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Fetal cerebral ventriculomegaly: outcome in 176 cases

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KEYWORDS: cerebral lateral ventricles; fetus; neurodevelopmental outcome; ventriculomegaly

ABSTRACT

Objective *To evaluate the outcome of fetuses affected by different degrees of ventriculomegaly.*

Methods *We studied 176 fetuses with ventriculomegaly and evaluated the pregnancy outcome and the neurodevelopmental outcome at age ⩾ 24 months. The population was divided into three groups according to ventricular width: A (mild ventriculomegaly, 10 to 12 mm); B (moderate, 12.1 to 14.9 mm) and C (severe, ⩾ 15 mm).*

Results *Ventriculomegaly was more often an isolated finding in Group A (44/75; 58.7%) than in Group B (10/41; 24.4%) and Group C (24/60; 40%). When the ventriculomegaly was an isolated finding, 97.7% of fetuses with mild, 80% with moderate and 33.3% of those with severe dilatation were alive at ⩾ 24 months. The neurodevelopmental outcome was normal in 93% of Group A, 75% of Group B and 62.5% of Group C.*

Conclusions *Our results suggest that the definition of borderline ventriculomegaly should be limited to ventricular width below 12 mm. Cases with measurements above this value are more often associated with malformations and have a normal neurodevelopmental outcome less frequently. Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

A standard examination of the fetus includes prenatal sonographic evaluation of the cerebral ventricles, which can be detected as early as 15 weeks' gestational age, and their measurement is part of the assessment of the central nervous system (CNS).

Severe ventriculomegaly (width of the atria of the lateral ventricles ⩾ 15 mm) is often associated with an unfavorable outcome[1]. However, the significance of lesser degrees of dilatation, also called borderline dilatations (between 10 and 15 mm), is still unclear: the dilatation may be associated with structural or chromosomal anomalies, or be a harmless finding with no pathological significance[2–6]. Therefore, the detection of dilatation raises several problems in obstetric management and counseling of prospective parents.

The aim of the present study was to assess the outcome of fetuses with different degrees of prenatally diagnosed ventricular dilatation.

METHODS

We reviewed 204 consecutive cases of ventriculomegaly referred to our ultrasound unit in a 10-year period (June 1990 to June 2000). Twin pregnancies ($n = 14$) and cases with incomplete follow-up ($n = 14$) were excluded, leaving 176 cases for analysis.

Indications for scanning were: suspected ventriculomegaly and/or other CNS malformations in 123 cases (70%), suspected non-CNS malformations in 30 cases (17%) and no risk factors (routine scanning) in 23 cases (13%). The scans were performed transabdominally with different ultrasound equipment: Aloka SSD-680, Aloka SSD-1700 (Aloka Company Ltd, Tokyo, Japan), ATL 3000 and ATL 5000 (Advanced Technology Laboratories, Bothwell, WA, USA). Ventriculomegaly was defined as the diameter of one or both lateral ventricles ⩾ 10 mm. The ventricular atria were measured on an axial plane at the level of the thalami by positioning electronic calipers on the internal margins of the ventricular wall perpendicular to the long axis of the ventricles[7].

In each case, a thorough sonographic evaluation of fetal anatomy was performed, including fetal echocardiography. Information about the fetal karyotype was available in 152 cases. Twenty-four mothers refused the cytogenetic analysis (17 had a normal child and seven had the pregnancy terminated because of multiple malformations of the fetus). Screening for infections (TORCH)

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was performed in only 30 cases. Data on pregnancy outcome were available in all cases: spontaneous miscarriage, termination of pregnancy (TOP), type of delivery, perinatal, neonatal and infant morbidity and mortality. In cases of miscarriage, TOP, neonatal or infant death the postmortem examination was available. A detailed clinical examination and instrumental examination, where appropriate, were obtained in liveborn infants. All the surviving neonates were at least 24 months old at the time of the study (range, 2–12 years).

