

Sonographic biometrical range of external genitalia differentiation in the first trimester of pregnancy: analysis of 2593 cases

V. Mazza^{1*}, I. Di Monte¹, M. Pati¹, G. Contu¹, C. Ottolenghi², A. Forabosco³ and A. Volpe¹

¹*Obstetric and Gynecology Unit, Department of Obstetric, Gynecologic and Pediatric Sciences, Modena and Reggio Emilia University, Modena, Italy*

²*Lab of Genetics, NIH/NIA, IRP, Baltimore, USA*

³*Medical Genetics Unit, Department of Obstetric, Gynecologic and Pediatric Sciences, Modena and Reggio Emilia University, Modena, Italy*

Objectives The aim of this study was to establish the accuracy of fetal gender assignment by sonography in the biometrical range of 18 to 29 mm of biparietal diameter (BPD).

Methods Transvaginal and/or transabdominal sonography was used to detect the sagittal sign as a marker of fetal gender in 2593 fetuses with BPD between 18 and 29 mm. The results of sonographic examination were compared with the gender at birth or with karyotype obtained from amniotic fluid cells or chorionic villus sampling.

Results Fetal gender assignment was feasible in 2374 of 2593 cases (91%). Of the 2188 fetuses with known fetal sex outcome, 1025 were males and 1157 were females, and 6 had genital anomalies. In fetuses without genital anomalies, an accuracy rate of 100% was achieved at a BPD of ≥ 24 mm. The results of the six cases with genital malformations were considered separately.

Conclusion Sonography is a reliable method for the study of the morphological development of the external genitalia in fetuses 'in vivo'; it is possible to assign fetal gender in 95 to 99% starting at a BPD of 20 mm and to achieve an accuracy rate of 99 to 100% from a BPD of 22 mm, but fetal sex assignment should not be undertaken below a BPD of 22 mm, and especially not in cases where fetal sexing affects pregnancy management. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS: fetal gender; prenatal diagnosis; sonography; biparietal diameter

INTRODUCTION

The knowledge of embryo-fetal gender is instrumental in prenatal screening of X-linked diseases and inherited sex-limited disorders in general, as well as for direct diagnosis of both isolated and syndromic sexual developmental anomalies (Mandell *et al.*, 1995; Sivan *et al.*, 1995; Mazza *et al.*, 2002a, 2003; Pinhas-Hamiel *et al.*, 2002). Noninvasive techniques such as sonography can be helpful to determine whether a pregnancy is at risk for disease, thereby requiring additional invasive testing (Mazza *et al.*, 2002b).

While the most conspicuous derivative of internal genitalia, the uterus, is not amenable to sonographic analysis until 19 weeks' gestation (Soriano *et al.*, 1999), external genitalia have been indicated as a useful target for routine investigations and their visualization is now assisted by progress in ultrasound technology.

In 1989, Emerson and colleagues described the 'sagittal sign' as a sonographic marker for the prediction of fetal gender starting from the 14th week of gestation. On the basis of the 'sagittal sign', we initially achieved an

average accuracy of 87% at 18 mm of biparietal diameter (BPD) corresponding to 11⁺⁴ weeks of gestation and of 100% at 23 mm of BPD corresponding to 12⁺⁴ weeks of gestation (Mazza *et al.*, 1999).

As an alternative to Emerson's method, Efrat *et al.* (1999) proposed to measure the angle of the genital tubercle to an horizontal line through the lumbosacral skin profile, achieving, by this method, an average 91% accuracy in gender assignment for the same gestational ages.

Whitlow *et al.* (1999) used an approach that combined sagittal and transverse views of the genitalia. His results reached an accuracy lower than 80% within 13 weeks' gestation and were operator independent. Pedreira (2000) also suggested the use of a transverse plane in order to assign sex with better accuracy and indicated that males could be recognized by the presence of a third echogenic point in addition to two echogenic points or lines that were present in both sexes on this plane. Right assignment varied from 77 to 90% from 11 to 11⁺⁶ weeks to 13⁺⁶ weeks' gestation (average 82%), out of a total 106 pregnancies.

In a small series of fetuses derived from *in vitro* fertilization, an absolute accuracy in gender prediction was achieved at 69 days from fertilization, corresponding to 11⁺⁶ weeks based on the last menstrual period (Mazza *et al.*, 2001).

*Correspondence to: V. Mazza, Dipartimento di Scienze Ostetriche, Ginecologiche e Pediatriche Sez. di Ginecologia e Ostetricia, Università degli Studi di Modena, Via del Pozzo, 71—41100 Modena, Italy. E-mail: mazza@unimo.it

Nowadays, the use of three-dimensional ultrasound for fetal gender determination in the first trimester is increasing. Michailidis *et al.* (2003) report that a correct prediction of fetal gender is achieved in 85% of cases. Lev-Toaff *et al.* (2000) have an accuracy of male and female gender assignment of 100% at 11 to 14 weeks of gestation, but they have only studied ten fetuses in a period of 4 weeks without specifying their distribution in this too large interval.

On the basis of distinct methods, some authors concluded that the sonographic approach may not be sufficiently accurate to be a useful alternative to invasive tests (Whitlow *et al.*, 1999). However, it was noted elsewhere that larger numbers of pregnancies should be tested before any conclusion could be reached on whether and which of these methods would be appropriate (Efrat *et al.*, 1999; Pedreira, 2000).

