Measurements in First-Trimester Abortion Products

A Pathologic Study

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• ***Context.***—**Related to the advances in prenatal diagnosis and the emergence of medically challenging situations, there has been an increased interest in conducting a pathologic study of first-trimester abortion products.**

Objective.—**To evaluate measurements across a large group of first-trimester spontaneous abortion specimens. Potential goals include a validation of prenatal embryo and gestational-sac measurements as a function of gestational age (GA).**

Design.—**A retrospective case study of first-trimester spontaneous abortions between June 2015 and April 2017 in Centro de Genética Clínica Embryo-Fetal Pathology Laboratory, Porto, Portugal. Considering the inclusion criteria, 585 complete gestational sacs, 182 embryos, and 116 umbilical cords were selected. We recorded the weight of the gestational sacs and embryos and measurements of gestational sacs, umbilical cords, and embryo crown-rump length. Models were computed using regression techniques.**

Results.—**Gestational-sac diameter percentiles 5, 25, 50, 75 and 95 were calculated according to GA, and at each 1-week interval the diameter increased an average of 3 mm. Umbilical cord length percentiles 5, 25, 50, 75 and 95 were calculated according to GA, and at each 1-week interval, the length increased an average of 1.35 mm. Embryo crown-rump length estimated mean ± SD values were GA 6 weeks, 5.3 ± 2.3 mm; GA 7 weeks, 9.4 ± 4.8 mm; GA 8 weeks, 13.7 ± 8.2 mm; GA 9 weeks, 20.8 ± 9.1 mm; GA 10 weeks, 22.6 ± 13.4 mm; GA 11 weeks, 29.4 ± 12.9 mm; and GA 12 weeks, 52 mm.**

Conclusions.—**Pathologic measurements obtained should be compared to expected measurements and correlated with ultrasound findings, clinical information, and microscopic findings. Deviations from expected values could lead to an understanding of early pregnancy loss.**

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Human embryogenesis is divided into 2 major periods, blastogenesis and organogenesis, happening from conception to the eighth week of development.[1,2]

Spontaneous abortion (SA) refers to spontaneous delivery before fetal viability. Clinically, SA is classified as early if it occurs at or before the 12th week of gestational age (GA).[2,3]

Prenatal growth evaluation is dated from the first day of the last menstrual period. This is termed GA (2 weeks longer than embryonic age).[2] A gestational sac (GS) can usually be identified at the fifth week and is an early indication of an intrauterine pregnancy.[2]

A precise incidence of first-trimester SA (FTSA) is not well established. Currently, it is accepted that up to 60% of all conceptions will be miscarried, most of these not being noticed by the woman.[3–6]

Etiology of SA is a complex process. Several causes, from maternal, paternal, or biparental to multifactorial, placental, and embryonic factors may be associated in the pathogenesis of SA.[7] All are well known, although the most common causes of early or very early pregnancy loss are aneuploidies or chromosomal aberrations. These often result in a growth-disorganized embryo and solitary or multiple malformations indicative of specific syndromes or associations.[7–12] Seventy percent of SAs at less than 8 weeks of GA exhibit an

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abnormal karyotype; the presence of an abnormal karyotype decreases at higher GA.[8,11]

Pathologic examination of FTSA specimens is important for diagnosis. Combined gross and microscopic findings provide crucial information for the management of subsequent pregnancies and maternal health in specific conditions and help guide the need for complementary genetic studies or others tests.[12–16]

