Prediction of small-for-gestational-age neonates: screening by biophysical and biochemical markers at 30–34 weeks

Spyros Bakalis, Gergana Peeva, Ricardo Gonzalez, Leona C. Poon*, Kypros H. Nicolaides*

Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK

*Joint senior authors

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Correspondence:
Leona C. Poon
Harris Birthright Research Centre for Fetal Medicine
Division of Women's Health
King's College London,
Denmark Hill, London SE5 9RS
Telephone +44 20 3299 8256
Fax +44 20 7733 9543
Mail: chiu_yee_leona.poon@kcl.ac.uk

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Abstract

Objective: To investigate the potential value of combined screening by maternal characteristics and medical history (maternal factors), estimated fetal weight (EFW), uterine artery pulsatility index (PI), mean arterial pressure (MAP) and serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) at 30-34 weeks' gestation in the prediction of small for gestational age (SGA) neonates, in the absence of preeclampsia (PE).

Methods: Screening study in singleton pregnancies at 30-34 weeks including 469 that delivered SGA neonates and 9,003 cases that were unaffected by SGA, PE or gestational hypertension (normal). Multivariable logistic regression analysis was used to determine if uterine artery PI, MAP and serum PlGF or sFlt-1, individually or in combination, improved the prediction of SGA neonates provided by screening with maternal factors and EFW.

Results: In the SGA group, compared to the normal group, the mean $\log_{10}$ multiple of the median (MoM) values of uterine artery PI, MAP and serum sFlt-1 were significantly higher and $\log_{10}$ MoM PlGF was lower. Multivariable logistic regression analysis demonstrated that in the prediction of SGA $<5^{th}$ delivering at <5 weeks and at $\geq$5 weeks of assessment there were significant independent contributions from maternal factors, EFW, uterine artery PI, MAP, serum PlGF and serum sFlt-1, but the best prediction was provided by a combination of maternal factors, EFW, uterine artery PI, MAP and serum PlGF without inclusion of sFlt-1 Combined screening predicted, at 10% false positive rate, 89%, 94%, 96% of SGA neonates delivering at 32-36 weeks' gestation with birth weight $<10^{th}$, $<5^{th}$ and $<3^{rd}$ percentiles, respectively; the respective detection rates of combined screening for SGA neonates delivering at $\geq$37 weeks were 57%, 65% and 72%.

Conclusion: Combined screening by maternal factors and biophysical and biochemical markers at 30-34 weeks' gestation can identify a high proportion of pregnancies that subsequently deliver SGA neonates.

Introduction

Small for gestational age (SGA) neonates are at increased risk of perinatal mortality and morbidity, but the risks can be substantially reduced if the condition is identified prenatally, because in such cases close monitoring and appropriate timing of delivery and prompt neonatal care can be undertaken [1]. The traditional approach of identifying pregnancies at high-risk of delivering SGA neonates is maternal abdominal palpation and/or serial measurements of symphysial-fundal height, but the performance of such screening is poor with detection of <30% of affected fetuses [2,3].

A routine third-trimester scan is by far superior to abdominal palpation in identifying pregnancies at high-risk of delivering SGA neonates. A study in 30,849 singleton pregnancies, examined the performance of routine screening for delivery of SGA neonates in the absence of preeclampsia (PE) by a combination of maternal characteristics and medical history (maternal factors) and estimated fetal weight (EFW) from the measurements of fetal head circumference (HC), abdominal circumference (AC) and femur length (FL) at 30-34 weeks' gestation [4]. Combined screening predicted, at 10% false positive rate (FPR), 87% and 58% of SGA neonates with birth weight <5th percentile (SGA<5th) delivering at <5 and at ≥5 weeks of assessment, respectively [4]. In the same study population of 30,849 pregnancies, in the SGA group uterine artery pulsatility index (PI) and mean arterial pressure (MAP) were increased and combined screening with maternal factors, EFW, uterine artery PI and MAP predicted 91% and 60% of SGA <5th, at 10% FPR, delivering at <5 and at ≥5 weeks of assessment, respectively [5]. A study of 9,850 pregnancies at 30-34 weeks, reported that in the SGA group maternal serum placental growth factor (PlGF) was decreased and soluble fms-like tyrosine kinase-1 (sFlt-1) was increased and that combined screening with maternal factors, EFW and serum biochemistry predicted 93% and 64% of SGA <5th percentile, at 10% FPR, delivering at <5 and at ≥5 weeks of assessment, respectively [6].

