OBSTETRICAL AND GYNECOLOGICAL SURVEY
Vol. 41, No. 4 – 187-199
INCAP PUBLICATION I-1442

The Evaluation of the Methods Used in the Diagnosis of Intrauterine Growth Retardation

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Several methods used in the diagnosis of intrauterine growth retardation (IUGR) were evaluated with epidemiologic techniques. The strong effect of IUGR prevalence on the positive predictive and false-positive values of these methods is discussed. If correctly used, the combination of clinical measurements and perinatal risk factors can have a predictive power as high as any of the other more sophisticated techniques. The data reviewed show that at present biparietal diameter measurements, nonstress test/oxytocin challenge test or hormone values do not contribute to a better IUGR prediction than when the above mentioned methods are applied. For IUGR detection, ultrasound evaluation should include ratios of anthropometric measurements and may be complemented with amniotic fluid volume assessment. It is suggested that these procedures be reserved to a selected high risk population. Efforts should be made to evaluate new technologies through randomized controlled trials before they are introduced to the general population, particularly in developing countries.

Since it was first described intrauterine growth retardation (IUGR) has attracted the attention of obstetricians and pediatricians alike in the past two decades (23). IUGR infants are recognized as having increased perinatal and infant morbidity and mortality (36) as well as higher prevalence of developmental and physical growth handicaps (13, 68). The early identification of intrauterine growth arrest and the evaluation of the well-being of growth retarded fetuses are accepted as the main objectives of antenatal care. When growth retardation is recognized, special management of pregnancy is required and therapeutic measures might be attempted.

A long list of methods and techniques for the diagnosis of IUGR has been proposed in the literature, and today many of them are included in the obstetrician's armamentarium. Yet, they seldom have been evaluated in the context of a screening program or using correct epidemiologic methods. This paper discusses the predictability of several techniques used to monitor fetal growth and intrauterine growth retardation. This information should help those involved in prenatal care programs to select the most appropriate technique for the population for which it will be used.

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This paper was partially presented at the PAHO/WHO Conference on Appropriate Technology for Prenatal Care, Washington D.C., November 1984.

Materials and Methods

Eighty-six reports of methods used in the diagnosis of IUGR published between 1975 and 1983 in English-language journals were reviewed. In order to be included in the review, the reports must have stated the detection of IUGR fetuses as a study objective; if the method(s) for detecting IUGR fetuses were studied in the context of a prenatal care program, IUGR must have been clearly identified as one of the outcomes. A report was included only if it yielded the necessary information to construct a two by two table (Table 1).

Methods were evaluated using sensitivity, specificity, false-positive and false-negative rates and their complementary positive and negative predictive values (14, 21, 66). Prevalence of the disease (in this case, IUGR) was also calculated for each reported population. Table 1 shows the data layout that was completed for each method as well as the formulas used for the calculation of the parameters. In short,

TABLE 1 **Data layout and definitions used**

		"True" birth weight status		
		IUGR	Normal	Total
Antepartum diagnosed status	IUGR	a	b	a + b
	Normal growth	c	d	c + d
	Total	a + c	b + d	N

Sensitivity = a/(a + c) *Specificity* = d/(b + d)
False-negative = c/(c + d) *False-positive* = b/(a + b)
"True" prevalence of IUGR = (a + c)/(a + b + c + d)
Positive predictive value (PPV) = a/(a + b)
Negative predictive value (NPV) = d/(c + d)
False-positive rate = 1 − PPV
False-negative rate = 1 − NPV
Positive predictive value (PPV) by prevalence level*

$$= \frac{\text{Sensitivity} \times \text{prevalence}}{\text{Sensitivity} \times \text{prevalence} + (1 - \text{specificity})(1 - \text{prevalence})}$$

* See Refs. 14 and 66.

sensitivity is the proportion of IUGR infants that were correctly detected by the test, and specificity the proportion of normal birth weight infants that were considered as having normal growth by the test. Positive predictive value (PPV) is the proportion of fetuses diagnosed as IUGR by the test that actually will be IUGR at birth; the complementary false-positive rate is the proportion of those fetuses diagnosed as IUGR by the test that actually will have normal birth weight. Finally, the false-negative rate is the proportion of those fetuses diagnosed as having normal intrauterine growth by the test, but who will be IUGR at birth. The Youden Index (76) was used as a summary measure to evaluate the performance of tests. It ranges from 0 to 1 with 1 being a test without any misclassifications and has the advantage of not being affected by the IUGR prevalence.

A given method with high sensitivity and positive predictive value would lead to accurate prediction of IUGR and consequently promote timely and appropriate management for those affected pregnancies. Conversely, a method with high false-positive rates will result in a large number of normally growing fetuses receiving treatment for a nonexisting complication with important cost and iatrogenic consequences. A high false-negative rate will imply that a large number of growth retarded fetuses will not be detected and will be managed as normal pregnancies.

The effect of the prevalence of IUGR on the PPV and false-positive rate was explored using regression analysis controlling for the sensitivity and specificity of the test. The Bayesian approach was used to calculate, for the same test, the PPV at two levels of IUGR prevalence (14, 66).

Definitions of abnormal intrauterine growth and the outcome at birth (normal birth weight or IUGR) were accepted as the original authors have stated. Fifty-five publications that met the criteria of having the required data are included here. Some reports discuss more than one test; in these cases each test was considered independently.

