# ISUOG
## Virtual World Congress
ON ULTRASOUND IN OBSTETRICS AND GYNECOLOGY

16–18 OCTOBER 2020

**3 DAY EVENT**

**5** streams — **170+** expert talks — **1200+** abstracts

Register to access a high tech virtual space enabling you to learn and interact with

**200+ world leading experts**

and global community

**Watch Live** OR **On Demand**

Earn CME/CPD points for attending

Benefit from reduced registration fees

Explore scientific program & register here

CELEBRATING THIRTY YEARS • ISUOG WORLD CONGRESS • 30

*Ultrasound Obstet Gynecol* 2011; **37**: 570–575
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.8847

# Role of three-dimensional ultrasound measurement of the optic tract in fetuses with agenesis of the septum pellucidum

J. P. BAULT*†‡, L. J. SALOMON†‡, L. GUIBAUD§ and R. ACHIRON¶

**Centre d'Echographies Ambroise Paré Les Mureaux, CHI Poissy Saint-Germain, Yvelines, France; †Maternité Necker-Enfants Malades, APHP, Université Paris Descartes, Paris, France; ‡SFAPE: Société Pour l'Amélioration des Pratiques en Echographie, Paris, France; §Imagerie Pédiatrique et Fœtale, Hôpital Femme Mère Enfant, Université Claude Bernard Lyon I, Lyon Bron, France; ¶Department of Obstetrics and Gynecology, Sheba Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel*

**KEYWORDS:** 3D ultrasound; measurements; optic tract; prenatal; septal agenesis

## ABSTRACT

***Objectives*** *To construct reference ranges for fetal optic tract mean diameter and to report measurements in fetuses with agenesis of the septum pellucidum (SP).*

***Methods*** *Three-dimensional volumes of the optic chiasm were acquired in 98 normal fetuses during routine sonographic examination at 21–36 weeks' gestation and the diameters of the posterior left and right optic tracts were measured offline. A polynomial regression approach (mean and SD model) was used to compute reference charts for the mean fetal optic tract diameter measurements. In addition, 23 volumes were acquired in fetuses with SP agenesis for offline measurement of optic tract diameter. Complete follow-up was obtained in 13 of these 23 cases.*

***Results*** *In normal fetuses, the optic tract diameter increased linearly throughout gestation. There was no evidence of increased variability with gestational age (constant SD). Normal charts and equations for Z-score calculation were constructed. Among the 13 fetuses with SP agenesis and complete follow-up, nine had normal measurements, of which eight had normal vision postnatally. Four had hypoplastic optic tract, defined as mean optic tract diameter Z-score below −3. Of these, two underwent termination of pregnancy and pathological examination confirmed hypoplasia of the tract, one showed signs of hypoplasia at magnetic resonance imaging and postnatal examination confirmed blindness, and one had a hypoplastic measurement for only one tract and was born with poor vision and abnormal bilateral eye movements.*

***Conclusion*** *We present new reference charts for mean fetal optic tract diameter. In fetuses with agenesis of the SP, sonography of the optic tract might be a useful tool to assess its development and may help in prenatal counseling. Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.*

## INTRODUCTION

Agenesis of the septum pellucidum (SP) is a rare cerebral malformation, with an incidence of 2–3/100 000 in the general population, and is characterized by partial or complete absence of the SP[1]. Although isolated agenesis of the SP may be present in normal individuals, it can be associated with severe neurological anomalies such as septo-optic dysplasia (SOD) or be a part of holoprosencephaly syndrome. Agenesis of the SP is also a clue to the diagnosis of De Morsier syndrome[2], which is characterized by fetal endocrinological deficiencies as well as various degrees of optic tract hypoplasia associated with visual impairment[3,4].

Detection of SP agenesis raises the possibility of there being additional midline defects and an abnormal optic tract[5]. Although anomalies of the optic tract have been described using magnetic resonance imaging (MRI) in children with SP agenesis, measurements with MRI are not possible due to the spatial resolution[6]. Ultrasound technology has only recently made it possible to visualize the fetal optic tract *in utero*[7]. In a preliminary study, we showed the feasibility of fetal optic tract measurement and its potential application in cases with SP agenesis[8,9].

