Association of First-Trimester Echogenicity of the Puborectalis Muscle with Mode of Delivery

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Short title: Association of echogenicity with mode of delivery

Précis:

Decreased ultrasonographic echogenicity of the puborectalis muscle in the first trimester is associated with increased cesarean delivery for failure to progress.

Abstract

Objective: To evaluate the association between mean echogenicity of the puborectalis muscle, measured using transperineal ultrasound, in women during their first pregnancy and the subsequent mode of delivery.

Methods: This is a secondary analysis of a prospective observational study on the association between stress urinary incontinence and levator muscle avulsion after delivery of a first pregnancy. In this study, 280 nulliparous women with a singleton pregnancy were examined with transperineal ultrasound examination at 12 and 36 weeks of gestation. Patients were recruited from an obstetrics practice associated with the university medical center in Utrecht, the Netherlands. Their mean echogenicity of the puborectalis muscle values were measured at rest, on pelvic floor muscle contraction, and on Valsalva maneuver. The subsequent mode of delivery was classified into five categories: spontaneous vaginal delivery, instrumental vaginal delivery, elective cesarean delivery, cesarean delivery due to nonreassuring fetal status and cesarean delivery due to failure to progress. Mean echogenicity of the puborectalis muscle values according to mode of delivery were compared by analysis of variance and Tukey's post-hoc test.

Results: Of the 254 women included 157 had a spontaneous vaginal delivery, 47 underwent a cesarean delivery (11 elective, 36 emergency) and 45 had a vacuum operative vaginal delivery and in 5 patient files the mode of delivery was not recorded. Of the analyzed women, those who delivered by cesarean because of failure to progress had a significantly lower mean echogenicity of the puborectalis muscle on pelvic floor contraction at 12 weeks of gestation (mean echogenicity of 116 ± 14) than women who had a

spontaneous vaginal delivery (132 ± 21; Tukey's post-hoc test, p = 0.03), instrumental vaginal delivery (138 ± 21; p= 0.004) and cesarean delivery due to nonreassuring fetal status (139 ± 20; p= 0.02).

Conclusion: Lower mean echogenicity of the puborectalis muscle values on pelvic floor contraction during the first pregnancy at 12 weeks of gestation are associated with a subsequent cesarean delivery due to failure to progress.

Introduction

Obstructed or dysfunctional labor, a failure to progress, is a common obstetrical problem, with an estimated incidence of 3 to 6 per 100 live births worldwide [1]. The cause can be mechanical like a cephalopelvic disproportion, but failure to progress can also be due to functional factors like inadequate uterine contractions or failure of the cervix to dilate [2,3,4]. A three dimensional (3D) computer model based on magnetic resonance imaging (MRI), demonstrated that the pelvic floor muscles must undergo extensive stretching during vaginal delivery [5]. However, the potential role of pelvic floor muscles in the progression of labor and mode of delivery has not been widely studied. Van Veelen and co-workers investigated the association between levator hiatal dimensions, measured with transperineal ultrasound, during pregnancy and subsequent mode of delivery in nulliparous women. They reported a significantly smaller levator anterior-posterior (AP) dimension on contraction at 12 weeks of gestation in women who subsequently had cesarean delivery due to failure to progress, as compared to women who had a normal or vaginal assisted delivery or emergency cesarean delivery due to non reassuring fetal status [6]. This finding raises the question if the puborectalis muscle is different structurally, functionally or both in the women who have a cesarean delivery due to failure to progress. Another way to look at the structure of muscles is to study it's echogenicity. Echogenicity is clinically used in children with neuromuscular disease as a diagnostic tool and monitoring tool for disease progression [7-9], so may well provide information of the puborectalis muscle.

The objective of the present study was to study the association between the mean echogenicity of the puborectalis muscle in pregnant nulliparous women and the subsequent mode of delivery. If changes in echogenicity reflect functional changes, as in neuromuscular diseases in children, we hypothesized that differences in the echogenicity could be linked to the mode of delivery.

