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Metopic suture in fetuses with Apert syndrome at 22–27 weeks of gestation

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KEYWORDS: 3D ultrasound; Apert syndrome; coronal suture; craniosynostosis; metopic suture

ABSTRACT

Objectives *To examine the possible association of skull deformity and the development of the cranial sutures in fetuses with Apert syndrome.*

Methods *Three-dimensional (3D) ultrasound was used to examine the metopic and coronal sutures in seven fetuses with Apert syndrome at 22–27 weeks of gestation. The gap between the frontal bones in the transverse plane of the head at the level of the cavum septi pellucidi was measured and compared to findings in 120 anatomically normal fetuses undergoing routine ultrasound examination at 16–32 weeks.*

Results *In the normal group, the gap between the frontal bones in the metopic suture at the level of the cavum septi pellucidi, decreased significantly with gestation from a mean of 2.2 mm (5th and 95th centiles: 1.5 mm and 2.9 mm) at 16 weeks to 0.9 mm (5th and 95th centiles: 0.3 mm and 1.6 mm) at 32 weeks. In the seven cases with Apert syndrome, two-dimensional ultrasound examination demonstrated the characteristic features of frontal bossing, depressed nasal bridge and bilateral syndactyly. On 3D examination there was complete closure of the coronal suture and a wide gap in the metopic suture (15–23 mm).*

Conclusion *In normal fetuses, cranial bones are believed to grow in response to the centrifugal pressure from the expanding brain and proximity of the dura to the suture is critical in maintaining its patency. In Apert syndrome, the frontal bossing may be a mere consequence of a genetically predetermined premature closure of the coronal suture. Alternatively, there is a genetically predetermined deformation of the brain, which in turn, through differential stretch of the dura in the temporal and frontal regions, causes premature closure of the coronal suture and impaired closure of the metopic suture.*

INTRODUCTION

Prenatal sonographic diagnosis of craniosynostosis, which is either syndromal or isolated, is based on the combination of identifying the premature closure of the sutures and the associated deformation of the skull. However, there is evidence that the deformation of the skull may not be a consequence of a primary closure of the sutures and the former may precede the latter by several weeks[1,2].

The objective of this study was to examine further the possible association of skull deformity and the development of the cranial sutures in fetuses with Apert syndrome. This autosomal dominant condition with a birth prevalence of about one in 65 000, is due to a mutation in one of two specific points in the fibroblast growth factor receptor 2[3]. Apert syndrome is characterized by coronal craniosynostosis, frontal bossing, midfacial hypoplasia and symmetric syndactyly of the hands and feet[4,5]. All newborns with Apert syndrome have coronal synostosis and a widely patent midline calvarial defect extending from the glabella to the posterior fontanelle[6].

METHODS

The metopic suture was examined by three-dimensional (3D) ultrasound in seven fetuses with Apert syndrome at

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22–27 weeks of gestation and the findings were compared to those in 120 anatomically normal fetuses undergoing routine ultrasound examination at 16–32 weeks. In the cases of Apert syndrome, the patients were referred to fetal medicine centers for further assessment and management following the identification of abnormal findings during a routine second-trimester scan in their local hospital.

The 3D ultrasound examinations were carried out with the specific aim of assessing the metopic sutures, as previously described[7,8]. The scans were performed transabdominally (RAB 4–8L probe, Voluson 730 Expert, GE Medical Systems, Milwaukee, WI, USA), by sonographers with extensive experience in 3D ultrasound. The 3D volumes were obtained with the fetuses in the mid-sagittal plane, the transducer being parallel to the direction of the nose. For postprocessing, the frontal bones and metopic suture were visualized in the coronal plane, using surface rendering with Transparent Maximum Mode (Voluson 730 Expert Operation Manual, GE Medical Systems, Milwaukee, WI, USA).

For the measurement of the gap between the frontal bones the three orthogonal sectional planes were displayed. The transverse plane was selected and scrolled up to the level of the cavum septi pellucidi, used routinely for the two-dimensional (2D) examination of the head. Two parallel lines were then used to measure the distance between the two frontal bones (Figure 1).

Regression analysis was used to determine the significance of the association between the gap in the metopic suture with gestation and biparietal diameter in the normal fetuses. The Kolmogorov–Smirnov test showed that the data were normally distributed. The analyses were performed with SPSS 11.5 (SPSS, Chicago, Illinois, USA). $P < 0.05$ was considered to be statistically significant.