The aim of this study was to construct new reference ranges for fetal optic tract mean diameter measured using three-dimensional (3D) ultrasound and to evaluate the potential value of such charts in analyzing measurements of fetuses with agenesis of the SP.

*Correspondence to:* Dr J. P. Bault, Centre d'Echographie Ambroise Paré, 68/70 rue Aristide Briand, 78130 Les Mureaux, Yvelines, France (e-mail: Jean-Philippe.BAULT@wanadoo.fr)

*Accepted: 3 September 2010*

## SUBJECTS AND METHODS

This was a cross-sectional study of morphologically normal fetuses in low-risk pregnancies undergoing routine ultrasound examination at 21–36 weeks. Only fetuses with known dates based on first-trimester crown–rump length and without growth restriction were included in the study[10]. Follow-up of all fetuses was carried out and demonstrated absence of vision impairment. Fetuses with abnormal karyotype or congenital malformation and multiple pregnancies were excluded from the study. No exclusion was made on the basis of abnormal optic tract measurement. Gestational age in weeks was used: fractions of weeks were computed to the nearest week, with fractions of $\leq 4$ days and $\geq 5$ days, assigned to the lower and higher weeks, respectively.

All measurements were performed with no time constraints by a single trained sonographer using a Voluson 730 or E8 Expert ultrasound machine (versions BT 04 to 09, GE Medical Systems, Zipf, Austria) equipped with the same transabdominal (4–8 MHz) volume probe, with a cine-loop facility. (A transvaginal approach may be used when the presentation is cephalic.) In 14 cases, measurements were then repeated by a second sonographer, blinded to the findings of the first, for the interobserver study. All optic tract measurements were performed according to the method published previously[7–9], to the nearest 0.1 mm.

Briefly, the transabdominal approach started from an axial plane slightly below the biparietal diameter plane, showing the circle of Willis. A volume was obtained using the surface program set on 'maximum quality'. A sweep was then performed in an axial plane with an angle of 30°. The volume acquired was then rotated by 90°, showing the region of interest (ROI) from above, in Plane A. The ROI was oriented by placing the green line at the upper part of the box and the green square on the left. A convex reduction of the volume was then performed in order to generate the thinnest possible volume. Scrolling from top to bottom allowed the X-shaped chiasm to be visualized. The optimal rendering settings usually consisted of the following combination: surface smooth/light gradient, 70/30 set-up.

The diameter of the optic tract was measured as shown in Figure 1. We chose to measure the posterior rather than the anterior tracts because they are free from shadowing from the sphenoid bone. The mean values of the right and left tract measurements were used in all cases for computing normal ranges. All measurements in this study were made using a transabdominal approach and took 3–5 min to perform. Statistical analysis was performed as previously recommended[11–13]. Variables were fitted using a polynomial such as $y = a + \Sigma b_i x_i$ where $x$ denotes gestational age and i goes from 1 to n[13]. Increasing order terms (1 to $n$) for gestational age were added in the model as long as they were significant as based on a sequence of likelihood-ratio tests. $R^2$ statistic and/or the subjective aspect of fitted curve were also studied to assess the quality of fit, together with the $Z$-score distribution. The variability, meaning SD, of the variables at each week of gestational age was modeled by first computing the mean week-specific absolute scaled residuals (absolute difference between the measurements and the predicted mean multiplied by $\sqrt{(\pi/2)}$), and then regressing them against gestational age. Once again, degrees higher than 1 for gestational age were added in the model only if they were significant as based on likelihood-ratio test. Statistical analysis was performed using Stata 9.2 for Windows (StataCorp LP, College Station, TX, USA) and STATISTICA data analysis software system, version 6 (2001; StatSoft, Inc., Tulsa, OK, USA).

We also collected retrospectively volumes of 23 fetuses with SP agenesis that were scanned between 2007 and 2009. None of these volumes was recorded originally in order to measure the optic tract; they were intended only to demonstrate the absence of the lateral walls of the SP. However, we tried and succeeded in measuring the optic tract mean diameter from these volumes. Measurements were compared with the visual appearance of the tract as seen on MRI whenever this was available in a coronal plane. Volumes and MR images were provided by colleagues for the purpose of this study.

