OBSTETRICS

Effects of exogenous progesterone on fetal nuchal translucency: an observational prospective study

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OBJECTIVE: Nuchal translucency (NT) seen ultrasonographically at 11-14 weeks' gestation is a sensitive marker for Down syndrome. Despite its important role for Down syndrome screening, its use is still considered controversial due to high false-positive rates. We speculated that progesterone could lead to abnormal blood flow patterns and, subsequently, to increased NT. Our primary endpoint was to evaluate the effects of exogenous progesterone on NT thickness compared to controls. The secondary endpoint was to evaluate these effects in a subgroup at low risk for fetal aneuploidies, identifying the strongest factors influencing NT variation. The tertiary endpoint was to evaluate, within the treatment group, if there is any difference in NT according to the type of progesterone administered, route of administration, and dose regimen.

STUDY DESIGN: All women who came to measure NT at 11-14 weeks' gestation (crown-rump length between 45-84 mm) were considered eligible. We divided patients into 2 groups: women receiving exogenous progesterone and controls. Afterwards, 3 NT scans were performed for each case, and the largest value, accurate to 2 decimal points, was recorded.

RESULTS: In all, 3716 women were enrolled and analyzed. In a crude analysis, NT ($P < .05$) increased in the exogenous progesterone group. The same results were obtained in the low-risk group ($P < .05$). The factorial analysis of variance model confirmed a correlation between altered NT and gestational age ($P < .0001$) and progesterone exposure ($P < .05$). The characteristics of treatment (route, formulation, dose) were examined separately and no statistically significant differences among the subgroups were observed.

CONCLUSION: Exogenous progesterone increases NT.

Key words: aneuploidy, embryo development, nuchal translucency, progesterone, ultrasound

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Nuchal translucency (NT) is a transient subcutaneous collection of fluids behind the fetal neck seen ultrasonographically at 11-14 weeks' gestation and is recognized as a sensitive marker for Down syndrome.[1] Despite its important role in the first trimester of pregnancy for Down syndrome screening, the use of NT measurement is still considered controversial[2] particularly due to the verification bias,[3] which is likely to cause overestimation of the detection rate. Furthermore, it is well known that increased NT is also present in euploid fetuses.[4] Many pathophysiological theories have been put forward to explain this increase, so that Allan[5] described fluid retention after exposure to many environmental factors early in pregnancy.

The presence of progesterone receptors has been demonstrated in the placenta and in the fetoplacental vascular tree, especially in the muscular layer of the vessel[6] working through nuclear receptor proteins. It has been demonstrated that progesterone could cause both rapid dose-dependent relaxation of the placental vascular smooth muscle[7] and the proliferation of cultured human vascular smooth muscle cells of the umbilical vein.[8]

With the increased use of progesterone, 2 metaanalyses evaluated its use in the first trimester of pregnancy for both prevention of miscarriage and for treating threatened miscarriage in a low-risk population and stated that it does not modify the outcome.[9,10] A more recent meta-analysis confirmed these data suggesting a possible but still not well-proven effect in patients with a history of recurrent abortion.[11] Actually low clinical evidence continues to support the use of progesterone in the first trimester even to treat threatened miscarriage.[11] Thus, today, the only robust clinical evidence for the use of progesterone is for assisted reproductive technology (ART) pregnancy[12] and for women at high risk for preterm birth.[13] We speculated that the use of exogenous progesterone in the first trimester of pregnancy could lead to abnormal blood flow patterns that may affect both the expression of the growth factors required for the normal development of the fetus and the deregulation of fetal blood pressure. Therefore, this investigation was carried out to make a prospective evaluation of NT thickness

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between 11-14 weeks' gestation among women receiving exogenous progesterone and to compare these findings with controls. The primary endpoint was to evaluate the effects of exogenous progesterone on fetal NT thickness compared to controls. The secondary endpoint was to evaluate these effects even in a subgroup at low risk for aneuploidies and other fetal abnormalities and to identify the strongest factors influencing NT variation. The tertiary endpoint was to evaluate, within the treatment group, if there is any difference in NT according to the type of progesterone administered, the route of administration, and the dose regimen.

Materials and Methods

From January 2008 through November 2009, at the "Altamedica" Fetal-Maternal Medical Center, in Rome, all women requesting the measurement of NT at 11-14 weeks' gestation were considered for the study. Inclusion criteria were: (1) age between 18-39 years; (2) body mass index (BMI) <30 kg/m^2; (3) crown-rump length (CRL) between 45-84 mm; and (4) no concomitant medications other than progesterone. In the enrolled group of women, we identified a cohort group at low risk for aneuploidies and other fetal abnormalities defined as NT <2.5 mm (which is roughly equivalent to the 95th percentile[1]) and those who underwent ART pregnancies.

