Use of Placental Growth Factor for Trisomy 21 Screening in Pregnancy: A Systematic Review

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Abstract

Background Prenatal serum screening is an important modality to screen for aneuploidy in pregnancy. The addition of placental growth factor (PLGF) to screen for trisomy 21 remains controversial.

Objective To determine whether the addition of PLGF to combined serum aneuploidy screening improves detection rates (DRs) for trisomy 21.

Study Design We performed a systematic review of the literature until October 2019 to determine the benefits of adding PLGF to prenatal screening. We performed a goodness-of-fit test and retrieved the coefficient of determinations (R^2) as a function of false positive rates (FPRs), providing mean-weighted improvements in the DRs after accounting for PLGF levels.

Results We identified 51 studies, of which 8 met inclusion criteria (834 aneuploidy cases and 105,904 euploid controls). DRs were proportional to FPR across all studies, ranging from 59.0 to 95.3% without PLGF and 61.0 to 96.3% with PLGF (FPR 1–5%). Goodness-of-fit regression analysis revealed a logarithmic distribution of DRs as a function of the FPR, with $R^2 = 0.109$ (no PLGF) and $R^2 = 0.06$ (PLGF). Two-sample Kolmogorov–Smirnov's test reveals a p-value of 0.44. Overall, addition of PLGF improves DRs of 3.3% for 1% FPR, 1.7% for 3% FPR, and 1.4% for 5% FPR, respectively.

Conclusion Addition of PLGF to prenatal screening using serum analytes mildly improves trisomy 21 DRs as a function of FPRs.

Keywords

► PLGF
► placental growth factor
► trisomy 21
► prenatal screening
► aneuploidy

Placental growth factor (PLGF) is a human protein encoded by the *PGF* gene, which is a member of the vascular endothelial growth factor family, and is implicated in the angiogenesis and trophoblastic invasion of the maternal spiral arteries during placentation in early pregnancy.[1] Maternal serum levels of PLGF at 11 to 13 weeks' gestation are decreased in pregnancies with impaired placentation resulting in increased risks for preeclampsia and delivery of small for gestational age (SGA) and growth restricted (intrauterine growth restriction) neonates.[2]

Like other proteins used for either the combined first-trimester screening (cFTS) or the integrated prenatal screening (IPS) of aneuploidies, such as serum-free human chorionic gonadotropin (hCG), pregnancy-associated plasma protein A (PAPP-A), unconjugated estriol (uE3), and inhibin-A, PLGF is a protein of placental origin.[3] Indeed, the main source of PLGF during pregnancy is the placental trophoblast, where it plays a key role in trophoblastic growth and differentiation.[4]

With the advent of noninvasive prenatal testing (NIPT) using maternal serum cell-free fetal DNA, the use of cFTS/IPS

for detection of aneuploidy has decreased. However, serum screening remains the mainstay test for prenatal screening in the majority of patients in modern obstetrical practice in North America.[5] Depending on maternal age (MA), this approach confers detection rates (DRs) for trisomy 21 between 86 and 95%, and false-positive rates (FPRs) between 4 and 10%, indicating that there exists room for clinical improvement.[5] However, whether the addition of serum PLGF improves the DR of conventional serum screening with cFTS/IPS is controversial.[6] It is conceivable that, where NIPT is unavailable or unaffordable, a more sensitive serum screening test may benefit a proportion of the population who lack access to cell-free DNA testing.

In this study, we conducted a systematic review to determine whether the measurement of serum PLGF improves the DRs of prenatal serum screen analytes while reducing the FPRs for aneuploidy screening.

Materials and Methods

Literature Search and Study Selection
We performed a Medline, Embase, Google Scholar, Scopus, Institute for Scientific Information Web of Science, and Cochrane database search, as well as PubMed (www.pubmed.gov) search until the end of October 2019 from the past 20 years using the following Boolean search criteria: placental growth factor OR PLGF, Trisomy OR aneuploidy, AND prenatal screening OR serum screening OR integrated screening OR combined screening. We restricted our research to studies in English, in humans, and made no distinction regarding country or journal of origin. The reference lists and bibliographies of included studies were then searched for other salient and pertinent articles. Finally, manual searches of studies belonging to research teams having prior PLGF and aneuploidy screening were reviewed, and other pertinent studies were retrieved. We used the Newcastle–Ottawa scale to assess the risk of bias in the studies included (►Table 1).

