Original Paper

Fetal Diagnosis and Therapy

Fetal Diagn Ther 2010;28:207–219
DOI: 10.1159/000319589

Received: May 10, 2010
Accepted after revision: July 19, 2010
Published online: September 18, 2010

Normal Ranges of Embryonic Length, Embryonic Heart Rate, Gestational Sac Diameter and Yolk Sac Diameter at 6–10 Weeks

George I. Papaioannou Argyro Syngelaki Leona C.Y. Poon Jackie A. Ross
Kypros H. Nicolaides

Harris Birthright Research Centre for Fetal Medicine and Early Pregnancy Unit, King's College Hospital, London, UK

Key Words
Early pregnancy · Embryo · Crown-rump length · Gestational sac · Yolk sac · Embryonic heart rate

Abstract
Objectives: To construct normal ranges for embryonic crown-rump length (CRL), heart rate (HR), gestational sac diameter (GSD) and yolk sac diameter (YSD) at 6–10 weeks of gestation. ***Methods:*** We examined 4,698 singleton pregnancies with ultrasound measurements of CRL, HR, GSD and YSD at 6–10 weeks and CRL at 11–13 weeks resulting in the live birth after 36 weeks of phenotypically normal neonates with birth weight above the 5th centile. Gestational age was derived from CRL at the 11- to 13-week scan using the formula of Robinson and Fleming. Regression analysis was used to establish normal ranges of CRL, fetal HR, GSD and YSD with gestation, and fetal HR, GSD and YSD with CRL. ***Results:*** At 6–10 weeks there were significant quadratic associations between CRL, GSD, YSD and gestation and between HR, GSD, YSD and CRL, and a cubic association between HR and gestation. The estimated gestation from CRL was the same as that of Robinson and Fleming for a CRL of 10.2–36.5 mm, but the formula of Robinson and Fleming underestimated the gestation by 1 day for a CRL 7.4–10.2 mm and this increased to 9 days for a CRL of 1 mm. ***Conclusion:*** This study established normal ranges for early pregnancy biometry.

Introduction

The measurements of embryonic length and heart rate (HR) and those of the gestational sac diameter (GSD) and yolk sac diameter (YSD) have been used for assessment of gestational age (GA) and prediction of adverse pregnancy outcome, such as miscarriage. Studies reporting normal ranges for these measurements with gestation have essentially derived their data from the examination of pregnancies in women with regular menstrual cycles and known date of the last menstrual period (LMP). However, in 15–45% of pregnancies, women are uncertain of their LMP, they have irregular menstrual cycles or they became pregnant soon after stopping the oral contraceptive pill [1, 2]. Additionally, because of considerable variations in the day of ovulation, in approximately 15% of women with certain dates and regular 28-day cycles, there is a discrepancy of more than 7 days in gestation calculated from the menstrual history and by ultrasound [3, 4]. For these reasons, accurate dating of pregnancy necessitates ultrasonographic measurement of the embryonic or fetal crown-rump length (CRL), and the most commonly recommended formula of estimating gestation from CRL is that of Robinson and Fleming [5–8]. Although the original formula was derived in 1975 from a study of 334 singleton pregnancies in women with regular menstrual cycles and certain LMP, several subsequent studies have generally confirmed the accuracy of the prediction [9–

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1015–3837/10/0284–0207$26.00/0

Accessible online at:
www.karger.com/fdt

Professor Kypros H. Nicolaides
Harris Birthright Research Centre for Fetal Medicine
King's College Hospital, Denmark Hill
London SE5 9RS (UK)
Tel. +44 20 3299 8259, Fax +44 20 7733 9534, E-Mail kypros@fetalmedicine.com

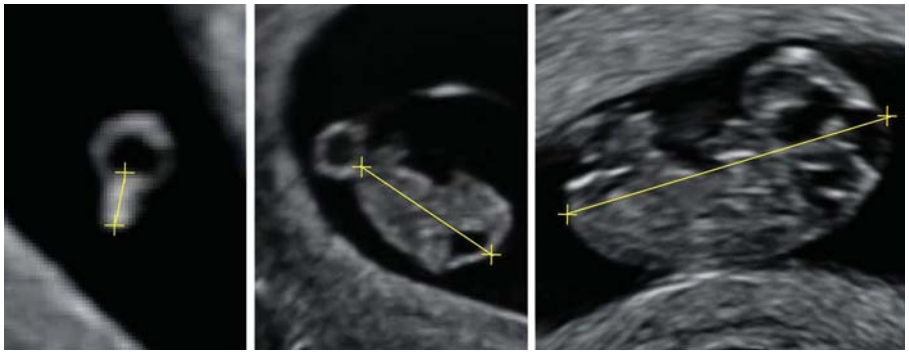


Fig. 1. Ultrasound pictures illustrating the measurement of embryonic length. In pregnancies at less than 7 weeks of gestation, the embryonic crown and rump cannot be visualised and therefore the greatest length of the embryo is measured (left, 3 mm). From 7 weeks onwards CRL is measured in a sagittal section of the embryo with care being taken to avoid inclusion of the yolk sac (middle, 14 mm; right, 25 mm).

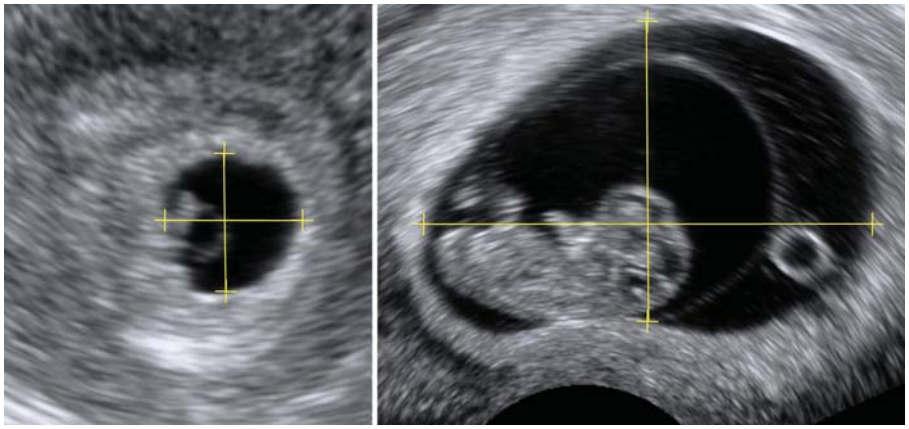


Fig. 2. Ultrasound pictures illustrating the measurement of GSD in embryos with CRL of 2 mm (left) and 25 mm (right). The callipers are placed at the inner edges of the trophoblast.

27]. Some studies, however, have suggested that in pregnancies below 8 weeks, the measurement of CRL underestimates the GA [17, 25]. Studies reporting reference ranges for embryonic HR, GSD or YSD have examined small numbers of either spontaneously conceived pregnancies in women with certain LMP or in vitro fertilisation pregnancies and reported their values either in relation to GA or embryonic CRL [14, 18, 26, 28–49].