Data on their neurodevelopmental condition were obtained in structured interviews with the parents. The questionnaire included the evaluation of: locomotor activities and co-ordination of movements; hearing and visual capacity (also activity of the oculomotor muscles); development and quality of speech and socialization skills; learning performance; evolution of diagnosed anomalies or new pathologies and their therapies (often chronic) (Figure 1).

We defined severe neurodevelopmental outcomes as: cerebral palsy (with or without the need for orthopedic help, urinary incontinence, daily enemas, etc.), epilepsy, bradyacusia with prothesis, mono/bilateral blindness and mental retardation. Mild anomalies were: moderate motor skill problems (with or without tone and reflex anomalies), squint, nystagmus, mild speech difficulty, moderate learning problems and ventricular-peritoneal shunt with normal motor development[8].

The population was divided into three groups according to the degree of ventricular dilatation: mild, from 10 to 12 mm (Group A), moderate, from 12.1 to 14.9 mm (Group B), and severe, $\geqslant 15$ mm (Group C). There were 75 cases (43%) in Group A, 41 (23%) in Group B and 60 (34%) in Group C. Outcomes in the three groups were compared by means of χ^2 test and Fisher's exact test.

QUESTIONNAIRE

Assessment of locomotor activity:

1) When did he/she begin crawling?
2) When did he/she begin to walk alone?
3) When did he/she start running?
4) Did he/she have any difficulty with hand use?
5) Did he/she ever have motor co-ordination problems (for instance when he/she was playing, running….)?
6) Did he/she have any difficulty with sitting?

Assessment of eye and hand co-ordination:

1) Did/Does he/she ever have visual disorders? If yes, of what degree?
2) Does he/she wear glasses? If yes, why?
3) Does he/she have ocular motility problems? If yes, which ones?
4) Does he/she have problems writing and/or drawing?
5) Is he/she able to reproduce with the drawing the images that are shown to him/her?

Assessment of hearing and speech capacity:

1) Did he/she ever have hearing disorders? If yes, what?
2) Must he/she use acoustic devices?
3) When did he/she start speaking?
4) Is he/she able to make him/herself understood?
5) Did he/she ever have language problems? If yes, is he/she supported by a speech therapist? How many times a week/month?

Assessment of learning performance:

1) Did/Does he/she go to kindergarten?
2) Did he/she regularly begin school? If not, how many years late did he/she begin school?
3) Has he/she ever been rejected at school?
4) Does he/she need a support teacher? If yes, how many times a week/month?
5) Does he/she find it difficult to study at home?
6) Does he/she have socialization problems (i.e. play with children)?
7) Is he/she able to memorize things?

Others:

1) From 3rd to 5th year of life, did he/she acquire the capacities to eat alone, to dress and wash him/herself?
2) Towards 2 years of age did the child acquire complete bowel control? And bladder control by day?
3) Does the child use walkers?
4) Does the child require bladder catheterizations and/or enemas? If yes, how many times a day?

Figure 1 Questionnaire on the neurodevelopmental condition of the surviving neonates.

RESULTS

The median gestational age at diagnosis of ventriculomegaly was 24 (range, 15–36) weeks in Group A, 29 (range, 16–39) weeks in Group B and 25 (range, 15–39) weeks in Group C. The number of cases diagnosed before 24 weeks was significantly higher ($P = 0.003$) in Groups A (46/75; 61%) and C (34/60; 57%) than in Group B (12/41; 29%). Different outcomes of the total population are summarized in Figure 2.

Ventriculomegaly was more often an isolated finding in Group A (44/75; 58.7%) than in Group B (10/41; 24.4%) ($P < 0.001$) and Group C (24/60; 40%) ($P = 0.047$). Structural and/or chromosomal anomalies were found in 31 fetuses (41.3%) of Group A, 31 (75.6%) of Group B and 36 (60%) of Group C (Table 1). All the malformations were diagnosed *in utero*, although not always at the first examination. In Group A, there were three cases of chromosomal anomalies not associated with structural malformations; the maternal age in these three cases was 25, 30 and 42 years. The ventriculomegaly was unilateral in five cases: four in Group A, one of which had associated malformations (spina bifida), and one in Group B (associated with a nasopharyngeal tumor).

