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Predicting the sex of fetus in first trimester based on the crown-rump length

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ABSTRACT

Introduction: Ultrasound examination of pregnant women to assess the anatomy and normal developmental parameters of the fetus has been a standard in obstetrics since the 1980s. Nowadays, attempts are being made to identify sex in early pregnancy. The method of fetal sex determination based on cytogenetic evaluation of fetal cells isolated from maternal blood and free fetal DNA detectable in pregnant women's blood, developed in recent years, requires a specialised laboratory. In view of these conditions, it seems obvious and necessary to search for alternative methods of fetal sex determination at the earliest possible stage of pregnancy.

Therefore, the aim of the present study was to determine the sex of the fetus in the I trimester of pregnancy.

Materials and methods: The initial study included 187 pregnant women who were between 5–10 weeks of gestation (model 1) and the actual study included 240 subjects who were between 5–13 weeks of singleton pregnancy (model 2). A logistic regression model was used to assess the probability of fetal sex based on crown-rump length (CRL), gestational sac volume (GSV), and gestational age.

Results: The study indicates that the sex of the fetus can be predicted with a high probability from ultrasound earlier than previously thought.

Conclusions: After 7 weeks of gestation, differences in the size of male and female fetuses start to become apparent. Male fetuses have on average higher CRL and GSV than female fetuses. This allows predicting male sex with a significantly higher probability.

Keywords: crown-rump length (CRL); gestational sac volume (GSV); sex of fetus; I trimester; ultrasonography.

INTRODUCTION

There are only a few publications in the world literature on methods and results of ultrasonographic diagnosis of fetal sex in the I trimester of pregnancy. Since the landmark publication of Efrat et al. in 2006 which demonstrated the possibility of fetal sex determination in the I trimester of pregnancy and indicated the method of examination, researchers dealing with this problem have been conducting research on the application of this method. The method used by Efrat et al. consists in visualising the fetus with the transabdominal ultrasound transducer in a precise midline dimension and then measuring the angle of the fetal genital cusp in relation to the line drawn through the skin of the lumbosacral region. An angle of less than 10 degrees corresponds to the female sex, while the male sex was diagnosed at an angle of more than 30 degrees. The accuracy of the male sex assignment in the entire study group reached 99–100% and was significantly higher than for the female sex, where it reached 91.5% at 12–12 + 3 weeks and 99–100% only after 12 + 4 weeks [1]. Studies using the same method were conducted by the following teams of researchers: Chelli et al. evaluated the feasibility and accuracy of fetal sex identification by transabdominal ultrasound during the I trimester of pregnancy. The feasibility of sex assignment was estimated at 89.7% and accuracy at 87.9%. Accuracy increased with the increasing crown-rump length (CRL) only in male fetuses. This is due to the observed fact that the measured angle of the genital cusp in male fetuses increased with increasing CRL, while it did not change significantly in female fetuses. At an intermediate angle of 10–30 degrees, the sex was not determined [2].

A broader catalogue of studies devoted to the issue of fetal sex determination in the I trimester of pregnancy using ultrasound techniques [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18] published in the world literature in 1998–2018 is presented in Table 1.

The aforementioned studies differ in the methods of fetal assessment used, such as viewing the genital region of the fetus proposed by the authors of the earliest studies, the method of Efrat et al. [1], the method of Arfi et al. [6], or the use of transverse sections additionally modified by Hsiao et al. [5]. At the same time, as ultrasound technology developed and improved, high-frequency transducers, transvaginal heads, as well as virtual reality and 3D apparatus of Bogers et al. [18] were used in the studies.

Another issue that appears in the literature in the context of estimating the probability of fetal sex is the volume of the gestational follicle. The gestational follicle in the I trimester

