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Fetal Age Estimation Using Orbital Measurements: 3D CT-Scan Study Including the Effects of Trisomy 21

ABSTRACT: This study evaluates a new method of fetal age estimation based on orbital measurement and including the potential trisomy 21 of the fetus. Six orbital and one facial CT-scan measurements were taken on 71 fetuses ranging from 14 to 41 weeks of gestational age. Forty-eight fetuses were "normal" and 23 fetuses presented the Down syndrome (trisomy 21). The anatomy/imagery correspondence was evaluated comparing our results to those obtained by direct bone measurements on the same fetuses and revealed no significant differences between the two kinds of measurements. Moreover, a multiple linear stepwise regression was realized to estimate fetal age and showed that the "trisomy 21 parameter" is not conserved in the final determination model. Therefore, we conclude that the good radio-anatomical correspondence offers an interesting alternative to direct bone measurement (necessitating dissections) and allows a reliable fetal age determination, whatever is the trisomy 21 condition of the fetus.

KEYWORDS: forensic science, fetus, age estimation, pathology, radiographic measurement, CT-scan, trisomy 21

Accurate identification of fetal age is important in clinical, forensic, and archaeologic contexts. Although age estimates of living fetuses are commonly made *in utero* through ultrasound measurements (1–7), many forensic and archaeologic situations present only limited material for examination (8). Clearly there is a need to maximize the number of potential gestational age estimators. In the former setting, radiographs often are available and may provide the only means for *post hoc* investigation (1,4,9–13). But radiographic measures of the skeleton are affected by image quality including parallax and enlargement. Moreover bone radiographic superposition may obscure from view some elements such as fetal orbit. Improved CT-scan imagery allows better visualization and measurements of fetal structures, including facial and orbital features.

Our study compares a large number of orbital measures obtained by CT-scan and tests their efficacy as fetal age predictors for the period between 14 and 41 weeks' gestational age. Comparing our results to those of Benso (14) who investigated the same fetuses and measured the same orbital parameters but with a sliding caliper directly on skull, we evaluate the anatomy/imagery correspondence.

Development of facial structures is intimately related to forebrain development (15). Thus, defects of the face and cerebral malformations are often associated (16). Fetal orbital biometry is therefore a useful ultrasound parameter in the early detection of the various anomalies and aneuploidy associated with orbital maldevelopment (17–24).

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To assess whether orbital measurements can be modified by pathology, we included fetuses with Down syndrome. We estimate therefore the influence of the trisomy 21 on fetal age prediction.

Methods

The study group includes 71 fetuses referred before 1999 to the prenatal diagnosis unit. All of them underwent a complete evaluation of potential dysmorphics including radiographic (skull CT-scan), karyotypic, gross anatomic, and histologic examination. A sample of 48 fetuses ranging from 14 to 41 weeks of gestational age was classified as nondysmorphic. The remaining fetuses, ranging from 19 to 27 weeks were diagnosed as abnormal with the same chromosomal aberration: trisomy 21. In order to take this pathology into account, we used T21 as an adjustment covariate and we coded "0" when the pathology was absent and "1" for fetuses with trisomy 21.

Age distribution for both normal and abnormal fetuses within the 14 to 41 weeks range is reported in Fig. 1.

Gestational age for all fetuses was based on accurate reports of mother's last normal menstrual period (LNMP) and the ultrasound examination of the fetal biometry. When conflicting reports of LNMP were in the records or where maternal report clearly conflicted with clinical and ultrasound evaluation, cases were excluded from the study.

Metrics

Complete skull and therefore orbital CT-scan were available for all specimens. A 3D reconstruction was obtained by using the MIMICS software (MATERIALISE, Leuven, Belgium). The choice of measured points was orientated by anthropological points in the skull and the orbits. All measurements were in millimeters. The following orbital landmarks and measurements were obtained in all cases (Figs. 2 and 3).

