Original Research

Associations between fetal biometric parameters and maternal characteristics in the prenatal screening phase for aneuploidies

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Abstract

Background and Aim. Aneuploidies are rare diseases with great impact on an individual's life, as well as on their families, the reason why prenatal screening is performed, allowing families to take an informed decision. Initial prenatal screening includes the double test, triple test, non-invasive prenatal testing and ultrasonography. Among these, ultrasonography plays an important role giving information regarding an elevated risk for aneuploidies.

Methods. Eighty-four pregnant women who underwent prenatal screening were included in this study, of whom 9 cases were diagnosed with an aneuploidy. A statistical analysis was performed to identify possible associations between morpho-fetal characteristics, estimated fetal growth, and other parameters, such as maternal characteristics or gestational age.

Results. As expected, based on the data available in the literature, an advanced maternal age was observed in the high-risk group, compared to the low-risk one (the risk was evaluated after the initial screening and influenced the decision of a further amniocentesis). A good correlation was observed in this study between the fetal biometric parameters and gestational age, as well as between fetal biometric parameters and maternal weight gain in healthy pregnancies, while low or no correlations were found in the aneuploid pregnancies.

Conclusions. The results of our study highlight the importance of ultrasonography evaluation and reveal possible correlations of fetal parameters with maternal characteristics. These findings, together with already well-established parameters, might suggest stronger clusters of soft markers and bring supplementary information regarding the risk level of pregnancy, in order to perform a better assessment of cases where invasive diagnosis is required.

Keywords: trisomy 21, trisomy 18, trisomy 13, monosomy X, prenatal screening, fetal biometry

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Introduction

Aneuploidies represent chromosomal abnormalities in which a cell has an abnormal number of chromosomes, meaning either extra copies or missing copies of one or more chromosomes. Down syndrome (DS; trisomy 21) results from the presence of an extra chromosome 21, typically due to meiotic nondisjunction during the first or second meiotic division in the oocyte. It is the most common autosomal trisomy associated with a genetic form of intellectual disability and represents a major cause of congenital anomalies worldwide. Approximately half of individuals with DS are diagnosed with cardiac or digestive malformations, while affected children are also at increased risk for leukemia and early-onset Alzheimer's disease [1,2].

The prevalence of DS is strongly influenced by maternal age and is relatively consistent across multi-ethnic

populations, estimated at 1 in 640 infants in the United States. However, variation exists among certain groups, likely due to complex gene–environment interactions. Higher prevalence rates have been reported among Jews of non-European origin in Israel and among U.S. residents of Mexican or Central American origin [2,3].

In contrast, trisomy 13 and trisomy 18 are less frequent, with live birth prevalence in the United States estimated at 1 in 12,340 and 1 in 6,670, respectively [4]. These syndromes can arise from complete trisomy or from partial trisomy due to unbalanced translocations [5]. Prognosis remains poor, with population-based studies reporting 1-year survival rates between 0 and 8% for both conditions [6,7].

In Romania, prenatal DS screening follows a combined approach based on maternal age, ultrasound parameters, and biochemical serum markers during the first or second trimester, with adjustments for maternal weight, ethnicity, smoking status, and patient history. For women not screened in the first trimester, second-trimester assessment (the "triple test") combines maternal age with biochemical parameters including alpha-fetoprotein (AFP), beta-hCG, and unconjugated estriol (uE3) between 15 and 18 weeks of gestation. Some strategies also integrate ultrasound parameters such as biparietal diameter (BPD). A risk assessment software such as Astraia or Prisca is generally used, with calculations based on maternal age, patient history, biochemical markers, and ultrasound findings (e.g., nuchal translucency, nasal bone, fetal heart rate, crown-rump length, PAPP-A, and beta-hCG). More recently, non-invasive prenatal testing (NIPT) using massive parallel sequencing of cell-free fetal DNA has been introduced as an alternative, especially for cases with intermediate risk. Depending on the outcome, patients are stratified into negative (follow-up ultrasound), positive (fetal karyotyping), or intermediate risk (further NIPT) categories.

