Study of Femoral Torsion During Prenatal Growth: Interpretations Associated With the Effects of Intrauterine Pressure

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ABSTRACT   The developing fetus is protected from external environmental influences by maternal tissues. However, these structures have a limited elasticity, such that the fetus must grow in a confined space, constraining its size at the end of pregnancy. Can these constraints modify the morphology of the fetal skeleton? The intensity of these constraints increases between 5 months and birth, making it the most appropriate period to address this question. A sample of 89 fetal femora was analyzed, and results provide evidence that during this period, the torsion of the femoral shaft (quantified by means of a new three-dimensional method) increases gradually. Two explanations were considered: this increase could signal effects of constraints induced by the intrauterine cavity, developmental patterning, or some combination of these two. Different arguments tend to support the biomechanical explanation, rather than a programming pattern formation. Indeed, the identification of the femur as a first degree lever, created by the hyperflexion of the fetal lower limbs on the pelvis, could explain the increase in femoral shaft torsion during prenatal life. A comparison with femora of infants is in accordance with this mechanical interpretation, which is possible through bone modeling/remodeling. Although genetic and epigenetic mechanisms may regulate timing of fetal development, our data suggest that at birth, the fetal skeleton also has an intrauterine mechanical history through adaptive bone plasticity. Am J Phys Anthropol 000:000–000, 2011.   ©2011 Wiley-Liss, Inc.

Already in 1892, Wolf noted the impact of biomechanical constraints on skeletal shape (Wolf, 1892; Chamay and Tschantz, 1972; Ruff et al., 2006). However, the role of the environment in shaping the phenotype of an organism was only fully accepted and its mechanisms clarified with the emergence of molecular biology at the end of the 20th century resulting in the emergence of the field of epigenetics. Numerous studies of postnatal growth describe how external forces may impact the shape and growth of the locomotor skeleton (Abitbol, 1987; Preuschoft et al., 1988; Ruff et al., 1994; Tardieu and Trinkaus, 1994; Sumner and Andriacchi, 1996; Macchiarelli et al., 1999; Shefelbine et al., 2001; Ruff, 2003a,b; Ryan and Krovitz, 2006; Tardieu et al., 2006; Cowgill and Hager, 2007; Volpato et al., 2008; Cowgill, 2010). Throughout this body of literature, strong relationships between changes in bones during postnatal growth, both in general shape and in microarchitecture, and weight-bearing behavior were demonstrated. During postnatal growth, gravity is a fundamental parameter. This factor can be considered negligible during fetal life *in utero*, whereas the question of whether fetal morphology can be shaped by mechanical influence remains.

Influences of physical forces generated by the differential growth of connected tissues have been described from the first stages of development based on cell–cell or cell–matrix physical interactions (Henderson and Carter, 2002). In humans, important changes in the mechanical environment of the skeleton were noted between the fifth and the seventh week when contractions of muscles appear (de Vries et al., 1982, 1984; Clavert, 1987). Based on finite element analyses, Carter and collaborators suggested that the mechanical environment has a dominant influence on skeletogenesis and more specifically on endochondral ossification (Carter and Wong, 1988; Carter and Orr, 1992; Carter et al., 1996; Carter and Beaupré, 2001). Experiments using artificial immobilization and studies exploiting the congenital lack of muscular systems in embryonic and fetal models have demonstrated the critical role of muscular loading in joint formation and rates of ossification (Hall, 1972; Hall and Herring, 1990; Pitsillides, 2006; Gomez et al., 2007). Profound changes in the skeletal shape of human fetuses with neuromuscular diseases were described (Rodriguez et al., 1988a,b), suggesting that despite a genetically determined pattern and architecture, bones need stimuli induced by a mechanical environment to reinforce their structure. However, as noted by Skedros and collaborators (2004), the results of these studies should be considered with caution because of the radical nature of the perturbations.

