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Uterine artery pulsatility index reference chart selection between 24 and 40 weeks of gestational age for a health institution in Lima, Peru

Selección de la curva de referencia del índice de pulsatilidad de las arterias uterinas entre las 24 y 40 semanas de gestación para una institución de salud en Lima, Perú

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ABSTRACT
Uterine artery resistance is assessed to detect inadequate placentation in pregnant women, that increases the risk to develop preeclampsia, intrauterine growth restriction and other complications associated with placental insufficiency. Objective: To identify the uterine arteries pulsatility index (UtAPI) reference chart that best fits our institutional data. Methods: Retrospective, cross-sectional study that evaluated 1 753 single pregnancies; 2 031 UtAPI measurements of the uterine arteries were obtained. Mean UtAPI was compared with the reference charts published by Gomez, Limay and Weichert. Results: There was a mild but significant (r=0.16) negative correlation between UtAPI and gestational age between 24 and 40 weeks of gestation; 6.5%, 7.5% and 15% of our measurements were above the 95 centile of respectively Weichert, Limay and Gomez reference charts. Conclusions: In our population, the UtAPI distribution fitted best with Weichert reference chart. More prospective studies are needed to validate this clinical finding.
Key words: Uterine arteries, Doppler color ultrasonography.

RESUMEN
La evaluación de la resistencia en las arterias uterinas es empleada para identificar a las gestantes con placentación inapropiada, que las pone en riesgo de desarrollar preeclampsia, restricción de crecimiento intrauterino (RCIU) y otras manifestaciones de insuficiencia placentaria. Objetivo. Identificar cuál de las curvas de referencia del índice de pulsatilidad de las arterias uterinas (IPAUt) publicadas coinciden con nuestros datos institucionales. Métodos. Estudio retrospectivo, transversal, en el que se obtuvo 2 031 evaluaciones del índice de pulsatilidad de las arterias uterinas en 1 753 gestantes. La resistencia promedio de las arterias uterinas fue comparada con las curvas de referencia publicadas por Gomez, Weichert y Limay. Resultados. El IPAUt tuvo una débil pero significativa correlación negativa (r=0,16) con la edad gestacional (EG), entre las 24 y 40 semanas. El 6,5%, 7,5% y 15% de nuestras mediciones superaron el percentil 95 de las curvas de Weichert, Limay y Gomez, respectivamente. Conclusiones. El índice de pulsatilidad promedio de las arterias uterinas en nuestra población se ajustó mejor a la curva de referencia de Weichert. Se requieren estudios prospectivos para validar este hallazgo clínico.
Palabras clave. Arterias uterinas, Ultrasonografía Doppler color.

INTRODUCTION

The uterine artery originates from the anterior trunk of the hypogastric artery (internal iliac artery). It runs 5 cm obliquely down and forward in the lateral pelvic wall, then curves inwards transversely towards the cervix. Two centimeters after reaching the cervix, it curves again (uterine artery arch) and finally directs forward and vertically following the lateral edge of the uterus, emitting a series of branches towards the frontal and posterior aspects of the uterine body (radial arteries). Shortly before the arch, it emits the cervical branches[(1)].

Campbell[2] described the method of identifying blood flow from the uterine arteries at the junction with the iliac arteries and constructed an indicator of S/Vm resistance (peak systolic velocity over average velocity; see Appendix 1), protodiastolic notches and low diastolic velocity. In this study he identified that uterine arteries resistance is higher in patients affected by placental insufficiency.

From then on, parameters used to evaluate flow resistance have been diverse: notches (protodiastolic notch)[2,3], resistance index (RI)[3-5], systolic-diastolic ratio (S/D)[6,7], pulsatility index (PI)[8,9]. Until Ochi[9], in arterial occlusion experiments in animals, showed that the PI has a greater correlation (r=0.95) with the actual uterine artery resistance than the RI (r=0.85) or the S/D (r=0.90), and that this relationship was linear, unlike the other indices which had a logarithmic relationship.

Other technical aspects involved in estimating resistance are the place where the flow velocity waves are obtained (crossing with the external iliac artery or in the uterine arch)[10-12], the via used (transvaginal or abdominal)[13] or the parameter recorded (if the measurement on the placental side or the average on both sides was taken into account)[14].

The assessment of uterine arteries resistance is still used to identify pregnant women with inadequate placentation and, therefore, at risk of developing second and third trimester adverse events, such as preeclampsia, intrauterine growth restriction (IUGR) and other manifestations of placental insufficiency[15-19]. It is critical to identify them as high obstetric risk pregnancies. These values should be compared with reference tables[20-23].

A basic analysis of the index reference formula [PI= (S-D) /m] shows that the PI distribution curve of any artery will not have a normal distribution, but will show right-hand asymmetry. For further explanation, see Appendix 1.

The aim of this paper is to compare our measurements in pregnant women with normal pregnancies and outcomes, with the forementioned reference curves, in order to select the most appropriate one for our service.

Methods

This is a study with data obtained prospectively and transversal data analyzed retrospectively. All pregnant women who attended the institution's ultrasound service between January 1, 2013 and March 15, 2020 were offered the evaluation of placental blood flow. Examinations performed on pregnant women over 24 weeks old were included. Multiple pregnancies, fetuses without gestational age confirmed by first trimester ultrasound, abnormal fetuses, fetuses with estimated weight below the 10th percentile, pregnant women with preeclampsia, diabetes or other complications, and fetuses with more than two assessments in that period were excluded. The examinations were performed with General Electric model Voluson E8 BT12 ultrasound equipment, with RAB4-8 or C 1-5 convex volumetric transducer.

Data were recorded in the institution database (Astraia). Both uterine arteries resistance was measured by the abdominal route below the junction with the external iliac artery. The pulsatility index was automatically calculated by the ultrasound equipment software and electronically transferred to the database. The uterine artery pulsatility index (UtAPI) was compared with the reference curves published by Gomez[20], Weichert[21] and Limay[22]. The uterine artery PI data were tabulated in Excel by week of gestational age.

