

**Risk stratification for early-onset fetal growth restriction in women with abnormal serum biomarkers: a retrospective cohort study.**

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20 **Supplementary table 1: Population prevalence of adverse pregnancy outcomes**

	N	%	95% C.I.
SMH births (2011-2018)	67065		
Total serum screening results	29796	44.4%	
Combined	20846	67.0%	
Second Trimester	8950	30.0%	
SMH Births with outcome >22 weeks	65192		
Live Birth	64729	99.3%	
Perinatal Death	436	0.7%	0.6-0.7
FGR (<3rd Centile)	4491	6.9%	6.7-7.1
SGA (<10th Centile)	12355	19.0%	18.6-19.2
Birth <34 weeks	1582	2.4%	2.4-2.6
eFGR	427	0.67%	0.6-0.7

21 C.I., confidence interval; SMH, St Mary's Hospital; EDD, estimated delivery date; FGR, fetal  
 22 growth restriction; SGA, small for gestational age; eFGR, early-onset fetal growth restriction  
 23

24 **Supplementary Table 2: Performance of maternal serum biomarker MoM thresholds for the prediction of FGR and early-onset FGR in SMH**

25 **hospital population 2011-2018.**

		All FGR					eFGR							
Threshold	Cut-off	AUC/prevalence	Sens	Spec	PPV	NPV	AUC/prevalence	Sens	Spec	PPV	NPV	Screen +ve 10,000*	Number of eFGR detected†	Number needed to screen to detect 1 case‡
	PAPP-A													
<5th(1–3)	0.415	0.602 1007/17882 (5.6%)	13.3	94.4	12.4	94.8	0.657 79/17882 (0.4%)	25.3	94	1.84	99.65	609	10/44	59
SMH 5th	0.392		11.9	95.5	13.6	94.8		24.0	95.1	2.13	99.65	500	10/44	51
SMH 3rd	0.341		8.8	97.3	16.5	94.7		17.7	97.1	2.65	99.63	300	7/44	41
	Inhibin													
SMH 95th (current)(1,3,4)	2.03	0.547 559/7628 (7.3%)	10.9	95.4	15.4	93.3	0.737 52/7628 (0.7%)	27.6	95.1	3.68	99.49	500	17/67	29
SMH 97th	2.31		7.8	97.3	17.8	93.2		20.7	97.1	4.6	99.45	300	13/67	23
SMH 99th	3.03		4.2	99.3	30.2	93.1		13.8	99.1	9.3	99.42	87	9/67	10
	αFP													
SMH 95th	1.74	0.575 561/7629 (7.4%)	11.8	95.5	16.9	93.4	0.705 52/7629 (0.7%)	22.4	95.1	3	99.45	500	14/67	36
SMH 97th	1.90		8.8	97.4	20.8	93.3		19.0	97.1	4.23	99.44	300	12/67	25
Current(1,3,4)	2.2		4.4	98.7	20.5	93.1		15.5	98.57	6.82	99.43	133	10/67	14

26 \*Theoretical population of 10,000 screened women.

27 †Based on SMH prevalence of eFGR of 44/10000 in women with a 1<sup>st</sup> Trimester screen & 67/10000 in women having a 2<sup>nd</sup> Trimester screen,  
28 and assuming all women attend a placental screen with a detection rate of 93% for eFGR (estimated fetal weight and uterine artery Doppler at  
29 21-24 weeks).  
30 ‡Number of placental screen scans (21-24) weeks which would need to be performed to detect 1 case of eFGR.  
31 FGR, fetal growth restriction; eFGR, early-onset fetal growth restriction; AUC, area under the curve; Sens, sensitivity; Spec, specificity; PPV,  
32 positive predictive value; NPV, negative predictive value; SMH, St Mary's Hospital; PAPP-A, pregnancy associated plasma protein-A,  $\alpha$ FP, alpha  
33 fetoprotein.