A complete gross examination in FTSA specimens is the first step to correctly identify different constituents.[15] In general, gross examination of nonembryonic tissue does not provide diagnostic information except in the case of gestational trophoblastic disease. The success of a gross approach is partially dependent on the skill and experience of the examiner. As with examination of any specimen, it is wise to follow a routine protocol that includes measurements and weight of various components of FTSA specimens and guides the choice and number of histologic sections submitted.[15] A complete and well-oriented gross examination of the first-trimester placenta must include the chorionic plate, villi and intervillous space, and basal plate. Gross vesicles are usually not present except for complete hydatidiform mole and partial hydatidiform mole. Early complete and partial hydatidiform moles may need to be examined under a dissecting scope to see the abnormal villi. Usually hydatidiform moles are more voluminous products and translucent vesicles are better identified in fresh specimens and under water, particularly in early moles (especially those less than 10 weeks).[15–17] Grossly, FTSAs are heterogeneous. Decidual tissue usually appears as a small, flattened sheet that is relatively smooth on one surface and granular or nodular on the opposite surface.[15] Microscopically, it is composed of an admixture of extravillous trophoblast, decidual cells, uteroplacental vessels, and endometrial glands usually embedded in fibrinoid material. The basal plate lesions as vascular, inflammatory, or implantation disorders are only evaluated on microscopic study.[15] Blood clot usually does not contain diagnostic material[15]; however, it should be submitted for histologic examination, particularly if it is granular or firm.[15] Many embryo and umbilical cord (UC) characteristics are diagnosed solely by gross examination.[13,15] Gross examination is crucial to achieve biometric parameters and to document suspected (or not) development anomalies and potential abnormal chorionic villi features, such as are seen in gestational trophoblastic disease.[5,12,13,15,17] Moreover, along with a histologic study, it can identify potential diseases and causes of early abortion. Together, these are crucial steps in assessing and predicting recurrent risk in future pregnancies as well as its impact for the mother and fetus.[14–17]

Growth is a highly complex process. It takes place in a completely ordered fashion in the biological system.[18] Knowledge of distinct intrauterine phases in which the growth and body composition of the fetus are related to the mode of nutrition are well documented.[1,2,18–22] Studies of human intrauterine growth usually are based on anthropometric measurements of infants born at various gestational periods. Weight is a nonspecific measurement of growth; however, it is still the most widely used single clinical measurement of growth in intrauterine and postnatal life.[19–23] Measurements of growth after birth at all ages are mainly longitudinal.[18–23] However, growth measurements of body composition are not longitudinal in early development.[18–23] Numerous percentile charts have been constructed that relate embryo-fetal measurements to GA.[23,24] Recent studies have sought to demonstrate the importance of embryo crown-rump length (CRL) and placental/GS parameters as potential predictors of early pregnancy loss or maternal risk diseases.[24–26] However, those studies must be validated with embryonic and GS histologic features seen in embryonic and placental disorders, such as chronic massive intervillositis and gestational trophoblastic disease, among others. The accurate measurement of embryo/fetal crown-heel length provides the best clinical measurement of skeletal growth.[18,22,23] Some studies investigated efficacy of first-trimester ultrasound parameters such as GS thickness for prediction of maternal risk disorders such as preeclampsia and/or the delivery of small-for-gestational-age neonates; however, there were no specific pathologic aspects reported.[24,25,27,28] Others have documented such parameters as median GS diameter to CRL ratio as better predictors of pregnancy loss than GS diameter and embryo CRL alone.[24,29]

Four types of growth disorganization have been established.[28] Type 1 consists of an intact chorionic or amniotic sac with no evidence of an embryo or body stalk.[28] Type 2 consists of a chorionic sac containing a nodular embryonic tissue 1 to 4 mm long, usually attached to the amnion.[28] Type 3 consists of a chorionic sac containing a disorganized embryo up to 10 mm long with recognizable cephalic and caudal poles; retinal pigment and a short body stalk may be present.[28] Type 4 consists of an embryo that has a CR length from 3 to 17 mm with major distortion of the body shape, always involving the head, which usually is small; cervical flexion is absent or abnormal. These embryos have a recognizable head, trunk, and limb buds, and the morphologic characteristics are not consistent with any one stage of development.[28]

Placenta, especially in the second and third trimester, loses some weight during storage by evaporation but predominantly by leakage of blood and serum, although weight loss is most significant in hydropic or edematous placentas.[30] On the other hand, the placenta gains approximately 5% in weight after formalin fixation, but small FTSA specimens are little or not affected.[30] Knowing the GA and growth of the embryo and GS are important to appropriately evaluate the measured parameters. The value of this paper is in the gross pathologic measurements and expected growth during GAs of 4 to 12 weeks. Our objective was to obtain measurements in a large group of FTSA specimens and compare them with published studies.

