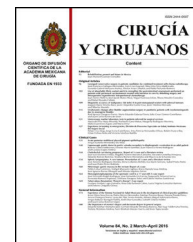




CIRUGÍA y CIRUJANOS

Órgano de difusión científica de la Academia Mexicana de Cirugía
Fundada en 1933

www.amc.org.mx www.elsevier.es/circir



CLINICAL CASE

Applicability of 3/4D transperineal ultrasound for the diagnosis of anal sphincter injury during the immediate postpartum[☆]



José Antonio García-Mejido^{a,*}, Laura Gutiérrez Palomino^b, Ana Fernández Palacín^c,
José Antonio Sainz-Bueno^a

^a Servicio de Ginecología y Obstetricia, Hospital Universitario de Valme, Seville, Spain

^b Servicio de Ginecología y Obstetricia, Hospital de Ceuta, Ceuta, Spain

^c Medicina Preventiva y Salud Pública, Universidad de Sevilla, Seville, Spain

Received 21 April 2015; accepted 4 September 2015

Available online 12 January 2017

KEYWORDS

3D transperineal
ultrasound;
Anal sphincter;
Anal sphincter
suture;
Anal sphincter
injuries

Abstract

Background: The most common cause of anal sphincter injuries in women is vaginal birth. Endo-anal ultrasound is currently used for the diagnosis of anal sphincter defect. However, due to the inconvenience caused, it is not an applicable technique during the immediate postpartum.

The aim of this study was to determine whether transperineal ultrasound in 3/4D is a useful diagnostic method for the assessment of anal sphincter during the immediate postpartum.

Material and methods: A prospective study was conducted on the vaginal deliveries performed between September 2012 and June 2013 in the Valme University Hospital (Seville). Obstetric and foetal parameters that could influence the onset of perineal tears were studied. The patients underwent a transperineal 3/4D ultrasound and a multislice study (48 h after birth).

Results: The study included 146 puerperal women. The sphincter complex was assessed in all of them during the immediate postpartum. External anal injuries were observed in 10.3% of the cases. In 8.2% of cases, the primary suture of the external anal sphincter was detected during ultrasound examination, and 2.1% of asymptomatic lesions were diagnosed only with postpartum ultrasound. None of the patients reported discomfort or pain.

[☆] Please cite this article as: García-Mejido JA, Palomino LG, Palacín AF, Sainz-Bueno JA. Aplicabilidad de la ecografía transperineal en 3/4D para el diagnóstico de lesiones del esfínter anal durante el posparto inmediato. Cir Cir. 2017;85:80–86.

* Corresponding author at: Carretera de Cádiz s/n, Hospital Universitario Valme, Seville, Spain. Telephone: +34 9550 15385.

E-mail address: jagmejido@hotmail.com (J.A. García-Mejido).

PALABRAS CLAVE

Ecografía
transperineal 3D;
Esfínter anal;
Sutura del esfínter
anal;
Lesiones del esfínter
anal

Conclusions: The 3-dimensional transperineal ultrasound is helpful in determining the primary repair of the anal sphincter during the immediate postpartum, with no discomfort for patients, as well as for establishing those early sphincter injuries that go unnoticed during vaginal delivery.

© 2015 Academia Mexicana de Cirugía A.C. Published by Masson Doyma México S.A. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Aplicabilidad de la ecografía transperineal en 3/4D para el diagnóstico de lesiones del esfínter anal durante el posparto inmediato

Resumen

Antecedentes: La causa más frecuente de lesiones del esfínter anal en mujeres es el parto vaginal. Actualmente el diagnóstico del defecto del esfínter anal es la ecografía endoanal. Sin embargo, debido a las molestias que ocasiona, no es una técnica aplicable durante el posparto inmediato.

El objetivo que nos planteamos es establecer si la ecografía transperineal en 3/4D es un método de diagnóstico útil para la valoración del esfínter anal durante el posparto inmediato.

Material y métodos: Se realizó un estudio prospectivo de los partos vaginales atendidos entre septiembre del 2012 y junio del 2013, en el Hospital Universitario de Valme (Sevilla). Se estudiaron parámetros obstétricos y fetales que pudiesen influir en la aparición de desgarreros perineales. A las pacientes se les realizó una ecografía transperineal en 3/4D y estudio multicortes ecográfico (48 h tras el parto).