TABLE 1. Ultrasonographic determination of fetal sex in the first trimester

Author	Year of survey	Head	Test criterion	Gestational age weeks	Gender identification impossible	Gender identification possible
Mielke et al. [7]	1998	transabdominal	sagittal and transverse sections	11–16	19.6%	80.3%
Benoit [8]	1999	transvaginal	sagittal section	12–12.6	46.2%	98.5%
Whitlow et al. [9]	1999	transabdominal and transvaginal	sagittal and transverse sections	11 12 13 14	41% 13% 8% 2%	78% 86% 87% 92%
Mazza et al. [10]	1999	transabdominal and transvaginal	sagittal section	11–11.6 12–12.6	13.4% 0%	76.5% 87.9%
Efrat et al. [11]	1999	transabdominal	sagittal section (1)	12–12.6 13–13.6	7.2% 12.2%	98.7% 100%
Pedreira [12]	2000	transabdominal	cross-section	11–11.6 12–12.6 13–13.6		77.4% 79.5% 90.3%
Pedreira et al. [13]	2001	transabdominal	cross-section	11–11.6 12–12.6 13–13.6	1.5%	80% 97% 90.9%
Mazza et al. [17]	2004	transabdominal and transvaginal	sagittal section	11–11.6 12–12.6 13–14	26% 4.5% 2.5%	73.8% 91.3% 99.8%
Hyett et al. [16]	2005	transabdominal	sagittal section (1)	10.5–11.4 12–12.6 13.2	2% 1% 0%	100% 100% 100%
Chi et al. [15]	2006	transabdominal	sagittal section (1)	11–11.6 12–12.6 13–14	1% 1% 0%	100% 100% 100%
Efrat et al. [1]	2006	transabdominal	sagittal section (1)	12–12.3 12.4–12.6 13–13.6	15% 4% 2.7%	95.5% 99% 100%
Hsiao et al. [5]	2008	transabdominal	saggital and cross-section	11 12 13	40.6% 5.35% 2.27%	71.9% 92% 98.2%
Chelli et al. [2]	2009	transabdominal	sagittal section (1)	11–11.6 12–12.6 13–14.3	10.8% M 8.1% F	68.4% 90.8% 83.9%
Lubusky et al. [3]	2012	transabdominal	sagittal section (1)	11.4–12 12–12.2 >12.2	36.5% 9.5% 2.6%	75% 96.6% 100%
Manzanares et al. [4]	2016	transabdominal	sagittal section (1)	11–13.6	9.5%	87.5
Arfi et al. [6]	2016	transabdominal	sagittal section (2)	<12 12–13 >13		66% M; 100% F 91% 100% M; 64% F
Bogers et al. [18]	2018		3D the angle of inclination of the genital cusp			<58%

Explanations: (1) angle > 30 degrees – male fetus; angle < 30 degrees – female fetus; (2) anogenital distance; M – male; F – female

consists of 2 cavities: the amniotic cavity and the extraembryonic cavity [19, 20]. It appears in the 5th week of normal pregnancy and by the time the embryo appears, in the 6th week of pregnancy, the average gestational sac diameter (GSD) is about 10 mm [21]. Gestational sac diameter is an important parameter of pregnancy growth in the I trimester. Robinson was the 1st to measure gestational sac volume (GSV) including embryonic structures, and gestational sac fluid volume (GSFV) using the planimetric method [22]. Gestational sac fluid volume was obtained by subtracting the embryonic volume derived

from Streeter data from GSV [23]. Robinson's results showed that GSFV increased from 1 mL at 6 weeks gestation to 28 mL at 10 weeks and to 80 mL at 13 weeks [22].

The identification in 1997 by Lo et al. of cell-free fetal DNA (cffDNA) in the plasma and serum of pregnant women, as a source of fetal genetic material, enables the identification of the Y chromosome sequence and thus early, reliable, and minimally invasive determination of fetal sex allowing the avoidance of conventional invasive prenatal diagnostic methods [24]. This method, due to its high cost, is not readily available and cannot be treated as a routine procedure. In view of these conditions, it seems obvious and necessary to search for alternative methods of fetal sex assessment in the earliest possible period of pregnancy. Therefore, the aim of the present study was to determine the fetal sex in the I trimester of pregnancy based on measurement of its CRL and gestational follicle volume on ultrasound examination.

MATERIALS AND METHODS

The study was divided into 2 parts: a preliminary study (model 1) and an extended study (model 2). The aim of the preliminary study was to identify the possibility of predicting fetal sex by taking into account 2 parameters: CRL and GSV, and to resolve the validity of excluding one of these parameters (in case of collinearity) or the need to observe both parameters simultaneously. The aim of the extension study was to obtain the best possible model for estimating the probability of fetal sex in early pregnancy.