Ultrasound remains an important tool for detecting chromosomal abnormalities through the identification of "soft markers", which are not pathological by themselves but are associated with increased risk of aneuploidy. Commonly assessed markers include choroid plexus cysts, echogenic intracardiac foci, mild ventriculomegaly, nuchal fold thickening, echogenic bowel, pyelectasis, shortened long bones, and absent or hypoplastic nasal bone. Novel markers, such as aberrant right subclavian artery, have also been proposed [8]. The cumulative presence of multiple markers further elevates the risk of chromosomal abnormalities.

Despite the availability of screening tests, the incidence of DS at birth in Romania has remained relatively constant, with reported rates of 1 in 1,606 births in 2000, 1 in 1,863 in 2015, and 1 in 1,975 in 2018 [1]. Large prospective international studies have shown that first-trimester combined screening can detect >90% of trisomy 21 cases, with a false-positive rate of 3–5% [9–12]. The accuracy of risk estimation can be further improved using different algorithms and combinations of nuchal translucency with biochemical markers such as PAPP-A and free beta-hCG [9,13–16].

Nonetheless, current screening strategies have limitations. Approximately 30% of DS cases remain undetected [17], and while the introduction of cell-free DNA testing has reduced the need for invasive procedures, its impact on overall detection rates is limited due to restricted availability, high cost, and insufficient systematic data [18,19]. Screening remains crucial, as it allows families to receive timely information, facilitates medical management, and enables termination of pregnancy before 24 weeks in accordance with Romanian legislation. Therefore, improving detection rates while minimizing false positives continues to be a priority in prenatal care.

Hence, the purpose of the present study was to investigate possible associations between morpho-fetal characteristics, such as BPD, occipito-frontal diameter, head circumference (HC), abdominal circumference (AC), femur length (FL), estimated fetal growth, and other parameters (maternal characteristics or gestational age (GA)) that could bring additional information over the risk of genetic disorders, by defining powerful clusters of soft markers, with increased sensibility and specificity, in order to identify cases where invasive diagnosis is required.

Methods

Data collection

We conducted a prospective study with cross-sectional data collection on 84 pregnant women in their first and second pregnancy trimester, who attended their antenatal check-up at the IMOGEN Research Institute, within the Cluj County Emergency Clinical Hospital, from July 2023 to May 2024. The study was approved by the Scientific Research Ethics Committee from Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca (253/14.07.2020).

Demographic data and other information regarding the medical history of the women included in the study or characteristics of the pregnancies, (gestational age (GA), complications) were registered at the moment of the initial screening (ultrasonography).

Inclusion criteria

The study included patients with a viable pregnancy, with the GA between 11 -22 estimated weeks of pregnancy.

Exclusion criteria

Patients with incomplete medical records, and patients who have not signed an informed consent for the study inclusion were excluded.

Measurement of parameters

Estimated fetal weight (EFW) was derived from the Hadlock formula, which combines BPD, HC, AC and FL.

GA was assigned per accepted criteria: a valid last menstrual period date, dates of negative and positive

pregnancy test results, first-trimester sonographic examination, and preamniocentesis fetal biometric measurements.

The biometric measurements were performed by two examinators on a GE Voluson E8 Expert ultrasound device, with variable frequency probes, according to the clinical guidelines developed by Romanian Society of Obstetrics and Gynecology, and hard copy images were printed.

The subgroup of patients at high risk was defined based on maternal age or the results obtained for the double test or non-invasive prenatal test (NIPT) on prior medical check-up. More specifically, the criteria that led to the inclusion on the high-risk group and further screening included: maternal age>35 years old; a high risk suggested by a double test or a NIPT; maternal infections that could increase the risk of malformations (cytomegalovirus), or malformations observed during the ultrasonography evaluation. Supplementary tests via amniocentesis were performed for this group of patients

Chromosomes 13, 18, 21, X, and Y were tested for aneuploidies using DNA extracted from amniotic fluid. The initial results from QF-PCR were then confirmed through karyotyping. Fetal karyotype was unknown at the time of the sonographic examination, but known at the time of retrospective review of sonographic images.