RESULTS

In the normal group, the median gestational age was 24 (range, 16–32) weeks and the median biparietal diameter was 60 (range, 37–88) mm. The gap between the frontal bones in the metopic suture at the level of the cavum septi pellucidi, decreased significantly with gestation from a mean of 2.2 mm (5^{th} and 95^{th} centiles: 1.5 mm and 2.9 mm) at 16 weeks to 0.9 mm (5^{th} and 95^{th} centiles: 0.3 mm and 1.6 mm) at 32 weeks (metopic gap in mm $= -0.079 \times$ gestational weeks $+$ 3.469, SD $= 0.4$ mm; $r = 0.661$, $P < 0.001$; metopic gap in mm $= -0.024 \times$ biparietal diameter in mm $+ 3.045$, SD $= 0.4$ mm; $r = 0.629$, $P < 0.001$; Figure 2).

In the seven cases with Apert syndrome, 2D ultrasound examination demonstrated the characteristic features of frontal bossing, depressed nasal bridge and bilateral syndactyly, and on 3D examination there was complete closure of the coronal suture and a wide gap in the

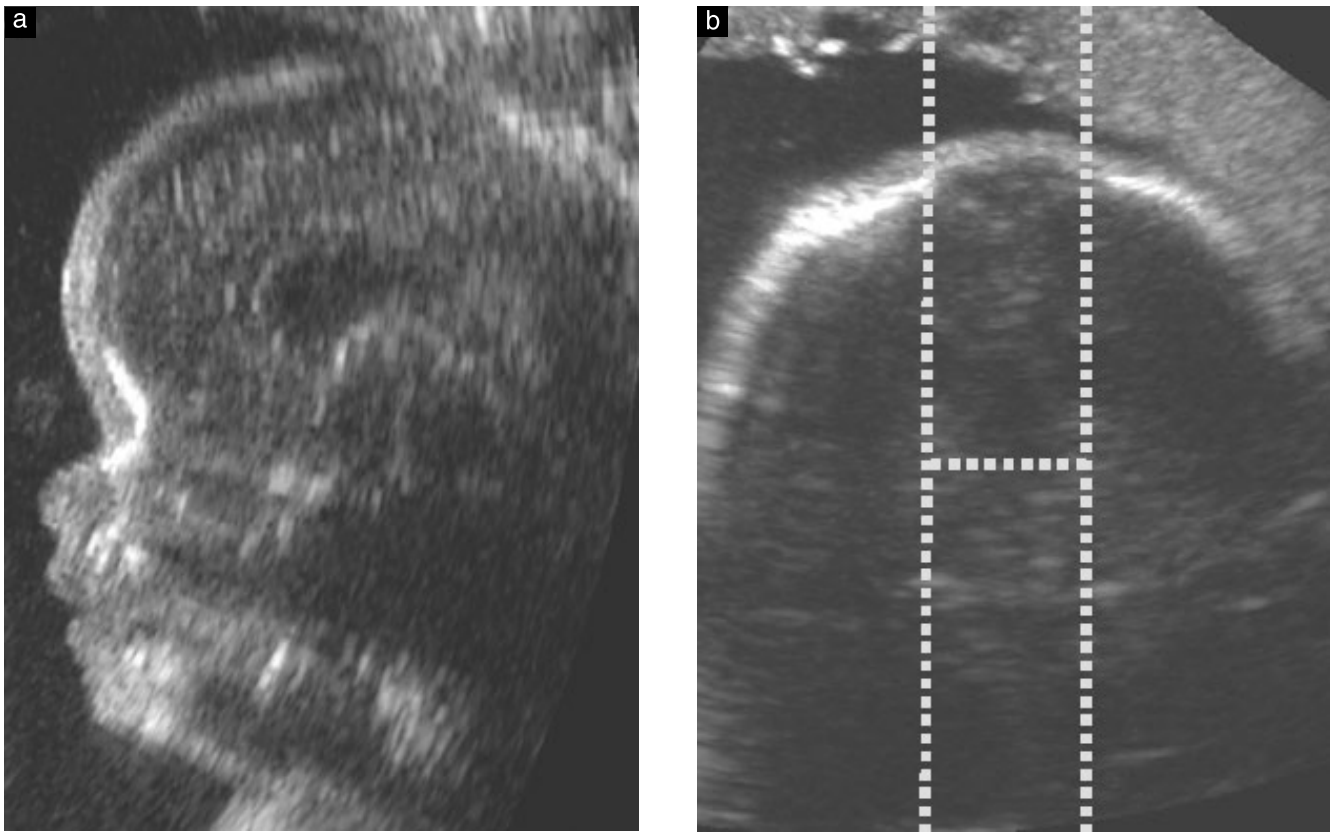

Figure 1 Two-dimensional ultrasound images of a fetus with Apert syndrome at 24 weeks showing characteristic frontal bossing and the clearly visible corpus callosum because of the absence of the frontal bones in the midline (a), and measurement of the large gap between the frontal bones in the transverse plane at the level of the cavum septi pellucidi (b).