## RESULTS

Optic tract measurements were obtained in all 98 normal fetuses at 21–36 weeks' gestation. Neonatal clinical examination including visual assessment was normal in all infants. The mean ± SD number of examinations performed at each week of gestation was 6 ± 3. Raw fetal optic tract (FOT) diameter measurements were fitted satisfactorily with a linear model[11,12], as follows:

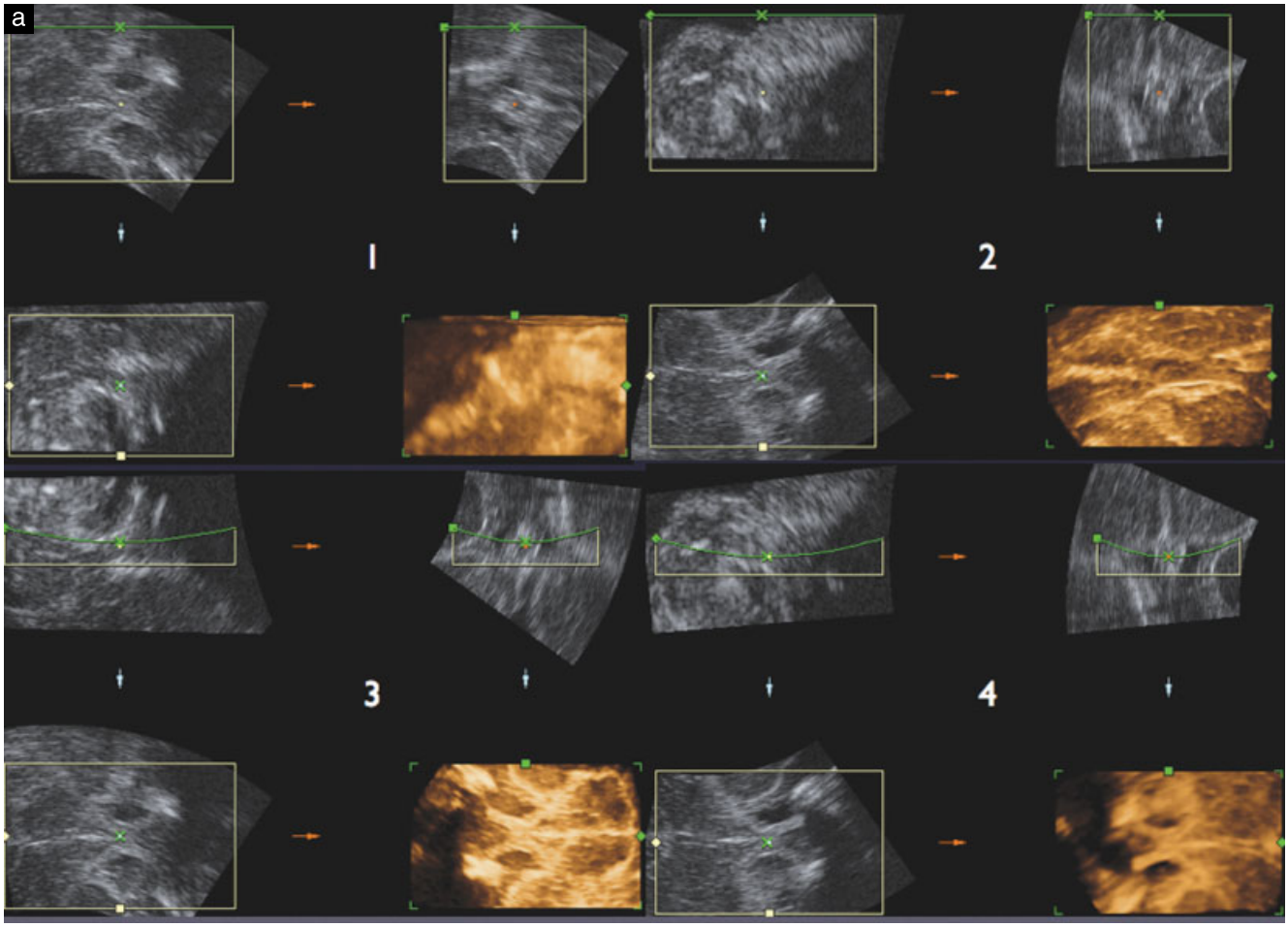
$$\text{FOT diameter} = 0.0451951 + 0.0925759 \times \text{GA},$$

where GA is gestational age to the nearest week and all measurements are in mm.