Statistical analysis

Statistical analysis and data visualization were performed in STATISTICA (Version 13.5, StatSoft, OK, USA), Jamovi (Version 2.6, Sydney, Australia) and Microsoft Excel for Microsoft 365 MSO (Version 2507). Normality of data was evaluated by descriptive indicators and Shapiro-Wilk test. We described the categorial variables as absolute and relative frequencies (n, %) and quantitative data as median, interquartile range (IQR, 25th percentile – 75th percentile) and {minimum to maximum values}, since they did not follow the Gaussian distribution. Fisher's Exact test was used to evaluate the bivariate association between qualitative variables followed by relative risk and its 95% confidence interval for the effect size measurement whenever appropriate, whereas Mann-Whitney U test was performed to determine the difference in the distributions of quantitative variables. Spearman's rank correlation coefficient (ρ) was used to describe the monotonic relationship between quantitative variables. All statistical tests we performed were two-sided tests, a significant result being considered for a p-value < 0.05.

Results

Descriptive analysis

The group of patients with increased risk in whom amniocentesis was recommended included 41 pregnant women, while the low-risk group consisted of 43 women (Figure 1). The distribution of criteria types based on which the amniocentesis was performed in the high-risk group, for both pathological and normal karyotypes is pictured in figure 2. The most frequent criteria were genetic in both subgroups, with a significantly higher percentage in the subgroup with pathological karyotypes (90% versus 40.6%, Fisher's exact test, p=0.01).

Maternal age registered in the high-risk group was significantly higher than in the low-risk group, with a median age of 36.9 years and 28.3 years, respectively (Mann-Whitney test, p<0.01, see table I).

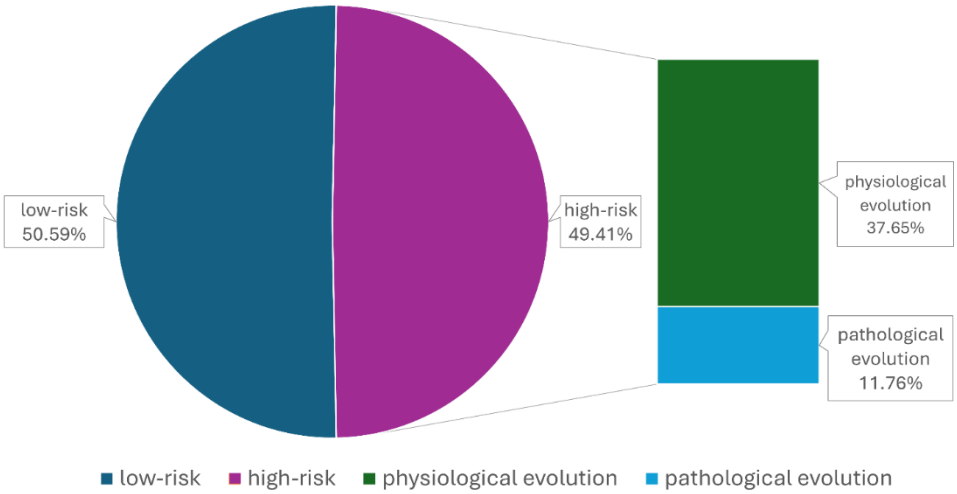

Figure 1. Distribution of the risk type and evolution of the pregnancy in the study group.

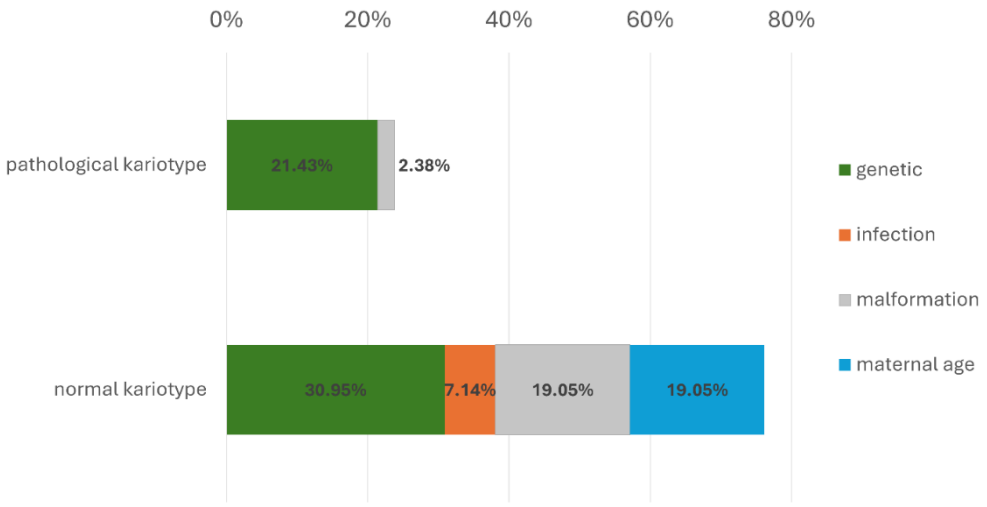

Figure 2. Prevalence of each risk criteria in the high-risk group.