Seven fetuses (23% of the 30 that were tested) presented with an underlying infection: five due to cytomegalovirus (two in Group A, one in Group B and two in Group C) and two due to *Toxoplasma gondii* (both in Group C). Major sonographic anomalies (hydrops, ascites, cerebral calcifications) were present in all these cases. The male/female ratio was close to 1 in Groups B and C, while males outnumbered females in Group A (46 vs. 29).

TOP was chosen in 65 cases (37% of the total population; 64% of the malformations diagnosed before

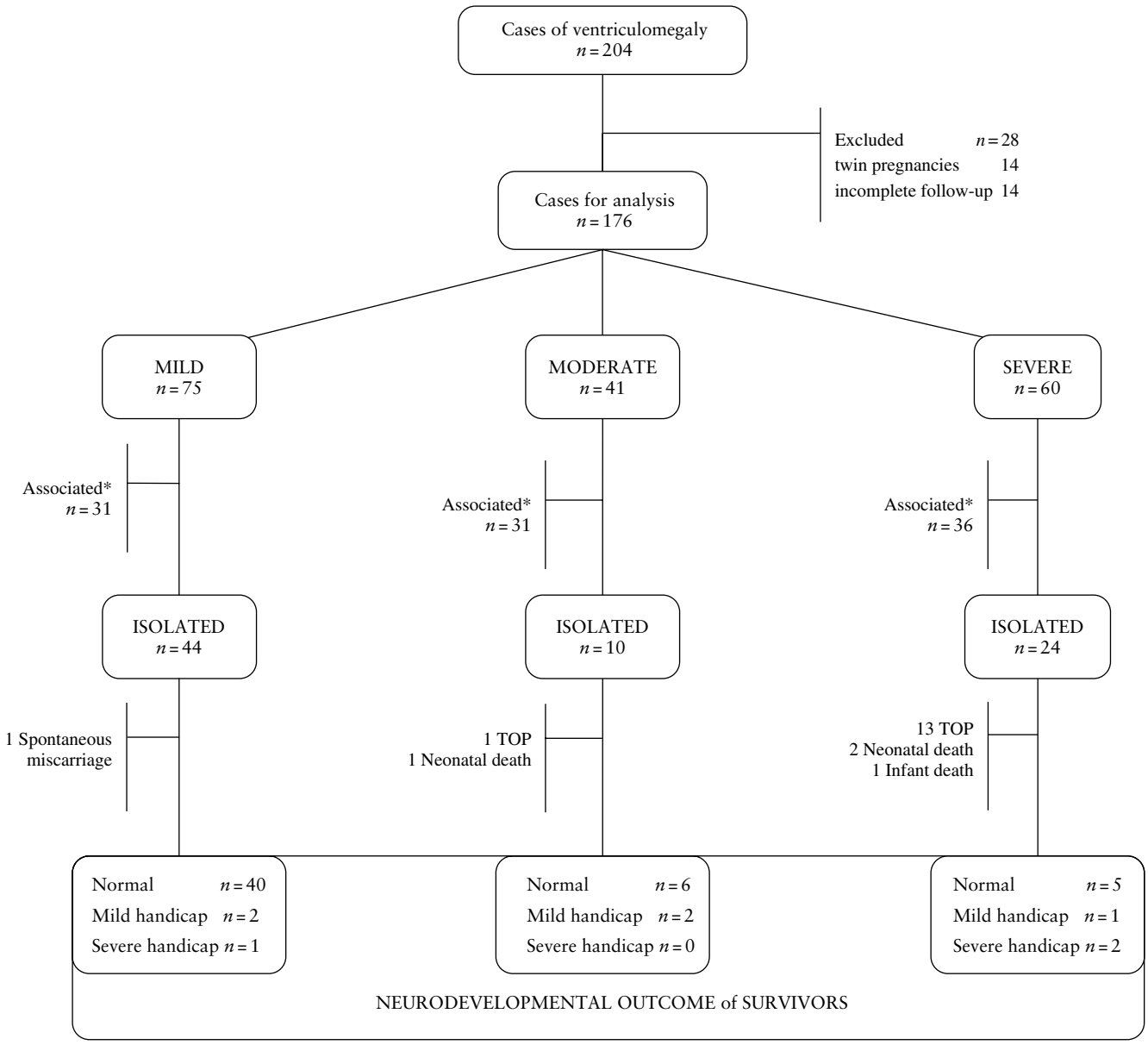

Figure 2 Flow chart showing the different outcomes of the total population. *Associated with structural and/or chromosomal malformations (see Table 1). TOP, termination of pregnancy.

24 weeks). Almost half of them (31) were in Group C, 22 in Group A and 12 in Group B. In 14 cases, ventriculomegaly was the only finding and 13 of them were in the severe form. Data on TOP, spontaneous miscarriage, intrauterine death, neonatal death and infant death in each group are reported separately for cases of isolated and non-isolated ventriculomegaly (Table 2).

Since the outcome in cases with structural and/or chromosomal anomalies depends on the type of the associated malformations, we further considered outcome data only for isolated cases. When ventriculomegaly was an isolated finding, 97.7% of fetuses with mild, 80% of those with moderate and 33% of those with severe dilatation were alive at $\geqslant 24$ months. The neurodevelopmental outcome at the age of $\geqslant 24$ months was normal in 93%, 75% and 62.5% of the surviving neonates, respectively (Table 3). There were two cases of mild handicap in Group A (language problems requiring a speech therapist; nystagmus), two cases in Group B (mild intellective impairment requiring a delay in starting primary school and the need for a support teacher; ventriculoperitoneal shunt with normal neurodevelopmental outcome and mild strabismus) and one in Group C (hydrocephalus with ventriculoperitoneal shunt and mild neurodevelopmental delay at 1 year of age).