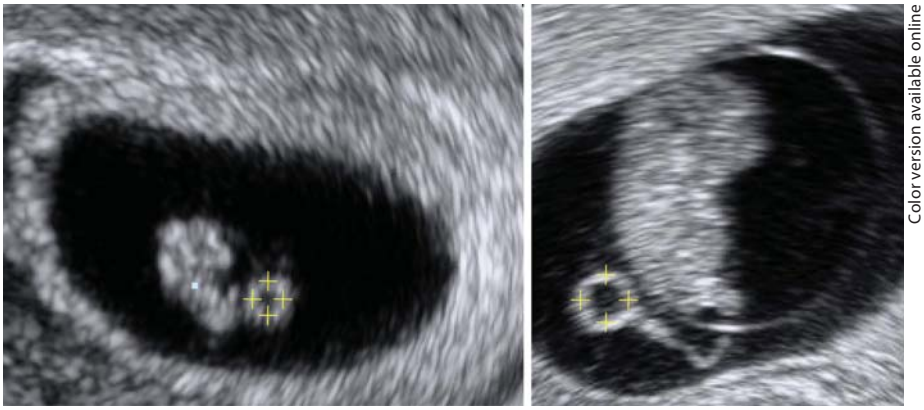
The aim of this study of 4,698 singleton pregnancies with normal outcome is to construct normal ranges for CRL, HR, GSD and YSD at 6–10 weeks of gestation. In these pregnancies, GA was derived from the measurement of fetal CRL at 11–13 weeks of gestation.

Materials and Methods

In our hospital there is an early pregnancy unit (EPU) which is freely accessible to pregnant women in our area. On arrival the demographic data and obstetric history are recorded in the EPU database and an ultrasound scan is carried out. The menstrual cycle and date of the LMP are recorded and classified as a regular cycle of 26–30 days with certain LMP, regular-uncertain, irregular-certain, unknown and conception within 3 cycles since a recent pregnancy or stopping the contraceptive pill. The indications for attending the EPU are classified as vaginal bleeding, abdominal pain, anxiety because of previous miscarriages or ectopic pregnancies, and pregnancy dating. The objectives of the ultrasound scan, which are performed by appropriately trained doctors, include the diagnosis of an intrauterine or extrauterine pregnancy and, where appropriate, recording of the number of live or dead embryos and measurement of embryonic CRL, HR, GSD, and YSD.

In pregnancies at less than 7 weeks of gestation, the embryonic crown and rump cannot be visualised and therefore the CRL was measured as the greatest length of the embryo (fig. 1). From 7 weeks onwards, the CRL was measured in a sagittal section of the embryo with care being taken to avoid inclusion of the yolk sac [50]. The HR was calculated as beats per minute by the software of the ultrasound machine after measurement by electronic callipers of the distance between two heart waves on a frozen M-mode image [28]. The GSD was calculated as the average of 3 perpendicular diameters with the callipers placed at the inner edges of the trophoblast (fig. 2) [49]. YSD was calculated as the average of 3 perpendicular diameters with the callipers placed at the centre of the yolk sac wall (fig. 3) [43].

In our hospital we routinely offer an ultrasound scan at 11–13 weeks in the fetal medicine unit (FMU) as part of the 1st trimester



Color version available online

Fig. 3. Ultrasound pictures illustrating the measurement of YSD in embryos with CRL of 8 mm (left) and 22 mm (right). The callipers are placed at the centre of the yolk sac wall.

Table 1. GA, ultrasound scan parameters and maternal characteristics in the study population

GA and ultrasound scan parameters	
GA, days	54 (50–61)
CRL, mm	13.0 (8.4–19.5)
Embryonic HR, bpm	155 (132–169)
Mean GSD, mm	26.0 (20.7–32.7)
YSD, mm	4.1 (3.7–4.7)
Maternal characteristics	
Maternal age, years	31.3 (26.4–35.5)
Maternal BMI	23.2 (21.2–26.9)
Racial origin	
White, n (%)	2,764 (58.8)
Black, n (%)	1,516 (32.3)
South Asian, n (%)	166 (3.5)
East Asian, n (%)	67 (1.5)
Mixed, n (%)	185 (3.9)
Nulliparous, n (%)	2,450 (52.1)
Cigarette smoker, n (%)	388 (8.3)
Conception	
Spontaneous, n (%)	4,599 (97.9)
Assisted, n (%)	99 (2.1)

Unless otherwise indicated, values are medians (interquartile ranges).

screening for chromosomal and other major fetal abnormalities, and the findings are recorded in the FMU database. The scan includes measurement of the fetal CRL. Data on pregnancy outcome are collected from the hospital maternity records or the general medical practitioners of the women and are then recorded in the FMU database.

We merged the EPU and FMU databases and searched the combined database to identify women fulfilling the following criteria: (1) scan in the EPU demonstrating a singleton pregnancy with a live embryo and measurements of embryonic CRL, HR, GSD and YSD; (2) scan in the FMU demonstrating a singleton pregnancy with a live fetus, no major defects and measurement of fetal CRL; and (3) live birth after 36 completed weeks of gestation of a phenotypically normal neonate with birth weight above the 5th centile for GA [51].

In all pregnancies fulfilling the entry criteria, GA at the visits to the EPU and FMU and at delivery were calculated from the formula of Robinson and Fleming using the fetal CRL at the FMU visit [7].

Statistical Analysis

Descriptive data are presented as medians (interquartile ranges) for continuous variables and number (percentage) for categorical variables. Square root (sqrt) transformation was applied to the measured CRL, FHR, GSD and YSD. Linear regression analysis was used, firstly, to determine the association of CRL, FHR, GSD and YSD with GA and to establish the normal ranges with GA, and, secondly, to determine the inter-relationship between GA, FHR, GSD and YSD with CRL and to establish the normal ranges with CRL. In summary, for each ultrasonographic measurement, polynomial regression models, either quadratic or cubic, were fitted separately to the mean and standard deviation (SD) as functions of GA or CRL. The 5th and 95th centiles were calculated as the mean $\pm$ 1.645 SD, with the value of 1.645 derived from the theoretical normal distribution.

The statistical software package SPSS 15.0 (SPSS Inc., Chicago, Ill., USA) was used for the data analyses.

Results

The data search identified 4,698 patients fulfilling the entry criteria. The patients were examined in the EPU between December 2002 and May 2009, and the indications for attending the EPU were vaginal bleeding in 1,515 (32.3%) cases, abdominal pain in 1,142 (24.3%), anxiety because of previous miscarriages or ectopic preg-

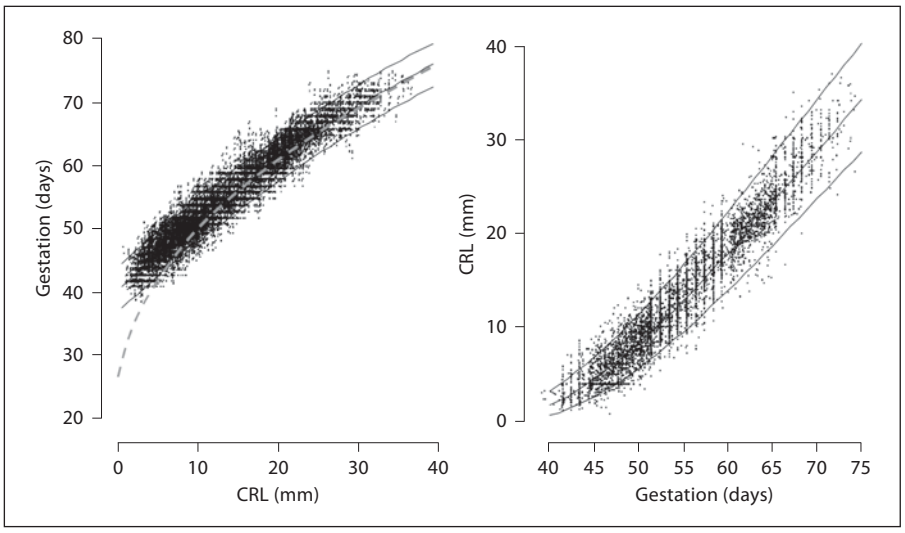


Fig. 4. Relationship between GA and embryonic CRL (left) and between embryonic CRL and GA (right; median, 95th and 5th centiles). The interrupted line on the left is the median value derived from the formula by Robinson and Fleming [7].

