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Tachysystole and risk of cesarean section after labor induction using misoprostol: a cohort study

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Faculté de biologie
et de médecine

UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE

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Service d'Obstétrique

Tachysystole and risk of cesarean section after labor induction using

misoprostol: a cohort study

THESE

préparée sous la direction du Docteur David Desseauve
(avec la co-direction du Professeur David Baud)

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

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par

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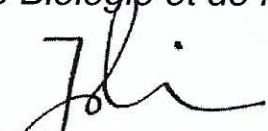
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***Tachysystole and risk of cesarean section after labor induction using
misoprostol: a cohort study***

Lausanne, le 24 septembre 2020

*pour Le Doyen
de la Faculté de Biologie et de Médecine*



*Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale*

Hypercinésie utérine et risque de césarienne après le déclenchement du travail par Misoprostol

Le déclenchement artificiel du travail est une pratique obstétricale courante, concernant 20 % des patientes dans le pays occidentaux. Le Misoprostol, un analogue synthétique de la prostaglandine E1, est un agent de déclenchement couramment utilisé en Suisse. Cependant, cet agent induit plus fréquemment que les autres des hypercinésies utérines. Il est craint qu'une fréquence trop élevée de contractions pendant le déclenchement du travail induise une diminution de la perfusion placentaire, une majoration des acidoses fœtales ainsi qu'une augmentation du taux de césarienne. Peu d'études sur le sujet ont été réalisées avec des résultats divergents. De plus, il n'a pas été démontré une augmentation du taux de césarienne ou une élévation de la morbidité néonatale lorsque le Misoprostol est comparé aux autres moyens de déclenchement dans la littérature.

L'objectif de notre étude est d'évaluer si la présence d'une hypercinésie lors du déclenchement du travail est associée à une augmentation du taux de césarienne ainsi que des issues maternelles et néonatales défavorables. Nous avons réalisé une étude de cohorte rétrospective au sein de la maternité du Centre Hospitalier Universitaire Vaudois, incluant 446 patientes à plus 37 semaines d'aménorrhées admises pour un déclenchement du travail par Misoprostol entre Mai 2016 et Mai 2017. Les données démographiques, obstétricales et néonatales ont été recueillies par consultation des dossiers médicaux informatisés des patientes. Chaque cardiotocogramme a été analysé et classé selon les recommandations de l'ACOG tant d'un point de vue du rythme cardiaque que des contractions. L'hypercinésie a été définie comme un nombre supérieur à 6 contractions par 10 minutes.

Au total 140 patientes (31.4%) ont présenté une hypercinésie. La durée moyenne de l'hypercinésie était de 2 heures et 12 minutes. Nous n'avons pas trouvé d'association entre la présence d'une hypercinésie et le taux de césarienne. La présence d'un rythme cardiaque fœtale suspect était plus fréquent chez les patientes ayant une hypercinésie, toutefois cela n'était pas associé à des issues néonatales défavorables. Les issues maternelles étaient similaires entre les patientes présentant une hypercinésie versus celles qui n'en n'avaient pas.

La définition actuelle de l'hypercinésie repose sur un seuil de contraction que la patiente expérimente sur 10 minutes. Une définition reposant uniquement sur la fréquence des contractions n'est pas suffisante pour évaluer l'impact d'une activité utérine excessive et n'est donc pas un prédicteur d'issues maternelles ou néonatales défavorables comme démontré dans notre étude. A ce jour, il n'existe pas de moyen d'investigation permettant de caractériser de manière fiable l'activité contractile utérine. Contrairement à l'étude de l'analyse du rythme cardiaque fœtale, que peu d'auteurs se sont intéressés à l'analyse des contractions et leurs associations aux issues néonatales et maternelles. Il nous semble indispensable de porter notre attention sur la caractérisation de l'activité utérine en salle d'accouchement et d'y développer de nouveaux outils permettant de mesurer la force utérine contractile et le tonus utérin de base afin d'y améliorer la sécurité des mères ainsi que des nouveau-nés.



