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New first trimester crown-rump length's equations optimized by structured data collection from a French general population

Marc Constant[*] Viet Chi Tran[†] Bernard Benoît[‡] Francis Vasseur[§]

October 29, 2011

Abstract

Objectives Prior to foetal karyotyping, the likelihood of Down's syndrome is often determined combining maternal age, serum free beta-HCG, PAPP-A levels and embryonic measurements of crown-rump length and nuchal translucency for gestational ages between 11 and 13 weeks. It appeared important to get a precise knowledge of these scan parameters' normal values during the first trimester. This paper focused on crown-rump length.

Methods 402 pregnancies from in-vitro fertilization allowing a precise estimation of foetal ages (FA) were used to determine the best model that describes crown-rump length (CRL) as a function of FA. Scan measures by a single operator from 3846 spontaneous pregnancies representative of the general population from Northern France were used to build a mathematical model linking FA and CRL in a context as close as possible to normal scan screening used in Down's syndrome likelihood determination. We modeled both CRL as a function of FA and FA as a function of CRL. For this, we used a clear methodology and performed regressions with heteroskedastic corrections and robust regressions. The results were compared by cross-validation to retain the equations with the best predictive power. We also studied the errors between observed and predicted values.

Results Data from 513 spontaneous pregnancies allowed to model CRL as a function of age of foetal age. The best model was a polynomial of degree 2. Datation with our equation that models spontaneous pregnancies from a general population was in quite agreement with objective datations obtained from 402 IVF pregnancies and thus support the validity of our model. The most precise measure of CRL was when the SD was minimal (1.83mm), for a CRL of 23.6 mm where our model predicted a 49.4 days of foetal age. Our study allowed to model the SD from 30 to 90 days of foetal age and offers the opportunity of using Zscores in the future to detect growth abnormalities.

Conclusion With powerful statistical tools we report a good modeling of the first trimester embryonic growth in the general population allowing a better knowledge of the date of fertilization useful in the ultrasound screening of Down's syndrome. The optimal period to measure CRL and predict foetal age was 49.4 days (9 weeks of gestational age). Our results open the way to the detection of foetal growth abnormalities using CRL Zscores throughout the first trimester.

Keywords: crown-rump length; foetal age; equation of the standard deviation; normal parameters; structured embryonic data collection.

Introduction

In France, prior to foetal karyotyping, the likelihood of chromosomal aneuploidy is determined with an algorithm that combines maternal age, serum free β-HCG, pregnancy-associated plasma protein A levels and scan embryonic measurements of first trimester crown-rump length (CRL) and nuchal translucency[1 2 3]. When the probability of aneuploidy exceeds 1/250, foetal karyotyping is proposed, whatever the woman's age. The window of screening requires scan measures for gestational age (GA) between 11 weeks + 0 day and 13 weeks + 6 days (CRL between 45 and 84 mm)[4], thus during and at the boundary of the first trimester. To date the most consensual reference regarding CRL according to the foetal age (FA)

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(FA=GA-14), arose from Robinson in 1973[5] on an Australian population. Regardless of their validity, Robinson's data were obtained using ultrasound technologies far from the modern ultrasound devices now routinely used and given the great potential impact of ultrasound measures on the medical decision in the aneuploidy diagnosis process, it appeared crucial to get a precise knowledge of CRL variations with current ultrasound technologies. Our study of the first trimester CRL variation in a French general population, completes the results of Salomon et al.[6] regarding the second and third trimesters.
Since Robinson, several CRL curves have been proposed. Hadlock[7] published an equation that integrates data from vaginal measurements, Verwoerd-Dikkeboom and al.[8] proposed an equation obtained with measures stemming from a three-dimensional acquisition. In 2008 Verbrug et al.[9] and in 2010 Papaioannou et al.[10] established new charts based on multiethnic samples taken by multiple operators with various devices. In 2010, Pexters and al.[11] established a multi-operator curve on a population sample close to that in our study. Our curves did not significantly differed from the classical Robinson curve, and those recently presented[8 10 11]. The present work provides a first trimester external validation of these recent charts and pleads for the use of our equations in routine foetal aneuploidy screening at least in the French population. Moreover, our work offers for the first time a modeling of the standard deviation, which is a prerequisite step towards the definition of normal foetal growth parameters.

Methods

Data

402 pregnancies from in-vitro fertilization (IVF) were ultrasound measured between February 1989 and September 2010 by a single operator (B.B.) in Nice and Monaco scan centers. In this sample, non-viable embryos were excluded. There were 78 (19.4%) twin and 8 (1.99%) triplet pregnancies. In case of a multiple pregnancy, only one embryo measurement was retained. Comparison of CRL between single and multiple pregnancies was performed with the Wilcoxon and Chow tests. Wilcoxon signed-rank test compares the two samples and tests whether their population means differ[12]. This was possible since the FA distributions were similar between groups. However, since the CRL clearly depends on FA, the Chow test was more suitable as it compares the modeling of CRL as a function of FA and checks whether the same regression can be applied to both samples or whether two different models are needed[13 14 15 12].

The general population sample consisted of 3846 spontaneous pregnancies examined in one center (Lambersart) by a single operator (M.C.) between January 2007 and February 2011. CRLs were measured for 2123 of them. Pregnancies from IVF were excluded. To determine as accurately as possible the date of fecundation, we included in the study only pregnancies of women who had regular periods with a cycle duration that was clearly expressed, and who knew the date of their last menstruations and who had no contraception for at least 3 months before pregnancy. As it is well known that CRL measurements are less accurate on large embryos, only CRL measures below 85 mm were kept. Thus 513 pregnancies fitted our selection criteria and were scored. As estrus occurs 14 days before menstruations rather than at half of the menstrual cycle (due to delayed ovulation[16]), the J0 of life for the foetus was determined as 14 days before the next estimated menstruation. In case of a multiple pregnancy, the measurement of only one embryo was kept.

As several examinations were sometimes performed during the follow-up of pregnancies, only the measurement from the first examination was selected for inclusion in the datasets. Both in-vitro fertilization (B.B. sample) and spontaneous (M.C. sample) pregnancy studies were performed with devices from the same manufacturer: Kretz/General Electric. IVF sample (B.B. sample) was performed with different versions of Kretz Voluson 530, 730, Expert, General Electric E8 (from 1989-02-16 to 2010-09-17). Spontaneous pregnancy studies (M.C. sample) were performed with Kretz Voluson Expert V5 (from 2006-01-02 to 2007-01-01) and General Electric E8 (from 2008-01-02 to 2010-12-23)). The measures were performed and collected with the software MEDISPHINX[1] which allows a precise collection of the clinical circumstances of the ultrasound examination.