Data Extraction
This review was modeled on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) statement. Our main inclusion criteria sought studies, which

directly assessed the effects of adding PLGF to the IPS by providing DRs and their corresponding FPR values. Given its greater incidence, we focused primarily on the effects of adding PLGF for the detection of trisomy 21 (Down's syndrome), and collected information on the different detection modalities and metabolites used in each study. We excluded studies which simply assessed levels of PLGF throughout pregnancy, as well as those which described methodologies for its measurement in the laboratory. Likewise, individual case reports and expert opinion articles were excluded.

Data Synthesis
We used SPSS 24.0.0 (IBM, 2017) to perform a goodness-of-fit test and retrieve a coefficient of determination (R^2) before and after the introduction of PGLF, as a function of FPRs. Finally, we performed a two-sample Kolmogorov–Smirnov's test to delineate differences in distributions of DR as function of FPR with and without PLGF and receiver-operating characteristic (ROC) curves are provided to illustrate sensitivities as a function of specificities in two studies. Forest plots were retrieved using Review Manager 5.3.5 (The Cochrane Collaboration, 2014). This study was exempted from Institutional Review Board approval because it is a systematic review and no identifiable patient data were used.

Results

We identified a total of 51 studies, of which 8 met inclusion criteria. A total of 3 prospective cohort studies and 5 case-control studies were included in our final analysis, for a total of 834 aneuploidy cases and 105,904 euploid control pregnancies. The search flowchart depicting the search strategy is illustrated in ►**Fig. 1**. All studies used the following modalities to estimate aneuploidy risk: MA, nuchal translucency (NT), PAPP-A, and β-hCG. One study by Wright et al[7] used α-fetoprotein (AFP) levels and Doppler evaluation of the ductus venosus (DV) in addition to the aforementioned modalities.

DRs were proportional to FPRs across all studies, and ranged from 59.0 to 95.3% without the use of PLGF and 61.0 to 96.3% after accounting for PLGF. Goodness-of-fit regression analysis revealed a distribution of DRs as a function of the FPR, which exhibited a logarithmic distribution with $R^2 = 0.109$ in the no PLGF group and $R^2 = 0.06$ in the

Table 1 Newcastle–Ottawa scale to assess the quality of studies included

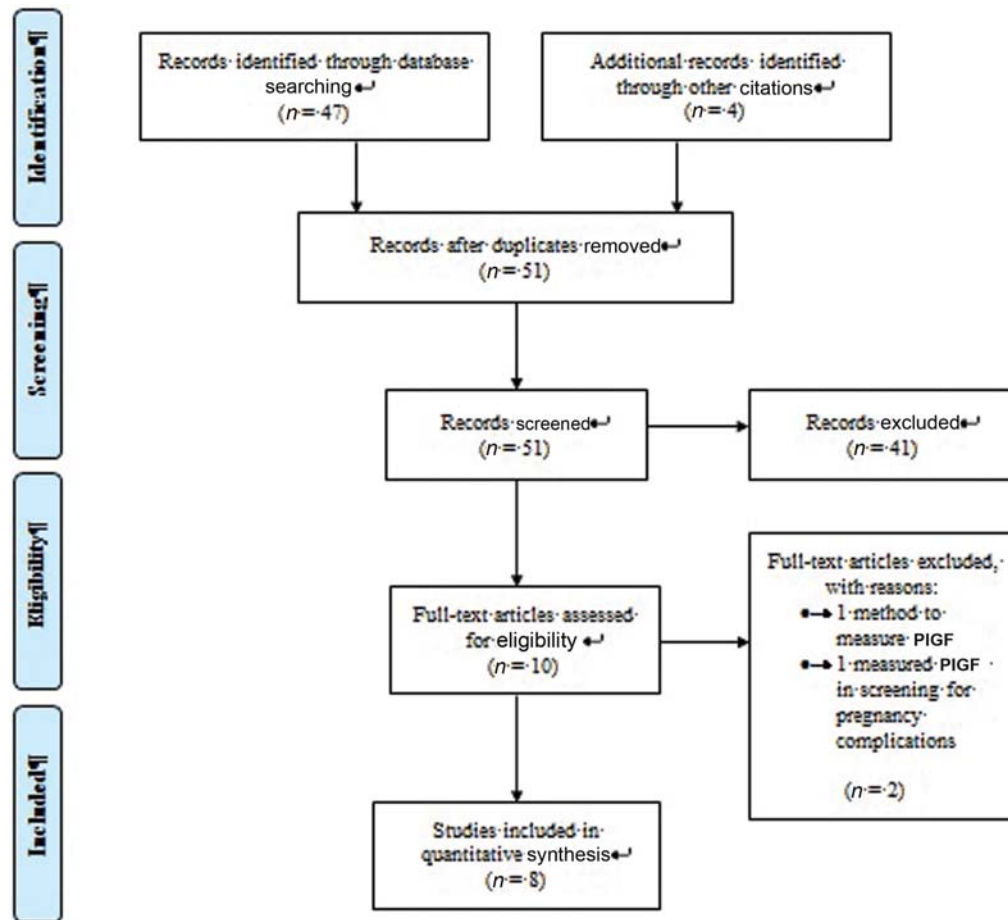| Study	Study design	Selection	Comparability	Exposure or outcome
Han et al (2016)[28]	Case–control	↓ ↓	–	↓ ↓
Pandya et al (2012)[32]	Prospective cohort	↓ ↓ ↓ ↓	–	↓ ↓ ↓
Cowans et al (2010)[21]	Case–control	↓ ↓	↓	↓ ↓
Kagan et al (2012)[18]	Case-control	↓	↓ ↓	↓ ↓
Zaragoza et al (2009)[22]	Case–control	↓	↓	↓ ↓
Wright et al (2014)[7]	Prospective cohort	↓ ↓ ↓ ↓	–	↓ ↓ ↓
Boutin et al (2018)[33]	Prospective cohort	↓ ↓ ↓ ↓	↓ ↓	↓ ↓ ↓
Koster et al (2011)[29]	Case–control	↓ ↓ ↓	↓ ↓	↓ ↓

