

Weqas
Unit 6, Parc Tŷ Glas
Llanishen, Cardiff, CF14 5DU

Tel: 02920 314750
Email: contact@weqas.com

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Preterm Labour Markers - which kits to use?

Gareth Davies

Deputy Director, Weqas

Preterm Labour Markers - Overview

Introduction

Introduction to Biomarkers for Preterm Labour and P-PROM

Diagnosis of Preterm Labour and P-PROM

Diagnostic Tests

Performance on Weqas Programmes

Preterm Labour Markers – Introduction

Premature labour is labour that happens before the 37th week of pregnancy. About 8 out of 100 babies will be born prematurely.

(Premature labour and birth, <https://www.nhs.uk/pregnancy/labour-and-birth>)

NICE guideline on preterm labour and birth {NG25} states that women reporting symptoms of preterm labour who have intact membranes should have a clinical assessment.

Preterm prelabour rupture of membranes (P-PROM)

A woman is described as having P-PROM if she has ruptured membranes before 37+0 weeks of pregnancy but is not in established labour (NG25)

Premature rupture of the membranes (PROM) at term occurs in 5 to 10% of pregnancies and pre-term PROM occurs in approximately a third of all premature births and is associated with significant neonatal morbidity and mortality.

Biomarkers for Preterm Labour Marker

Fetal fibronectin

- Fetal fibronectin is an adhesive glycoprotein that holds the membranes of the uterus to the fetal membranes. After 35 weeks of pregnancy, it begins to break down naturally and is detectable in vaginal secretions.

Phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1)

- Phosphorylated IGFBP-1 is a protein made by the cells lining the uterus. When delivery is imminent, small amounts of phosphorylated IGFBP-1 leak into the cervix.

Placental alpha microglobulin-1 (PAMG-1) (PartoSure)

- Placental alpha microglobulin-1 (PAMG-1) is a protein released from the lining of the uterus into the amniotic cavity throughout pregnancy. It is found in very high concentrations in amniotic fluid and in very low concentrations in normal vaginal discharge

Biomarkers for P-PROM

Insulin-like growth factor binding protein-1 (IGFBP-1)

- IGFBP-1 is a 25kD protein synthesized in the decidual cells and foetal liver and is secreted into amniotic fluid. Amniotic fluid is normally not found in the vagina, but when foetal membranes rupture, amniotic fluid leaks into the vagina and the IGFBP-1 concentration quickly rises and remains high until delivery.

Placental alpha microglobulin-1 (PAMG-1) (AmniSure)

- Placental alpha microglobulin-1 (PAMG-1) is a protein released from the lining of the uterus into the amniotic cavity throughout pregnancy. It is found in very high concentrations in amniotic fluid and in very low concentrations in normal vaginal discharge

Diagnosis of Preterm Labour

1.7 Diagnosing preterm labour for women with intact membranes

Offer a clinical assessment to women reporting symptoms of preterm labour who have intact membranes. This should include

- clinical history taking
- the observations described for the initial assessment of labour in NICE's guideline on intrapartum care
- a speculum examination (followed by a digital vaginal examination if the extent of cervical dilatation cannot be assessed; be aware that if a swab for fetal fibronectin testing is anticipated the swab should be taken before any digital vaginal examination).

If the clinical assessment suggests that the woman is in suspected preterm labour and she is 30+0 weeks pregnant or more, consider transvaginal ultrasound measurement of cervical length as a diagnostic test to determine likelihood of birth within 48 hours.

Diagnosis of Preterm Labour

Consider fetal fibronectin testing as a diagnostic test to determine likelihood of birth within 48 hours for women who are 30+0 weeks pregnant or more if transvaginal ultrasound measurement of cervical length is indicated, but is not available or not acceptable.

Act on the results as follows:

- if fetal fibronectin testing is negative (concentration 50 ng/ml or less), it is unlikely preterm labour
- if fetal fibronectin testing is positive (concentration more than 50 ng/ml), view the woman as being in diagnosed preterm labour and offer treatment as described in the sections on tocolysis and maternal corticosteroids.

Fetal Fibronectin

Fetal fibronectin detected between 22 and 35 weeks of pregnancy is an indicator of preterm birth risk (DG33).

A positive result indicates an increased risk of pre-term labour and is useful in aiding patient management.