The objective of this study is to examine the potential value of combined screening by maternal factors, EFW, uterine artery PI, MAP, serum PLGF and serum sFlt-1 at 30-34 weeks' gestation in the prediction of pregnancies that deliver SGA neonates in the absence of PE.

Methods

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for their routine hospital visit at 30^{+0}-34^{+6} weeks' gestation at King's College Hospital, London, and Medway Maritime Hospital, Kent, between June 2011 and December 2013. The visit included first, recording of maternal characteristics and medical history, second, calculation of EFW from ultrasound measurements of fetal HC, AC and FL, third, measurement of uterine artery PI at the apparent crossover with the external iliac arteries by transabdominal color Doppler ultrasound [7], fourth, measurement of MAP by automated devices [8], and fifth, measurement of maternal serum concentrations of PlGF and sFlt-1 (Cobas e411, Roche Diagnostics, Penzberg, Germany). Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal HC at 19-24 weeks [9,10]. Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the Ethics Committee of each participating hospital.

Patient characteristics

Patient characteristics recorded included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous or

assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes or no), medical history of chronic hypertension (yes or no), diabetes mellitus (yes or no), systemic lupus erythematosus (SLE) or anti-phospholipid syndrome (APS), family history of PE in the mother of the patient (yes or no) and obstetric history including parity (parous or nulliparous if no previous pregnancies at $\geq$ 24 weeks' gestation), previous pregnancy with PE (yes or no), previous pregnancy with SGA (yes or no) and the time interval between the last delivery and conception of the current pregnancy in years. The maternal weight and height were measured.

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The primary outcome of the study was SGA without PE. The newborn was considered to be SGA if the birth weight was less than the 5th percentile after correction for gestational age at delivery (SGA <5th) [11]. The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy [12]. The obstetric records of all women with pre-existing or pregnancy associated hypertension were examined to confirm if the condition was chronic hypertension, PE or GH.

Statistical analysis

The observed measurements of EFW were expressed as Z-scores, corrected for gestational age [11]. The values of uterine artery PI, MAP and serum PlGF and sFlt-1 were $\log_{10}$ transformed to make their distributions Gaussian. Each measured value in the outcome groups was expressed as a multiple of the normal median (MoM) after adjustment for those characteristics found to provide a substantial contribution to the $\log_{10}$ transformed value [13-16]. Mann Whitney-U test was used to compare the median MoM values of the biomarkers between the outcome groups and regression analysis was used to determine the significance of association between $\log_{10}$ MoM of each biomarker with assessment to delivery interval and birth weight Z-score.

The *a priori* risk for SGA <5th delivering at <5 weeks of assessment was determined using the algorithm derived from the multivariable logistic regression analysis of maternal characteristics and history as previously described [4]. Multivariable logistic regression analysis was then used to determine if the maternal factor-derived logit (*a priori* risk), EFW Z-score and $\log_{10}$ MoM value of each biomarker had a significant contribution in predicting SGA <5th delivering at <5 and at $\geq$5 weeks of assessment. The performance of screening was determined by receiver operating characteristic (ROC) curves. Similarly, the algorithm was used to determine the performance of screening for SGA defined by birth weight <10th percentile (SGA <10th) and SGA with birth weight <3rd percentile (SGA <3rd).

The statistical software package SPSS 22.0 (SPSS Inc.,Chicago, IL) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for all data analyses.

