Indication of prenatal diagnosis in pregnancies complicated by undetectable second-trimester maternal serum estriol levels

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Summary

Objectives. Undetectable maternal serum unconjugated estriol levels in the second-trimester screening test have been associated with congenital pathology and an adverse pregnancy outcome. We reviewed outcomes of pregnancies with undetectable levels of estriol (<0.25 ng/ml) in the triple-marker screening test and assessed the clinical value of this finding.

Methods. We studied estriol values in 6,018 pregnant patients who underwent a triple-marker screening test during a seven-year period.

Results. 26 women had estriol levels at or below the sensitivity of the assay. The most common explanations were dating errors, prematurity, growth restriction and X-linked ichthyosis. We also observed one fetal death at 16 weeks, one severe threatened fetal abortion, one case of multiple congenital anomalies and one case of isolated adrenocorticotropin hormone deficiency. There were 6 women remaining with unexplained undetectable estriol.

Conclusion. Undetectable maternal estriol values may indicate a severe fetal pathology and should lead to further investigations.

KEY WORDS: low estriol, X-linked ichthyosis, triple-marker screening, isolated ACTH deficiency.

Objectives

The primary purpose of the second-trimester triple-marker screening test is the detection of trisomy 21 and neural tube defects by combining α-fetoprotein (αFP), human chorionic gonadotropin (hCG) and unconjugated estriol (uE3). However, very low (< 0.5 MoM) and undetectable (≤ 0.25 ng/ml) second-trimester maternal serum uE3 levels have been associated with congenital pathology and an adverse pregnancy outcome, independently of the value of the other analytes (1-8). The most common diagnosis is X-linked ichthyosis (XLI). This entity is characterized by steroid sulfatase (STS) deficiency and provokes keratinization troubles and scaly skin in boys. The importance of detecting low estriol levels should be assessed in light of outcome. We therefore reviewed outcomes of 26 pregnancies with undetectable levels of estriol (<0.25 ng/ml) in the triple-marker screening test and assessed the clinical value of this finding.

Methods

From January 1, 2000 through January 1, 2007, 6,018 pregnant patients underwent a triple-marker screening test, including αFP, hCG and uE3, between 14 and 22 weeks’ gestation, in the Centre Hospitalier Universitaire Tivoli, Third Level, Public Hospital. All pregnant patients under the age of 35 years are offered this test, and patients older than 35 years if they wished to avoid amniocentesis. Pregnancies were dated according to the date of last menstrual period, and the gestational age was modified by the first trimester or the early second trimester ultrasound scan if the difference exceeded 1 week. Acceptance was voluntary and was almost 100%. Undetectable uE3 was defined as less than 0.25 ng/ml, as this was the lowest limit of sensitivity of our method. uE3 was assayed by immunochemoluminescence in a DPC Immulite One instrument. Values were given in ng/ml and multiples of median (MoM, multiples of median), adjusted for smoking, weight, ethnic origin, diabetes and medically assisted reproduction. All measurements were calculated using Prisca software.

Pregnancy outcomes were obtained from obstetrical and pediatric medical records, and patients were later reached by means of telephone calls if follow-up data was incomplete. The follow-up time ranged from 1 to 7 years. This study was approved by the local Ethics Committee and required a signed informed consent form. Descriptive statistics were performed using STATA IC10 software.

Results

6,018 estriol measurements were obtained. After excluding 90 pregnancies with datation errors, 5928 women remained. Of these pregnancies with dating errors, 43 were found to be too late for screening (above 22 weeks at screening) and 47 were found to be 13 weeks at screening and were tested again later.

26 women had estriol levels at or below the sensitivity of
the assay (≤0.25 ng/ml). Dating errors accounted for 8 cases. Our results are summarized in Table I. Five of these pregnancies were also associated with either low (< 0.5 MoM) or high (>2 MoM) levels of hCG or αFP. We could not find any trend toward poorer pregnancy outcome as 3 pregnancies were uneventful and the patients delivered normal babies. The other 2 cases included a fetal death and a severe threatened abortion (Table I). After all exclusions, there were 6 women remaining with unexplained undetectable estriol. Follow-up evaluation was available in all cases (4 girls and 2 boys) and revealed no anomalies. Boys were tested negative for STS deficiency through genetic analyses. Measurements were on average obtained at 15 weeks gestational age, with a median of 15 (15-17). In the undetectable estriol group, the median age was 14.5 weeks (14-16).