Among the 106 liveborn fetuses, the ventricular dilatation improved and eventually disappeared during intrauterine life in 50 cases, remained unchanged in 37 cases and increased in 19 cases. A normal outcome was found significantly more often when ventriculomegaly improved (92%) than when it remained unchanged (35%) ($P < 0.001$) or worsened (21%) ($P < 0.001$) (Table 4).

Table 1 Structural and chromosomal anomalies in Groups A, B and C

Group	*No. of cases*	*Structural malformations*	*Chromosomal anomalies*
A	3		47,XY,+21
			47,XX,+21
			47,XX,+21
	5	Omphalocele, ascites, heart malformations	47,XY,+18
		Pyelectasis (Potter 4)	46,XY/47,XY,+8 (mosaicism)
		Clinodactyly, dysmorphia	47,XX,+21
		Common atrioventricular canal	47,XX,+21
		Brachycephaly, single umbilical artery, polydactyly, VSD, Dandy–Walker syndrome	47,XY,+13
	5	Spina bifida/myelomeningocele	
	4	Agenesis of the corpus callosum	
	3	Dandy–Walker syndrome	
	1	Cerebral hemorrhage	
	10	Non-CNS malformations: multiple malformations (7), congenital heart disease (1), others (2)	
B	1	Closed choanas, hand deformations, renal cysts and pyelectasis, heart anomalies	47,XY,+21
	10	Spina bifida/myelomeningocele	
	6	Agenesis of the corpus callosum	
	2	Dandy–Walker syndrome	
	3	Other CNS malformations: nasopharyngeal tumor, cephalocele, pachygyria	
	9	Non-CNS malformations: genetic syndromes (5), multiple malformations (3), congenital heart disease (1)	
C	2	Dysmorphia, sacral meningocele	47,XXX
		Dysmorphia, clubfoot, claw hands (Klinefelter)	47,XXY
	10	Spina bifida/myelomeningocele	
	11	Agenesis of the corpus callosum	
	1	Dandy–Walker syndrome	
	1	Cerebral hemorrhage	
	1	Heterotopia	
	10	Non-CNS malformations: multiple malformations (8), diaphragmatic hernia (1), esophageal atresia (1)	