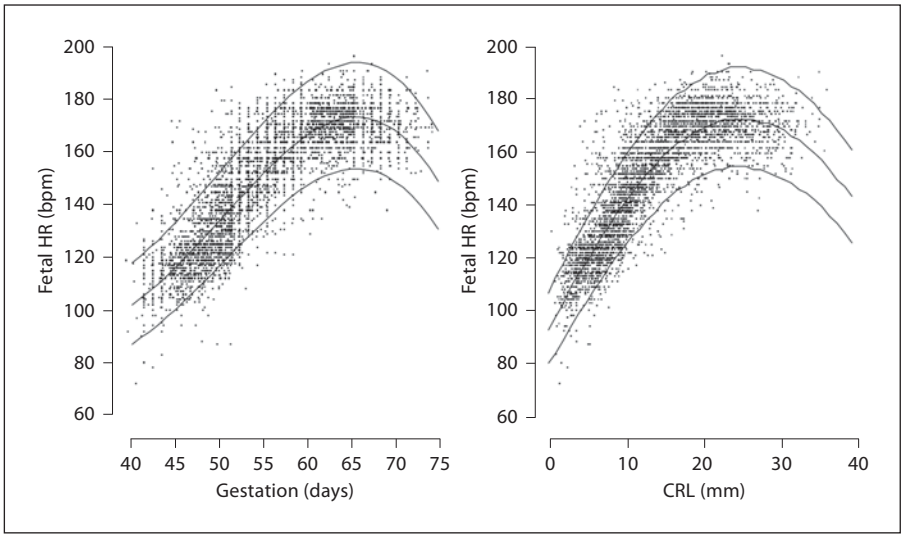


Fig. 5. Relationship between embryonic HR and GA (left) and embryonic CRL (right; median, 95th and 5th centiles).

nancies in 1,355 (28.8%), and pregnancy dating in 686 (14.6%). Details of maternal characteristics and ultrasound findings in the EPU are shown in table 1.

CRL versus Gestation

There was a significant quadratic association between GA and CRL (fig. 4, table 2): expected GA = 39.811963 (SE = 0.122316) + 1.155896 (SE = 0.017045) × CRL – 0.006429 (SE = 0.000519) × CRL^2; $R^2 = 0.916$, SD = 2.084, $p < 0.0001$.

There was a significant quadratic association between CRL and GA (fig. 4, table 3): expected sqrt CRL = –6.662367 (SE = 0.233173) + 0.246741 (SE = 0.008481) × GA – 0.001046 (SE = 0.000076) × GA^2; $R^2 = 0.909$, SD = 0.299, $p < 0.0001$.

Embryonic HR versus Gestation

There was a significant cubic association between HR and GA (fig. 5, table 2): expected sqrt HR = 26.617171 (SE = 2.368948) – 1.090044 (SE = 0.130018) × GA + 0.026235 (SE = 0.002356) × GA^2 – 0.000184 (SE = 0.000014) × GA^3; $R^2 = 0.743$, SD = 0.467, $p < 0.0001$.

There was a significant quadratic association between HR and CRL (fig. 5, table 3): expected sqrt HR = 9.654134

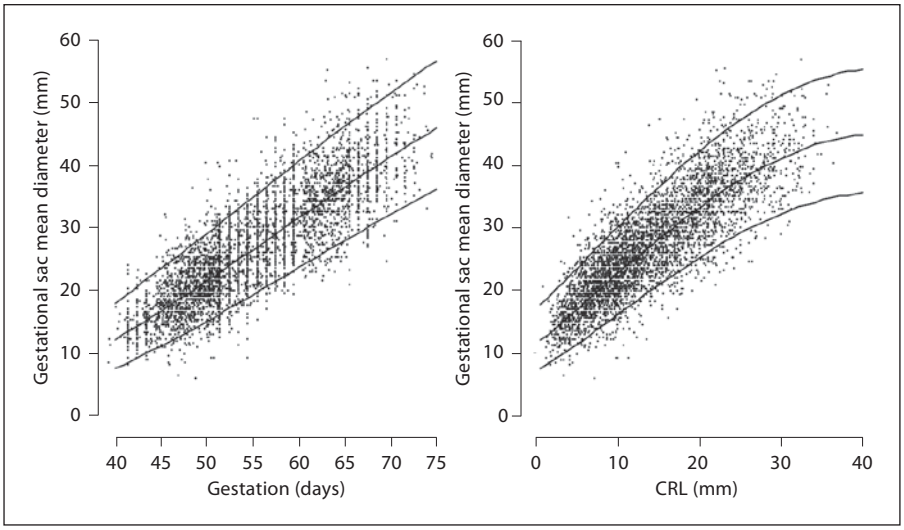


Fig. 6. Relationship between GSD and GA (left) and embryonic CRL (right; median, 95th and 5th centiles).

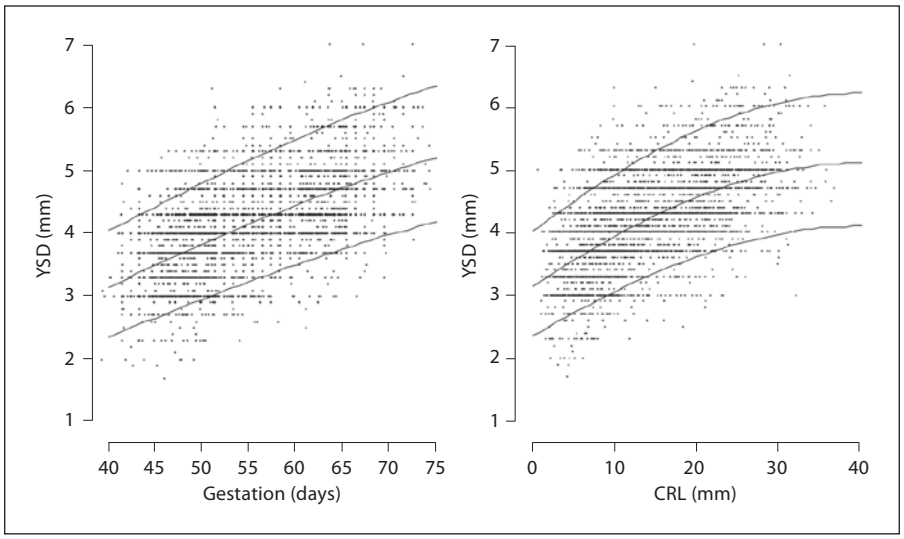


Fig. 7. Relationship between YSD and GA (left) and embryonic CRL (right; median, 95th and 5th centiles).

(SE = 0.026480) + 0.278977 (SE = 0.003668) × CRL – 0.005519 (SE = 0.000111) × CRL^2; $R^2 = 0.773$, SD = 0.439, $p < 0.0001$.

Mean GSD versus Gestation

There was a significant quadratic association between GSD and GA (fig. 6, table 2): expected sqrt GSD = –2.612095 (SE = 0.368632) + 0.188464 (SE = 0.013425) × GA – 0.000836 (SE = 0.000121) × GA^2; $R^2 = 0.693$, SD = 0.459, $p < 0.0001$.

There was a significant quadratic association between GSD and CRL (fig. 6, table 3): expected sqrt GSD = 3.438705 (SE = 0.026845) + 0.151436 (SE = 0.003758) × CRL – 0.001763 (SE = 0.000115) × CRL^2; $R^2 = 0.707$, SD = 0.447, $p < 0.0001$.

