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Choosing the Equation for Estimated Gestational Age With Crown-Rump Length

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Abstract

Background: The aim of our study was to approach the equation most robust for gestational age (GA) estimation in our clinical setting. Six recent equations are assessed.

Methods: A total of 484 single normal pregnancies, from the trisomy screening program at Consorci Hospital General Universitari of Valencia, Spain were assessed for differences in GA estimations, with duplicated crown-rump length (CRL) measurements taken at least 1 week apart. Regression and Chi-square test was applied for comparing results, considering significant if P < 0.05.

Results: The differences in GAs using the same CRL were as high as 11 days at 90 mm, but at 20 to 65 mm are only 1 - 2 days. The GA estimation has low reproducibility when based on two CRL measurements, but one equation achieved a GA difference of ± 5 days in 97.1% of cases, which is significantly higher than any other equation. Five equations are influenced by the interval between the CRL measurements.

Conclusions: The differences between GA estimations based on successive CRL measurements could be clinically significant. Understanding the equation's behavior is essential to choose the optimal equation for a specific clinical setting. We identified an equation with higher reproducibility.

Keywords: Gestational age estimation; Crown-rump length; Equations for gestational age; Crown-rump growth

Introduction

The relationship between crown-rump length (CRL) and gestational age (GA) was described 47 years ago [1]; and the first equation based on this relationship was proposed subsequently [2].

The importance of CRL measurements for screening chromosome alterations has led to studies on the effects of inaccuracies in these measurements on the corresponding risk evaluations [3]. However, the influence of CRL-based equation behavior for GA calculations is also important.

The equations used in the 70s were proposed based on images from static machines, with the menstrual age as reference. Subsequent advancements in sonography and more accurate identification of the GA have yielded newer equations [4-6]. Nevertheless, the equation proposed by Robinson and Fleming [2] continues to be widely applied after 45 years. In fact, many clinics accept the results provided by the software of their sonography machine, regardless of the equation it uses and how it behaves.

Thus, we aim to highlight the differences in CRL-based GA estimations by six equations proposed in the last 10 years [4-6] and the Robinson and Fleming equation [2]. To this end we compared the differences in GA values calculated using two CRL measurements performed on the same patient with an interval of at least 1 week, searching the equation with most reproducible results.

Materials and Methods

We used data from clinical practice, with all patients providing written consent. Our Institutional Review Committees considered that this analysis was exempt from obtaining approval because of its retrospective character. The study was performed in accordance with the ethical standards of the committee and the Declaration of Helsinki and its later revisions. The data were obtained from the database of the trisomy screening program at the Consorci Hospital General Universitari of Valencia, Spain, based on nuchal translucency (NT) and CRL measurements at week 12. Because some patients were tested before the right CRL for NT estimation or it was difficult to obtain an adequate image, sonography was repeated several days after.

All evaluations were performed using transabdominal sonography with a GE Logic 400 CL unit using a convex probe with frequencies between 3.5 and 5 MHz. For inclusion in this study, the interval between the two measurements had to be greater than 1 week, with a CRL value of at least 10 mm. CRL measurements were based on appropriate embryo extension images and the sagittal section. Four sonographers performed all measurements

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Table 1. Main Characteristic of Sonographies

	N	%
CRL at first sonography (mm)		
10 - 20	147	30.4
20 - 30	161	33.3
30 - 40	134	27.7
40 - 50	42	8.7
Total	484	100
CRL at second sonography (mm)		
40 - 50	39	8.1
50 - 60	276	57.0
60 - 70	152	31.4
> 70	17	3.5
Total	484	100
BPD at second sonography (mm)		
15 - 20	239	49.3
20 - 25	229	47.3
25 - 30	12	2.5
Not available	4	0.8
Total	484	100

CRL: crown-rump length; BPD: biparietal diameter.

A total of 484 single normal pregnancies were available for analysis. Table 1 shows data of the first and second sonographies.