The entry point for the study was a live pregnancy. Aborted pregnancies or spontaneous miscarriages were excluded from the study. There were no abnormalities related to the course of the pregnancy, its termination or the health of the mother in the study group that could in any way affect the results of the study. Table 2 shows the basic descriptive statistics of anthropometric characteristics of the patients participating in the study. The patients are a heterogeneous group on average in terms of age, weight, height, BMI, and number of pregnancies, but such heterogeneity reflects well the anthropometric characteristics of the general population of women of childbearing age. According to the Kolmogorov–Smirnov test with the Lilliefors correction, the studied variable distributions are normal with $p < 0.05$.

TABLE 2. Anthropometric characteristics of the studied patients

Features	Descriptive statistics		
	min.	mean	max.
Age (years)	16	26.2	41
Weight (kg)	40	63.2	90
Height (cm)	150	166.2	182
BMI	15.4	22.9	34.6
No. of pregnancies	1	1.8	7

The initial study included 187 pregnant women who were at 5–10 weeks of gestation (model 1) and the actual study included 240 subjects who were at 5–13 weeks of singleton pregnancy (model 2).

Ultrasound examinations were performed with a GE Voluson 730-Pro ultrasound machine by an FMF-certified ultrasonographer. Up to the 11th week of pregnancy, examinations were performed with a vaginal transducer and from the 11th week of pregnancy with a transabdominal convex transducer. Fetal CRL and GSV were assessed in relation to gestational age (GA) calculated from the date of last menstrual bleeding and the sex of the baby at birth. The women included in the study gave birth to 104 boys and 83 girls.

The CRL measurements obtained were initially divided into pregnancies up to 7 weeks and after 7 weeks. The rationale for this division was the finding that up to 7 weeks in the boys' group, CRL is weakly dependent on GA.

A logistic regression model was used to assess the probability of fetal sex based on CRL, GSV, and GA:

$$P(X = male) = \frac{e^{a_0 + a_1 \mathrm{GA} + a_2 CRL + a_3 GSV}}{1 + e^{a_0 + a_1 \mathrm{GA} + a_2 CRL + a_3 GSV}}$$

when: GA – gestational age; CRL – crown-rump length; GSV – gestational sac volume

A quasi-Newton estimation procedure was used. The significance of the model as a whole was tested using the χ^2 test, while the significance of individual model parameters was tested using the Student's t-test and the Wald χ^2 test. Calculations were performed using the Statistica 13.3 software.

The odds ratio, which is the product of correctly classified cases to incorrectly classified cases, was also assessed for the study population.

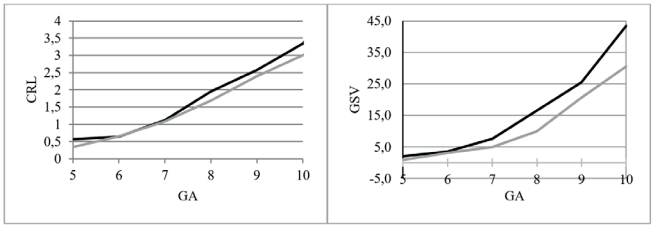
RESULTS

Model 1a

The study of the relationship between the CRL parameter by sex and week of gestation can be presented at mean levels. In Figure 1, a progressive difference in the size of CRL between male and female fetuses can be observed from the 8th week of gestation onwards. Hence, week 7 of gestation was considered crucial in the study. Up to the 7th week, the development of male and female fetuses was similar, i.e. there was no clear difference in CRL dimensions. The GSV parameter was similar, although the difference between male and female fetuses started to be visible from the 6th week of gestation but the difference increased from the 7th week of gestation.

The model as a whole is close to being statistically significant ($p = 0.15$). However, the individual parameters of the model are statistically insignificant, as for the GA parameter we obtained $p = 0.49$, for CRL parameter $p = 0.38$, and for GSV parameter $p = 0.30$. It is worth noticing the signs next to GA parameters – negative, and CRL and GSV – positive; on the basis of them we can conclude that the higher CRL and GSV dimension with

lower GA gestational week, the higher probability that the fetus is male.



GA – gestational age
Explanations: black line – male, grey line – female

FIGURE 1. Mean levels of crown-rump length (CRL) and gestational sac volume (GSV) at successive weeks of gestation

A logistic regression model was used to estimate the probability of the sex of the baby based on the parameters of the gestational week, CRL, and gestational follicle volume. This model, based on the combination of GA, CRL and GSV parameters for the whole sample population, allows estimating the sex of the fetus. It takes the following form:

$$P(X = male) = \frac{e^{0,7713-0,1491GA+0,3163CRL+0,0153GSV}}{1+e^{0,7713-0,1491GA+0,3163CRL+0,0153GSV}}$$

when: GA – gestational age; CRL – crown-rump length; GSV – gestational sac volume

The odds ratio for the model is 2.09, which is clearly better than for random sex assignment, for which the odds ratio is 1.

