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Assessment of Human Fetuses Undergoing Acute Pain: Validation of the Fetal-7 Scale

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Abstract: **Improvements in fetal ultrasound have allowed for the diagnosis and treatment of fetal diseases in the uterus, often through surgery. However, little attention has been drawn to the assessment of fetal pain. To address this gap, a fetal pain scoring system, known as the Fetal-7 scale, was developed. The present study is a full validation of the Fetal-7 scale. The validation involved 2 steps: 1) 4 fetuses with the indication of surgery were evaluated in 3 conditions perioperatively: acute pain, rest, and under loud sound stimulation. Facial expressions were assessed by 30 raters using screenshots from 4D high-definition ultrasound films; 2) assessment of sensitivity and specificity of the Fetal-7 scale in 54 healthy fetuses and 2 fetuses undergoing acute pain after preoperative anesthetic intramuscular injection. There was high internal consistency with Cronbach's alpha (α) of .99. Intrarater reliability of the Fetal-7 scale (test-retest) calculated by intraclass correlation coefficient was .95, and inter-rater reliability was .99. The scale accurately differentiated between healthy fetuses at rest and those experiencing acute pain (sensitivity of 100% and specificity of 94.4%). The Fetal-7 scale is a valid tool for assessing acute pain-related behavior in third-trimester fetuses and may be of value in guiding analgesic procedures efficacy in these patients. Further research is warranted to explore the presence of postoperative pain in fetuses and its effects after birth.**

Perspective: ***Recordings with 3-dimensional ultrasound of human fetuses undergoing preoperative anesthetic injections revealed complex facial expressions during acute pain, similar to those collected in newborns. This study presented the validation process and cut-off value of the Fetal-7 scale, paving the way for the study of pain before birth in humans.***

Key words: *Acute pain, Fetus, Pain measurement, Obstetric surgical procedures, Validation study*

The recognition and knowledge about pain in newborns went from a dubious and greatly ignored phenomenon to an undisputable fact within a few decades.[1] In a similar route, pain in the human fetus, especially in the later weeks of gestation, has been increasingly discussed in academic, scientific, and society grounds.[2-4] With the development of ultrasonography technology, it was possible to recollect in

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fetuses the same facial expressions seen in newborns experiencing acute pain.[5-7] With the fast development of fetal surgery, the issue of pain in the fetus has moved from the neuroscience and theoretical helm into a pragmatic and clinical entity. While it is increasingly acknowledged that procedural and postprocedural pain is likely to occur, currently no assessment tools are validated to measure it.[8-10] Without reliable measures, analgesic treatment cannot be monitored or tailored to avoid the suffering and stress response related to surgery, which can additionally lead to worse long-term outcomes related to uncontrolled pain in the human fetus.[3,11]

Recently, it was shown that fetal expressions of acute pain triggered by the intramuscular injection of anesthetics prior to the performance of fetal surgery (tracheal fetal occlusion and fetal aortic valve dilation) could be recorded by 4D high-definition ultrasound (US) directed to the fetal face.[12] Strikingly, all the facial expressions of acute pain validated for neonates could be clearly identified in third-trimester fetuses. In a later study, it was shown that, with the exclusion of redundant items and the addition of 2 additional ones, a fetal pain scoring system in third-trimester fetuses could be produced (the Fetal-7 scale), comprising of 7 items derived from facial and head movements and expressions: 1) "brow lowering," 2) "eyes squeezed shut," 3) "deepening of the nasolabial furrow," 4) "open lips," 5) "horizontal mouth stretch," 6) "vertical mouth stretch," 7) "neck deflection.[13] Furthermore, to dissect acute pain from the nonspecific engagement of salience effects of surprise, facial expression scores in 3 different conditions were compared 1) after the preprocedural anesthetic shot, 2) after intense sound stimulation, and 3) at rest. The sum of the 7 items above a cut-off score of ≥5 differentiated acute pain from the other 2 control conditions.[13] This approach was further shown to detect acute pain expressions in also second-trimester fetus undergoing pain due to preprocedural anesthetic.[14] Despite these efforts, the Fetal-7 was not yet fully validated, which led us to conduct a formal full psychometric validation for the assessment of acute pain in third-semester human fetuses.

