 mmol/L) within 60 minutes before delivery were used as the reference group. The two DDI groups (≤20 and >20 minutes) were also compared directly to determine the effect of the time to delivery on adverse neonatal outcomes.

We applied logistic regression to estimate crude and adjusted odds ratios of the adverse neonatal outcomes of interest, with associated 95% confidence intervals. We adjusted for maternal age (categorical variable: <20, 20–24, 25–29, 30–34, or ≥35 years), parity (dichotomous variable: nulliparous or parous), birthweight (continuous variable, in hectograms), mode of delivery (dichotomous variable: operative vaginal delivery or cesarean section), and FBS lactate concentration (dichotomous variable: 4.8–5.1 mmol/L or ≥5.2 mmol/L). Kaplan–Meier survival plots and the log-rank test were used to assess the effect of the time from indication of high FBS lactate concentration to delivery on the risk of adverse neonatal outcomes, with the DDI as a continuous variable. The effect of the lactate level on the time consumption was evaluated by linear regression.

The level of statistical significance was set at 0.05.

All statistical analyses were performed with STATA 17 (StataCorp. 2021. Stata Statistical Software: Release 17).

2.5 | Ethics statement

The User Council at the Division of Gynecology and Obstetrics at Oslo University Hospital was involved in the planning of the study. The Regional Committee for Medical and Health Research Ethics South East Norway (Reference number: 2017/1561. Approval date: December 20, 2017) and the Data Protection Officer at Oslo University Hospital approved the study.

3 | RESULTS

A flowchart of the study inclusion is displayed in Figure 1. A total of 10 000 women were invited to participate in the study, of whom only 321 actively opted out. Another 1623 women were excluded for other reasons, such as preterm labor and breech delivery (Figure 1). Ten women gave birth twice during the study period, but none of them had more than one delivery that met the criteria for inclusion in the analyses.

Of the 8056 included women, 2425 (30.1%) had at least one lactate measurement during labor, and 2046 (25.4%) had lactate measured during the final 60 minutes before delivery.