**Supplementary Table 3: Univariate associations between baseline characteristics and 21-24 week ultrasound findings for early-onset FGR.**

Variable	N	P	OR	95% C.I.
Customised EFW centile† (increment 5 centiles)	1196	<0.001*	0.66	0.58-0.75
Non-customised EFW centile (increment 5 centiles)	1196	<0.001*	0.63	0.54-0.73
Umbilical artery PI (increment 0.1)	1186	<0.001*	1.98	1.55-2.51
Umbilical artery RI (increment 0.1)	1182	<0.001*	7.08	3.06-16.26
Uterine artery PI† (increment 0.1)	1196	<0.001*	1.47	1.34-1.60
Uterine artery RI (increment 0.1)	1196	<0.001*	6.48	3.93-10.70
Placental depth	1196	0.001*	1.76	1.27-2.44
Placental surface area	1196	<0.001*	0.97	0.96-0.98
PEC (width x width / depth)	1196	<0.001*	0.93	0.91-0.96
Maternal BMI	914	0.848	1.01	0.92-1.10
Maternal sBP at first prenatal visit	1135	0.031*	1.03	1.00-1.06
Maternal dBP at first prenatal visit	1132	0.045*	1.04	1.00-1.09
Maternal ethnicity (compared to white)	1196			
Black	692	0.606	1.35	0.43-4.19
Asian	211	0.220	1.79	0.71-4.55
Other	134	0.782	1.20	0.34-4.26
Maternal parity (nullip vs multip)	1196	0.335	0.68	0.31 – 1.49

OR, odds ratio; C.I., confidence interval; EFW, estimated fetal weight; PI, pulsatility index; RI, resistance index; PEC, placental efficiency coefficient; BMI, body mass index; sBP, systolic blood pressure; dBP, diastolic blood pressure.

\*Statistically significant

†Retained for use in the multivariable model

**Supplementary Table 4: 21-24 week placental screen test performance for early-onset**

**FGR, with and without PSA.**

	Without placental surface area		
	True +ve	True -ve	
Test +ve	25	127	PPV=16.5%
Test -ve	2	1042	NPV=99.8%
	Sensitivity=92.6%	Specificity=89.1%	
	+LR = 8.53	-LR = 0.08	
	With placental surface area		
	+ve	True -ve	
Test +ve	26	120	PPV=17.8%
Test -ve	1	1049	NPV=99.9%
	Sensitivity=96.3%	Specificity=89.7%	
	+LR = 9.38	-LR = 0.04	

PPV, positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; -LR, negative likelihood ratio.

**Supplementary Table 5: Multivariable logistic regression coefficients for 1196 women who underwent a 21-24 week placental screen.**

	Coefficient	Standard Error	z	P	95% C.I.
Log mean uterine artery PI	4.39	0.77	5.66	<0.001	2.87 – 5.91
Log EFW centile	-0.71	0.17	-4.24	<0.001	-1.04 – -0.38
Constant	-2.08	0.66	-3.17	0.002	-3.37 – -0.79

C.I., confidence interval; PI, pulsatility index; EFW, estimated fetal weight; PSA, placental surface area.

**Supplementary Table 6: Prevalence of adverse pregnancy outcomes in the test-negative and test-positive groups**

Outcome	Negative placental screen (n=1044)	Positive placental screen (n=152)	
	N (%)	N (%)	OR [95% C.I.]
<b>SGA &lt;10<sup>th</sup> centile</b>	203 (19.4%)	90 (59.2%)	6.01 [4.20-8.60]
<b>FGR &lt;3<sup>rd</sup> centile</b>	66 (6.3%)	57 (37.5%)	8.89 [5.89-13.43]
<b>Preterm &lt;36 weeks</b>	57 (5.5%)	50 (32.9%)	8.49 [5.52-13.06]
<b>Preterm &lt;34 weeks</b>	17 (1.6%)	34 (22.4%)	17.41 [9.43-32.12]
<b>Iatrogenic preterm &lt;34 weeks</b>	7 (0.7%)	24 (15.8%)	27.78 [11.73-65.75]
<b>Preterm FGR (3<sup>rd</sup> centile) &lt;34 weeks</b>	2 (0.2%)	25 (16.5%)	102.56 [24.01-438.10]
<b>Stillbirth</b>	5 (0.5%)	7 (4.6%)	10.03 [3.14-32.02]
<b>Stillbirth &lt; 34 weeks</b>	2 (0.2%)	7 (4.6%)	25.15 [5.18-122.24]

OR, odds ratio; C.I., confidence interval; SGA, small for gestational age; FGR, fetal growth restriction.