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for the systematic review of studies. PLGF, placental growth factor.

PLGF group. These results indicate a poor fit of the model and large variation between DR for a given FPR across studies.

Two-sample Kolmogorov–Smirnov's test reveals a *p*-value of 0.44 indicating that curves with and without PLGF share a similar distribution. ►**Table 2** shows individual study data. ►**Fig. 2** reveals the improvements in DRs in serum screening samples containing PLGF. Upon addition of PLGF to the combined serum screening, average improvements in the DRs of 3.3% for a 1% FPR, 1.7% for a 3% FPR, and 1.4% for a 5% FPR were observed. Forest plot of DRs by study for a FPR of 3% is provided in ►**Fig. 3**. Finally, receiver-operating characteristic (ROC) curves pre/post-PLGF for studies by Han et al and Koster et al are shown in ►**Fig. 4**.

Discussion

The first-trimester prenatal screening based on MA, NT, and biomarkers such as PAPP-A and β-hCG has shown great efficacy, and this screening modality remains one of the main approach used in modern obstetrical practice.[8] In this study, we sought to determine whether the measurement of serum PLGF improves the DRs of prenatal serum screen analyses while reducing the FPRs for aneuploidy screening. Our findings suggest that the addition PLGF to prenatal screening test mildly improves trisomy 21 DRs between 1.4 and 3.3%.

PLGF is produced during pregnancy primarily in placental trophoblasts.[9] As mentioned previously, PLGF plays a significant role in trophoblast growth and differentiation. Trophoblast cells, especially extravillous trophoblast cells, are responsible for invading maternal arteries,[10] where proper development of blood vessels in the placenta is critical for embryonic development. Under normal physiologic conditions, PLGF is secreted at lower levels in other organs as well, including the thyroid, heart, lung, and skeletal muscle, where PLGF levels are affected by gestational age and maternal characteristics, including age, body mass index, racial origin, and smoking status.[11,12] In an uncomplicated pregnancy, PLGF concentrations are low in the first trimester and increase from weeks 11 to 12 and reach the peak at week 30, after which it decreases once again.[11]

In preeclampsia, PLGF levels are significantly lower at the time of diagnosis as well as during the progression of the clinical syndrome. The decrease in PLGF concentration is likely due to both a combination of reduced primary expression of PLGF and reduced free PLGF due to binding with soluble fms-like tyrosine kinase-1, which is raised in affected women.[13–15] Women are recognized at high risk for preeclampsia by using a combination of biomarkers, including PLGF, maternal characteristics, and uterine artery Doppler can benefit from using prophylactic aspirin in early