MATERIALS AND METHODS

Sample Definition

We conducted a retrospective case study of 1561 FTSA specimens sent to Centro de Genética Clínica Genetics Embryo-Fetal Pathology Laboratory (Porto, Portugal). The specimens had been sent for pathologic examination to determine pregnancy loss etiology between June 2015 and April 2017. Inclusion criteria were complete intrauterine FTSA until 12th week of GA and gross parameters appropriately available for at least one component: GS, UC, or embryo. Exclusion criteria were gestational trophoblastic diseases, abortion specimens relating to a medical termination of pregnancy, twin pregnancy, ectopic pregnancy, assisted reproductive technology pregnancy loss abortion products, known and well documented maternal disorders, incomplete specimens, and unknown GA.

All the samples used in the present study were unlinked and unidentified from their donors. Because of the retrospective nature of the study, the local ethical review committees of the involved

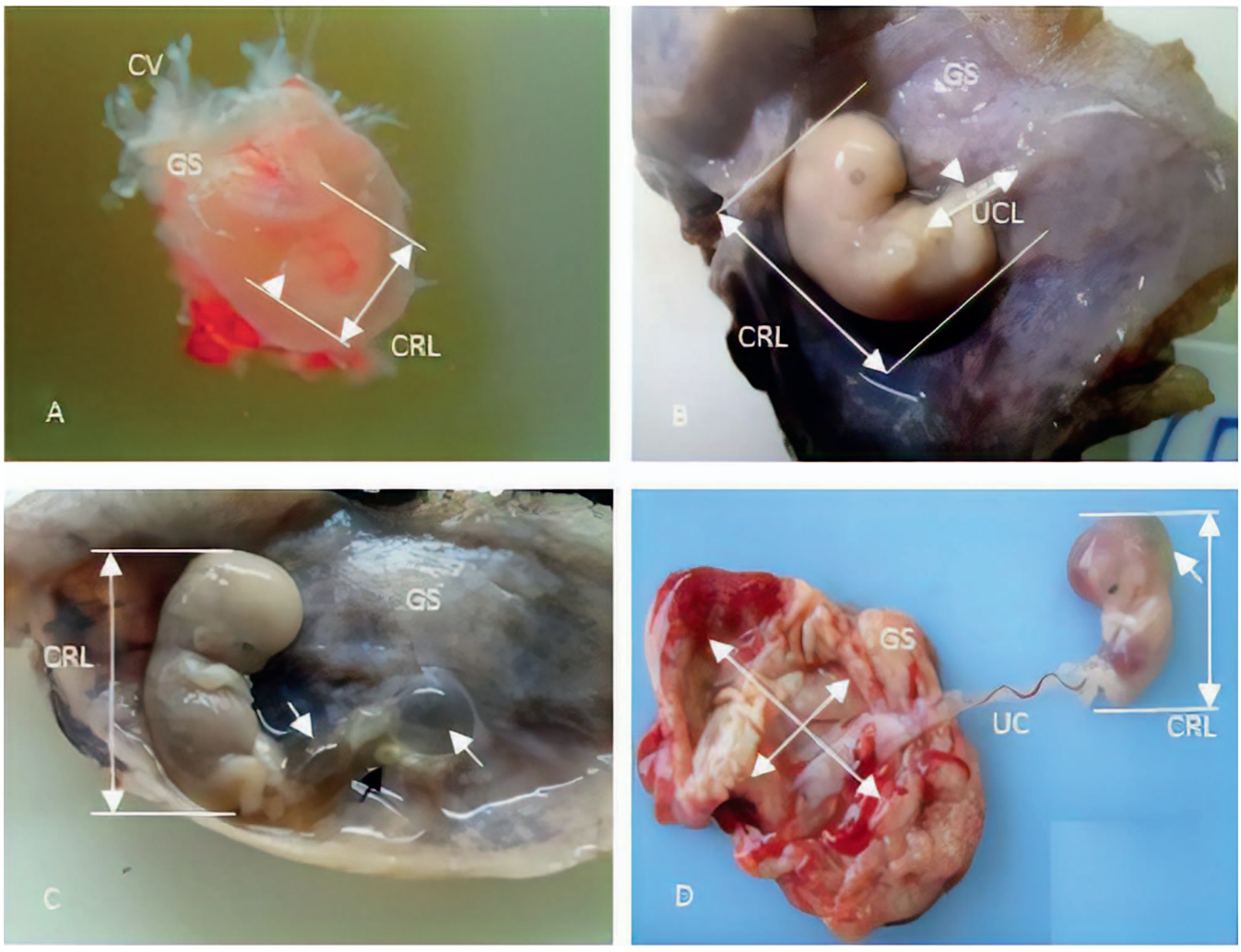

Figure 1. *Examples of complete first-trimester spontaneous abortion pathologic specimens. Gross parameters were taken of each individual component: gestational sac (GS), embryo crown-rump length (CRL), and umbilical cord (UC). A, Intact GS with sparse chorionic villi (CV) containing an early embryo (development age 32 days) with recognizable cephalic pole (arrowhead) and caudal pole without other recognizable external features. B, Opened GS containing an embryo with a small head and retinal pigment, chin fused to chest, paddle-shaped hand plate and lower limb bud showing inconsistent development, short UC length (UCL) (arrowhead). This embryo is a growth-disorganized type IV with 47,XY,+16 karyotype. C, Opened GS with a normal embryo at week 7, with pigmented eye, auricular hillocks, elbow, and free fingers. Umbilical cord cysts (white arrows) and yolk sac remnant (black arrow). D, Opened GS showing a normal coiling UC, an intact fetus at beginning of the fetal period (9th development week), and nuchal thickening translucency (white arrow).*

institutions and Minho University Medicine School (Braga, Portugal) approved the work and waived the need for written informed consent.

Collecting Data