Considering the maternal characteristics, we found no significant differences in the educational level, background, smoking or marital status between high- and low-risk subgroups (Table I). Among the most relevant characteristics of maternal medical history, dysmenorrhea and past oral contraceptive treatments were significantly associated with a high risk of aneuploidies (Table II). As far as the most relevant medical conditions of the pregnancies are concerned, a higher rate of miscarriage was found in low-risk subgroup, thus requiring medical treatment with progesterone (Table III). Likewise, there was a tendency towards a statistical significance for the association of folic acid and a decrease in the risk of a genetic disorder. The women who received folic acid supplementation had almost a two-fold decrease in genetic disorder risk (RR=0.58 (IC95% 0.38; 0.89)).

Table I. Maternal characteristics of patients included in the study.

Characteristic	High-risk group (n_1=41)	Low-risk group (n_2=43)	p-value
Maternal age (years)	36.9 [31.3-40.3] {17.8-45}	28.3 (24.5-31.8) {15.8-37.6}	<0.001*
Educational level • High • Low	 19 (45.2) 23 (54.8)	 21 (48.8) 22 (51.2)	0.740**
Smoker status	14 (34.1)	10 (23.3)	0.155**
Marital status • Unmarried	 14 (35)	 16 (37.2)	0.834***
Background • Rural areas	 20 (48.8)	 16 (37.2)	0.284***

Quantitative variables were described as median (quartile 1- quartile 3) {minimum value- maximum value}, and the qualitative ones were described as absolute frequency (percentage, %); *Mann-Whitney U test, **Fischer test, ***Chi-square test.

Table II. Maternal medical history.

Characteristic	High-risk group (n_1=41)	Low-risk group (n_2=43)	p-value*
History of genetic diseases in the family	3 (7.3)	1 (2.3)	0.112
Pregnancy losses	9 (22)	7 (16.3)	0.507
Complications of anterior pregnancies	5 (11.9)	4 (9.3)	0.738
General medical history of the patient**			
• Thrombophilia	1 (2.4)	4 (9.3)	0.175
• Thrombocythemia	1 (2.7)	-	0.773
• Hypothyroidism	1 (2.4)	5 (11.6)	0.202
• Dysmenorrhea	7 (16.7)	-	**0.005**
• Conization	3 (7.1)	-	0.074
Gynecological treatment before pregnancy			
• Oral contraceptives	12 (28.6)	-	**<0.001**
• Fertility treatment	-	1 (2.3)	0.320

Variables were described as absolute frequency (percentage, %); *Fischer test; **Only the most frequent pathologies within the study group were reported.

Table III. Characteristics of the present pregnancies.

Characteristic	High-risk group (n_1=41)	Low-risk group (n_2=43)	p-value*
Impending miscarriage treatment (progesterone)	2 (4.8)	10 (23.3)	**0.014**
Folic acid treatment	34 (82.9)	41 (95.3)	0.085
Gynecological conditions			
• Pre-eclampsia	1 (2.4)	1 (2.4)	0.987
• Impending miscarriage	2 (4.8)	10 (23.3)	**0.014**

Variables were described as absolute frequence (percentage, %); *Fischer test.

Of all the 84 pregnancies evaluated in our study, in 9 pregnancies a prenatal diagnosis of aneuploidy was established: 3 pregnancies with monosomy X, 2 pregnancies with trisomy 13, one pregnancy with trisomy 18 and 4 pregnancies with trisomy 21 (Figure 1 and Figure 3). The information regarding the GA at the moment of evaluation was missing in one case for each group (pathological and healthy pregnancies). A significantly higher gestational age was found in patients with pathological pregnancies, with a median value of 16.7 (16.3-17.1) {15.6-17.6} weeks, than in patients with normal karyotype, in whom the median gestational age was 13.1 (12.4-17) {11.7-22.3} weeks (Mann Whitney U, p=0.03).