The negative predictive value (NPV) of the test at 10 ng/mL is quoted as 100%, with a NPV at 50 ng/mL of 99.2%.

The manufacturers quote a cut-off of >50 ng/mL as a positive result; indicating the likelihood of a preterm birth within the following 14 days.

Diagnosis of Preterm Labour

NICE Diagnostic guidance [DG33] **Biomarker tests to help diagnose preterm labour in women with intact membranes**

Recommendation 1.1

- There is currently insufficient evidence to recommend the routine adoption of Actim Partus and PartoSure to help diagnose preterm labour in women with intact membranes when transvaginal ultrasound measurement of cervical length is not available or not acceptable.

However:

- November 2024: There is a problem with the supply of cassettes used for fetal fibronectin testing. We will review our guidance and use our topic prioritisation process to decide whether to update it. For more information, see the NHS England letter on the discontinuation of Hologic fetal fibronectin testing.

It is recommended that women presenting in threatened preterm labour should be assessed with an alternative test (Actim Partus):

- If this test is negative, the woman can be assumed to be at low risk of preterm birth and as such would not require in-utero transfer or optimisation medications.
- If the test is positive, the woman should be recommended to deliver in an appropriate unit and receive optimisation medications

phIGFBP-1

phIGFBP-1 is a biochemical marker used as an aid in assessing the risk of preterm delivery in pregnant women with signs and symptoms of preterm labour and intact amniotic membranes, after 22 weeks plus 0 days of pregnancy.

IGFBP-1 is present in amniotic fluid primarily as a non-phosphorylated form. The phosphorylated form is produced mainly by human decidual cells and is present between the chorion and decidua.

As the cervix matures and labour approaches, the chorion and decidua detach and decidual proteins, including phIGFBP-1, leak into the cervical secretion.

The test has a limit of detection of 10 ng/mL and a measuring range of 10 to 8,000 ng/mL.

- If this test is negative, the woman can be assumed to be at low risk of preterm birth and as such would not require in-utero transfer or optimisation medications.
- If the test is positive, the woman should be recommended to deliver in an appropriate unit and receive optimisation medications.

PAMG-1 - Partosure

PartoSure is a CE-marked qualitative lateral flow, immunochromatographic point-of-care test designed to detect placental alpha microglobulin-1 (PAMG-1) in vaginal secretions during pregnancy

PartoSure is for use in pregnant women with signs and symptoms of preterm labour, intact amniotic membranes and minimal cervical dilatation (3 cm or less), between 20 weeks plus 0 days and 36 weeks plus 6 days of pregnancy.

The test can be used if vaginal infections, urine, semen and trace amounts of blood are present, but should not be used if there is significant discharge of blood.

It can also be used shortly after a vaginal examination.

The test has a limit of detection of 1 ng/ml and a measuring range of 1 to 40,000 ng/ml.

Preterm prelabour rupture of membranes (P-PROM)

NICE guideline [NG25] Preterm labour and birth (last updated June 2022)

1.3 Diagnosing preterm prelabour rupture of membranes (P-PROM)

If pooling of amniotic fluid is not observed, perform an IGFBP-1 or PAMG-1 test of vaginal fluid.

1.3.2 If the result of the test is positive, do not use the test results alone to decide what care to offer the woman, but also take into account her clinical condition, medical and pregnancy history and gestational age, and either: offer care consistent with the woman having P-PROM or re-evaluate the woman's diagnostic status at a later time point.

1.3.3 If the result of the IGFBP-1 or PAMG-1 test is negative and no amniotic fluid is observed: do not offer antenatal prophylactic antibiotics, unlikely to be P-PROM, return for reassessment if there are any further symptoms suggestive of P-PROM or preterm labour.

IGFBP-1

IGFBP-1 is a 25kD protein synthesized in the decidual cells and foetal liver and is secreted into amniotic fluid. Amniotic fluid is normally not found in the vagina, but when foetal membranes rupture, amniotic fluid leaks into the vagina and the IGFBP-1 concentration quickly rises and remains high until delivery.