The way embryonic lengths were measured was optimized for every examination, according to the size of the embryo and the prevailing technical conditions. Below 20 mm, the greatest length is a neck-rump measurement[11]. As often as possible, the measure tried to get closer to a sagittal section. This criterion is less important for small embryos. For many measures, a sagittal section was often obtained in 2D mode by vaginal or abdominal access. In case of difficulties, this sagittal section was be built with triplan mode from a 3D acquisition[9] (Figure 1). Below 45 mm, the measure was almost essentially the one of an embryo in flexion. Beyond, we looked for a neutral position of the embryo with presence of an amniotic liquid triangle

[1] http://www.isisphinx.com/

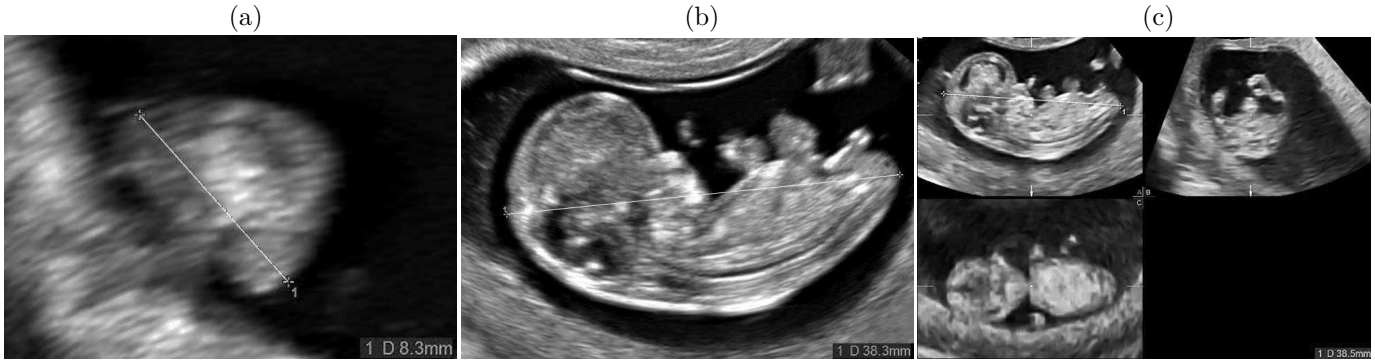

Figure 1: *Ultrasound pictures illustrating the embryonic length measurement. (a) Sagittal section of an 8 mm embryo. (b) Sagittal section of a 38 mm embryo. (c) Same embryo, sagittal section build with triplan mode from a 3D acquisition.*

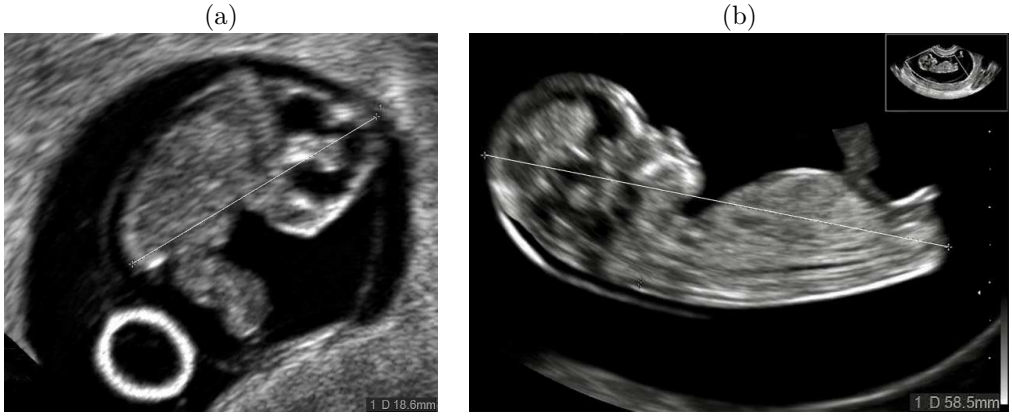

Figure 2: *(a) Ultrasound picture illustrating quality criteria for CRL below 45 mm (right, 19 mm). (b) Quality criteria beyond 45 mm (left, 59 mm).*

between the chin and the breastbone.

The quality criteria researched for the measures of the CRL were as follows:

For CRL< 45 mm (Figure 2 (a))

1. Sagittal section: visibility as soon as possible of the fourth ventricle and of the origin of the umbilical cord. Then, we added the rachis and the genital tuber.
2. Favorable locations of calipers: crown and rump were well defined, without edge contact, and the calipers were placed at the outer side of the interface (greatest length). Note that at this age, the biggest length is obtained by placing the cephalic caliper in the crown-neck junction[11].
3. Zoom of the image: do that the image of the foetus filled at least 3/4 of the screen.

For CRL> 45 mm (Figure 2 (b))

1. Foetus in neutral position: presence of a triangle of amniotic liquid between the chin and the breastbone.
2. Sagittal section: ideally, visibility of hard plate or nasal bone, rachis and genital tuber (Figure 2).
3. Favorable locations of calipers: as in the previous case.
4. Zoom of the image: as in the previous case.

To clean the data, we used non parametric tolerance limits[17 18]. In this context if the consensus reference values for a Gaussian distributed parameter are usually those comprised between -2SD and +2SD (95% of the whole population), for a non Gaussian distributed parameter as is probably the case here, there is no consensus range[19]. The 3rd and 97th or the 5th and 95th or the 10th and 90th percentiles are chosen as reference values according to the biological or physiological parameter under investigation, thus excluding either 6, 10 or 20% of the population with extreme values[20 21 22]. We performed a preliminary robust regression, that is not sensitive to outliers, and provided weights which were used to clean the data. This led us

to exclude 8.4% of the pregnancies with extreme values, 3.9% above and 4.5% below.