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Tachysystole and risk of cesarean section after labor induction using misoprostol: A cohort study

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ABSTRACT

Objectives: To investigate if tachysystole was associated with an increased risk of cesarean section or unfavorable maternal or neonatal outcomes following induction of labor by misoprostol vaginal inserts. **Study design:** We conducted a retrospective cohort study of 446 women over 37 weeks of gestation admitted for labor induction by misoprostol vaginal inserts between May 2016 and May 2017. Fetal heart rate and uterine activity tracings were assessed for tachysystole, defined as ≥ 6 contractions per 10 min, averaged over a 30-minute window. Univariate analysis was performed by using *t*-test and Chi-square, comparing demographics, pregnancy characteristics, intrapartum monitoring, mode of delivery, neonatal outcomes (Apgar score < 7 at 5 min, umbilical cord artery pH < 7.10, neonatal intensive care unit admission) and maternal outcomes, with regard to the presence of tachysystole. The association between tachysystole and cesarean section was evaluated after adjusting for potential confounders by a modified Poisson regression model, expressed as an adjusted risk ratio and 95 % confidence intervals. **Results:** A total of 140 women (31.4 %) presented with tachysystole. The median duration of tachysystole was 2 h 12 min. The rate of cesarean section was 25.0 % (N = 35) among patients with tachysystole and 19.6 % (N = 60) for those without tachysystole. Presence of tachysystole during induction of labor with misoprostol vaginal inserts was not associated with cesarean section (adjusted risk ratio, 1.0; 95 % confidence interval, 0.7–1.4). Neonatal and maternal outcomes were similar between mothers who did and did not experience tachysystole.

Conclusions: This study illustrates that tachysystole is not associated with an increased risk of cesarean section after induction of labor by misoprostol vaginal inserts. The impact of excessive uterine activity on the fetal wellbeing defined by the frequency of uterine contraction alone is probably insufficient. Further research on the development of accurate measures of uterine contractility is necessary to better understand its effect on fetal well-being.

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Introduction

Induction of labor is a common obstetrical intervention. The rate of induction of labor in the United States has increased in the last twenty years from 9.5 % to 23 % of births [1]. A misoprostol vaginal insert, releasing 7 mcg per hour, was introduced to the market in 2014. It is the only licensed prostaglandin E1 analogue approved for induction of labor in many countries. However, compared to other means of induction of labor, increased rates of

tachysystole with misoprostol vaginal inserts (MVI) have been reported by several authors [2–4].

Presence of tachysystole during induction of labor is a concern as it is feared to lead to fetal blood deoxygenation due to decreased placental perfusion [5]. This in turn could lead to non-reassuring fetal heart traces, fetal acidosis, and hence higher rates of medical intervention and poorer neonatal outcomes [5]. Despite the high frequency of tachysystole after induction of labor with MVI, no difference in cesarean section rate or neonatal outcomes has been observed between MVI and other induction methods [2–4]. Currently, there is conflicting evidence regarding the clinical impact of tachysystole, as some authors have reported an increase in cesarean section rates, operative vaginal delivery and neonatal morbidity [6–8] while others found no significant differences [9–11]. More information is therefore needed on the association between tachysystole and progression to cesarean section. Furthermore, a

Abbreviations: NICU, neonatal intensive care unit; MVI, misoprostol vaginal inserts; RR, unadjusted risk ratios; aRR, adjusted risk ratios; CI, confidence interval.

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study illustrated that managing cases of uterine tachysystole with fetal heart rate changes was more challenging due to the longer half-life of MVI (approximately 40 min) [12]. The optimal approach to manage concurrent tachysystole and fetal heart rate alterations after induction of labor is as yet undetermined.

The aim of our study was to evaluate if the presence of tachysystole after induction of labor by MVI is associated with an increased risk of cesarean section and unfavorable maternal or neonatal outcomes.