There was no evidence of increased variability with increasing GA ($P = 0.37$ for a change with GA). A constant SD model was therefore used, with SD = 0.1737 mm. The normal range is shown in Figure 2.

Table 1 provides the mean and 3rd, 5th, 95th and 97th centiles for posterior optic tract diameter measurements at 20–36 weeks'. The mean and SD of the $Z$-score distribution were $-4.10^{-6}$ and 1.0001, very close to the theoretical values of 0 and 1, respectively[13].

The intraclass correlation coefficients (ICC) were: 0.80 (95% CI, 0.62–0.98) for intraobserver and 0.94 (0.88–1) for interobserver measurements. The mean and 95% limits of agreement were 0.027 (−0.454; 0.508) for intraobserver and 0.053 (−0.159; 0.265) for interobserver repeatability. The Bland–Altman[14] plot for interobserver variability is shown in Figure 3. Our method demonstrated good intra- and interobserver reproducibility, with no systematic bias and limited random error.



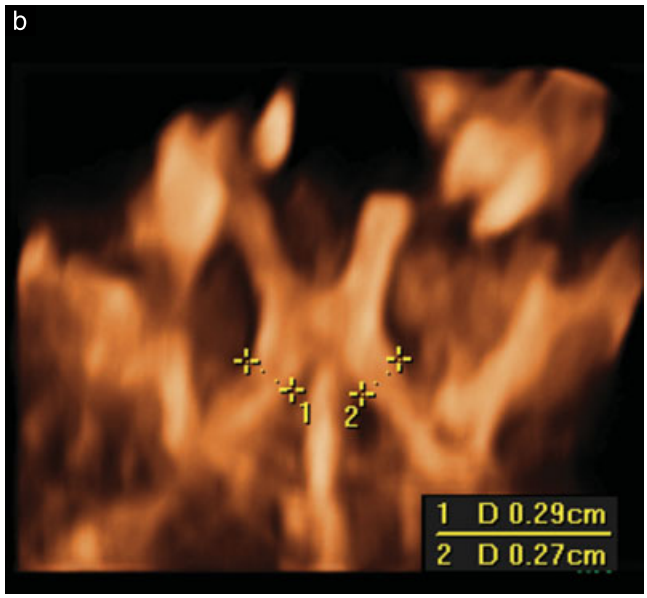




**Figure 1** Measurement of optic tract diameter using a transabdominal approach in a 28-week fetus. (a) 1: Acquisition in the axial plane. 2: Adjustment to obtain the axial plane of the optic chiasm. 3: Rotation by 90° to visualize the chiasm from the upper green line. 4: Adjustment to visualize the optic tract. (b) Measurement of optic tract diameter.

Regarding the 23 volumes obtained from fetuses with SP agenesis, we were able to identify and measure the optic tract in 22 (96%) cases; in one case, optic tract measurement was not possible because the whole chiasm was not included in the volume. In six of the 22 cases, MRI was performed. In only 13 of the 22 cases were we able to obtain pregnancy outcome; in the other nine cases the pregnancy was terminated without pathological examination or patients were lost to follow-up. The results are summarized in Table 2: among the 13 cases with a known outcome, four had hypoplasia of the tract, with mean optic tract diameter Z-scores below −3 (hypoplastic group), and nine had normal measurements (normal group, Table 2).

In the hypoplastic group, two patients (Cases 1 and 4) elected to terminate the pregnancy and pathological examination confirmed hypoplasia of the optic tract (Figure 4c). In one fetus (Case 2) 3D ultrasound and MRI were performed and both showed hypoplastic tract (Figures 4a,b). The measurement in 3D ultrasound in this case was confirmed by a second operator with no knowledge of the initial measurement: no significant difference in measurements was found between the operators (1.3 and 1.3 mm vs. 1.3 and 1.2 mm). Postnatally, this infant demonstrated blindness at the age of 1 year. In the last case (Case 3), both 3D ultrasound and MRI showed unilateral hypoplasia of the optic tract. Postnatally, this infant demonstrated major impairment of vision with abnormal movements of the eyes. In these