Table 2 Studies included in the systematic review

Author (year)	Study design	Number of patients		Screening modalities	Detection rate of screening *before* adding PLGF data	FPR	Detection rate of screening *after* adding PLGF data	FPR
		Trisomy 21	Euploid					
Han et al (2016)[28]	Case–control	42	558	MA+ NT + PAPP-A + β-hCG + PLGF	88.4% 93.4% 95.3%	1% 3% 5%	89.9% 94.6% 96.3%	1% 3% 5%
Pandya et al (2012)[32]	Prospective cohort	44	11,414	MA+ NT + PAPP-A + β-hCG + PLGF	85.0%	2.7%	88.0%[a]	2.6%
Cowans et al (2010)[21]	Case–control	70	375	MA+ NT + PAPP-A + β-hCG + PLGF	92.9% 94.5%	3% 5%	93.3% 94.9%	3% 5%
Kagan et al (2012)[18]	Case–control	100	409	MA+ NT + PAPP-A + β-hCG + PLGF	85.0%	2.7%	87.0%	2.6%
Zaragoza et al (2009)[22]	Case–control	90	609	MA+ NT + PAPP-A + β-hCG + PLGF	71.1% 76.7%	3% 5%	70.0% 80.0%	3% 5%
Wright et al (2014)[7]	Prospective cohort	324	86,917	MA+ NT + PAPP-A + β-hCG + PLGF + AFP + DV	87.0%	2.2%	93.3%	1.3%
Boutin et al (2018)[33]	Prospective cohort	13	4,765	MA+ NT + PLGF	–	–	92.0%	5%
Koster et al (2011)[29]	Case–control	151	847	MA+ NT + PAPP-A + β-hCG + PLGF	59.0% 71.0% 77.0%	1% 3% 5%	61.0% 73.0% 78.0%	1% 3% 5%

Abbreviations: AFP, α-fetoprotein; β-hCG, β human chorionic gonadotropin; DV, ductus venosus; FPR, false-positive rate; MA, maternal age; NT, nuchal translucency; PAPP-A, pregnancy-associated plasma protein; PLGF, placental growth factor.
[a]Risk cutoff of 1/100.

pregnancy.[16,17] Although in screening for preeclampsia, PLGF gives higher DRs than PAPP-A and free β-hCG, the study by Kagan et al[18] has shown that the replacement of PAPP-A or free β-hCG by PLGF results in a significant reduction in the DR of trisomy 21 as a consequence. A low level of PLGF is apparently both a consequence of early abnormal placentation and a causative factor to continued abnormal growth during the latter half of pregnancy. Therefore, in women without preeclampsia, who give birth to SGA infants also have, on average, lower levels of PLGF.[15]

In trisomy 21, several studies have examined PLGF, but disagreement exists on how levels differ in cases relative to controls. In the first trimester, some of the studies reported that PLGF levels in trisomy 21 increased,[19,20] and others reported decreased[21,22] relative to expected baseline. Likewise, in the second trimester, PLGF has also been found to be increased,[23] decreased,[24] and unchanged[25,26] in cases of trisomy 21. However, these inconsistencies in the literature may be due to which immunoassay methods were used to measure PLGF as mentioned in the article by Cowans et al.[27]

In our study, we focused primarily on the effects of adding PLGF for the detection of trisomy 21 and we found a large variation between DR for a given FPR across studies as a poor fit of the model. Also, our analysis reveals average improves trisomy 21 DRs between 1.4 and 3.3% for FPRs between 5 and 1%, respectively. Among the studies that were included in our research, we found only two studies that reported FPR as 1, 2, and 5%, which are Han et al[28] and Koster et al.[29] We performed ROC curves for these studies.

While PLGF may be a beneficial addition to the classical combined screening for preeclampsia and trisomy 21, it would increase the direct cost of such screening. However, one must consider the potential long-term savings associated with increased detection of trisomy 21 and subsequent termination of affected pregnancies. For example, care of an individual with trisomy 21 entails numerous medical visits and lifelong access to health care services, as well as to several social and housing services. The assessment of cost–benefit is also confounded by cost attributed to the care of a trisomy 21 affected child. Care for a child affected with trisomy 21 is assumed to bring about a cost of approximately U.S. $700,000 for the first 4 years of medical care in the United States,[30] with up to U.S. $125,000[31] depending on whether the child at birth did or did not have a heart defect. Which figure is used is going to have a significant impact of any cost–benefit analysis.