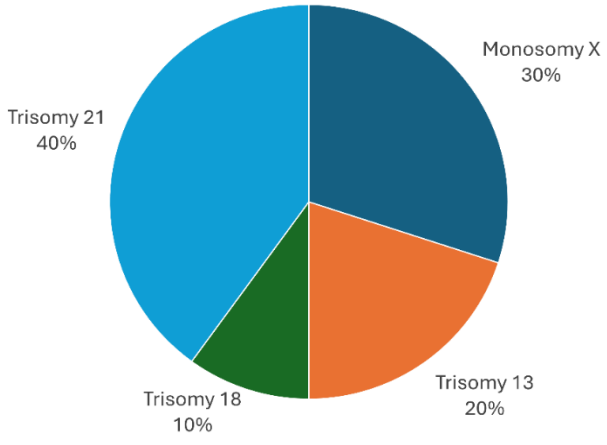

Figure 3. The incidence of aneuploidies in the study group.

Associations between fetal biometric parameters, screening results and maternal characteristics

Regarding the differences between the fetal biometric parameters in pathological and physiological pregnancies, we found that the median values of all parameters (BPD, occipito-frontal diameter, HC, AC, FL, estimated fetal weight and maternal weight gain), were smaller in the pathologic pregnancies group than in the healthy pregnancies group, even though the comparisons did not reach statistical significance (Mann Whitney tests, $p>0.05$, see table IV).

However, all fetal biometric parameters were strongly correlated with gestational age (Spearman's rank correlation coefficient > 0.85, $p<0.05$) and moderate to very good correlation was found between all materno-fetal characteristics in the healthy pregnancies group (Table V). On the other hand, in the pathological pregnancies group, weak and insignificant correlations were observed between morpho-fetal parameters and maternal characteristics or GA, while only cranial measurements, femur length and estimated fetal weight, respectively, were significantly correlated (Table VI).

Table IV. Fetal biometric parameters in pathological versus physiological pregnancies.

Materno-fetal characteristic	Pathological pregnancies (n_1=7)	Physiological pregnancies (n_2=28)	p-value*
biparietal diameter (cm)	3.59 (3.49-3.70) {3.17-3.85}	3.67 (3.49-4.46) {3.03-5.73}	0.257
occipitofrontal diameter (cm)	4.62 (4.39-4.66) {4.03-4.81}	4.77 (4.46-5.59) {3.91-7.30}	0.132
cranial circumference (cm)	13.30 (13-13.70) {11.80-13.90}	13.70 (12.90-16.60) {11.50-21.10}	0.274
abdominal circumference (cm) [(a)]	11.6 (11.0-12.50) {10.90-12.90}	11.70 (10.40-14.30) {8.97-19.10}	0.946
femur length (cm)	2.04 (2.02-2.31) {1.61-2.73}	2.33 (1.99-3.04) {1.47-4.10}	0.274
estimated fetal weight (g) [(a)]	176 (160-202) {158-224}	185 (148-286) {113-567}	0.769
maternal weight gain (kg) [(a)]	5 (3.25-6.75) {2-11}	3.75 (2-6) {-3-10}	0.318

Variables were described as median (quartile 1-quartile 3) {minimum value-maximum value};[(a)] complete case data (pathological pregnancy) =6; *Mann Whitney U test.

Table V. Association between fetal biometric parameters and maternal characteristics in healthy pregnancies

	Parameter	gestational age (weeks)	biparietal diameter (cm)	occipito-frontal diameter (cm)	head circumference (cm)	abdominal circumference (cm)	femur length (cm)	estimated fetal weight (g)	maternal weight gain (kg)
biparietal diameter (cm)	ρ	0.858	N/A						
	p-value	<0.001							
occipito-frontal diameter (cm)	ρ	0.902	0.941	N/A					
	p-value	<0.001	<0.001						
cranial circumference (cm)	ρ	0.893	0.969	0.979	N/A				
	p-value	<0.001	<0.001	<0.001					
abdominal circumference (cm)	ρ	0.951	0.891	0.944	0.923	N/A			
	p-value	<0.001	<0.001	<0.001	<0.001				
femur length (cm)	ρ	0.944	0.933	0.949	0.955	0.961	N/A		
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001			
estimated fetal weight (g)	ρ	0.964	0.918	0.957	0.948	0.990	0.985	N/A	
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001		
maternal weight gain (kg)	ρ	0.376	0.512	0.505	0.463	0.510	0.474	0.500	N/A
	p-value	0.001	0.009	0.010	0.020	0.009	0.017	0.011	

ρ=Spearman rank coefficient value, complete case values=28, except for weight growth and gestational age=69, N/A-not applicable.