Although there is evidence that intrinsic genetic and epigenetic factors control neonatal morphology, influences

Fig. 1. Photograph in proximal view of a fetal osteocartilaginous femur from the collection of the Muséum National d'Histoire Naturelle (Paris). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of extragenetic factors are unclear. The term "extragenetic" (Skedros et al., 2004) is defined as a subset of the epigenetic factors corresponding to the mechanical stimuli induced by the exterior environment of the individual. The influences of the external forces applied to the embryo by the surrounding environment in normal pregnancy are less explored (Le Damany, 1903, 1905; Seringe and Kharrat, 1982; Jouve et al., 2005), and some authors suggested that these can be considered negligible (Hendersen and Carter, 2002; Nuzzo et al., 2003). However, while maternal tissues protect the fetus from environmental dangers, they also limit the space available for growth, causing compression of the fetus at the end of normal pregnancy (Hicks, 1871; Seringe and Kharrat, 1982; Abitbol, 1993; Hieber et al., 1997). During the second half of an asymptomatic pregnancy, fetal movements are more and more limited in amplitude and duration with an advancing gestational age (Roodenburg et al., 1991), thus illustrating the increase in feto-maternal conflict over time. In this work, changes in femoral torsion are considered in relation to such extragenetic factors.

Different levels of canalization (Waddington, 1942) can be observed in different skeletal features. Although some features appear to be more genetically determined, a significant influence of the mechanical environment was demonstrated for other features (Ruff, 2003a; Cowgill and Hager, 2007). The orientation of the femoral neck is known to be strongly influenced by environmental factors (Heimkes et al., 1993; Lovejoy et al., 1999; Lovejoy, 2005; Skuban et al., 2009). The three-dimensional orientation of the femoral neck is often described in both clinical and evolutionary studies (Dunlap et al., 1953; Tayton, 2007) using the angle of anteversion. This angle corresponds to the angle between the three-dimensional axis of the femoral neck and its projection on the frontal plane. However, a characteristic of fetal femora is the poor development of the femoral neck making measurements in fetuses very complex (see Fig. 1). Some methods, such as the one proposed by Rigaud and collaborators (1965), use the center of the femoral head and the center of the greater trochanter to draw the axis of the femoral neck in a proximal view. There are several problems with such methods, however. On one hand, the femoral head and the greater trochanter are structures with their own morphologies, independent of the one of the femoral neck. In other words, the head and the greater trochanter are not positioned systematically at the center of the axis of the femoral neck (Kingsley and Olmsted, 1948). On the other hand, in fetal femora, the proximal and distal epiphyses are largely cartilaginous. In museum collections, osteological specimens are more common because of the difficulty of preserving cartilaginous tissues, and thus the femoral head and the greater trochanter are absent.

In this work, a new protocol is proposed to assess twisting or torsion of the proximal femur in fetal specimens, using measurements of femoral shaft torsion. Changes in the proximal part of the femur during the last months of pregnancy based on the femoral torsion data are analyzed, and two potential explanations are discussed. These changes are also compared to changes observed during earlier and later stages of development.

MATERIALS

This study included 97 fetal femora (50 right and 47 left) of modern *Homo sapiens* located in different collections acquired by French museums during the second half of the 19th and 20th centuries. Because the intensity of the intrauterine constraints increases between 5 months and birth, this is the most appropriate period to address the question of whether the intrauterine environment affects skeletal growth. Consequently, when the precise fetal age was unknown, only femora with a shaft length measurement between 35 and 76 mm were used as this length corresponds to the period between 22 and 40 weeks of gestation (see Adalian, 2002). This is in accordance with the data based on ultrasound measurements found in the literature (Hadlock et al., 1982; Guihard-Costa et al., 1991; Thiebeaugeorges et al., 2006).

Our sample was composed of two different series of specimens:

Series 1 included 27 osteocartilaginous femora of known sex and age. Thirteen right and 14 left femora (13 of which were pairs) were obtained through dissections of fetuses from the fluid-preserved specimens located at the Laboratoire d'Anatomie Comparée of the Muséum National d'Histoire Naturelle of Paris in 2002. During dissections, all fetuses with a pathological skeleton were excluded. After dissections, the femora were conserved in fluid that prevented desiccation and maintained the shape of the cartilaginous parts (see Fig. 1). Such samples are rare but fundamental to any study of the shape of the fetal skeleton. Only osteocartilaginous femora allow us to observe the transition between cartilage and bone.

Series 2 included 70 dry osteological femur specimens lacking the distal and proximal epiphyses. Eighteen right and 18 left femora (16 of which were pairs) were obtained from the osteological collections of the Musée de l'Homme (MNHN, Paris). The age was known for 14 individuals and the sex for 9 individuals. Nineteen right and 15 left femora (five of which were pairs) came from the osteological collections of the Muséum des Confluence in Lyon. Sex and age of these specimens were unknown.