Mathematical methods

Regressions: Several regression models were tested. Numerical tests, based on comparisons of R^2 statistics, led us to describe CRL by polynomials of degree 2 in FA. Fisher's significance tests for the highest degree coefficients were performed and showed significant coefficients. The choice of degree 2 polynomials avoided overfitting of the model to the data and was in agreement with the settings of Robinson[5], Verwoerd-Dikkeboom et al.[8] or Pexters et al.[11]. Papaioannou et al.[10] used a polynomial of degree 2 in FA to describe the square root of the CRL. Whereas classical least square estimators assume a constant variance of the residuals, the discrepancy between predictions and observations in our case, clearly depended on the FA at the time of measure. Thus, we corrected the heteroskedasticity to account for the varying variance of the residuals and to obtain an equation for the latter. For this, we applied generalized least squares regressions[23 12]. The modeling of the standard deviation was very important since our purpose was to further define Z-scores and normal parameters.
Our dataset exhibited outliers due among other to imprecision on the fecundation time, which could compromise the quality of the regression results. The robust regression methods we used are designed to be unsensitive to the presence of outliers[15 24]. We used the `lmRob` function from the `R Cran` robust package[25]. The study was completed by a modeling of the residuals' variance in time. Also, the observations corresponding to CRLs smaller or higher than 45mm were reweighted so that these two periods had equivalent importance in the regression.

Validation of the results: We considered two criteria to compare the results provided by the different regressions. The cross-validation reveals methods with good predictive power, whereas the study of the differences between predictions and measurements provides information on the accuracy of prediction.
The idea behind cross-validation is to separate the observations into two samples: the first one, the training sample, was used to obtain the regression formula that express the explained variable as a function of explanatory variables ; the explanatory variables of the second sample, the test sample, were used in these regressions to provide predictions of the explained variable. These predictions were compared with the true measurements. We chose a leave-one-out cross-validation that uses test samples of size 1 and repeats the procedure by successively excluding each observation from the training data. We did this for each regression that had been proposed (heteroskedastic, robust, Robinson's curve) and ranked the methods according to the number of times their predictions were the best ones.
To ensure that the methods did not perform too badly when they did not provide the best predictions, we also studied the distribution of the deviations between the predictions and the measurements.

Results

Pregnancies from IVFs

Out of the 402 pregnancies, there were 78 (19.40%) twin pregnancies and 8 (1.99%) triple pregnancies. Preliminary tests (Wilcoxon and Chow, data not shown) showed that multiple pregnancies did not required to be separated from single pregnancies and that the measures made in Nice and Monaco could be considered simultaneously.

Heteroskedastic and robust regressions were realized. We performed cross-validation with the obtained regressions (see Table 1). Globally, the robust regression gave the best prediction in 64.56% cases:

$$\mathbf{CRL} = -3.3108 - 0.2087\ \mathbf{FA} + 1.5250\,10^{-2}\ \mathbf{FA}^2, \quad (1)$$
$$\text{with } R^2 = 73.79\%$$
$$\sigma^2 = 46.2354 - 2.0194\ \mathbf{FA} + 0.0230\ \mathbf{FA}^2,$$

Tabulated values are given in the electronic supplementary materials (ESM).

We used robust tests that generalize the Wald test for linear hypothesis[15]. The null assumptions that the coefficients in (1) were equal to the coefficients of Robinson, Pexsters or Verwoerd-Dikkeboom models were all rejected with p-values smaller than 0.01.

We saw from the cross-validation (Table 1) that the CRLs predicted with our model were closer to the true values in 64.56% of the cases when compared with Robinson's prediction (67.72% of the cases when compared with Papaioannou's curve, 63.68% when compared with Pexsters' curve, 54.56% when compared with Verwoerd-Dikkeboom's curve). Predictions errors, with (1), had also a smaller standard deviation (3.43 mm).

Pregnancies after spontaneous conception

Using the same methodology as reported above, we performed heteroskedastic and robust regressions with the

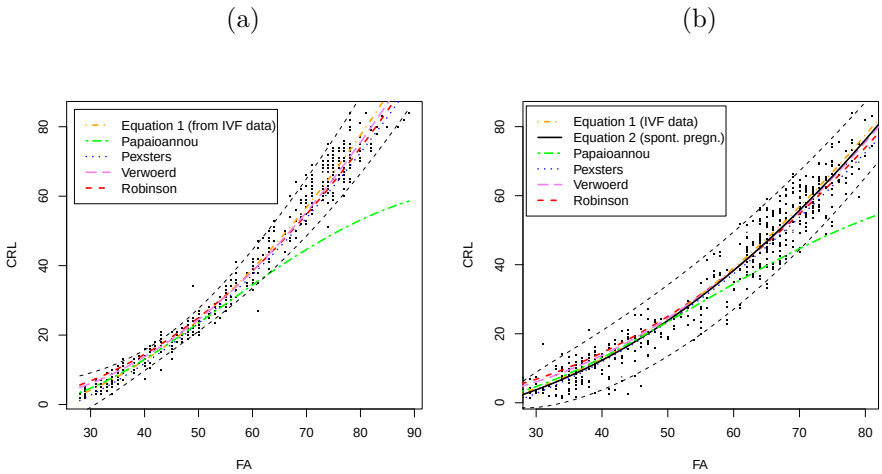

Figure 3: *(a) Predictions of the CRL values with equation* (1) *and with Papaioannou's, Pexsters's, Verwoerd-Dikkeboom's and Robinson's models. IVF data are represented. The confidence interval associated with equation* (1) *and obtained with our IVF data is represented in black dotted line.*
(b) Predictions of the CRL values using equation (1) *(from our IVF data), equation* (2) *(from our spontaneous pregnancies data) and using Papaioannou's, Pexsters', Verwoerd-Dikkeboom's, Robinson's models. The data from spontaneous pregnancies are represented. The confidence intervals associated with* (2)*, with* $\kappa = 1.96$*, are drawn in dotted black lines.*

CRL measures from spontaneous pregnancies.

$$\mathbf{CRL} = -4.1212 - 0.1824\ \mathbf{FA} + 0.0148\ \mathbf{FA}^2, \quad (2)$$
$$\text{with } R^2 = 78.48\%$$
$$\sigma^2 = -53.1054 + 2.5634\ \mathbf{FA} - 0.0189\ \mathbf{FA}^2,$$

The CRL 95% confidence interval was also determined:

$$CI = [-4.1212 - 0.1824\ \mathbf{FA} + 0.0148\ \mathbf{FA}^2 \pm \kappa \times \big(-53.1054 + 2.5634\ \mathbf{FA} - 0.0189\ \mathbf{FA}^2\big)^{1/2}].$$

The constant κ was calibrated so that 95% of the observations were included in the confidence interval, thus $\kappa = 1.85$.