Resultados: Se analizó a 146 púrpas y en todas se valoró el complejo esfinteriano durante el posparto inmediato. El 10.3% presentaron lesiones del esfínter anal externo. En el 8.2% de los casos se detectó la sutura primaria del esfínter anal externo durante la exploración ecográfica y en el 2.1% de las pacientes se observaron lesiones asintomáticas diagnosticadas solamente con la ecografía posparto. Ninguna de las pacientes refirió molestias ni dolor.

Conclusiones: La ecografía transperineal 3D es útil para determinar la reparación primaria del esfínter anal durante el posparto inmediato sin molestias para las pacientes, además de establecer precozmente aquellas lesiones esfinterianas que pasan desapercibidas durante el parto vaginal.

© 2015 Academia Mexicana de Cirugía A.C. Publicado por Masson Doyma México S.A. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Background

The most common cause of anal sphincter lesions in women is vaginal birth.¹ This has a major affect on the quality of life of these patients, as approximately one-third of them develop anal incontinence in spite of repair of the lesion following birth.² The majority of symptomatic patients have mild incontinence,^{3,4} so that many of them do not consult their doctor about it.

The diagnosis of external and internal anal sphincter defect is currently by means of endoanal ultrasound scan. This is due to the good sensitivity and specificity of this test.⁵ Nevertheless, this technique cannot be used to evaluate anal sphincter suture during the immediate postpartum period because of its intrinsic discomfort and the need for staff who know the technique and how to use it. This is why some authors recommend reserving it solely for research purposes.⁶ We therefore have the aim of establishing whether 3/4D transperineal ultrasound scan is a useful diagnostic tool during the immediate postpartum period,

to evaluate the anal sphincter and its repair after giving birth.

Material and methods

A prospective study was carried out from 1 September 2012 to 30 June 2013, in patients admitted to the Maternity Unit of Valme Hospital Universitario (Seville). This included those patients with the gestation of a single foetus to term, with no history of previous pregnancy or previous surgical operations to correct pelvic floor disease, in the active phase of the birth, with the foetus in head presentation, and having given their written acceptance of the informed consent. Pregnancies with severe disease of the mother or foetus were excluded.

Births were attended by the staff of the Maternity Unit, with at least 3 years' experience in obstetric practice.

The following obstetric parameters were studied: gestational age, induction of birth, epidural anaesthesia,

instrumentation, duration of the second phase of the birth, episiotomy and perineal tears. The foetal parameters quantified after birth are head perimeter and foetal weight.

For ultrasound evaluation a Toshiba Aplio 500® (Toshiba Medical Systems Corp., Tokyo, Japan) ultrasound scanner was used, with a PVT-675MV 3D abdominal probe. The probe was enclosed in a powder-free cover for reasons of hygiene.⁷

The postpartum ultrasound scan was performed by the same examiner who was specifically trained in transperineal 3/4D ultrasound scanning. The images were recorded within the first 48 h postpartum; they were acquired when the patients were lying in dorsal lithotomy on a gynaecological examination table with an empty bladder and rectum.^{8,9} The transducer was placed on the perineum carefully, with as little pressure as possible, with the main axis of the transducer placed in the introitus in the central sagittal plane.

Study of the echographic volume of the anal sphincter permits access to the axial plane. This analysis used what is known as the plane of minimum dimensions described in previous studies.^{9–13} Slices were taken at intervals of 2.5 mm after the plane of minimum dimensions, studying 3 slices under this plane and 4 slices above it, obtaining a total of 8 slices equivalent to a thickness of 12.5 mm. The anal sphincter was evaluated in 6 central slices, and the existence was determined of undiagnosed lesions which had been produced during birth, or sutures made in the context of a major tear.

The descriptive statistical analysis of the quantitative variables is summarised in the form of averages and typical deviations or, in the case of asymmetrical distributions, with medians and percentiles (P25 and P75) while qualitative variables are shown as percentages. The statistical analysis was performed using version 15 of the SPSS program (SPSS, Chicago, IL, USA).