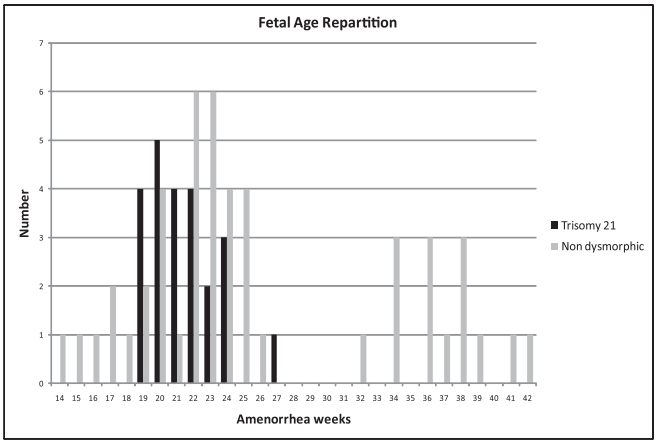

FIG. 1—*Age distribution of the studied fetuses. Ages are expressed in weeks of Amenorrhea (Gestational weeks + 2).*

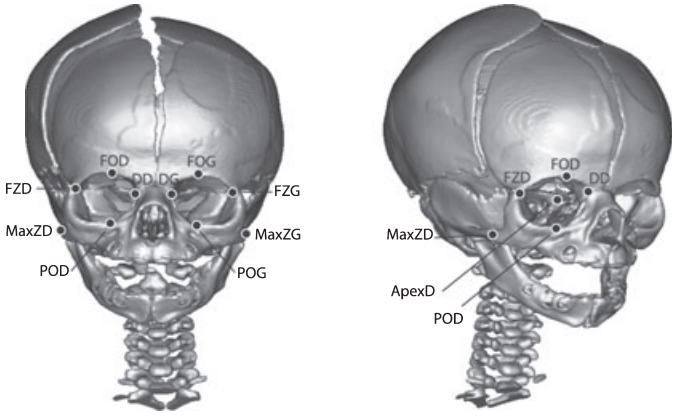

FIG. 2—*Landmarks used for orbital and facial measurements.*

Orbital Parameters

OD: Orbital diameter corresponds to the distance between the dacryon and the lateral border of a single orbit (25).

HO: Height of the orbital entrance is determined at right angles to the orbital diameter and passes by the junction of the maxilla and the malar bone.

MDO: The measurement points for the medial depth of the orbit, strictly speaking, the length of the medial wall, are the dacryon anteriorly and posteriorly the lower radix of the ala minor in the superior orbital fissure (26).

LDO: The lateral depth of the orbit is defined as the distance between the lower radix of the ala minor and the lateral border of one orbit.

OI: Orbital index is evaluated by the formula "HO/OD × 100."

Facial Parameters

IOD: Interocular distance is measured between the right and left dacryon (26).

BOD: Binocular distance is measured between the lateral border of one orbit and the lateral border of the opposite orbit (20). The lateral border is defined as the junction of the frontal and the malar bone.

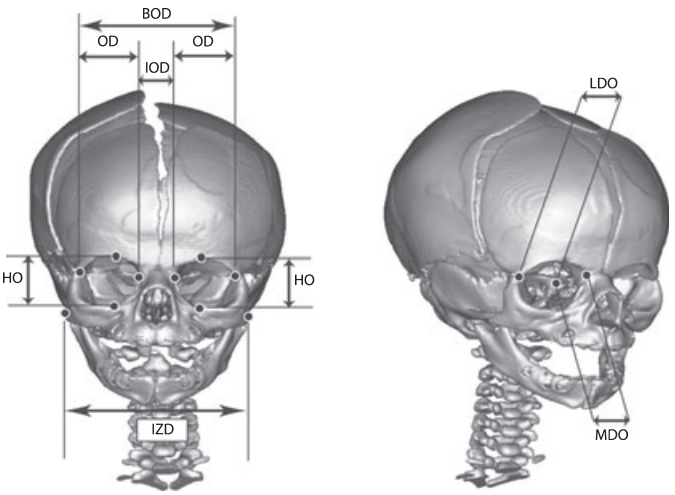

FIG. 3—*Measurements of the orbit and the face. IOD, interocular distance; BOD, binocular distance, OD, orbital diameter; HO, height of the orbital entrance; MDO, medial depth of the orbit; LDO, the lateral depth of the orbit; IZD, inter-zygomatic distance.*

IZD: Inter-zygomatic distance is measured between the both junctions of the malar and temporal bone.

