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Systematic review of maternal Placental Growth Factor levels in late pregnancy as a predictor of adverse intrapartum and perinatal outcomes

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ABSTRACT

Aim: This systematic review evaluates the utility of maternal Placental Growth Factor (PlGF) when measured in late pregnancy (>20 weeks) as a predictor of adverse obstetric and perinatal outcomes.
Methods: Pubmed and Embase were searched using the term "placental growth factor" in combination with relevant perinatal outcomes. Studies were included if they measured PlGF levels in pregnant women after 20 + 0 weeks gestation and reported relevant adverse obstetric or perinatal outcomes related to placental insufficiency (excluding pre-eclampsia).
Results: Twenty-six studies were eligible for inclusion with 21 studies investigating the relationship between PlGF and small for gestational age (SGA) and 7 studies investigating PlGF for the prediction of other adverse perinatal outcomes. In all studies, maternal PlGF levels were significantly lower in the SGA group compared to controls. Other outcomes investigated included caesarean section (CS) for fetal compromise, low Apgar score, neonatal intensive care unit (NICU) admission, neonatal acidosis, stillbirth, and intrapartum fetal compromise. The results generally showed a significant association between low PlGF levels and CS for fetal compromise, NICU admission and stillbirth.
Conclusion: Low maternal PlGF levels in late pregnancy are strongly associated with SGA. Findings across studies were variable in relation to PlGF and the prediction of other adverse intrapartum and perinatal outcomes, however there was a consistent association between low PlGF levels and CS for fetal compromise, NICU admission and stillbirth. This review suggests that the use of PlGF for the prediction of adverse outcomes is promising. Its predictive value may potentially be enhanced if used in combination with other biomarkers or biophysical measures of fetal well-being.

Introduction

Over recent years there have been a large number of studies which have provided strong evidence that levels of placentally derived angiogenic proteins are perturbed particularly in women who develop pre-eclampsia [1–7] as well as other obstetric and perinatal complications [8–12]. Many, if not all of these conditions share a similar aetiology characterised by placental dysfunction.

One such protein is Placental Growth Factor (PlGF), levels of which are reduced in women with poor perinatal outcomes [8,13,14]. PlGF is a member of the vascular endothelial growth factor (VEGF) family and was first isolated from the human placenta in 1991 [15]. Although the precise mechanisms by which PlGF exerts its various effects are still unclear it is known to play a pivotal role in angiogenesis and vasculogenesis, both vital steps for the creation of a low resistance placental circulation [16].

In normal pregnancy, maternal PlGF levels have a non-linear association with gestation, peak at around 30 weeks and then progressively fall towards term [17,18]. During the first and second trimesters of pregnancy, low levels of PlGF are linked to impaired placental development and angiogenesis, which is associated with various pregnancy complications including pre-eclampsia, miscarriage, stillbirth, low birth weight and fetal growth restriction (FGR) [12,16,19,20]. More recently, low maternal PlGF levels in the third trimester appear to be associated with late onset FGR, gestational hypertension and pre-eclampsia as well as intrapartum fetal compromise and adverse perinatal outcomes [8,21].

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The aim of this systematic review was to evaluate the utility of maternal Placental Growth Factor (PlGF) levels when measured in late pregnancy (>20 weeks) as a predictor of adverse obstetric and perinatal outcomes **other than** pre-eclampsia.

Methodology

Data sources

The search strategy was developed in accordance with the Centre for Reviews and Disseminations' Guidance for Systematic Reviews in Health Care [22] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [23]. The PubMed and Embase databases were searched for papers published between January 1997 and June 2017 using the key words: ("PLGF" OR "placental growth factor") AND ("neonat*" OR "perinat*" OR "intrapartum" OR "SGA" OR "small for gestational age" OR "FGR" OR "fetal growth restriction" OR "growth restriction" OR "IUGR"). The search was restricted to English as the language; human as the species and female as the gender. The Cochrane Library and Clinicaltrials.gov databases were also searched to identify any relevant reviews or studies.