CNS, central nervous system; VSD, ventricular septal defect

Table 2 Outcome of 176 fetuses with ventriculomegaly

	Group A (75)		*Group B (41)*		*Group C (60)*		
	Isolated (44)	*Associated (31)*	*Isolated (10)*	*Associated (31)*	*Isolated (24)*	*Associated (36)*	*Total (176)*
Termination of pregnancy	0	22	1	11	13	18	65
Spontaneous miscarriage	1	2	0	1	0	1	5
Intrauterine death	0	0	0	0	0	0	0
Neonatal death	0	2	1	2	2	2	9
Infant death	0	0	0	2	1	1	4
Alive at $\geqslant$ 24 months of age	43	5	8	15	8	14	93

DISCUSSION

Abnormal dilatation of the cerebral lateral ventricles was one of the first malformations to be recognized prenatally in the late seventies. The diagnosis of hydrocephaly was made when the ventricle/hemisphere ratio was above the upper limits of reference ranges. Subsequent studies characterized the *in utero* growth of different parts of the ventricular system and reference values of ventricular width were established throughout pregnancy[7,9–11]. The accepted standard today is the measurement of atrial width at the level of the choroid plexus.

Table 3 Neurodevelopmental outcome of survivors with isolated ventriculomegaly

Outcome n *(%)*	*A*	*B*	*C*
n	43	8	8
Normal	40* (93)†	6 (75)	5 (62.5)†
Mild handicap	2 (4.6)	2 (25)	1 (12.5)
Severe handicap	1‡ (2.3)	0 (0)	2 (25)

*Three cases of unilateral ventriculomegaly. †Group A vs. C, $P = 0.042$. ‡A case of retinoblastoma.

Table 4 Outcome of the liveborn fetuses according to the evolution of ventriculomegaly *in utero*

Evolution of ventriculomegaly	*Normal*	*Mild handicap*	*Severe handicap*	*Dead*	*Total (106)*
Improved in:					
Group A	37	2	1		40
Group B	5	1			6
Group C	4				4
Total *n* (%)	46 (92)	3 (6)	1 (2)		50
Stable in:					
Group A	7		1	2	10
Group B	2	1	7	4	14
Group C	4	1	3	5	13
Total *n* (%)	13 (35)	2 (5)	11 (30)	11 (30)	37
Worsened in:					
Group A					0
Group B	2	1	4	1	8
Group C	2	1	7	1	11
Total *n* (%)	4 (21)	2 (10.5)	11 (58)	2 (10.5)	19

Atrial width above 15 mm from 14–16 weeks onward is usually associated with a poor prognosis[1]. Our study confirms previous data: 60% of the cases with ventricular width $\geqslant 15$ mm had associated structural malformations of the CNS and/or other organs. Pregnancy was terminated in most cases diagnosed before 24 weeks (88%) and there was one case of spontaneous miscarriage. Of the 60 fetuses with severe ventriculomegaly, only 10 (16%) were alive and normally developed at the age of at least 2 years. Even when the analysis was limited to cases of isolated ventriculomegaly, the rate of normal neurodevelopmental outcome was 62.5%. Graham *et al.*[12] found major neurological morbidity at pediatric follow-up in 33% (3/9) of survivors with isolated severe ventriculomegaly. It is noteworthy that we diagnosed only a relatively small percentage of cases (57%) before 24 weeks of gestational age; since it is easy to diagnose severe ventriculomegaly, this means that almost half of severe ventricular dilatations developed later in prenatal life.

The published reports on borderline ventriculomegaly, defined as ventricular width between 10 and 15 mm, are relatively few and often not comparable, especially with regard to neurodevelopmental outcome because of the variable length of follow-up and different methodological approaches[4–6,11–16].