FI: Facial index is evaluated by the formula "BOD/IZD × 100."

Statistical Analysis

In order to investigate the reproducibility (interobserver variations), the repeatability (intraobserver variations), the side influence and the relationship between our radiographic measurements and the direct skull measurement (14), we used the intraclass correlation coefficient (ICC) ($\alpha = 5\%$) as defined by Fleiss and Shrout (27). As classical covariate selection, univariate analysis was provided, calculating Pearson's correlation tests ($\alpha = 20\%$) between age and each orbital measurement. As multivariate analysis, multiple linear regression (with stepwise procedure) was realized to predict fetal age ($\alpha = 5\%$), with T21 adjustment. To evaluate the potential link between the trisomy 21 and the orbit, we employed the logistic regression, estimating odd ratio (OR) for each risk factor ($\alpha = 5\%$), with age adjustment. The quality of the prediction was evaluated by cross-validation, and the goodness-of-fit by the R^2 coefficient. Data analysis was performed using SPSS version 11.5.1 (SPSS Inc., Chicago, IL).

Results

For each measurement, intraclass correlation coefficient tests showed a significant concordance between right and left sides. Therefore, we chose to work only on left-side data, which were computer-stored and analyzed.

The inter- and intraobserver coefficients of intraclass correlation (ICC) are exposed in Tables 1 and 2. They ranged respectively from 0.7451 to 0.9983 and from 0.7725 to 0.9979 ($p < 0.0001$). Our orbital measurements are repeatable and reproducible.

Moreover, significant concordance could be found between the values of the interocular distance, the binocular distance, the orbital diameter, and the height of the orbital entrance of our study and those obtained by direct skulls measurements by Benso. ICC ranged from 0.4454 to 0.8881 (Table 3), and was significantly different from zero.

The univariate analysis showed very high correlation between all measurements and age (Table 4).

TABLE 1—*Intraobserver variation.*

Measure	ICC (95% CI)	*p*-Value
BOD	0.9959 (0.9911–0.9981)	<0.0001
IOD	0.9409 (0.8747–0.9726)	<0.0001
HO	0.9661 (0.927–0.9844)	<0.0001
OD	0.975 (0.9459–0.9885)	<0.0001
LDO	0.9037 (0.7973–0.9557)	<0.0001
MDO	0.7725 (0.5549–0.8912)	<0.0001
FI	0.9269 (0.8462–0.966)	<0.0001
OI	0.9064 (0.8054–0.9562)	<0.0001
IZD	0.9979 (0.9955–0.9991)	<0.0001

ICC, intraclass correlation coefficient; CI, confidence interval.

TABLE 2—*Interobserver variation.*

Measure	ICC (95% CI)	*p*-Value
BOD	0.998 (0.996–0.999)	<0.0001
IOD	0.745 (0.515–0.875)	<0.0001
HO	0.987 (0.97–0.994)	<0.0001
OD	0.9434 (0.88–0.9738)	<0.0001
LDO	0.8535 (0.7002–0.9315)	<0.0001
MDO	0.7628 (0.5383–0.8862)	<0.0001
FI	0.9409 (0.8746–0.9726)	<0.0001
OI	0.8619 (0.7161–0.9356)	<0.0001
IZD	0.9973 (0.9941–0.9988)	<0.0001

ICC, intraclass correlation coefficient; CI, confidence interval.

TABLE 3—*Comparison with direct skull measurements (Ref. [14]).*

Measure	ICC (95% CI)	*p*-Value
BOD	0.8881 (0.7396–0.9542)	<0.0001
IOD	0.4961 (0.0805–0.7647)	0.0111
HO	0.4454 (0.0155–0.7363)	0.0215
OD	0.5055 (0.093–0.7699)	0.0097

ICC, intraclass correlation coefficient; CI, confidence interval.

Pathology

We used a logistic regression in order to take into account the effect of the trisomy 21 pathology. The parameters of the regression are shown in Table 5.