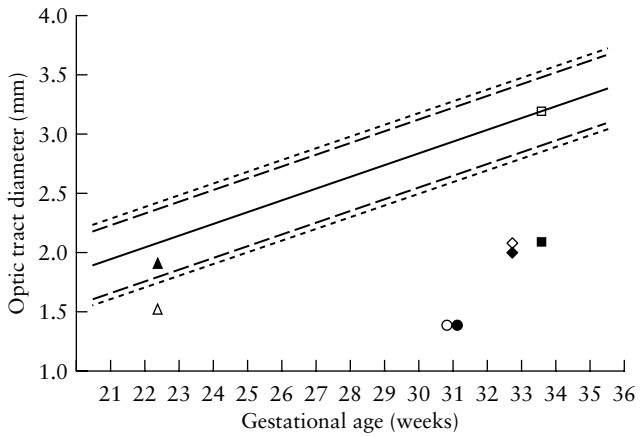



**Figure 2** Reference range for fetal optic tract diameter at 21–36 weeks, calculated by linear regression (3rd, 5th, 50th, 95th and 97th centiles), showing the four hypoplastic cases (Case 1, ▲△; Case 2, ●○; Case 3, ■ □; Case 4, ◆◇; filled symbols are left optic tract and unfilled symbols are right optic tract).

latter two cases, the diagnosis of SP agenesis and SOD was confirmed.

Eight of the nine infants in the normal group had normal vision. In one of these eight cases there was an associated commissural dysplasia; the fetus was liveborn and the child had good vision at the time of writing. In the ninth case, the child had minor ophthalmological complications with a ptosis of one eye. In all nine cases, the diagnosis of SP agenesis was confirmed.

## DISCUSSION

Our study confirms the feasibility of 3D ultrasound in evaluating the fetal optic tract and suggests that it could be of prognostic value in cases with agenesis of the SP.

**Table 1** Reference ranges for fetal optic tract diameter (in mm)

| GA (weeks) | n | Centile | | | | |
|---|---|---|---|---|---|---|
| | | 3rd | 5th | 50th | 95th | 97th |
| 21 | 5 | 1.6 | 1.7 | 2.0 | 2.3 | 2.3 |
| 22 | 7 | 1.7 | 1.8 | 2.1 | 2.4 | 2.4 |
| 23 | 6 | 1.8 | 1.9 | 2.2 | 2.5 | 2.5 |
| 24 | 7 | 1.9 | 2.0 | 2.3 | 2.6 | 2.6 |
| 25 | 5 | 2.0 | 2.1 | 2.4 | 2.6 | 2.7 |
| 26 | 5 | 2.1 | 2.2 | 2.5 | 2.7 | 2.8 |
| 27 | 6 | 2.2 | 2.3 | 2.5 | 2.8 | 2.9 |
| 28 | 4 | 2.3 | 2.4 | 2.6 | 2.9 | 3.0 |
| 29 | 5 | 2.4 | 2.4 | 2.7 | 3.0 | 3.1 |
| 30 | 5 | 2.5 | 2.5 | 2.8 | 3.1 | 3.2 |
| 31 | 5 | 2.6 | 2.6 | 2.9 | 3.2 | 3.3 |
| 32 | 17 | 2.7 | 2.7 | 3.0 | 3.3 | 3.3 |
| 33 | 5 | 2.8 | 2.8 | 3.1 | 3.4 | 3.4 |
| 34 | 6 | 2.9 | 2.9 | 3.2 | 3.5 | 3.5 |
| 35 | 5 | 2.9 | 3.0 | 3.3 | 3.6 | 3.6 |
| 36 | 5 | 3.0 | 3.1 | 3.4 | 3.7 | 3.7 |

GA, gestational age.

In the case of absence of the SP, detailed ultrasound examination should exclude midline malformations, i.e. holoprosencephaly, corpus callosum agenesis, rhombencephalosynapsis, obstructive hydrocephaly or ischemic destructive lesions[15–17]. Even when it is isolated, absence of the SP raises the possibility of SOD. SOD is a heterogeneous condition comprising various optic disc and nerve abnormalities as well as pituitary hypoplasia[3,18,19]. The most severe form can present total blindness, panhypopituitarism and psychomotor delay.