Results

The characteristics of the study population are presented in Table 1. Uterine artery PI, MAP and serum PlGF were measured in 9,472 pregnancies, including 469 (5.0%) with SGA neonates.

Normal pregnancy outcome

In the unaffected pregnancies with birth weight >5th percentile, the mean, standard deviation

and 5th, 10th, 90th and 95th percentiles of log_{10} MoM values of each biomarker are shown in sTable 1.

Correlations between log_{10} MoM values of uterine artery PI, MAP, PlGF and sFlt-1 in the normal group are shown in sTable 2 and correlations between log_{10} MoM values of each biomarker with gestational age at delivery, assessment to delivery interval and birth weight Z-score are shown in sTable 3.

Small for gestational age

In the SGA <5th group delivering at <5 weeks and ≥5 weeks of assessment, compared to the normal group, the mean log_{10} multiple of the median (MoM) values of uterine artery PI, MAP and serum sFlt-1 were significantly higher and log_{10} MoM PlGF was lower (sTable 4). Correlations between log_{10} MoM values of each biomarker with gestational age at delivery, assessment to delivery interval and birth weight Z-score are shown in sTable 3.

Prediction of SGA delivering at <5 and ≥5 weeks from screening

Multivariable logistic regression analysis demonstrated that in the prediction of SGA <5th delivering at <5 weeks and at ≥5 weeks of assessment there were significant independent contributions from maternal factors, EFW, uterine artery PI, MAP, serum PlGF and serum sFlt-1, but the best prediction was provided by a combination of maternal factors, EFW, uterine artery PI, MAP and serum PlGF without inclusion of sFlt-1 (sTable 5 and 6).

The areas under ROC (AUROC) and the DRs, at FPRs of 5% and 10%, of SGA <10th, SGA <5th and SGA <3rd delivering at <5 and at ≥5 weeks of assessment in screening by maternal factors, EFW Z-score, uterine artery PI, MAP and serum PlGF are given in sTable 6.

Performance of screening for SGA delivering at 32-36 and ≥37 weeks

In combined screening by maternal factors, EFW, uterine artery PI, MAP and serum PLGF at 30-34 weeks' gestation, the DRs at FPR of 5% and 10% and FPR for DR of 80%, 90% and 100%, of SGA neonates with birth weight <10th, <5th and <3rd percentiles delivering at 32-36 and ≥37 weeks are shown in Table 2 and the ROC curves are shown in Figures 1 and 2.

Discussion

Main findings of the study

The findings of this study confirm that in pregnancies that deliver SGA neonates in the absence of PE, uterine artery PI, MAP and serum sFlt-1 at 30-34 weeks' gestation are increased and EFW and serum PLGF are decreased [4-6]. The alterations in serum metabolites were related to the severity of the disease reflected in the birth weight Z-score. In the prediction of SGA the only biochemical marker with significant contribution, in addition to maternal factors, fetal biometry, uterine artery PI and MAP, was PLGF.

Combined screening by maternal factors, fetal biometry, uterine artery PI, MAP and serum PlGF at 30-34 weeks' gestation, predicted, at 10% FPR, 89%, 94%, 96% of SGA neonates delivering at 32-36 weeks' gestation with birth weight <10th, <5th and <3rd percentiles, respectively; the respective DRs of combined screening for SGA neonates delivering at ≥37 weeks were 57%, 65% and 72%.

Strengths and limitations of the study

The strengths of this third-trimester screening study for SGA in the absence of PE are first, examination of a large population of pregnant women attending for routine care in a gestational age range which is widely used for the assessment of fetal growth and wellbeing, second, use of a specific methodology and appropriately trained doctors to measure uterine artery PI and MAP, third, measurement of maternal serum concentration of metabolites that have been shown to be altered in pregnancies associated with impaired placentation, fourth, expression of the values of biomarkers as MoMs after adjustment for factors that affect the measurements and fifth, use of Bayes theorem to combine the prior risk from maternal characteristics and medical history with biomarkers to estimate patient-specific risks and the performance of screening for SGA of different severities delivering at selected intervals from the time of assessment.