Results

The Prediction of IUGR During Pregnancy

Table 2 presents the characteristics of the sampled populations, the criteria for sample selection, sample size and the prevalence of IUGR according to the publications included. It also shows the sensitivity, specificity, positive predictive values, and false-negative rates for each method. Methods are oriented to identification of maternal risk factors, indirect or direct monitoring of fetal growth or its activity, measurement of metabolites produced totally or partially by the fetal-placental unit or assessment of maternal metabolic functions.

Methods based on fundal height measurements have a sensitivity ranging from 46 to 86 per cent (mean 67 per cent) and a false-negative rate between 4 and 12 per cent (mean 7 per cent). Endocrine tests showed a sensitivity range from 27 to 95 per cent (mean 63 per cent) and from 0.8 to 56 per cent (mean 21 per cent) for false-negative rates. Overall measurements based on ultrasound techniques range from 7 to 100 per cent (mean 67 per cent) for sensitivity and from 0 to 13 per cent (mean 5 per cent) for false-negative rates. The measurement of biparietal diameter by ultrasound showed a sensitivity range from 7 to 100 per cent (mean 55 per cent) and from 0 to 13 per cent (mean 6 per cent) for false-negative rates.

Table 3 shows the best reported values for each technique obtained from studies with sample size of at least 100, the Youden Index (76) as a summary measure, and for comparison, the PPV calculated using a standard prevalence of IUGR of 10 per cent (formula given at the bottom of Table 1) (14, 21, 66). As can be seen from Tables 2 and 3, the combination of maternal risk factors and several clinical characteristics including fundal height and weight gain by the 34th week of gestation, and amniotic fluid volume or fetal ultrasound measurements are the procedures that can better identify IUGRs. The three least likely of these groups of techniques to identify IUGR

TABLE 2 **The prediction of IUGR by several methods**

Method	Sample selection criteria	Sample size	Incidence IUGR (%)	Sensitivity (%)	Specificity (%)	Predictive positive value %	False-negative rate (%)
I. *Risk Factors*							
Galbraith et al. (18)	Unselected series	8030	4.9	69.1	67.1	9.8	2.3
II. *Clinical Indices*							
A. Clinical inspection and palpation							
Hall et al. (24)	Unselected series	1884	10.0	43.9	87.8	28.7	6.6
B Symphysial fundal height	≤37 W known by LMP* or GA*	138	29.7	73.2	79.4	60.0	12.5
Quaranta et al. (51)							
Westin (70)	Unselected series 37–42 W	428	11.0	68.1	89.2	43.8	4.2
Belizan et al. (3)	Known LNMP*	139	31.7	86.4	89.5	79.2	6.6
Calvert et al. (7)	Unselected known LM, prenatal care started <16 weeks	381	11.8	64.0	79.0	29.0	6.0
Canttingius et al. (8)	With risk factors	527	11.2*	46–58	82–95	29–52	6.0
C. Roll-over test							
Verma et al. (67)	28–34 weeks gestation, no renal, metabolic, or vascular disease	130	6.9	88.9	76.0	21.6	1.1
D. Risk factors and clinical indices							
Wennergren and Karlsson (69)	Unselected series	611	2.3	100.1	95.5	34.1	0.
III. *Endocrine Test*							
A. Plasma estriol							
Odendaal et al. (48)	Positive stress test	53	56.6	43.3	87.0	81.2	45.9
Arias (1)	Abnormal BPD*; known LMP	24	45.8	27.3	61.5	37.5	50.0
B. Placental-lactogen hormone							
Odendaal et al. (48)	Positive stress test	77	55.8	81.4	52.9	68.6	30.8
Gohari et al. (20)	Subnormal uterine growth or complications associated with IUGR	111	34.2	36.8	90.4	66.7	26.7
Hensleigh et al. (27)	High-risk volunteers	58	36.2	71.4	48.6	44.1	25.0
C. Urinary estrogen							
Odendaal et al. (48)	Positive stress test	46	60.9	21.4	94.4	85.7	56.4
Ryden (54)	High-risk pregnancy	583	7.4	58.1	91.3	34.7	3.5
Wolfrum et al. (74)	High-risk pregnancy, no renal disease or penicillin treatment	222	28.4	90.5	63.5	49.6	5.6
D. Pregnanediol							
Wolfrum et al. (74)	High-risk pregnancy	222	28.4	90.5	45.3	39.6	7.7
E. Estrogen and pregnanediol							
Wolfrum et al. (74)	High-risk pregnancy, no renal disease or penicillin treatment	222	28.4	81.0	74.2	55.4	9.2
Wolfrum et al. (75)	High-risk pregnancy, no renal disease or penicillin treatment	500	3.6	83.3	78.4	12.6	0.8
F. Cystine aminopeptidase							
Ryden (54)	High-risk pregnancy	583	7.4	34.9	94.6	34.1	5.2
G Exogeneous DHA-S half life							
Tanguy et al. (64)	Suspected IUGR	59	33.9	95.0	89.7	82.6	2.8