Moreover, one possible advantage of adding PLGF to serum screening exists in screening programs which only offer NIPT screening for a given risk level in the cFTS/IPS. As an example, in one of our clinics, we only offer NIPT contingent on the serum screen if the cFTS/IPS risk is more than 1:2,500. The implementation of that cutoff led to a reduction in the number of NIPT offered to around 3%, largely reducing cost and personnel use. This could represent a significant saving when applied to a provincial/state/national screening program. Thus, despite the mildly increased DR of trisomy 21 by adding PLGF to first-trimester screening, there may in fact be long-term cost savings of routinely adding this marker
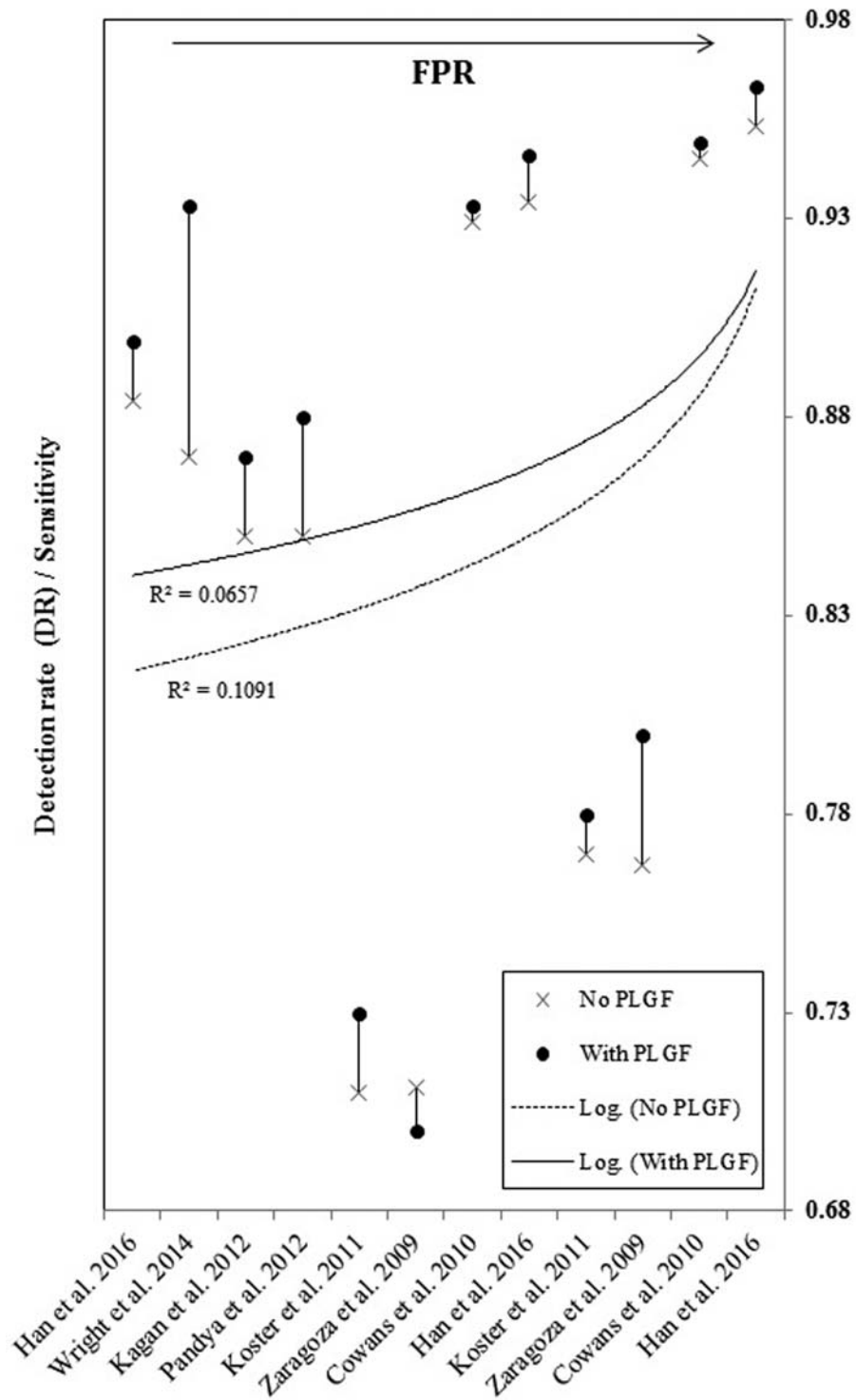
Fig. 2 Aneuploidy detection rates before and after PLGF from 1% to 5% FPR. FPR, false-positive rate; PLGF, placental growth factor.