# Supplementary Table 7: Details of the pregnancies with false negative placental screens

(n=2) and those who had negative screens who delivered <34 weeks >3<sup>rd</sup> centile

Mean uterine artery PI	EFW centile	Abnormal maternal serum biomarker	Birth gestation (weeks + days)	BW centile	Indication for delivery	Placental histology
1.06	22.2	PAPP-A	26+3	0.0	Elective Caesarean Section for absent umbilical artery EDF, static growth and abnormal NST	No histology available
0.65	88.6	βHCG	25+3	0.7	Emergency Caesarean Section for placental abruption; EFW at placental screen was incorrect	No histology available
0.69	0.7	PAPP-A	32+0	4.6	Elective Caesarean Section for abnormal umbilical artery Dopplers and reduced fetal movements	MVM
0.68	29.0	βHCG	30+2	4.6	Premature rupture of membranes and abnormal NST	No histology available
1.16	24.9	PAPP-A	32+4	5.8	Stillbirth following placental abruption	Focal area of CHIV; evidence of abruption; no MVM.
0.99	49.3	PAPP-A	32+2	6.1	Spontaneous preterm labour	No histology available
0.85	32.4	PAPP-A	33+2	9.1	Spontaneous preterm labour; large fibroid	No histology available
0.56	64.5	PAPP-A	33+2	14.3	Spontaneous preterm labour	No histology available
1.09	86.9	PAPP-A	23+5	16.5	Spontaneous preterm labour	No histology available
0.91	51.0	PAPP-A	33+2	17.4	Planned Caesarean Section due to absent umbilical end diastolic flow	Inconclusive - possible CHIV or possible MVM
1.07	59.0	Inhibin	32+5	19.2	Planned Caesarean section for pre-eclampsia; normal fetal growth trajectory	MVM
0.65	61.4	PAPP-A	33+2	20.6	Normal fetal growth trajectory; stillbirth 1 week after a follow-up scan	CHIV
0.77	13.4	Inhibin	25+0	27.2	Spontaneous preterm labour	CHIV
1.11	80.8	PAPP-A	31+6	46.9	Spontaneous preterm labour	
1.05	88.5	Inhibin	32+4	50.1	Spontaneous preterm labour	No histology available
0.79	50.7	αFP & inhibin	26+2	58.1	Spontaneous preterm labour	Chorioamnionitis
0.65	64.8	PAPP-A	32+0	100.0	Spontaneous preterm labour	No histology available

PI, pulsatility index; EFW, estimated fetal weight; BW, birthweight; βHCG, beta human chorionic gonadotropin; PAPP-A, pregnancy-associated plasma protein-A; αFP, alpha-fetoprotein; EDF, end-diastolic flow; NST, non stress test; MVM, maternal vascular malperfusion; CHIV, chronic histiocytic intervillitis.