In each case, after estimating the GA with the first CRL measurement, the estimated day of delivery (EDD) was determined. The same extrapolation was performed with the second measurement, and the difference in the dates in relation to the first assessment was determined.

Table 2 [2, 4-6] shows the seven equations tested, ordered by the year of their publication.

Follow-up assessments of the 484 pregnancies were performed until week 20, when sonography excluded fetal defects and confirmed that the pregnancy had progressed well. Subsequently, 59 cases were lost to follow-up. For the remaining 425 cases, delivery took place in the hospital at term. All newborns were normal, vigorous, and weighed between 3,000 and 4,230 g.

The patient and examination data were stored in FileMaker Pro 5 (Claris Corporation Santa Clara, CA). The same database was used to calculate the GA, EDD, and CRL daily growth between the two measurements. Microsoft Excel 2016 was used for regression analysis, and the Chi-square test was applied for the analysis of the distribution of differences in GA with two CRL measurements.

Results

Table 3 [2, 4-6] shows the GAs estimated by the seven equations for CRL values ranging from 10 to 90 mm, at intervals of 5 mm. The last column shows the correlation coefficients with the CRL values. Minor differences can be observed for CRLs from 20 to 65 mm; then, the differences increased to up to 11 days.

Table 4 shows the variations in the daily CRL growth in relation to the CRL during the first sonographic assessment. The rate of growth appeared to accelerate from a CRL of 20 mm. The linear correlation coefficient for this tendency was 0.333 ($P < 0.001$).

Table 5 analyzes the daily CRL growth variation in relation to the interval between the two sonographic assessments. The growth variation decreased as the interval increased. The correlation coefficient was 0.363 ($P < 0.001$).

Table 6 shows the CRL growth according to the maternal body mass index (BMI) in the second sonographic assessment. No influence was detected.

Table 7 [2, 4-6] shows the equations' clinical performance for predicting the EDD with the two CRL measurements. In comparing results distribution, with the Chi-square test no differences between the Robison and Fleming [2], and Papaioannou et al [4] equations were observed, but differences were present among all other equations. The highest and most equilibrated agreements were obtained with Constant's equation 6 [5], in which 97% of the predictions were within ± 5 days, which is higher ($P < 0.05$) than all other equations. Also are shown the R^2 values for the interval between the CRL measurements and the GA differences. Robinson and Fleming [2] and Constant et al [5] equations are independent of this effect.

Discussion

The equations we studied were meant for estimation of the GA

Table 2. The Equations

1. Robinson [2]	GA = (8.052 × sqrtCRL + 23.73)
2. Papaiouannou [4]	GA = (39.811963 + 1.155896 × CRL - 0.006429 × CRL^2)
3. Constant a [5]	GA = ((19.1732 + 6.0266 × sqrtCRL + 0.0955 × CRL) + 14)
4. Constant b [5]	GA = ((18.0739 + 5.6925 × sqrtCRL + 0.1549 × CRL) + 14)
5. Constant c [5]	GA = ((17.8994 + 5.7617 × sqrtCRL + 0.1471 × CRL) + 14)
6. Constant d [5]	GA = ((19.2702 + 5.7804 × sqrtCRL + 0.1271 × CRL) + 14)
7. Papageorghiou [6]	GA = 40.9041 + (3.21585 × $CRL^{1/2}$) + (0.348956 × CRL)

CRL: crown-rump length; GA: gestational age; sqrt: square root.