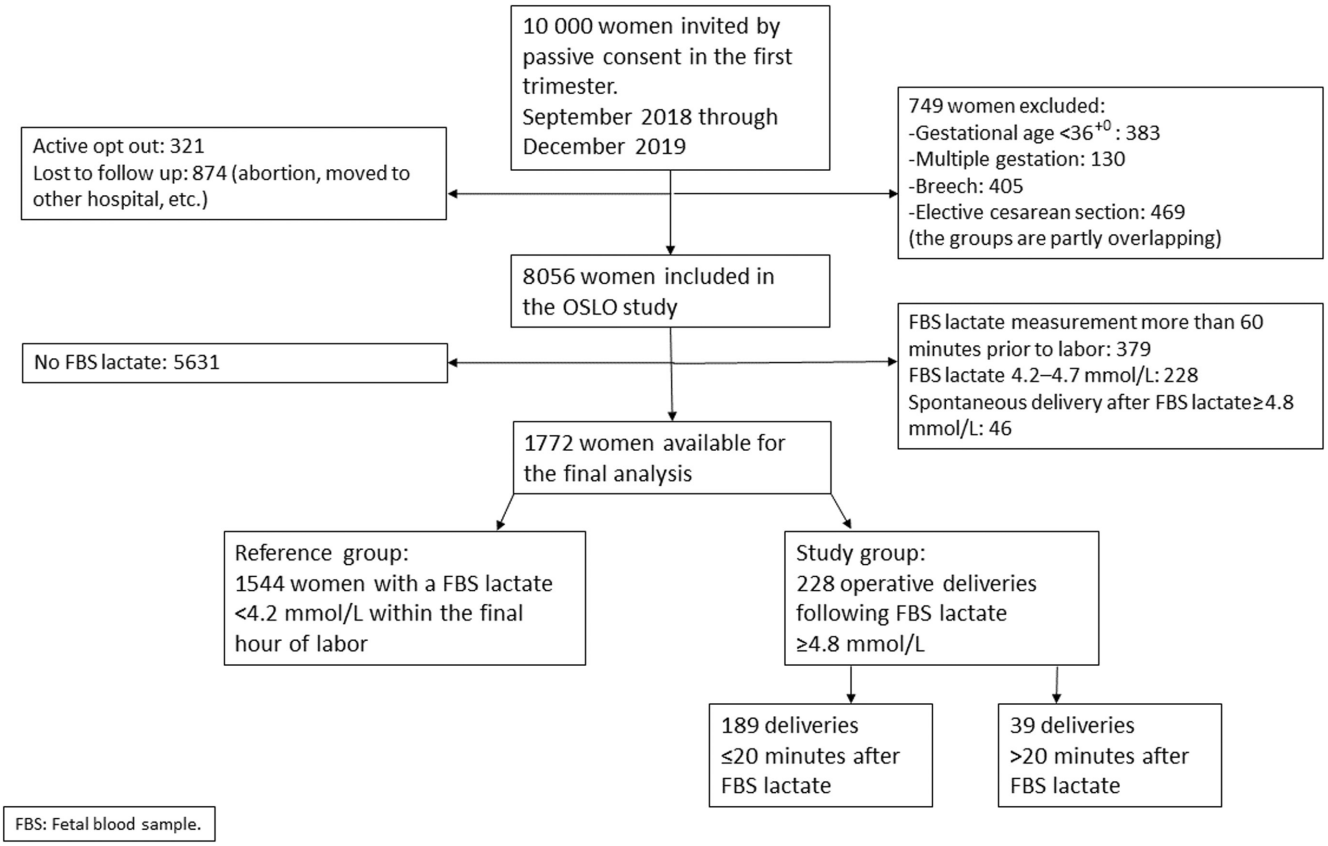

FIGURE 1 Flowchart of participant inclusion.

There were 265 (3.3%) cases of umbilical cord acidemia (pH ≤7.10).

During the study period, 228 women had an operative delivery after an FBS lactate concentration of 4.8 mmol/L or greater. The reference group (FBS lactate concentration <4.2 mmol/L within 60 minutes before delivery) included 1544 women (Figure 1).

Table 1 displays the characteristics of the included mothers and their newborns. The reference group and the study group (FBS lactate concentration ≥4.8 mmol/L) were comparable with regard to all background information, except for gestational age, stage of labor at delivery, and mode of delivery (Table 1). The two DDI groups did not differ from each other with regard to any background information, except for mode of delivery and stage of labor at delivery (Table 1). They were also comparable to each other with regards to the median concentration of the final FBS lactate measurement (Table 2).

Delivery was accomplished within a time frame of 20 min for 83% of the operative deliveries following an FBS lactate concentration of 4.8 mmol/L or greater. The DDI was, as expected, significantly shorter for women delivered in the second stage of labor, with 90% delivered within 20 minutes in the second stage of labor, compared with 47% in the first stage of labor.

As a supplementary analysis, we calculated the effect of the FBS lactate concentration on the length of the DDI using linear regression. There was a statistically significant inverse correlation between the lactate concentration and the time consumption. The DDI decreased by 65 seconds for each 1 mmol/L increase of FBS lactate ($p = 0.04$).

Results of the analyses are shown in Table 3. As expected, the risks of a 5-minute Apgar score less than 7, cord pH level of 7.10 or less, transfer to the neonatal intensive care unit, and combined neonatal morbidity were increased for the study group, compared with the reference group. This applied both for DDI of 20 minutes or less and for DDI of more than 20 minutes. We found a statistically significant increase in the risk of a 5-minute Apgar score less than 7 when the DDI exceeded 20 minutes (adjusted odds ratio 8.1, 95% confidence interval 1.1–60.9). There was a statistically non-significant increase in the risk of umbilical cord pH of 7.10 or less, transfer to the neonatal intensive care unit, and combined neonatal morbidity with DDI more than 20 minutes (Table 3).

Unfortunately, we were not able to estimate crude and adjusted odds ratios of metabolic acidosis because there were no cases in the reference group (FBS lactate concentration <4.2 mmol/L within 60 minutes before delivery), nor in the group with a DDI exceeding 20 minutes. There were three cases in the group with lactate of 4.8 mmol/L or more and delivery within 20 minutes from indication of high FBS lactate concentration.

The same applied for neonatal encephalopathy. There were 10 cases of moderate to severe neonatal encephalopathy in the study period. Five of them had FBS within the last 60 minutes of labor. One had a normal FBS lactate concentration and a spontaneous delivery, but the delivery was complicated by shoulder dystocia and umbilical

TABLE 1 Patient characteristics.