Materials and Methods

This study is a secondary analysis of a prospective observational study on the association between stress urinary incontinence and levator muscle avulsion after delivery of a first pregnancy. The Medical Ethics Committee of the University Medical Center Utrecht approved this study (reference 08-299) and all women gave written informed consent. Patients were recruited from an obstetrics practice, associated with the university medical center in Utrecht, the Netherlands. A total of 280 nulliparous pregnant women were examined with 4D transperineal ultrasound assessment of their pelvic floor anatomy during pregnancy at 12 and 36 weeks of gestation and 6 months postpartum. Pregnancy was confirmed and dated based on the crown-rump length measured with early ultrasound in regular care. The ultrasound datasets at 12 and 36 weeks were used for the purpose of this study. Women were excluded when they had a medical history of incontinence (urinary, fecal or both), previous pelvic organ prolapse or anti-incontinence surgery, connective tissue disease or neurological disorders [10]. Clinicians who managed the patients' labor were blinded to the ultrasound data. Delivery data were retrieved by one of the authors (KW) from the medical reports and the institutional database.

The mode of delivery was classified according to the Dutch nationwide perinatal register into five categories: spontaneous vaginal delivery, instrumental vaginal delivery, elective cesarean delivery, emergency cesarean delivery due to nonreassuring fetal status and emergency cesarean delivery due to failure to progress [11].

The assessment consisted of 4D transperineal ultrasound imaging using a GE Voluson 730 Expert system (GE Healthcare, Zipf, Austria) with RAB 4-8 MHz curved array volume transducer placed on the perineum in the sagittal plane. Two experienced sonographers performed all the ultrasound examinations [12]. All ultrasound system settings were kept identical during all examinations [13]. The pelvic floor ultrasound examinations were performed with the participants in supine position and with an empty bladder. Echogenicity was measured with the puborectalis muscle in rest, during maximal pelvic floor muscle contraction (PFMC) and Valsalva [13].

Offline analysis of the data was performed using 4D View 7.0 (GE Medical Systems Kretztechnik, Zipf, Austria) and Matlab R2010a (MathWorks, Natick, MA). The plane of minimal hiatal dimensions, resulting in the axial plane, is selected following the worldwide consensus [14]. The puborectalis muscle was delineated using the software Matlab (function 'imfreehand') as described previously and shown in Figure 1 [15]. The mean echogenicity of the puborectalis muscle was determined automatically by calculating the sum of the echogenicity of all pixels and dividing that sum by the number of pixels. Observers were blinded to delivery mode during post processing of the data.

Mean echogenicity of the puborectalis muscle values at 12 weeks and 36 weeks of gestation were compared between the different modes of delivery by analysis of variance (ANOVA), followed by a Tukey's post-hoc test when appropriate. **To determine the magnitude of the effect we calculated the effect size of the statistically significant findings by Cohen's d.** A post-hoc ROC-curve was derived to evaluate the ability of mean echogenicity of the puborectalis muscle to correctly classify the need for an emergency cesarean delivery due to failure to progress. Statistical analysis was carried out using SPSS versions 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Of the 280 women recruited from the clinic, 26 were excluded. Two women were incorrectly included (based on a twin pregnancy and a neurological disorder), one woman had a premature delivery at 19.9 weeks of gestation, 17 women were excluded based on loss to follow-up, or missing ultrasound volume datasets because of technical errors during file saving (at least two out of three datasets were missing), and six datasets were excluded because the symphyses was located outside the view of the ultrasound images.

The mean age of the women was 31.1 years (SD: 4.1) and their mean body mass index (BMI) at 12 weeks and 36 weeks of gestation was 23.4 (SD 3.9) and 27.6 (SD 3.8) kg per m^2, respectively. Mean gestational age at first visit was 13.3 weeks (SD 1.9) and 36.0 weeks (SD 0.9) at second visit.