This regression (2) was compared to Robinson's, Papaioannou's, Pexsters', Verwoerd-Dikkeboom's equations and to equation (1) (obtained with IVFs). Robust Wald-type tests[15] showed that with the variance of our observations, our equation (2) could be considered as significatively different from Robinson's regression (p-value=0.0261). The equations of Pexsters, Verwoerd-Dikkeboom and equation (1) were not statistically different from equation 2 (p-values of 0.0768, 0.3969 and 0.8189 respectively), although the cross-validation and the study of the errors between predictions and observations (see Table 2) showed that there were closest predictions with our equation 2.

Using spontaneous pregnancies data, for FA = 28 days, equation (2) (from spontaneous pregnancies) predicted CRL = 2.39 mm, equation (1) CRL=1.98 mm, thus a -0.41 mm difference with IVF equation (1). Likewise for FA=28 days Robinson's curve predicted CRL = 3.23 mm (+0.84 mm) with equivalent to an overestimation of 1 day by the latter, Papaioannou's curve predicted CRL = 1.86 mm (-0.53 mm), Pexsters' curve predicted CRL=1.16 mm (-1.23 mm) and Verwoerd-Dikkeboom's curve predicted CRL=2.51 mm (-0.12 mm).
For FA=70 days, equation (2) (from spontaneous pregnancies) predicted CRL=55.77 mm. We found a difference of 1.03 mm with the equation (1) (IVF equation), -1.00 mm with Robinson's curve, -11.11 mm with Papaioannou's curve, -2.03 mm with Pexsters' curve and -0.35 mm with Verwoerd-Dikkeboom's curve.

For CRL < 20 mm, no significant difference was noticed between equation (1) (built on IVF) and equation (2) (built on spontaneous pregnancies) , p = 0.8713. For CRL = 20 mm the mean difference between the predictions of equation 1 and equation 2 was 0.43 mm (median of 0.42 mm and standard deviation of 0.039 mm, p-value<0.05) and fits with less than 1 day difference for foetal age. Thus, on this period, datations predcited by these equations were either similar or negligible (see datation tables in ESM). However, for CRL = 20 mm, the deviation between equation (1) and equation (2) slightly increased. Graphically (Fig. 3 (b)), the equation (1) (built on IVF) over-estimated the CRL.

	Equation (1) (from IVF data)	Robinson's curve (5)	Papaioannou's curve 7	Pexsters's curve (9)	Verwoerd-Dikkeboom's curve (10)
Number of best performances					
Frequency (Percentage) (%)	192 (33.68)	85 (14.91)	63 (11.05)	156 (27.37)	74 (12.98)
	368 (64.56)	202 (35.44)	*	*	*
	386 (67.72)	*	184 (32.28)	*	*
	363 (63.68)	*	*	207 (36.32)	*
	311 (54.56)	*	*	*	259 (45.44)
Absolute error					
Min	0.01702	0.0350	0.0193	0.0020	0.0086
Median	1.7690	2.1670	2.9560	2.1380	1.9150
Mean	2.4650	2.9400	7.9240	3.0470	2.6530
Max	14.9200	14.1100	32.3800	15.4400	12.9900
Error					
Min absolute error	-10.9900	-14.1100	-32.3800	-15.4400	-12.75
Median absolute error	-0.0879	0.4710	-2.5120	-1.8900	0.2488
Mean absolute error	0.0481	-0.3087	-7.2090	-2.170	-0.2373
Max absolute error	14.9200	12.9700	8.5150	11.9100	12.990
Std dev.	3.4393	3.8680	8.9772	3.5432	3.587

Table 1: *In the first part of the table, we compared the different equations by cross-validation. In line 1, we computed the predictions for all the models and count, for each method, the number of times it gave the best prediction. In lines 2 to 5, we compared equation* (1) *with each of the other model (for instance, in line 2, we compared the predictions of equation* (1) *and of Robinson's model and indicated how many times each of them gave the best prediction). In the second and third parts of the table, summary of the absolute error and of the signed error were computed. The data used for the cross-validation were the IVF measures. Our equation* (1) *provided the best predictions. Papaioannou's curve was efficient for GA under 75 days (FA under 61 days) but not for larger embryos (see ESM).*

A t-test showed that, for the spontaneous pregnancies, the proportion of over-estimations by the equation (1) (built on IVF) was statistically higher than when equation (2) (built on spontaneous pregnancies) was used (p-value= 0.0330). The mean difference between the CRL prediction by equation (1) and equation (2) was 0.94 mm, with a median of 0.94 mm and a standard deviation of 0.223 mm.

Predicting FA with the ultrasound measure of CRL

Up to now, the determination of FA from the ultrasound measure of CRL is based on Robinson's equation[26] or on the equation by Papaioannou et al.[10] (see equations in the ESM). As these authors, we opted to build a mathematical model from our data predicting FA from CRL. Indeed, in a stochastic setting, inverting the equations linking measures of CRL to FA may not be optimal. We built mathematical models from our data using the same regression methods and validation procedures as described in the previous sections.

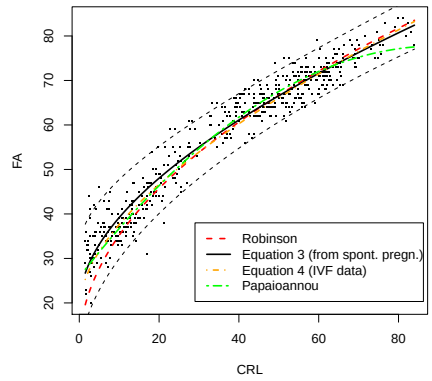

Figure 4: *Predictions of the foetal age (time since fecundation) from the measurements of the CRL using the equations found with various methods. We represented data from the sample of spontaneous pregnancies.*