TABLE 2—*Continued*

Method	Sample selection criteria	Sample size	Incidence IUGR (%)	Sensitivity (%)	Specificity (%)	Predictive positive value %	False-negative rate (%)
IV. *Ultrasound*							
A. BPD							
Lee and Chard (34)	BPD 18–21 W delivery after 36 W	1025	6.4	24.2	92.5	18.2	5.3
Sabbagha (55)	BPD 20–40 W	458	13.3	63.9	87.7	44.3	5.9
Crane et al. (11)	Consecutive series, referred patients	88	10.2	100.0	93.7	64.3	0.
Queenan et al. (52)	Known dates, uncomplicated pregnancy	100	16.0	43.8	89.3	43.8	10.7
Hohler et al. (28)	Consecutive series	311	6.1	63.2	97.3	55.6	3.1
B. BPD pattern	Clinical diagnosis of:						
Sholl et al. (60)	Dates discrepancy, possible IUGR	121	9.9	75.0	84.4	34.6	3.2
Sabbagha (55)	1st BPD <26W	458	13.3	6.6	96.0	20.0	13.0
Hohler et al. (28)	Consecutive series	311	6.1	52.6	97.3	55.6	3.1
C. BPD or BPD pattern							
Sabbagha (55)	BPD 20–40 W	458	13.3	63.9	86.1	41.5	6.0
Queenan et al. (52)	Known dates, uncomplicated pregnancy	100	16.0	56.2	89.3	50.0	8.5
D. Total intravolume							
Gohari et al. (19)	Complicated pregnancy, date discrepancy	96	29.2	75.0	100.0	100.0	9.3
E. Abdominal area							
Varma et al. (65)	Suspected IUGR	186	18.8	80.0	90.1	65.1	4.9
F. Head/abdominal area							
Varma et al. (65)	Suspected IUGR	186	18.8	82.9	92.1	70.7	4.1
Crane and Kopta (10)	Suspected IUGR or Abnormal BPD	47	21.3	100.0	100.0	100.0	0.
G. Crown-rump length							
Neilson et al. (43)	Referred high-risk and low-risk volunteers	474	7.6	69.4	87.9	32.1	2.8
H. Crown-rump length × trunk area							
Neilson et al. (43)	Referred high-risk and low-risk volunteers	474	7.6	94.4	87.9	39.1	0.5
I. Crown-rump length × trunk circumference							
Neilson et al. (43)	Referred high-risk and low-risk volunteers	474	7.6	88.9	91.1	45.1	1.0
J. Head area × trunk area							
Neilson et al. (43)	Referred high-risk and low-risk volunteers	474	7.6	44.4	91.1	29.1	4.8
K. BPD and placental grade							
Kazzi et al. (30)	High-risk pregnancy	191	20.4	59.0	86.0	52.0	11.0
L. Amniotic fluid volume							
Philipson et al. (49)	Clinical indication	192	24.0	82.6	60.3	39.6	8.3
Manning et al. (40)	Clinical diagnosis of IUGR	120	25.8	83.9	96.6	89.7	5.5
V. Two-Stage BPD and AFPG*							
Gross et al. (22)	Clinical suspicion of IUGR	249	19.7	79.6	79.5	48.8	5.9
BPD and foam stability Index test	All cases were LBW, preterms used as a reference	57	35.1	80.0	91.9	84.2	10.5
Sher et al. (59),							
VI. *Fetal Breathing*							
Manning et al. (39)	Random sample high-risk pregnancy	223	4.5	60.0	85.9	16.7	2.1

TABLE 2—*Continued*

Method	Sample selection criteria	Sample size	Incidence IUGR (%)	Sensitivity (%)	Specificity (%)	Predictive positive value %	False-negative rate (%)
Platt et al. (50)	High-risk pregnancy	136	10.3	71.4	91.8	50.0	3.4
Manning et al. (38)	W/AI*	789	6.5	92.2	94.7	54.7	0.6
VII. *Fetal movement*							
Rayburn (53)	W/AI	1161	4.0	29.0	97.0	28:0	3.0
Jarvis and MacDonald (29)	W/AI	90	14.0	77.0	86.0	48.0	4.0
VIII. *Oxytocin Challenge Test*							
Lin et al. (35)	Suspected IUGR for abnormal BPD or F.H.	583	14.6	40.0	92.0	45.9	10.0
Schulman et al. (57)	Authors experience	298	10.4	48.4	86.1	28.8	6.5
Freeman et al. (17)	Complicated pregnancy	390	14.6	43.9	87.7	37.9	9.9
Bhakthavathasalan et al. (5)	High-risk pregnancy	100	9.0	22.2	67.0	6.2	10.3
Hayden et al. (26)	High-risk, placental insufficiency	105	3.8	50.0	94.1	25.0	2.1
Schifrin et al. (56)	Postdates, hypertension, suspected IUGR	110	1.8	100.0	93.5	22.2	0.
IX. *Nonstress test*							
Lin et al. (35)	High-risk pregnancy + prenatal height and BPD	441	19.3	35.3	84.6	35.3	15.4
Manning et al. (39)	Random sample high-risk pregnancies	223	4.5	60.0	77.5	11.1	2.4
Flynn et al. (15)	Suspected IUGR	247	23.1	93.0	—	—	—
X. *Other*							
A. GTT							
Sokol et al. (61)	Clinical indication for test	55	10.9	100.0	71.4	30.0	0.
Khouzami et al. (31)	Clinical indication for test excluding gestational diabetes	71	22.5	37.5	89.1	50.0	16.9
B. Placental Protein-S							
Obiekwe et al. (47)	Unselected population 36-40 W	400	10.2	17.1	90.2	16.7	9.5
C. VIII/R Ag/VIII C							
Whigham et al. (71)	Clinically suspected IUGR	21	42.9	66.7	91.7	85.7	21.4
D. 3-Methyl histidine to creatinine Ratio							
Miodovnik et al. (41)	Clinical indication	42	35.7	86.7	85.2	76.5	8.0