We reviewed 116 such cases which makes ours the largest study. We separately analyzed cases of mild (10 to 12 mm) and moderate (12.1 to 14.9 mm) ventriculomegaly and found that the latter ones were significantly more often associated with structural anomalies (75%) than mild cases (41%). The large variation in the frequency of associated anomalies reported in the literature on borderline ventriculomegaly[2,3,5,6,14,15], ranging from 10%[6] to 76%[2], might be due to variation in the proportion of cases with mild and moderate ventriculomegaly; unfortunately, in most studies data were not separately analyzed for cases with atrial width < 12 mm or > 12 mm. Only Vergani *et al.*[5] found that an atrial width < 12 mm was associated with other anomalies in 6% of the cases, compared with 56% when the atrial width was $\geqslant 12$ mm.

Once structural malformations are ruled out, there is still a risk of chromosomal anomalies. The frequency of chromosomal anomalies reported in the literature in these cases ranges from 0 to 14%[3,5,6,12,14,15,17,18]; separate analysis for mild and moderate ventriculomegaly is never carried out. Although our sample is too small to draw any final conclusion, our data suggest that, at variance with structural anomalies, the degree of ventriculomegaly is not predictive of the risk of aneuploidies. None of the cases with ventricular width > 12 mm had isolated chromosomal anomalies; there were three isolated aneuploidies in cases of mild ventriculomegaly.

Screening for infections (usually TORCH) is recommended when ventriculomegaly is diagnosed[5,6,13,19]. However, there are few data to argue in favor or against such an approach. Although it suggests that TORCH infections are frequent (23%), our study is not conclusive because the number of screened cases was small ($n = 30$).

We collected follow-up data when the infants were at least 24 months old by means of interviews with the parents. Although this way of obtaining information about the condition of infants produces a very high rate of follow-ups, the results must be viewed with caution because parents are sometimes not objective. A strength of our study is that the infants were 24 months or older at the time of the interviews. It is well-known that this age must be reached in order to exclude moderate to severe neuromotor disabilities, and parents usually report this type of damage. A longer follow-up, to school age, and a neurological evaluation are needed to exclude mild motor or behavioral abnormalities which are often not reported by the parents.

Another strength of our study is that we analyzed the data separately according to the degree of ventriculomegaly: mild (10 to 12 mm) and moderate (12.1 to 14.9 mm). Neither group had severe neurodevelopmental outcomes, if we exclude the case of retinoblastoma, which is most likely a chance association. However, the overall

outcome was better when the ventriculomegaly was mild: it was normal in 93% of the cases compared with 75% in moderate cases. Vergani *et al.*[5] reported similar results in isolated cases: a significantly lower rate of developmental delay when atrial width was < 12 mm (3%) than when it was 12–15 mm (23%). Pilu *et al.*[6], in a review of the literature on 141 cases, reported a 3.8% rate of abnormal neurodevelopmental outcome when the atrial width was < 12 mm, compared to 14% when it was 12–15 mm[6]. Recently, Signorelli *et al.*[16] published results in 60 cases of mild isolated ventriculomegaly ⩽ 12 mm, reporting normal neurodevelopmental outcome in 100% of the cases. They suggested considering this atrial width a variant of the norm, once structural and chromosomal anomalies have been excluded. The fact that only in Group A there was a prevalence of male fetuses (61%) would support the observation that male fetuses have a slightly greater atrial width compared to females[6].

The evolution of ventriculomegaly *in utero* seems to be related to the outcome, with better prognosis when ventriculomegaly improves or disappears, independently of the severity at first presentation (mild, moderate or severe).

In conclusion, our results suggest that the definition of mild ventriculomegaly should be limited to a ventricular width below 12 mm. Cases with measurements above this value, but below 15 mm, are more often associated with structural malformations. Moreover, they have a normal neurodevelopmental outcome less frequently, although numbers are too small to reach statistical significance. We suggest that they should be considered separately (and defined as moderate). When ventriculomegaly is found, the diagnostic work-up must include targeted ultrasound examinations and fetal echocardiography since the rate of associated malformations is high and CNS or extraneural anomalies may be present. It must be underscored that in some cases associated structural malformations may be diagnosed later in pregnancy. Although the rate of chromosomal anomalies in isolated ventriculomegaly is fairly low, it still justifies offering fetal karyotyping.

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