This time, the heteroskedastic regression was shown to

	Equation (2) (from spont. pregn.)	Equation (1) (from IVF)	Robinson (5)	Papaioannou (7)	Pexsters (9)	Verwoerd (10)
Number of best performances						
Frequency (Percentage) (%)	269 (52.44)	244 (47.56)	*	*	*	*
	286 (55.75)	*	227 (44.25)	*	*	*
	338 (65.89)	*	*	175 (34.11)	*	*
	283 (55.17)	*	*	*	230 (44.83)	*
	258 (50.29)	*	*	*	*	255 (49.71)
	*	282 (54.97)	231 (45.03)	*	*	*
	*	337 (65.69)	*	176 (34.31)	*	*
	*	266 (51.85)	*	*	247 (48.15)	*
	*	266 (51.85)	*	*	*	247 (48.15)
Absolute error						
Min	0.0055	0.0137	0.0358	0.0450	0.0100	0.0232
Median	3.3200	3.1800	3.5510	5.4840	3.3620	3.3070
Mean	4.1150	4.1430	4.2950	7.6410	4.2330	4.1610
Max	14.6000	15.8800	15.8600	32.3800	15.4400	15.2000
Error						
Min	-12.4800	-12.1200	-14.1100	-32.3800	-15.4400	-12.7500
Median	-0.07181	0.6235	0.8910	-3.7620	-1.2900	0.7229
Mean	0.1997	1.0320	0.6668	-5.6230	-1.0830	0.7166
Max	14.6000	15.8800	15.8600	14.5600	13.7000	15.2000
Std dev.	5.2175	5.2102	5.4044	8.3903	5.2563	5.2565
Absolute relative error (Percentages)						
Median	11.0700	11.1200	10.2200	19.6100	11.4400	10.5000
Mean	24.9900	26.0400	32.0300	31.5900	24.2500	29.1900

Table 2: *Comparison of the predictions of Equations* (2) *and* (1) *with Robinson's, Pexters's and Verwoerd-Dikkeboom's equations, using the reweighted sample of 513 women with regular cycles. In the first part of the table, cross-validation with the data from spontaneous pregnancies was conducted, as in Table 1 ; in the second and third parts, summaries of the absolute and signed errors are provided.*

be more accurate when compared with the equation obtained by robust regression (with a cross-validation and a study of the prediction error, data not shown). These equations were:

$$\mathbf{FA} = 19.1732 + 6.0266\ \sqrt{\mathbf{CRL}} + 0.0955\ \mathbf{CRL}, \quad (3)$$
$$\text{with } R^2 = 99.71\%$$
$$\sigma^2 = 33.1275 - 4.9440\ \sqrt{\mathbf{CRL}} + 0.2270\ \mathbf{CRL}.$$

and showed relatively small heteroskedasticity.

Using the IVF data, we obtained the following equation for predicting FA from CRL:

$$\mathbf{FA} = 18.0739 + 5.6925\sqrt{\mathbf{CRL}} + 0.1549\mathbf{CRL}, \quad (4)$$
$$\text{with } R^2 = 99.87\%$$
$$\sigma^2 = 7.3281 - 1.6397\sqrt{\mathbf{CRL}} + 0.1688\mathbf{CRL}.$$

Fisher's tests with heteroskedastic corrections showed that the coefficients of (3) and those of Robinson[26] were statistically different (p-value=0.0321). The difference between the coefficients of (3) and (4) was not statistically significant (p-value=0.9943). Papaioannou et al.[10] used a polynomial of degree 2 to express FA as a function of CRL and CRL^2 thus the coefficients could not be compared to the ones of (3).

We compared the equation (3) (built on the spontaneous pregnancies), with the equation (4) (built on IVFs), Robinson's equation and Papaioannou's equation (see Table 4). This comparison showed that Equation (3) and Papaioannou's equations had similar predictive powers and equivalent precision in the predictions. Both outperformed Robinson's equation, but the latter still provided correct predictions for CRL larger than 45 mm, with an average error of 3.5 days (against 3 days for Equation (3)

Regression	Equation (3) (Spont. pregn.)	Equation (4) (IVF)	Robinson (6)	Papaioannou et al. (8)
Number of best performances				
Frequency (Percentage) (%)	262 (51.07)	251 (48.93)	*	*
	304 (59.26)	*	209 (40.74)	*
	251 (48.93)	*	*	262 (51.07)
	*	281 (54.78)	232 (45.22)	*
	*	246 (47.95)	*	267 (52.05)
	*	*	208 (40.55)	305 (59.45)
Absolute error				
Min absolute error	0.0071	0.0033	0.0100	0.0075
Median absolute error	2.5410	2.3220	2.4310	2.2660
Mean absolute error	2.9180	2.9310	3.3550	2.8490
Max absolute error	15.1400	16.5400	21.5400	15.3400
Error				
Min error	-15.1400	-16.5400	-21.5400	-15.34
Median error	0.2091	-0.4440	-0.8924	-0.2494
Mean error	-0.0023	-0.8233	-1.4820	-0.5261
Max error	14.7000	13.1800	11.9300	12.60
Std dev.	3.7200	3.7352	4.3729	3.6717
Relative error (Percentages)				
Median absolute error	4.1790	4.2970	4.3940	4.1870
Mean absolute error	5.9990	5.8790	6.9990	5.6700

Table 3: *Comparison of the predictions of the different equations for* **FA** *based on observations of the* **CRL**. *The first part of the table describes the cross-validation with the data from spontaneous frequencies. The first line gives for each model the number and percentage of times they provided the best prediction, when compared all together. The lines 2 to 5 compare the models two by two. The second, third and fourth part of the table provide summary statistics for the absolute error, the signed error and the relative error.*

and Papaioannou's equation, see Figures 4).

Optimal period to predict the FA with CRL

From equation (4), the foetal age at which the width of the confidence interval of FA predicted from the CRL was the smallest, was obtained for CRL=23.5950 mm, corresponding to FA=49.38 days. The CRL standard deviation at this time was estimated to be 1.8292 mm. This corresponds to the period where there is a trade-off between measuring large dimensions and adequate position of the embryo. Around FA=50 days, the embryo is indeed quite curved in shape and motionless.

Breakpoint

As the graphical representation of CRL by FA (Fig. 3 (a)) evoked a breakpoint in foetal growth, instead of using polynomials of degree 2 to model the CRL as a function of FA, we searched to reproduce the curvature of the graph by modeling a breakpoint between two subperiods. We looked for breakpoints from mixed regressions and used the package `flexmix`[27]. We obtained two groups (Fig. 5)that may be modeled respectively with:

$$\mathbf{CRL} = -21.15 + 0.7642\ \mathbf{FA} + 2.820\ \mathbf{FA}^2$$
$$\mathbf{CRL} = -28.1408 + 0.7106\ \mathbf{FA} + 7.364\ 10^{-3}\mathbf{FA}^2,$$

with R^2-statistics of 99.15% and 97.36%. Both equations disclosed a breakpoint at FA=45.56 days.

The methods distinguished two samples of respectively 211 and 359 observations, which differed from their FA, the first sample being composed of small FAs.