* Abbreviations used in the table: W = weeks' gestation; LMP = last menstrual period; GA = gestational age; BPD = biparietal diameter; IUGR = intrauterine growth retardation; AFPG = amniotic fluid phosphatidylglycertol; DHAS = dehydroisoandrosterone-sulfate; W/AI = without available information. VIII E Ag/VIII C = ratio: factor VIII related antigen/factor VIII coagulant activity.

fetuses are the use of risk factors alone, the nonstress test, and urinary estrogen.

The Effect of IUGR Prevalence on its Prediction

Figure 1 describes the relationship between the positive predictive value calculated for 66 different procedures and the prevalence of IUGR in their respective populations. As the IUGR prevalence increases, so does the PPV of the test ($r = 0.70$, $\beta = 1.08$, $P < 0.001$). Furthermore, when sensitivity and specificity were controlled in a regression model, or when the PPV—IUGR prevalence relationship was studied at two levels of sensitivity, the same linear relationship was present. Therefore, regardless of the sensitivity or specificity of the procedure, the prevalence of IUGR in the population under consideration is responsible for about 50 per cent ($r^2 = 49$ per cent) of the PPV variability.

As an example, data are presented from Miodovnik et al. (41), on the predictability of IUGR by the use of amniotic fluid 3-methyl histidine to creatinine molar ratio are 3 MH:CM $\times 10^{-3}$ (Table 4). A ratio of eight or higher was considered to be a good predictor of an IUGR infant in this group of high-risk mothers. In this selected population with an IUGR prevalence of 36 per cent, the obtained PPV is 76 per cent (Table 4). This means that 76 per cent of all infants with 3 MH:CM $\times 10^{-3}$ of at least eight will be IUGR at birth.

TABLE 3 **Selected methods for the diagnosis of IUGR infants***

Method	Reference	Sensitivity	Specificity	Youdens Index†	PV at 10% IUGR prevalence (%)
Maternal risk factors	(18)	69.1	67.1	0.36	19
Symphysis fundal height	(3)	86.4	89.5	0.75	48
Risk factors and clinical indices	(69)	100.0	95.5	0.95	69
Ultrasound measures					
Head/abdominal circumferences	(65)	82.9	92.1	0.75	
Crown-rump-length × trunk area	(43)	94.4	87.9	0.82	51‡
Crown-rump-length × trunk circumference	(43)	88.9	91.1	0.80	
Amniotic fluid volume	(40)	83.9	96.6	0.85	73
Fetal movement (N = 90)	(29)	77.0	86.0	0.63	38
Urinary estrogen	(74)	90.5	63.5	0.54	20
Estrogens and pregnanediol	(75)	83.3	78.4	0.62	30
OCT	(26)	50.0	94.1	0.44	48
NST	(39)	60.0	77.5	0.37	23

* The best published report for each technique is included; sample size larger than 100.
† Youdens index, summary measure of sensitivity and specificity, range, 0–1; 1 = no misclassification (76).
‡ Average of a, b, and c.