YSD versus Gestation

There was a significant quadratic association between YSD and GA (fig. 7, table 2): expected sqrt YSD = 0.785479 (SE = 0.118913) + 0.031223 (SE = 0.004337) × GA – 0.000148 (SE = 0.000039) × GA^2; $R^2 = 0.351$, SD = 0.143, $p < 0.0001$.

There was a significant quadratic association between YSD and CRL (fig. 7, table 3): expected sqrt YSD = 1.772616

Table 2. Relationship between GA and embryonic CRL, embryonic HR, mean GSD and mean YSD

Gestation days	CRL, mm			Embryonic HR, bpm			GSD, mm			YSD, mm		
	50th	5th	95th	50th	5th	95th	50th	5th	95th	50th	5th	95th
40	2.4	1.1	4.1	105	90	121	12.9	8.0	18.9	3.2	2.4	4.1
41	2.9	1.4	4.8	108	92	124	13.8	8.7	19.9	3.3	2.5	4.2
42	3.4	1.9	5.5	111	95	127	14.7	9.4	21.0	3.4	2.6	4.3
43	4.1	2.3	6.3	114	98	131	15.6	10.2	22.1	3.4	2.6	4.4
44	4.7	2.8	7.1	117	101	134	16.5	10.9	23.2	3.5	2.7	4.4
45	5.4	3.4	7.9	120	104	138	17.4	11.7	24.3	3.6	2.7	4.5
46	6.1	3.9	8.8	124	107	141	18.4	12.5	25.4	3.6	2.8	4.6
47	6.9	4.5	9.7	127	111	145	19.3	13.3	26.6	3.7	2.9	4.7
48	7.7	5.2	10.6	131	114	149	20.3	14.1	27.7	3.8	2.9	4.7
49	8.5	5.9	11.6	135	117	153	21.3	14.9	28.8	3.8	3.0	4.8
50	9.4	6.6	12.6	138	121	157	22.3	15.7	30.0	3.9	3.0	4.9
51	10.2	7.3	13.6	142	124	161	23.3	16.6	31.1	4.0	3.1	5.0
52	11.2	8.1	14.7	146	128	165	24.3	17.4	32.3	4.0	3.1	5.0
53	12.1	8.9	15.7	149	131	168	25.3	18.3	33.4	4.1	3.2	5.1
54	13.0	9.7	16.8	153	134	172	26.3	19.1	34.6	4.2	3.3	5.2
55	14.0	10.6	17.9	156	137	176	27.3	20.0	35.8	4.2	3.3	5.2
56	15.0	11.4	19.1	159	140	179	28.3	20.8	36.9	4.3	3.4	5.3
57	16.0	12.3	20.2	162	143	182	29.3	21.7	38.1	4.3	3.4	5.4
58	17.1	13.2	21.4	165	146	185	30.3	22.6	39.2	4.4	3.5	5.4
59	18.1	14.2	22.5	167	148	188	31.3	23.4	40.4	4.5	3.5	5.5
60	19.1	15.1	23.7	169	150	190	32.3	24.3	41.5	4.5	3.6	5.6
61	20.2	16.0	24.9	171	152	192	33.3	25.2	42.6	4.6	3.6	5.6
62	21.3	17.0	26.1	173	153	193	34.3	26.0	43.7	4.6	3.7	5.7
63	22.4	18.0	27.3	174	154	194	35.3	26.9	44.9	4.7	3.7	5.8
64	23.5	18.9	28.5	174	154	195	36.3	27.8	46.0	4.7	3.8	5.8
65	24.6	19.9	29.7	174	154	195	37.3	28.6	47.1	4.8	3.8	5.9
66	25.7	20.9	30.9	174	154	195	38.2	29.5	48.2	4.8	3.9	5.9
67	26.8	21.9	32.1	173	153	194	39.2	30.3	49.2	4.9	3.9	6.0
68	27.9	22.9	33.3	171	152	192	40.2	31.2	50.3	4.9	4.0	6.0
69	29.0	23.9	34.5	169	150	190	41.1	32.0	51.4	5.0	4.0	6.1
70	30.1	24.9	35.7	167	147	187	42.0	32.8	52.4	5.0	4.0	6.2
71	31.2	25.9	36.9	163	144	183	43.0	33.6	53.4	5.1	4.1	6.2
72	32.3	26.9	38.1	159	141	179	43.9	34.4	54.4	5.1	4.1	6.3
73	33.3	27.9	39.3	155	136	174	44.8	35.2	55.4	5.2	4.2	6.3
74	34.4	28.9	40.4	150	131	169	45.6	36.0	56.4	5.2	4.2	6.4
75	35.5	29.9	41.6	144	126	163	46.5	36.8	57.4	5.3	4.2	6.4

(SE = 0.008804) + 0.024340 (SE = 0.001236) × CRL – 0.000304 (SE = 0.000038) × CRL^2; R^2 = 0.358, SD = 0.142, $p < 0.0001$.

Discrepancy between CRL and Menstrual Dates in the Calculation of GA

The menstrual cycle and LMP as recorded in the EPU database were unknown in 340 (7.2%) of the 4,698 cases. There were 2,703 (57.5%) cases with a regular cycle and certain LMP, 571 (12.2%) with a regular cycle but uncertain LMP, 517 (11.0%) with an irregular cycle but certain LMP, and 567 (12.1%) where conception occurred within 3 cycles since a recent pregnancy or stopping the contraceptive pill.

The frequency distribution of the discrepancy in gestational days at the visit to EPU between the gestation calculated from the LMP and that calculated from the CRL in our new formula is illustrated in figure 8. The discrepancy was 7 days or more in 334 (12.4%) of the 2,703 cases with a regular cycle and certain LMP, 202 (35.4%) of the 571 with a regular cycle but uncertain LMP, 240 (46.4%) of the 517 with an irregular cycle but

Table 3. Relationship between embryonic CRL and GA, embryonic HR, mean GSD and YSD