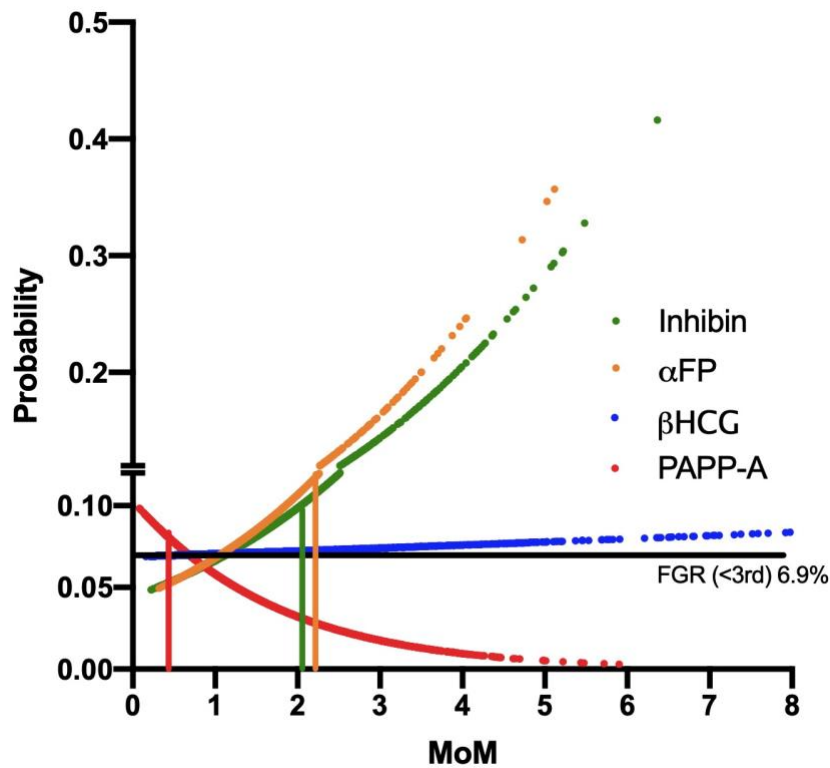


68 **Supplementary table 8: Details of the pregnancies complicated by stillbirth**

Placental screen	Gestation at birth (weeks + days)	Birthweight centile	Placental histology	Preventable?	Other details
Positive	22+6	0.0	Nil available	Not preventable	Mother had CREST syndrome
Positive	27+2	0.9	Nil available	Not preventable	Mother was homozygous for Factor V Leiden
Positive	26+0	0.0	MVM	Not preventable	Mother had antiphospholipid syndrome
Negative	40+3	3.9	Nil available	Possibly preventable	Normal scan at 35+6 weeks; transferred care; no growth after last scan
Negative	32+4	5.8	Focal area of CHIV; no MVM; abruption	Not preventable	Placental abruption
Positive	25+2	0.0	Nil available	Not preventable	-
Negative	37+3	54.0	Nil available	Possibly preventable	Delivered elsewhere
Positive	25+2	0.0	Possible MVM (inconclusive)	Not preventable	-
Negative	42+1	8.7	MVM	Preventable	-
Positive	33+6	35.7	No focal pathology seen	Possibly preventable	-
Negative	33+2	20.6	Fresh haemorrhage; no MVM	Not preventable	Placental abruption
Positive	33+2	0.1	MVM	Possibly preventable	-

69 CREST, limited scleroderma; MVM, maternal vascular malperfusion; CHIV, chronic histiocytic  
70 intervillitis.

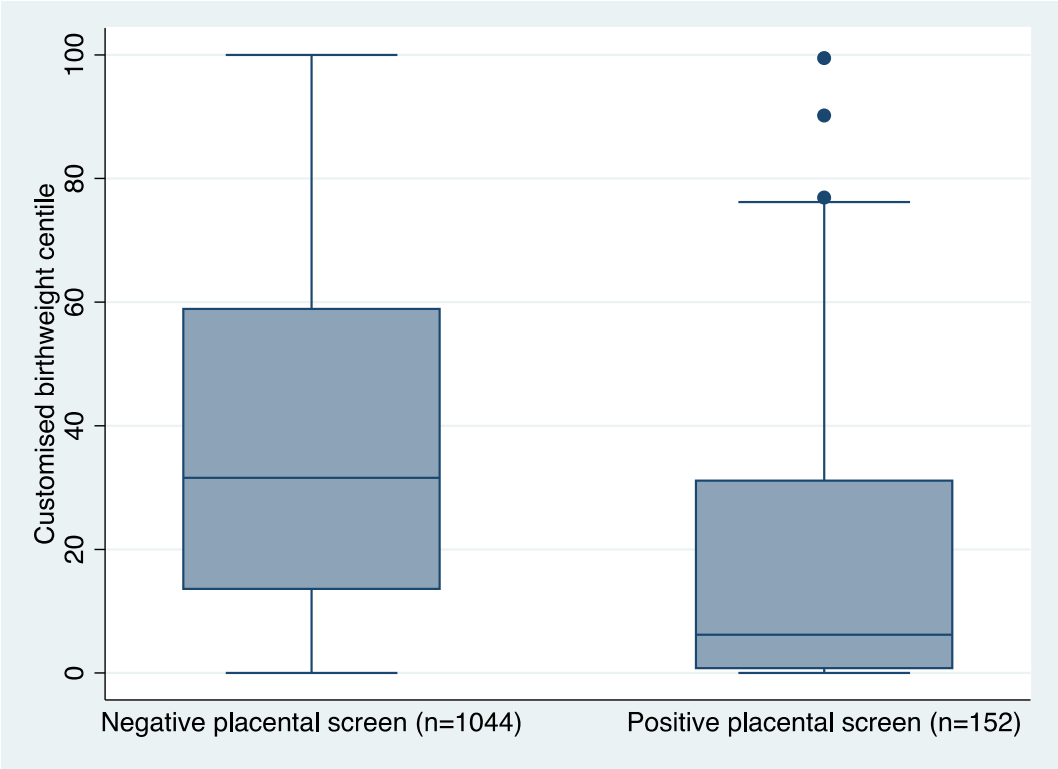
**Supplementary Figure 1: Probability of fetal growth restriction (<3rd centile) generated from univariate analysis of each biomarker.**