Of the 254 women included, data analysis at 12 weeks of gestation was possible for 247 cases at rest, 240 on contraction, and 223 on Valsalva. At 36 weeks of gestation these numbers were 219, 206 and 194 respectively. Of the included women 157 (61.8%) had a spontaneous vaginal delivery, 47 (18.5%) underwent a cesarean delivery (11 elective, 36 emergency) and 45 (17.7%) had a vacuum operative vaginal delivery and in 5 (2.0%) patient files the mode of delivery was not recorded [14]. In the operative vaginal delivery group, 15 deliveries were based on nonreassuring fetal status, 15 based on failure to progress, 9 based on a combination of failure to progress and nonreassuring fetal status and 6 with unknown reason for vacuum extraction. In the emergency cesarean delivery group due to nonreassuring fetal status, 15 women were in the first stage of labor, one in the second stage of labor, while in three cases the stage of labor was missing from the records. In the emergency cesarean delivery group due to failure to progress, 13 were in the first stage of labor (median cervical dilation 5cm, range 1 to 10 cm), four in the second [14].

In Table 1, the mean echogenicity of the puborectalis muscle values at 12 weeks and 36 weeks of gestation are shown for rest, contraction and valsalva. At 12 weeks of gestation, during rest and valsalva no statistical significant differences in mean echogenicity of the puborectalis muscle between groups were found. However, during contraction there was a statistical significant lower mean echogenicity of the puborectalis muscle for the women who had a cesarean delivery based on failure to progress as compared to vaginal deliveries (p=0.03), assisted vaginal deliveries (p=0.004) and cesarean delivery based on nonreassuring fetal status (p=0.02), with effect sizes of 0.90, 1.23 and 1.33 respectively. The results of the post hoc tests are shown in Table 2 and Figure 2. At 36 weeks of gestation no statistically significant differences in mean echogenicity of the puborectalis muscle between groups were observed for all maneuvers.

The area under the curve (Figure 3), representing the performance of mean echogenicity of the puborectalis muscle in distinguishing between vaginal deliveries and the need for an emergency cesarean delivery based on failure to progress, is 0.75 (**STD: 0.049, 95% CI bounds: 0.656 -0.848)**.

<u>Discussion</u>

Women who delivered by cesarean delivery due to failure to progress had a statistically significant lower mean echogenicity of the puborectalis muscle on pelvic floor contraction at 12 weeks of gestation than women who had a spontaneous or instrumental vaginal delivery or women with a cesarean delivery due to nonreassuring fetal status. No differences in mean echogenicity of the puborectalis muscle between modes of delivery groups at 36 weeks of gestation were found.

Echogenicity, or grey scale value analysis, is a parameter derived from imaging tools like ultrasound and varies between 0 (black) and 255 (white). In case of muscle tissue it represents the ratio between muscle cells that appear dark in grey scale imaging and the brighter extracellular matrix. The two major components of this extracellular matrix are collagen and fat. Higher echogenicity values are associated with increased amounts **of either fat in** muscle **tissue or connective tissue** [16,17]. The echogenicity provides us with structural information and in case of neuromuscular disease in children it is also used as a diagnostic tool and monitoring tool for disease progression [7-9].

During the course of pregnancy the extracellular matrix of the pubrectalis muscle changes. One of the greatest challenges lies within a pathophysiological explanation of the echogenicity changes, since it cannot be based on human histology data. In a recent study by Alperin and co-workers it was demonstrated that the collagen content of the intramuscular extracellular matrix increases during pregnancy [18]. This adaptation already started in early pregnancy and returned to non-pregnant virgin rat levels after delivery [18]. This is in line with our clinical observation that the mean echogenicity of the puborectalis muscle increases over time during pregnancy and decreases after delivery [15]. The significantly lower mean echogenicity of the puborectalis muscle in women who had an emergency cesarean section due to failure to progress may be an indication of a disturbed early adaptation of this collagen metabolism, with less collagen being formed. One of the key factors in the preparation for childbirth is the weakening of collagen in the pelvic tissues [19]. Less intramuscular collagen during pregnancy may be associated with the inability of the pelvic floor to stretch during delivery. With respect to failure to progress at the second stage of labor this is an intriguing explanation. However, it is unlikely that the puborectalis muscle itself limits first stage of labor progression, which was shown to be the cause of failure in the majority of women. In order to explain this, the low echogenicity of the puborectalis needs to be considered as a constitutional difference in muscle cell to extracellular matrix balance. Although hypothetical, a diminished amount of connective tissue in the cervix may be associated with poor weakening and dilatation. This possible association is currently under investigation at our institute.