Material and methods

Study population

We conducted a retrospective cohort study at the obstetrics service of the University Hospital of Lausanne, between May 2016 and May 2017. We included all pregnant women above 37 weeks of gestation and parity of three or less, admitted for induction of labor by MVI. The exclusion criteria were the following: women under 18 years old, previous uterine scar, uterine malformation, fetal growth restriction, application of more than one MVI, pregnancy complicated by non-vertex presentation, modified Bishop’s score ≥ 7 , multiple gestation, major fetal anomaly, non-viable foetus, pre-existing contraindications for labor or vaginal delivery, and cases where the paper fetal heart trace was unavailable.

Demographic, obstetrical and neonatal characteristics were gathered from the admission chart available on the hospital electronic database. The following data were recorded: maternal age, parity, gestational age, maternal BMI, maternal smoking, modified Bishop’s score at admission, indication for induction of labor, presence of tachysystole, Bishop’s score at occurrence of tachysystole, duration of tachysystole, use of tocolytics, fetal heart patterns, use of early epidural anesthesia, mode of delivery, time of delivery from the onset of induction, labor dystocia, presence of meconium stained amniotic fluid, postpartum hemorrhage (≥ 500 ml after vaginal delivery and ≥ 1000 ml after cesarean section),

neonatal umbilical cord blood gases and Apgar score at birth, transfer to neonatal intensive care unit (NICU).

The MVI was applied to the posterior fornix. The vaginal insert was extracted under the following conditions: onset of active labor, painful regular contractions, tachysystole, non-reassuring fetal heart monitoring, at 24 h post insertion, or at maternal request.

Exposure

The contractions patterns were independently reviewed by two authors (JS, DD), and classified according to the American College of Obstetrics and Gynecology and the National Institute of Child Health and Human Development workshop report [13,14]. During the review process, authors were blinded for the mode of delivery and the neonatal issues. Any assessment discordances or difficulty of interpretation, were discussed between the authors. Tachysystole was defined as ≥ 6 contractions per 10 min, averaged over a 30-minute window [13,14].

Outcomes

A positive primary outcome was considered for every patient with cesarean section noted in their chart as the mode of delivery.

In our service, fetal heart rate monitoring is recorded at regular intervals before labor (20 min before insertion; 1 h following insertion; every 4 h thereafter), as well as in cases of painful uterine contractions. During labor, a continuous fetal heart rate monitoring is performed. Following the same blinded review process as for the definition of tachysystole, fetal heart patterns were assessed using the available information. Non-reassuring fetal heart rate patterns, a secondary outcome, were defined as either Category II or Category III using the classification of the American College of Obstetrics and Gynecology and the National Institute of Child Health and Human Development workshop report [13,14]. The use of tocolytics with time to resolution after administration was reported as another secondary outcome. Intrapartum fetal resuscitation was performed