To compare data before and after birth, our sample also included 13 femora of very young infants (see Fig. 2). Five osteocartilaginous femora, including three right and two left femora (two of which were paired) were derived from the collections of the Laboratoire d'Anatomie Comparée of the Muséum National d'Histoire
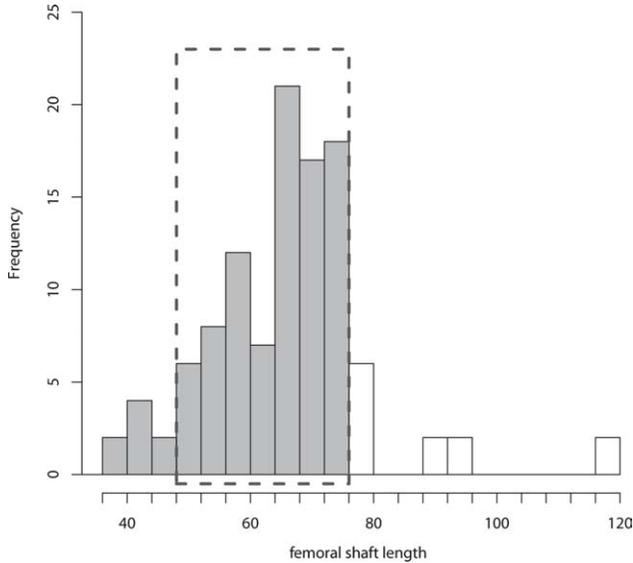
Fig. 2. Histogram illustrating the femoral shaft length distribution of the entire sample. The 97 fetuses are represented in gray and the 12 infants in white. At a size less than 48 mm, the base of the femoral neck is cartilaginous, resulting in nonhomologous measurements. Thus, only the 89 femora with a femoral shaft length between 48 and 76 mm were used to study the changes in the femoral shaft torsion during the last months of the pregnancy (gray box).

Naturelle of Paris. They correspond to stillbirths of known sex. Two additional left femora of stillbirths located in the osteological collections of the Musée de l'Homme (MNHN, Paris) were included in the study. Six femora of very young infants, including three right and four left femora (three of which were paired), also came from the latter collection. They correspond to two infants aged of 6 months and one aged of 1 year and 7 months. Sex was known.

METHODS

The lengths of the bony femoral shafts were measured using calipers (precision ±0.50 mm). These measurements were taken twice on a sample of 32 femora by a first observer, and they were also measured by a second observer. Paired t-tests were computed to estimate intra- and interobserver measurement errors.

The femoral shaft torsion was measured using the anteroposterior flattening of the proximal and distal femoral shaft. Digitizations were performed using a Micro-Scribe® G2 (Immersion) with a precision of ±0.38 mm according to the constructor. This allowed us to record the three-dimensional coordinates of two outlines perpendicular to the femoral shaft located at the proximal and distal ends. In the proximal region of the femoral shaft, the outline was recorded anteriorly at the base of the femoral neck (see Fig. 3). The distal outline was also acquired in the anterior part at a distance of 10% of the femoral shaft length away from the distal growth plate to eliminate the influence of the prominence of the lateral lip of the femoral trochlea (see Fig. 3). Each outline was acquired by recording the coordinates (x, y, z) of successive points 2 mm apart. The angle between the two axes corresponding to the minimal curvature of the two outlines was computed and reported as the femoral shaft

torsion. To be able to apply this protocol, the base of the femoral neck has to be ossified. Based on our personal observations of the sample of osteocartilaginous femora, in addition to radiographic samples where the transition between cartilage and bone is very clear, we determined that the base of the femoral neck is ossified at the age of 28 weeks of gestation. Only osteological femora with a femoral shaft length greater than or equal to 48 mm (Adalian, 2002) were thus measured, resulting in 89 femora. The osteocartilaginous femora conserved the cartilaginous epiphysis allowing us to acquire the proximal outline on the cartilaginous base of the neck on femora with a shaft length smaller than 48 mm. The measurements on the eight smallest femora (see Fig. 2) were compared to the sample of the 89 femora but were not included in the correlation analysis.