General maternal parameters were collected: mother's age, clinical data, obstetric history, and pregnancy GA. Gross parameters were taken of each individual component: gestational sac diameter and weight, embryo CRL and weight, and umbilical cord length and diameter. Measurements were acquired using a digital caliper with measuring range 0 to 150 mm (0–6 inches; Würth International AG). Gestational sac diameter was evaluated by measuring distance between the curved membranes in the chorionic plate. Embryo CRL was measured in its natural position, from the outer edge of the cephalic pole to the outer edge of the embryo rump in younger embryos and from the crown to the rump in older embryos as they began to straighten. Any potential gross embryo malformations were identified as growth disorganized. Umbilical cord length was measured only in those cases where the embryo remained attached to the GS. After removal of the clots and decidua and formalin fixation during 24 hours, the weights of GS and embryo separately were acquired using a GS620 balance with measuring range 0.01 to 620 g (serial number 12105085, Kern).

Statistical Analysis

Data analysis was performed using descriptive statistics and linear regression techniques, determining the mean, median, standard deviation, minimum, and maximum as well as the percentiles of the different parameters analyzed (diameter and weight of the GS, UC length and diameter, embryo CRL and weight). Data tabulation and graphical construction were performed using the statistical software IBM SPSS Statistics version 24.0. According to the nature of the variables, we conducted a descriptive study using charts and/or tables; an analytical study (95% confidence intervals for the mean values); a causation study (regression models to estimate parameters according to GA); or a distribution adjustment to verify the normality assumption (Shapiro-Wilk test).

Table 1. Summary Statistics for Gestational Sac (GS) Diameter

		GS Diameter, mm								
							Percentile			
GA, wk	No. Valid	Mean	SD	Median	Min	Max	5th	25th	75th	95th
4	2	5	—	5	5	5	—	—	—	—
5	32	11.2	6.1	10	4	25	4	6	15	25
6	89	20.7	9.4	20	2	50	10	15	25	40
7	91	24.5	9	25	4	60	10	20	30	40
8	119	28.4	8.9	30	6	60	15	20	30	40
9	93	32.9	11.9	35	4	60	15	25	40	50
10	83	34	13.5	30	10	90	15	25	41	50
11	48	37	14	37.5	10	60	15	25	50	60
12	20	40.9	15	40	10	60	15	30	55	60

Abbreviations: GA, gestational age; Min, minimum; Max, maximum.

RESULTS

Sample Characterization

One thousand three hundred ninety-one specimens were sent to pathology; based on clinical and pathologic exclusion criteria, 883 cases remained with 1, 2, or 3 of the inclusion criteria: 585 with complete GS, 182 with embryo, and 116 with UC. Of the 585 GSs, diameter was available for 577 (98.6%) and weight for 478 (81.7%). Of the 182 embryos, weight was available for 64 (35.2%) and CRL for 109 (59.8%). Of the 116 UCs, length was available for all and diameter was available for 19 (14.1%) (Figure 1, A through D).

