sFlt-1/PIGF RATIO

BACKGROUND

Preeclampsia is a common multisystem disorder of pregnancy with significant adverse effects on both mother and baby.[1,2] It is thought to be a disease of the vasculature driven by placental hypoperfusion/hypoxia and the production of anti-angiogenic factors.[3,4] Placental growth factor (PlGF) is one of a family of vascular endothelial growth factors (VEGF) that promote angiogenesis and help maintain endothelial and vasculature function. PlGF is key to the development and maturation of placental vasculature, with levels increasing throughout a healthy pregnancy peaking at 28-30 weeks gestation. Soluble fms-like-tyrosine kinase 1 (sFlt-1) is a freely circulating VEGF receptor, which exerts an antiangiogenic effect by sequestering PlGF and other circulating VEGFs reducing their bioavailability. In pregnancy, the placenta is the main source of both PlGF and sFlt-1.[5, 6]

In placental insufficiency, low PlGF is associated with fetal growth restriction, while excess sFlt-1 production results in widespread endothelial dysfunction and the syndrome of preeclampsia.[5, 7] The median time between a sharp rise in sFlt-1 levels and the onset of clinical disease is 5 weeks.[3] Both the degree of elevation and delta change in the sFlt-1/PlGF ratio correlate with disease activity.[8-12] A trial of utilising PlGF testing in clinical practice demonstrated a reduction in average time to preeclampsia diagnosis and a reduced incidence of severe adverse antenatal maternal outcomes such as eclampsia, stroke and death.[13]

In mothers with symptoms or signs suspicious for preeclampsia, a normal sFlt-1/PlGF ratio is a useful 'rule out' test. The sFlt-1/PlGF ratio can also discriminate between preeclampsia and other maternal conditions that present similarly such as worsening chronic hypertension, renal disease, or SLE.[14-16] Comorbid conditions do not elevate the sFlt-1/PlGF ratio in the absence of superimposed placental dysfunction. Cost-benefit analyses indicate that using the sFlt-1/PlGF ratio as a 'rule out' test for preeclampsia will aid resource allocation by reducing the intensity of monitoring in pregnancies deemed at low risk.[17-25] For the mother, a normal sFlt-1/PlGF ratio may prevent disruption to family and work life from unnecessary hospital appointments or admission.

IN PREGNANCIES AT 20 TO 36^{+6} WEEKS GESTATION

- **A sFlt-1/PlGF ratio ≤38 RULES OUT** preeclampsia for at least one week with a negative predictive value of 99%, in studies requiring both new or worsening proteinuria and hypertension for diagnosis,[26-27] and 96% in a NZ study[28] using SOMANZ criteria[1] for diagnosis. The negative predictive value for excluding preeclampsia remains high out to 4 weeks ≥94%.[29]
- **A sFlt-1/PlGF ratio >38 is suggestive of placental insufficiency.** A sFlt-1/PlGF ratio >38 measured in pregnancies <37^{+0} weeks gestation has a 75% positive predictive value for preeclampsia diagnosis within 4 weeks using SOAMNZ/ISSHP criteria.[28,30] In a NZ study,[28] most of those who did not progress to preeclampsia developed other features of placental insufficiency including isolated fetal growth restriction, postpartum preeclampsia, and placental abruption. Adverse maternal and neonatal outcomes are several times higher in pregnancies with a sFlt-1/PlGF ratio >38 versus ≤38.[28, 30]
- **A PlGF ≤100 pg/ml at 20-34 weeks gestation is suggestive of placental insufficiency.** A low PlGF can be found in / and may predict the recurrence of: Maternal Vascular Malperfusion (MVM), Chronic Histiocytic Intervillousitis (CHI), and Massive Perivillous Fibrinoid Deposition (MPFD).[37-39]

In pregnancies <35^{+0} weeks gestation with suspected preeclampsia, an elevated sFlt-1/PlGF ratio >38 is associated with a shorter test to birth interval. The positive predictive value for birth within 14 days of an elevated sFlt-1/PlGF ratio is >50%.[28,31]