The distribution of the number of data by gestational age was tabulated. We made a graph of the average uterine arteries PI distribution, to compare it with the normal curve (per week and over the entire period). Characteristics of this distribution curve were evaluated. A significance level of 5% was chosen. Analysis of variance (ANOVA) was used to compare averages and 95th percentiles of our sample with the reference curves. The 95th percentile was considered to select pregnant women at risk of poor perinatal outcomes (preeclampsia, IUGR, placental abruption, among others). As our population had normal results, values above the 95th percentile were considered false positive. The rate of false positives in our population was compared with the different reference curves (see Appendix 2).

Results

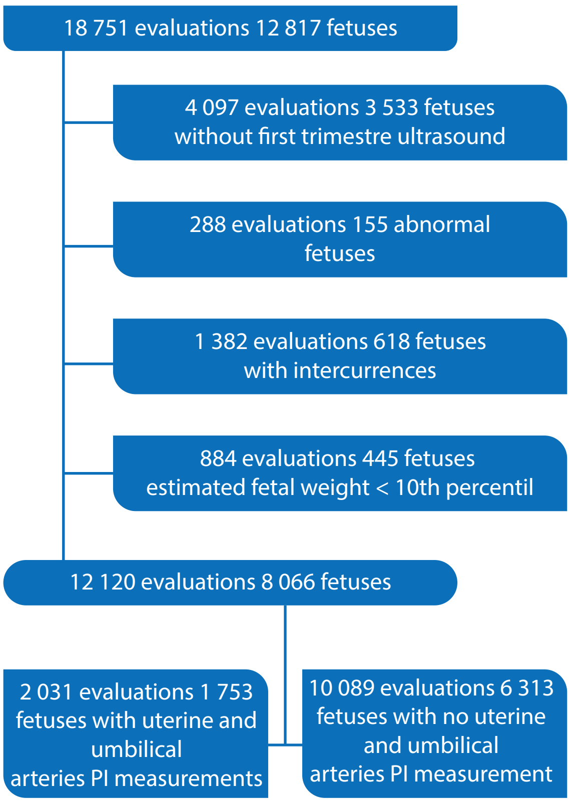
18 751 consecutive ultrasounds were performed in 12 817 singleton pregnancies with 24 weeks gestational age or more. After excluding patients and fetuses according to protocol, there were 12 120 assessments on 8 066 fetuses between 24 and 40 weeks, with a maximum of two assessments per fetus. Among them, 1 753 fetuses had 2 031 evaluations of both the uterine and umbilical arteries resistance, data that is presented (Figure 1). This article will be limited to the presentation of uterine arteries resistance.

1 172 (67%) women were carrying their first pregnancy (average 1.4 pregnancies, counting the current one; maximum 5). Average age of the pregnant women was 33.9 years (18-47.5 years). The correlation between resistance of the uterine artery and the umbilical arteries was weak (r=0.1), but significant.

The distribution of the UtAPI showed right asymmetry (1.9 Fisher coefficient, 6.5 kurtosis), as theoretically expected (Figure 2), with 0.80 average, 0.76 median and 0.77 mode (range 0.34 to 2.62, SD 0.25, IQ 0.649 to 0.895, *p* 5= 0.515, *p* 95= 1.22, outliers 1.264). The average UtAPI varied significantly according to gestational age (anova $p<0.05$). There was a significant negative correlation ($p<0.01$) but weak correlation of UtAPI with gestational age (r=0.16) between 24 and 40 weeks.

The 5th and 50th percentiles of our population and those of Gómez, Weichert and Limay tables coincide ($p>0.05$), but the 95th percentiles are discordant, as can be seen on Figure 3. Table 1 shows that the proportion of cases over the 95th percentile is significantly different to 5% in all weeks of gestational age, when using Gómez's reference curve.

Figure 1. Protocole of selection and exclusion of patients.



Discussion

The analysis done is important to select the curve more suitable to our reality. When using the Gomez curve, 15% of single pregnancies with normal outcome would have been qualified as pregnancies at risk. If the Weichert curve would had been used as reference, 5% of the pregnancies with normal outcomes would have been selected.

The Gomez curve was constructed on the basis of a cross-sectional study that included 20 pregnancies per week of gestational age. The 5th, 50th and 95th percentiles were calculated based on Royston's publication[25.26]. However, the measurements were made transvaginally in the first trimester, at the level of the uterine artery arch, and abdominally, one centimeter below the junction with the iliac arteries, after 15 weeks of pregnancy. This information is important because it has been found that the uterine artery resistance is higher at the level of the arch than even 3 cm above it[10.27], and is higher if measured transvaginally rather than abdominally[26].

The Weichert curves, on the other hand, were obtained from more than 100 000 measurements in normal clinical practice at three cen-

Figure 2. Distribution of the uterine arteries pulsatility index (UtAPI) between 14-39 weeks of gestational age.