Fetal Age Determination

We established a stepwise linear regression using the least squares method (Table 6). The obtained formula was as follows (Determination coefficient: $R^2 = 94\%$):

$$\text{Fetal age} = 0.152 + 0.736 \times \text{BOD} - 0.396 \times \text{IOD} - 0.782 \times \text{T21}$$

In this formula, fetal age is in amenorrhea weeks, BOD and IOD are in millimeters, and the "T21" parameter's value is "0" when the pathology is absent and "1" when the pathology is present.

Cross validation indicated small prediction errors, with an error mean of 0.004 weeks (−0.297; 0.305).

TABLE 5—*Logistic regression considering pathology.*

Measure	OR (95% CI)*	*p*-Value
BOD	1.44 (1.072–1.936)	0.016
IOD	3.008 (1.693–5.345)	0.0001
HO	5.994 (2.449–14.671)	0.0001
IZD	1.623 (1.200–2.195)	0.002
FI	0.00001 (0.0001–0.105)	0.026
OI	1.239 (1.105–1.389)	0.0001

The FI odd ratio was inferior to 1: it can be considered as a predictive factor of trisomy 21 when its value decreases.

CI, confidence interval.

*Estimations of OR were adjusted on age.

TABLE 6—*Multiple linear least squared regression (stepwise) for age determination.*

	Linear Regression Coefficients (95% CI)	*p*-Value
Constant	0.152 (−1.6; 1.91)	
BOD	0.736 (0.65; 0.82)	<0.001
IOD	−0.396 (−0.75; −0.04)	0.029
T21	−0.782 (−1.73; 0.17)	0.106

CI, confidence interval.

Discussion

Metrics

Our study is the first one based on fetal skull 3D CT-scan reconstruction and which focuses on orbital measurements. The most common method is ultrasound examination in early pregnancy. There are several reports in the literature on ultrasound fetal orbital measurements (17–24). In two cases, orbital parameters were directly measured on skulls (14,26).

Measures taken during ultrasound examination are frequently used as estimators of fetal age (28). It has been suggested that these measures also may provide a noninvasive means for diagnosis of pathologies such as trisomy 21 (29). Moreover, evaluating biometrics parameters obtained early in pregnancy by ultrasound examination, such as orbital measurements, may be useful as fetometric markers in an attempt to improve the detection rate of fetal anomalies (16,30,31).

Nevertheless, Cronk (32) and Sherwood et al. (28) detailed several possible sources of methodological errors in ultrasound studies, including the lack of standardized methodology and the poor reliability of measurement of some fetal dimensions. They also identified errors due to "the inherent technical limitation of ultrasound

TABLE 4—*Coefficient correlation of orbital parameter with age.*

Age	BOD	IOD	HO	IZD	OD	LDO	MDO	FI	OI
r	0.962	0.733	0.874	0.969	0.933	0.904	0.883	−0.470	−0.054
p-Value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.652
n	71	71	71	71	71	70	70	71	71

r, Pearson's correlation coefficient; *n*, number of fetuses.
$\alpha = 0.20$.

measurement." Others have identified technical errors such as incorrect identification of measurement planes (33,34). Mayden et al. (20) and Goldstein et al. (18) noted the importance of this plane to explore orbital region. "Tangential cuts through the orbits can easily produce erroneous measurements and in some fetal head position, it's difficult to define accurately the distal orbital margin because of acoustic shadowing from the nose."

An error also is associated with radiographic measures. Bone junctions, which are used in this study to define the measurements points, are not ossified yet. So, they are invisible for radiographic technique.

On the one hand, for the simple junctions (*i.e.,* between only two bones), the difficulty is easily solved. We just have to notify which visible ossified part of which bone forming the future junction is used as landmark. Thus, for BOD and OD, where junction between frontal and malar bone is implicated, it was the frontal ossified part of the junction which was chosen. In the same manner, for the HO and the IZD, it was respectively the maxillary and the temporal part of the junction which were chosen. In all cases, it was not the malar part of the junction which was selected. Indeed, fetal skeleton is flexible and deformable. However, malar bone, because of its external position in the face and its tripod disposition between frontal bone, temporal bone, and maxilla, is very exposed to displacement. To optimize the measurement precision, we used anatomically more stable bones.