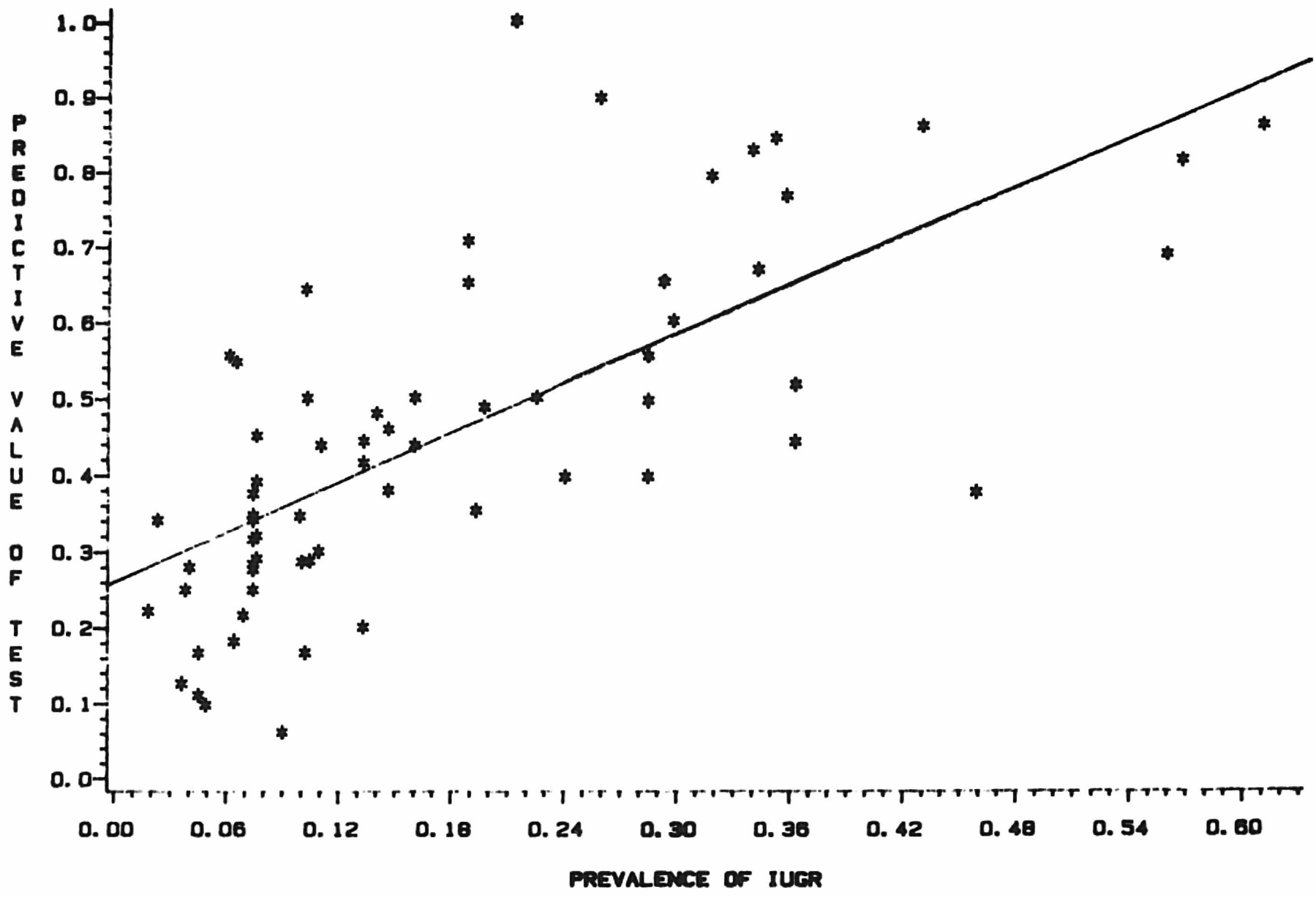

Fig. 1. Relationship between IUGR prevalence and the predictive value of the test. Sixty-six different procedures were included. The higher the IUGR prevalence the better the predictability of the method ($r = 0.70$, $\beta = 1.08$, $P < 0.001$).

Using the formula provided at the bottom of Table 1, it can be calculated that the PPV of the method is reduced to 39 per cent in a low-risk population with an IUGR prevalence of 10 per cent. Thus, only 39 per cent of those fetuses with abnormal 3 MH:CM $\times 10^{-3}$ will be IUGR at birth. Similar values are obtained using the regression line presented in Figure 1.

TABLE 4 **The effect of the population risk level on the predictability of pregnancy outcome (IUGR)**

		"True" birth weight status		
		IUGR	Normal	Total
Antepartum diagnosed status (3 MH:CR × 10^{-3})*	IUGR	13	4	17
	Normal fetal growth	2	23	25
	Total	15	27	42

PPV: 76% FP: 25%
FN: 8% IUGR prevalence: 36%

$$\text{PPV at a IUGR prevalence of 10\%} = \frac{\text{Sensitivity} \times \text{prevalence}}{\text{Sensitivity} \times \text{prevalence} + (1 - \text{specificity})(1 - \text{prevalence})}$$

$$= \frac{0.87 \times 0.10}{0.87 \times 0.10 + 0.15 \times 0.90} = 0.39 \text{ or } 39\%$$

* 3 MH:CR × 10^{-3}: Amniotic fluid 3-methyl histidine to creatinine molar ratio (Ref. 41)

Randomized Controlled Trials

One of the most significant questions in monitoring fetal growth is: can the use of the information obtained during pregnancy (normal/abnormal fetal growth) improve fetal outcome? The best study design to answer this question appears to be a randomized controlled trial (RCT). The following results could be expected in the intervention group in such a trial: a) no change or small reduction in IUGR incidence, given that fetal jeopardy is already established when diagnosis is done; b) an increase in induced labors and/or cesarean birth rates; and c) a reduction in fetal and neonatal mortality and morbidity.

Table 5 summarizes the results of five RCTs using ultrasound imaging for monitoring of fetal growth at different periods during pregnancy. The sample sizes were not large enough to show significant differences in fetal or perinatal mortality. In four of them (2, 4, 42, 73) no differences among groups were observed in the incidence of IUGR, Apgar score distribution, resuscitation rate, induced labor, elective cesaren section, and perinatal mortality. There was a significantly higher proportion of women admitted to hospitals in the ultrasound group in Bakketeig's study (2), however, "suspected IUGR" as a reason for admission was similar in the two groups (2.0 per cent ultrasound vs. 0.8 per cent controls).

Data from the Wladimiroff and Laar trial (73) showed that the sensitivity of one ultrasound measurement of the fetal chest area was 87.5 per cent, significantly higher than the 42.4 per cent reported for the group with no screening scan. Furthermore, when two stages of ultrasound examination were used (42) the sensitivity was 94 per cent and the specificity 90 per cent.