Results

166 expectant mothers with no previous vaginal birth were evaluated during birth. 16 cases were considered to have been lost: 10 patients terminated pregnancy with an intrapartum cesarian section (4 due to the suspicion of foetal discomfort and 6 due to lack of progression), while ultrasound study was not performed in 5 patients due to a fault in follow-up by the researcher (one case was ruled out because of defects in image capture and 4 cases were excluded as following processing of the axial image not all of the structures within the sphincter complex were identifiable due to intense perineal oedema).

Table 1 shows the general and intrapartum obstetric characteristics of the population that was finally studied.

Lesions occurred to the external anal sphincter in 10.3% (15 cases) of the births. In 8.2% (12 patients) of the cases a primary suture of the external anal sphincter was detected during the ultrasound scan, and in 2.1% of these (3 cases) they were not diagnosed during birth but were detected in the subsequent ultrasound scan.

Table 2 shows the data corresponding to the 12 patients who were diagnosed with perineal tears in the anal sphincter during birth. All of the tears were of the 3a or 3b types, according to the classification established by the Royal College of Obstetricians and Gynaecologists.¹⁴ Type 3a tears in the external anal sphincter were repaired by end to end

Table 1 General obstetric and intrapartum characteristics of the 146 patients studied.

	Average ($\pm$ SD) or %
Average age at maternity	29.26 ($\pm$ 5.60)
Gestational age	39.37 ($\pm$ 1.18)
BMI	23.52 ($\pm$ 3.78)
Induced births	19.9
Epidural analgesia	91.8
Epidural anaesthesia time in minutes	386 ($\pm$ 205.68)
Duration of the second phase of the birth in minutes	105.73 ($\pm$ 72.95)
Instrument assisted births (vacuum)	50
Head circumference (cm)	34.67 ($\pm$ 1.94)
Episiotomy	66.4
III grade perineal tears	8.2
Neonatal weight (g)	3294 ($\pm$ 385.65)

BMI: body mass index.

technique, while those of type 3b were sutured using the overlap technique. After the surgical repair of these high-grade tears a check was performed to ensure that they had been made correctly by means of bi-digital palpation of the suture, inserting the index finger into the anal channel and the thumb into the vaginal region. This check of the primary repair of the sphincter was performed by 2 independent examiners, and suture of the tear did not continue until both gynaecologists agreed that the external anal sphincter had been correctly repaired. A total of 4 of the cases which had presented high-grade tears were assisted births, and of these only 2 patients had not received episiotomy. The lesions of these 2 patients were of the 3a type, justified by precipitated expulsion that did not permit perineal protection during birth.

The ultrasound scan diagnosis of the primary suture of the anal sphincter was based on detecting a thickening of the external anal sphincter with a more hyperechoic appearance than the rest of the sphincter ring, as may be seen in Fig. 1. This ultrasound examination was performed by an external gynaecologist who had no connection with the birth and was unaware of the existence of a tear in each patient.

The obstetric data of the patients in whom high-grade tears had not been detected during birth and who presented lesions during the ultrasound scan are shown in Table 3. Although after birth all an examination of the anal sphincter of the women had been exhaustively performed in 2 examinations prior to the perianal suture, in 3 patients the lesions were diagnosed by ultrasound scan. These 3 cases were instrument-assisted births in which an episiotomy had been performed. The lesions were detected after 12 h and showed as a loss of external anal sphincter continuity, with retraction of the remaining muscle ends, while the internal anal sphincter remained intact, as may be seen in Fig. 2. The lesions in these 3 patients were confirmed by transperineal 3/4D ultrasound scan 6 months after the birth. In this check-up all 3 women were asymptomatic.

During the ultrasound scan none of the patients mentioned discomfort or pain, in spite of the fact that the evaluation took place within 48 h after giving birth, while

Table 2 Patients diagnosed with high grade tear during birth.