The association we found at 12 weeks of gestation was only significant during muscle contraction, although there was a same, non-significant trend with the puborectalis muscle in rest and Valsalva. Our explanation for this finding is that during contractions, the number of muscle cells per square cm in the contracting part increases, increasing the ratio between muscle cells and extracellular matrix in favor of the first [20]. The net effect is that the ultrasound image becomes darker. Therefore, the effect of the limited collagen amount on mean echogenicity of the puborectalis muscle may be more expressed during contraction as compared to rest and Valsalva.

The significant differences between groups in mean echogenicity of the puborectalis muscle we found at 12 weeks were not present at 36 weeks. We hypothesise that this is the effect of intramuscular fat storage. With respect to fat metabolism it was shown, both in humans as in rats, that the increased pregnancy levels of progesterone and increased intake of nutrients increase intracellular and intramuscular fat storage [21,22]. It was also demonstrated that fat replacement causes a substantial increase in muscle echogenicity [23]. An increasing mean echogenicity of the puborectalis muscle as a resultant of intramuscular fat storage during pregnancy may well obscure a limited increase in intramuscular collagen.

If we test the diagnostic characteristics of the mean echogenicity of the puborectalis muscle between women who had a vaginal delivery and those who had a cesarean delivery due to failure to progress, we found an area under the curve in the receiver operating characteristics curve of 0.75. Stated otherwise, in our population, 75% of participants who had cesarean delivery due to failure to progress had a lower mean echogenicity of the puborectalis muscle than their normal vaginal delivery counterpart. In its current form the mean echogenicity of the puborectalis muscle is not suitable as a clinical prognostic test and does not provide a single optimal cutoff value. Additionally, there are promising new techniques to analyse ultrasound images, like strain and elasticity becoming available for pelvic floor ultrasound. These may, in combination with clinical characteristics and mean echogenicity of the puborectalis muscle measurements, provide a better predictive clinical tool in the future.

A possible limitation of this study is the discrimination between different types of delivery. Worldwide there is a large variation in cesarean delivery rates [1]. Varying incidence in obstructed labour per country is likely to be due to a number of factors including variations in case definition and case ascertainment [1, 24, 25]. Since we undertook a single-center study, this may have resulted in bias based on delivery type indication. The second limitation of this study is that it is a secondary analysis and therefore it was not powered for the outcome under study. However, the differences in mean echogenicity of the puborectalis muscle between delivery type groups were found to have an effect sizes of >0.8, indicating a very strong effect. However, we would like to emphasize the preliminary nature of this novel study. It needs corroboration with a larger, preferably multi-center series

One of the major strengths of our study is its prospective design, including measurements at 12 and 36 weeks of gestation. Furthermore, we used 4D transperineal ultrasound, which is a reliable technique for measuring echogenicity in pregnant women [13]. Additionally, the fixed ultrasound device settings are key elements of this study.

In conclusion, this study shows that mean echogenicity of the puborectalis muscle at 12 weeks of gestation in women who need an emergency cesarean delivery due to failure to progress in nulliparous women differs from mean echogenicity of the puborectalis muscle in women with a different mode of delivery.