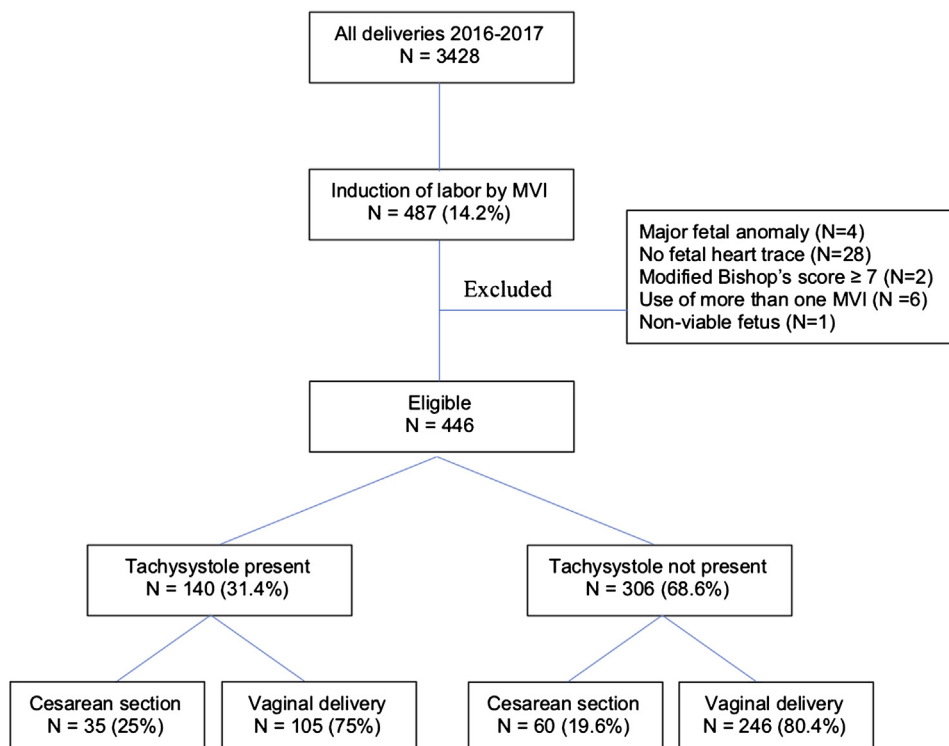


Fig. 1. Flowchart.

by rolling the patient to their left side, with administration of tocolytics in case of tachysystole associated with a Category III fetal heart pattern, in accordance with our unit's protocol. Tocolysis was effected using either Atosiban (6.75 mg administered IV over a 1-minute period) or Hexoprenaline (5 µg administered IV over a 5-minute period) at the physician's discretion.

Postpartum hemorrhage, transfer to neonatal intensive care unit (NICU), umbilical artery pH \leq 7.10 mmHg, umbilical lactate value, and five-minute Apgar score $<$ 7 were considered as other positive secondary outcomes.

Statistical analysis

Patients were divided into two subgroups according to presence of tachysystole. Student *t*-test and Chi-square or Fisher's exact test were used for comparison of continuous and categorical data, respectively. Cohen's kappa coefficient was used [15] to assess interobserver agreement after fetal heart and contractions patterns review. A Wilcoxon rank sum test was used to compare resolution time of tachysystole between the types of tocolytics.

Proportions were compared for potential confounders among women with tachysystole or without. Absolute risks and unadjusted risk ratios (RR) with their 95 % confidence interval (CI) were calculated. Adjusted RR (aRR) and 95 % CI were estimated using generalized linear models (Poisson regression with robust variance estimates). All analyses were performed using STATA software (version 14IC; Stata corporation, College Station, TX).

Results

Study population

During the study period, amongst 3428 deliveries, there were 487 patients (14.2 %) induced by MVI. The overall induction of labor rate was 20.2 %. A total of 446 patients were included in the analysis, as 41 women (8.4 %) did not meet our inclusion criteria as illustrated in Fig. 1. In the cohort of enrolled patients, 296 (66.4 %) were nulliparous. The mean maternal age was 31.6 years, ranging from 18 to 49, and the mean gestational age was 40.2 weeks, ranging from 37 to 42. The most common indication for induction of labor was post-term pregnancy in 126 women (28.3 %). Further indications included premature rupture of membranes (110 women, 24.7 %), oligohydramnios (39 women, 8.7 %), diabetes (29 women, 6.5 %), suspected macrosomia (22 women, 4.9 %), preeclampsia/hypertension (19 women, 4.3 %), fetal movement diminution (12 women, 2.7 %), cholestasis of pregnancy (7 women, 1.6 %), bleeding of unknown origin (6 women, 1.3 %) and miscellaneous others (44 women, 9.9 %). 32 women (7.2 %) were induced at their request. The median time between onset of induction of labor and any mode of delivery was 15 h 6 min. The median time between insertion and removal of MVI was 7 h.

Amongst the included women, 140 (31.4 %) presented with an episode of tachysystole. Demographics and baseline characteristics of the study population were compared according to the presence of tachysystole (Table 1). There were several differences in the baseline characteristics between the groups. Women with tachysystole were more likely to present with the following characteristics: younger age, older gestational age at induction, lower BMI, post-term pregnancy, intact membranes, cholestasis of pregnancy, Bishop's modified score $<$ 4 at induction, use of tocolytics, meconium stained amniotic fluid, and use of epidural anesthesia.