To test the intraobserver measurement error of this new method, the first observer took measurements twice for the 32 osteocartilaginous femora. The interobserver measurement error was estimated using measurements taken by the second observer on this same sample.

The dataset was analyzed using the freeware R 2.9.0 (R Development Core Team, 2008). The correlation test used the Pearson method. A linear least squared regression was calculated between the femoral shaft torsion and the total femoral length based on the femora with a length shaft between 48 and 76 mm. To assure independence between the two parameters used in the regression, one side was randomly chosen for the paired specimens (i.e., 30 pairs), resulting in a regression based on 59 femora. The representation of each side in the different age ranges was checked. Regression parameters were used to calculate theoretical values of the femoral shaft torsion from the femoral shaft length according to the equation $y = ax + b + \varepsilon$. Not enough femora of known sex were available, and consequently we did not test for differences between sexes.

RESULTS
Methodological validation

There was no significant intraobserver difference for the length of the femoral shaft ($t = 0.4146$; $P = 0.681$; $n = 32$). The interobserver difference was also nonsignificant ($t = 0.827$; $P = 0.221$; $n = 32$).

There was no significant intraobserver difference in femoral shaft torsion values ($t = -0.015$; $P = 0.988$; $n = 32$), and the interobserver difference was also nonsignificant ($t = 0.869$; $P = 0.392$; $n = 32$). The mean difference between the measurements of the first and the second operator was 0.9°.

Biometric analysis

The distribution of the femoral shaft length, which is used here as a proxy for the age of the subject (Adalian, 2002), measured for the entire sample is presented in Figure 2.

On the fetal sample with femoral shaft lengths between 48 and 76 mm, the linear model calculated by regressing log (femoral shaft torsion) on log (femoral shaft length) showed a significant correlation ($r_{Pearson} = 0.261$; $P = 0.026$; $n = 59$; see Fig. 4), with residuals normally distributed. The regression equation based on this sample was $y = 0.2398x + 11.682$. A 48 mm femoral shaft length, that is, 28 weeks of gestation (Adalian, 2002), corresponds to a predicted femoral shaft torsion of
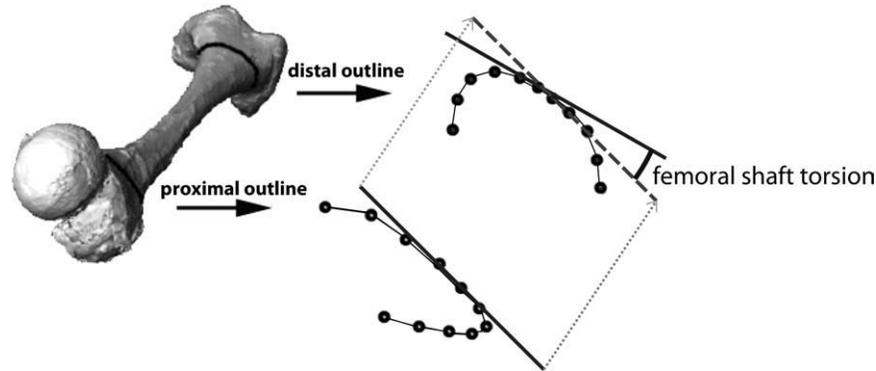
Fig. 3. Acquisition of the shaft torsion based on a novel three-dimensional method. Using a MicroScribe®, the anterior outlines (full line on illustration of the femur) of the proximal and distal extremities of the bony shaft are digitized. The angle between the two axes corresponding to the minimal curvature of the two outlines was computed and reported as the femoral shaft torsion.
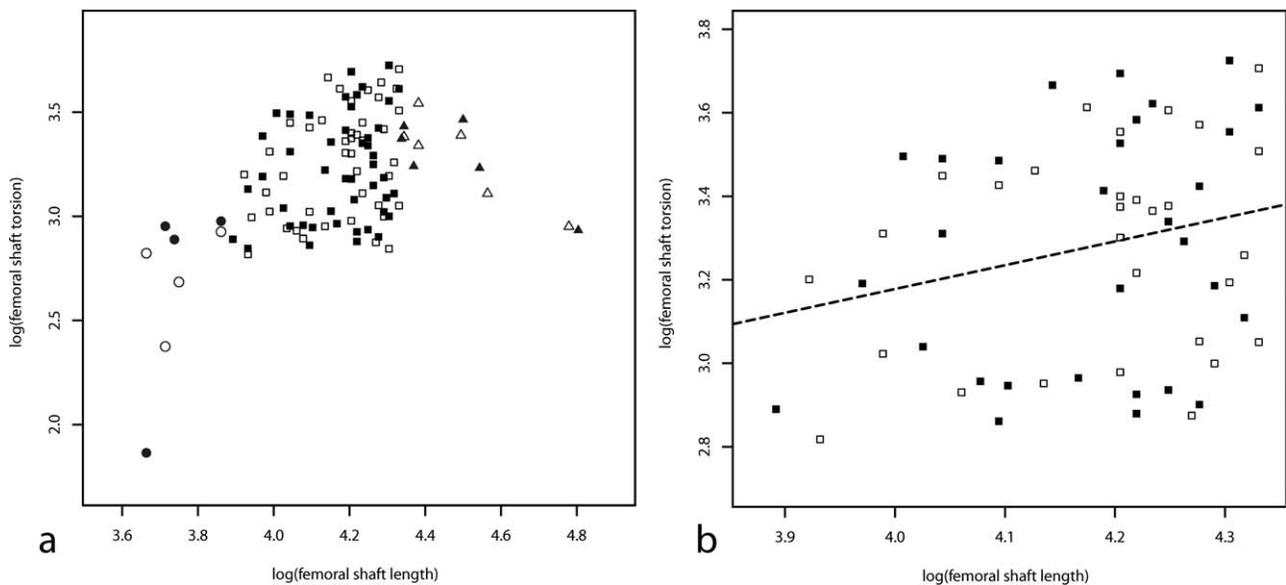