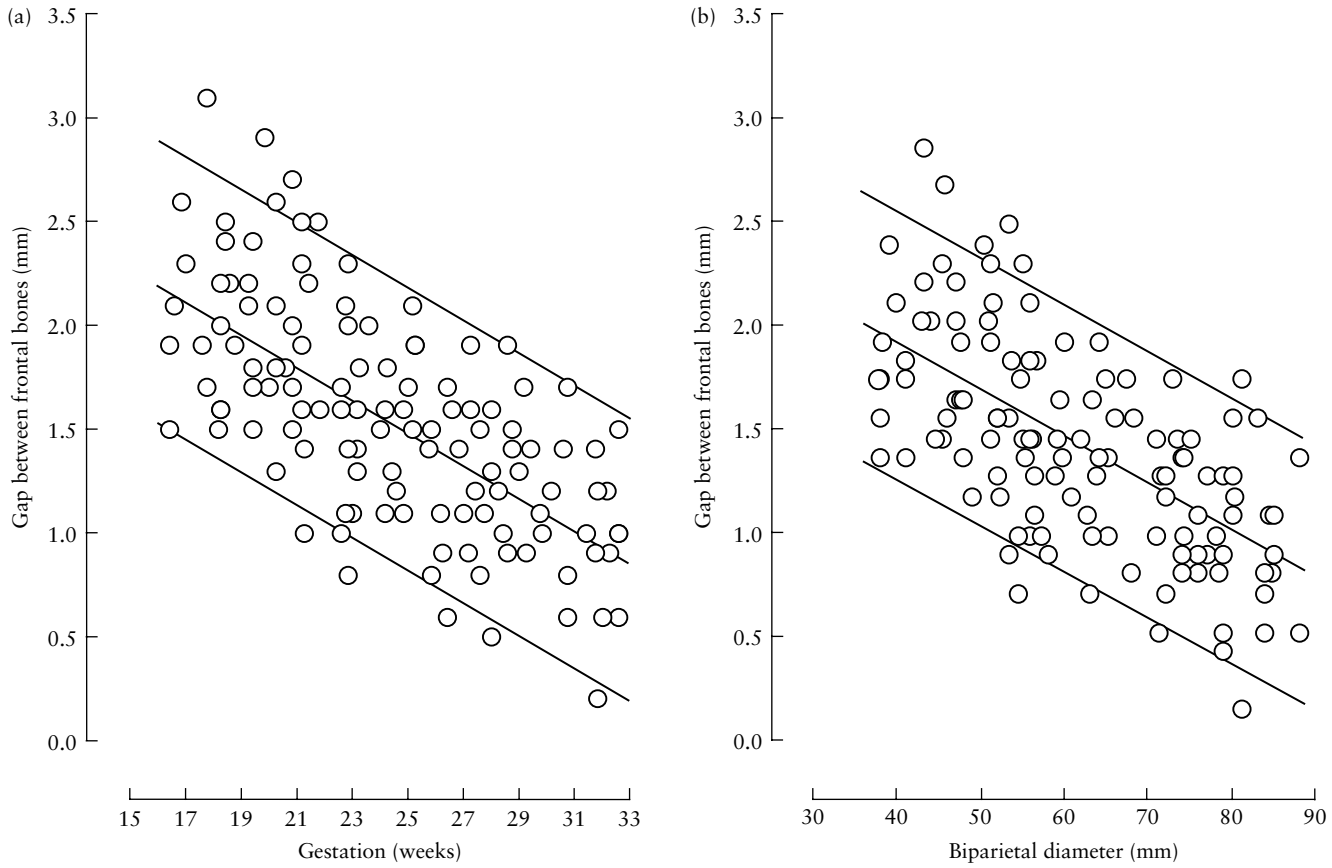

Figure 2 Reference ranges of the gap between the frontal bones in the transverse plane at the level of the cavum septi pellucidi (median, 5th centile and 95th centile) with gestation (a) and biparietal diameter (b).