The major limitation of the study is that the results of the 30-34 weeks' scan were made available to the obstetricians of the patients who would have taken specific actions of further monitoring for the cases of suspected SGA and consequently the performance of screening, especially for severe SGA delivering at <5 weeks from assessment, would be positively biased.

Comparison with findings from previous studies

Previous studies examining pregnancies with SGA fetuses in the third-trimester reported that the outcome was worse in cases with Doppler evidence of increased, than normal, impedance to flow in the uterine arteries [17,18]. Several, mainly case-control studies, in the second- and third-trimesters of pregnancy reported that in pregnancies delivering SGA neonates serum PLGF is decreased and sFlt-1 is increased [19-24].

In our previous third-trimester screening studies we reported the performance of screening for SGA neonates by maternal factors and fetal biometry [4] and how this performance was improved by the addition of uterine artery PI and MAP [5] or serum PLGF and sFlt-1 [6]. In this study we examined the performance of screening by a combination of biophysical and biochemical markers.

Implications for clinical practice

In the proposed new pyramid of pregnancy care [25], an integrated clinic at 11-13 weeks' gestation, in which biophysical and biochemical markers are combined with maternal characteristics and medical history, aims to identify pregnancies at high-risk of developing PE and / or SGA and through pharmacological intervention, with such medications as low-dose aspirin, to reduce the prevalence of these complications [26,27]. In pregnancies with impaired placentation the use of low-dose aspirin beyond 16 weeks' gestation does not prevent the subsequent development of PE and / or SGA [26-28]. Consequently, the objective of screening at 22 weeks and in the third-trimester is not to prevent SGA, but rather to identify the high-risk group and through close monitoring of such pregnancies to minimize adverse perinatal events by determining the appropriate time and place for iatrogenic delivery.

This study has shown that in the assessment at 30-34 weeks, measurement of uterine artery PI, MAP and serum PlGF improves the performance of screening for SGA achieved by the combination of maternal factors and fetal biometry alone. Future studies will define the best approach for the management of the high-risk pregnancies identified by third-trimester screening and the extent to which such management could reduce the adverse perinatal outcome associated with such pregnancies.

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Table 1. Characteristics of the study population.

Characteristic	Normal (n=9,003)	SGA without PE	
		Delivery <5w (n=51)	Delivery ≥5w (n=418)
Maternal age in years, median (IQR)	31.1 (26.8-34.8)	31.2 (26.1-36.1)	29.6 (25.0-33.9)*
Maternal weight in Kg, median (IQR)	76.9 (68.9-87.0)	72.4 (65.9-86.0)	70.0 (62.6-79.5)*
Maternal height in cm, median (IQR)	165 (160-169)	162 (158-167)*	162 (157-166)*
Gestation at screening in weeks, median (IQR)	32.2 (32.0-32.5)	32.1 (31.9-32.6)	32.1 (32.0-32.4)*
Racial origin			
Caucasian, n (%)	6,658 (74.0)	31 (60.8)	254 (60.8)*
Afro-Caribbean, n (%)	1,644 (18.3)	13 (25.5)	112 (26.8)*
South Asian, n (%)	332 (3.6)	2 (3.9)	33 (7.9)*
East Asian, n (%)	176 (2.0)	1 (2.0)	8 (1.9)
Mixed, n (%)	203 (2.3)	4 (7.8)	11 (2.6)
Past obstetric history			
Nulliparous, n (%)	4,338 (48.2)	28 (54.9)	241 (57.7)*
Parous with no prior PE and SGA, n (%)	4,139 (46.0)	17 (33.3)	136 (32.5)*
Parous with prior PE no SGA, n (%)	271 (3.0)	1 (2.0)	7 (1.7)
Parous with prior SGA no PE, n (%)	230 (2.6)	4 (7.8)	29 (6.9)*
Parous with prior SGA and PE, n (%)	25 (0.3)	1 (2.0)	5 (1.2)*
Inter-pregnancy interval in years, median (IQR)	3.1 (2.1-5.1)	3.4 (2.4-8.2)	3.4 (2.3-5.6)*
Cigarette smoker, n (%)	844 (9.4)	9 (17.6)	94 (22.5)*
Conception			
Spontaneous, n (%)	8,712 (96.8)	48 (94.1)	406 (97.1)
Ovulation drugs, n (%)	81 (0.9)	2 (3.9)	4 (1.0)
In vitro fertilization, n (%)	210 (2.3)	1 (2.0)	8 (1.9)
Chronic hypertension	97 (1.1)	2 (3.9)	5 (1.2)
Diabetes mellitus, n (%)	90 (1.0)	2 (4.0)	3 (0.7)
Type 1, n (%)	38 (0.4)	1 (2.0)	0 (0.0)
Type 2, n (%)	52 (0.6)	1 (2.0)	3 (0.7)
SLE or APS, n (%)	15 (0.2)	0 (0.0)	1 (0.2)
Gestation at delivery in weeks, median (IQR)	40.1 (39.0-40.9)	36.5 (35.1-37.0)*	40.0 (39.0-40.9)
Birth weight in grams, median (IQR)	3,430 (3,144-3,750)	1,936 (1,770-2,198)*	2,604 (2,434-2,770)*
Birth weight in percentile, median (IQR)	50.6 (27.1-75.7)	2.2 (0.9-3.5)*	2.6 1.5-3.7)*