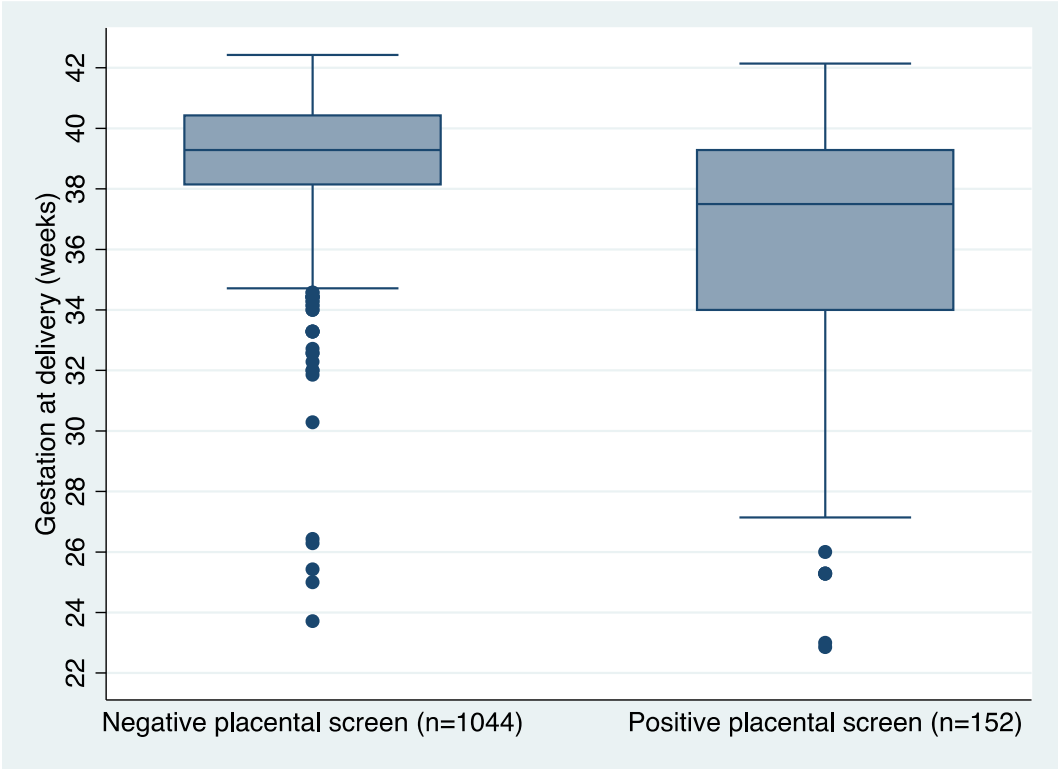
The vertical markers indicate the threshold used to trigger referral for a 21-24 placental screen scan.

$\alpha$ FP, alpha fetoprotein,  $\beta$ HCG, beta-human chorionic gonadotrophin; PAPP-A, pregnancy-associated plasma protein-A; ; FGR, fetal growth restriction; MoM, multiple of the median.

80 **Supplementary Figure 2: Difference in customised birthweight centile between those who**  
81 **test negative and those who test positive ( $p<0.001$ )**



84 **Supplementary Figure 3: Difference in gestational age at delivery between those who test**  
85 **negative and those who test positive ( $p<0.001$ )**



## References

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