Twin pregnancies – less data exist, and further validation is required. A retrospective analysis of 164 twin pregnancies with suspected preeclampsia at 30-35.2 weeks gestation, proposed that a sFlt-1/PlGF ratio cut-off of 38 is also applicable in twin pregnancies with suspected preeclampsia.[32] They reported a sFlt-1/PlGF ≤38 ruled out birth within 1 and within 2 weeks (NPV 99% and NPV 96.4% respectively), and that a ratio >38 was highly predictive of birth <1 and <2 weeks (PPV 55% and 61% respectively). An analysis of data from three prospective studies,[33] including 269 healthy twin pregnancies, confirmed that for twin pregnancies <29 weeks gestation the median, 5th, and 95th sFlt-1/PlGF ratio percentiles were the same as for singleton pregnancies. In twin pregnancies 29 to <34 weeks gestation the 95th percentile sFlt-1/PlGF was 33.9, however from 34 weeks gestation to birth the sFlt-1/PLGF ratio percentiles were substantially higher, median ratio 38.7. We can deduce therefore, that for twin pregnancies up to 34 weeks gestation a sflt-1/PlGF ratio cut-off of 38 remains discriminatory for placental health versus disease.

TEST PERFORMANCE

Canterbury Health Laboratory is offering this test through the Endocrinology Laboratory.

METHOD

sFlt-1 and PlGF immunoassay by Roche Diagnostics International ltd.

TURNAROUND TIME

For samples arriving in the laboratory before 3pm Monday to Friday (public holidays excluded) same day results will be available. For samples arriving outside these times, results will be available on the next working day.

SAMPLE REQUIREMENTS

Serum sample, minimum 1ml in a plain/red top serum gel tube.

TEST INDICATION

Where there is equipoise about admission or instigating intense outpatient surveillance in mothers ≥20 weeks gestation with:

- Symptoms or signs suspicious for preeclampsia including:
  - New or labile hypertension
  - Unexplained epigastric or upper abdominal pain, headache or visual scintillations
  - Renal impairment, proteinuria, thrombocytopenia, or liver dysfunction.
  - Where an alternate diagnosis to preeclampsia is being considered, eg. SLE, or underlying renal or liver disease
- Isolated suspected intrauterine fetal growth restriction to rule out placental insufficiency.
- Previous preeclampsia onset <32 weeks, or previous fetal growth restriction onset <32 weeks secondary to MVM, CHI, or MPFD. Request PlGF alone (not the ratio) at 20-24 weeks gestation to predict recurrence and aid management plan.

DO NOT REQUEST A TEST IF

- There is a firm diagnosis of preeclampsia and birth is imminent. However, the test may be useful in 'mild' manifest preeclampsia diagnosed <35 weeks gestation in planning location of care by using the traffic-light system to interpret the result.
- Postpartum

TEST REQUESTING

Please use the designated laboratory request form. Approval for the request is required from either an Obstetric SMO or Obstetric Physician.

The clinical indication must be included on the request form by selecting one of:

- Suspected preeclampsia
- Isolated new or worsening hypertension
- Isolated new or worsening proteinuria (after excluding a UTI)
- Isolated fetal growth restriction

INTERPRETATION OF RESULTS

Interpret sFlt-1 and PlGF in combination as the sFlt-1/PlGF ratio. Interpretation can be guided by following the traffic-light system employed and validated by other centres for use in singleton pregnancies (Appendix A). In cases of previous pre-eclampsia onset <32 weeks or isolated fetal growth restriction onset <32 in previous or current pregnancy, then PlGF may be requested and interpreted in isolation. A PlGF <100 mg/dL between 20-36 weeks gestation is very low (less than the 2.5th percentile).

There is ongoing research into the clinical utility of these biomarkers. These test results are for guidance and should be carefully interpreted in the clinical context and along other investigations currently used for diagnosing preeclampsia/placental insufficiency.