On the other hand, for complex junction (*i.e.,* where more than two bones are implicated), the radiographic identification of the landmark was more difficult. For example, the superior orbital fissure, which was the landmark for MDO and LDO, is a real bony cross-road between the great wings, the small wings, the body of the sphenoid bone, and the frontal bone! This identification difficulty was reflected by the reproducibility and repeatability tests results (Tables 1 and 2). They ranged respectively from 0.7628 to 0.7725 ($p < 0.0001$) for the MDO and from 0.8535 to 0.9037 ($p < 0.0001$) for the LDO whereas they ranged from 0.9434 to 0.9983 ($p < 0.0001$) for the other orbital parameters. The same phenomenon occurred for IOD. Another bony cross-road is implicated: the dacryon, convergence of the maxilla, the lachrymal, and the frontal bones. In the same manner, ICC of the reproducibility and repeatability tests was lowered: 0.7451 and 0.9409 ($p < 0.0001$).

Nevertheless, with these caveats in mind, this measurement technique was statistically validated and must be considered as reliable. The measurement point determination (*i.e*., landmarks) must just be performed precisely according to anatomical definitions.

Comparison with Direct Measurements (Ref. [14])

A significant concordance was found between orbital measures obtained by both methods, *i.e.,* there is a good anatomo-radiographic correspondence. That means that measurements obtained by CT-scan acquisition were as accurate as those obtained by dissection. Nevertheless, the radiographic method was quicker and easier. This conclusion is important, particularly in comparison with ultrasound estimators of fetal age. Several studies have compared ultrasound and postnatal measurements (reviewed in Ref. [32]). These studies reported a range of errors in some fetal measures that may be attributed to differences in plane of measure, tape pressure, or respiration in the case of abdominal measure. There is a lack of anatomo-ultrasound correspondence versus anatomo-radiographic (CT-scan) correspondence.

However, we noted that the ICC values are not very high (Table 3): 0.4454–0.5055 ($p < 0.05$) except for the BOD: 0.8881.

The technique used by Benso was aggressive for the orbital region and included a periost ablation. Since this tissue is a real connective tissue membrane, which connects the bony structures, the periost ablation could entail bony dehiscence and displacement. This periost ablation could partially explain the ICC decrease.

We noticed that the ICC of the BOD is particularly high; this distance was calculated from two measurement points depending from frontal bone. Thanks to the metopic suture, the two sides of this bone constitute just one unique bone. Therefore, it was less exposed to instability or displacement.

BOD seemed to be a particularly stable and reliable parameter, adapted to forensic context.

Age Univariate Correlation

As expected, all orbital parameters showed very high univariate correlations with age (Table 4). These results confirm those already published in the literature either by ultrasound measurements or by direct bone investigation.

IZD provided the strongest univariate correlation with age. It was identified as the best univariate predictor of gestational age. But, contrary to BOD, IZD did not seem to be adapted to forensic context. Connected bony structures are necessary to measure this parameter, and this condition is rarely present in the former setting. Therefore, IZD was excluded from the multiple regressions where only strictly orbital parameters were analyzed. In this case, both BOD and IOD provided the strongest univariate correlation: 0.962 and 0.733.

Nevertheless, according to Benso and Mayden data, age was less correlated with IOD. Several possible explanations, including IOD measurement difficulty and its low increase during pregnancy, could explain these results.

Effects of Pathology

The many ultrasound studies published in the literature provided data concerning the normal growth of the orbit. Reference abacuses were developed that can be helpful in the detection of syndromes with orbital growth defects and other associated fetal abnormalities. Trout et al. (35) and Guariglia and Rosati (19,30), published studies which purposes were to assess whether orbital biometric parameters obtained in early pregnancy by sonography could be useful screening tools for the detection of aneuploidy. The orbital values of fetuses with trisomy 21 were in the range of normality. However, a good correlation with an orbital abnormality (hypotelorism) and trisomy 13 was found, suggesting that this may be a very good morphologic marker for suspecting trisomy 13.