References

1. Dolea C, AbouZahr C. Global burden of obstructed labour in the year 2000. Evidence and information for Policy (EIP) World Health Organization Geneva, July 2003.
2. Lenhard MS, Johnson TR, Weckbach S, Nikolaou K, Friese K, Hasbargen U. Pelvimetry revisited: Analyzing cephalopelvic disproportion. *European Journal of Radiology* 2010; 74: e107-e111
3. Wray S. Insights into the uterus. *Exp Physiol* 2007; 92.4:621-631
4. Antonucci MC, Pitman MC, Eid T, Steer PJ, Genevier ES. Simultaneous monitoring of head-to-cervix forces, intrauterine pressure and cervical dilation during labour. *Med Eng Phys* 1996; 19(4): 317-326
5. Lien KC, Mooney B, DeLancey JO, Ashton-Miller JA. Levator ani muscle stretch induced by simulated vaginal birth. *Obstet Gynecol* 2004; 103: 31-40.
6. Van Veelen GA, Schweitzer KJ, van Hoogenhuijze NE, van der Vaart CH. Association between levator hiatal dimensions on ultrasound during first pregnancy and mode of delivery. *Ultrasound Obstet Gynecol* 2015; 45: 333-338.
7. Pillen S, Verrips A, van Alfen N, Arts IM, Sie LT, Zwarts MJ. Quantitative skeletal muscle ultrasound: Diagnostic value in childhood neuromuscular disease. *Neuromuscul Disord* 2007; 17: 509-516.
8. Maurits NH, Beenakker EAC, Van Schaik DEC, Fock JM, van der Hoeven JH. Muscle ultrasound in children: normal values and application to neuromuscular disorders. *Ultrasound Med Biol* 2004 30: 1017–1027.

9. Maurits NM, Bollen AE, Windhausen AEJ, de Jager A, van der Hoeven JH. Muscle ultrasound analysis: normal values and differentiation between myopathies and neuropathies. *Ultrasound Med Biol 2003*; 29: 215–225.

10. Van Veelen GE, Schweitzer KJ, van der Vaart CH. Ultrasound imaging of the pelvic floor: changes in anatomy during and after first pregnancy. *Ultrasound Obstet Gynecol* 2014; 44:476-480.

11. Stichting Perinatale Registratie Nederland. **http:www.perinatreg.nl**

12. van Veelen GA, Schweitzer KJ, van der Vaart CH. Reliability of pelvic floor measurements on three- and four-dimensional ultrasound during and after first pregnancy: implications for training. Ultrasound Obstet Gynecol 2013; 42(5):590-5.

13. Grob ATM, Veen AAC, Schweitzer KJ, Withagen MIJ, van Veelen GA, van der Vaart CH. Measuring echogenicity and area of the puborectalis muscle: method and reliability. *Ultrasound Obstet Gynecol* 2014; 44(4): 481-485.

14. Dietz HP, Shek C, Clarke B. Biometry of the pubovisceral uscle and levator hiatus by three-dimensional pelvic floor ultrasound. *Ultrasound Obstet Gynecol* 2005; 25:580-585.

15. Grob ATM, Withagen MIJ, van de Waarsenburg MK, Schweitzer KJ, van der Vaart CH. Changes in the Mean Echogenicity and Area of the Puborectalis Muscle during Pregnancy and Postpartum. Int Urogynecol J. 2015;16. [Epub ahead of print]

16. Pillen S, Tak RO, Zwarts MJ, Lammens MM, Verrijp KN, Arts IM, van der Laak JA, Hoogerbrugge PM, van Engelen BG, Verrips A. Skeletal muscle ultrasound: Correlation between fibrous tissue and echo intensity. *Ultrasound Med Biol* 2009; 35, 443–446

17. Reimers K, Reimers CD, Wagner S, Paetzke I, Pongratz DE. Skeletal muscle sonography: A correlative study of echogenicity and morphology. *J Ultrasound Med* 1993;12 73–77

18. Alperin M, Lawley DM, Esparza MC, Lieber RL. Pregnancy-induces adaptations in the intrinsic structure of rat pelvic floor muscles. *Am J Obstet Gynecol* 2015; 213 191.e1-7

19. Yu SY, Tozzi CA, Babiarz J, Leppert PC. Collagen changes in rat cervix in pregnancy – polarized light in microscopic and electron microscopic studies. *Proc Soc Exp Biol Med* 1995; 209 (4), 360-368

20. Peetrons P. Ultrasound of muscles. *Eur Radiol* 2002; 12:35-43.

21. Herrera E. Metabolic adaptations in pregnancy and their implications for the availability of substrates to the fetus. Eur J Clin Nutr. 2000; 54 (1): S47-51.

22. Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N Engl J Med* 2014; 371: 1131-1141.

23. Reimers K, Reimers CD, Wagner S, Paetzke I, Pongratz DE. Skeletal muscle sonography: a correlative study of echogenicity and morphology. *J Ultrasound Med* 1993; 12(2): 73-77.

24. Barber EL, Lundsberg L, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Contributing indications to the rising cesarean delivery rate. *Obstet Gynecol* 2011; 118(1): 29–38.

25. Lydon-Rochelle MT, Gardella C, Cárdena V, Easterling TR. Repeat cesarean delivery: what indications are recorded in the medical chart? *Birth* 2006; 33(1):4-11.

Table 1 Mean echogenicity of the puborectalis muscle at 12 and 36 weeks of gestation per delivery type and per maneuver. SD= standard deviation.

Type of delivery	Mean echogenicity of the puborectalis muscle at rest Mean ± SD		Mean echogenicity of the puborectalis muscle at contraction Mean ± SD		Mean echogenicity of the puborectalis muscle at Valsalva Mean ± SD	
	12weeks	36 weeks	12weeks	36 weeks	12weeks	36 weeks
Vaginal (n=157)	139 ± 20	148 ± 20	132 ± 21	139 ± 21	133 ± 20	135 ± 22
Assisted vaginal (vacuum) (n=45)	146 ± 18	148 ± 20	138 ± 21	136 ± 21	141 ± 25	128 ± 23
Elective cesarean (n=11)	150 ± 15	155 ± 10	137 ± 18	142 ± 13	139 ± 24	148 ± 15
Cesarean based on nonreassuring fetal status (n=19)	144 ± 28	147 ± 19	139 ± 20	140 ± 20	142 ± 20	138 ± 19
Cesarean based on failure to progress (n=17)	134 ± 15	145 ± 26	116 ± 14	133 ± 14	128 ± 20	138 ± 31

Table 2 ANOVA (Tukey post-hoc) analysis - Mean difference in mean echogenicity of the puborectalis muscle at 12 weeks of gestation between different types of delivery. SD= standard deviation. Vaginal delivery n=157; operative vaginal delivery n=45; elective cesarean delivery n=11; cesarean delivery based on nonreassuring fetal status n=19; cesarean delivery based on failure to progress n=17.

Types of delivery compared	Mean echogenicity of the puborectalis muscle difference ± SD	p-value
Puborectalis muscle in rest		
CS-FTP – Vaginal Delivery	-5.1 ± 5.1	0.917
CS-FTP – Operative Vaginal Delivery	-12.7 ± 5.7	0.228
CS-FTP – Elective CS	-16.6 ± 7.9	0.299
CS-FTP – CS- nonreassuring fetal status	-10.6 ± 7.1	0.677
Puborectalis muscle in contraction		
CS-FTP – Vaginal Delivery	-15.9 ± 5.5	0.032
CS-FTP – Operative Vaginal Delivery	-21.7 ± 6.1	0.004
CS-FTP – Elective CS	-20.8 ± 8.4	0.098
CS-FTP – CS- nonreassuring fetal status	-22.2 ± 7.6	0.023
Puborectalis muscle in Valsalva		
CS-FTP – Vaginal Delivery	-4.7 ± 5.5	0.955
CS-FTP – Operative Vaginal Delivery	-12.9 ± 6.3	0.310
CS-FTP – Elective CS	-10.8 ± 8.4	0.803
CS-FTP – CS- nonreassuring fetal status	-13.7 ± 7.8	0.506

CS-FTP= Cesarean delivery based on failure to progress; CS= Cesarean delivery; SD=standard deviation

Figure 1. Delineation of the puborectalis muscle by hand.