Methods

Study Design and Participants

This study represents the subsequent phase in the validation process of the F7[13] (Fig 1). The study was approved by the institutional ethics review board (2.649.528). All patients gave written informed consent to participate in the study and to record the behavioral reactions of the fetuses. US scanning was performed during the third trimester of pregnancy by a fetal-medicine specialist using a 4D-USmachine (Voluson E8 by GE Healthcare, Zipf, Austria or Samsung WS80 by Samsung Medison Co Ltd, Seoul, South Korea). Two fetal-medicine centers participated of the data collection: SEPACO Hospital, and Clinics Hospital—University of São Paulo, both in São Paulo, Brazil. The validation of the scale was divided into 2 steps: 1) we assessed the internal consistency, inter-rater, and intrarater reliability, and 2) we performed the external validity and the criterion validity of the F7 scale (Fig 1). This investigation conformed to the Standards for Reporting of Diagnostic Accuracy Studies 2015 guidelines.[15]

Step 1: Internal Consistency, Inter-rater Reliability, and Intrarater Reliability

In the first step, we recorded US images from 4 different third-trimester fetuses that were sequentially invited to join the study when attending preplanned visits to the fetal care centers: 2 were recorded during a painful stimulus related to the intramuscular mid-thigh injection of anesthetics as part of their preplanned surgery due to congenital left diaphragmatic hernia of poor prognosis (acute pain group [AP]), 1 fetus was recorded during undisturbed rest (control group at rest [Co-Re]), and 1 fetus was recorded during external acoustic stimulation (control group acoustic startle) as part of his usual vitality assessment. Acoustic stimulation is used in some fetal-medicine groups as a method to trigger changes in heart rate, which are markers of fetal health and well-being.[16,17] These fetuses underwent US recordings to provide images for the validation of the scale in raters. Details of the recording procedure are reported elsewhere.[13] Briefly, 5 representative images were drawn from the recordings of each fetus,

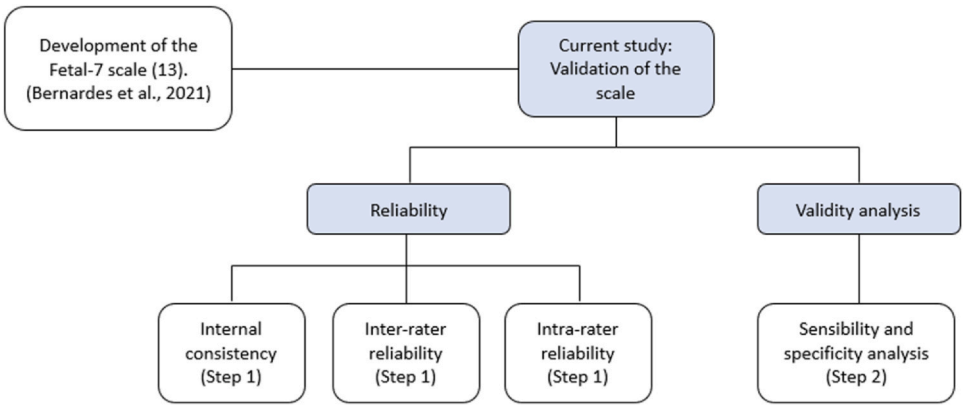

Figure 1. Study design.