SGA = small for gestational age with birth weight <5th percentile; PE = preeclampsia; IQR = interquartile range; SLE = systemic lupus erythematosus; APS = antiphospolipid syndrome.

* Comparisons between outcome groups: Chi square test or Fisher exact test for categorical variables and Mann Whitney-U test or student t-test for continuous variables, with Bonferroni correction: * P<0.025

Table 2. Performance of screening for small for gestational age neonates with birth weight <10th, <5th and <3rd percentile delivering at 32-36 and ≥37 weeks' gestation in the absence of preeclampsia by a combination of maternal factors, estimated fetal weight, uterine artery pulsatility index, mean arterial pressure and serum placental growth factor at 30-34 weeks' gestation.

Outcome	DR (%)		FPR (%)		
	FPR 5%	FPR 10%	DR 100%	DR 90%	DR 80%
Delivery at 32-36 weeks					
SGA <10th percentile	81.5 (70.0-90.1)	89.2 (79.1-95.6)	59.8 (58.7-60.8)	13.5 (12.8-14.2)	4.7 (4.2-5.1)
SGA <5th percentile	82.9 (66.4-93.4)	94.3 (80.8-99.3)	24.0 (23.1-24.9)	6.0 (5.5-6.5)	3.6 (3.2-4.0)
SGA <3rd percentile	86.4 (65.1-97.1)	95.5 (77.2-99.9)	16.1 (15.3-16.8)	6.0 (5.5-6.5)	1.1 (0.9-1.4)
Delivery at ≥37 weeks					
SGA <10th percentile	43.9 (40.6-47.2)	57.4 (54.1-60.7)	99.9 (99.8-100.0)	42.2 (41.1-43.3)	27.2 (26.2-28.1)
SGA <5th percentile	49.4 (44.5-54.3)	65.3 (60.5-69.9)	89.6 (88.9-90.2)	34.5 (33.6-35.5)	20.8 (20.0-21.7)
SGA <3rd percentile	55.0 (48.6-61.3)	71.5 (65.4-77.0)	78.6 (77.8-79.5)	30.2 (29.3-31.2)	15.3 (14.5-16.0)

DR = detection rate; FPR = false positive rate; SGA = small for gestational age.

Figure legends

Figure 1. Receiver operating characteristics curves of maternal factors (black line), maternal factors with estimated fetal weight (blue line) and maternal factors, estimated fetal weight, uterine artery pulsatility index, mean arterial pressure and serum placental growth factor (red line) in the prediction of small for gestational age neonates with birth weight 10th (left) <5th (middle) and 3rd (right) percentile delivering at 32-36 weeks' gestation.