	All patients ($n=8056$)	Reference group (Lactate <4.2 mmol/L within the final hour of labor) ($n=1544$)	Study group (operative delivery after FBS lactate ≥4.8 mmol/L) ($n=228$)	
			DDI ≤20 min ($n=189$)	DDI >20 min ($n=39$)
Average age at delivery (y)	31.6	31.6	31.1	31.0
Gestational age at delivery (wk)	40^{+0}	40^{+2}	40^{+4}	40^{+5}
Parity				
0	4314 (54%)	1210 (78%)	157 (83%)	33 (85%)
≥1	3742 (46%)	334 (22%)	32 (17%)	6 (15%)
Hypertensive complications	285 (4%)	57 (4%)	9 (5%)	0 (0%)
GDM or pre-existing diabetes	407 (5%)	76 (5%)	9 (5%)	2 (5%)
Induced delivery	2180 (27%)	506 (33%)	75 (40%)	14 (36%)
Epidural	4220 (52%)	1195 (77%)	148 (78%)	30 (77%)
Oxytocin	2859 (35%)	976 (63%)	112 (59%)	26 (67%)
Stage of labor at delivery				
First	615 (8%)	69 (4%)	17 (9%)	20 (51%)
Second	6995 (87%)	1470 (95%)	172 (91%)	19 (49%)
Missing	446 (6%)	5 (0%)	0 (0%)	0 (0%)
Mode of delivery				
Spontaneous	6259 (78%)	1116 (72%)	0 (0%)	0 (0%)
Operative vaginal	942 (12%)	351 (23%)	171 (90%)	7 (18%)
Cesarean section	855 (11%)[a]	77 (5%)	18 (10%)	32 (82%)
Birthweight (grams)	3542	3511	3516	3488

Note: Hypertensive complications include chronic (pre-existing) hypertension, gestational hypertension, and pre-eclampsia.

Abbreviations: DDI, decision-to-delivery interval; FBS, fetal blood sampling; GDM, gestational diabetes.

[a]A proportion of our elective cesarean sections is delivered at Rikshospitalet, Oslo University Hospital. The cesarean section rate, including these patients was 14.3%.

cord blood gases were normal. One had an operative vaginal delivery after an FBS lactate concentration of 4.7 mmol/L. Three had an FBS lactate concentration of at least 4.8 mmol/L and underwent operative delivery (one by cesarean section, two by vacuum) with a DDI of less than 20 minutes. There were no cases of neonatal encephalopathy with DDI of more than 20 minutes.

Arterial umbilical cord pH values recorded for the cases with neonatal encephalopathy were between pH 6.8 and pH 7.2.

Complications to the lactate sampling procedure were not registered systematically, but to our knowledge, none occurred during the study period.

In addition to the main study group analyses, we also investigated the larger study group with an operative delivery indicated by an FBS lactate concentration of 4.2 mmol/L or more in combination with clinical suspicion of fetal distress. For this group, we found a statistically significant increase in the risk of low 5-minute Apgar score, acidemia (pH ≤7.10), transfer to the neonatal intensive care unit, and combined neonatal morbidity for both DDI groups compared with the reference group. There was a tendency toward increased risk of all these adverse neonatal outcomes with increased time consumption, but these associations did not reach statistical significance (Tables S1 and S2).

In Figure S1, we illustrate by Kaplan-Meier survival plots that there were no statistically significant differences in the risk of adverse neonatal outcomes across the study groups with elevated FBS according to time to delivery (ie DDI), when time was considered as a continuous variable.

4 | DISCUSSION

In this large prospective observational study from an unselected pregnant population, we examined the associations between the length of the DDI and the risk of adverse neonatal outcomes in deliveries monitored with CTG and FBS lactate measurements. High FBS lactate identified fetuses at risk of short-term adverse outcomes.

There was a statistically significant increase in the risk of a low 5-minute Apgar score (<7) if the DDI exceeded 20 minutes. The respective risks of a pH of 7.10 or less, transfer to the neonatal intensive care unit, and combined neonatal morbidity also increased, but these associations did not reach statistical significance. These results are in line with the findings in previous studies.[14,24] Kessler et al. found an association between DDI and low 5-minute Apgar score, transfer to the neonatal intensive care unit, and neonatal

TABLE 2 Median number of lactate samples, median final lactate value, median DDI and quality of umbilical cord samples related to DDI group.