Descriptive Parameter Analysis

Maternal Age.—The mean maternal age was 32.9 years with a standard deviation of 6 years. It was also found that 50% of mothers were younger than or equal to 33 years.

Gestational Sac.—Gestational sac parameters were calculated according to the GA. For GS diameter and weight, the mean, SD, and percentile curves are shown in Tables 1 and 2 and Figures 2 and 3. At 10 weeks' gestation the mean diameter of the GS was 30 mm, and it increased 3 mm each week.

Umbilical Cord.—After evaluation of UC length and diameter, the mean, SD, and percentile curves were calculated according to the GA. Tables 3 and 4 and Figure 4 explain these values. At 10 weeks' gestation the mean UC length was 13.5 mm, and it increased 1.35 mm each week.

Embryo.—A complete embryo was present in 182 cases, with parameters obtained from GA weeks 5 to 12. Table 5 and Figure 5 explain embryo weight values. At 10 weeks' gestation, the mean embryo weight was 2 g, and it increased 0.2 g each week.

Table 6 and Figure 6 explain embryo CRL. The estimated mean ± SD values obtained were GA 6 weeks, 5.3 ± 2.3 mm; GA 7 weeks, 9.4 ± 4.8 mm; GA 8 weeks, 13.7 ± 8.2 mm; GA 9 weeks, 20.8 ± 9.1 mm; GA 10 weeks, 22.6 ± 13.4 mm; GA 11 weeks, 29. 4 ± 12.9 mm; and GA 12 weeks, 52 mm. At 10 weeks' gestation the mean embryo CRL was 22.6 mm, and it increased 2.26 mm each week.

DISCUSSION

Evaluation of these specimens is enhanced by an understanding of the purpose of pathologic examination and how it may be helpful to both patients and clinicians.

First-trimester abortion samples are a common pathologic specimen. The specimens have a varied composition and are often disrupted and intermixed.[13,15,16] A complete gross examination will allow appropriate assessment of the maternal, placental, and embryonic components and guide submission of tissue for histologic examination. Microscopic study may show abnormalities, which suggest possible etiologies for the pregnancy failure.[12–14,17,23]

Table 2. Summary Statistics for Gestational Sac (GS) Weight

		GS Weight, g								
							Percentile			
GA, wk	No. Valid	Mean	SD	Median	Min	Max	5th	25th	75th	95th
4	1	—	—	—	0.8	0.8	—	—	—	—
5	15	4.7	6.7	1.5	0.1	26	0.1	0.7	6	26
6	73	7.7	7.9	5	0.3	51	1	3	10	20
7	70	9.1	7.7	6.5	0.4	34	1.8	4	10	25
8	103	10.6	11.1	7	1	62	2	4	12	32
9	85	14.9	11.8	12	1.5	50	2	6	20	42
10	70	13	11.1	10.5	1	56	3	5	16	35
11	43	19.4	12.4	18	2	49	2.7	7	28	40
12	18	18.3	13.8	14.5	1	49	1	7	25	49

Abbreviations: GA, gestational age; Min, minimum; Max, maximum.