Case	Age at maternity	BMI	Gestational age at birth	Epidural duration (min)	Duration of second phase of birth (min)	Instrumentation (vacuum)	Episiotomy	Type of tear	Neonatal weight (g)	External anal sphincter repair (ultrasound scan)	Internal anal sphincter repair (ultrasound scan)
1	36	23.31	40	360	360	—	—	3a	2.390	+	—
2	32	29.05	38	325	15	+	+	3a	2.430	+	—
3	28	22.86	41	300	60	+	+	3b	4.000	+	—
4	33	24.09	38	195	40	+	+	3a	3.000	+	—
5	30	18.37	40	193	30	—	—	3a	2.830	+	—
6	33	23.62	40	240	60	+	+	3b	3.300	+	—
7	19	24.09	41	525	35	+	+	3b	3.495	+	—
8	29	20.96	38	345	60	—	+	3a	3.380	+	—
9	29	24.91	39	205	165	+	+	3b	3.930	+	—
10	40	24.54	40	620	180	+	+	3b	3.660	+	—
11	37	21.56	41	330	30	+	+	3b	3.910	+	—
12	25	18.07	39	525	135	—	+	3b	3.625	+	—

BMI: body mass index.

Table 3 Patients with high grade tears that were not detected during birth that presented lesions during ultrasound scan.

Case	Age at maternity	BMI	Gestational age at birth	Epidural duration (min)	Duration of second phase of birth (min)	Instrumentation (vacuum)	Episiotomy	Type of tear	Neonatal weight (g)	External anal sphincter (ultrasound scan)	Internal anal sphincter (ultrasound scan)
1	31	24.98	41	550	70	+	+		3.350	+	—
2	27	28.91	41	540	35	+	+		3.710	+	—
3	31	31.59	40	710	110	+	+	2	3.795	+	—

BMI: body mass index.

many of them had perineal sutures. Following the examination all of the patients stated that before the ultrasound scan they had thought that the scan would cause pain in the perineal region, but that this had not occurred.

None of the women studied presented clinical data showing anal incontinence during the postpartum period.

Discussion

Obstetric sphincter tears are the most frequent cause of anal incontinence in healthy women.^{6,15,16} A direct relationship has been found to exist between the degree of the sphincter defect after repair and the degree of anal incontinence.¹⁷ It is therefore important that the coloproctological surgeon diagnose these defects as soon as possible, to commence the appropriate treatment as early as is feasible.

Different approaches have been described for the evaluation of the anal sphincter by ultrasound scan, including endoanal, transvaginal and transperineal approaches.¹⁸ Classically endoanal ultrasound scan is now the main test for the diagnosis of these lesions, due to its good sensitivity and specificity.¹⁹ However, it is not a useful technique for evaluating the primary sutures of the sphincter during the immediate postpartum period because of the discomfort it may cause to patients. We also have to take into account the

difficulty of accessing specialised personnel who are able to perform an examination of this type during the immediate postpartum period.⁶ Some authors therefore advise that postpartum endoanal ultrasound scan should be reserved solely for research purposes.⁶

With the aim of finding an imaging technique that is easier to perform, accessible and non-invasive, the role of transperineal ultrasound scan was studied in the diagnosis of internal and external lesions of the anal sphincter.¹⁸ Previous studies have described that the location and extension of the anal sphincter lesions diagnosed using 3/4D transperineal ultrasound scan were compatible with those obtained using magnetic resonance imaging.²⁰

Evaluation of sphincters by transperineal ultrasound scan has been described with the use of different ultrasound probes. Different authors have established the usefulness of endovaginal probes for this type of examination.^{18,21-23} Peschers et al.,²⁴ as is the case in our work, used convex transducers, and they described all of the layers in the anal sphincter complex, in the same way as had been established using endoanal ultrasound scan.

Transperineal ultrasound scan has not only been able to describe the anatomical structures of the anal sphincter, as it has also made it possible to identify traumatic obstetric lesions in the sphincter complex,²¹ as we observed in our study.