Table 3. Gestational Age (Days) Obtained by the Seven Equations (CRL Range: 10 - 90 mm at Intervals of 5 mm)

CRL (mm)	Gestational age (days) by seven equations							Extreme values difference (days)
	1. Robinson [2]	2. Papaiounnou [4]	3. Constant a [5]	4. Constant b [5]	5. Constant c [5]	6. Constant d [5]	7. Papageorghiou [6]	
10	49	51	53	52	52	53	55	6
15	55	56	58	56	56	58	59	4
20	60	60	62	61	61	62	62	2
25	64	65	66	64	64	65	66	2
30	68	69	69	68	68	69	69	1
35	71	72	72	71	71	72	72	1
40	75	76	75	74	74	75	75	2
45	78	79	78	77	77	78	78	2
50	81	81	81	80	80	81	81	1
55	83	84	83	83	83	84	84	1
60	86	86	86	85	85	86	87	2
65	89	88	88	88	88	88	90	2
70	91	89	90	90	90	90	92	3
75	93	90	92	93	93	93	95	5
80	96	91	95	95	95	95	98	7
85	98	92	97	98	97	97	100	8
90	100	92	99	100	100	99	103	11
R	0.990*	0.966*	0.993*	0.994*	0.995*	0.995*	0.999*	

*P < 0.001. R: correlation coefficient between gestational age and CRL measurement. CRL: crown-rump length.

from CRL measurements; thus, within the appropriate range of CRL values, the two measurements should have yielded similar results. However, we instead observed low agreements for all equations. We investigated the sources of the disagreements.

The differences outlined in Table 3 can be primarily attributed to the equations' behavior, since no other sources of variability can influence these differences.

Table 7 shows the differences in estimating the date corresponding to the EDD by using two CRL measurements; this measurement is influenced by other sources of variability. The interval between the two measurements exerted an influence in five equations.

The intra- and interobserver variability of CRL measurements is not usually high, but in chromosomal screening programs, it is sufficient to modify the estimated risk [3]. Instrumentation also plays a role in causing variability, but modern ultrasound machines have diminished this effect. Standardization of images [7] and sonographers' specific training [8] is the mainstay to decrease measurements variability. Then the quality control of the CRL measurement appears essential, with a direct approach that ensures immediate application to prevent daily errors [9], or a delayed approach, more useful for

Table 4. Initial CRL and CRL Growth

First CRL (mm)	N	Growth rate (mm/day), mean (SD)	95% CI
10 - 15	60	1.46 (0.22)	1.40 - 1.52
15 - 20	87	1.53 (0.24)	1.48 - 1.58
20 - 25	71	1.64 (0.24)	1.58 - 1.70
25 - 30	90	1.72 (0.28)	1.66 - 1.78
30 - 35	73	1.80 (0.38)	1.71 - 1.89
35 - 40	61	1.72 (0.37)	1.62 - 1.81
> 40	42	1.86 (0.73)	1.63 - 2.01
Total	484		

R^2 = 0.333 (P < 0.001). CI: confidence interval; CRL: crown-rump length; SD: standard deviation.

Table 5. Sonography Interval and CRL Growth

Interval (days)	N	Growth rate (mm/day), mean (SD)	95% CI
7 - 14	121	1.82 (0.52)	1.73 - 1.91
14 - 21	142	1.73 (0.31)	1.68 - 1.78
21 - 28	125	1.60 (0.24)	1.56 - 1.64
28 - 35	84	1.47 (0.18)	1.43 - 1.51
≥ 35	12	1.31 (0.17)	1.20 - 1.42
Total	484		

R^2 = 0.363 (P < 0.001). CI: confidence interval; CRL: crown-rump length; SD: standard deviation.

Table 6. Maternal BMI and CRL Growth

BMI (kg/m^2)	N	Growth rate (mm/day), mean (SD)	95% CI
20 - 25	237	1.63 (0.33)	1.59 - 1.67
25 - 30	130	1.70 (0.49)	1.61 - 1.67
30 - 35	43	1.69 (0.35)	1.58 - 1.79
≥ 35	21	1.66 (0.26)	1.54 - 1.77
Not available	53		
Total	484		

R^2 = 0.009 (P > 0.05). CI: confidence interval; BMI: body mass index; CRL: crown-rump length; SD: standard deviation.

deferred control [10].