A recent preliminary report (12), however, contradicts these results. In this trial, a two-stage ultrasound examination was performed (Table 5) on the intervention group. A nonsignificant reduction in perinatal mortality, late neonatal death, with no increase in the use of hospital facilities was observed. Although severe growth retardation when detected was associated with more postnatal days of hospital care for "dysmaturity," a reduction in neonatal death among IUGR infants was reported in the ultrasound group (12).

Finally, it should be noted that these studies enrolled women early in pregnancy and an initial biparietal diameter (BPD) for gestational age evaluation was performed. This scheme may not be feasible in high-risk populations living in less developed countries or for poor urban women in developed societies.

Four RCTs evaluating the nonstress test have recently been presented (6, 16, 32, 37). Three of them used IUGR as one of the outcome measures. A nonsignificant reduction in the incidence of IUGR (birth weight < 5th percentile) (17.9 to 11.8 per cent) was reported by Flynn and colleagues (16) and no effect on IUGR rates, as either <5th or <10th percentile was shown by Lumley et al. (37). No significant differences were observed in the percentage of newborns with Apgar scores less than 7 at 1 minute and in other morbidity and mortality outcomes, although the sample sizes used were not large enough for the detection of significant differences in the mortality outcomes. An increased labor induction rate and higher cesarean birth rate were evident in the study group in only one report (6).

Screening Programs for IUGR

The first objective of a screening program for IUGR should be to identify a subgroup of the pregnant population that has an increased prevalence of the outcome under consideration (IUGR). It is also expected that those being screened will have a better outcome than those which did not receive the test(s). The former objective appears to have already been reached; the latter remains to be shown (4).

Based on the information available to clinicians and public health workers, it is possible to describe a hypothetical multistep screening program for IUGR. Ultimately, this sequence should be tested by a randomized controlled trial, as only the assessment

TABLE 5 **Randomized controlled trials of ultrasound in pregnancy, with emphasis in the diagnosis of IUGR**

Reference	Total sample size	Gestational age at screening (weeks)	Ultrasound measure	Incidence of IUGR (%)		Induced labor (%)		Outcome	Comments
				Study groups	Controls	Study groups	Control		
Wladimiroff and Laar (73)	745	25 32–36	Chest area	8 2	9.1	Not given		Not given	BPD at 25th week for gestational age
Bennett et al (4)	1062	16	BPD	9 0	8 3	19.6	20.2	No difference in perinatal mortality and Apgar scores	161 controls had known BPD results. BPD for gestational age assessment.
Bakketeig et al. (2)	1009	19 and 32	BPD (19 W) BPD + abdominal circumference.	8.4	5.7	6.5	7.9	No difference in resuscitation rates, perinatal mortality, Apgar scores, newborn BW, L, and H.C.	Prenatal care started < 17 weeks. Examiners had limited training. A.C. not used for IUGR diagnosis. Admissions for IUGR similar.
Neilson et al. (42)	877	< 24 W 34–36.5 W	BPD for gestational age and crown to rump length and trunk area.	4.0	4.0	31.0	29.0	No difference in Apgar score, neonatal deaths, BW × gestational age in total population or in SGA pregnancies.	Low risk population; sensitivity 94%, specificity 90%.
Eik-Nes et al., (12)	1628	18 W 32 W	BPD for gestational age BPD, Abdominal diameter.					Reduction in total perinatal death and in the IUGR group. Reduction in treatment for postterm pregnancies.	No increase in hospital admissions 28% of hospital days due to IUGR detected by ultrasound.

BW, birth weight; L&HC, length and head circumference; AC, abdominal circumference; and SGA, small for gestational age.

of the joint effect of the screening program and the treatment implemented can provide information concerning its effectiveness in the general population. Nevertheless, until such an RCT is performed, this sequence and the data presented here can be used by those providing prenatal care as a point of reference.

What follows is a theoretical screening program with two steps. The first screening step is based on maternal risk factors evaluated two times during pregnancy and on fundal height measurements. In the second step, fetuses suspected as IUGR during the risk scoring and clinical evaluation will be examined by ultrasound using anthropometric ratios (10, 43, 65).

A theoretical model of a population of 10,000 pregnant women with an incidence of IUGR (< 10th percentile weight/gestational age) of 11.8 per cent was developed. The incidence of IUGR of 11.8 per cent is derived from one of the studies reviewed using an unselected population (7). The first step will identify 25 per cent of the population as possible IUGR (using a conservative figure from the fundal height data) (7) and 75 per cent as having normal fetal growth. Those fetuses detected as IUGR will then be screened using ultrasound anthropometric ratios. The group initially diagnosed as having normal fetal growth will be followed by fundal height monitoring and risk factor assessment and those suspected as IUGR will be referred for ultrasound evaluation.

Of the 2500 women referred for ultrasound evaluation, it is expected that 725 (PPV 29 per cent) (7) will have, at delivery, an IUGR infant. Of these 725, the ultrasound evaluation will correctly diagnose 645 and the remaining 80 will be incorrectly diagnosed as non-IUGR. On the other hand, among the 7500 women without risk factors or clinical evidence of IUGR, 455 will have at delivery an IUGR fetus (6 per cent false-negative rate). The continuous monitoring

of this low-risk population using clinical methods and risk factors will further identify a subgroup of 1771 women that are referred for ultrasound evaluation. Ultrasound screening will classify 407 of them as IUGR, among which a total of 259 will actually be growth retarded (PPV 64 per cent). Of the 5729 women not referred as IUGR, 164 will deliver an IUGR infant (false-negative rate 3 per cent).