Study selection

An initial title and abstract review was performed on all publications from the search to exclude duplicated and ineligible manuscripts. The first reviewer (HS) screened all titles and extracted those citations requiring more detailed examination. A second review of abstracts and citations was then performed by two reviewers (HS and LD) who went on to read and select all relevant studies for inclusion and extract the study data. When any disagreement between the opinions of the two reviewers arose, a further assessment of that study was performed by a third reviewer (SK). Studies were eligible for inclusion if they reported maternal PlGF levels in pregnant women >20 + 0 weeks gestation and relevant obstetric or perinatal outcomes (excluding pre-eclampsia) or the association between low maternal PlGF levels and adverse outcomes. The adverse outcomes included in the review were those that could be putatively linked to underlying placental insufficiency. The gestational age cut-off (>20 + 0 weeks) was chosen to reflect placental insufficiency developing in later pregnancy. This threshold has also been used by other investigators [10]. Specific obstetric and perinatal outcomes investigated were, small for gestational age, fetal growth restriction, preterm birth, intrapartum fetal compromise, emergency caesarean delivery for fetal distress, stillbirth, neonatal acidosis and NICU admission. All selected full-text manuscripts were then reviewed in detail. A manual search of the reference lists of these articles was carried out to identify relevant papers not captured by the initial search strategy. Systematic and expert reviews, case series and reports, abstracts, book chapters, opinion pieces and guidelines were excluded. Publications were also excluded if they only reported PlGF solely in relation to pre-eclampsia or if PlGF was only measured at <20 weeks gestation.

The specific outcomes investigated in this systematic review were: small for gestational age (SGA), FGR, preterm birth, intrapartum complications (fetal compromise, emergency operative birth) and neonatal complications (low Apgar score at 5 min, neonatal intensive care unit admission (NICU), acidosis) and stillbirth.

Results

Fig. 1 outlines the PRISMA flow chart for the identification of relevant studies for this review. Three hundred and forty-three publications were initially identified using the aforementioned search strategy and 44 full text articles were then reviewed.

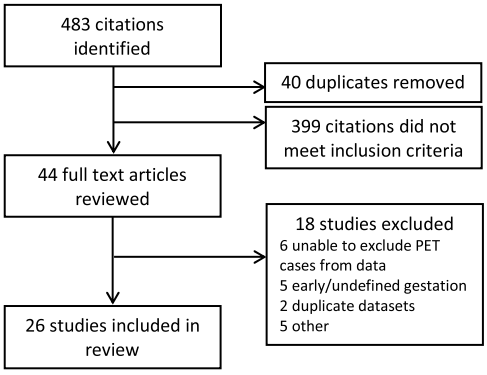

Fig. 1. Selection of studies.

Twenty-six studies (total participants, N = 42,609) were deemed to be eligible for final inclusion. Of these, 21 studies reported the relationship between PlGF and SGA or FGR infants with a participant total of N = 41,837 [10,13,24–42], seven studies detailed the predictive value of PlGF for other adverse perinatal outcomes with a participant total of N = 13,401 [8,10,13,14,25,38,43] and three studies described the role of PlGF in distinguishing between placentally-mediated FGR and constitutionally SGA infants with a participant total of N = 841 [10,44,45].

Study characteristics are presented in Table 1 and include the type of study, populations of recruited women, total number of participants, gestation at which PlGF was measured, type of PlGF assay, criteria for abnormal maternal PlGF levels if defined and specific outcomes investigated. Most studies were prospective cohort by design [10,13,14,24,25,27–32,35–38,40,43,44]. There were seven either nested or retrospective case-control studies [26,33,34,39,41,42,45] and one prospective cross-sectional [8]. The majority of studies recruited participants with uncomplicated pregnancies [8,13,14,24–26,29,31–34,36–38,41,42] with seven of these recruiting from the third trimester only. Five studies recruited participants with a suspected or confirmed SGA fetus on antenatal ultrasound [10,30,39,44,45], two recruited those at risk of either FGR or pre-eclampsia [27,43], and one study recruited women with abnormal uterine artery Dopplers [40]. Two studies investigated specific populations – women with Type 1 Diabetes Mellitus [35] and those living at high altitude [28]. Participant numbers in the individual studies ranged from N = 31 in a small retrospective case-control study [39] to N = 9850 in a large prospective cohort study [32].

Although all the included studies collected PlGF samples >20 weeks gestation, eight studies collected samples exclusively in the third trimester (>30 weeks gestation) [8,13,14,25,26,31,32,44]. The included studies used a variety of PlGF assay platforms from various manufacturers – R&D Systems® [14,24,26,27,35,38–42,44], Roche Diagnostics® [13,25,28,29,31,32,34,36], Alere® [8,10,30,43,45], PerkinElmer® [37] and BRAHMS KRYPTOR® [33]. Only half of the included studies reported the definition of an abnormal PlGF criterion [10,13,14,24,25,29–32,38,40,43,45]; of these the majority used <5th centile for gestational age as the defined threshold [10,13,25,29–32,45]. Most studies reported median PlGF levels [8,24,29–32,34–36,42,45], some reported the mean and standard deviation (SD) [26,28,39–41], others used multiples of the median (MoM) [13,14,25,33,37,44] and two studies calculated logarithmic means [27,38]. Individual studies did not routinely report gestation-specific PlGF ranges for their study cohorts.

Small for gestational age

The association between maternal PlGF levels and SGA or FGR was reported in 21 studies (Table 2). The definition of SGA or FGR