Prenatal diagnosis of severe forms of SOD should focus on pituitary insufficiency and abnormal development of the optic structures[19–22]. Lepinard *et al.*[4] have shown that a low level of maternal serum estriol is suggestive of fetal

**Table 2** Details of 13 fetuses with agenesis of the septum pellucidum and complete follow-up

| Case | GA (weeks) | Optic tract measurement (mm) | Z-score | Antenatal MRI | Outcome |
|---|---|---|---|---|---|
| Normal optic tract | | | | | |
| 1 | 22 | 2* | 1.6 | — | LB, vision normal |
| 2 | 32 | 2.8/3.2 | −1.1/1.1 | — | LB, vision normal |
| 3 | 29 | 2.7* | 2.9 | — | LB, vision normal† |
| 4 | 30 | 3.1* | 3.1 | — | LB, vision normal |
| 5 | 23 | 2.2* | 1.1 | — | LB, vision normal |
| 6 | 32 | 3.2/2.9 | 1.1/−1.0 | Normal | LB, vision normal |
| 7 | 22 | 2.1* | 0.1 | — | LB, vision normal |
| 8 | 26 | 2.2/2.3 | −1.1/−1.0 | Normal | LB, vision normal |
| 9 | 22 | 1.9/1.6 | −1.2/−2.2 | Normal | LB, minor complications: ptosis |
| Hypoplastic optic tract | | | | | |
| 1 | 22 | 1.5/1.9 | −3.3/−1.0 | — | TOP: hypoplasia of optic tract |
| 2 | 31 | 1.3* | −5.0 | Bilateral hypoplasia | LB, blind |
| 3 | 34 | 3.2/2.1 | −0.5/−4.5 | Unilateral hypoplasia | LB, major complications |
| 4 | 33 | 2.1/2.0 | −4.0/−4.1 | Bilateral hypoplasia | TOP: hypoplasia of optic tract |

*In cases with only one measurement value, measurements were equal for the two branches. †In one case (Case 3) there was an associated anomaly: comissural dysplasia. GA, gestational age; LB, live birth; MRI, magnetic resonance imaging; TOP, termination of pregnancy.

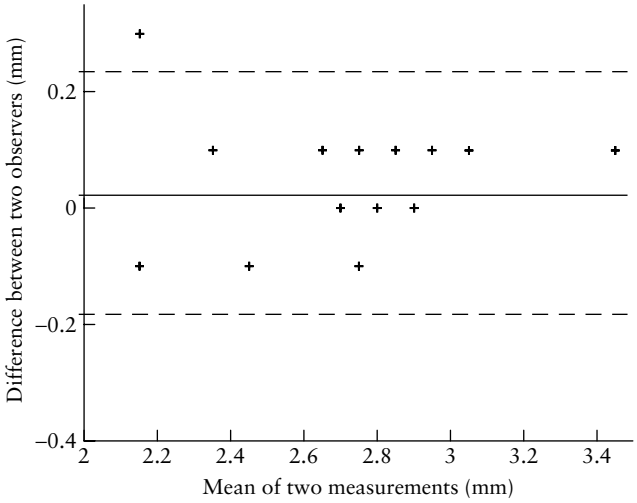



**Figure 3** Bland–Altman plot for interobserver variability, showing the difference between pairs of fetal optic tract diameter measurements plotted against their mean. Mean difference (——) and 95% limits of agreement (– – –) are shown.

ACTH (adrenocorticotropic hormone) deficiency and can help to diagnose the most severe endocrinological forms of SOD with panhypopituitarism.

Our study suggests that when 3D ultrasound and MRI indicate optic nerve hypoplasia, there is a high risk of postnatal visual impairment. However, there were several weaknesses in our study. Although normal optic nerves can be assessed by 3D ultrasound evaluation, SOD cannot be strictly excluded, partly because of the low spatial resolution of the technique but also due to potential progressive atrophy postnatally. Our study was retrospective and included volumes that had not been acquired for fetal optic tract measurement. Finally, these measurements can be difficult to obtain.

Our study describes new tools with which to visualize and assess optic tract development prenatally. However, even if prenatal diagnosis of optic nerve hypoplasia becomes feasible, counseling for SOD remains one of the biggest difficulties in the field.