Model 1b

After restricting the model to data from the 7th week of pregnancy, the logistic regression equation changes its form as follows:

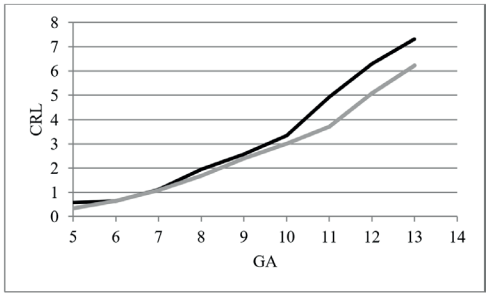
$$P(X = male) = \frac{e^{1,7360-0,2594GA+0,3580CRL+0,0123GSV}}{1+e^{1,7360-0,2594GA+0,3580CRL+0,0123GSV}}$$

when: GA – gestational age; CRL – crown-rump length; GSV – gestational sac volume

The model as a whole is not statistically significant (p = 0.31), as well as the individual parameters, for GA we obtained p = 0.32, for CRL parameter p = 0.34, and for GSD parameter p = 0.40. The interpretation of the signs of the parameters is analogous to that described above. However, the quotient for this model is much higher, i.e. 2.74. Thus, the model allows better estimation of the sex of the child; this happens with the sample limited from the 7th week of pregnancy and therefore limited in terms of numbers. It follows that 2 potential problems of model significance are revealed here, the 1st relates to the size of the sample population and the 2nd to the range of GAs adopted.

Model 2

By increasing the size of the sample population and also allowing for patients at 10–13 weeks of gestation, a statistically significant model can be obtained [25]. Figure 2 presents data on the association between CRL and GA. The presented data show that after the 10th week of pregnancy there is a further increase in the difference in CRL between male and female fetuses.



GA – gestational age
Explanations: black line – male, grey line – female

FIGURE 2. Mean crown-rump length (CRL) in the consecutive weeks of pregnancy

Due to the collinearity of the relationship between CRL and GSV parameters, the model was performed only for the combination of GA and CRL, for pregnant women at over 7 weeks of gestation. Its formula is presented as follows:

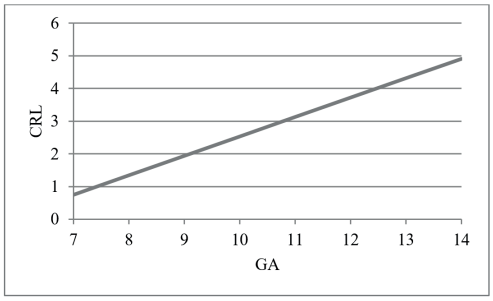
$$P(X = male) = \frac{e^{1,9926-0,3479GA+0,5873CRL}}{1+e^{1,9926-0,3479GA+0,5873CRL}}$$

when: GA – gestational age; CRL – crown-rump length

The model as a whole is statistically significant (p = 0.01). Also, individual parameters of the model were either statistically significant, for the CRL variable p = 0.01, or close to statistical significance, for the GA variable p = 0.06.

The presented model shows that the higher the value of the CRL parameter with a lower value of GA, the higher the probability that the child will be male and lower the probability that the child will be female. Conversely, the lower the value of the CRL parameter with a higher value of the GA parameter, the less likely the child will be male and the more likely the child will be female.

Figure 3 shows the combinations of GA and CRL parameters at which the probability that the fetus is male and female is the same. The greater the difference between the GA and CRL combinations and the equal probability line, the greater the probability that the fetus is female (for combinations below the line) or male (for combinations above the line).



CRL – crown-rump length; GA – gestational age

FIGURE 3. The equal probability line

DISCUSSION

Estimating the sex of the fetus in early pregnancy is still an unsolved issue. The main difficulty comes from the rather late development of the genitalia. The present work is part of the body of research that attempts to estimate the sex of the fetus in very early pregnancy.