On the basis of our four-year experience, we present our new and large report about the high accuracy of sonography in noninvasive early fetal gender prediction.

MATERIALS AND METHODS

A total of 2311 pregnant women were examined in our ultrasound unit by the same operator (V.M.) between June 1999 and June 2003.

2035 pregnant women had a single pregnancy and 276 had multiple pregnancies. 270 had twins and 6 had triplets. All triplet pregnancies were trichorionic, whereas of the 270 twin pregnancies, 88 were mono-chorionic and 182 were bichorionic.

A total number of 2593 fetuses have been included in the study. If some of these were examined more than once, only the first examination was included. We have excluded all the pregnancies derived from *in vitro* fertilization because these were in another study, which have been partially published already (Mazza *et al.* 2001). The BPD was measured from the proximal edge to the proximal edge of the fetal skull (outer-inner) in a transaxial plane.

Ultrasound examination was performed using an ESAOTE AU4 machine (Genoa, Italy) with a transabdominal transducer of 5 MHz and a transvaginal transducer of 6.5 MHz frequency, and by an Acuson Sequoia

(Mountain View, CA, USA) with a transabdominal transducer of 6 MHz and a transvaginal transducer of 8 MHz frequency, and a Philips HDI 5000 Sono CT (Bothell, WA, USA) with a broadband transabdominal transducer of 5-2 MHz and a broadband transvaginal transducer of 8-4 MHz.

Transabdominal or transvaginal ultrasound investigation, or both, were performed in order to obtain a correct sagittal section. Ultrasound criteria according to Emerson *et al.* (1989) and Mazza *et al.* (1999) were used for fetal sex assignment. Briefly, the sagittal sign is obtained by fetal scanning in the midline sagittal plane. Following around the contour of the rump, from dorsal to ventral, a focal bulge reflecting the penis or clitoris is encountered ventrally. A 'caudal acute angle' between the axis of the ventral surface of the fetus and the long axis of the clitoris indicates female genitalia, whereas a 'cranial acute angle' between the axis of ventral surface of the fetus and the long axis of the penis indicates male genitalia.

The fetal gender defined by sonography was compared to neonatal sex at birth or to the karyotype obtained from amniotic fetal cells or chorionic villus sampling (CVS).

Cross-tabulations about the ratio between assigned and real sex allowed us to evaluate the method in terms of accuracy for male, female and overall fetal sex prediction.

The accuracy for the male was defined as the number of male fetuses correctly identified (true males) relative to the total number of males. The accuracy for the female was defined as the number of female fetuses correctly identified (true females) out of the total number of females.

The results were then stratified for BPD values. The overall accuracy rate was calculated as the total number of correct fetal sex assignments divided by the total number of examinations when fetal sex assignment was possible.

RESULTS

Of the 2593 investigated fetuses, sex assignment was possible in 2374 cases, with a failure rate of 9%.

Of the 2374 cases assigned, 186 (7.8%) were lost to follow-up.

Table 1—Gender assignment by sonography in genital anomalies (6 cases)

Genital anomalies	1st sonographic gender assignment	Karyotype	2nd sonography gender assignment	Phenotype	Figure
FPH (LP)	Male BPD: 23 mm	Female	Male (2nd trimester)	Male	1
MPH (PGD)	Female BPD: 21 mm	Male	Female (2nd trimester)	Female	2
Penoscrotal transposition	Female BPD: 23 mm	Male	Male with micropenis (2nd trimester)	Male with penoscrotal transposition	3
Bladder exstrophy	Female BPD: 23 mm	Male	Male with epispadias and bladder exstrophy (2nd trimester)	Male	4
Bladder exstrophy	Male BPD: 23 mm	Not performed	Not performed	Male with epispadias and bladder exstrophy	
Hypospadias	Male BPD: 23 mm	Not performed	Male with hypospadias (3rd trimester)	Male with hypospadias	5

FPH, female pseudohermaphroditism; LP, luteoma of pregnancy; MPH, male pseudohermaphroditism; PGD, partial gonadal dysgenesis.

Of the remaining 2188 fetuses with known fetal sex outcome, 1025 were males and 1157 were females, and 6 had genital anomalies. The data of these six cases are separately described in Table 1.

In all the multiple pregnancies, examined once in this study, the agreement between the assigned and the real gender concern both the two fetuses of the twin pregnancy and all the three fetuses of the triplet ones.

In the 2182 cases without genital anomalies, considering fetal gender assignment in relation to BPD, this increased from 60% at 18 mm to 98% at 22 mm of BPD (Table 2).

The accuracy of male prediction was of 32% at 18 mm and reached 100% at 22 mm of BPD. The accuracy for female was of 97% at 18 mm and reached 100% at 24 mm BPD.

The overall accuracy increased from 74% at 18 mm to 100% at 24 mm of BPD or greater (Table 3).