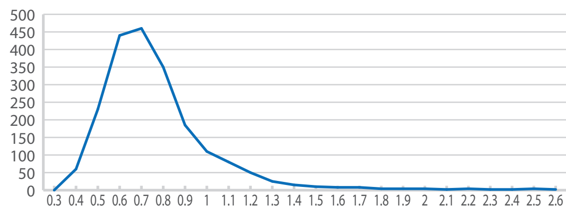
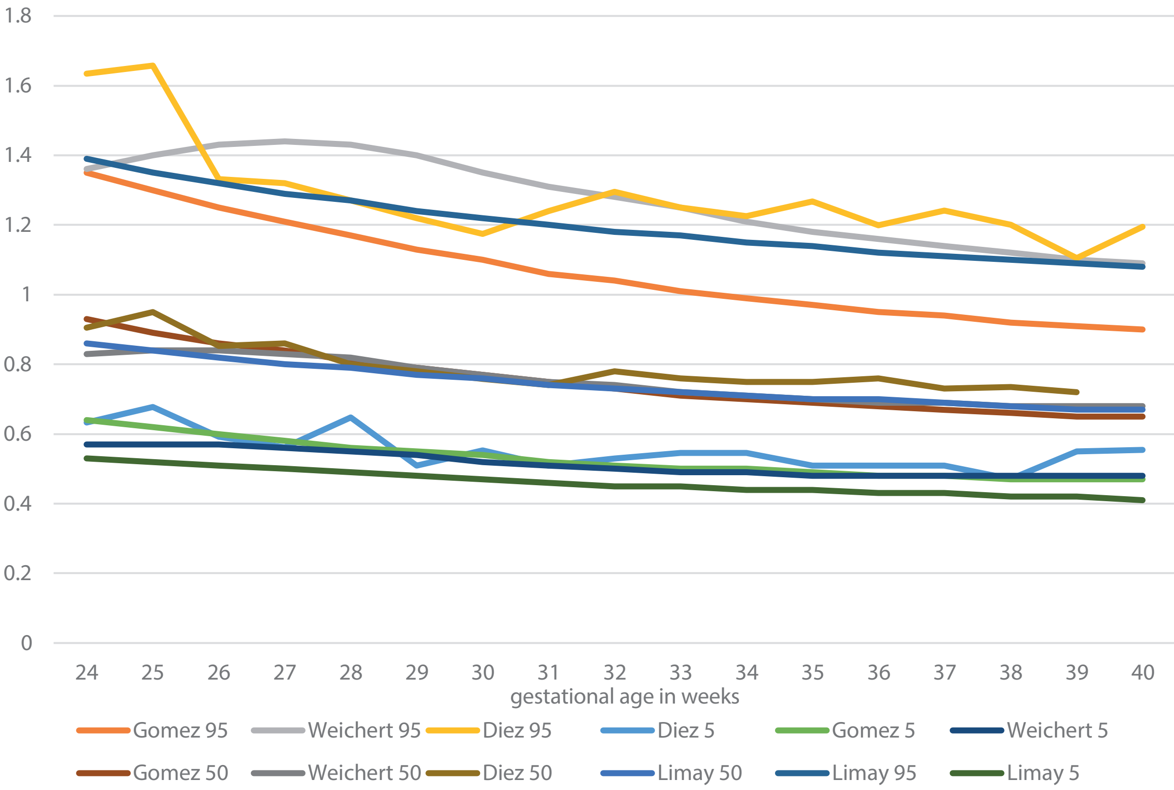


Table 1. Comparison of the proportion of UtAPI values over the 95th percentile.

GA	N	Percentile 95				Number (%) > 95th percentile		
		Gomez	Weichert	Diez	Limay	Gomez	Weichert	Limay
24	22	1.35	1.36	1.64	1.39	5 (23)*	4 (18)	4 (18)
25	31	1.3	1.40	1.66	1.35	6 (19)*	5 (16)*	5 (16)*
26	32	1.25	1.43	1.33	1.32	3 (9)	2 (6)	2 (6)
27	26	1.21	1.44	1.32	1.29	5 (19)	3 (12)	5 (19)
28	11	1.17	1.43	1.27	1.27	1 (9)	1 (9)	1 (9)
29	21	1.13	1.4	1.22	1.24	3 (14)*	1 (5)	1 (5)
30	52	1.1	1.35	1.17	1.22	4 (8)	1 (2)	3 (6)
31	99	1.06	1.31	1.24	1.2	12 (12)*	5 (5)	7 (7)
32	163	1.04	1.28	1.30	1.18	27 (17)*	14 (9)	15 (9)
33	172	1.01	1.25	1.25	1.17	24 (14)*	9 (5)	10 (6)
34	255	0.99	1.21	1.23	1.15	33 (13)*	11 (4)	12 (5)
35	315	0.97	1.18	1.27	1.14	51 (16)*	21(7)	24 (8)*
36	298	0.95	1.16	1.20	1.12	42 (14)*	17 (6)	19 (6)
37	259	0.94	1.14	1.24	1.11	47 (18)*	23 (9)	24 (9)
38	143	0.92	1.12	1.20	1.1	21 (15)*	8 (6)	11 (8)*
39	81	0.91	1.1	1.11	1.09	10 (12)*	4 (5)	4 (5)
40	49	0.9	1.09	1.20	1.08	9 (18)*	4 (8)	4 (8)
	2 029					303 (15)*	133 (6.5)*	151 (7.4)*

$p<0.05$
** GA= gestational age*
**N=number*

Figure 3. 5th, 50th and 95th percentiles of the uterine arteries reference index in our population, compared to those published by Weichert, Gomez and Limay.



tres, in single pregnancies, and considering only patients with a maximum of 3 measurements, to eliminate those with pathology. Their filter was the Viewpoint database. Therefore, the number of measurements per week of gestational age is not uniform as in Gomez's, but it has peaks of data accumulation in the periods 11 to 13 and 20 to 24 weeks, as well as nadires between 13 to 20 and 24 to 28 weeks. Weichert lists other technical reasons that explain the possible reasons for the discrepancy of his measurements with the published curves, among them, early collaterals appearing in the curve with the highest flow and the angle of insonation.

The design of our study, similar to Weichert's, may explain the similarity of the results. However, they excluded only patients with multiple tests and we excluded pregnant women with preeclampsia, IUGR, complications and fetuses with abnormalities.

Between 2010 and 2016, there were about 100 000 births at the National Maternal Perinatal Institute. Limay[22] constructed a curve in low-risk mothers with healthy fetuses; and excluded small and macrosomic fetuses. It is not very clear how only 7 020 pregnant women were selected. But, he obtained between 24 and 408 uterine artery PI measurements for each gestational age between 11 and 41 weeks, with accumulations in the first and second trimesters (1 800 measurements between 12 and 15 weeks and 2 300 between 19 and 26), similarly to Weichert's study.