Abbott ACTIM PROM

- Can be used at any gestational age, test results in 5 minutes
- Visual read or option for digital interpretation with the Actim 1ngeni Instrument

BHR Amnioquick Test

- Cut-off 5 ng/mL, 10 minute test, visual read

Laborie ROM Plus Rupture of Membranes Test

- Dual Protein Markers: IGFBP-1 & AFP
- effective in the presence of blood at a 10% concentration

PAMG-1 - AmniSure

99% sensitive and 98% specific to support accuracy of negative and positive ROM clinical results
No gestational age limit
Not affected by urine, semen, vaginal infections and trace amounts of blood on the swab
Visual read, 10 minute test

Weqas Programmes

Weqas fFN programme

Bimonthly, 2 samples per distribution

Liquid stable samples ready to use; no pre-analytical preparation required.

Linear related panel distributed covering the clinically relevant range.

Programme assesses both site and device performance

Qualitative and Quantitative reporting available, qual interpretations based on cut-offs of 50 and 200 ng/mL (EQUiPP study 2014).

Weqas ph-IGFBP-1 programme

Bimonthly, 2 samples per distribution

Liquid stable samples ready to use; no pre-analytical preparation required.

Linear related panel distributed covering the clinically relevant range.

Programme assesses both site and device performance

Weqas POCT PROM programme (IGFBP-1)