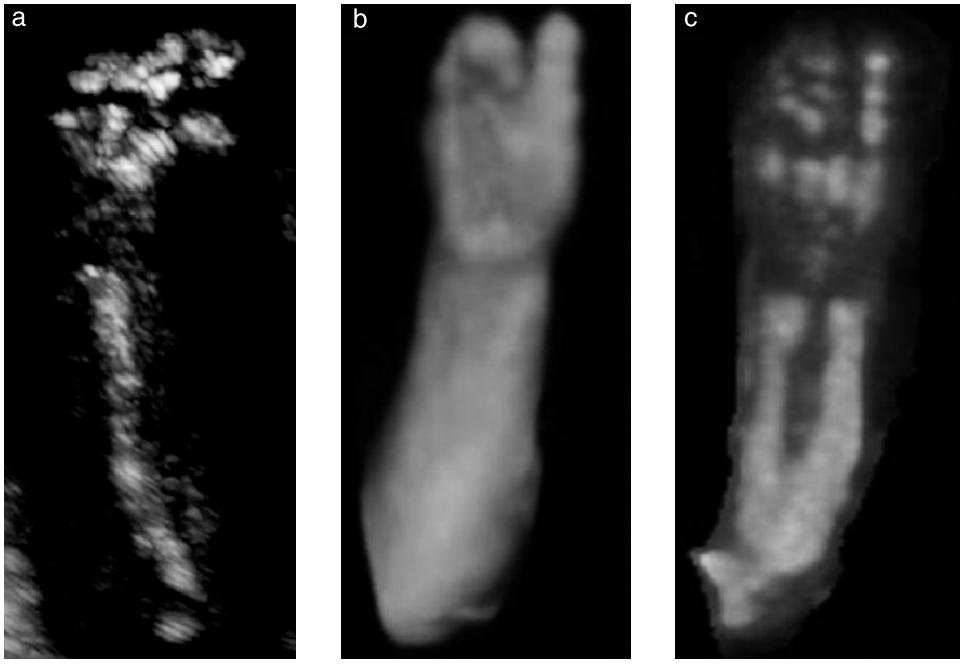

Figure 3 Syndactyly and 'mitten-like' posture of the hand in a fetus with Apert syndrome at 22 weeks, demonstrated by two-dimensional ultrasound (a), three-dimensional ultrasound with surface rendering mode (b), and transparent maximum mode (c).

metopic suture (Figures 1, 3–5; Table 1). The parents chose to have a termination of pregnancy and the diagnosis was confirmed by postmortem examination. In two of the cases amniocentesis and DNA analysis was carried out, and in both cases the specific mutations in the fibroblast growth factor receptor 2 were demonstrated. None of the parents had a family history of the condition.