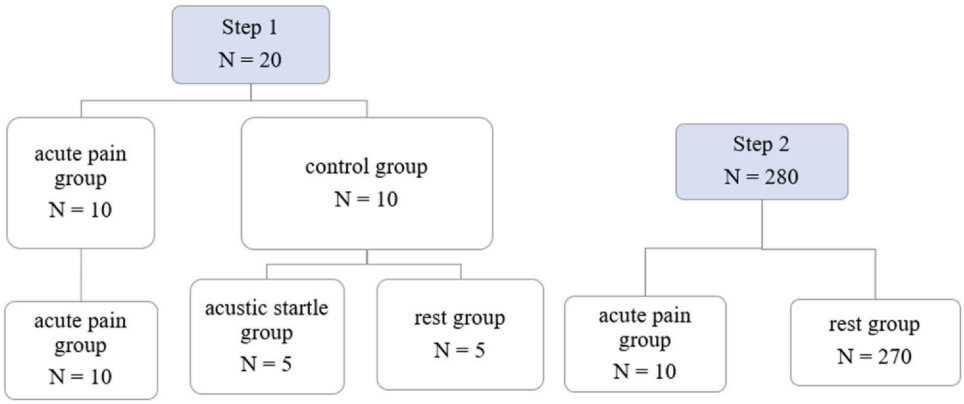

Figure 2. Flowchart of fetuses' US images assessed in the 2 steps of the study. N = number of US images available for each assessment. One US video provided 5 images each.

totalizing 20 images, which were subsequently evaluated by 30 raters (20 fetal-medicine specialists, 7 specialists in gynecology and obstetrics, 1 physiotherapist, 1 nurse, and 1 neurologist), which were blind to the fetal group belonging (Fig 2).

Invitations to participate as a rater were sent via email to members of the hospitals staff. If accepted to participate, the raters underwent a training program consisting of watching 1 tutorial video (https://www.youtube.com/watch?v=KZjqf0HU8B8), which lasts 3 minutes and 9 seconds, twice on 2 different days a week. Videos were prepared using representative real dynamic video images from patients included in our previous studies,[13] with accompanying audio, written legends, and explanatory texts. Raters were then requested to assess 2 cases with a tutor via an online meeting. Cases included 5 images of a fetus experiencing acute pain related to anesthetic puncture and 5 images of a fetus recorded at rest. After training, every rater assessed the facial movement images from each fetus and rated using the Fetal-7 scale. Images were evaluated twice by each rater after a 30 day-interval for intrarater reliability assessment.

Step 2: Sensitivity and Specificity Analysis

In the second step, we calculated the sensitivity and specificity of F7 scale by assessing third-trimester healthy fetuses recorded during undisturbed rest in usual care routine USs (Co-Re, n = 54) and third-trimester 2 fetuses undergoing surgery due to congenital left diaphragmatic hernia of poor prognosis (AP group) (Fig 2). Sensitivity and specificity were calculated according to the presence or absence of nociceptive stimulus (ie, images from Co-Re compared to those from the AP group). These assessments were performed within 30 days by the raters.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS IBM Corp, Armonk, NY), version 25. Initially, variables were analyzed by descriptive statistics. Internal consistency was analyzed using Cronbach's alpha.[18] The minimum value considered acceptable for the Cronbach's alpha coefficient was .7.[19,20] This evaluation reflects the extent to which questionnaire items are intercorrelated, or whether they are consistent in measurement of the same construct. For intrarater and intrarater reliability, we measured the intraclass correlation coefficient (ICC) by using a 2-way mixed model with absolute agreement.[19,21,22] ICC values less than .5 are indicative of poor reliability, values between .5 and .75 indicate moderate reliability, values between .75 and .9 indicate good reliability, and values greater than .90 indicate excellent reliability.

Sensitivity and specificity analyses were assessed as sensitivity and specificity of F7 scale to detect fetal reaction to the painful stimulus were calculated. The significance level adopted was 5%. The sample size was calculated to provide 300 images from US recordings and the number of raters corresponding to 10% of this sample (n = 30).[23]

Results

Participants

Gestational ages of the fetuses evaluated in step 1 were 26.2 weeks and 28.8 weeks in the 2 fetuses in the acute pain group (1 male and 1 female) and 28.2 weeks and 32.1 weeks in the fetuses in the control group (1 male and 1 female). All mothers were South American women. Step 2 included 52 control fetuses 34.4 weeks gestational age (34 female) and 2 fetuses undergoing anesthesia before surgery with a mean gestational age of 28.1 (1 male and 1 female).