Figure 2. Receiver operating characteristics curves of maternal factors (black line), maternal factors with estimated fetal weight (blue line) and maternal factors, estimated fetal weight, uterine artery pulsatility index, mean arterial pressure and serum placental growth factor (red line) in the prediction of small for gestational age neonates with birth weight 10th (left) <5th (middle) and 3rd (right) percentile delivering at $\geq$37 weeks' gestation.

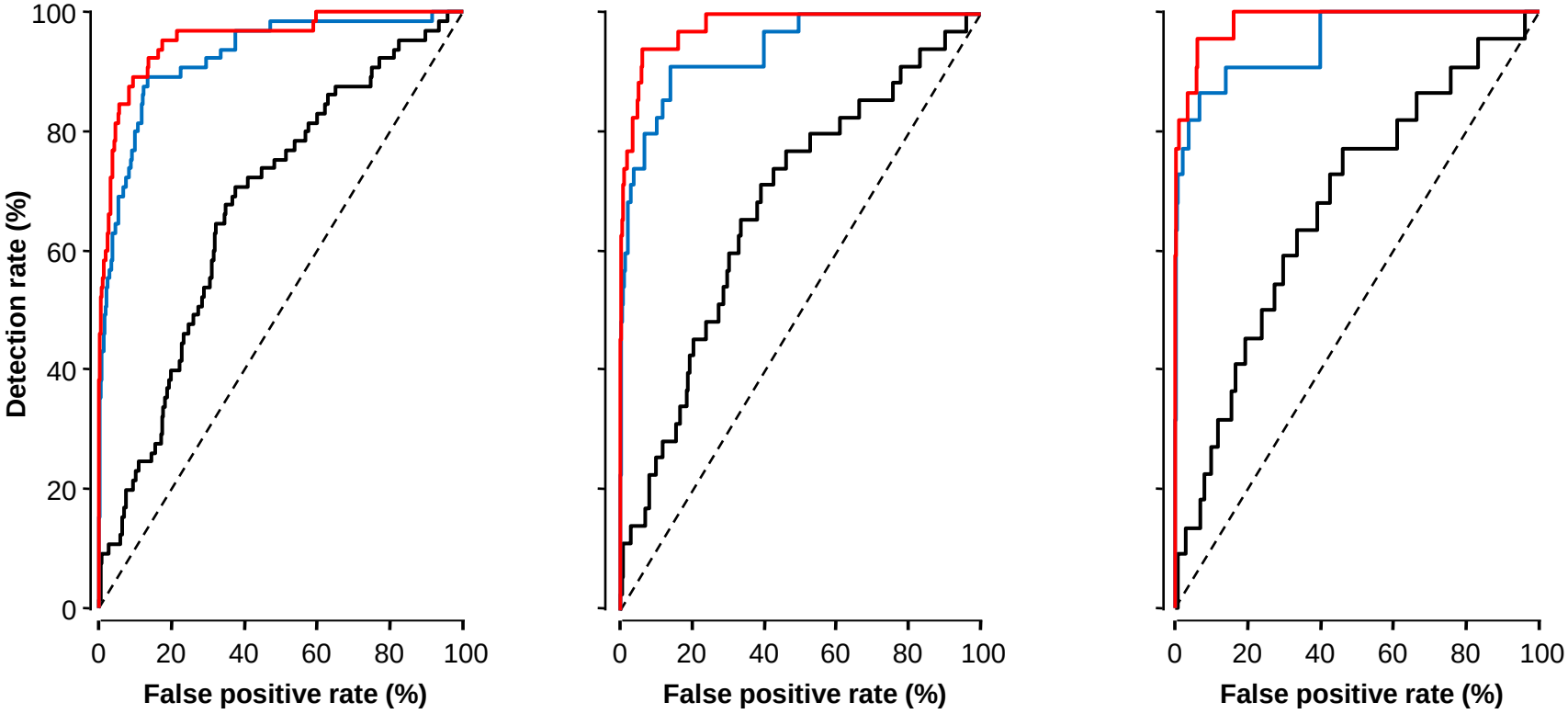
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Figure 1