CRL mm	Gestation, days			Embryonic HR, bpm			GSD, mm			YSD, mm		
	50th	5th	95th	50th	5th	95th	50th	5th	95th	50th	5th	95th
1	41	38	44	99	85	113	12.9	8.1	18.7	3.2	2.4	4.1
2	42	39	46	104	90	119	13.9	9.0	20.0	3.3	2.5	4.2
3	43	40	47	109	94	125	15.0	9.9	21.3	3.4	2.6	4.3
4	44	41	48	114	99	130	16.1	10.8	22.6	3.5	2.7	4.4
5	45	42	49	119	104	135	17.2	11.7	23.9	3.6	2.7	4.5
6	47	43	50	124	108	140	18.4	12.6	25.2	3.6	2.8	4.6
7	48	44	51	129	113	145	19.5	13.5	26.5	3.7	2.9	4.7
8	49	45	52	133	117	150	20.6	14.5	27.8	3.8	2.9	4.8
9	50	46	53	137	121	155	21.7	15.4	29.1	3.9	3.0	4.8
10	51	47	54	141	125	159	22.8	16.3	30.4	3.9	3.1	4.9
11	52	48	55	145	128	163	23.9	17.3	31.7	4.0	3.1	5.0
12	53	49	56	149	132	167	25.0	18.2	32.9	4.1	3.2	5.1
13	54	50	57	152	135	171	26.1	19.1	34.2	4.2	3.3	5.2
14	55	51	58	156	138	174	27.2	20.0	35.4	4.2	3.3	5.2
15	56	52	59	159	141	177	28.2	21.0	36.6	4.3	3.4	5.3
16	57	53	60	161	144	180	29.3	21.9	37.8	4.3	3.4	5.4
17	58	54	61	164	146	183	30.3	22.7	38.9	4.4	3.5	5.4
18	59	55	62	166	148	185	31.3	23.6	40.1	4.5	3.5	5.5
19	59	56	63	168	150	187	32.3	24.4	41.2	4.5	3.6	5.6
20	60	57	64	170	151	189	33.2	25.3	42.2	4.6	3.6	5.6
21	61	58	65	171	153	190	34.1	26.1	43.3	4.6	3.7	5.7
22	62	59	66	172	154	192	35.0	26.8	44.3	4.7	3.7	5.7
23	63	60	66	173	154	192	35.9	27.6	45.2	4.7	3.8	5.8
24	64	60	67	173	155	193	36.7	28.3	46.2	4.8	3.8	5.8
25	65	61	68	174	155	193	37.5	29.0	47.0	4.8	3.8	5.9
26	66	62	69	174	155	193	38.2	29.7	47.9	4.8	3.9	5.9
27	66	63	70	173	155	193	39.0	30.3	48.7	4.9	3.9	6.0
28	67	64	71	173	154	192	39.6	30.9	49.5	4.9	3.9	6.0
29	68	64	71	172	153	191	40.3	31.5	50.2	4.9	4.0	6.0
30	69	65	72	170	152	190	40.9	32.0	50.8	5.0	4.0	6.1
31	69	66	73	169	151	188	41.5	32.5	51.5	5.0	4.0	6.1
32	70	67	74	167	149	186	42.0	33.0	52.1	5.0	4.0	6.1
33	71	68	74	165	147	184	42.5	33.4	52.6	5.0	4.0	6.1
34	72	68	75	163	145	182	42.9	33.8	53.1	5.1	4.1	6.2
35	72	69	76	160	142	179	43.3	34.1	53.5	5.1	4.1	6.2
36	73	70	77	157	140	176	43.6	34.4	53.9	5.1	4.1	6.2
37	74	70	77	154	137	173	43.9	34.7	54.2	5.1	4.1	6.2
38	74	71	78	151	134	169	44.2	34.9	54.5	5.1	4.1	6.2
39	75	72	79	147	130	165	44.4	35.1	54.7	5.1	4.1	6.2
40	76	72	79	144	127	161	44.6	35.3	54.9	5.1	4.1	6.2

certain LMP, and 178 (31.4%) of the 567 where conception occurred within 3 cycles since a recent pregnancy or stopping the contraceptive pill. The respective percentages for discrepancy of 5 days or more were 23.9, 47.5, 57.8 and 43.6%.

Comparison of Gestation from CRL by the Formula of Robinson and Fleming and the Formula from this Study

The GAs derived from embryonic CRL using the 2 formulas are plotted in figure 9. In the 3,003 cases with CRL of 10.2–36.5 mm, the estimated gestation by the 2 formulas was the same. In the 785 cases with CRL 7.4–10.2 mm, the estimated gestation from Robinson and Fleming was

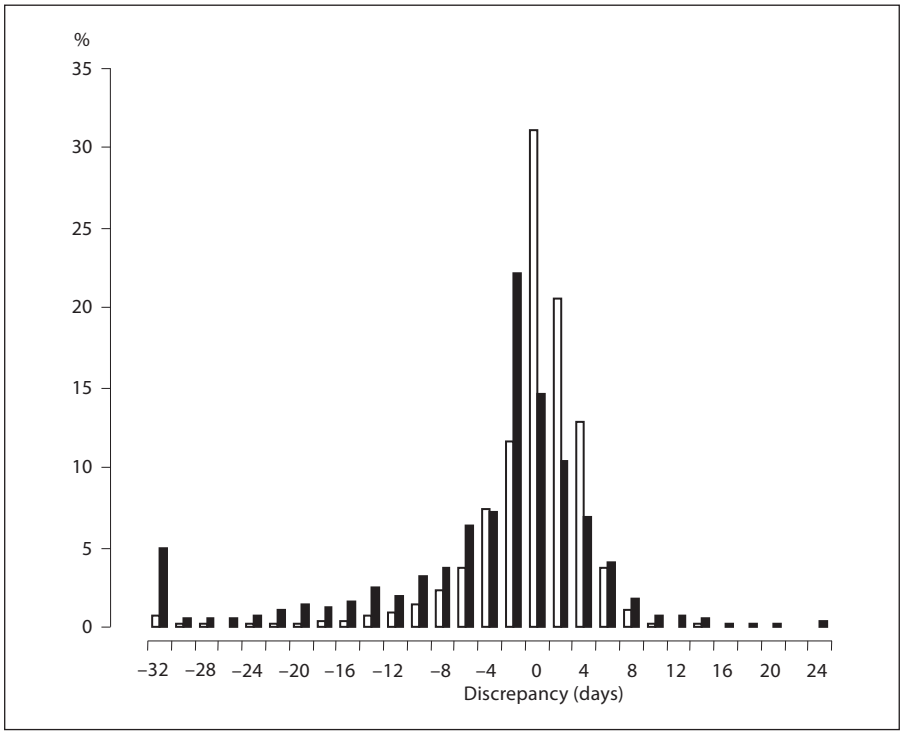


Fig. 8. Frequency distribution of the discrepancy in gestational days between the gestation calculated from the first day of the LMP and that calculated from CRL in our new formula. White histograms = regular cycle and certain LMP; black histograms = irregular cycle, uncertain LMP or conception within 3 cycles since a recent pregnancy or stopping the contraceptive pill.

Table 4. Relationship between GA and embryonic CRL in previous reports and in our study

Author	Gestation weeks	n	Inclusion criteria	Gestation (days) according to CRL			
				2 mm	10 mm	20 mm	30 mm
Dating from regular cycles							
Robinson and Fleming, 1975 [7]	6–14	314	no information about outcome	35	49	60	69
Drumm et al., 1976 [9]	6–14	253	no bleeding	–	48	60	68
Bovicelli et al., 1981 [10]	7–13	237	no information about outcome	–	–	59	69
Nelson, 1981 [11]	7–17	83	normal live birth	–	–	63	69
Pedersen, 1982 [12]	6–14	101	normal live birth	–	49	60	68
Hadlock et al., 1992 [13]	5–18	416	normal scan	40	50	60	69
Grisolia et al., 1993 [14]	5–12	248	normal live birth	–	49	60	69
Verburg et al., 2008 [15]	<17	3,760	normal live birth	–	53	60	70
McLennan and Schluter, 2008 [16]	5–14	396	normal live birth	37	49	60	68
Assisted reproduction							
MacGregor et al., 1987 [17]	7–13	72	no information about outcome	–	54	61	69
Rossavik et al., 1988 [18]	7–12	19	no information about outcome	–	55	61	67
Vollebergh et al., 1989 [19]	6–13	47	normal live birth	42	55	60	71
Silva et al., 1990 [20]	5–12	36	normal live birth	42	51	60	69
Koornstra et al., 1990 [21]	6–13	128	normal live birth	–	50	60	67
Evans, 1991 [22]	8–11	33	normal live birth	–	53	61	71
Lasser et al., 1993 [23]	6–10	144	normal live birth	41	51	61	69
Daya, 1993 [24]	6–14	94	no information about outcome	43	51	61	69
Guirgis et al., 1993 [25]	6–13	224	normal live birth	–	53	63	69
Wisser et al., 1994 [26]	5–14	139	normal live birth	40	51	61	70
Coulam et al.,1996 [27]	5–8	361	normal live birth	37	52	–	–
This study	6–10	4,698	normal live birth	42	51	60	69