Step 1

a. Internal Consistency

Cronbach's alpha was calculated for internal consistency using the data from all 30 raters of the first application of the instrument: .99 (95% (confidence interval) CI: .98–1.0).

b. Inter-rater Reliability

Absolute agreement between all 30 raters for the total score of the first application of the instrument was measured with mean inter-class coefficient .99 (95% CI: .97–.99) indicating a high reliability.

Table 1. Intrarater Reliability (Test-Retest) Calculated by ICC

RATER	ICC
1	.983
2	.889
3	.987
4	.988
5	1.000
6	.930
8	.978
9	.967
10	.941
11	.964
12	1.000
13	.973
14	.987
15	.545
16	.986
17	.984
18	.976
19	.983
20	.935
21	.966
22	.989
23	.976
24	.889
25	.990
28	.937
29	.994
30	.972
Mean ICC	.952

NOTE. Intrarater reliability assessed by ICC for total score in the Fetal-7 scale at the first and second score time points.

c. Intrarater Reliability

Twenty-seven raters performed the first and second applications of the F7 scale. The absolute agreement between them showed a mean ICC of .95 (95% CI: .91–.98) indicating that the test-retest reliability was high (Table 1).

Step 2: Sensitivity and Specificity Analyses

Raters evaluated US-derived images from 54 healthy fetuses at rest. Three (5.55%) of the 54 healthy fetuses were classified with a score ≥5 on the F7 scale. In the pain group, 1 fetus was classified with a score of 6, and 1 fetus was classified with a score of 7 (Table 2). The frequencies of Fetal-7 score items among the healthy and pain fetuses are shown in Table S1. Fetal-7 accuracy was .946 for the F7 scale. The sensitivity and specificity of the F7 scale were 100% and 94.4%, respectively. The positive predictive value was 57%, and the negative predictive value was 100% calculated based on 2-by-2 table (Table S2).

Table 2. Frequencies of Fetal-7 Final Scores in Fetuses in Control-Rest and Acute Pain Groups

SCORE	CONTROL-REST n (%)	ACUTE PAIN n (%)
0	25 (46.3)	0 (0)
1	9 (16.7)	0 (0)
2	6 (11.1)	0 (0)
3	8 (14.8)	0 (0)
4	3 (5.6)	0 (0)
5	1 (1.9)	0 (0)
6	1 (1.9)	1 (50)
7	1 (1.9)	1 (50)
Total	54	2

Discussion

The present study reported the validation of the Fetal-7 scale for evaluating acute fetal pain. The scale had high sensitivity and specificity to differentiate acute fetal pain from rest or sound stimulus and an excellent internal consistency and intrarater reliability. This work stems from initial reports of fetal behavior evaluated by 4-dimensional sonography.[24,25] Reislland et al,[26] described, in an innovative approach, potential pain-related expressions in normal fetuses under unprovoked rest ("gestalt pain"). This original approach was the first to report that fetuses at rest may present facial expressions and behavior that could be similar to those of neonates, and it was hypothesized that this could represent fetal pain. However, the lack of a temporal trigger such as a painful stimulus limits the assumptions of causality between the experience of discomfort or pain and the facial expression. In 2018, we reported on the evaluation of fetal facial expressions during acute pain (during fetal intramuscular anesthetic injection before fetal surgery),[12] and further on, we developed a scale capable of distinguishing fetal pain expressions from rest and acoustic startle, the F7 scale.[13] This approach allowed the painful stimulus to serve as an event linking the phenomenological responses to pain and the recordings, thus providing direct causal connections between the expected and observed behaviors. Interestingly, the score in the undisturbed rest fetuses is not 0, and fetuses indeed produce facial expressions of pain during rest. While the valency and lived experience behind these expressions are unknown, they further support the original reports from Reislland et al.[26]