Development of facial structures is intimately related to forebrain development (15). Thus, defect of the face and cerebral malformations are often associated (16). Therefore, because anomalies of the central nervous system, particularly holoprosencephaly, are typically associated with trisomy 13, orbital anomalies are often presented by this pathology.

Down's syndrome includes different physical features including a characteristic face: flattening of the back of the head, slanting of the eyelids, small skin folds at the inner corner of the eyes, depressed nasal bridge, slightly smaller ears, and small mouth (36). Because anomalies of the central nervous system are not classically associated with Down's syndrome, it seems logical that these individuals do not show orbital anomalies. Our statistical analysis (using logistic regression with age adjustment) goes together with this fact. Most of the orbital measurements were either not correlated with trisomy 21 (MDO, LDO, OD), or with an OR value near

1 (neutral influence) (BOD, IZD, and OI). But three parameters seemed to be influenced by the pathology: IOD, OH, and FI.

FI (OR = 0.00001 [0.0001–0.105], OR was smaller than 1): the more the BOD/IZD ratio increased, the risk that the fetus was pathologic decreased. On the other hand, as IZD increased versus BOD, the risk increased. Morphologically, this translated into a round face, a common characteristic of Down's syndrome. FI may be a very good morphologic marker for suspecting trisomy 21. However, because of the small number of cases in this study, this assertion must be validated by further study.

OH and IOD (OR = 5.99 [2.449–14.671] and 3 [1.693–5.345]): the more the values increased regarding the age, the more the risk that fetus was pathologic (trisomy 21) was important. Concerning OH, we did not find any study where this parameter was investigated. This result must be confirmed by further studies. Concerning IOD, these data were contrary to the findings of the precedent ultrasound studies. This discrepancy was most likely due to the following factor: we just concluded that FI was correlated with trisomy 21. Moreover, FI is the ratio BOD/IZD. However, IOD measurement was included in BOD measurement. Then, because IOD was linked with a parameter correlated with trisomy 21 (BOD and by the way, FI), IOD appeared to be influenced by the pathology. In fact, we attributed this result to a measurement bias.

In conclusion, except OH and IOD, orbital parameters may not be influenced by trisomy 21. On the opposite, FI, which included facial parameter (IZD), seemed to be correlated with this pathology.

Fetal Age Determination

The linear regression kept only two significant parameters in the final model: IOD and BOD, and we kept T21 as a factor of adjustment ($p = 0.106$). Trisomy 21 may not be a fetal age determination influencing factor. However, caution must be exercised. There is an age repartition difference in samples of pathologic fetuses versus healthy fetuses (respectively 19 to 27 amenorrhea weeks, and 14 to 41) (Fig. 1). Indeed, the pathologic fetuses were medical abortions resulting from second trimester sonography which diagnosed the pathology. Ages of pathologic fetuses are closer and effects of trisomy 21 on its determination are only evaluated during this short period.

Influence of trisomy 21 may be underestimated in this study. Therefore we kept the T21 variable as adjustment factor in the final regression equation for age estimation.

Conclusion

There are many applications for accurate fetal aging. In this study, we provided a new innovative method which includes the pathologic condition of the fetus. Moreover, we showed that the method is statistically valuable and reliable. It can be used either with CT-scan imagery, therefore saving a lot of time, or directly on anatomical pieces after dissection.

One of the parameters we investigated, FI, seems to have a clinical application. Further studies are needed to determine the validity of this morphological marker for suspecting trisomy 21: studies investigating FI on newborns or children presenting Down syndrome to confirm the correlation between this orbital parameter and the trisomy 21, or studies based on large sample and sonography measurements to evaluate the FI interest for the prenatal diagnosis.

Finally, we plan to realize the same study with fetuses which are known to present other orbital abnormalities, like those presenting trisomy 13. At this time, we would see if the "pathology" parameter would be useful for fetal age determination, increasing therefore the validity of our methodology in the field of forensic sciences, where age determination is needed but where the pathologic condition of the fetal remains is not always known.

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