What the authors do not mention is their inappropriate statistical analysis. In non-normal distributions such as those of the PI, the central boundary theorem allows conversion to Z-scores or standardization of the curve to estimate the average, but not to estimate the standard deviation. An average close to the population mean can be achieved with a small amount of data per week (20 or 30). However, to estimate a 95th percentile value that truly identifies the top 5% of the population at risk and with an error margin of less than 5% would require at least 384 measurements for each week of gestational age (see Appendix 3). This explains the discrepancies in this estimate between the different authors.

We have yet to demonstrate the clinical utility of selecting Weichert's curve. To do this it will be necessary to compare the evolution of pregnant women with UtAPI greater than the 95th percentile of Weichert and Gomez and to do more follow-ups on patients with UtAPI between the 95th percentile of Gomez and the 95th percentile of Weichert (patients in the gray area), to assess whether their maternal-perinatal outcomes are different from those of the population below the 95th percentile of Gomez.

An alternative to this approach is to use the 90th percentile of the UtAPI distribution corresponding to 1.1 between 30+0 and 39+0 weeks instead of the Gomez 95th percentile. The UtAPI distribution between these gestational ages is normal in the range 0.4 to 1.1, with an average of 0.79 (Figure 4). With this protocol, any patient with UtAPI >1.1 after 30 weeks would require further evaluation, and the evaluation of other arteries or additional controls should be considered.

All in all, all services should conduct a quality control of the measurements of Doppler's fetal and maternal parameters, analyze its results, verify if there is an appropriate reference curve or creating one.

In our study, Weichert's curve produced the least false positives in our normal population.

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Appendix 1. Mathematical evaluation of the pulsatility index formula.

PI = (S-D) /mV

S = Maximum speed during systole

D = Minimum speed during diastole

mV= Average speed in a 'cardiac' cycle

By definition, 'S' (maximum value) is greater than 'm' (median), which is greater than 'D' (minimum value). This way, we will analyze the distribution of the curve, i.e., which shape the curve will take with the variation of its parameters.

The first step is to know in which quadrant of a Cartesian curve the parameters move. Hence, we return to theory:

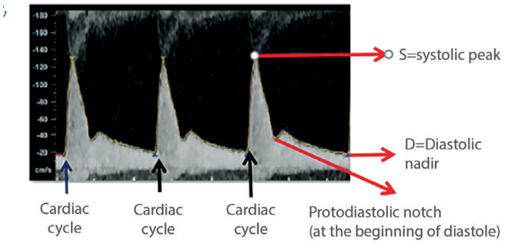
In an artery, S is the maximum blood speed measured in the direction it flows away from the heart. We define this as positive, its minimum value is 0 (zero) when there is no blood flow from the heart (cardiac arrest), and its maximum value is reached in the areas where the body wants to direct more blood, for example, in an aortic narrowing or a uterus at term, when there is transitory narrowing and low resistance (siphon effect).

D, is the minimum speed of blood, measured in the same way, in high resistance blood systems; in the external iliac arteries, for example, it takes negative values. In contrast, when we approach the capillaries, the resistance decreases to a minimum, and the blood flow tends to be laminar, similar to that of a vein, which makes the D value approach the S value.

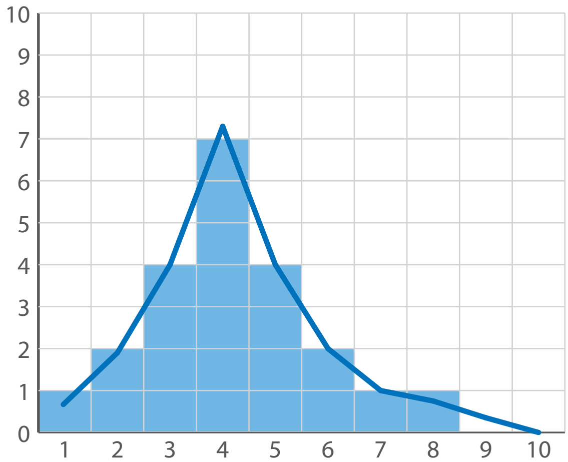
'm', the average speed over time, indicates the net flow of blood through the artery in a cardiac cycle; if there is no hemodynamic decompensation, the net flow should be positive. It is calculated by making an integral of the flow under the curve in a cardiac cycle, divided by the number of cycles of time. See Graph A1.2

In this graph, S (the peak velocity) would be 7; D (the minimum speed) will be 0; the cardiac cycle length would be 10. The calculation of m is not (S-D) /2 = (7-0) /2 =3.5, but is calculated in the following way:

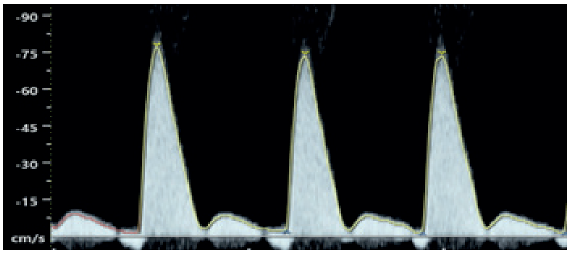
Graph A1.1. Flow velocity wave of a uterine artery



Graph A1.2. Diagram showing how the median speed is measured in time (integral under the curve/ time units)

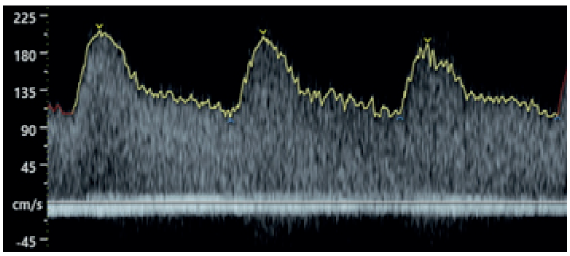


Graph A1.2. PI of the uterine artery at 7 weeks.