Discussion

Robinson's curve remains a historical benchmark that is still widely used. Since 1973, many other studies have been performed. Our first purpose was to propose new

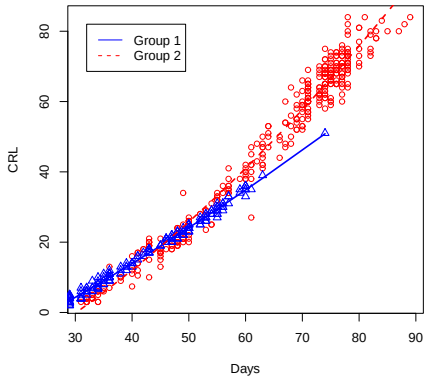

Figure 5: *Estimation of mixed linear regression with the Flexmix package, with the two clusters that have been identified. IVF data are used.*

equations for the modeling of CRL as a function of FA using modern equipment and following the standardized procedures for ultrasound measurements in the context of Down syndrome's detection in a general population. We obtained two equations. For IVF data, equation (1) and equation (4) respectively gave the predictions of CRL by FA and of FA by CRL. Likewise with spontaneous pregnancies, we obtained equation (2) and equation (3).
The accuracy of these new main equations we propose relies on several factors. First, each of our datasets (from IVFs and from spontaneous pregnancies) was obtained by a single operator using the same manufacturer devices: Kretz/General Electric. The computerized data collection was done on interfaces that had been specially developed for this work. Measurements were optimized by the choice of the best method, transabdominal or transvaginal scan, for every examination. The difficult measures benefitted from 3D triplan reconstructions. Moreover, we used an explicit methodology to clean our data. The statistical accuracy of our equation was established by a cross-validation and by studying the errors of the different predictions. Comparisons between the various predictions showed that for CRLs between 45 and 85 mm, the differences between "ancient" and "recent" charts were small. On the other hand, the recent equations benefitted from a larger number of data for the initial period, collected by vaginal access. The new equations we propose are more precise, and allow moreover to follow up in time embryos that are measured with CRL smaller than 45 mm. The beginning of the curve is much more accurate and is more in adequation with the practice, for instance when considering the predicted size after 28 days since conception.
Moreover, we provided models for the evolution of the residuals, which allows for building confidence intervals and Z-scores. As a byproduct we showed that the best period to predict FA is to measure embryo around day 50, when its size is around 24 mm.

For CRL <20mm there is not difference between equations built on IVF data and on spontaneous pregnancies data. This objectively suggests that the age at which an embryo of 1 to 2mm becomes visible in the gestational sac, as well as the embryonic growth for foetuses between 1 and 20 mm, are in average independent from the mode. For CRL≥20mm the small difference between both models increased suggesting that IVF embryos could have a slightly higher growth rate than spontaneous pregnancies embryos as was already reported[28 29].

Finally, models where the CRL is expressed as a polynomial of degree 2 are convenient for practical uses. However, searching a model with a break point showed that there is a change in the growth regime around day 46, when the CRL is around 20 mm. This could correspond to the beginning of the maternal connection.

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Electronic Supplementary Materials

Equations of Robinson (1973, 1975)

Robinson[5] calibrated CRLs from 334 measures of natural pregnancies with known and significant last menstruations:

$$\mathbf{CRL} = 7.295 - 0.6444\ \mathbf{GA} + 0.0144\ \mathbf{GA}^2, \tag{5}$$

where we recall that $\mathbf{GA} = \mathbf{FA} + 14$ represents the gestational age. A corrective factor of (1 mm +3.7%) was substracted by par Robinson to account for the calibration of his machine.

In[26], Robinson established the following equation for computing the gestational age from measurements of the CRL.

$$\mathbf{GA} = 8.052\sqrt{\mathbf{CRL}} + 23.73. \tag{6}$$

Equation of Papaioannou et al. (2010)

Papaioannou et al.[10] obtain a curve for the **CRL** as a function of **GA** for **GA** between 40 and 75 days.

$$\sqrt{\mathbf{CRL}} = -6.662367 + 0.246741\ \mathbf{GA} - 0.001046\mathbf{GA}^2. \tag{7}$$

Their curve is correct for $\mathbf{GA} \leq 75$ days, but from the negative coefficient of $\mathbf{GA}^2$, we can guess that the fit for larger time will deteriorate (see Fig. 4).

They could also predict the GA as a function of the CRL.

$$\mathbf{GA} = 39.811963 + 1.155896\ \mathbf{CRL} - 0.006429\ CRL^2. \tag{8}$$

Equation of Pexters et al. (2010)

Using a large population of pregnancies, Pexsters et al.[11] proposed a new curve to re-estimate the CRL curve from 5.5 weeks' gestation and obtained:

$$\mathbf{CRL} = -9.09 - 0.26\ \mathbf{GA} + 0.012\ \mathbf{GA}^2. \tag{9}$$

Equation of Verwoerd-Dikkeboom et al. (2010)

Verwoerd-Dikkeboom et al.[8] use 3D measurements from 6 to 14 weeks GA in 32 pregnancies to calibrate an equation of the CRL.

$$\mathbf{CRL} = 9.0963 - 0.751165\ \mathbf{GA} + 0.015508\ \mathbf{GA}^2. \tag{10}$$

$$\sigma^2 = 0.2814 - 0.006087\ \mathbf{GA} + 0.000043\ \mathbf{GA}^2. \tag{11}$$

Robust regression for the prediction of FA as a function of CRL

The robust regression gave, on our IVF data:

$$\mathbf{FA} = 17.8994 + 5.7617\ \sqrt{\mathbf{CRL}} + 0.1471\ \mathbf{CRL}, \tag{12}$$

$$\sigma^2 = 7.3281 - 1.6397\ \sqrt{\mathbf{CRL}} + 0.1688\ \mathbf{CRL}.$$

Cross validation showed that on IVF data, the regression with heteroskedastic regression (4) gave the best prediction. Compared with Robinson's regression, it gave the best prediction in 343 cases out of 570 (60.18%).

On spontaneous pregnancies data, we obtained:

$$\mathbf{FA} = 19.2702 + 5.7804\sqrt{\mathbf{CRL}} + 0.1271\mathbf{CRL}, \tag{13}$$

$$\sigma^2 = 41.8353 - 8.3486\sqrt{\mathbf{CRL}} + 0.5198\mathbf{CRL}. \tag{14}$$

Cross-validation showed that on spontaneous pregnancies data, the heteroskedastic regression presented in (3) gave better prediction in 263 (51.27%) cases versus 250 (48.73%) cases for the Robust regression. However, in term of precision, these two methods were comparable. For the heteroskedastic (resp. robust) regression, the mean absolute error was 2.9180 (resp. 2.9120), the median absolute error was 2.5410 (resp. 2.5000) and the standard deviation was 3.7199 (resp. 3.7169).