Using this flow tree the two by two table presented in Table 6 was developed. As can be seen, this theoretical program identified 12.3 per cent of the population as IUGR; of those 1,230 women, 73.4 per cent (904) (PPV) had IUGR infants. Further, of the 1180 truly IUGR fetuses 76.6 per cent (904) were correctly identified by the program (sensitivity). Finally, 94 per cent of all infants were correctly diagnosed as either normal birth weight or IUGR, respectively (904 + 8,494/10,000).

With the implementation of qualified management of IUGR infants, this screening program could have a positive effect on the outcome of pregnancies. The perinatal and neonatal mortality rates of IUGR infants have been reported to be between four and eight times higher than that of the non-IUGRs (33). Using a relative risk of eight for neonatal mortality of all IUGR infants obtained from Koops and colleagues (33), and supposing a population with an IUGR incidence of 11.8 per cent (7), we obtained an IUGR attributable risk for neonatal mortality of 45.2 per cent in the total population. This means that in such a population, 45.2 per cent of the neonatal mortality can be associated with IUGR. Supposing a reduction of one-half in the mortality among the IUGR infants with screening-intervention programs, a decrease from 12.9 (33) to 10.0 per cent in neonatal mortality could be expected.

TABLE 6 **Predictability of a screening program for IUGR infants using clinical variables and ultrasound measures**

		True Birth weight Status		
		IUGR	Normal	Total
Antepartum	IUGR	904	326	1,230
	Normal fetal growth	276	8,494	8,770
	Total	1,180	8,820	10,000
	Sensitivity:	76.6		
	Specificity:	96.3		
	PPV:	73.4		
	F.P.:	26.5		
	FN:	3.1		
Antepartum	First step, risk factors, clinical indices; 2nd step, anthropometric ultrasound ratios.			

Discussion

We have offered here a review of methods currently in use for the monitoring of fetal growth. Some limitations of the present information should be discussed. We could not include all publications, given that appropriate data were not always available to perform the calculations offered here. The definitions of IUGR, particularly the use of weight for gestational age standards, are based on assumptions that may not be totally valid (21).

Problems arise when cut-off points for the definition of normal birth weight IUGR are established. Infants can be above the 5th or 10th percentiles or any given standard deviation of birth weight for gestational age yet also be growth retarded. The use of weight for length standards or Ponderal Index values could help to identify these IUGR infants.

Changes in the cutoff points used can affect the evaluation of the screening test. If modifications occur in the definition of the test results (normal or abnormal intrauterine growth patterns) the sensitivity and specificity of the test will be affected in opposite directions (63). On the contrary, if changes occur in the definition of the outcome measure (IUGR), then its prevalence will increase or decrease depending on, for example, the cutoff percentile that was employed. Prevalence changes, as this review shows, dramatically influence the PPV, FP and FN rates (Fig. 1 and Table 4). Furthermore, although, sensitivity and specificity are said not to be influenced by the prevalence of the disease, IUGR may represent one special case where this effect may be observed (63).

The formula for PPV presented at the bottom of Table 1 is an important tool of simple applicability that helps to evaluate a test under different IUGR prevalence rates. It should be used when tests are developed in a high-risk group and then introduced to the general pregnant population. Figure 1 provides a graphic demonstration of this effect and can be applied to calculate the expected PPV for a given population.

Two additional problems are present in the interpretation of the data in this review. First, a relatively wide variation in predictability is observed among reports of the same method, which may be due either to differences in the underlying populations or to the instrumentation of such a technique. Second, once the diagnosis is made, interventions are generally attempted. An effective treatment can influence the outcome under study (IUGR), thus elevating the false-positive rate of the screening test.

Clinicians and public health workers must consider

these limitations when evaluating the literature or when decisions have to be made about the technique and the steps to be implemented. The review presented here can benefit those involved in this process. For example, the correct calculation of the positive predictive value and false-positive rate for a particular population IUGR prevalence can help estimate realistic expectations and prepare the resources to accommodate the increased referral of patients at risk for IUGR.

A summary evaluation of the methods judged to be most accurate is presented in Table 3. The inclusion in the table of the best report is a bias that gives a more positive view of the technique that may not be always true. From this table, it is evident that when combining maternal risk factors with clinical indices (e.g., fundal height, weight gain monitoring), as in the Wennergren and Karlsson report (69), an excellent IUGR predictability is obtained, however the study included only 14 IUGR infants. Unfortunately, the use of risk scores may be limited because clinicians may not always analyze available data, for example IUGR history (9) or clinical indices like fundal height are seldom plotted in normal charts despite evidence that this practice can help to identify abnormal fetal growth.

It is also clear, from the data shown, that the measurement of biparietal diameter by ultrasound is not a better screening technique than other clinical measurements like fundal height. The recent National Institutes of Health report on ultrasound supports this interpretation (46).

In contrast, the use of the ratio of two morphometric measurements using ultrasound (42, 43) gives an excellent prediction rate of IUGR. Unfortunately, when evaluated in the context of a RCT, although the predictability remained high, the positive impact in pregnancy outcome was not present (42). Furthermore, these reports (42, 60) had a 15-week biparietal diameter measurement for gestational age assessment, practice that requires early contact with patients plus the systematic use of BPD, which is not recommended at this time (46).