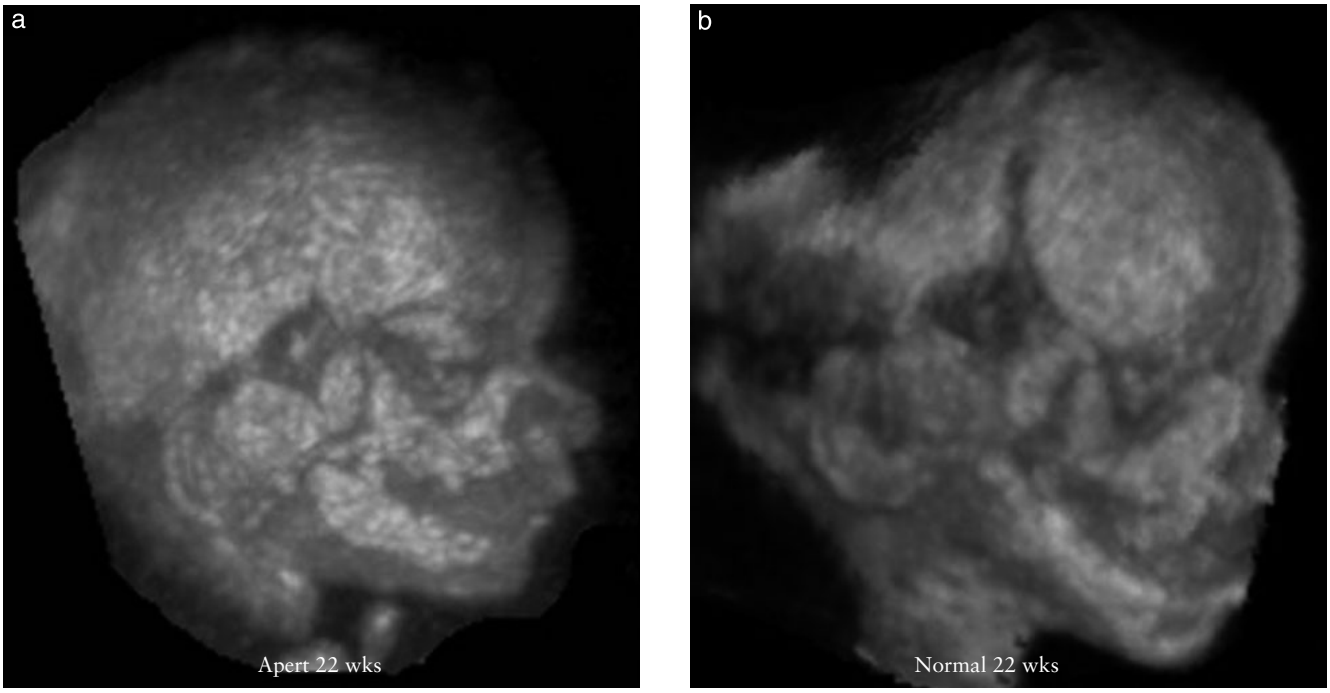

Figure 4 Three-dimensional ultrasound with transparent maximum mode demonstrating the closed coronal suture in a fetus with Apert syndrome at 22 weeks (a) and the open suture in a normal fetus at 22 weeks (b). wks, weeks.