The difficulties associated with the determination of sex in early pregnancy have already been encountered by Lubusky et al. In their study based on the evaluation of the genital area in the medial sagittal plane, the sex of the fetus was assessed. A close, directly proportional relationship was found between CRL increasing with GA and the feasibility and accuracy of sex determination. At a CRL of less than 50 mm, corresponding to a gestation of less than 11 + 4 weeks, due to a feasibility of assessment of 39.1%, with an accuracy of 30.5% (40.9% in males and 24.3% in females), the sex of the fetus could not be reliably predicted. Only at a CRL above 60 mm (GA above 12 + 2 weeks) did the feasibility reach 97.4% and accuracy 100% in both sexes. Thus, the key point in that study appeared to be the 12th week of pregnancy [3]. In our study, we attempt to push this boundary towards 7 weeks of gestation.

Other studies also take the higher GA as the cut-off. Manzanares et al. attempted to evaluate the feasibility and accuracy of determining fetal sex on transabdominal ultrasound at 11–13 + 6 weeks of gestation and the factors that affect the accuracy of the assessment. The method of the study was to assess the angle of the genital cusp in the sagittal plane. The accuracy of fetal sex prediction was favored by an increase in fetal CRL above 55.7 mm, GA above 12 + 2 weeks, and a pregnant woman's BMI below 23.8. None of the other factors analyzed affected the ability and accuracy of fetal sex assessment [4]. Similar results were also obtained by Hsiao et al. [5]. Arfi et al. proposed their own different method of fetal sex identification subject to the measurement of the anogenital distance, i.e. the distance between the caudal end of the fetus and the base of the genital cusp. This distance, from the 11th week of gestation, varies according to the sex of the fetus. A distance of 4.8 mm or more allows the identification of a male fetus, while a distance less than 4.8 mm characterizes female fetuses [6].

It can therefore be asked whether it is necessary to estimate the sex of the fetus at such a preliminary stage. The answer to this question is most positive. Unlike in female fetuses, male genital differentiation is preceded by gonadal maturation. The male phenotype depends on the presence of testosterone and anti-miller hormone secreted in the fetal testes, whereas the female phenotype depends on their absence. The beginning of the differentiation of the testis occurs in the 6th–7th week of gestation, when the sex cords formed by the Sertole cells are formed. In the 8th week of gestation, testosterone-producing Leydig cells, differentiated from mesenchyme, are observed in the testis. Testosterone production is stimulated by high levels of human chorionic gonadotropin. The absence of testicular development at 6–8 weeks of gestation is the evidence of a primary, temporarily inactive ovary [26]. Early diagnosis of fetal sex is especially important in the context of genetic diseases related to the X chromosome. In the world literature of the last 15 years, several attempts to assess fetal sex on the basis of ultrasound examination performed in the I trimester of pregnancy have been presented [1, 2, 3, 4, 5, 6]. All these studies focused on the final weeks of the I trimester and covered the range of 11–13.6 weeks of gestation. The authors assessed the distance between the caudal end of the fetus and the base of the genital cusp [6], the angle of the genital cusp measured in the sagittal plane [1, 2, 3, 4, 5], or the combined CRL and genital area of the fetus [3]. The authors of the presented studies agree that the accuracy of fetal sex assessment increases significantly with GA. They set the cut-off point for reliable results at 11 weeks of gestation [6], 12.2 weeks of gestation and CRL 56.7 mm [4] and 11.4–12 weeks of gestation and CRL 50–54.9 mm [1, 2, 3].

Our study indicates that the sex of the fetus can be predicted with a high probability from ultrasound earlier than previously thought. Obviously, the error made in estimating the sex of the fetus in very early pregnancies is greater than in later pregnancies, but given the possible applications, this issue is worth discussing.

CONCLUSIONS

In the presented study, the research problem was the relationship between GA, fetal length, and gender. The obtained results subjected to statistical analysis allow us to state that:

1. up to 7 weeks, there is no clear difference in the size of male and female fetuses; after 7 weeks of gestation differences in the size of male and female fetuses start to become apparent. Male fetuses have on average higher CRL and GSV parameters than female fetuses;
2. compared to random sex assignment, the determined logistic model allows predicting male sex with a significantly higher probability;
3. better results were obtained from the combinations of GA and CRL than those of GA and GSD. However, it is worth continuing research on much larger populations using these combinations, as the results are promising;
4. early diagnosis of fetal sex is especially important in the context of genetic diseases related to the X chromosome. The presented approach to fetal sex estimation is a cheap and non-invasive method for further diagnostics.

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