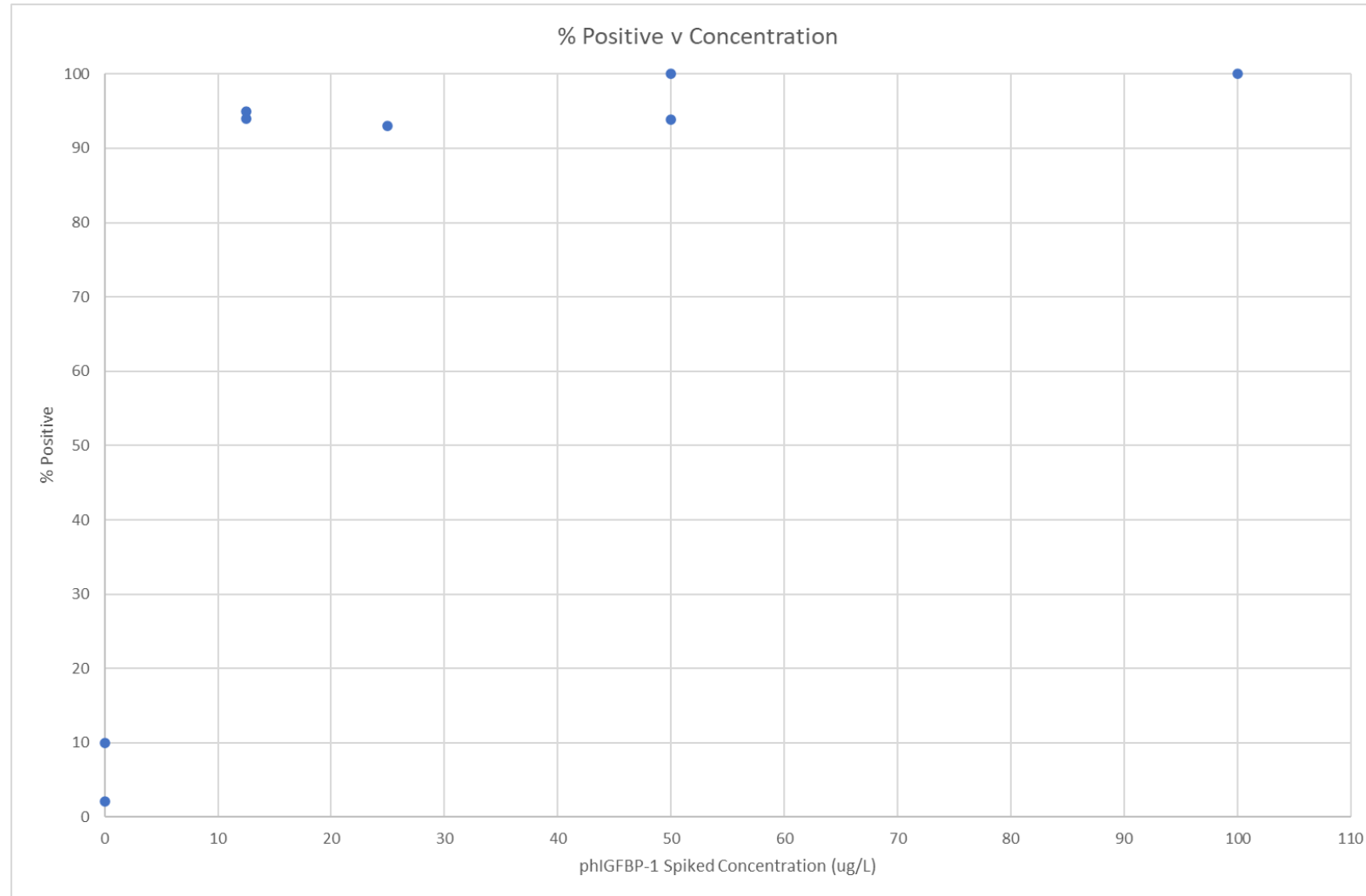
Bimonthly, 2 samples per distribution

Liquid stable samples ready to use; no pre-analytical preparation required.

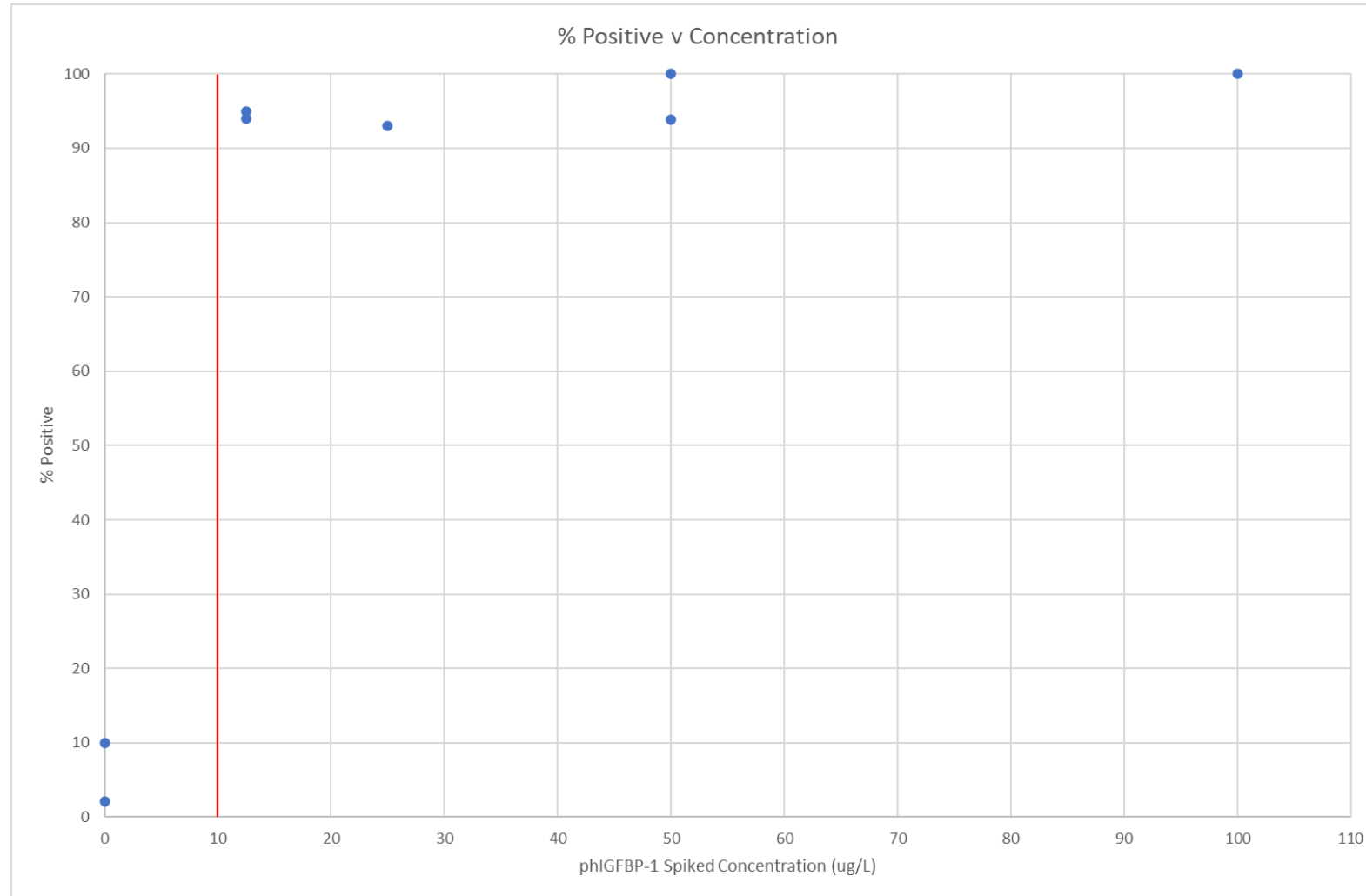
Linear related panel distributed covering the clinically relevant range.