Fig. 4. Scatter plots illustrating the relationship between ln-transformed femoral shaft length and femoral shaft torsion. (a) Graph illustrating all data of the three age groups combined, including femora for which the ossification of the base of the femoral neck was not complete (gray circles), femora for which the ossification of the base of the femoral neck was complete (black squares), and femora of individuals after birth including stillborns and very young infants (gray triangles). Open symbols represent right femurs and filled symbol left femurs. (b) Graph illustrating only femora with a shaft length between 48 and 76 mm. One of the two sides was randomly chosen for paired specimens (30 pairs). The regression line (black dotted line) indicates the result of linear least square model fitted through the 59 specimens between 28 and 40 weeks of gestation ($r_{Pearson} = 0.261$; $P = 0.026$; $n = 59$).

$23.2°$. Similarly, a 76 mm femoral shaft length, that is, 40 weeks of gestation, corresponds to a predicted femoral shaft torsion of $29.9°$, suggesting an increase of $6.6°$ during the last months of the pregnancy.

The mean value of the femoral shaft torsion of the eight femora with a shaft length less than 48 mm was $15.5°$ (range = $6.5°$–$19.6°$). The mean value for the 13 femora corresponding to individuals after birth was $27.1°$ (range = $18.8°$–$34.6°$).

DISCUSSION

In *Homo sapiens*, feto-maternal conflicts appear at the end of the second trimester of an asymptomatic pregnancy, with the intensity of space constraints on the fetus increasing until birth (Hicks, 1871; Seringe and Kharrat, 1982; Roodenburg et al., 1991, Abitbol, 1993).

Here, we examine whether the functional influences imposed by the intrauterine cavity upon the fetus affect the growth of the femur. Ideally, a longitudinal study analyzing changes of the shape directly during increase of maternal constraints would be conducted. However, there is currently no method other than ultrasound allowing for longitudinal studies. As ultrasound data are, unfortunately, not precise enough if we decided to undertake a cross-sectional study on osteocartilaginous and osteological femora. One limitation of such an approach is that femoral shaft length is used as a proxy of intensity of the intrauterine constraints. Although there are always constraints at the end of the pregnancy in humans, their intensity at a given age is difficult to estimate because of the numerous parameters that may come into play. Not only fetal growth parameters such as placental volume (Thame et al., 2004), but also maternal

parameters including maternal morphology, health, and tissue elasticity will come into play (Hieber et al., 1997; Benson-Martin et al., 2006; Kiss et al., 2006; Jabareen et al., 2009). Although femoral shaft length is a good parameter to evaluate fetal growth, variation in maternal parameters determining the intensity of the biomechanical constraints on the fetus may result in two fetuses of similar femoral shaft length differing in their degree of shaft torsion.