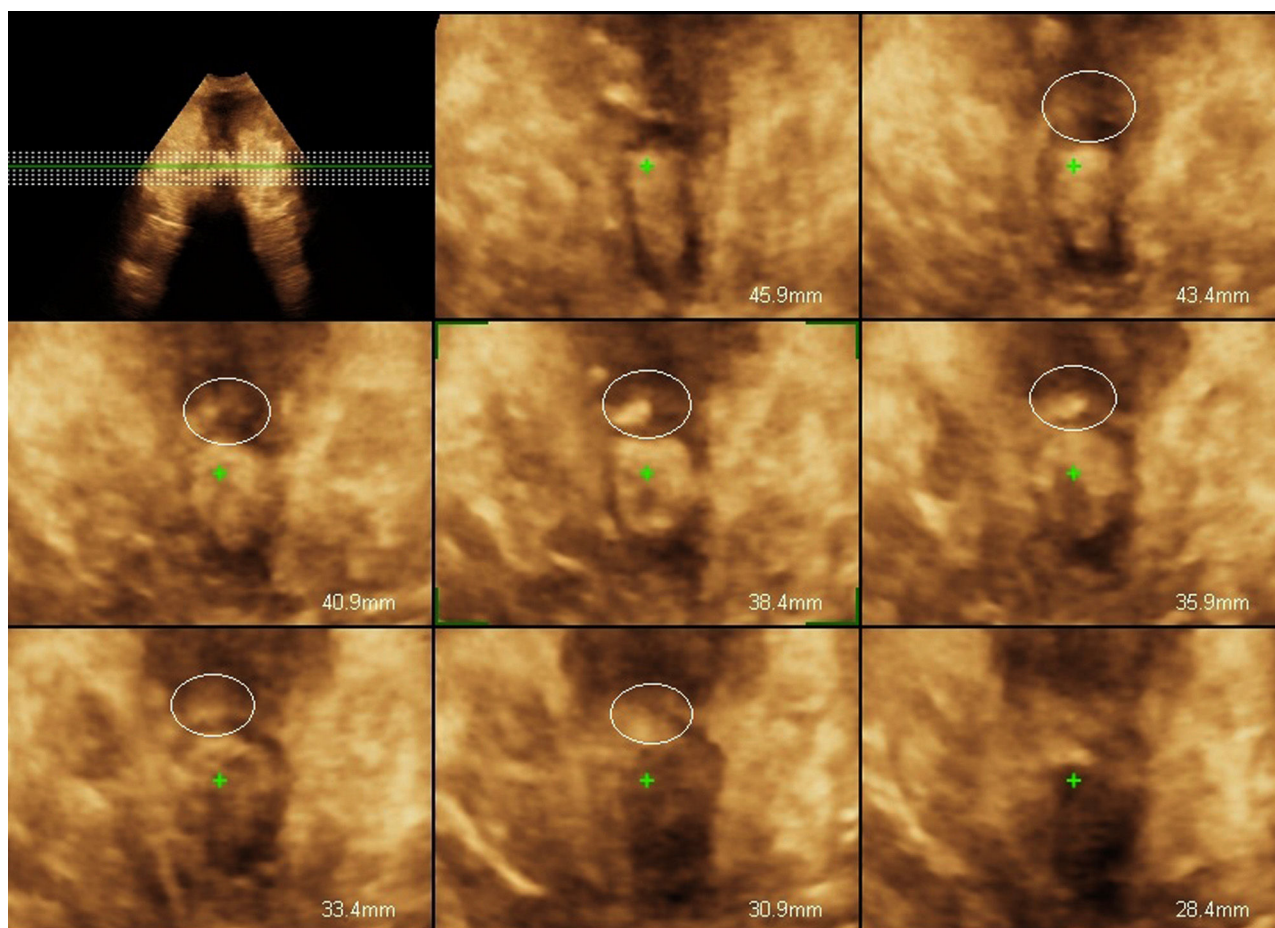


Figure 1 The circle marks thickening at 12 o'clock in the external anal sphincter caused by the primary suture of the sphincter using overlap technique in the 6 central slices.