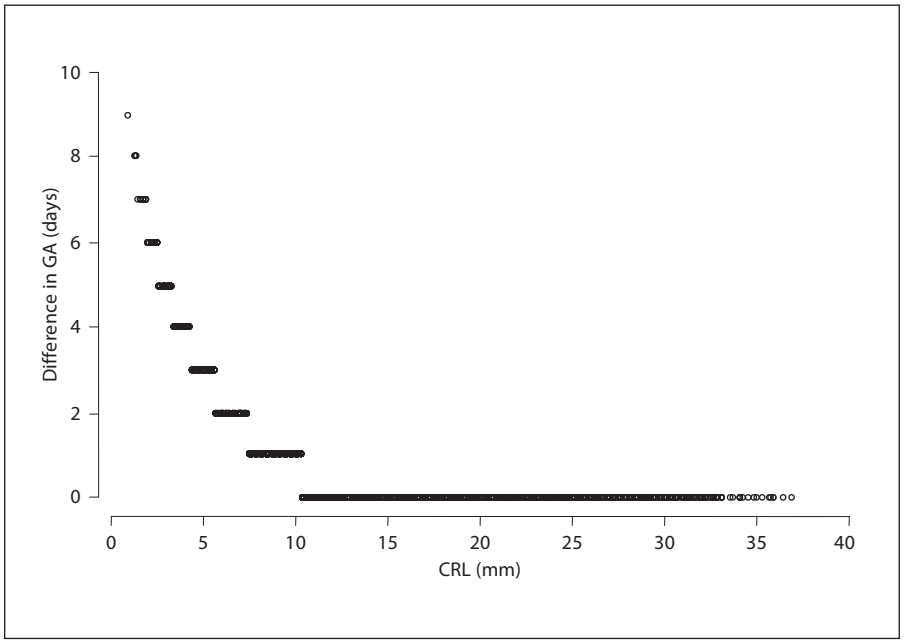


Fig. 9. Difference in GA according to embryonic CRL derived from the formula by Robinson and Fleming [7] and the formula from this study. At low CRL the formula by Robinson and Fleming underestimates GA.

Table 5. Relationship between embryonic HR and embryonic CRL or GA in previous reports and in our study

Author	Gestation weeks	n	Inclusion criteria	HR (bpm) according to CRL			
				2 mm	10 mm	20 mm	30 mm
Schats et al., 1990 [28][1]	5–8	45	normal scan at 13 weeks	95	135	–	–
Achiron et al., 1991 [29]	6–11	580	normal scan at 13 weeks	–	146	170	171
Yapar et al., 1995 [30]	6–13	1,331	no information about outcome	106	139	175	175
Falco et al., 1996 [31]	6–13	105	normal scan at 20 weeks	116	128	140	147
Britten et al., 1994 [32] [1]	5–8	361	normal live birth	98	152	–	–
Coulam et al., 1996 [27] [1]	5–8	361	normal live birth	105	140	–	–
Tannirandorn et al., 2000 [33]	5–14	547	normal live birth	134	155	177	177
Makrydimas et al., 2003 [34]	6–10	619	normal live birth	108	147	173	174
This study	6–10	4,698	normal live birth	102	135	170	171
				HR (bpm) according to gestation			
				42 days	49 days	56 days	63 days
Robinson and Shaw-Dunn, 1973 [35]	6–15	97	no information about outcome	–	132	158	177
Merchiers et al., 1991 [36]	5–12	141	normal scan at 13 weeks	98	126	155	163
Tezuka et al., 1991 [37]	5–8	133	normal scan at 13 weeks	112	132	161	–
Wisser and Dirscheld, 1994 [38][1]	5–14	160	normal live birth	102	130	158	169
Yapar et al., 1995 [30]	6–13	1,331	no information about outcome	116	140	168	179
Tannirandorn et al., 2000 [33]	5–14	547	normal live birth	141	155	165	172
This study	6–10	4,698	normal live birth	108	131	156	173

[1] In vitro fertilisation study.

Table 6. Relationship between YSD and embryonic CRL or GA in previous reports and in our study

Author	Gestation weeks	n	Inclusion criteria	Measurement	YSD (mm) according to CRL			
					2 mm	10 mm	20 mm	30 mm
Lindsay et al., 1992 [39]	6–10	357	normal at 6–12 weeks	in-to-in	2.3	2.9	3.6	4.4
Küçük et al., 1999 [40]	6–10	219	normal at 12 weeks	in-to-in	2.1	2.7	3.6	–
Makrydimas et al., 2003 [34]	6–10	619	normal live birth	no information	4.4	5.0	5.7	6.4
This study	6–10	4,698	normal live birth	middle-to-middle	3.2	4.0	4.6	5.0
					YSD (mm) according to gestation			
					42 days	49 days	56 days	63 days
Crooij et al., 1982 [41]	6–12	100	no exclusion	no information	3.0	4.1	4.8	5.1
Reece et al., 1988 [42]	6–12	77	normal live birth	no information	–	–	4.4	4.1
Jauniaux et al., 1991 [43]	5–12	145	normal live birth	middle-to-middle	3.0	4.0	4.7	5.2
Lindsay et al., 1992 [39]	6–10	357	normal at 6–12 weeks	in-to-in	2.4	2.9	3.1	3.4
Grisolia et al., 1993 [14]	5–12	248	normal live birth	no information	4.2	4.6	4.8	5.0
Stampone et al., 1996 [44]	5–11	117	normal live birth	in-to-in	3.6	4.1	4.5	4.8
Cepni et al., 1997 [45]	6–11	110	normal at 6–12 weeks	out-to-out	4.5	4.7	5.2	5.4
Küçük et al., 1999 [40]	6–10	219	normal at 12 weeks	in-to-in	2.1	2.5	3.1	3.6
Blaas et al., 1998 [46]	7–12	29	normal live birth	middle-to-middle	–	4.2	4.3	4.8
This study	6–10	4,698	normal live birth	middle-to-middle	3.3	3.8	4.2	4.6

Table 7. Relationship between GSD and embryonic CRL or GA in previous reports and in our study

Author	Gestation weeks	n	Inclusion criteria	GSD (mm) according to CRL			
				2 mm	10 mm	20 mm	30 mm
Bromley et al., 1991 [47]	6–10	52	normal at 6–10 week	13	24	34	42
Makrydimas et al., 2003 [34]	6–10	619	normal live birth	15	22	31	40
This study	6–10	4,698	normal live birth	14	23	33	41
				GSD (mm) according to gestation			
				42 days	49 days	56 days	63 days
Helman et al., 1969 [48]	5–13	103	no info about follow-up	17	24	31	38
Rossavik et al., 1988 [18][1]	7–12	19	no info about follow-up	12	19	26	33
Goldstein et al., 1991 [49]	5–12	137	no info about follow-up	14	26	29	33
Grisolia et al., 1993 [14]	5–12	248	normal live birth	16	23	29	35
Coulam et al., 1996 [27][1]	5–8	235	normal live birth	14	23	–	–
This study	6–10	4,698	normal live birth	15	21	28	35

[1] In vitro fertilisation study

1 day less than by our formula. For lower CRL, the discrepancy between the 2 formulas increased exponentially with decreasing CRL from 2 days for CRL of 5.6–7.4 mm to 9 days for CRL of 1 mm.

Comparison of Reference Ranges with Previous Studies

A literature search of PubMed was carried out to identify all previous studies that constructed reference ranges of embryonic CRL with GA and embryonic HR, GSD

and YSD with CRL or gestation. The results of these studies are summarized and compared with our findings in tables 4–7.