Tachysystole management

The median duration of tachysystole was 2 h 12 min. Tachysystole arose after removal of the MVI in 33 women (23.6 %) and occurred

Table 1
Demographic and baseline characteristics of the study population.

	Tachysystole		p value
	Yes n = 140	No n = 306	
Maternal age, years			0.001
< 25	27 (19.3)	27 (8.8)	
25–34	89 (63.6)	189 (61.8)	
\geq 35	24 (17.1)	90 (29.4)	
Gestational age at induction, weeks			0.06
37	4 (2.9)	10 (3.3)	
38	16 (11.4)	27 (8.8)	
39	18 (12.9)	54 (17.6)	
40	19 (13.6)	70 (22.9)	
$>$ 41	83 (59.3)	145 (47.4)	
Nulliparity	98 (70.0)	198 (64.7)	0.27
BMI, kg/m²			0.14
18.5–24.9	12 (8.6)	26 (8.5)	
25–29.9	115 (82.1)	230 (75.2)	
\geq 30	13 (9.3)	50 (16.3)	
Indication for induction			0.05
Post-term pregnancy	50 (35.7)	76 (24.8)	
Rupture of membrane	20 (14.3)	90 (29.4)	
Diabetes	8 (5.7)	21 (6.9)	
Oligohydramnios	13 (9.3)	26 (8.5)	
Fetal movement diminution	3 (2.1)	9 (2.9)	
Preeclampsia/Hypertension	5 (3.6)	14 (4.6)	
Suspected macrosomia	8 (5.7)	14 (4.6)	
Maternal request	11 (7.9)	21 (6.9)	
Cholestasis of pregnancy	4 (2.9)	3 (1.0)	
Bleeding of unknown origin	2 (1.4)	4 (1.3)	
Other	16 (11.4)	28 (9.2)	
Modified Bishop's score $>$ 4	11 (7.9)	39 (12.7)	0.13
Labor dystocia	15 (10.7)	30 (9.8)	0.78
Use of tobacco during pregnancy	19 (13.6)	46 (15.0)	0.63
Epidural anesthesia	110 (78.6)	212 (69.3)	0.05
Meconium stained amniotic fluid	37 (26.4)	63 (20.6)	0.18
Tocolysis	21 (15.0)	17 (5.6)	0.0001

All data shown as n (%).

^ap value obtained via Chi-square test of Fisher's exact test as appropriate.

BMI, body mass index.

more frequently at low Bishop's score, between 0 and 2 (58 % of patients). Tocolytics were administered to 21 women (15.0 %) who presented with tachysystole and category III fetal heart tracing; 9 women (42.9 %) received Atosiban while 12 (57.1 %) received Hexoprenaline. 17 women (5.6 %) without tachysystole received tocolytics; Hexoprenaline in all cases.

No significant difference in rates of cesarean section between the administration of Atosiban compared to Hexoprenaline was observed (46.2 % vs 53.9 %, $p = 0.70$), nor in the difference in time to resolution of tachysystole (1 h 12 min vs 1 h 43 min, $p = 0.93$).

Association between tachysystole and cesarean section

The risk of cesarean section was 25.0 % in the tachysystole group and 19.6 % in the other group ($p = 0.20$). The unadjusted RR for cesarean section associated with the presence of tachysystole after induction of labor versus absence of tachysystole was 1.4 (95 % CI, 0.8–2.2). After adjustment for confounders using generalized linear models, the adjusted RR was 1.0 (95 % CI, 0.7–1.4) (Table 2).

A satisfactory agreement between the two reviewers with regards to the classification of the contraction patterns was observed, with a Cohen's kappa value of 85 % (CI 95 %: 0.79–0.91).

Association between tachysystole and other maternal or neonatal outcomes

Women who experienced tachysystole were more likely to present non-reassuring fetal heart monitoring during induction of labor or labor (aRR, 3.5; 95 % CI, 2.8–4.4). However, no associations

Table 2

Adjusted risk ratio for cesarean section among patients induced with misoprostol vaginal inserts in the presence of tachysystole.