S 75 cm/S
D -3 cm/s
M 20 cm/s
IP 3.9

Graph A1.3. Flow velocity wave of a uterine artery at 24 weeks



Right Ut-PS	198.20 cm/s
Right Ut-ED	105.52 cm/s
Right Ut-S/D	1.88
Right Ut-PI	0.67
Right Ut-RI	0.47
Right Ut-MD	101.95 cm/s
Right Ut-TAmax	137.98 cm/s

The speed is added in each fraction of the heart rate cycle and divided between by the cycle length. That is, (1+2+4+7+4+2+1+1+0+0) /10 = 2.2

Then, the range (R) of these variables in different clinical conditions will be:

RS= (0, ∞), RD= (-∞, S), Rm = (0, ∞)

What will be the range of the PI? For that purpose we will analyze the numerator (S-D) and the denominator (m):

In a high resistance artery, S will be small (close to zero) and D, very negative (close to -∞); therefore, (S-D) will be close to (0 - (-∞)) = ∞. The net flow (m), even in a high-resistance artery, must be antegrade, which would mean that the negative (or reverse) phase of the blood flow is very short, so m will be close to ∞; except in states of hemodynamic decompensation. See Graph A1.2.

In contrast, in a low-resistance artery, S will be very large, but D will have a value similar to S; so, (S-D) will be close to (S-S) = 0. M will have a large value, but greater than half of S. This way, the PI will be close to zero. Graph A1.3.

Note the small negative diastolic phase. IP = (S-D) / m) = (75 – (-3)) / 20 = 3.9.

Therefore, the range of the IP will be (0, ∞) and its distribution curve will be shown as in Graph A1.4. That is, a curve that seems normal, for IP values between 0.48 (2.5 percentile) and 1.09 (90 percentile), after which there is a right asymptote (bias) going towards infinity, but with few measurements in that range.

Graph A1.4. Average PI distribution curve of the uterine arteries between 25 and 39 weeks of gestation

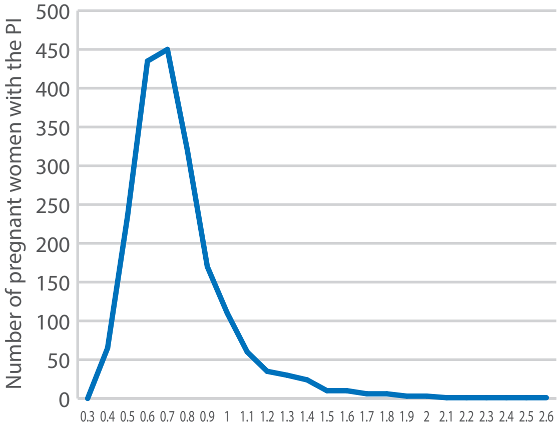


Table A1.1 Percentiles of the average of uterine arteries PI.

Percentil	IP
2.5	0.48
5.0	0.52
10.0	0.56
25.0	0.65
50.0	0.76
75.0	0.89
90.0	1.09
95.5	1.28
97.5	1.26

Appendix 2. Percentiles and percents.

Centiles or percentiles originate by ordering 100 measurements of similar objects in increasing values. They are a measure of dispersion. Percents, on the other hand, are a measure of proportion, measuring what proportion of the population has a given attribute.

To better understand this, let us look at the maximum size reached by a person, i.e. the size of an adult. We have 100 adult persons, we put them in a row in order of size, the smallest one first and the tallest one at the end. The position they occupy is their size percentile. The percentiles help us to identify a proportion of the population. For example, the 5th percentile of size should identify the smallest 5%; but this will not always be the case. Let us take an example by comparing two samples of 100 pregnant women at 'Loayza' and 'Dos de Mayo' hospitals. The height (in centimeters) of the ten smallest in sample one (at Loayza hospital) are: 141, 142, 143, 144, 145, 146.147, 148.149 and 150; and in sample two (at Dos de Mayo hospital), 143, 144, 145, 145, 145, 145, 148, 149, 150, 151. The 5th percentile in both samples would be 145 cm, but below the 5th percentile at Loayza hospital there would be 4 people (4%), and at Dos de Mayo hospital, 2 pregnant women (2%). This should not happen when the size is distributed normally.

Let's see it with real data in a local clinic, based on the size referred by 2 318 pregnant women at the beginning of their prenatal control. The 5th percentile was 150 cm, the 50th or median percentile, 160 cm, and the 95th percentile, 171 cm (Figure A1.1). In this population, 87 (3.8%) women reported measuring 150 cm; therefore, only 30 (1.5%) will be below the 5th percentile. In contrast, 24 (1%) women reported being 171 cm long, so 97 (4%) will have a height above the 95th percentile. When we look at the referred length distribution curve, we see that it is not a normal curve, but it has a bias to the right.

Let us compare these data with those obtained from systematic measurements of maternal height: the 5th percentile would be 150 cm, height of 13 pregnant women (2%); but, 4.3% of pregnant women measure less than 150 cm. The 95th percentile is 170 cm, size of 13 pregnant women (2%), and 4% of pregnant women measured more than 170 cm.

Graph A2.1. Number of pregnant women according to the height referred to at the beginning of prenatal control.

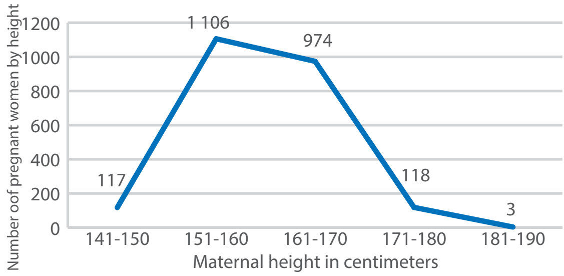
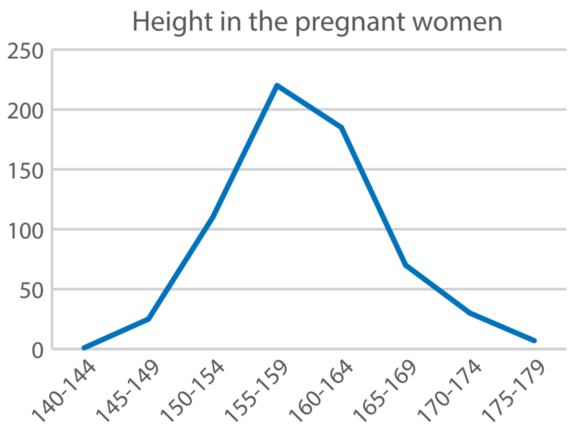


Table A2.1. Statistics on maternal height.