Tabel VI. Association between fetal biometric parameters and maternal characteristics in pathological pregnancies

	Parameter	gestational age (weeks)	biparietal diameter (cm)	occipito-frontal diameter (cm)	head circumference (cm)	abdominal circumference (cm)	femur length (cm)	estimated fetal weight (g)	maternal weight gain (kg)
biparietal diameter (cm)	ρ	-0.110	N/A						
	p-value	0.814							
occipito-frontal diameter (cm)	ρ	0.073	0.560	N/A					
	p-value	0.877	0.191						
cranial circumference (cm)	ρ	0.198	0.800*	0.685	N/A				
	p-value	0.670	0.031	0.090					
abdominal circumference (cm)	ρ	-0.058	0.294	0.290	0.600	N/A			
	p-value	0.913	0.571	0.577	0.242				
femur length (cm)	ρ	0.427	0.376	0.518	0.487	0.203	N/A		
	p-value	0.339	0.406	0.233	0.268	0.700			
estimated fetal weight (g)	ρ	-0.059	0.209	0.441	0.522	0.638	0.868*	N/A	
	p-value	0.912	0.691	0.381	0.288	0.173	0.025		
maternal weight gain (kg)	ρ	0.348	-0.154	0.154	0.300	0.800	0.205	0.949	N/A
	p-value	0.499	0.805	0.805	0.683	0.333	0.741	0.051	

ρ=Spearman rank coefficient value, complete case values=7, except for abdominal circumference and estimated fetal growth=6, N/A-not applicable.

Discussion

Almost half of the patients included in this study (48.2 %) were considered to have increased risk for genetic fetal disorders as indicated by the initial screening based on maternal age, double test or NIPT (Figure 1). This high rate could be explained partly by the role of the clinical and research center in which the study was performed in our region, as a tertiary unit. Even though the initial screening could have been performed in other clinical centers, some patients with obvious risk factors (e.g. maternal age, history of a genetic disorder in the family) presented themselves directly to this research center, motivated by the possibility of further exploration (amniocentesis, chorionic villus sampling).

Despite the small number of the study sample, and thus of the aneuploidies identified, the previously reported prevalence of each aneuploidy in larger samples [20] is partly in accordance with the results of our study, where DS was the most frequent genetic disorder diagnosed, followed by monosomy X and trisomies 13 and 18 (Figure 3). Since the advanced maternal age (>35 years old) is considered one of the main criteria for high-risk pregnancies, this is also reflected by our results which showed a significantly higher maternal age in the high-risk group compared with the low-risk group (Table I). The association between the advanced maternal age and DS is well-known and was reported back in the first half of the 20th century, primarily resulting from increased meiotic nondisjunction [20]. Regarding the higher GA in the pathologic group in comparison with the group with physiological evolution, a possible explanation is the hesitancy of women to undergo this screening when they present with some known risk factors, such as the maternal age.

Our results reveal a trend toward statistical significance of the association between folic acid supplementation and reduced risk of genetic disorders (Table III). Our findings are in accordance with the available recommendation regarding the use of folic acid during pregnancy. Folic acid is important in DNA and RNA synthesis, hematopoiesis and neuronal function. It is recommended in the periconceptional phase due to its benefits in the prevention of fetal neural tube defects and chromosomal fragility. Besides neural tube defects, inadequate folate intake has been linked to a higher risk of DS, cardiovascular disease, Alzheimer's disease, and several types of cancer [21,22]. Therefore, the increased use of folic acid in the euploid pregnancies group compared to the aneuploid ones, could reinforce the importance of this nutrient in the physiological evolution of pregnancy.

In industrialized countries, there is a strong trend toward advanced maternal age as an important risk factor for aneuploidies, particularly for first pregnancies. As advanced maternal age is associated with a higher risk of fetal trisomies, the need for accurate, non-invasive methods of prenatal chromosomal abnormality detection has become increasingly significant. Ultrasound-detectable soft markers continue to play a critical role in the non-invasive assessment of fetal trisomies, particularly trisomy 21, trisomy 18, and trisomy 13.