Discussion

This study of a large number of pregnancies with well-documented normal outcomes has established normal ranges for CRL, HR, GSD and YSD at 6–10 weeks of gestation. The study has confirmed that in a high proportion of women, the use of LMP cannot be used for assessment of GA because of irregular menstrual cycles, uncertain LMP or conception within 3 months of a previous pregnancy or stopping the contraceptive pill. Even in women with regular cycles and certain LMP, there was a discrepancy in the gestation calculated from the LMP and CRL of more than 5 days in one fourth of the cases. These results provide further support for the recommendation that pregnancy dating should be based on CRL rather than LMP [5]. Similarly, they emphasize the need to rely on the CRL for establishing GA-related normal ranges for HR, GSD and YSD.

In this study we chose to include only pregnancies with a normal outcome and to establish normal rather than reference ranges because, firstly, a high proportion of pregnancies attending an EPU result in miscarriage and, secondly, several studies reported that several pregnancy complications are associated with abnormal measurements of HR, GSD and YSD [52–55].

The relation between CRL and GA in this and previous studies is similar to that of the report by Robinson and Fleming except for CRL below 10 mm where their formula underestimates gestation. Our findings are similar to those in previous reports examining pregnancies conceived by in vitro fertilisation [19, 20, 23, 24, 26]. Although this underestimate is only 1 day for CRL 7.4–10.2 mm, it increases exponentially for lower CRL and reaches 9 days for CRL of 1 mm. A possible explanation for the discrepancy between the 2 formulas is the very low number of cases with low CRL examined by Robinson and Fleming, which was 15 for CRL below 10 mm and none below 5 mm. In our study, we examined more than 1,500 and 400 pregnancies with CRL below 10 and 5 mm, respectively. In addition, in all cases we used high frequency transvaginal ultrasound compared to the transabdominal static approach used by Robinson and Fleming that is likely to be less accurate when the CRL is very small.

The embryonic HR increased with gestation from a mean of about 110 bpm at 6 weeks to a maximum of about 175 bpm at 9 weeks and decreased thereafter. The early increase in HR coincides with the morphological development of the heart, and the subsequent decrease may be the result of functional maturation of the parasympathetic system [35, 38, 56]. This decrease continues throughout pregnancy and during the first 10 years of postnatal life [57]. Possible explanations for discrepancies between our findings and those of previous reports include different methods of pregnancy dating and the small number of cases, especially in very early gestation, in the previous studies.

In normal pregnancy, the gestational sac appears during the 5th gestational week. The yolk sac appears 5–6 days later and lies in the coelomic cavity which occupies the whole gestational sac before the appearance of the embryo [43, 58]. The mean YSD and GSD when the embryo first appears at 6 weeks of gestation are about 3 and 10 mm, respectively. The YSD and GSD increase with gestation, but at between 10 and 12 weeks the yolk sac degrades [43]. Discrepancies between studies in the reported YSD with gestation may be accounted for by differences in the method of measurement. In general, the YSD was lower when the calipers were placed at the inner edges rather than the middle or outer edges of the yolk sac wall. We chose to use the middle because the thickness of the yolk sac wall may vary with the use of image compounding, harmonics and gain setting, resulting in systematic under- or overestimation of YSD when the measurements are taken in-to-in or out-to-out. Our findings on GSD are similar to those of the largest and most recent of the previous studies [14, 27, 34, 47, 49].

This study involving a large number of normal pregnancies established normal ranges for early pregnancy biometry. The measurements of CRL can be used for pregnancy dating and those of HR, GSD and YSD for further research to investigate their possible role in the prediction of miscarriage and other pregnancy complications.

Acknowledgement

This study was supported by a grant from the Fetal Medicine Foundation (Charity No. 1037116).

References

1 Campbell S, Warsof SL, Little D, Cooper DJ: Routine ultrasound screening for the prediction of gestational age. Obstet Gynecol 1985; 65:613–620.
2 Hall MH, Carr-Hill RA: The significance of uncertain gestation for obstetric outcome. Br J Obstet Gynaecol 1985;92:452–460.
3 Geirsson RT, Busby-Earle RM: Certain dates may not provide a reliable estimate of gestational age. Br J Obstet Gynaecol 1991;98:108–109.
4 Hoffman CS, Messer LC, Mendola P, Savitz DA, Herring AH, Hartmann KE: Comparison of gestational age at birth based on last menstrual period and ultrasound during the first trimester. Paediatr Perinat Epidemiol 2008;22:587–596.
5 National Institute for Clinical Excellence. Antenatal Care: Routine Care for the Healthy Pregnant Woman. Clinical Guideline CG62. London, NICE, 2008. http://guidance.nice.org.uk/CG62 (accessed May 6, 2010).
6 Robinson HP: Sonar measurement of fetal crown-rump length as means of assessing maturity in first trimester of pregnancy. BMJ 1973;4:28–31.
7 Robinson HP, Fleming JE: A critical evaluation of sonar crown rump length measurements. Br J Obstet Gynaecol 1975;82:702–710.
8 Loughna P, Chitty L, Tony Evans T, Chudleigh T: Fetal size and dating: charts recommended for clinical obstetric practice. Ultrasound 2009;13:161–167.
9 Drumm JE, Clinch J, MacKenzie G: The ultrasonic measurement of fetal crown-rump length as a method of assessing gestational age. Br J Obstet Gynaecol 1976;83:417–421.
10 Bovicelli L, Orsini LF, Rizzo N, Calderoni P, Pazzaglia FL, Michelacci L: Estimation of gestational age during the first trimester by real-time measurement of fetal crown-rump length and biparietal diameter. J Clin Ultrasound 1981;9:71–75.
11 Nelson LH: Comparison of methods for determining crown-rump measurement by real-time ultrasound. J Clin Ultrasound 1981;9:67–70.
12 Pedersen JF: Fetal crown-rump length measurement by ultrasound in normal pregnancy. Br J Obstet Gynaecol 1982;89:926–930.
13 Hadlock FP, Shah YP, Kanon DJ, Lindsey JV: Fetal crown-rump length: reevaluation of relation to menstrual age (5–18 weeks) with high-resolution real-time US. Radiology 1992;182:501–505.
14 Grisolia G, Milano K, Pilu G, Banzi C, David C, Gabrielli S, Rizzo N, Morandi R, Bovicelli L: Biometry of early pregnancy with transvaginal sonography. Ultrasound Obstet Gynecol 1993;3:403–411.
15 Verburg BO, Steegers EA, De Ridder M, Snijders RJ, Smith E, Hofman A, Moll HA, Jaddoe VW, Witteman JC: New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. Ultrasound Obstet Gynecol 2008;31:388–396.
16 McLennan AC, Schluter PJ: Construction of modern Australian first trimester ultrasound dating and growth charts. J Med Imaging Radiat Oncol 2008;52:471–479.
17 MacGregor SN, Tamura RK, Sabbagha RE, Minogue JP, Gibson ME, Hoffman DI: Underestimation of gestational age by conventional crown-rump length dating curves. Obstet Gynecol 1987;70:344–348.
18 Rossavik IK, Torjusen GO, Gibbons WE: Conceptual age and ultrasound measurements of gestational sac and crown-rump length in in vitro fertilization pregnancies. Fertil Steril 1988;49:1012–1017.
19 Vollebergh JHA, Jongsma HW, van Dongen PWJ: The accuracy of ultrasonic measurement of fetal crown-rump length. Eur J Obstet Gynecol Reprod Biol 1989;30:253–256.
20 Silva PD, Mahairas G, Schaper AM, Schauberger CW: Early crown-rump length. A good predictor of gestational age. J Reprod Med 1990;35:641–644.
21 Koornstra G, Wattel E, Exalto N: Crown-rump length measurements revisited. Eur J Obstet Gynecol Reprod Biol 1990;35:131–138.
22 Evans J: Fetal crown-rump length values in the first trimester based upon ovulation timing using the luteinizing hormone surge. Br J Obstet Gynaecol 1991;98:48–51.
23 Lasser DM, Peisner DB, Vollebergh J, Timor-Tritsch I: First-trimester fetal biometry using transvaginal sonography. Ultrasound Obstet Gynecol 1993;3:104–108.
24 Daya S: Accuracy of gestational age estimation by means of fetal crown-rump length measurement. Am J Obstet Gynecol 1993; 168:903–908.
25 Guirgis RR, Alshawaf T, Dave R, Craft IL: Transvaginal crown-rump length measurements of 224 successful pregnancies which resulted from gamete intra-Fallopian transfer or in-vitro fertilization. Hum Reprod 1993;8:1933–1937.
26 Wisser J, Dirschedl P, Krone S: Estimation of gestational age by transvaginal sonographic measurement of greatest embryonic length in dated human embryos. Ultrasound Obstet Gynecol 1994;4:457–462.
27 Coulam CB, Britten S, Soenksen DM: Early (34–56 days from last menstrual period) ultrasonographic measurements in normal pregnancies. Hum Reprod 1996;11:1771–1774.
28 Schats R, Jansen CAM, Wladimiroff WT: Embryonic heart activity: appearance and development in early human pregnancy. Br J Obstet Gynaecol 1990;97:989–994.
29 Achiron R, Tadmor O, Mashiach S: Heart rate as a predictor of first-trimester spontaneous abortion after ultrasound-proven viability. Obstet Gynecol 1991;78:330–334.
30 Yapar EG, Ekici E, Gökmen O: First trimester fetal heart rate measurements by transvaginal ultrasound combined with pulsed Doppler: an evaluation of 1331 cases. Eur J Obstet Gynecol Reprod Biol 1995;60:133–137.
31 Falco P, Milano V, Pilu G, David C, Grisolia G, Rizzo N, Bovicelli L: Sonography of pregnancies with first-trimester bleeding and a viable embryo: a study of prognostic indicators by logistic regression analysis. Ultrasound Obstet Gynecol 1996;7:165–169.
32 Britten S, Soenksen DM, Bustillo M, Coulam CB: Very early (24–56 days from last menstrual period) embryonic heart rate in normal pregnancies. Hum Reprod 1994;9:2424–2426.
33 Tannirandorn Y, Manotaya S, Uerpairojkit B, Tanawattanacharoen S, Wacharaprechanont T, Charoenvidhya D: Reference intervals for first trimester embryonic/fetal heart rate in a Thai population. J Obstet Gynaecol Res 2000;26:367–372.
34 Makrydimas G, Sebire NJ, Lolis D, Vlassis N, Nicolaides KH: Fetal loss following ultrasound diagnosis of a live fetus at 6–10 weeks of gestation. Ultrasound Obstet Gynecol 2003;22:368–372.
35 Robinson HP, Shaw-Dunn J: Fetal heart rates as determined by sonar in early pregnancy. J Obstet Gynaecol Br Commonw 1973;80: 805–809.
36 Merchiers EH, Dhont M, De Sutter PA, Beghin CJ, Vandekerckhove DA: Predictive value of early embryonic cardiac activity for pregnancy outcome. Am J Obstet Gynecol 1991;165:11–14.
37 Tezuka N, Sato S, Kanasugi H, Hiroi M: Embryonic heart rates: development in early first trimester and clinical evaluation. Gynecol Obstet Invest 1991;32:210–212.
38 Wisser J, Dirscheld P: Embryonic heart rate in human dated embryos. Early Hum Dev 1994;37:107–115.
39 Lindsay DJ, Lovett IS, Lyons EA, Levi CS, Zheng XH, Holt SC, Dashefsky SM: Yolk sac diameter and shape at endovaginal US: predictors of pregnancy outcome in the first trimester. Radiology 1992;183:115–118.
40 Küçük T, Duru NK, Yenen MC, Dede M, Ergün A, Başer I: Yolk sac size and shape as predictors of poor pregnancy outcome. J Perinat Med 1999;27:316–320.
41 Crooij MJ, Westhuis M, Schoemaker J, Exalto N: Ultrasonographic measurement of the yolk sac. Br J Obstet Gynaecol 1982;89: 931–934.