The discrepancies between real and assigned gender demonstrated that female gender was documented in

Table 2—Fetal gender assignment in relation to biparietal diameter (2593 cases)

BPG (mm)	Cases (n°)	Assigned (n°)	%	Follow up (n°)
18	332	201	60	175
19	249	220	88	195
20	230	221	96	207
21	277	263	95	244
22	306	300	98	280
23	301	295	98	282
24	228	221	97	212
25	203	197	97	184
26	172	168	98	155
27	107	104	97	92
28	95	92	97	84
29	93	92	99	78
Total	2593	2374	91	2188

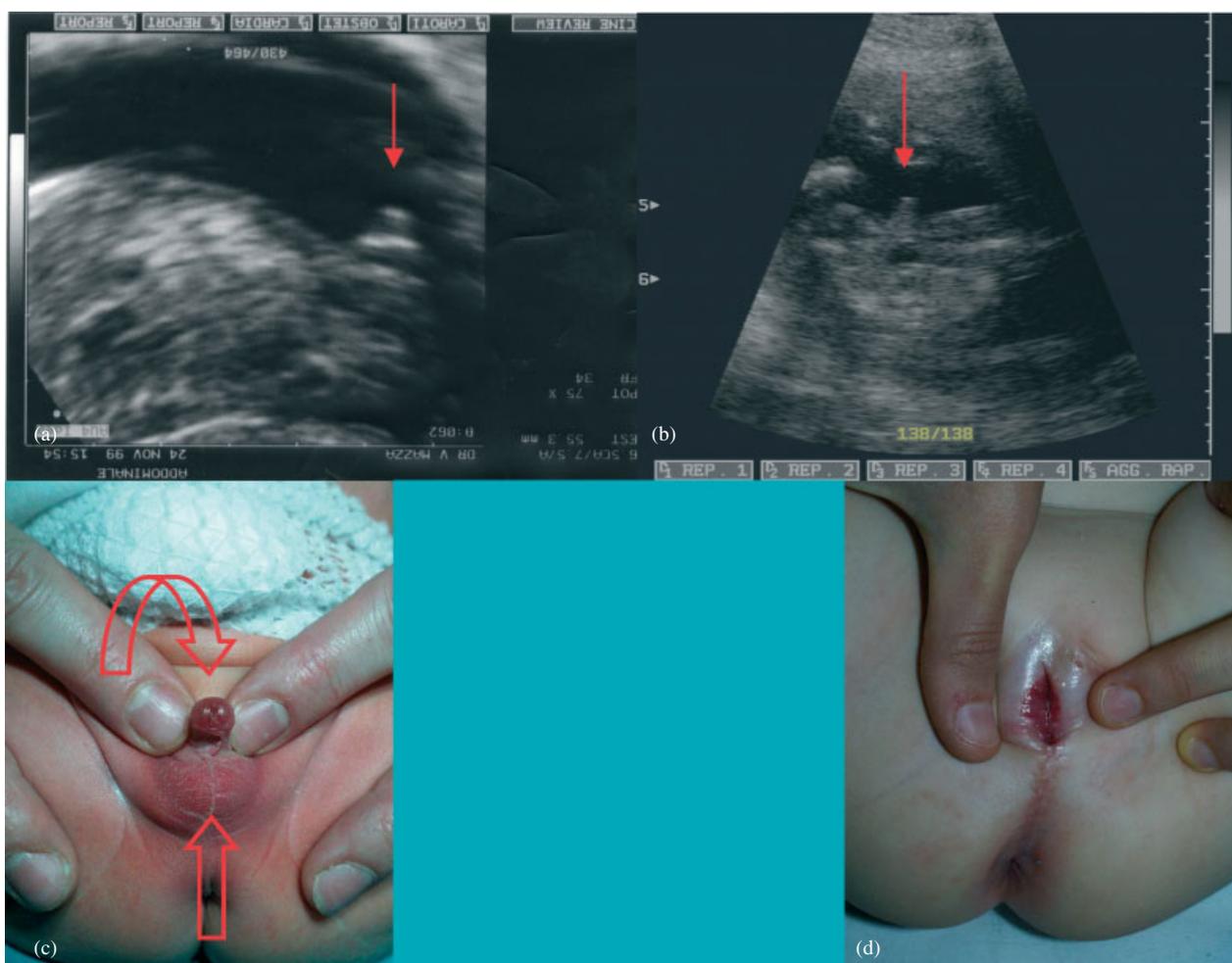


Figure 1—Sonography for the fetal gender assignment. (a) Sagittal section of external genitalia at 23 mm of BPD. The red arrow points to the bulge/penis: male gender assignment. (b) Coronal section of external genitalia at 22 weeks gestation. The red arrow points the penis and the scrotum-like structures: male gender assignment. (c) External genitalia of the girl at birth with a complete masculinization (Prader, 1986). The straight arrow indicates the completely fused labioscrotal-swellings, the curved arrow indicates the urethral meatus opening at the apex of the penis. (d) External genitalia after feminizing genitoplasty. Mazza *et al.* Prenatal diagnosis of female pseudohermaphroditism associated with bilateral luteoma of pregnancy: case report. *Human Reproduction*, 2002, **17**: 821–824. European Society of Human Reproduction and Embryology. Reproduced by permission of Oxford University Press/Human Reproduction