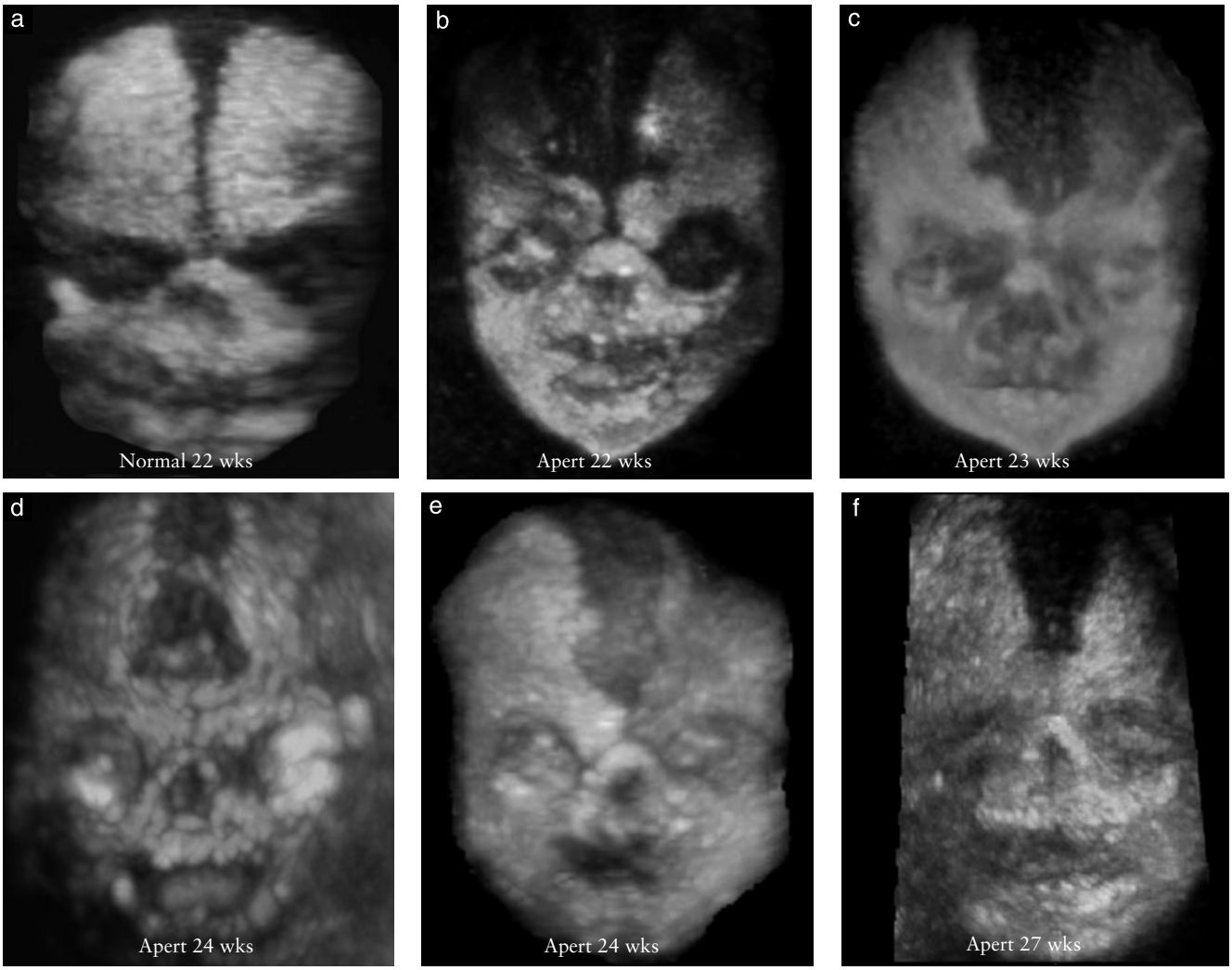

Figure 5 Three-dimensional ultrasound with transparent maximum mode demonstrating the narrow gap between the frontal bones in a normal fetus at 22 weeks (a) and the wide gap in fetuses with Apert syndrome at 22–27 weeks (b–f). wks, weeks.

Table 1 Gestation at diagnosis, two-dimensional (2D) ultrasound findings, and size of the gap between the frontal bones in the transverse plane at the level of the cavum septi pellucidi in seven fetuses with Apert syndrome

Case	*Gestation (weeks)*	*2D ultrasound findings*	*Metopic gap (mm)*
1	22	Frontal bossing, depressed nasal bridge, bilateral syndactyly, duplex kidneys	18
2	23	Frontal bossing, depressed nasal bridge, bilateral syndactyly	23
3	24	Frontal bossing, nasal hypoplasia, bilateral syndactyly	20
4	24	Frontal bossing, depressed nasal bridge, bilateral syndactyly	20
5	25	Frontal bossing, depressed nasal bridge, bilateral syndactyly	20
6	26	Frontal bossing, depressed nasal bridge, bilateral syndactyly	19
7	27	Frontal bossing, depressed nasal bridge, bilateral syndactyly	15

DISCUSSION

The findings of this study demonstrate that in fetuses with Apert syndrome at 22–27 weeks of gestation the characteristic features of frontal bossing, midfacial hypoplasia and syndactyly are associated with closure of the coronal suture and a wide gap between the frontal bones.

In normal fetuses, the gap between the frontal bones at the level of the cavum septi pellucidi decreased with gestation from a mean of 2.2 mm at 16 weeks to 0.9 mm at 32 weeks. This is compatible with the findings of previous anatomical and 3D ultrasound studies on the normal development of the frontal bones and metopic suture[7,9–12]. Thus, the frontal bones are ossified in membrane from two primary centers in the supraorbital region, which first appear at 9 weeks of gestation. Between 11 and 20 weeks, ossification spreads upwards in a radial fashion. At about 16 weeks, the frontal bones reach the midline in the supranasal region, and with advancing gestation the two bones enlarge and converge as if being zipped upwards together. In the third trimester there is apparent closure of the metopic suture, which again starts from the glabella and then moves upwards towards the anterior fontanelle.

In the fetuses with Apert syndrome, the gap between the frontal bones at the level of the cavum septi pellucidi was 15–23 mm rather than the normal size of 1–2 mm. In normal fetuses, the cranial bones are believed to grow in response to the centrifugal pressure from the expanding brain, and proximity of the dura to the suture is critical in maintaining its patency[13,14]. For example, in shunted hydrocephaly the normal expansion of cranial contents is abruptly halted and the resultant lack of stretch of the dura leads to craniosynostosis[15]. Similarly, in holoprosencephaly, which is associated with microcephaly, there is premature ossification of the frontal bones and closure of the metopic suture, possibly due to lack of brain growth and absence of a normal stretch stimulus across the suture[16].

Apert syndrome is associated with frontal bossing and megalencephaly[17], which would result in stretching of the dura in the frontal bones and continuing patency of the metopic suture. It is possible that the frontal bossing is a mere consequence of a genetically predetermined premature closure of the coronal suture. This is certainly compatible with the finding that in all of our affected fetuses the coronal suture was closed. However, in a previously reported fetus with Apert syndrome at 20 weeks there was frontal bossing with widely open metopic and coronal sutures[1]. Similarly, in fetuses with other craniosynostoses the deformation of the skull preceded the closure of the sutures by several weeks[2]. It is therefore possible that, in Apert syndrome, there is a genetically predetermined deformation of the brain, which in turn, through differential stretch of the dura in the temporal and frontal regions, causes premature closure of the coronal suture and impaired closure of the metopic suture.

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