	Cesarean section n (%)	RR (95 % CI)	Adjusted RR (95 % CI) ^a
Tachysystole	35 (25.0)	1.4 (0.8–2.2)	1.0 (0.7–1.4)

RR, risk ratio; CI, confidence interval.

^a Adjusted for maternal age, gestational age, indication of induction, body mass index, modified Bishop's score > 4, use of epidural anesthesia, presence of meconium stained amniotic fluid by a modified Poisson regression.

were found between unfavorable neonatal outcomes and tachysystole: Apgar scores < 7 at 5 min (aRR, 1.4; 95 % CI, 0.8–2.3), cord arterial pH < 7.10 (aRR, 1.0; 95 % CI, 0.6–1.6), umbilical lactate value (aRR, 1.0; 95 % CI, 0.9–1.0) and NICU admission (aRR, 1.0; 95 % CI, 0.7–1.6). These results were not adjusted for indications of labor induction where differences between groups were non-significant. Women with tachysystole were not at increased risk of postpartum hemorrhage (aRR, 1.1; 95 % CI, 0.8–1.6) (Table 3).

Discussion

In this retrospective cohort study, we did not observe an association between tachysystole after induction of labor by misoprostol vaginal inserts and cesarean section, despite its frequent occurrence (31.4 %). Non-reassuring fetal heart patterns during induction of labor or labor were more common amongst women who presented with tachysystole; however, tachysystole was not found to be associated with unfavorable neonatal outcomes. This was in line with recent findings [3,16–20].

Why do some women experience tachysystole for hours with no impact on the fetal heart pattern, while others rapidly manifest grave repercussions? Current evidence cannot provide an adequate answer. Heuser et al., retrospectively examined 48,529 women who underwent spontaneous, induced or augmented labor during a 28-month period [6]. 11 % of women presented with tachysystole, with an associated increase in operative delivery, NICU admissions and composite adverse neonatal outcomes. However, 60 % of women presenting with tachysystole did not necessitate any interventions or present fetal heart rate alterations. In another retrospective study, by Ahmed et al., 11 % of 8008 women in spontaneous labor presented with tachysystole [8]. This study illustrated an increased risk of cesarean section for non-reassuring fetal heart tracings and NICU admissions. The overall absolute risk was increased by only 2% or less, as 96 % of women with tachysystole presented normal fetal heart monitoring. For both studies there were no individual associations between tachysystole and low Apgar score, and umbilical cord pH data were unavailable. Frey et al., conducted a case-control study of 2355 women, and showed that while tachysystole was common in cases

of unfavorable composite neonatal outcomes, rates of tachysystole were not significantly different compared to women with normal umbilical artery pH [21]. In line with our results, Bofill et al. demonstrated, in an analysis of six randomized clinical trials involving 905 women undergoing induction or augmentation of labor, that while non-reassuring fetal heart tracings were more common in the tachysystole group, there were no adverse effects observed on Apgar scores, umbilical cord pH or NICU admissions [11]. Two separate studies examining tachysystole have not shown greater incidence of low Apgar scores, umbilical artery pH or other adverse neonatal outcomes: Stewart et al. [9] who examined cases in the initial 4 h of induction of labor, and Smith et al. [10] who investigated cases during the final 4 days before delivery.

Clinical debate on the issue centers on uterine contraction frequency, but perhaps examination of uterine contractile force bears more importance. Could the compression of the spiral arteries leading to reduced fetal oxygenation be a consequence, not alone of tachysystole, but also of differences in uterine contraction intensity? It is our belief that defining tachysystole only by the number of contractions per 10 min intervals is not a reliable marker to predict adverse neonatal and maternal outcomes, as external tocodynamometers are useless in the measurement of uterine contractile force or baseline uterine tone [22]. Bakker et al. demonstrated by using intrauterine pressure catheter that an increased uterine activity was associated with lower umbilical cord arterial [7]. In contrast, a Cochrane review found insufficient evidence for the routine use of intrauterine pressure catheter during induction of labor or augmentation with oxytocin as it did not show an improvement in maternal and neonatal outcomes [23], with some complications reported [24]. Recently, a promising non-invasive alternative technique for uterine contraction monitoring has been developed. Electrohysterography measures the uterine electrical currents through contact electrodes placed on the abdomen, and has higher sensitivity than external tocodynamometers for uterine contraction detection [25]. Electrohysterography has been investigated as a tool to measure intrauterine pressure [26], and should discriminate clinical settings e.g. labor vs non-labor [27], prediction of preterm deliveries [28], or prostaglandins effect on uterine activity during induction of labor [29]. With further study, electrohysterography monitoring could provide further insight on uterine contractions' capacity to alter placental perfusion, and thus fetal outcomes.