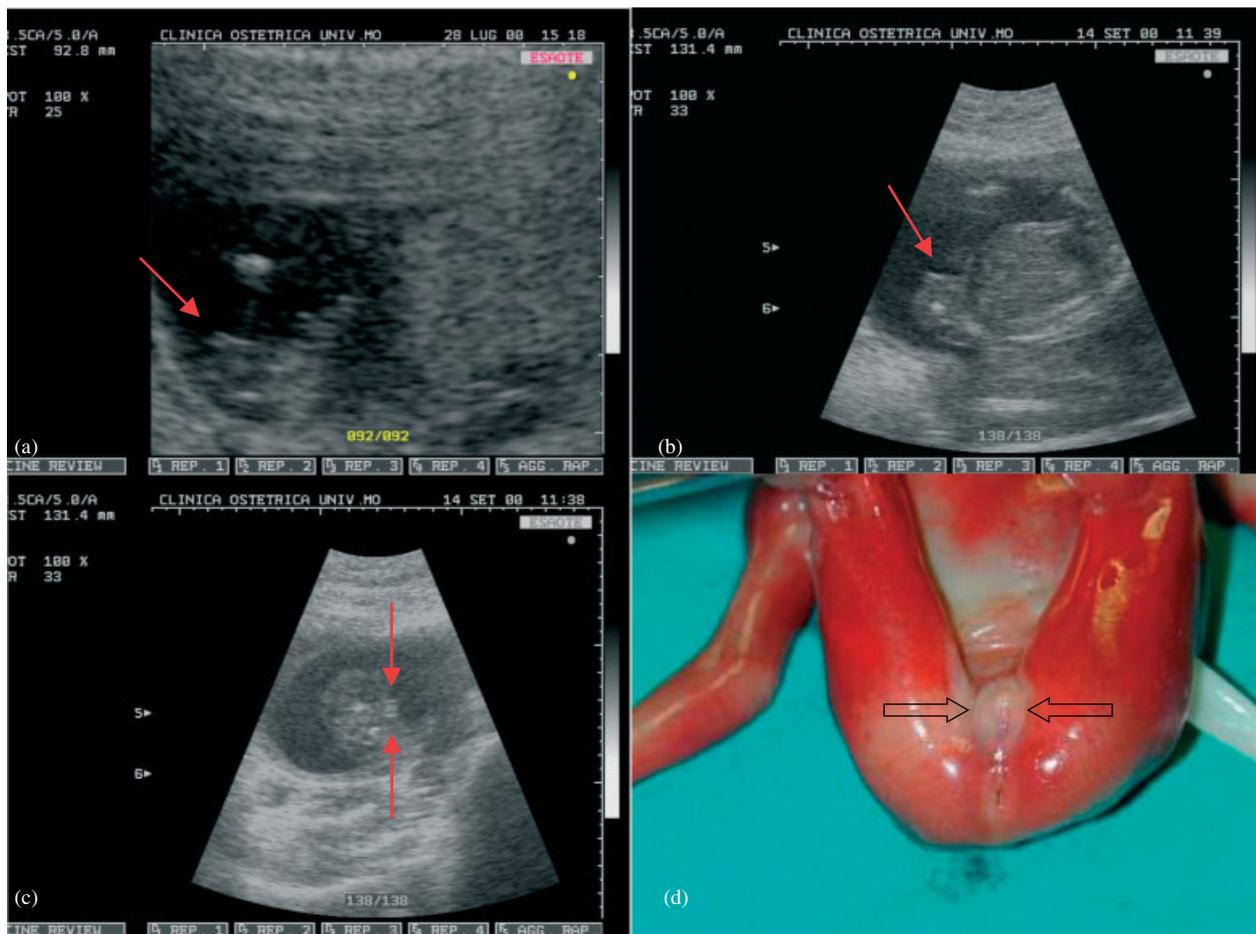


Figure 2—Sonography for fetal gender assignment. (a,b) Sagittal section of external genitalia at 21 mm and 41-mm BPD respectively. The arrows point to the bulge/clitoris. (c) Coronal section of external genitalia at 41 mm of BPD. The arrows point to the labia majora and minora. (d) External genitalia of the fetus with 46 XY, partial gonadal dysgenesis after therapeutic abortion. The arrows point to the unfused labia majora. Early prenatal diagnosis of recurrent 46, XY partial gonadal dysgenesis. Mazza *et al.* 2003. *Prenatal Diagnosis* 23(9): 716–721. Copyright John Wiley & Sons Ltd. Reproduced with permission

Table 3—Accuracy of fetal gender assignment (in 2182 cases without genital anomalies) in relation to biparietal diameter

BPD (mm)	Male accuracy		Female accuracy		Total accuracy	
	Cases (n°)	%	Cases (n°)	%	Cases (n°)	%
18	26/82	32	90/93	97	175	74
19	56/91	62	101/104	97	195	84
20	78/99	79	106/108	98	207	91
21	100/116	87	127/127	100	243	94
22	135/135	100	144/145	99	280	99
23	133/133	100	143/144	99	277	99.5
24	103/103	100	109/109	100	212	100
25	90/90	100	94/94	100	184	100
26	38/38	100	82/82	100	155	100
27	46/46	100	46/46	100	92	100
28	50/50	100	50/50	100	84	100
29	42/42	100	55/55	100	78	100
Total	1025		1157		2182	

male fetuses in 128/388 cases (33%) more frequently than male gender being documented in a female fetuses in 10/721 cases (1.4%).