Characteristics of the parents

Characteristics of parents of spontaneous pregnancies data are presented the characteristics in Table 4.

	Whole sample		Women with regular cycles	
Variable	Mean	Standard deviation	Mean	Standard deviation
Mother's age	29.69	6.18	29.46	6.05
Mother's size (cm)	164.58	9.30	164.47	9.09
Mother's weight (kg)	64.42	14.31	64.14	13.93
Mother's Mass Corporal Index (MCI)	24.51	14.73	24.16	12.69
Father's age	30.69	6.88	30.79	6.93
Father's size (cm)	177.51	19.17	177.27	8.44
Father's weight (kg)	81.13	40.30	81.96	45.34
Father's MCI	26.52	19.58	26.40	17.19

Table 4: *Characteristics of the parents.*

Tabulation of the CRL predicted by the IVF equation (1)

FA days	FA weeks+days	CRL mm	SD of the CRL (mm)	FA days	FA weeks+days	CRL mm	SD of the CRL (mm)
26	3 + 5	1.572894	3.047959	56	8 + 0	32.82732	2.308587
27	3 + 6	2.172470	2.913853	57	8 + 1	34.34187	2.431273
28	4 + 0	2.802544	2.781558	58	8 + 2	35.88692	2.557076
29	4 + 1	3.463118	2.651343	59	8 + 3	37.46247	2.685558
30	4 + 2	4.15419	2.523531	60	8 + 4	39.06852	2.816352
31	4 + 3	4.875762	2.398507	61	8 + 5	40.70507	2.949151
32	4 + 4	5.627834	2.276729	62	8 + 6	42.37212	3.083695
33	4 + 5	6.410404	2.158747	63	9 + 0	44.06967	3.219766
34	4 + 6	7.223474	2.045217	64	9 + 1	45.79771	3.357179
35	5 + 0	8.067043	1.936924	65	9 + 2	47.55626	3.495774
36	5 + 1	8.941112	1.834795	66	9 + 3	49.34530	3.635417
37	5 + 2	9.84568	1.739914	67	9 + 4	51.16485	3.775992
38	5 + 3	10.78075	1.653531	68	9 + 5	53.01489	3.917398
39	5 + 4	11.74631	1.577043	69	9 + 6	54.89544	4.059548
40	5 + 5	12.74238	1.511952	70	10+ 0	56.80648	4.202367
41	5 + 6	13.76894	1.459782	71	10 + 1	58.74802	4.345789
42	6 + 0	14.82601	1.421958	72	10 + 2	60.72006	4.489756
43	6 + 1	15.91357	1.399643	73	10 + 3	62.7226	4.634218
44	6 + 2	17.03163	1.393582	74	10 + 4	64.75564	4.779128
45	6 + 3	18.18019	1.403985	75	10 + 5	66.81918	4.924449
46	6 + 4	19.35925	1.430494	76	10 + 6	68.91322	5.070144
47	6 + 5	20.56881	1.472238	77	11 + 0	71.03775	5.216183
48	6 + 6	21.80887	1.527970	78	11 + 1	73.19279	5.362536
49	7 + 0	23.07943	1.596224	79	11 + 2	75.37833	5.50918
50	7 + 1	24.38049	1.675472	80	11 + 3	77.59436	5.656091
51	7 + 2	25.71204	1.764232	81	11 + 4	79.8409	5.803249
52	7 + 3	27.0741	1.861145	82	11 +5	82.11793	5.950636
53	7 + 4	28.46666	1.965003	83	11 + 6	84.42546	6.098235
54	7 + 5	29.88971	2.074765	84	12 + 0	86.76349	6.246032
55	7 + 6	31.34326	2.189542	85	12 + 1	89.13202	6.394012

Table 5: *Predictions of the CRL as a function of FA for IVF data. We use Equations* (1) *and the associated equation for the standard deviation (SD).*

Tabulation of the FA predicted by the IVF equation (4)

CRL mm	FA days	SD of FA days	CRL mm	FA days	SD of FA days
1	23.92126	2.420171	43	62.06217	1.957944
2	26.43405	2.312322	44	62.64861	1.969268
3	28.39823	2.234829	45	63.23018	1.980882
4	30.07841	2.173452	46	63.80702	1.992769
5	31.57711	2.122639	47	64.37931	2.004914
6	32.9469	2.079527	48	64.94718	2.017301
7	34.21900	2.042402	49	65.51077	2.029915
8	35.41377	2.010139	50	66.07021	2.042745
9	36.54533	1.981947	51	66.62562	2.055776
10	37.62399	1.957245	52	67.17713	2.068998
11	38.65749	1.93559	53	67.72484	2.082398
12	39.65189	1.916631	54	68.26886	2.095966
13	40.61198	1.900084	55	68.8093	2.109691
14	41.54165	1.885717	56	69.34624	2.123565
15	42.44410	1.873333	57	69.87979	2.137577
16	43.32203	1.862764	58	70.41003	2.151719
17	44.1777	1.853865	59	70.93705	2.165983
18	45.01304	1.846509	60	71.46093	2.180362
19	45.82972	1.840584	61	71.98175	2.194847
20	46.62921	1.835989	62	72.49958	2.209431
21	47.41277	1.832634	63	73.0145	2.224109
22	48.18154	1.830438	64	73.52656	2.238874
23	48.9365	1.829326	65	74.03585	2.25372
24	49.67856	1.829231	66	74.54242	2.268641
25	50.4085	1.830088	67	75.04634	2.283632
26	51.12706	1.831841	68	75.54766	2.298688
27	51.83487	1.834435	69	76.04645	2.313803
28	52.53254	1.837822	70	76.54275	2.328975
29	53.2206	1.841953	71	77.03662	2.344197
30	53.89954	1.846786	72	77.52812	2.359466
31	54.56982	1.852281	73	78.01728	2.374779
32	55.23185	1.858398	74	78.50416	2.390131
33	55.88601	1.865103	75	78.9888	2.405518
34	56.53267	1.872362	76	79.47126	2.420939
35	57.17215	1.880142	77	79.95157	2.436388
36	57.80475	1.888415	78	80.42977	2.451864
37	58.43076	1.897152	79	80.9059	2.467364
38	59.05045	1.906327	80	81.38001	2.482884
39	59.66406	1.915915	81	81.85213	2.498423
40	60.27183	1.925892	82	82.3223	2.513977
41	60.87396	1.936236	83	82.79055	2.529545
42	61.47068	1.946927	84	83.25691	2.545124