Maternal height (cm) (95,0%)	
Mean	159
Typical error	0.23
Median	159
Mode	160
Standard deviation	5.94
Sample variance	35.30
Kurtosis	0.27
Asymmetry coefficient	0.28
Range	39
Minimum	140
Maximum	179
Addition	104 150
Count	655
Confidence level (95,0%)	0.46

Graph A2.2. Distribution of maternal height.



When looking at the maternal size distribution graph, we see that it does have a normal and symmetrical distribution, i.e. the size is normally distributed, symmetrically, with an average of 159 cm and standard

deviation of 6 cm.

To make the percentiles more useful, the distribution of the parameter should be normal in the population.

In a small study using the Student t-test in 200 pregnant women to compare the difference in length between size referred and measured, we find a significant difference ($p<0.05$; mean 159 vs 161 cm).

To construct or use a reference curve, measurements have to be conducted in an appropriate manner.

In another example, birth size at 38 weeks of gestational age the median is 49 cm, the 5th percentile is 46 cm, the 10th percentile is 47 cm and the 95th percentile is 51 cm. In this case, 4.3% of the female newborns are below the 5th percentile, 7% below the 10th percentile and 5% above the 95th percentile. The distribution of newborn length is also normal. The curve serves to identify the population at risk.

Graph A2.3. Size distribution of 38 week newborn girls.

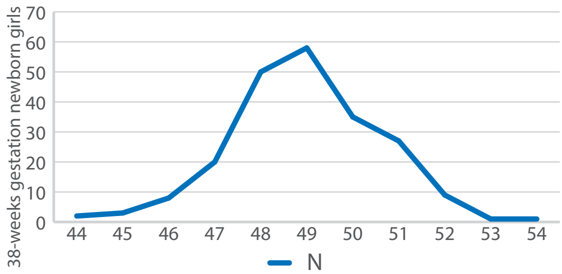


Table A2.2. Size statistics of 38-week newborns

Mean	48.8
Typical error	0.1
Median	49
Mode	49
Standard deviation	1.60
Sample variance	2.55
Curtosis	0.58
Asymmetry coeficient	-0.15
Range	10
Minimum	44
Maximum	54
Addition	10 548
Count	216
Confidence level (95.0%)	0.21

Appendix 3. Tables and reference curves of percentiles.

In Appendix 2, we saw that the distribution curve of a variable serves to identify a proportion of the population that we qualify as population at risk. But we also saw that it is useful at a certain point in time, in the examples at birth and in adulthood.

During development, these values vary, so reference curves or tables are developed in which the 2.5, 5, 10, 25, 50, 75, 90, 95 and 97.5 percentiles are recorded as they change over time. These tables can be reistered by periods of days, weeks, months or years, depending on their variation over time. Graph A3.1 shows the distribution curves for each week of gestational age. The process of making this reference curve throughout pregnancy is simple, since the percentiles for each week only need to be linked.

However, in the specific case of the pulsatility index of the uterine and umbilical arteries, we have two problems:

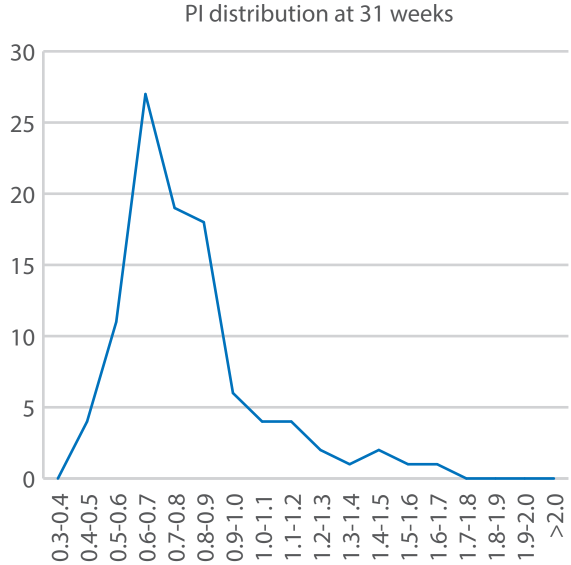
1. The weekly distribution curves do not have a normal distribution, as in the case of the referred size in appendix 2; the curve has a bias to the right, which we expected according to the analysis made in Appendix 1.

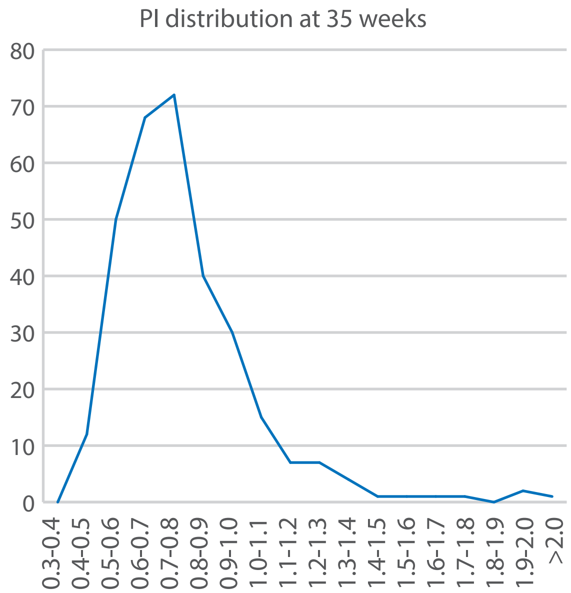
2. Reference curves of PI measurements have been done in different sites and by different vias; this increases dispersion.

Point one can be solved by increasing the number of measurements per week (to 384) and eliminating outliers.