The BPD in all these cases was between 18 and 23 mm.

DISCUSSION

In humans, sexual development is genetically determined and requires appropriate differentiation of the gonads in order to acquire a sexually dimorphic phenotype (George and Wilson, 1994).

Secretion of at least three testicular hormones: Anti-Müllerian Hormone (AMH), testosterone (T) and insulin like Hormone (INSL 3) is necessary for proper male sexual development, whereas *in utero* hormonal requirement for fetal feminization is not conspicuous and still debated (Nef and Parada, 2000). Testis sexual dimorphism becomes histologically apparent at 6 to 8 weeks' gestation. By about 12 weeks in human male embryos, secretion of AMH has induced regression of Müllerian derivatives, which otherwise will generate uterus and tubes (Jost, 1972). INSL3 induces proper transabdominal migration of testes (Nef *et al.*, 1999), and testosterone and/or other androgens are required for the development

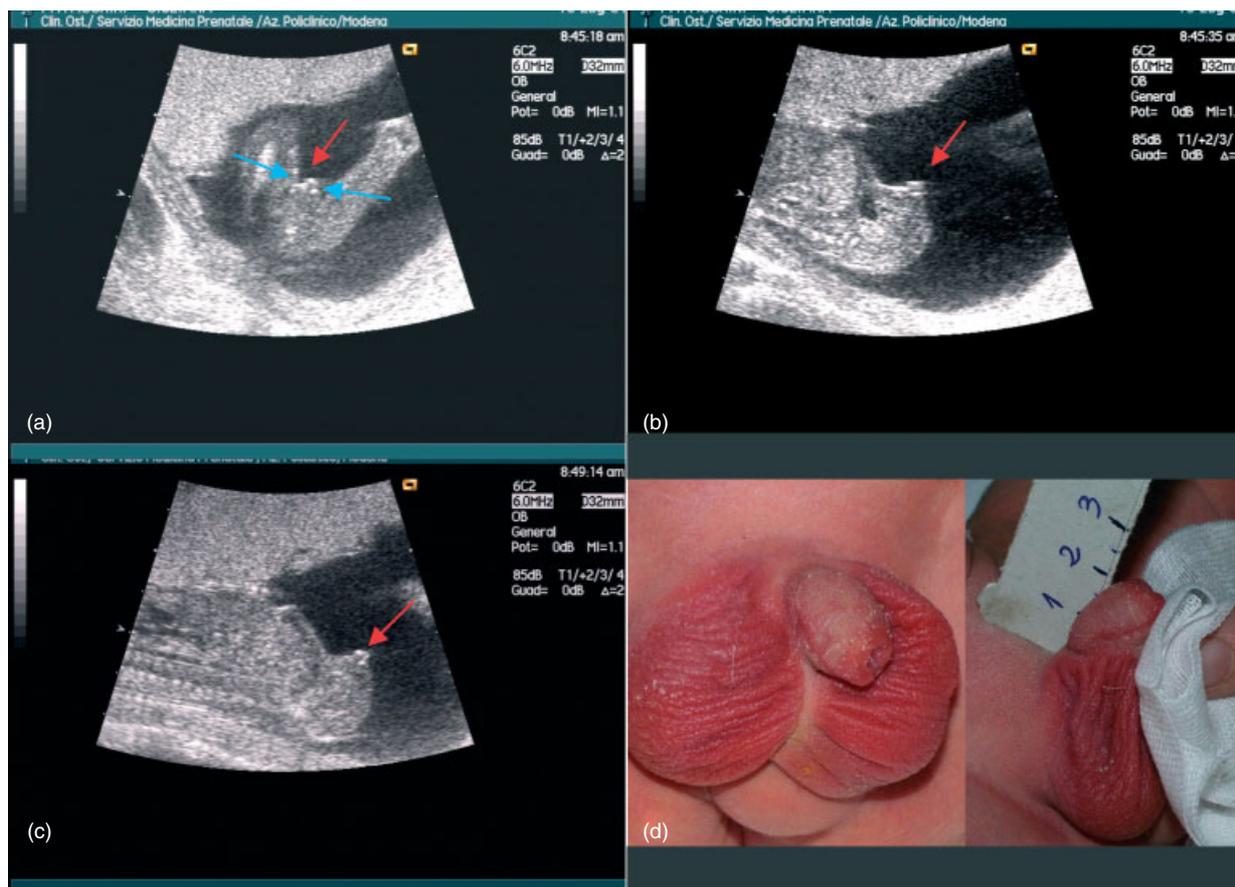


Figure 3—*Penoscrotal transposition*. (a) Coronal section and (b,c) sagittal section of the external genitalia of the fetus at 35 mm of BPD, erroneously assigned as female at 23 mm of BPD. (a) The red arrow points to the micropenis-like structure. The green arrows point to the unfused hemiscrotum. (b,c) Sagittal section. The arrow point to the micropenis like-structure. (d) The external genitalia at birth

of male internal and external genitalia (Wilson *et al.*, 2002).

In our study, we have evaluated a large number of cases, about 2500, in a strict biometrical range (from 18 to 29 mm of BPD) so that we have been able to observe the development of male genitalia.