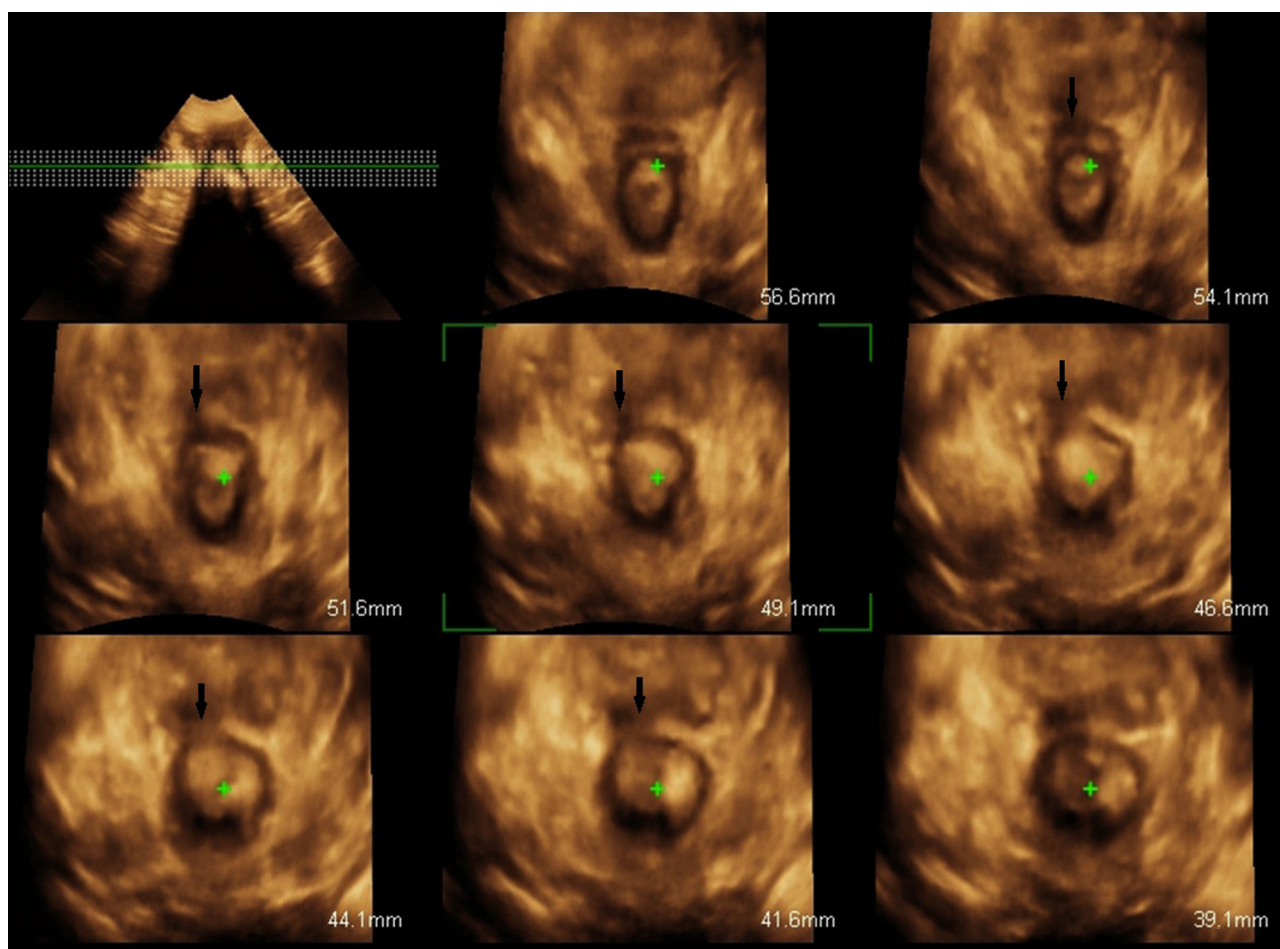


Figure 2 The arrow indicates a discontinuity in the external anal sphincter that corresponds to a sphincter lesion in the 6 central slices, established immediately after the birth.