Table 6: *Predictions of the FA as a function of CRL by using Equations* (4) *and the associated equation for the standard deviation (SD).*

Tabulation of the CRL predicted by the equation built on spontaneous pregnancies (2)

FA days	FA weeks+days	CRL mm	SD of the CRL (mm)	FA days	FA weeks+days	CRL mm	SD of the CRL (mm)
26	3 + 5	1.160552	0.8733835	56	8 + 0	32.1681	5.582057
27	3 + 6	1.764087	1.524546	57	8 + 1	33.66139	5.620191
28	4 + 0	2.397282	1.961599	58	8 + 2	35.18434	5.654726
29	4 + 1	3.060135	2.309479	59	8 + 3	36.73695	5.685728
30	4 + 2	3.752647	2.604172	60	8 + 4	38.31922	5.713254
31	4 + 3	4.474817	2.862153	61	8 + 5	39.93114	5.737353
32	4 + 4	5.226645	3.092623	62	8 + 6	41.57273	5.75807
33	4 + 5	6.008133	3.301349	63	9 + 0	43.24397	5.77544
34	4 + 6	6.819278	3.492232	64	9 + 1	44.94488	5.789494
35	5 + 0	7.660083	3.668060	65	9 + 2	46.67544	5.800255
36	5 + 1	8.530546	3.830904	66	9 + 3	48.43566	5.807742
37	5 + 2	9.430667	3.982359	67	9 + 4	50.22553	5.811968
38	5 + 3	10.36045	4.123679	68	9 + 5	52.04507	5.81294
39	5 + 4	11.31989	4.255875	69	9 + 6	53.89426	5.810659
40	5 + 5	12.30898	4.379772	70	10+ 0	55.77312	5.805122
41	5 + 6	13.32774	4.496057	71	10+ 1	57.68163	5.796319
42	6 + 0	14.37615	4.605306	72	10+ 2	59.6198	5.784235
43	6 + 1	15.45422	4.708009	73	10 + 3	61.58763	5.76885
44	6 + 2	16.56196	4.804586	74	10 + 4	63.58512	5.750137
45	6 + 3	17.69935	4.895399	75	10 + 5	65.61226	5.728064
46	6 + 4	18.86639	4.980764	76	10 + 6	67.66907	5.702591
47	6 + 5	20.0631	5.060957	77	11 +0	69.75553	5.673673
48	6 + 6	21.28947	5.136219	78	11+ 1	71.87165	5.641257
49	7 + 0	22.54549	5.206765	79	11 + 2	74.01743	5.605281
50	7 + 1	23.83117	5.272784	80	11 + 3	76.19287	5.565678
51	7 + 2	25.14651	5.334444	81	11 + 4	78.39797	5.522369
52	7 + 3	26.49151	5.391894	82	11 + 5	80.63273	5.475266
53	7 + 4	27.86617	5.445268	83	11 + 6	82.89714	5.424271
54	7 + 5	29.27049	5.494685	84	12 + 0	85.19121	5.369271
55	7 + 6	30.70446	5.54025	85	12 +1	87.51494	5.310144

Table 7: *Predictions of the CRL as a function of FA for spontaneous pregnancies. We use Equations* (2) *and the associated equation for the standard deviation (SD).*

Tabulation of the FA predicted by the equation built on spontaneous pregnancies (3)

CRL mm	FA days	SD of FA days	CRL mm	FA days	SD of FA days
1	25.29526	5.330148	43	62.79687	3.235434
2	27.887	5.156509	44	63.34921	3.212509
3	29.89792	5.024458	45	63.89639	3.190083
4	31.60820	4.914002	46	64.43858	3.168145
5	33.12633	4.817394	47	64.97593	3.146684
6	34.50799	4.730656	48	65.50861	3.125689
7	35.78624	4.651428	49	66.03676	3.105150
8	36.98260	4.578167	50	66.56052	3.085059
9	38.11206	4.509806	51	67.08001	3.065407
10	39.1855	4.445563	52	67.59537	3.046185
11	40.21114	4.384852	53	68.10671	3.027386
12	41.19538	4.327215	54	68.61414	3.009001
13	42.14330	4.272289	55	69.11778	2.991024
14	43.05901	4.219779	56	69.61772	2.973448
15	43.94591	4.169442	57	70.11407	2.956267
16	44.80685	4.121076	58	70.60691	2.939473
17	45.64421	4.074508	59	71.09635	2.923062
18	46.46006	4.029594	60	71.58246	2.907028
19	47.25616	3.986206	61	72.06532	2.891364
20	48.03405	3.944234	62	72.54503	2.876067
21	48.79508	3.903583	63	73.02165	2.861130
22	49.54045	3.864167	64	73.49525	2.846549
23	50.2712	3.825912	65	73.96591	2.832319
24	50.98829	3.78875	66	74.4337	2.818435
25	51.69256	3.752622	67	74.89868	2.804894
26	52.38477	3.717474	68	75.3609	2.791691
27	53.06561	3.683256	69	75.82045	2.778822
28	53.7357	3.649925	70	76.27736	2.766283
29	54.39563	3.617441	71	76.7317	2.754070
30	55.0459	3.585767	72	77.18352	2.742179
31	55.687	3.554868	73	77.63288	2.730607
32	56.31936	3.524715	74	78.07982	2.71935
33	56.94341	3.495280	75	78.52439	2.708405
34	57.5595	3.466535	76	78.96665	2.697768
35	58.16799	3.438456	77	79.40662	2.687436
36	58.7692	3.411022	78	79.84437	2.677406
37	59.36343	3.384211	79	80.27994	2.667675
38	59.95097	3.358004	80	80.71335	2.658239
39	60.53208	3.332383	81	81.14466	2.649096
40	61.107	3.307330	82	81.5739	2.640242
41	61.67596	3.282831	83	82.00112	2.631674
42	62.23918	3.258870	84	82.42634	2.623390

Table 8: *Predictions of the FA as a function of CRL by using Equations* (3) *and the associated equation for the standard deviation (SD).*