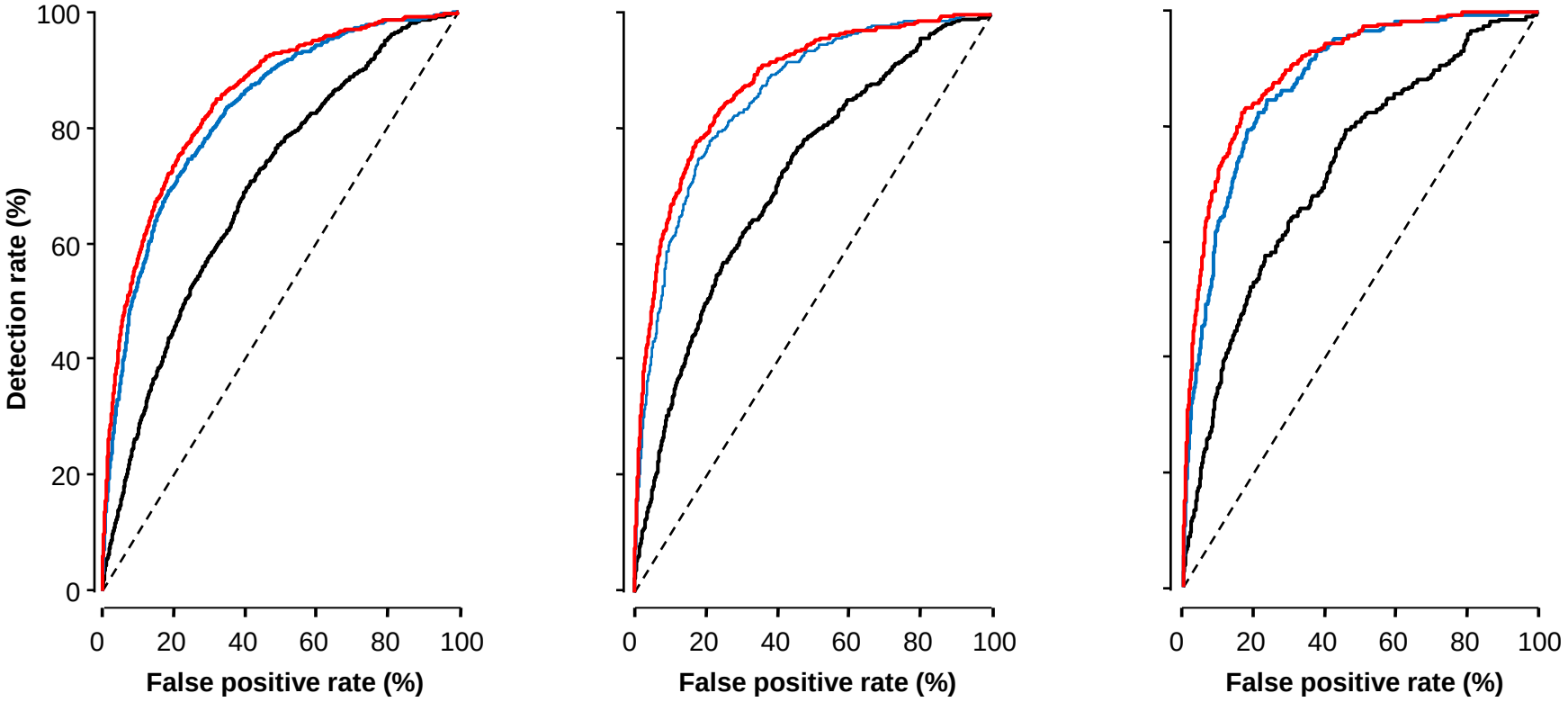
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Figure 2