In the case of patients with anal sphincter lesions it is important that they be given an ultrasound scan following the repair of the sphincter after the birth. They should also receive periodical check-ups to evaluate the healing process and to detect possible symptoms of incontinence.²⁵ Nevertheless, ultrasound is not only useful in the evaluation of the scarring process, as it is also useful in the diagnosis and follow-up of hidden lesions of the anal sphincter that were not diagnosed during the birth.⁶ These hidden lesions have been described in 7.9% of vaginal births.²¹ These types of hidden trauma were also detected in our study, with a frequency of 2.1%, which is lower than the figure established in previous studies.²¹

However, the incipient diagnosis at such an early stage which we performed in this work may be restricted by oedema, haemorrhaging and lacerations in the genital area.²⁶ To attempt to reduce these erroneous diagnoses it was decided to undertake a single axial plane tomographic ultrasound study. This established the diagnosis of sphincter lesion if the said trauma was present in the 5 central slices of the multislice mode.

Sphincter lesions that go unnoticed during birth and are identified during the subsequent ultrasound scan are the cause of some cases of postpartum anal incontinence.²⁷ Asymptomatic sphincter defects have been detected in patients with reduced sphincter thickness at the 12 o'clock

position and with an intact perineal body.²⁸ This is due to the fact that the body of the perineum stabilised the remaining muscle fibres of the external sphincter.²⁸

The chief objective following a complete ultrasound examination must be to advise women after they have suffered anal sphincter obstetric trauma.²⁵

To conclude, we can say that 3D transperineal ultrasound scan is useful for determining the primary repair of the anal sphincter during the immediate postpartum period. It causes the patients no discomfort and also offers early indication of those sphincter lesions that went unnoticed during vaginal birth.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or

subjects mentioned in the article. The corresponding author is in possession of this document.

Conflict of interests

The authors declare that they received no financing of any type and that they have no conflict of interests to declare.