Our results suggest a significant increase in femoral shaft torsion of 6.6° (23.2°–29.9° between 28 and 40 weeks of gestation) during the last months of pregnancy. Although significant, the r-value of the regression is weak ($r = 0.26$). However, this could be explained by the interindividual variation introduced by the cross-sectional nature of the data. Thus, in our cross sectional sample, 7% (i.e., r^2) of the variance of the femoral shaft torsion is related to femoral length. These results are consistent with the data in the literature. Indeed, an increase of the anteversion angle during prenatal growth has been documented previously (Le Damany, 1903, 1905; Altmann, 1924; von Lanz and Mayet, 1953; Watanabe, 1974; Jouve et al., 2005). This increase in torsion could signal effects of extragenetic factors, a programmed developmental patterning or some combination of these two.

One potential explanation of this increase in femoral torsion involves the biomechanical constraints induced by the intrauterine cavity. Although numerous positions are adopted by the fetus, in all cases, flexion, followed later by hyperflexion, of the femur on the pelvis is observed (Seringe et al., 1981, 1982). This hyperflexion is caused by the increasing compression constraints during pregnancy and creates a mechanical force on the femur that can be represented by a first degree lever. For a first degree lever to be realized, a rigid bar rotating about a fulcrum under the effect of a motive and a resistive force needs to be identified. In the fetus (see Fig. 5), the rigid bar is the femoral shaft. When hyperflexion appears because of the compression of the fetus in the uterus, the femoral shaft touches the anterior superior iliac spine through soft tissues, thus creating a fulcrum. The proximal part of the femoral shaft is not free to move, because the femoral head is held in place by the acetabular socket. Consequently, a resistive force is created on the proximal femur. The femoral neck is located between the femoral head—which in this posture cannot rotate more in the acetabulum and is thus locked—and the greater trochanter, on which the resistive force is applied. Thus, the femoral neck creates a lever arm and increases the moment of the resistive force resulting in a force tending to cause torsion (see Fig. 6). The soft tissues of the articular capsule and the coxo-femoral articular ligaments (Seringe, 1998) cause a distribution of this force along the proximal part of the shaft thus causing femoral shaft torsion.

Le Damany (1903, 1905) already described these mechanical influences of the intrauterine constraints to explain the increase of the anteversion angle of the femoral neck. Le Damany (1906) suggested a rotation of the growth cartilage around the shaft axis to explain the increase in the anteversion angle. Indeed, he observed an area of lesser resistance between the growth cartilage and the bony part of the shaft and inferred that the cohesion between these two parts would be based on the periosteum. The periosteum is an elastic membrane and could support small rotations. However, several observa-
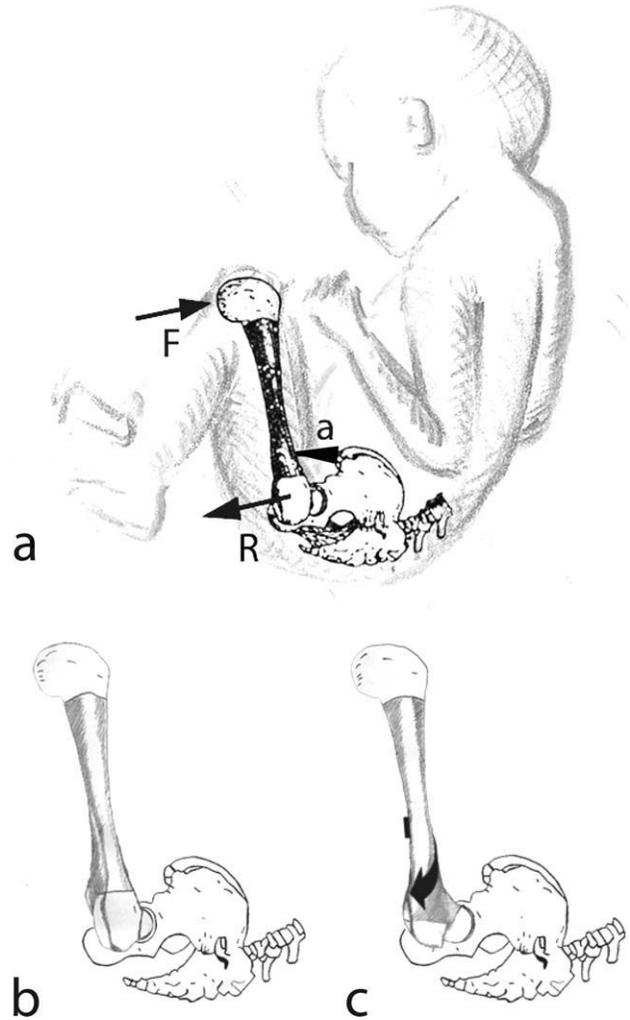