One way to qualify a value as an outlier is to add to the 75th percentile, 1.5 times the difference with the 25th percentile. For example, table A1.1 shows that, for the average of uterine arteries PI, the 75th percentile is 0.89, the 25th percentile is 0.65. The difference between them is 0.24. We add 0.89 + 1.5*(0.24) = 0.89 + 0.36 = 1.35. Any value above 1.25 should not be considered in the construction of the reference curve. The equivalent is to consider 1.35 as the 100th percentile.

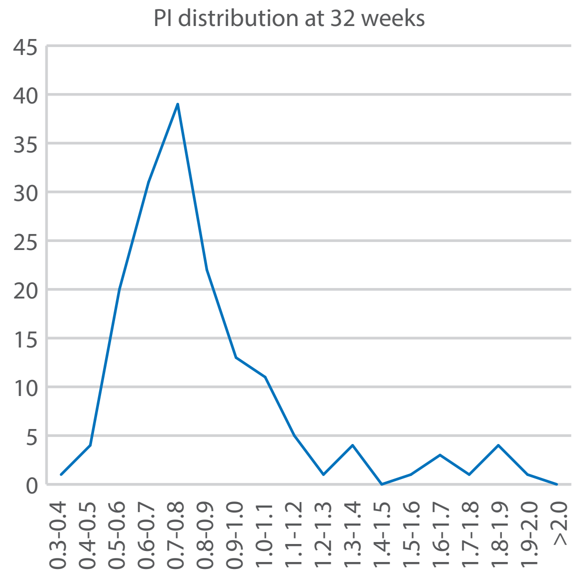
Graph A3.1. Distribution curves of the average of the uterine artery PI per week of gestational age, central tendency values, 5th and 95th percentile curves between 31 and 38 weeks.

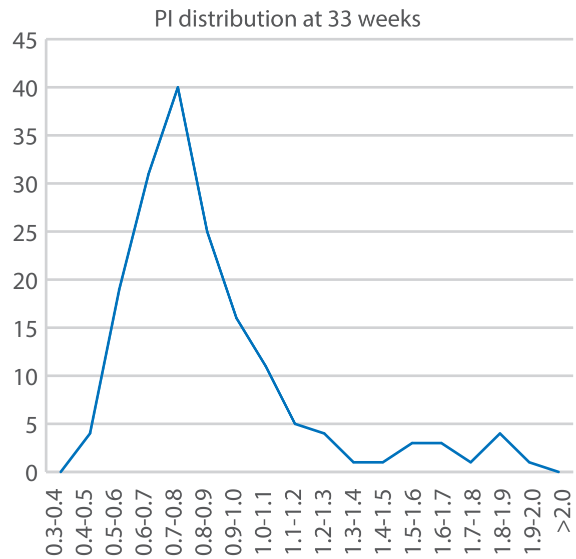


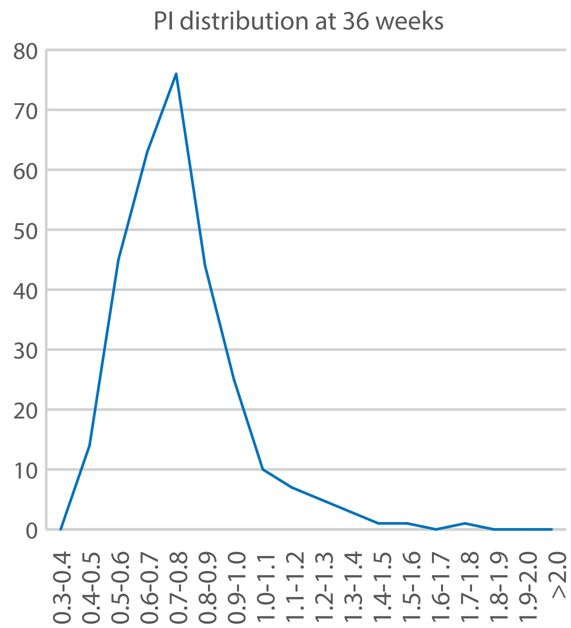


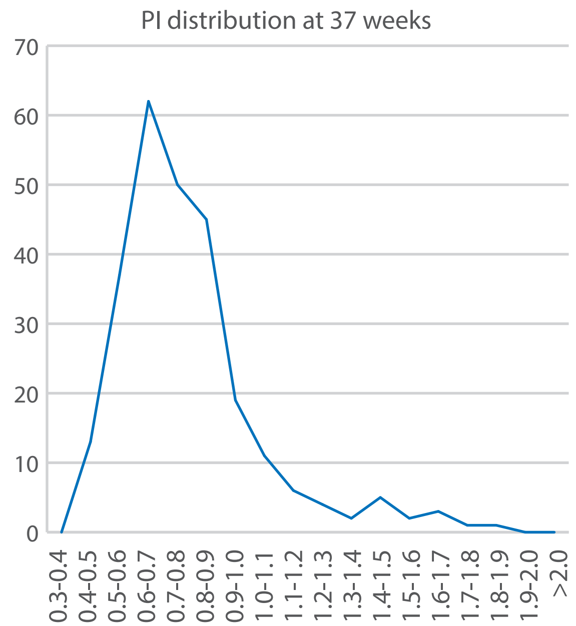
Uterine arteries mean PI				
GA	Mean	Median	Mode	SE
31	0,80	0,74	0,64	0,02
32	0,84	0,78	0,68	0,02
33	0,80	0,76	0,70	0,02
34	0,79	0,75	0,77	0,01
35	0,79	0,75	0,69	0,02
36	0,77	0,76	0,79	0,01
37	0,79	0,73	0,67	0,02
38	0,75	0,74	0,75	0,02
Total	0,79	0,75	0,70	0,01