Temporary elevations in the sFlt-1/PlGF ratio have been observed with an associated preeclampsia-like syndrome and/or a short-term decline in fetal growth interval.[28] Although COVID-19 can raise the sFlt-1 level and a temporary pre-eclampsia-like syndrome,[34-35] a raised sFlt-1/PlGF ratio is thought to be indicative of preeclampsia.[36]

In twin pregnancies, it appears that the same sFlt-1/PlGF cut-off of 38 can be reliably used up to 33+6 weeks gestation. However further studies are needed to validate current findings. (see background information above).

RECOMMENDED FREQUENCY OF SFLT-1/PLGF RATIO TESTING

INITIAL sFlt-1/PlGF RATIO ≤ 38 (NORMAL) AND PlGF ≥100

- Suspected preeclampsia –stop testing if symptoms and signs resolve or if there is an alternative diagnosis. If a suspicion for preeclampsia remains and there is no alternative diagnosis, repeat the test in 3-4 weeks. If the clinical suspicion is suddenly heightened by a rapid deterioration in maternal condition, then a test can be ordered sooner, maximum once per week.
- Isolated but worsening hypertension or proteinuria – repeat in test in 4 weeks if symptoms evolve and ongoing concern about pre-eclampsia.

INITIAL sFlt-1/PIGF RATIO ≤ 38 (NORMAL) AND PIGF <100 PG/ML (LOW)

- Indicates placental pathology. Usually reflects maternal vascular malperfusion. Also low in some cases of fetal vascular malformation if there is associated infarction, Chronic Histiocytic Intervillousitis, or Massive Perivillous Fibrinoid Deposition. No need to repeat the test. Monitor fetal growth, check for features of pre-eclampsia at each visit.

INITIAL sFlt-1/PIGF RATIO > 38 (HIGH)

- Stop testing if birth is indicated or if ≥35 weeks gestation.
- If the sFlt-1/PIGF ratio result is in the 'amber' category (Appendix A) and <35 weeks gestation with both a stable mother and baby, a repeat test in 7 days may aid management decisions.

ENQUIRIES

Endocrine Laboratory	80885
Clinical Biochemistry	86968
Obstetric team or Obstetric Physician	on call

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APPENDIX 1 sFlt-1/PIGF RATIO INTERPRETATION

sFlt-1/PIGF Ratio in Suspected Preeclampsia	Rule Out Preeclampsia	Short-term Prediction Placental Dysfunction +/- Preeclampsia	Rule In Placental Dysfunction +/- Preeclampsia
20^{+0} to 33^{+6} weeks gestation	≤38	>38 to <85	≥85
≥34 to 36^{+6} weeks gestation	≤38	>38 to <110	≥110
Clinical implications	• Preeclampsia is excluded and unlikely to develop for at least one week • NPV 96-99%[1-2] for preeclampsia ≤1 wk • NPV 94-96%[1,3] for preeclampsia ≤4 wks • NPV 95-96%[1,4] for birth ≤2 weeks if $<35^{+0}$ gestation	• Clinically associated with ≥ 1 of impending: preeclampsia, FGR, preterm birth, and placental abruption • The degree of elevation and the rate of change are proportional to clinical severity • PPV 37-75%[1-2] for preeclampsia ≤4 weeks • PPV 51-56%[1,4] for birth ≤2 weeks if $<35^{+0}$ gestation • Occasionally transient elevations occur and are associated with temporary signs of preeclampsia or a decline in fetal growth velocity (eg. seen with severe sepsis and viral infections such as COVID-19)	• In suspected preeclampsia the diagnosis is confirmed • In the absence of preeclampsia eg. isolated FGR, please refer to the clinical implications and management plan in the amber box
Management plan	• Continue usual outpatient care • Admit only if additional maternal or fetal concerns, eg. uncontrolled hypertension • If ongoing clinical suspicion of preeclampsia consider a repeat test at 3-4 weekly intervals	• Frequent outpatient review 2-3 times per week • Admit if additional maternal or fetal concerns, eg. uncontrolled hypertension • Repeat sFlt-1/PIGF test on day 3 and weekly thereafter. A rapid rise (vs a stable result) correlates with disease activity and an increased likelihood of birth <14 days	• Admit • Do not repeat the sFlt-1/PIGF ratio

NPV, negative predictive value; PPV, positive predictive value; FGR, fetal growth restriction

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