Fig. 5. When compressive constraints become important inside the maternal abdomen, the fetus adopts a position requiring a hyperflexion of the fetal lower limbs on the pelvis. (a) This hyperflexion creates a first degree lever when the femur leans against the pelvis and associated soft tissues. The first degree lever is symbolized by the motive force F, the resistive force R, and the fulcrum a. (b) The angle of femoral shaft torsion in femur in a young fetus (in the picture, 23 weeks of gestation) is small. When the femur is viewed in sagittal view, the greater trochanter hides the femoral head nearly completely. (c) The femoral head is locked in the acetabular cavity. Consequently, the forces generated in the femoral neck by the resistive force of the first degree lever may explain the increase in femoral shaft torsion, which attains important values at the end of the pregnancy (in the picture, 40 weeks of gestation; modified after Le Damany).

tions allow us to refute the hypothesis put forward by Le Damany. First, histological observations show a continuity between the growth cartilage and the primary and secondary bone of the shaft, which does not allow physical rotation (Kember and Sissons, 1976; Pous et al., 1980). Moreover, this rotation would be impossible without disturbing the organization of the proximal femur. The senior coauthor (Seringe) observed *in situ* the organization of the ligaments, the muscular insertions, the articular capsule, and the position of the small trochanter during numerous surgeries performed on the hips of newborns. The disturbance of these elements of the prox-
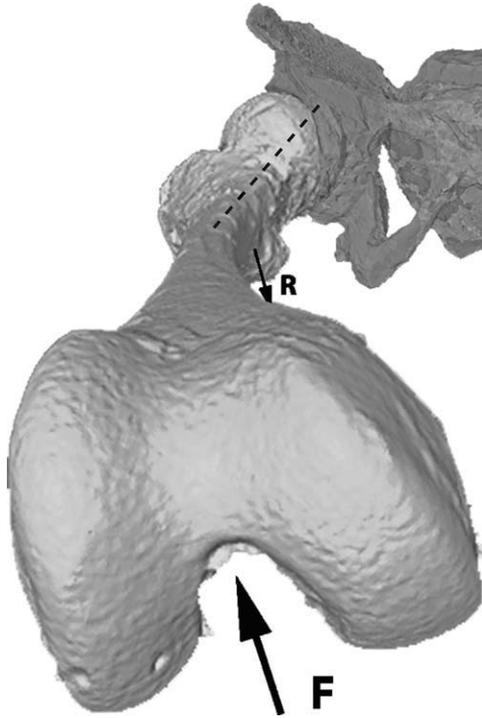
Fig. 6. A superior view of the situation described in Figure 5a illustrating the axis of the femoral neck (black-dotted line) increasing the moment of the resistive force (R) and causing torsion in the femoral shaft, because the femoral head is locked in the acetabular socket.

imal femur was never observed, suggesting that the hypothesis of Le Damany is not correct and leading us to present an alternative hypothesis. Current knowledge on the cellular mechanisms of bone growth allows us to identify the processes, which would be implied in femoral torsion formation during the last trimester of the pregnancy. Indeed, both bone modeling and remodeling are well known and allow the bone to adapt its structure to its mechanical environment (Amtman, 1979; Frost, 1982, 2004; Ingber, 1998; Martin, 2000; Lieberman et al., 2001; Van der Meulen and Huiskes, 2002; Pearson and Lieberman, 2004; Ruimerman et al., 2005; Ruff et al., 2006). In these early stages, these cellular mechanisms are very active. A histological morphometric study based on fetal femora of 16–41 weeks of gestation demonstrated a growth speed of 16 mm/day in the proximal epiphysis (Salle et al., 2002). This implies that cell proliferation and differentiation in the growth cartilage as well as the maturation of primary into secondary bone could respond very rapidly to changes in intrauterine constraints. Given the much slower nature of the remodeling process through apposition and resorption, the response by the secondary bone would be less rapid. As mechanotransduction pathways are sensitive to dynamical changes in the loading environment, the Braxton–Hicks contractions, which prepare the uterus for delivery (Hicks, 1871; Dunn, 1999) and imply a punctuated increase in intrauterine compression, could play a role in this process.