	All patients (Lactate measured in 2425 women [30%]) ($n=8056$)	Reference group (Lactate <4.2 mmol/L within the final hour of labor) ($n=1544$)	Study group (operative delivery after FBS lactate ≥4.8 mmol/L) ($n=228$)	
			DDI ≤20 min ($n=189$)	DDI >20 min ($n=39$)
Number of lactate measurements, median (range)	0 (0–13)	2 (1–13)	2 (2–10)	3 (1–6)
Final lactate measurement (mmol/L), median (range)[a]	2.8 (0.5–11.5)	2.6 (0.5–4.1)	5.2 (4.8–11.5)	5.2 (4.8–7.3)
DDI (minutes), median (range)[a]				
Total	20 (0–1468)	20 (0–60)	11 (1–20)	25 (21–41)
If delivered in first stage	49 (5–800)	36 (5–60)	17 (10–20)	25 (21–41)
If delivered in second stage	19 (0–1468)	19 (0–60)	10 (1–20)	25 (21–38)
DDI ≤20 min[a]				
Total	50%	53%	100%	0%
If delivered in first stage	15%	19%		
If delivered in second stage	54%	55%		
Cord acid base data				
Two vessels (%)	5034 (62%)	1076 (70%)	141 (75%)	21 (54%)
One vessel (%)	1863 (23%)	398 (26%)	43 (23%)	16 (41%)
No data (%)	1159 (14%)	70 (5%)	5 (3%)	2 (5%)

Abbreviations: DDI, decision-to-delivery interval; FBS, fetal blood sampling.

[a]Values for the "all patients" group are restricted to the fraction that had at least one FBS lactate measurement during labor.

TABLE 3 Crude and adjusted odds ratios, with 95% CIs, of neonatal outcomes for DDI >20 minutes compared with DDI ≤20 minutes, in operative deliveries after an FBS lactate ≥4.8 mmol/L, estimated by logistic regression.

	DDI ≤20 min	DDI >20 min				
Outcome	*N* (%)	*N* (%)	OR	95% CI	aOR	95% CI
5-min Apgar score <7	7 (4)	4 (10)	2.9	0.8–10.6	8.1	1.1–60.9
Cord pH ≤7.10	21 (13)	6 (20)	1.7	0.6–4.6	2.0	0.5–8.4
Metabolic acidosis	3 (2)	0 (0)	NA	NA	NA	NA
Transfer to NICU	40 (21)	10 (26)	1.3	0.6–2.9	1.1	0.4–3.5
Neonatal encephalopathy	3 (2)	0 (0)	NA	NA	NA	NA
Combined neonatal morbidity	56 (30)	14 (36)	1.3	0.6–2.8	1.7	0.6–4.7

Note: Adjusted for maternal age, birthweight, mother's parity (primipara or parous), mode of delivery (operative vaginal delivery or cesarean section), and lactate (as dichotomous variable: 4.8–5.1 mmol/L or ≥5.2 mmol/L).

Metabolic acidosis: umbilical cord pH <7.00 and base deficit in the extracellular fluid ≥12 mmol/L.

Combined neonatal morbidity: 5-min Apgar score <7, umbilical cord pH ≤7.10, and/or transfer to the neonatal intensive care unit.

Abbreviations: aOR, adjusted odds ratio; CI, confidence intervals; DDI, decision-to-delivery interval; FBS, fetal blood sampling; *N*, number of cases in the group (cases as percentage of the group); NA, not available; NICU, neonatal intensive care unit; OR, odds ratio.

encephalopathy in labors monitored by STAN.[14] Heller et al. found statistically significant associations between DDI exceeding 20 minutes and low 5- and 10-minute Apgar scores in labors monitored by CTG with optional FBS.[24] They did not, however, find a statistically significant association between DDI and severe acidemia (pH <7.0). They did not define the start of their DDI, nor did they perform a separate subgroup analysis for deliveries with FBS measurements. This makes a direct comparison with our results challenging.

Our results differ from the results found by Murphy and Koh, who found no statistically significant relation between the length of the DDI and risk of adverse neonatal outcomes.[25] Their study was, however, limited to operative vaginal deliveries, and FBS was only performed in 34.5% of the cases with fetal distress.

Previous studies that have examined the effect of DDI in deliveries with obstetric emergencies such as uterine rupture and placental abruption found statistically significant associations between DDI and neonatal outcomes.[26] The lack of statistically significant associations between DDI and some of the examined adverse neonatal outcomes in the present study could be due to confounding by indication, as fetuses with more severe signs of fetal distress are delivered more rapidly. Despite a shorter DDI, those obstetrical emergencies still carry risk of significant neonatal morbidity. However, fetuses with severe signs of fetal distress (umbilical cord prolapse, suspected uterine rupture, suspected placental abruption, severe bradycardias, or preterminal CTG patterns) are delivered without spending time on FBS. As the analyses in the present study are restricted to deliveries with an FBS lactate concentration measured within 60 minutes before delivery, we do not believe that this effect had a substantial impact on our results.