42 Reece EA, Sciosca AL, Pinter E, Hobbins JC, Green J, Mahoney MJ, Naftolin F: Prognostic significance of the human yolk sac assessed by ultrasonography. Am J Obstet Gynecol 1988;159:1191–1194.
43 Jauniaux E, Jurkovic D, Henriet Y, Rodesch F, Hustin J: Development of the secondary human yolk sac: correlation of sonographic and anatomical features. Hum Reprod 1991; 6:1160–1166.
44 Stampone C, Nicotra M, Muttinelli C, Cosmi EV: Transvaginal sonography of the yolk sac in normal and abnormal pregnancy. J Clin Ultrasound 1996;24:3–9.
45 Cepni I, Bese T, Ocal P, Budak E, Idil M, Aksu MF: Significance of yolk sac measurements with vaginal sonography in the first trimester in the prediction of pregnancy outcome. Acta Obstet Gynecol Scand 1997;76: 969–972.
46 Blaas HG, Eik-Nes SH, Bremnes JB: The growth of the human embryo. A longitudinal biometric assessment from 7 to 12 weeks of gestation. Ultrasound Obstet Gynecol 1998;12:346–354.
47 Bromley B, Harlow BL, Laboda LA, Benacerraf BR: Small sac size in the first trimester: a predictor of poor fetal outcome. Radiology 1991;178:375–377.
48 Helman LM, Kobayashi M, Fillisti L, Lavenhar M: Growth and development of the human fetus prior to the twentieth week of gestation. Am J Obstet Gynecol 1969;103: 789–900.
49 Goldstein I, Zimmer EA, Tamir A, Peretz BA, Paldi E: Evaluation of normal gestational sac growth: appearance of embryonic heartbeat and embryo body movements using the transvaginal technique. Obstet Gynecol 1991;77:885–888.
50 Robinson HP: The diagnosis of early pregnancy failure by sonar. Br J Obstet Gynaecol 1975;82:849–857.
51 Poon LCY, Karagiannis G, Staboulidou I, Shafiei A, Nicolaides KH: Reference range of birth weight with gestation and first-trimester prediction of small for gestation neonates. Prenat Diagn, in press.
52 Choong S, Rombauts L, Ugoni A, Meagher S: Ultrasound prediction of risk of spontaneous miscarriage in live embryos from assisted conceptions. Ultrasound Obstet Gynecol 2003;22:571–577.
53 Varelas FK, Prapas NM, Liang RI, Prapas IM, Makedos GA: Yolk sac size and embryonic heart rate as prognostic factors of first trimester pregnancy outcome. Eur J Obstet Gynecol Reprod Biol 2008;138:10–13.
54 Ivanisević M, Djelmis J, Jalsovec D, Bljajic D: Ultrasonic morphological characteristics of yolk sac in pregnancy complicated with type-1 diabetes mellitus. Gynecol Obstet Invest 2006;61:80–86.
55 Berdahl DM, Blaine J, Van Voorhis B, Dokras A: Detection of enlarged yolk sac on early ultrasound is associated with adverse pregnancy outcomes. Fertil Steril 2010;94:1535–1537.
56 Wladimiroff JW, Seelen JC: Fetal heart action in early pregnancy. Development of fetal vagal function. Eur J Obstet Gynecol 1972;2: 55–63.
57 Finley JP, Nugent ST: Heart rate variability in infants, children and young adults. J Auton Nerv Syst 1995;51:103–108.
58 Oh JS, Wright G, Coulam CB: Gestational sac diameter in very early pregnancy as a predictor of fetal outcome. Ultrasound Obstet Gynecol 2002;20:267–269.