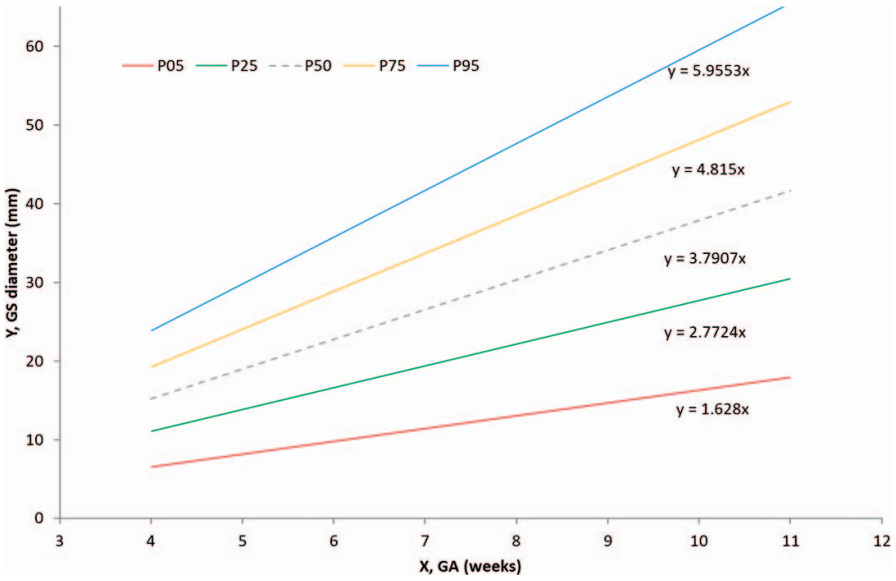

Figure 2. *Percentiles (P) for gestational sac (GS) diameter according to gestational age (GA).*

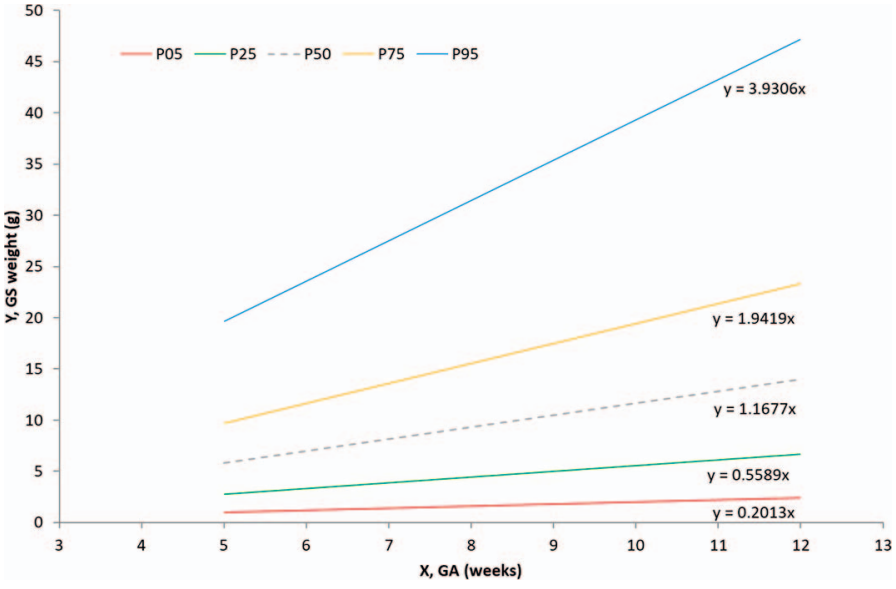

Figure 3. *Percentiles (P) for gestational sac (GS) weight according to gestational age (GA).*

Table 3. Summary Statistics for Umbilical Cord (UC) Length

		UC Length, mm								
							Percentile			
GA, wk	No. Valid	Mean	SD	Median	Min	Max	5th	25th	75th	95th
6	2	10.5	—	10.5	6	15	—	—	—	—
7	7	7	2.9	6	3	10	3	5	10	10
8	19	12.5	8.4	10	2	40	2	7	15	40
9	31	10.8	8.1	10	3	43	3	5	15	24
10	26	19.6	17	13.5	2	80	4	10	25	45
11	23	20.9	22.1	10	2	80	3	6	30	70
12	8	26.5	25.3	16	5	80	5	10	37.5	80

Abbreviations: GA, gestational age; Min, minimum; Max, maximum.

Table 4. Summary Statistics for Umbilical Cord (UC) Diameter										
		UC Diameter, mm								
							Percentile			
GA, wk	No. Valid	Mean	SD	Median	Min	Max	5th	25th	75th	95th
8	2	4	—	—	3	5	—	—	—	—
9	5	3	1	3	2	4	2	2	4	4
10	8	3.3	1.3	3	2	5	2	2	4.5	5
11	2	4.5	—	—	4	5	—	—	—	—
12	2	3	—	—	2	4	—	—	—	—

Abbreviations: GA, gestational age; Min, minimum; Max, maximum.