The use of a fetal scale to evaluate fetal pain has many potential implications. The first direct implication is the potential to evaluate pain after surgical fetal procedures to control analgesia. It has been widely discussed and nowadays accepted that fetal anesthesia is mandatory during fetal procedures.[27] However, studies about pain control after these procedures are still incipient. Animal studies show a strong fetal pain and stress reaction after surgery,[28] and the same fetal surgeries, when performed during the neonatal period, require multidisciplinary pain treatment.[29-31] One example of surgery that is performed both in the neonatal and prenatal period is myelomeningocele correction. When the surgery is performed in the neonatal period, it is mandatory to evaluate and treat neonatal pain, while there is still incipient discussion about evaluating

and treating fetal pain in the days/weeks after intrauterine surgery is performed.[32] The systematic use of a dedicated pain scale has the potential to enable the monitoring of postsurgical pain and its short- and long-term effects. Some analgesic drugs cross the hematoplacental barrier and can be used to treat fetal pain,[33-35] which could not only acutely relieve pain but might additionally hamper the undesirable long-term consequences of pain experienced during early life.[36] In order to propose postsurgical interventions for fetal pain handling, be it pharmacological or non-pharmacological, one needs to assess pain behaviors in order to guide the duration of the intervention in time and in a way to avoid both under- and overtreatment in terms of dosing.

This study has also shown that it was possible for specialists to be trained and apply the scale with online didactic material and that the evaluation of the Fetal-7 scales is feasible under US-trained hands. The next step would be to study if fetal face evaluations could be obtained and interpreted by health professionals with less experience in US recordings. However, since the fetal treatment setting is usually performed in tertiary care centers, the validation of the scale allows it to be used in the precise clinical setting where it is indeed expected to be used. Furthermore, since the scale is image-based, it could be implemented in a semiautomatic use added to US machines and would pave the way for prospective exploring the correlations between intraoperative pain behaviors with postnatal pain sensitivity. There are some ongoing discussions about the future use of robots to help healthcare personnel in performing obstetric US.[37] Artificial intelligence has also been studied in the US setting to help in the identification of fetal malformations,[38] and new solutions in this area are expected. In the future, the association of robot-assisted US acquisition and artificial intelligence interpretation could lead us to the perspective of automatic calculation of fetal pain status, which could lead to an easier and more personnel-friendly identification of painful status in the womb.

One limitation of this study is the evaluation of fetuses in the third trimester. Some fetal conditions can indicate fetal surgery in the late second trimester, but although this scale has been used to previously describe fetal facial pain response in the second trimester,[14] it is unknown if facial expressions would have the same pattern before 24 weeks, and weather sensibility and specificity would be the same. Therefore, it would be important, that further studies focus on the use of the scale in younger fetuses in the analysis of fetal pain. Additionally, because data collection in step 2 occurred during the third-trimester vitality assessment in the control group, these fetuses' gestational age was higher than those of fetuses undergoing anesthesia for surgery. We actually believe these discrepancies raised the threshold for the detection of changes in the Fetal-7 score between groups, and if they influenced our results, it would be in the direction of underestimating the properties of the Fetal-7, not the other way around.

Conclusions

In conclusion, the Fetal-7 scale opens the possibility of analyzing and quantifying fetal pain after fetal surgery (eg, intrauterine myelomeningocele correction, thoracic drain, and fetal diseases that can cause pain). After the scale is tested for these conditions, its use would allow the proper identification and treatment of pain in an early stage of life and potentially allow for fetal pain treatment and the prevention and its potential long-term consequences after birth.

Disclosures

The authors have no conflicts of interest to disclose. The Center for Neuroplasticity and Pain is supported by the Danish National Research Foundation. DCA is supported by a Novo Nordisk Grant NNF21OC0072828 and European Research Council grant 101087925.

Data Availability

The data that support the findings of this study are available from the corresponding author, LSB, upon reasonable request.

Appendix A. Supplementary Data

Supplementary data related to this article can be found in the online version at doi:10.1016/j.jpain.2024.104527.

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