both to patients and the health care system. Future studies should be aimed at addressing the cost–benefit analysis of implementing PLGF into routine prenatal screening. Furthermore, it is imperative that any time the efficacy of a treatment/technology/process is evaluated, that it be compared with a gold standard. Nowadays, the screening gold standard remains NIPT with cell-free DNA, with sensitivity and specificity for trisomy 21 approaching 100%. As we have reported in this study, unfortunately, the addition of PLGF to serum screening analytes does not approach these values. The difference in efficacy might be nevertheless justified in the lesser cost of serum analytes screening and the lack of widespread availability of NIPT as described earlier.

Strengths and Limitations

The strengths of this study are multiple and include the large number of patients analyzed, the consistency of findings
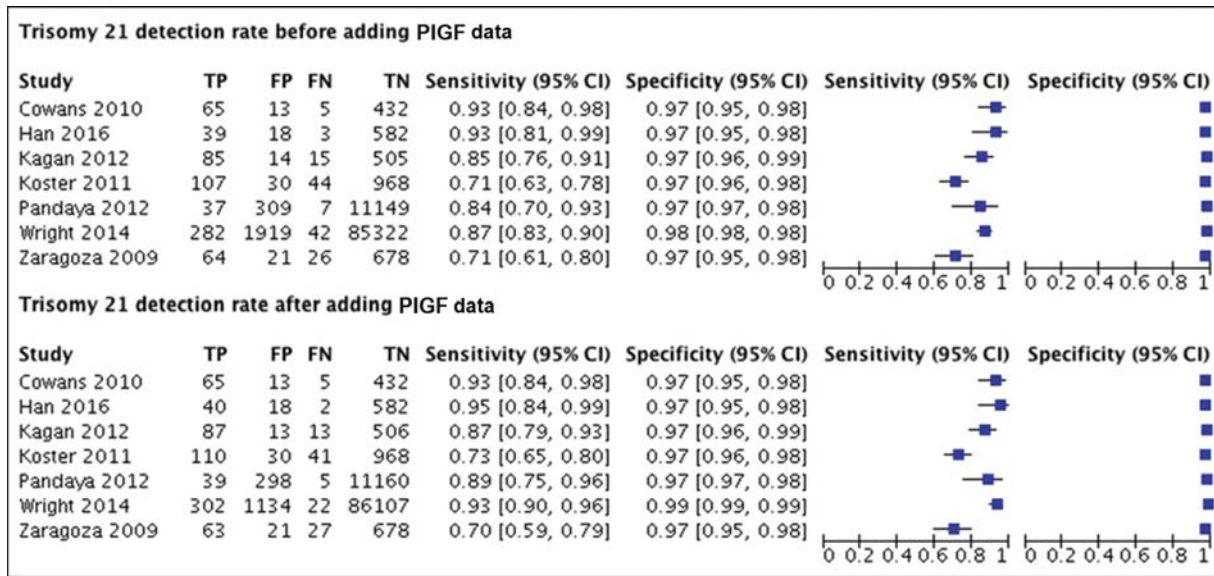
Trisomy 21 detection rate before adding PIGF data

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cowans 2010	65	13	5	432	0.93 [0.84, 0.98]	0.97 [0.95, 0.98]
Han 2016	39	18	3	582	0.93 [0.81, 0.99]	0.97 [0.95, 0.98]
Kagan 2012	85	14	15	505	0.85 [0.76, 0.91]	0.97 [0.96, 0.99]
Koster 2011	107	30	44	968	0.71 [0.63, 0.78]	0.97 [0.96, 0.98]
Pandaya 2012	37	309	7	11149	0.84 [0.70, 0.93]	0.97 [0.97, 0.98]
Wright 2014	282	1919	42	85322	0.87 [0.83, 0.90]	0.98 [0.98, 0.98]
Zaragoza 2009	64	21	26	678	0.71 [0.61, 0.80]	0.97 [0.95, 0.98]