References

1. Zhuang RR, Song YF, Chen ZQ, Ma M, Huang HJ, Chen JH, et al. Levator avulsion using a tomographic ultrasound and magnetic resonance-based model. *Am J Obstet Gynecol*. 2011;205:232e1–8e, <http://dx.doi.org/10.1016/j.ajog.2011.03.052>.
2. Starck M, Bohe M, Valentin L. Results of endosonographic imaging of the anal sphincter 2–7 days after primary repair of third- or fourth-degree obstetric sphincter tears. *Ultrasound Obstet Gynecol*. 2003;22:609–15.
3. Zetterström J, López A, Anzén B, Norman M, Holmström B, Mellgren A. Anal sphincter tears at vaginal delivery: risk factors and clinical outcome of primary repair. *Obstet Gynecol*. 1999;94:21–8.
4. Fornell EK, Berg G, Hallböök O, Matthiesen LS, Sjö Dahl R. Clinical consequences of anal sphincter rupture during vaginal delivery. *J Am Coll Surg*. 1996;183:553–8.
5. Frudinger A, Halligan S, Bartram CI, Spencer JA, Kamm MA. Changes in anal anatomy following vaginal delivery revealed by anal endosonography. *Br J Obstet Gynaecol*. 1999;106:233, 227.
6. Folch M, Parés D, Castillo M, Carreras R. Practical issues in the management of third and fourth degree tears to minimise the incidence of faecal incontinence. *Cir Esp*. 2009;85:341–7.
7. Falkert A, Endress E, Weigl M, Seelbach-Göbel B. Three-dimensional ultrasound of the pelvic floor 2 days after first delivery: influence of constitutional and obstetric factors. *Ultrasound Obstet Gynecol*. 2010;35:583–8.
8. Dietz HP, Simpson JM. Levator trauma is associated with pelvic organ prolapse. *BJOG*. 2008;115:979–84.
9. Dietz HP, Shek KL. Tomographic ultrasound imaging of the pelvic floor: which levels matter most? *Ultrasound Obstet Gynecol*. 2009;33:698–703.
10. Dietz HP, Shek C, Clarke B. Biometry of the pubovisceral muscle and levator hiatus by three-dimensional pelvic floor ultrasound. *Ultrasound Obstet Gynecol*. 2005;25:580–5.
11. Guaderrama NM, Liu J, Nager CW, Pretorius DH, Sheean G, Kassab G, et al. Evidence for the innervation of pelvic floor muscles by the pudendal nerve. *Obstet Gynecol*. 2005;106:774–81.
12. Braekken IH, Majida M, Ellstrom-Eng M, Dietz HP, Umek W, Bo K. Test–retest and intra-observer repeatability of two-, three- and four-dimensional perineal ultrasound of pelvic floor muscle anatomy and function. *Int Urogynecol J Pelvic Floor Dysfunct*. 2008;19:227–35.
13. Yang JM, Yang SH, Huang WC. Biometry of the pubovisceral muscle and levator hiatus in nulliparous Chinese women. *Ultrasound Obstet Gynecol*. 2006;28:710–6.
14. Royal College of Obstetricians and Gynaecologist, Guideline No. 29. Management of third- and fourth-degree perineal tears following vaginal delivery. Londres: RCOG Press; 2001.
15. Folch M, Parés D, Castillo M, Carreras R. Aspectos prácticos en el manejo de las lesiones obstétricas perineales de tercer y cuarto grado para minimizar el riesgo de la incontinencia fecal. *Cir Esp*. 2009;85:341–7.
16. Rodríguez R, Alós R, Carceller MS, Solana A, Frangi A, Ruiz MD, et al. Incontinencia fecal posparto. Revisión de conjunto. *Cir Esp*. 2014;2:4, <http://dx.doi.org/10.1016/j.ciresp.2014.10.002>. S0009-739X(14)00328-5.
17. Norderval S, Markskog A, Rossaak K, Vonen B. Correlation between anal sphincter defects and anal incontinence following obstetric sphincter tears: assessment using scoring systems for sonographic classification of defects. *Ultrasound Obstet Gynecol*. 2008;31:78–84.
18. Hall RJ, Rogers RG, Saiz L, Qualls C. Translabial ultrasound assessment of the anal sphincter complex: Normal measurements of the internal and external anal sphincter at the proximal, mid-, and distal levels. *Int Urogynecol J Pelvic floor Dysfunct*. 2007;18:881–8.
19. Shek K, Dietz H. The effect of childbirth on hiatal dimensions. *Obstet Gynecol*. 2009;113:1272–8.
20. Huang WC, Yang SH, Yang JM. Three-dimensional transperineal sonographic characteristics of the anal sphincter complex in nulliparous women. *Ultrasound Obstet Gynecol*. 2007;30:210–20.
21. Valsky DV, Messing B, Petkova R, Savchev S, Rosenak D, Hochner-Celnikier D, et al. Postpartum evaluation of the anal sphincter by transperineal three-dimensional ultrasound in primiparous women after vaginal delivery and following surgical repair of third-degree tears by the overlapping technique. *Ultrasound Obstet Gynecol*. 2007;29:195–204.
22. Lee JH, Pretorius DH, Weinstein M, Guaderrama NM, Nager CW, Mittal RK. Transperineal three-dimensional ultrasound in evaluating anal sphincter muscles. *Ultrasound Obstet Gynecol*. 2007;30:201–9.
23. Huang WC, Yang SH, Yang JM. Three dimensional transperineal sonographic characteristics of the anal sphincter complex in nulliparous women. *Ultrasound Obstet Gynecol*. 2007;30:210–20.
24. Peschers UM, DeLancey JO, Schaer GN, Schuessler B. Exoanal ultrasound of the anal sphincter: normal anatomy and sphincter defects. *Br J Obstet Gynaecol*. 1997;104:999–1003.
25. Valsky DV, Cohen SM, Lipschuetz M, Hochner-Celnikier D, Yagel S. Three-dimensional transperineal ultrasound findings associated with anal incontinence after intrapartum sphincter tears in primiparous women. *Ultrasound Obstet Gynecol*. 2012;39:83–90.
26. Faltin DL, Boulvain M, Stan C, Epiney M, Weil A, Irion O. Intraobserver and interobserver agreement in the diagnosis of anal sphincter tears by postpartum endosonography. *Ultrasound Obstet Gynecol*. 2003;21:375–7.
27. Sultan AH, Kamm MA, Hudson CN, Thomas JM, Bartram CI. Anal-sphincter disruption during vaginal delivery. *N Engl J Med*. 1993;329:1905–11.
28. Starck M, Bohe M, Fortling B, Valentin L. Endosonography of the anal sphincter in women of different age and parity. *Ultrasound Obstet Gynecol*. 2005;25:169–76.