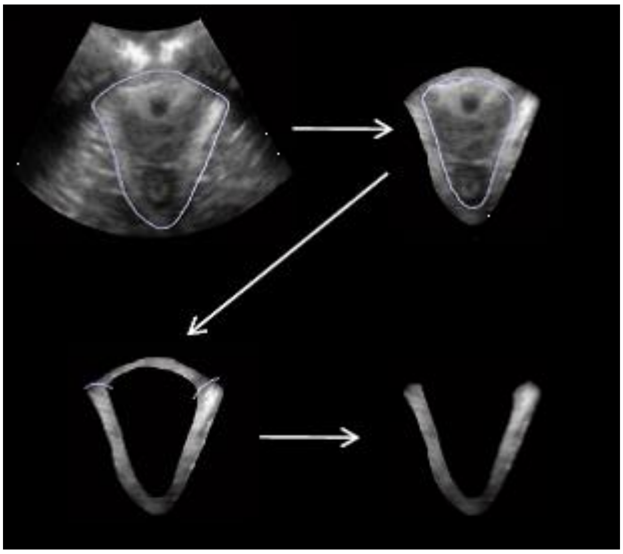


Figure 2. Distribution of mean echogenicity of the puborectalis muscle at 12 weeks of gestation, pelvic floor in contraction. CI, confidence interval.