We have used the sagittal sign for the gender assignment.

At early gestational age, in some cases, a notch could be seen both caudally and cranially depending on the orientation of the ultrasound beam on the very small target. This led to no or mis-assignment of gender in a proportion of cases that was high at 18 mm BPD but fell rapidly at 19 mm BPD.

It is likely that the high proportion of unassigned fetuses at early gestational age corresponds to males (whose follow-up is not available), since the sex ratio of assigned fetuses is consistently biased towards females.

Moreover, our high rate of unassigned male fetuses and wrong male assignment of female ones at 18 and 21 mm of BPD can be explained by the observation of Pedreira *et al.* (2001): In 25 percent of the cases he studied, the angle between the phallus and the spine changed during the examination, both for male and female fetuses, as we have also observed in some cases

(Figure 6). The phenomenon was observed at 11 and 12 weeks and in only one case at 13 weeks.

Our data demonstrate how sonographic accuracy is unreliable in the biometrical range 18 to 21 mm of BPD in predicting fetal sex (accuracy for males 32 to 87%). From 22 to 23 mm of BPD, the accuracy reached 99.5% because of two misdiagnosis: A female fetus assigned as male, that we can consider as an operator's mistake, and a male fetus assigned as female, that can be interpreted as a delay in male differentiation (Figure 7).

From 24 mm of BPD, a perfect concordance with an accuracy rate of 100% exists.

As we know, the interest in the morphogenesis of the external genitalia in the human embryo/early fetus arose in the early part of the last century.

Besides, many authors (Herzog, 1904; Spaulding, 1921) asserting that through the identification of the external genitalia it was possible to recognize the sex of an embryo/early fetus at about the beginning of the third month, Wilson in 1926 demonstrated that these results were inaccurate. He studied some of Spaulding's embryos/early fetuses of the Carnegie Laboratory of Embryology, not limiting himself to make a diagnosis of sex from an evaluation of the external genitalia but histologically examining the early fetal gonads. He concluded that 'while it is true that in this rather large