## ACKNOWLEDGMENTS

We express our gratitude to B. Benoit, C. Bisch, R. Chaoui, G. L. Pilu, H. Laurichesse, J. M. Levaillant, D. Moeglin and Y. Ville for their help in the course of the study and in the writing of the manuscript. This study was performed in Centre d'Echographie Ambroise Paré. The volumes were acquired in Hopital Princesse Grace, Monaco (B. Benoit), Hopital Croix Rousse, Lyon, France (C. Bisch), Prenatal and Human Genetics, Berlin, Germany (R. Chaoui), Departments of Obstetrics and Gynecology, University of Bologna, Italy (G. L. Pilu), CHU Clermont Ferrand, France (H. Laurichesse), CHU Antoine Béclère, Clamart, France (J. M. Levaillant) and CHU, Nice, France (D. Moeglin) as well as in the institutions of the authors.

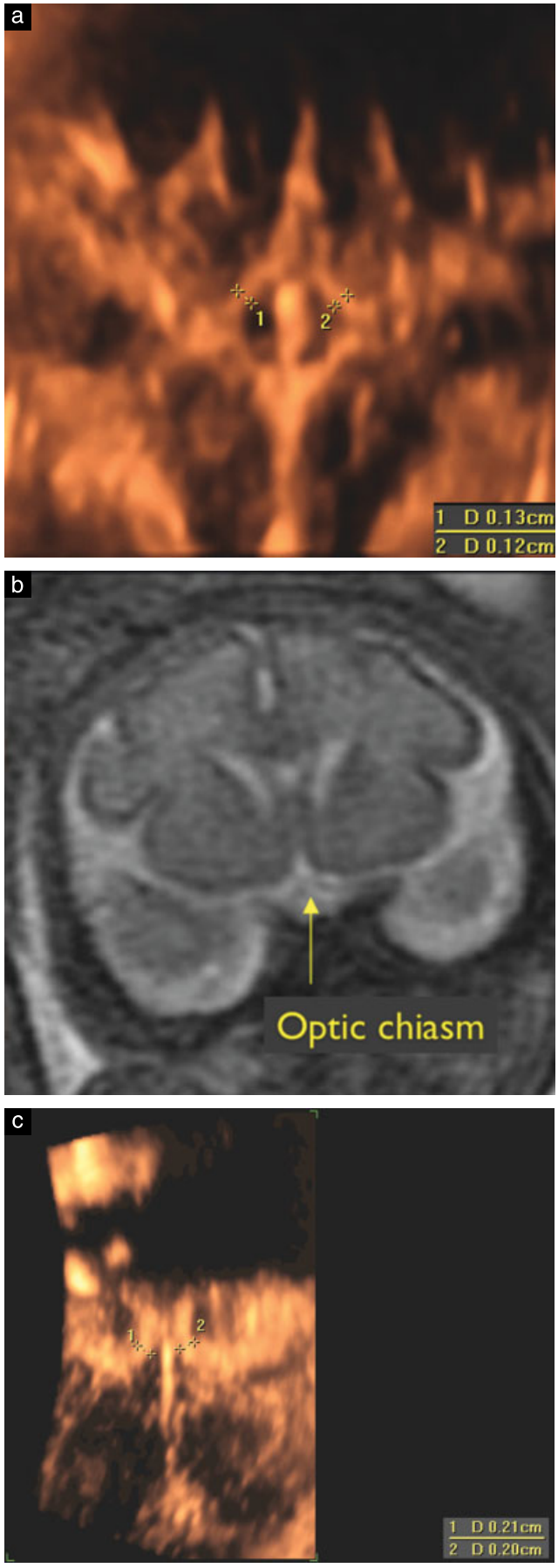



**Figure 4** Optic tract diameter measurement in two fetuses with hypoplastic tract: Case 2 (31 weeks), shown on three-dimensional ultrasound (a) and magnetic resonance imaging (b), and Case 4 (33 weeks) (c).