Both the FBS lactate cut-off values for fetal acidemia and the recommended speed of intervention in case of diagnosed fetal acidemia may affect neonatal morbidity. The proportion of adverse neonatal outcomes was low in our study, supporting the short DDI for operative intervention due to fetal distress recommended in the Norwegian guidelines.[12] Corresponding limits were advocated in the study by Heller et al.[24] Whether those recommendations (DDI ≤20 minutes) could have been extended without the cost of increased neonatal morbidity cannot be answered by the present study.

It could be argued that the low rate of severe neonatal morbidity in the group with FBS lactate concentration of 4.8 mmol/L or greater in our study may indicate that a lactate threshold of 4.8 mmol/L for fetal acidemia is too strict. On the other hand, such a threshold might also be one of the reasons for the low proportions of neonatal morbidity in our study sample. Our study cannot answer this clinical question. Performing a randomized controlled trial to determine an optimal lactate threshold for intervention would be challenging in any institution with low rates of adverse neonatal outcomes.

As previously pointed out by Holzmann et al., it is important to use a cut-off value specified for the lactate meter in use.[27] At the time of the clinical observational part of our study, no such recommendation existed for the StatStrip Xpress Lactate Hospital Meter. A recently published Swedish observational study recommends a higher cut-off value of 5.2 mmol/L for labor intervention,[28] but no prospective comparative study has been performed to test the optimal FBS lactate concentration. A sub-analysis of our data, with an FBS lactate concentration of 5.2 mmol/L as cut-off value, revealed higher adjusted odds ratio for all outcomes, but no difference in the effect of the DDI, compared with the results with the cut-off value of 4.8 mmol/L (data not shown).

The tendency towards increased risk of adverse neonatal outcomes with increased time from indication of high FBS lactate concentration to delivery was present for all the examined outcomes in the present study. However, it was only statistically significant for the risk of low 5-minute Apgar score. As a high percentage of the labors with indication were delivered within the recommended DDI of 20 minutes, the group with a longer DDI is rather small, limiting the statistical power of our study.

The frequency of FBS lactate sampling was high in the present study, compared with previous studies.[19,28–30] It is possible that this liberal use of FBS lactate as a marker of fetal distress is one of several explanations for the high rate of favorable neonatal outcomes and the low proportions of operative deliveries in our delivery unit. On the other hand, the high frequency may potentially entail unnecessary interventions. The high FBS lactate measurement frequency might reduce the external validity of our study. Only 11% of the included women had a final FBS lactate of 4.8 mmol/L or more. This was lower than in the study by Kruger et al.,[19] in which 25% of the women had a final measurement above this concentration, but comparable to the 15% found by Holzmann et al.[30] A direct comparison of negative and positive predictive values is challenging because different lactate meters were used in these three studies.

The main strength of our study is the high number of prospectively included deliveries and a longstanding clinical experience with the use of FBS lactate in our clinic.[31] Further, the use of passive consent limits inclusion bias; only 3.2% of the women opted out. Minority groups have in general lower recruitment in studies with active consent.[32] Our study design with passive consent reduces this risk of selection bias and improves external generalization of the results. None of the included women decided to opt out after labor, which minimizes the risk of exclusion bias due to negative outcomes.

Limitations of our study include missing umbilical cord blood data, related to known difficulties in sampling analysis. In the present study, 71% of the included women with an operative delivery indicated by a high FBS lactate concentration had a valid sample from both the artery and the vein, and 26% had only one vessel sampled. This limitation is partially compensated through the inclusion of additional neonatal outcomes other than neonatal acidemia and metabolic acidosis. Furthermore, in the clinical setting of the present study, FBS lactate measurements could be missed through lack of documentation in the electronic patient records. Another limitation of the present study is the definition of the DDI, which differs from that used in other research.[15,25] We used the time of the final FBS lactate measurement as the start of the DDI (sampling-to-delivery interval) as it represents the time when fetal distress was objectively diagnosed. The decision to deliver (used for DDI in other studies) will commonly be made later, which limits the direct comparability with other data.

5 | CONCLUSION

In the present study, based on a general delivery population, we found a statistically significant increase in the risk of a 5-minute Apgar score less than 7 if the DDI exceeded 20 minutes in operative deliveries following a high FBS lactate concentration. There was a tendency toward increased risks of the other examined adverse

neonatal outcomes with increased DDI, but these associations did not reach statistical significance. Our study supports currently recommended time limits for intervention due to fetal distress.

AUTHOR CONTRIBUTIONS

The study was initialized by JK and BY. All authors contributed to the planning of the study. MB collected the clinical data. NG and MB performed the statistical analyses. All authors contributed to and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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