Experimental studies using long bones of young rabbits are in agreement with these interpretations (Arkin and Katz, 1956; Moreland, 1980). Indeed, changes in growth cartilage proliferation and secondary trabecular

orientation were observed when artificial constraints on rabbit tibias were applied. To complete the present study, microarchitectural analyses of the trabecular bone in the proximal part of the human fetal femora are ongoing (Peyrin et al., 2005).

An alternative explanation would be that increase of femoral torsion reflects a general pattern of developmental programming. However, several arguments work against this hypothesis. On one hand, a comparison with the values obtained for femora of the youngest fetuses demonstrates that in early stages, the architecture of the cartilaginous epiphysis results in limited femoral shaft torsion. Because the ossification of the base of the femoral neck could induce a change in the shape of the proximal part of the femur (Roberts, 1962), correlations were only computed on femora with a shaft length greater than or equal to 48 mm. From this stage onward, the base of the femoral neck is ossified. Thus, our measurements of the base of the femoral neck were not influenced by a change in the nature of tissues. The earlier fetuses included in the correlation, that is, with the base of the femoral neck ossified, have a femoral shaft torsion, which is smaller than that observed for fetuses around birth. The hypothesis that the increase of the femoral shaft torsion during the last months of the pregnancy is influenced more by the intrauterine pressure than by the process of ossification is thus put forward here.

On the other hand, our small sample of young infants appears to trend off in a negative direction after birth (Fig. 4a). This present sample was too small to calculate a regression and to draw any definitive inferences but is consistent with data in the literature reporting a decrease of femoral torsion during the first year of life. Indeed, very early anatomical observations of both Mikulicz (1878) and Le Damany (1903) showed a postnatal decrease in femoral torsion during the first year of life. Later, this decrease was documented by radiological and ultrasound studies on large samples (Dunlap et al., 1953; Shands and Steele, 1958; Crane, 1959; Upadhyay et al., 1990). Staheli and collaborators (1968) established a positive correlation between the maximal values of the internal rotation of the hip based on direct measurements and radiological measurements of femoral anteversion. Thus, the decrease of the maximal internal rotation, observed radiologically by them (Staheli et al., 1985) during the first year of life, based on 48 subjects, is in accordance with the discussed decrease of femoral anteversion. This reversal of femoral anteversion or torsion after birth provides an additional argument in favor of increasing femoral torsion *in utero* corresponding to modeling/remodeling activities in response to intrauterine pressure, rather than reflecting a genetically determined pattern.

CONCLUSION

The study of development is largely complicated by a tangle of genetic and epigenetic factors. Prior studies provided evidence that genetic and epigenetic factors control prenatal development. There are, however, also lines of evidence suggesting that extragenetic factors such as maternal hormonal or nutritional factors influence the growth of the fetus. However, the external forces applied to the embryo by the surrounding environment (e.g., maternal tissues) during normal pregnancy are less clear. Because the fetus develops in the amniotic environment, it may be assumed that the fetal skeleton

is shielded from external mechanical influences. However, the limited space available inside the uterus results in a feto-maternal conflict and constraints on the development of the fetus. In this study, an increase of femoral torsion during the last months of pregnancy was shown, and two explanations were considered. Different arguments tend to support a mechanical explanation rather than a programming pattern formation. A biomechanical rationale was developed, and a comparison with earlier and later stages of development tends to support the idea that the observed femoral shaft torsion is due to intrauterine constraints. Although genetic mechanisms may regulate timing of fetal development, our data suggest that at birth, the fetal skeleton also has an extragenetic mechanical history.

ACKNOWLEDGMENTS

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