Amongst the strengths of our research, our patient cohort presented tachysystole at a high incidence and of relatively long duration, with these fetuses exposed to greater uterine activity than those in any comparable study. Our research was not limited to specific intrapartum periods, instead encompassing the entire labor process. Fetal heart trace analysis was performed according to current definitions of tachysystole. Our work is homogenic,

Table 3

Intrapartum monitoring, neonatal and maternal outcomes.

	Tachysystole		RR (95 % CI)	Adjusted RR (95 % CI) ^a
	Yes N = 140	No N = 306		
NRFT	52 (37.1)	84 (27.5)	15.9 (8.3–30.5)	3.5 (2.8–4.4)
Neonatal outcomes				
Apgar < 7 at 5 min	7 (5.0)	6 (2.0)	2.6 (0.9–8.0)	1.4 (0.8–2.3)
Cord artery pH < 7.10	14 (10.0)	17 (5.6)	1.9 (0.9–4.0)	1.0 (0.6–1.6)
Umbilical lactate	4.8 ± 3.2	4.3 ± 2.4	1.0 (1.0–1.1)	1.0 (0.9–1.0)
NICU admission	18 (12.9)	26 (8.5)	1.6 (0.8–3.0)	1.1 (0.7–1.6)
Maternal outcome				
Postpartum hemorrhage	31 (10.1)	16 (11.4)	1.1 (0.6–2.2)	1.1 (0.8–1.6)

All data shown as n (%) or mean ± SD.

NRFT, non-reassuring fetal heart tracing; NICU, neonatal intensive care unit.

^a Adjusted for presence of non-reassuring fetal heart tracing, Apgar < 7 at 5 min, cord artery pH < 7.10, umbilical lactate value, neonatal intensive care unit admission, postpartum hemorrhage by a modified Poisson regression.

using a single protocol of induction of labor in a tertiary center. Furthermore, this study is original as, contrary to some other works reporting on tachysystole, we report the tocolytic agents administered, and their impact. [2,11,16,17] The major limitation of this study is its retrospective design. Retrospective chart review inhibits our capacity to control for other potential confounding factors. We have endeavored to mitigate this by dual independent analysis and correlation testing. Hidden bias may be produced by charts presenting deficient data.

Conclusion

In summary, we illustrated that tachysystole after induction of labor by MVI is not associated to an increased rate of cesarean delivery. However, the impact of excessive uterine activity on the fetal wellbeing defined by the frequency of uterine contraction alone is probably insufficient. While prediction of neonatal outcomes according to fetal heart patterns is currently in vogue, the repercussions of uterine activity on these outcomes has largely been ignored. Further attention is required to the characterization of excessive uterine activity, and the effective application of such knowledge by the obstetrician to optimize the safety of mother and child.

Authors' contributions

Conception and design: JS, DD and YV. Data collection: JS. Data analysis: JS, DD and AP. Manuscript drafting: JS. Revision of the manuscript and/or editing: YV, DB, AP, DD. All authors read and approved of the final manuscript.

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Ethical approval and consent for publication

The study was approved by the local IRB (Ethical Commission of the Canton of Vaud, Switzerland, 2018-01761), on November 21st 2018. As routinely collected data was accessed, no written consent from women was obtained.

Declaration of Competing Interest

The authors report no conflict of interest.

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