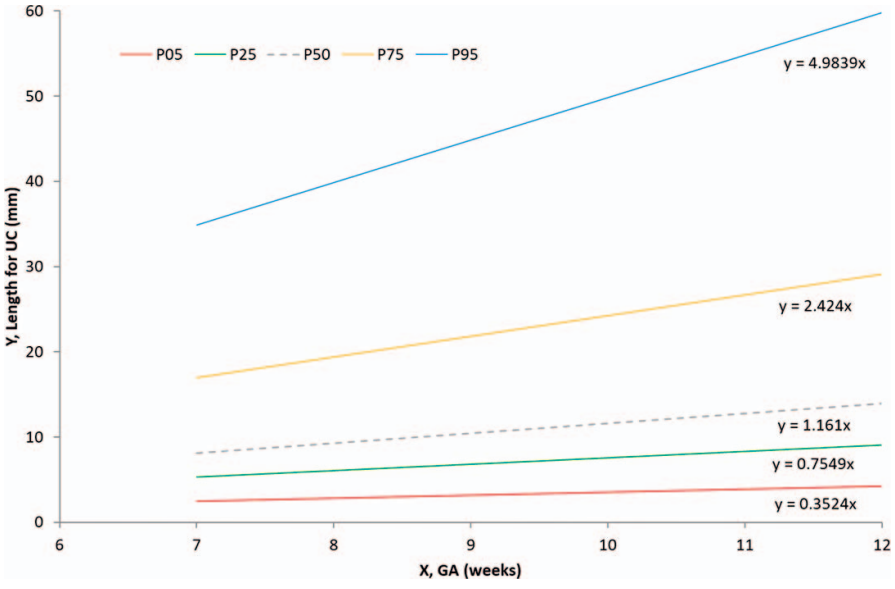

Figure 4. *Percentiles (P) for umbilical cord (UC) length according to gestational age (GA).*

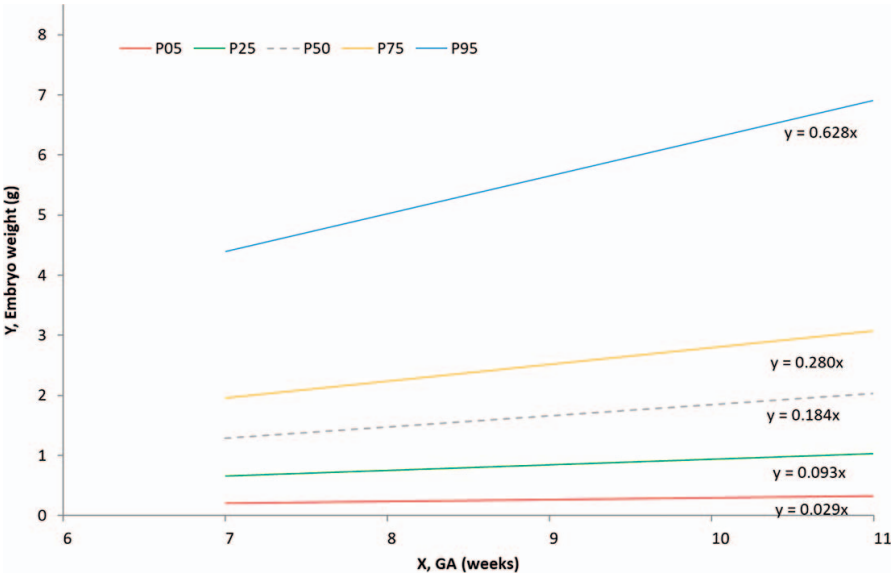

Figure 5. *Percentiles (P) for embryo weight according to gestational age (GA).*

Table 5. Summary Statistics for Embryo Weight

		Embryo Weight, g								
							Percentile			
GA, wk	No. Valid	Mean	SD	Median	Min	Max	5th	25th	75th	95th
6	1	—	—	—	0.1	0.1	—	—	—	—
7	3	0.3	0.3	0.1	0.1	0.6	0.1	0.1	0.6	0.6
8	8	1	0.7	0.7	0.1	2	0.1	0.5	1.8	2
9	22	2.5	3.5	1.3	0.5	14	0.6	1	2	12
10	13	2.2	1.1	2	0.3	4	0.3	1.4	3	4
11	16	3.2	2.4	3.5	0.2	8.4	0.2	1	4.5	8.4
12	1	—	—	—	10	10	—	—	—	—

Abbreviations: GA, gestational age; Min, minimum; Max, maximum.