## REFERENCES


1. Barkovich AJ, Norman D. Absence of the septum pellucidum: a useful sign in the diagnosis of congenital brain malformations. *AJR Am J Roentgenol* 1989; **152**: 353–360.
2. Barkovich AJ, Fram EK, Norman D. Septo-optic dysplasia: MR imaging. *Radiology* 1989; **171**: 189–192.
3. De Morsier G. Etudes sur les dystrophies cranio-encéphaliques III. Agenesie du septum pellucidum avec malformation du tractus optique: la dysplasie septo-optique. *Schweiz Arch Neurol Psychiatr* 1956; **77**: 267–292.
4. Lepinard C, Coutant R, Boussion F, Lo'l D, Delorme B, Biquard F, Bonneau D, Guichet A, Descamps PL. Prenatal diagnosis of absence of the septum pellucidum associated with septo-optic dysplasia. *Ultrasound Obstet Gynecol* 2005; **25**: 73–75.
5. Pilu G, Tani G, Carletti A, Malaigia S, Ghi T, Rizzo N. Difficult early sonographic diagnosis of absence of the fetal septum pellucidum. *Ultrasound Obstet Gynecol* 2005; **25**: 70–72.
6. Garel C. *MRI of the Fetal Brain*. Springer: Berlin, 2003.
7. Bault JP. Visualization of the fetal optic chiasma using three-dimensional ultrasound imaging. *Ultrasound Obstet Gynecol* 2006; **28**: 862–864.
8. Bault JP. OC76: prognostic value of fetal optic chiasm measurements in fetuses with septal agenesis. *Ultrasound Obstet Gynecol* 2007; **30**: 390.
9. Bault JP, Salomon LJ. P38.13: fetal optic chiasm measurements: reference range at 22–36 weeks of gestation. *Ultrasound Obstet Gynecol* 2007; **30**: 596.
10. Wisser J, Dirschedl P, Krone S. Estimation of gestational age by transvaginal sonographic measurement of greatest embryonic length in dated human embryos. *Ultrasound Obstet Gynecol* 1994; **4**: 457–462.
11. Altman DG, Chitty LS. Charts of fetal size: 1. Methodology. *Br J Obstet Gynaecol* 1994; **101**: 29–34.
12. Royston P, Wright EM. How to construct 'normal ranges' for fetal variables. *Ultrasound Obstet Gynecol* 1998; **11**: 30–38.
13. Silverwood R, Cole TJ. Statistical methods for constructing gestational age-related reference intervals and centile charts for fetal size. *Ultrasound Obstet Gynecol* 2007; **29**: 6–13.
14. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307–310.
15. Comité National Technique de l'Echographie de Dépistage Prénatal. Rapport du comite national technique de l'echographie de depistage prenatal. 2005; 81.
16. Miller SP, Shevell MI, Patenaude Y, Poulin G, O'Gorman AM. Septo-optic dysplasia plus: a spectrum of malformations of cortical development. *Neurology* 2000; **54**: 1701–1703.
17. Malinger G, Lev D, Kidron D, Heredia F, Hershkovitz R, Lerman-Sagie T. Differential diagnosis in fetuses with absent septum pellucidum. *Ultrasound Obstet Gynecol* 2005; **25**: 42–49.
18. Belhocine O, Andre C, Kalifa G, Adamsbaum C. Does asymptomatic septal agenesis exist? A review of 34 cases. *Pediatr Radiol* 2005; **35**: 410–418.
19. Birkebaek NH, Patel L. Optic nerve size evaluated by magnetic resonance imaging in children with optic nerve hypoplasia, multiple pituitary hormone deficiency, isolated growth hormone deficiency, and idiopathic short stature. *J Pediatr* 2004; **145**: 536–541.
20. Adamsbaum C, Chaussain JL. Diagnostic strategies in pediatric imaging. *Horm Res* 1996; **46**: 165–169.
21. Hellstrom A, Aronsson M, Kyllerman M, Kopp S, Steffenburg S, Strömland K, Westphal O, Wiklund L, Albertsson Wickland K. Children with septo-optic dysplasia – how to improve and sharpen the diagnosis. *Horm Res* 2000; **53** (Suppl. 1): 19–25.
22. Celentano C, Prefumo F, Liberati M, Tartaro A, Gallo G, Lattanzio G, Rotmensch S. Prenatal diagnosis of septal agenesis with normal pituitary function. *Prenat Diagn* 2006; **26**: 1075–1077.