Discussion

The rate of estriol values at or below 0.25 ng/ml is 0.4% (26/6,018) in our population. Previous series of undetectable second-trimester maternal estriol values are shown in Table I (1-8). There are only four series of uE3 expressed in [ng/ml]. These results must be interpreted with caution as inclusion criteria and pathologic and genetic analyses vary greatly among studies. However, the estimated rate of anomalies reaches 50% in every setting.

The rate of perinatal complications in the presence of undetectable estriol, was assessed in several studies and was found to be increased (2,8). Those data are consistent with our series, as 5 babies out of 18 (28%) were either premature or small for gestational age, or both. Undetectable estriol levels are also associated with congenital pathology and fetal demise. The most common anomaly is XLI. The incidence of XLI in our population is about 2/6000, which is similar to other reports.

XLI is transmitted on a recessive basis in more than two thirds of the cases (9). This genetic disturbance involves the distal end of the short arm of the X chromosome, Xp22.3ter region. Complete deletion is seen in 90% of patients with XLI (10) including rare cases of translocations X/Y (11) and is thus easily detectable through FISH.

MoM: multiples of median , NR: not reported.
* All measurements were below 0.4 MoM.
** Diaphragmatic hernia, premature, diabetic mother – this case is also included in preterm births.
*** The sum of anomalies is greater that the total because some babies had more than one diagnosis.
Analysis. Few cases of partial deletion have been reported and require PCR amplification (12). A dozen of point mutations have been observed (13). XLI might appear as of no importance as it is not a life-threatening condition but in up to 10% of cases, this anomaly is part of a contiguous gene deletion syndrome with additional severe anomalies including Kallman Syndrome, Chondrodysplasia punctata, mental retardation and short stature (10).

The prenatal finding of STS deficiency is also of interest because it eliminates the diagnosis of other severe disorders; if family history suggests ichthyosis, as it is observed here, STS deficiency is from far the most likely diagnosis and may be confirmed by genetic studies. If past history of the family does not support ichthyosis but a deletion is confirmed in the male fetus, it is necessary to exclude the carrier state of the mother. If the mother is not a carrier, the fetus can carry a de novo mutation, and contiguous gene syndrome cannot be excluded. There is no agreement to which test should be offered in that case. Some authors propose pregnancy termination (14) whereas others suggest performing selective genetic studies to detect other associated anomalies (12). However, the gene encoding for mental retardation associated with XLI has not yet been identified and these cases cannot be reliably differentiated (15). If STS deficiency is not confirmed, and after excluding gender reversal and morphologic anomalies, a work-up to evaluate differential diagnoses should be pursued. Rare conditions associated with undetectable estriol values have now been described (Table II) and should not be ignored as proper early diagnosis is achievable and can prevent neonatal death. Useful information can be obtained through genetic biochemical assays in maternal blood and urine and amniotic fluid (16) as these entities are all characterized by specific biochemical and steroid profiles.

Reports of undetectable estriol levels in pregnancies of neonates born with isolated adrenocorticotropic hormone (ACTH) insufficiency are extremely rare (17), and this is the first series mentioning ACTH insufficiency. We also observed a case of diaphragmatic hernia but this is the first series mentioning ACTH insufficiency. We confirm that undetectable maternal serum second-trimester estriol values indicate a fetal anomaly in more than half of cases. We recommend that pregnant women with an unexplained isolated undetectable estriol level of undetectable etiology be referred for additional evaluation to a geneticist and a pediatric endocrinologist. If not, infants born to mothers with undetectable estriol levels of unexplained cause should undergo early postnatal evaluation to enable early diagnosis.

Synopsis

Undetectable maternal serum second-trimester estriol values indicate a fetal anomaly in more than half of cases and should lead to further investigation.

References


Table II - Reported conditions with undetectable maternal estriol values.

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<tr>
<th>Condition</th>
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<tr>
<td>Anencephaly</td>
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<tr>
<td>EctoGem corticoids</td>
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<tr>
<td>Adrenal insufficiency</td>
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<td>– ACTH deficiency</td>
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<tr>
<td>– Congenital panhypopituitarism</td>
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<td>– Congenital adrenal hypoplasia</td>
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<td>– Congenital adrenal hyperplasia</td>
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<td>– 17α-hydroxylase</td>
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<tr>
<td>Lipoid adrenal hyperplasia</td>
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<td>Antley-Bixler syndrome</td>
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<tr>
<td>Other inborn errors of metabolism</td>
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<tr>
<td>– Steroid sulfatase deficiency</td>
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<td>– Multiple sulfatase deficiency</td>
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<tr>
<td>– Zellweger syndrome</td>
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<td>– Smith-Lemli-Opitz syndrome</td>
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<td>– Aromatase deficiency</td>
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