Maternal factors and fetal growth

Maternal anthropometric characteristics, such as height and weight gain during pregnancy, influence

fetal growth. Significant positive correlations have been already reported between maternal height and fetal growth parameters in the second trimester of pregnancies; however, evidence linking maternal height with fetal aneuploidy is lacking [23]. Our results showed a positive correlation between maternal weight gain and fetal biometry during second trimester in the control group of healthy pregnancies, as pictured in Table V, while in the aneuploid cohort, there was a weak or insignificant correlation between evaluated maternal weight gain and fetal biometry (Table VI). Maternal weight gain is also an important determinant of neonatal birth weight. Infants born to mothers with inadequate weight gain are at higher risk of being small-for-gestational-age (SGA), while excessive maternal weight gain increases the likelihood of large-for-gestational-age infants. These associations have been observed across low-, middle-, and high-income countries [24]. Insufficient maternal weight gain is associated with low birth weight at term and should be considered of high importance in clinical practice.

Screening for fetal aneuploidy

Second-trimester screening for fetal aneuploidies has gained considerable popularity, aided by advances in sonographic technology. Sonographic markers include both structural anomalies and non-anomalous variations in fetal anatomy and are collectively referred to as sonographic markers of fetal aneuploidy (SMFA) [25]. While not specific for aneuploidy, individual markers or combinations occur more frequently in aneuploid than in euploid fetuses. Detection rates of SMFA vary among centers and are dependent on the type of aneuploidy. GA and fetal sex have also been associated with variations in detection rates, though findings are inconsistent [25].

Advanced GA correlates positively with the detection rate of SMFA. Additionally, certain markers tend to appear in clusters, increasing in this manner the detection rates for pathological pregnancies. Similar to known patterns in genetic syndromes, understanding clustering may enhance insights into pathophysiologic mechanisms. Clinically, this information is relevant for guiding counseling: women at higher risk for aneuploidy, who decline invasive testing and rely on biochemical and sonographic screening, may benefit from delayed evaluation after 18 weeks of gestation in order to maximize SMFA detection. Repeated scanning may be warranted if image quality is suboptimal, preferably between 21–22 weeks to allow timely karyotyping [26].

Most patients included in this study were carrying euploid fetuses, and the prevalence of SMFA in this population allows estimation of the relative risk of aneuploidy. Further studies including both euploid and aneuploid fetuses are needed to refine risk assessment, particularly considering GA, fetal sex, and concurrent SMFA. The observation of clustered SMFA among trisomic fetuses should also be investigated in a general second-trimester population.

Fetal growth restriction and biometric parameters

Fetal growth restriction (FGR), defined as failure to achieve intrauterine growth potential due to placental insufficiency, intrinsic genetic growth limitation, and usually associated structural anomalies, increases perinatal morbidity and mortality, as well as long-term health risks [27,28]. Classification based on HC and AC ratios distinguish symmetrical (Type I), asymmetrical (Type II), and mixed-pattern (Type III) FGR. Type I reflects early, proportional growth restriction; Type II represents late-onset asymmetrical growth restriction due to placental insufficiency; Type III combines features of both and is associated with infections or toxic exposures.

Our results demonstrate that fetal biometric parameters—such as BPD, HC, AC, FL increase predictably with advancing GA in euploid pregnancies (Spearman's correlation coefficient >0.75, Table V), while there is a weak correlation between these parameters regarding aneuploid pregnancies (Table VI). All individual measured values for fetal biometric parameters were reduced compared with control group, even if the GA at the moment of evaluation was higher. These measures are foundational to ultrasound-based estimations of fetal age and growth trajectory.

As previously shown, and in accordance with our results, chromosomal abnormalities, particularly trisomies 13, 18, and 21, contribute to 5–20% of FGR cases, especially in early-onset FGR [27].

Femur length

FL is a standard long-bone measurement during second-trimester scans. FL varies with maternal ethnicity: Asian fetuses typically show shorter FL, whereas Black fetuses may exhibit longer FL. Short FL can indicate aneuploidy, skeletal dysplasia, intrauterine growth restriction, or be influenced by uteroplacental insufficiency [29]. In our cohort, measured values for FL were smaller in the affected group, but with no significant difference from the physiological pregnancies (Table IV).