The institutional review board (Comitato Etico per la Ricerca Scientifica) of "Altamedica" Fetal-Maternal Medical Center approved the study and written informed consent was obtained from all patients. Women were asked if they were taking progestinic therapy. Patients were then divided into 2 groups: women who do not take exogenous progesterone (control group) and women receiving exogenous progesterone (treatment group). Progesterone formulations (micronized, 17-alpha-hydroxyprogesterone, progesterone), routes of administration (intramuscular, intravaginal, orally), and dosing regimens (standard, high) were recorded. We considered as "standard dose" that recommended by the pharmaceutical company: (1) 200 mg-d of the micronized form; (2) 100 mg-d of progesterone; and (3) 682 mg per week of 17-alpha-hydroxyprogesterone. Higher doses were considered as "high dose." Then we excluded women with a progesterone treatment period of <1 week and patients who took progesterone at a dose that was less than the standard dose.

Afterwards, patients were asked about ART or spontaneous pregnancy, medical history and comorbidities, smoking habits, age, and weight and height to calculate the BMI. We excluded patients who used chronic therapies, those affected by chronic hypertension, or those with a history of diabetes mellitus before or during pregnancy.

All women were subsequently submitted to ultrasound evaluation. In all women the gestational age was calculated by fetal CRL[14] at the time of NT measurement by a well-trained sonographer (among a group of 13 operators who were certified according to the Italian College of Fetal Maternal Medicine). In all cases, the General Electric Medical System Voluson 730 Pro or General Electric Medical System Voluson E8 (General Electric, Fairfield, CT) with a 2-dimensional (4.5-16.5 MHz) transabdominal probe was used at the "Altamedica" institution. When the visualization of the fetus was difficult (ie, high BMI) the examination was performed with a 2-dimensional (5-9 MHz) transvaginal probe. Each operator used both ultrasound systems during the study period. We included only fetuses with a CRL between 45-84 mm, which corresponds to a gestational age of between 11^{+0} and 13^{+6} weeks. We excluded patients who had a nonviable fetus, major fetal abnormalities (defined as lethal, incurable, or curable severe abnormalities with a high risk of residual handicap, eg, anencephaly or spina bifida),[15] or multiple pregnancies.

In each eligible woman, 3 NT scans were performed, and the largest value was recorded. In the assessment of fetal NT, the calipers placed on the white lines (on-to-on)[1] provide measurements that are accurate to 2 decimal points. The NT was measured in a neutral position, in midsagittal view, away from amnion, with a maximum lucency and image size $>75\%$.[1]

Statistical analysis

Categorical variables were reported as absolute frequencies and percentages and association between variables was measured by the χ^2 test. Continuous variables were reported as mean $\pm$ SD and multiple of the median (MoM) (95% confidence interval [CI]) and differences were analyzed by the Student t test.

The MoMs were determined based on medians from 19,198 unselected samples.[16]

Normality was assessed by the Shapiro-Wilk test. The effect of progesterone treatment on NT thickness was examined by factorial analysis of variance (ANOVA). The Tukey post hoc test was used for the comparison of mean $\pm$ SD and MoM NT between groups. All data were expressed as mean $\pm$ SD and MoM (95% CI). Factors were included in the model as fixed effects. The significant covariates included in the final model were maternal age, gestational age, BMI, smoking, and therapy with progesterone. A logistic regression model was also used to confirm the independent predictors of NT thickness using the median NT of the whole group. The Wald test was used to determine the significance of each variable in the model. The identification of the strongest factors influencing NT variation was performed in the low-risk cohort group. Furthermore, we excluded women who underwent ART to avoid possible biases.

To standardize the analysis, the characteristics of the treatment were grouped a priori into 3 categories. The categories were decided by the investigators participating in the study. Women were classified according to the type of progesterone administered (micronized, progesterone, 17-alpha-hydroxyprogesterone), by the route of administration (intramuscular, oral, vaginal), and by the dose regimen (standard, high). The mean $\pm$ SD and MoM NT was calculated for each subgroup of the 3 categories considered and the resulting values were then compared.

A 2-sided P value $<.05$ was considered significant. Software (SPSS statistical program, version 16; IBM Corp, Armonk, NY) was used for analysis.