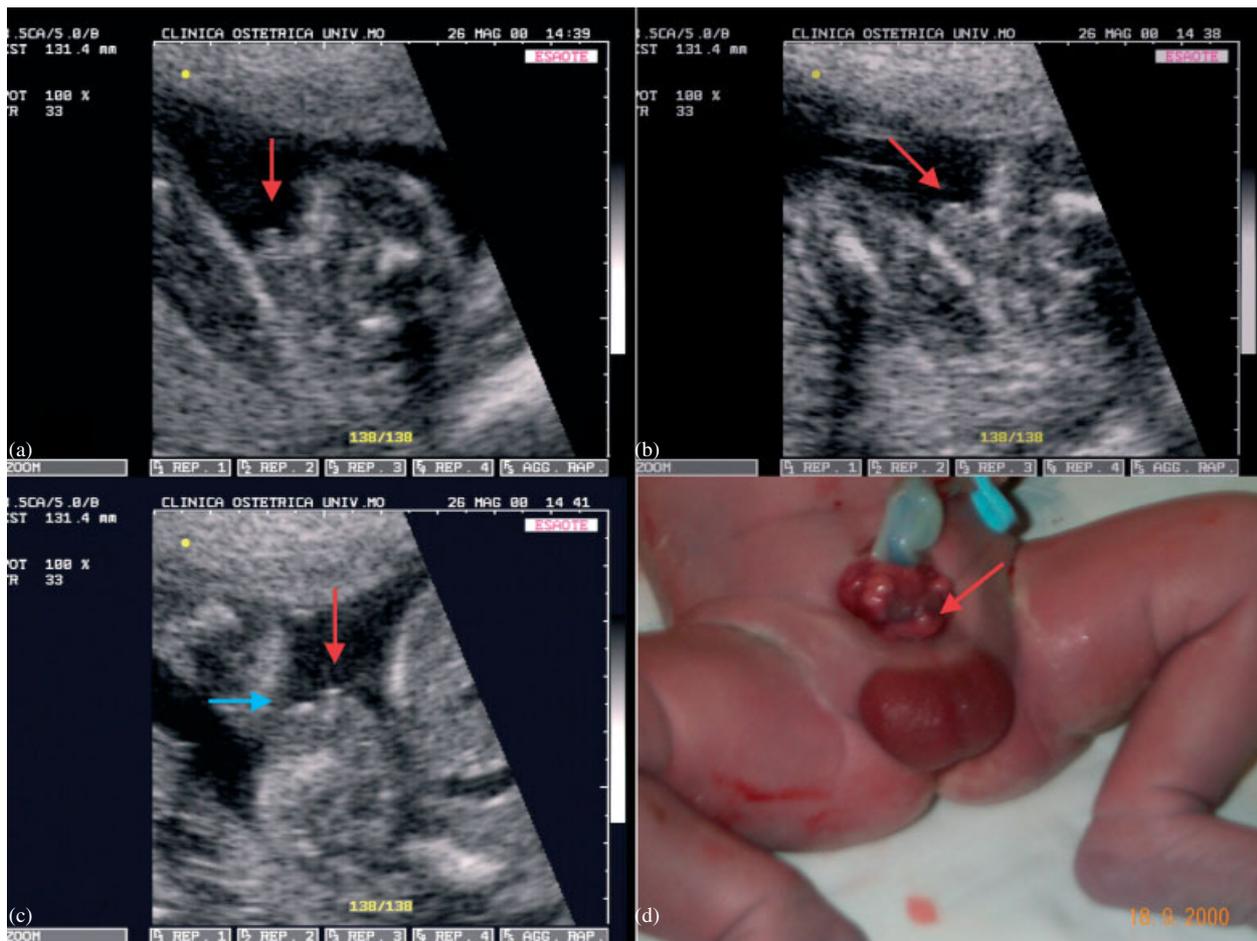


Figure 4—Bladder exstrophy. (a,b) coronal section (c) sagittal section of the external genitalia in the fetus at 21 weeks of gestation with bladder exstrophy erroneously assigned as female at 23 mm of BPD. (a,b) Ambiguous genitalia with a penis like-structure (red arrow). (c) The arrow points a scrotum like-structure. (d) External genitalia with bladder exstrophy at birth. The arrow points to a penis with complete epispadias



Figure 5—Hypospadias. Sagittal section of the penis in the third trimester: the curved arrow indicates an anomalous distal morphologic characteristic with ventral incurving of the penis. The fetus was correctly assigned as male at 23 mm of BPD

series of specimens the diagnosis of sex, made from an examination of the external genitalia, has been confirmed in a fairly high percentage of the specimens by an

examination of the gonads, on the other hand a high percentage of error has also been noted, the errors in diagnosis being particularly numerous in embryos from 21 mm to 40 mm in length'. According to him, it is quite impossible to diagnose the sex of a given embryo/early fetus by examination of the sex of a given embryo/early fetus until the embryo/early fetus has attained a crown-rump length of 50 mm and, as revealed by histological study of the gonads, the errors have been in diagnosing males as females. This fact would apparently indicate that in many instances, the development and differentiation of the external genitalia are markedly retarded as compared with the development of the gonads and particularly so in the male embryo/early fetuses.

In 1997, Ammini agreed with Wilson that differential development (female/male) started after 50 mm. He studied 97 embryos/early fetuses obtained after medical termination of unwanted pregnancies in the range of 15 to 30 to 221 to 250 mm of crown rump length (CRL) corresponding to 6 to 26 weeks' period. As we know, moreover, there is not a reliable correlation between biometrical data in fixed fetuses and in fetuses obtained by artificially induced abortion (Iffy *et al.*, 1967; Jakobovits *et al.*, 1972).



Figure 6—Change with time in the angle between bulge/penis-clitoris and ventral surface. Sagittal section of external genitalia at 19 mm of BPD. (a) the angle between the ventral surface and the long axis of the bulge/penis suggests male gender assignment. (b) After 47 seconds there is a slight change in orientation of the bulge/clitoris with evident caudal notch, that suggests female gender assignment. (c) At 16 weeks' gestation: male gender assignment confirmed by karyotype



Figure 7—Sonography for fetal gender assignment. (a) External genitalia of the fetus at 23 mm of BPD, assigned as female according to the 'sagittal sign'. The red arrow points to the bulge/clitoris. The curved green arrow points to the caudal notch. (b) Sagittal section. The red arrow points to the penis: male gender assignment. Interpretation: delay in male differentiation

We have to say that Wilson and Ammini's studies consider a limited number of cases and they use a biometrical range of distribution that is too wide to make a reliable description of the dynamics of the masculinization phenomena.

Sonography can be used to predict fetal gender in early pregnancy. Moreover, the discordance between the phenotypic fetal gender assigned by sonography and the genotypic sex, as we have described in the case of female pseudohermaphroditism-luteoma of pregnancy (FPH-LP) and of male pseudohermaphroditism-partial gonadal dysgenesis (MPH-PGD), has given us the possibility to make an early correct diagnosis.

On the other hand, in some cases of external genitalia disorders, such as penoscrotal transposition and bladder exstrophy, early fetal gender assignment is of great difficulty (Table 1).

Finally, sonography is a reliable method for the study of the morphological development of the external genitalia in the fetuses 'in vivo'.

We agree with Blaas who has even said that the embryonic development visualized by ultrasound is in

good agreement with 'developmental time schedule' of human embryos, as described in the Carnegie staging system (Blaas, 1999).

In conclusion, our data demonstrate that fetal sex assignment should not be undertaken below a BPD of 22 mm, and especially not in cases where fetal sexing affects pregnancy management, for example, in patients at risk of X-linked disorders and congenital adrenal hyperplasia, since the sex assignment below a BPD of 22 mm is consistently biased towards females.

REFERENCES

- Ammini AC, Sabherwal U, Mukhopadhyay C, Vijayaraghavan M, Pandey J. 1997. Morphogenesis of the human external male genitalia. *Pediatr Surg Int* **12**: 401–406.
- Blaas HG. 1999. The examination of the embryo and early fetus: how and by whom? *Ultrasound Obstet Gynecol* **14**: 153–158.
- Efrat Z, Akinfenwa OO, Nicolaides KH. 1999. First-trimester determination of fetal gender by ultrasound. *Ultrasound Obstet Gynecol* **13**: 305–307.