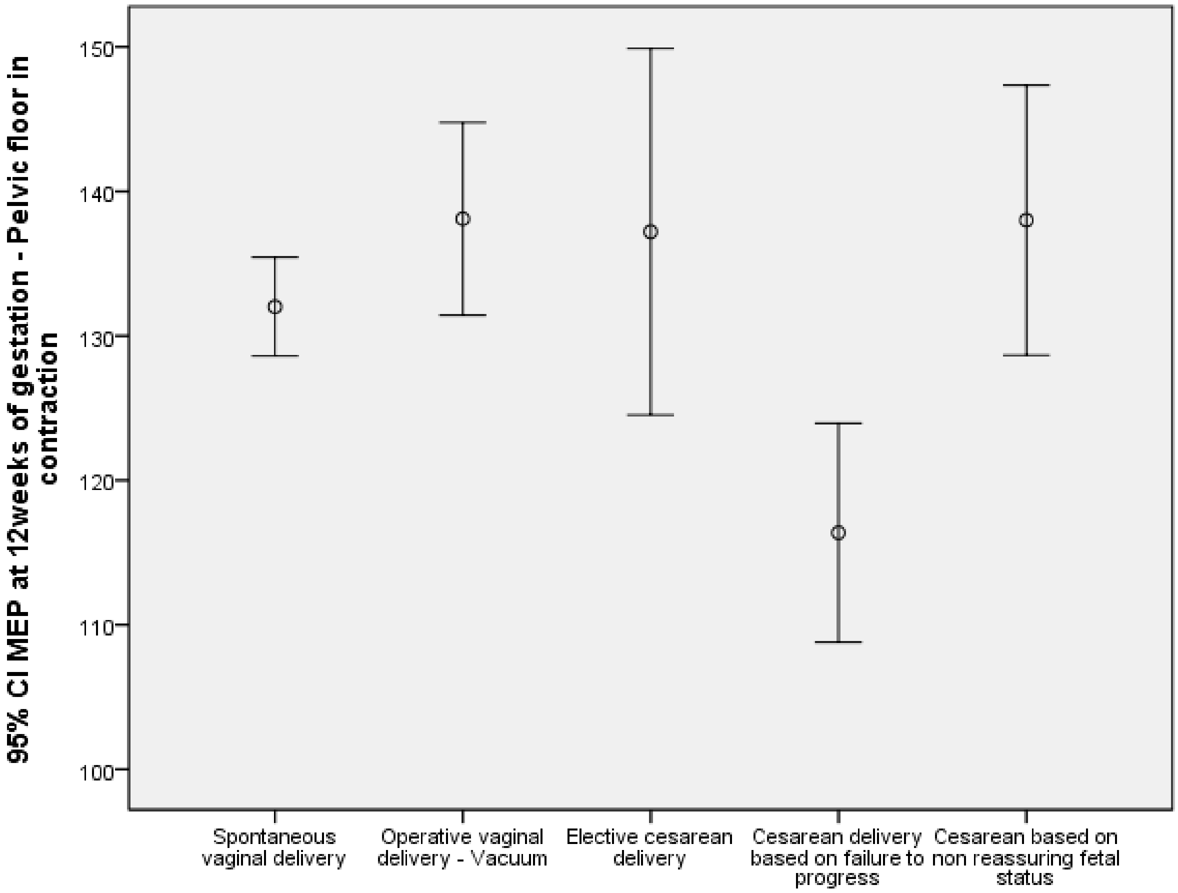
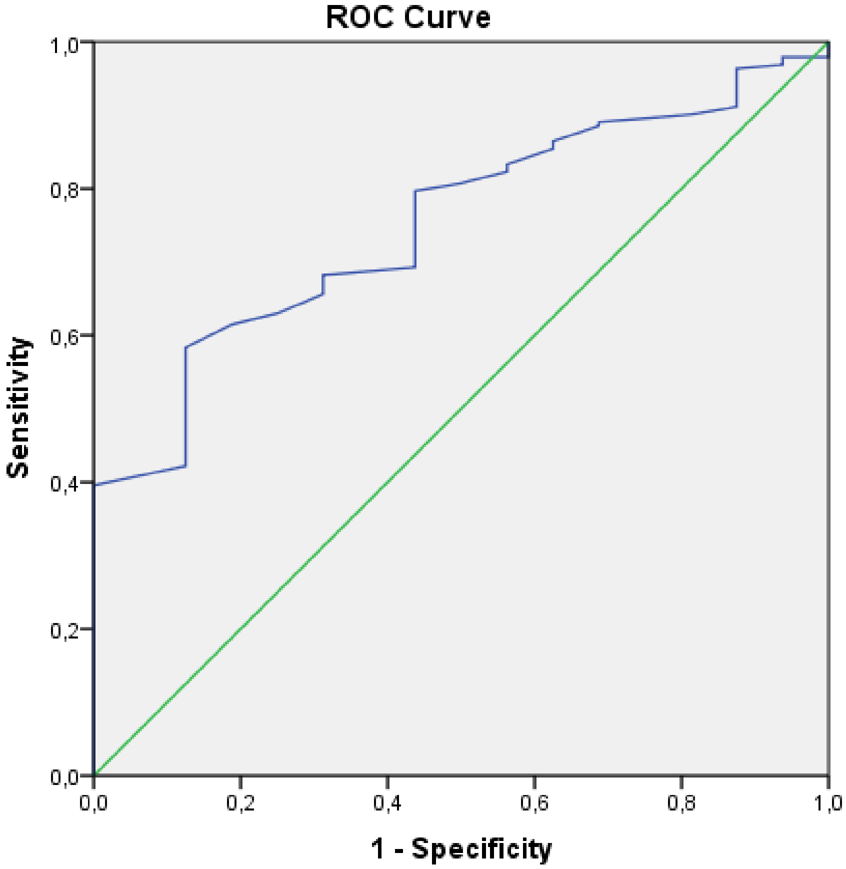


Figure 3. Receiver operating curve of mean echogenicity of the puborectalis muscle. Vaginal deliveries (n=192) compared with cesarean delivery, failure to progress (n=16) at 12 weeks of gestation, pelvic floor in contraction. Area under curve: 0.752; standard error: 0.049, 95% confidence interval: 0.656 -0.848



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