Abdominal circumference and estimated fetal weight

As was observed before, low AC (<5th percentile) in the second trimester is associated with chromosomal abnormalities, most commonly trisomy 18 or 21 [30,31]. Our results tend to show reduced values of AC in the affected fetuses, even though the difference achieved no statistical significance (Table IV).

Biparietal diameter

The utility of BPD and related ratios as markers for aneuploidy remains controversial. Some studies show weak correlations between BPD and trisomy 13 or 21, while other parameters, such as BPD-to-shoulder ratios, demonstrate statistical significance for trisomy 18 [32]. Targeted sonography can identify abnormal biometric findings in nearly all trisomy 18 fetuses, with measurements below the 5th percentile observed in approximately half of cases [33].

Table VII. Fetal sonographic soft markers across studies evaluating aneuploidies.

Study (year)	Country	Gestational age at screening	Sample size (main characteristics)	Fetal marker
Engelbrechtsen et al. (2013) [38]	Denmark	12-16 weeks	25 (high risk for trisomy 13, 18 or 21/structural abnormalities)	Biparietal diameter: 20 (16–25.7)* mm
Herrera et al. (2020) [39]	Texas (United States of America)	16–21 weeks	144 (Down syndrome)	femur length: 38 fetuses (26%) < 3rd percentile
Kataguiri et al. (2014) [40]	Brazil	17.7 ± 3.1 weeks**	30 (Down syndrome)	femur length: 1/30 observed/expected < 0.90
Bronshtein et al. (2003) [41]	Israel	14–16 weeks	13 (Turner syndrome)	femur length: 12/13 shortened
Papp et al. (2006) [42]	Hungary	11-23 weeks	69 (Turner syndrome)	femur length: 7 fetuses (10.1%) with length below the 10th centile

Data given as mean (range) and mean± standard deviation**.

In our study, lower measurements were observed for individual BPD diameter in the affected group, in spite of a lack of statistical significance (Table IV). Odibo et al. showed that combined approaches, such as BPD-to-nasal bone ratios, may improve sensitivity and specificity for Down syndrome detection [34]. There is substantial inter-study variability in the sonographic markers evaluated in fetuses at risk of aneuploidy. Most studies evaluated maxillofacial or mandibular measurements in trisomies 18 and 13 [35,36] and nuchal thickening, hyperechoic bowel, and intracardiac echogenic foci in fetuses with Down syndrome [37]. Table VII summarizes studies that have identified shortened femur length and reduced biparietal diameter as soft sonographic markers in aneuploid fetuses.

Although definitions for abnormal values vary and are gestational-age dependent, the reported findings are consistent with our results and prove that these measurements may enhance the detection of aneuploidy in affected pregnancies.

Limitations

The present study has several limitations. First, the relatively small cohort size, particularly the limited number of aneuploid cases, may reduce the statistical power and applicability of the findings. Secondly, variation in GA at admission could have influenced the detection rate of sonographic markers. In addition, incomplete documentation of medical records, such as the absence of percentile values for certain biometric measurements, restricted the depth of analysis. Finally, the reduced incidence of aneuploidy within this cohort is likely attributable to the widespread uptake of first-trimester screening, which allows for earlier diagnosis and subsequent exclusion of many affected pregnancies from second-trimester evaluation.

Another potential limitation of our study is the involvement of two independent sonographers in performing the ultrasound examinations. Given that the detection of soft markers and biometric measurements is inherently operator-dependent, inter-observer variability may have influenced the results. Differences in technical expertise, image acquisition, and interpretation could introduce measurement bias and affect reproducibility. Although both examiners were experienced and followed standardized protocols, subtle variations in technique may limit the generalizability of our findings and should be considered when interpreting the results.

Conclusions

Ultrasonography evaluation is of particular importance in the prenatal screening of aneuploidies, giving reliable results about the fetal growth related to gestational age in healthy pregnancies and raising a suspicion over a possible genetic disorder when the measurements are not correlated to gestational age. Besides these, based on the results we obtained, other maternal parameters like maternal height and weight gain seem to correlate also with the fetal biometric parameters, suggesting a possible supplemental input of these parameters in the evaluation of the genetic disorder risk, with the aim of reducing the cases of invasive prenatal test, with all the well-known associated risks, by defining new complex and powerful clusters of soft markers. In spite of the small number of aneuploidies cases identified in this study, our findings might still serve as an incentive for further research.

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