The type of CRL growth could be also a source of variability. Rabelink et al [11] described significant individual differences in CRL growth. These differences may be influenced by maternal characteristics (ethnic, constitutional and environmental), embryo origin (spontaneous, *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), cryopreserved), and fetal sex.

Among maternal characteristics, the BMI at the second sonographic assessment (Table 6) did not influence our findings, but was found to be an influencing factor in other studies [12]. The effects of maternal age, tobacco use, and alcohol consumption have also been described previously [13]. The low number of non-Caucasian pregnant women prevented us from approximating ethnic influences [14].

Tunon et al [15] found no differences between embryos from natural cycles or assisted reproduction (IVF and embryo transfer, ICSI, or frozen embryos). Some studies have found discrepancies in embryos from assisted reproduction and proposed specific references for IVF embryos [16].

In 2014, Napolitano et al [17] published a systematic review focused on the methodology applied for developing the equations. Their review covered research published up to 2011, so they did not consider the six equations that we have included here (Table 2) [2, 4-6]: equation 2 by Papaioannou et al [4], equations 3 to 6 by Constant et al [5], and equation 7 by Papageorghiou et al [6]. These six equations were based on heterogeneous populations, but were analyzed using rigorous and complex methodologies. Equation 5 by Constant et al [5] and 7 by Papageorghiou et al [6] achieved less than 40% agreement for a coincidence of ± 1 day, while equations 3, 4, and 6 by Constant et al [5] exceeded the 40% agreement benchmark. The best result was obtained by equation 6 by Constant et al [5], which yielded 47% for ± 1 day and 97% for ± 5 days and a perfect balance in both positive and negative results; these estimations overcome the other equations.

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Table 7. The Difference of GA (Days) Between First and Second Sonography (Σ (%) of Summaries of Previous Results of the Row)

Days of difference	0	1	-1	Σ (%)	2	-2	Σ (%)	3	-3	Σ (%)	4	-4	5	-5	Σ (%)	≥ 6	≤ -6	R^2	Chi-square
1. Robinson [2]	16	7	27	50 (10.3)	1	51	102 (21.1)	2	67	171 (35.3)	1	68	0	59	299 (61.8)	0	185	0.000	307*
2. Papaiounnou [4]	14	6	34	54 (11.2)	3	50	107 (22.1)	2	69	178 (36.8)	1	66	0	56	301 (62.2)	0	183	0.087*	295*
3. Constant a [5]	75	52	76	203 (41.9)	26	68	297 (61.4)	22	48	367 (75.8)	11	34	8	27	447 (91.7)	5	32	0.107*	16*
4. Constant b [5]	80	66	60	206 (42.6)	45	50	301 (62.2)	37	37	375 (77.5)	18	25	13	16	449 (92.3)	17	20	0.052*	14*
5. Constant c [5]	66	70	51	187 (38.6)	72	33	292 (60.3)	55	25	372 (76.8)	30	16	19	6	443 (91.5)	33	8	0.227*	20*
6. Constant d [5]	81	92	57	230 (47.5)	55	57	342 (70.7)	41	25	408 (84.3)	20	19	14	9	470 (97.1)	5	9	0.000	Reference
7. Papageorghiou [6]	71	62	56	189 (39.0)	47	58	294 (60.7)	31	27	352 (72.7)	20	33	13	18	436 (90.0)	19	29	0.121*	26*

R^2: regression on the interval of the two CRL measurements and the differences in gestational age, *P < 0.01. Chi-square of GA distribution: equation 6 reference, *P < 0.01. GA: gestational age; CRL: crown-rump length.

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Conflict of Interest

The authors have no conflict of interest to declare

Informed Consent

All subjects provided written informed consent.

Author Contributions

Elena de la Fuente Diez performed the study and participated in the article's redaction and approval. Francisco Tomas-Bosch selected the cases, supervised the study, and participated in the article's redaction and approval. Jose J. Santonja-Lucas planned the study and performed the final redaction.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

GA: gestational age; CRL: crown-rump length-References

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