Table 6. Summary Statistics for Embryo Crown-Rump Length (CRL)

		Embryo CRL, mm								
							Percentile			
GA, wk	No. Valid	Mean	SD	Median	Min	Max	5th	25th	75th	95th
5	4	9.8	7.6	8	3	20	3	4	15.5	20
6	8	5.3	2.3	5	2.3	10	2.3	4	6	10
7	7	9.4	4.8	11	3	15	3	4	14	15
8	19	13.7	8.2	13	2	30	2	6	20	30
9	27	20.8	9.1	20	2	42	6	15	27	35
10	23	22.6	13.4	28	2	40	2.8	6	35	40
11	19	29.4	12.9	30	12	58	12	20	40	58
12	2	52	—	52	44	60	—	—	—	—

Abbreviations: GA, gestational age; Min, minimum; Max, maximum.

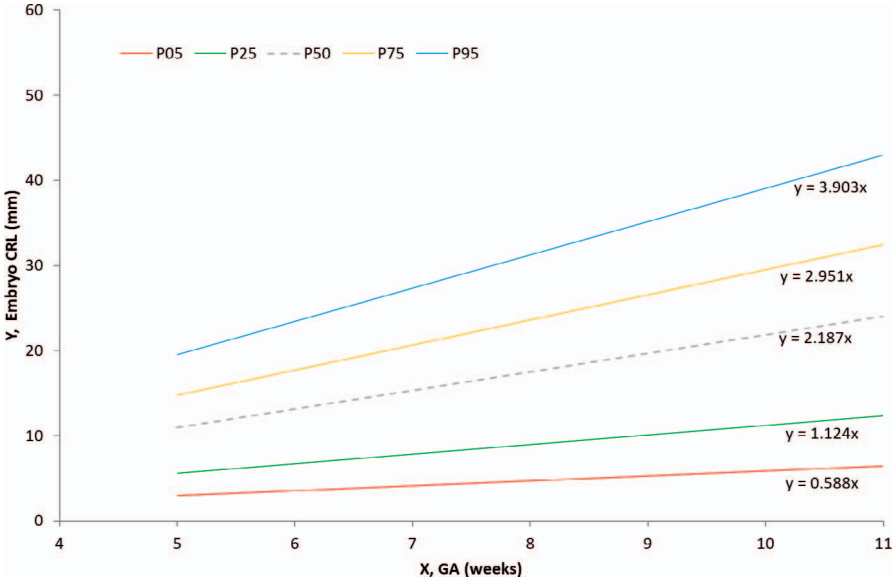

Figure 6. *Percentiles (P) for embryo crown-rump length (CRL) according to gestational age (GA).*

Given the GS and embryo measurements between weeks 5 and 12 that were performed in this study, a comparison of these measurements with prenatal ultrasound findings would be helpful to identify the accuracy of the latter modality.[15,26,27–29] Pathologic study is important for understanding causes of early pregnancy loss and counseling and treatment of patients during subsequent pregnancies. Multidisciplinary studies on early abortion have been increasing.[8,12,15,18,24–29] However, the correlation studies, especially in biometrics, are not yet well established.

Pathologic examination in FTSA is critical to validate ultrasound findings, including measurements, and also to understand the etiology of early abortion. Any value deviations in ultrasound and pathologic features may be important in determining embryonic, placental, or maternal disorders.[8,14,15,17,23–29]

CONCLUSIONS

The pathologic study of first-trimester abortion samples adds information to prenatal ultrasound, which may be helpful to parents and clinicians. Deviation from normal expected growth of the embryo, GS, or UC may be the etiology of first-trimester abortion.

The extension of the series with a greater number of cases is important for a sample validation and to determine a table of biometric values in early pregnancy loss. As a future perspective, it would be critical to continue the exploration of this topic, looking for the precise percentage of early SA worldwide and a shortage of pathologic studies evaluating the gross and microscopic etiologies of FTSA.

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