- Emerson DS, Felker RE, Brown DL. 1989. The sagittal sign. An early second trimester sonographic indicator of fetal gender. *J Ultrasound Med* **8**: 293–297.
- George FW, Wilson JD 1994. *Sex Determination, Differentiation. The Physiology of Reproduction*, Knobil E, Neill ID (eds). Raven Press: New York.
- Herzog F. 1904. Beitrage zur Entwicklungsgeschichte und histologie der mannlichen Harnrohre. *Arch F Mikr Anat* **63**: 710–747.
- Iffy L, Shepard TH, Jakobovits A, Lemire RJ, Kerner P. 1967. The rate of growth in young human embryos of Streeter's horizons XIII to XXIII. *Acta Anat* **66**: 178–186.
- Jakobovits A, Iffy L, Wingate MB, Slate WG, Chatterton RT Jr, Kerner P. 1972. The rate of early fetal growth in the human subject. *Acta Anat* **83**: 50–59.
- Jost A. 1972. A new look at the mechanisms controlling sex differentiation in mammals. *Johns Hopkins Med J* **130**: 38–53.
- Lev-Toaff AS, Ozhan S, Pretorius D, Bega G, Kurtz AB, Kuhlman K. 2000. Three dimensional multiplanar ultrasound for fetal gender assignment: value of the mid-sagittal plane. *Ultrasound Obstet Gynecol* **16**: 345–350.
- Mandell J, Bromley B, Peters CA, Benacerraf BR. 1995. Prenatal sonographic detection of genital malformations. *J Urol* **153**: 1994–1996.
- Mazza V, Contu G, Falcinelli C, et al. 1999. Biometrical threshold of biparietal diameter for certain fetal sex assignment by ultrasound. *Ultrasound Obstet Gynecol* **13**: 308–311.
- Mazza V, Falcinelli C, Paganelli S, et al. 2001. Sonographic early fetal gender assignment: a longitudinal study in pregnancies after *in vitro* fertilization. *Ultrasound Obstet Gynecol* **17**: 513–516.
- Mazza V, Di Monte I, Ceccarelli PL, et al. 2002a. Prenatal diagnosis of female pseudohermaphroditism associated with bilateral luteoma of pregnancy: case report. *Hum Reprod* **17**: 821–824.
- Mazza V, Falcinelli C, Percesepe A, Paganelli A, Volpe A, Forabosco A. 2002b. Non-invasive first trimestre fetal gender assignment in pregnancies at risk for X-linked recessive diseases. *Prenat Diagn* **22**: 919–924.
- Mazza V, Ottolenghi C, Di Monte I, et al. 2003. Early prenatal diagnosis of recurrent 46, XY partial gonadal dysgenesis. *Prenat Diagn* **23**(9): 716–721.
- Michailidis GD, Papageorgiou P, Morris RW, Economides DL. 2003. The use of three-dimensional ultrasound for fetal gender determination in the first trimester. *Br J Radiol* **76**: 448–451.
- Nef S, Parada LF. 1999. Cryptorchidism in mice mutant for Ins13. *Nat Genet* **22**: 295–299.
- Nef S, Parada LF. 2000. Hormones in male sexual development. *Genes Dev* **14**: 3075–3086.
- Pedreira DA. 2000. In search for the 'third point'. *Ultrasound Obstet Gynecol* **15**(3): 262–263.
- Pedreira DA, Yamasaki A, Czeresnia CE. 2001. Fetal phallus 'erection' interfering with the sonographic determination of fetal gender in the first trimester. *Ultrasound Obstet Gynecol* **18**(4): 402–404.
- Pinhas-Hamiel O, Zalel Y, Smith E, et al. 2002. Prenatal diagnosis of sex differentiation disorders: the role of fetal ultrasound. *J Clin Endocrinol Metab* **87**(10): 4547–4553.
- Prader A. 1986. Disorders sexual differentiation (intersexuality). In *Clinical Endocrinology Theory, Practice*, Labhart A (ed.). Springer-Verlag: New York; 715–747.
- Sivan E, Koch S, Reece EA. 1995. Sonographic prenatal diagnosis of ambiguous genitalia. *Fetal Diagn Ther* **10**(5): 311–314.
- Soriano D, Lipitz S, Seidman DS, Maymon R, Mashiach S, Achiron R. 1999. Development of the fetal uterus between 19 and 38 weeks of gestation: in utero ultrasonographic measurements. *Hum Reprod* **14**(1): 215–218.
- Spaulding MH. 1921. The development of the external genitalia in the human embryo. *Contribs Embryol* **13**: 69–88 (Carnegie Inst Wash Publications).
- Whitlow BJ, Lazanakis MS, Economides DL. 1999. The sonographic identification of fetal gender from 11 to 14 weeks of gestation. *Ultrasound Obstet Gynecol* **13**: 301–304.
- Wilson KM. 1926. Correlation of external genitalia and sex-glands in the human embryo. *Contribs Embryol* **91**: 25–30 (Carnegie Inst Wash Publications).
- Wilson JD, Leihy MW, Shaw G, Renfree MB. 2002. Androgen physiology: unsolved problems at the millennium. *Mol Cell Endocrinol* **198**: 1–5.