GA=gestational age; SE=standard error



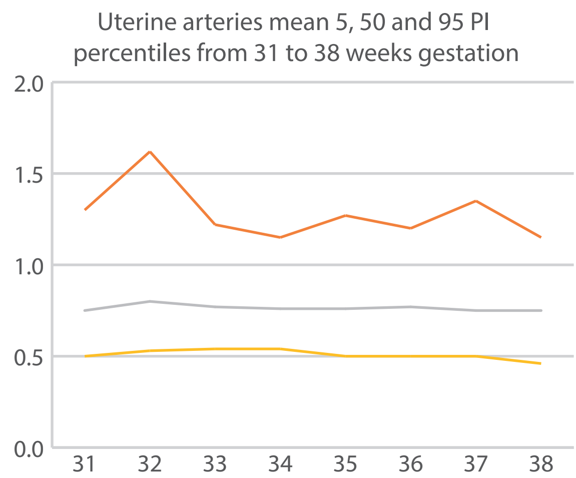


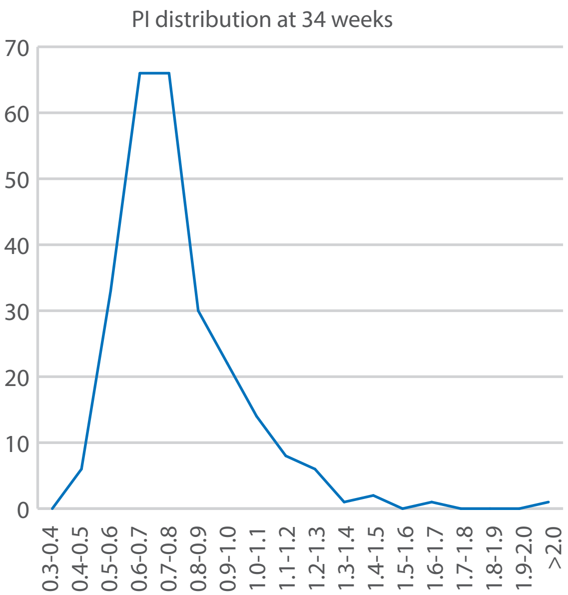


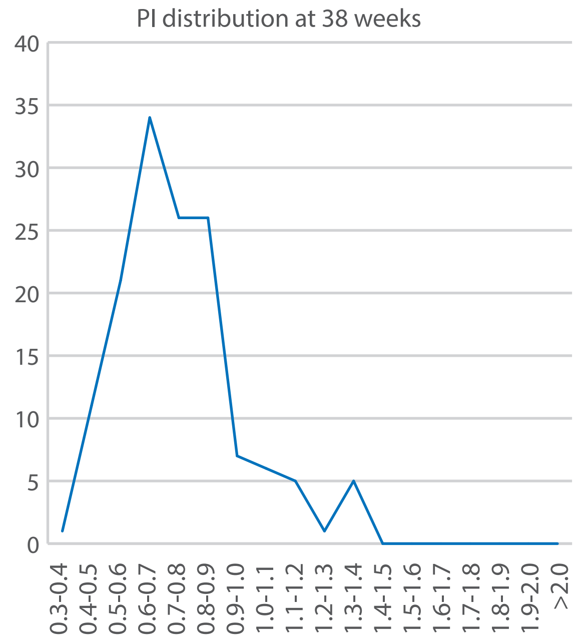


Uterine arteries average PI percentiles				
GA	Mean	Median	Mode	SE
31	1.25	0.74	0.51	99
32	1.61	0.78	0.53	163
33	1.21	0.76	0.55	170
34	1.15	0.75	0.55	255
35	1.25	0.75	0.51	313
36	1.19	0.76	0.51	298
37	1.34	0.73	0.51	259
38	1.13	0.74	0.47	143

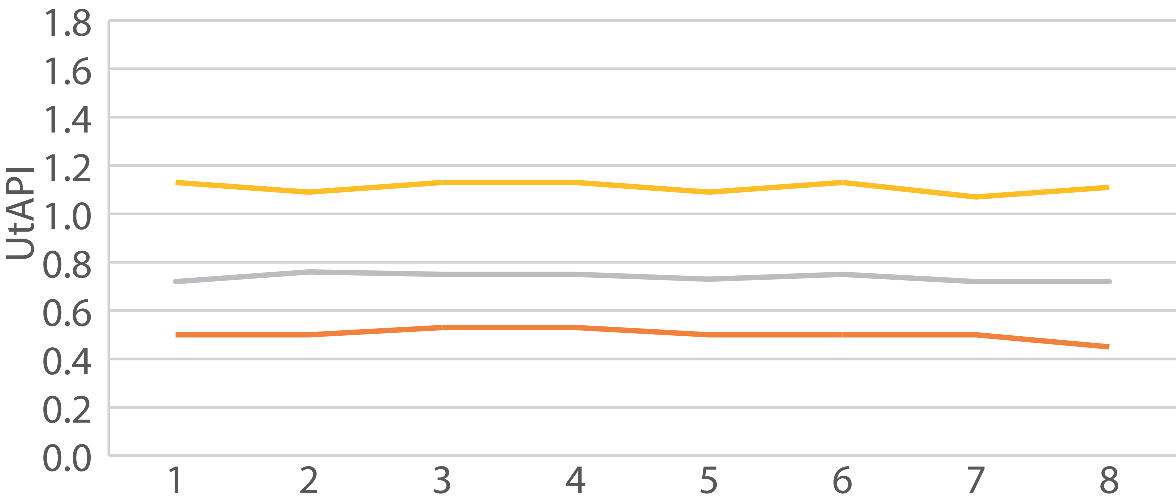
GA=gestational age; SE=standard error







Graph A3.2. Transformation of the reference curve after eliminating atypical values.



GA/Percentiles	5	50	95
31	0.5	0.73	1.1
32	0.5	0.76	1.1
33	0.5	0.76	1.1
34	0.5	0.75	1.1
35	0.5	0.74	1.1
36	0.5	0.75	1.1
37	0.5	0.72	1.1
38	0.5	0.72	1.1
39	0.55	0.72	1.1

GA=Gestational age