The qualitative amniotic fluid volume determination (40) and the sonographically detected oligohydramnios (62) appear to be good complements to the ultrasound technique. However, these results should be replicated in larger studies and the methodology better standardized before application of the technique is recommended.

In short, combination of morphometric measurements with the evaluation of amniotic fluid volume represent the best ultrasound alternative for IUGR detection. The need for accurate dating, the use of real-time ultrasound (not always available), the cost and, to some extent, the concern that has been raised about its safety, limit the utility of these techniques for routine screening and reserve them for specific medical indications (46).

Fetal movement counting has been suggested as an attractive method for monitoring fetal well-being (45). A recent completed randomized clinical trial has shown a significant reduction in the intrauterine death rate among those women in the "treatment" group (44). Based on information on malnourished children, a reduction in activity could be an adaptive mechanism among IUGR fetuses, although the use of fetal movement counting in the referred report (44) did not show any effect on the incidence of newborns with low weight for gestational age. Its simple and inexpensive implementation appears very attractive for first level care, yet its noncompliance rate of about 20 per cent also suggests that its use may be limited to a well-motivated population (25, 44).

IUGR is a condition for which a screening program is appropriate: it is an important perinatal problem, it has an identifiable preclinical phase (the length of which varies with the methods), and there are screening tests that can be applied on a continuous basis during pregnancy. Fetuses at risk of IUGR can receive appropriate antenatal management including earlier delivery (effective treatment).

On the contrary, the limitations in the outcome measure (e.g., birth weight for gestational age) (72) is a shortcoming of the implementation and evaluation of screening programs for IUGR. Nonetheless, overall IUGR appears to be a suitable entity for a screening program.

In Table 6 the overall predictive power of a two-step theoretical screening program is shown. This program, based on a preliminary clinical screening and a subsequent ultrasound diagnosis, may correctly predict 73 per cent of all IUGR infants. These calculations are assuming that the two steps are independent, which may not be the case. Underestimation of the program impact can result if both steps are detecting the same IUGR cases, while overestimation of the results is present if uterine height and clinical evaluation detect totally different IUGR fetuses than ultrasound screening.

In the first step, the most conservative figure for fundal height (PPV = 29 per cent) was used (7). When adequately used, clinical and risk factors have

shown better predictive figures, thus a reduction in false-negative and false-positive rates can be expected. Clinicians should be trained to interpret obstetrical histories and clinical information correctly, carefully measure maternal weight and fundal height, and plot those values on normal charts at each prenatal visit. The resulting clinically selected high-risk group can then be provided with a more detailed ultrasound follow-up (a combination of anthropometric measures and amniotic fluid evaluation). This approach should improve the cost/benefit and risk/benefit analyses of ultrasound techniques.

Randomized controlled trials appear to be the ideal study design to evaluate the impact of IUGR screening programs. They should be focused on the following central questions:

a. Is the IUGR detection rate of a screening program higher than the one of routine practice?
b. Are the morbidity and mortality rates of IUGR fetuses-newborns monitored by the screening program lower than those of IUGRs cared for by routine practice?
c. Are the morbidity and mortality rates of the total population in the screening program lower than that of the population under routine care?

The implementation of such a RCT is not without limitations and several major problems are present. Among them, for example, is that if a reduction of neonatal mortality from 12.9 per 1,000 to 10.00 per 1,000 is expected, 19,800 pregnancies in each group will be necessary to show significant differences ($\alpha = 0.05$; $\beta = 0.20$). With similar proportional reduction but with a neonatal mortality of 20 per 1,000, a sample size of 9,780 in each group is required.

Furthermore, the expectation that the morbidity and mortality rates will be reduced has the assumption of availability of effective "treatments." It appears that among those treatments currently practiced, the principal one is the early delivery of a subgroup of IUGR fetuses judged to be most at risk, while the remaining subgroup, although experiencing growth retardation, can be allowed to remain *in utero*. Perhaps it is the latter group, the proportionately growth retarded, that will benefit the most from the proposed screening program.

Conclusions

Methods used for monitoring fetal growth should always be evaluated using epidemiologic procedures. The strong effect of disease (IUGR) prevalence on the positive and false-positive predictive values should always be taken into consideration in this process. When correctly used, the combination of clinical measurements and risk factors can produce a predictive power as high as any of the other more sophisticated techniques. Efforts should be devoted to improve the utilization of this information by health care personnel.

For IUGR detection, ultrasound should be performed only in a high-risk population and should include ratios of anthropomorphic measurements complemented by the evaluation of amniotic fluid volume. At the present time biparietal diameter measurements, nonstress test/oxytocin challenge tests or hormone values do not contribute to a better prediction of IUGR than the above mentioned methods.

Fetal movements count appears to be a promising component of the first step of IUGR monitoring, yet this may have to be reserved to a highly motivated population that is already receiving basic prenatal care. Efforts should be made to evaluate screening methods in the context of randomized controlled trials before they are implemented to the general population, particularly in developing countries.

Acknowledgments—We express our gratitude to Dr. Adrian Grant for the critical review of this manuscript.

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