Trisomy 21 detection rate after adding PIGF data

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cowans 2010	65	13	5	432	0.93 [0.84, 0.98]	0.97 [0.95, 0.98]
Han 2016	40	18	2	582	0.95 [0.84, 0.99]	0.97 [0.95, 0.98]
Kagan 2012	87	13	13	506	0.87 [0.79, 0.93]	0.97 [0.96, 0.99]
Koster 2011	110	30	41	968	0.73 [0.65, 0.80]	0.97 [0.96, 0.98]
Pandaya 2012	39	298	5	11160	0.89 [0.75, 0.96]	0.97 [0.97, 0.98]
Wright 2014	302	1134	22	86107	0.93 [0.90, 0.96]	0.99 [0.99, 0.99]
Zaragoza 2009	63	21	27	678	0.70 [0.59, 0.79]	0.97 [0.95, 0.98]

Fig. 3 Forest plot of detection rates by study for a FPR of 3%. FPR, false-positive rate; PLGF, placental growth factor.
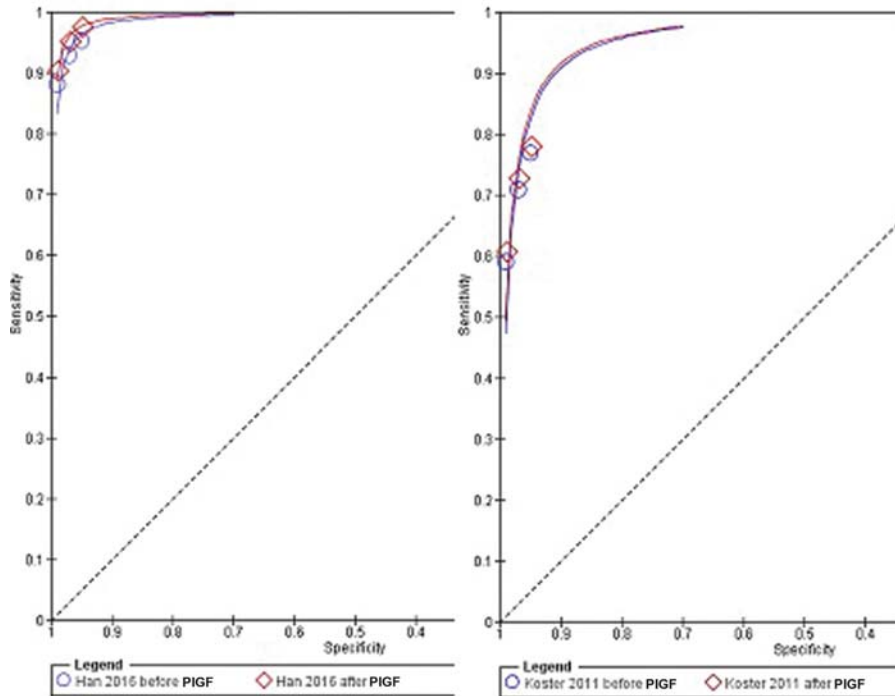

Fig. 4 Receiver-operating characteristic curves pre/post-PLGF for studies by Han et al and Koster et al. FPR, false-positive rate; PLGF, placental growth factor.

across studies, and the statistical methodology used. Likewise, to the best of our knowledge, this it is the first systemic review discussing the use of PLGF for aneuploidy screening in pregnancy. On the contrary, several limitations are worth noting. First, though the improvements in DRs following the introduction of PLGF were consistent across studies, the actual DRs between reports were significantly different, indicating significant heterogeneity between studies. Second, differences between the analytes studied in two out of the eight studies, which included the use of AFP and DV may have introduced significant bias. Finally, given the nature of the literature

available, we combined different study designs to arrive at our conclusions, which may have impacted our results.

Conclusion

In conclusion, addition of PLGF to prenatal screening using serum analytes mildly improves trisomy 21 DRs between 1.4 and 3.3% for FPRs between 5 and 1%, respectively. As the use of NIPT becomes increasingly widespread, future studies should address the cost–benefit analysis of introducing PLGF for prenatal screening with serum analytes.

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