Programme assesses both site and device performance

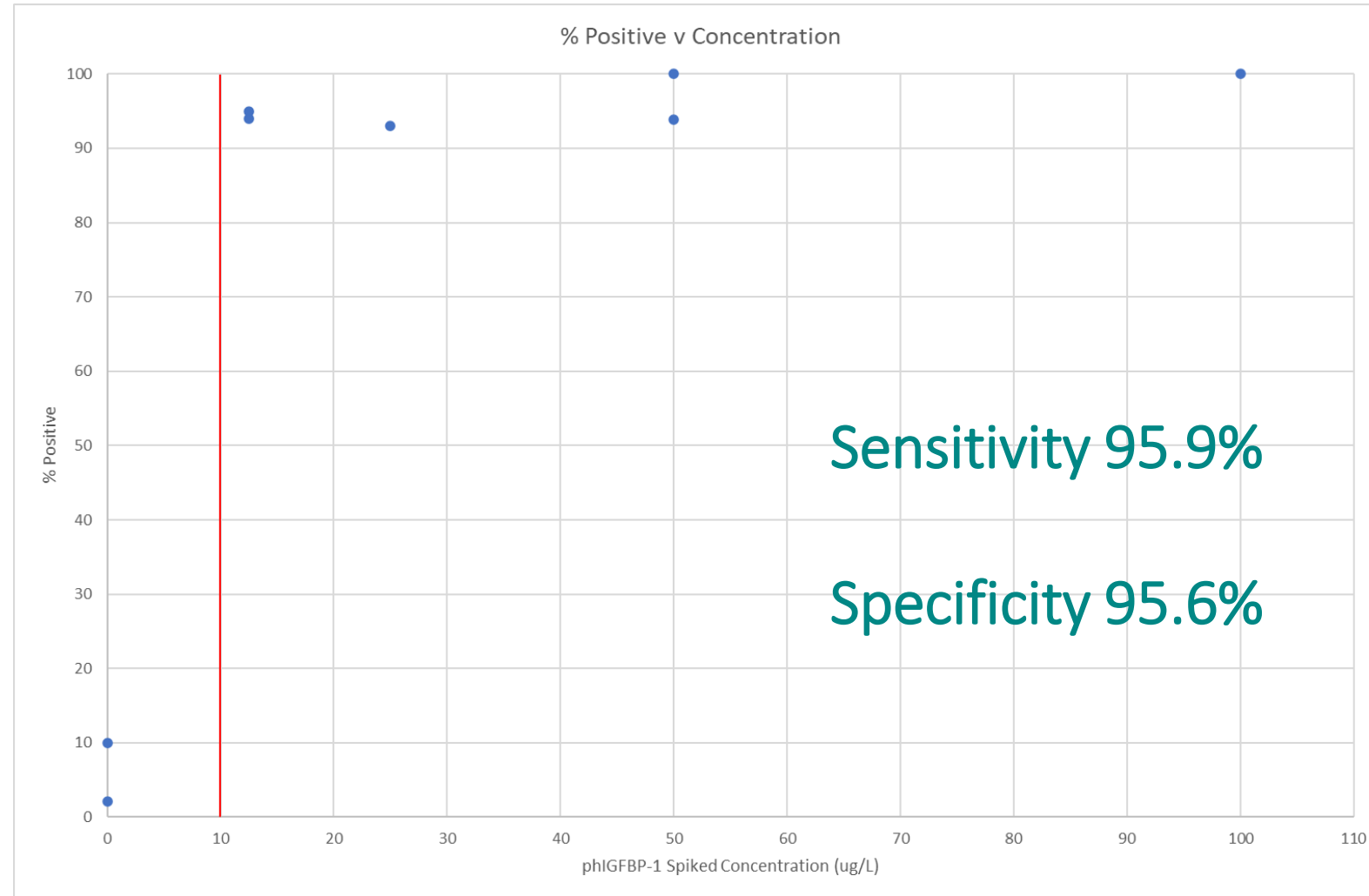
Performance on Weqas ph-IGFBP-1 Programme



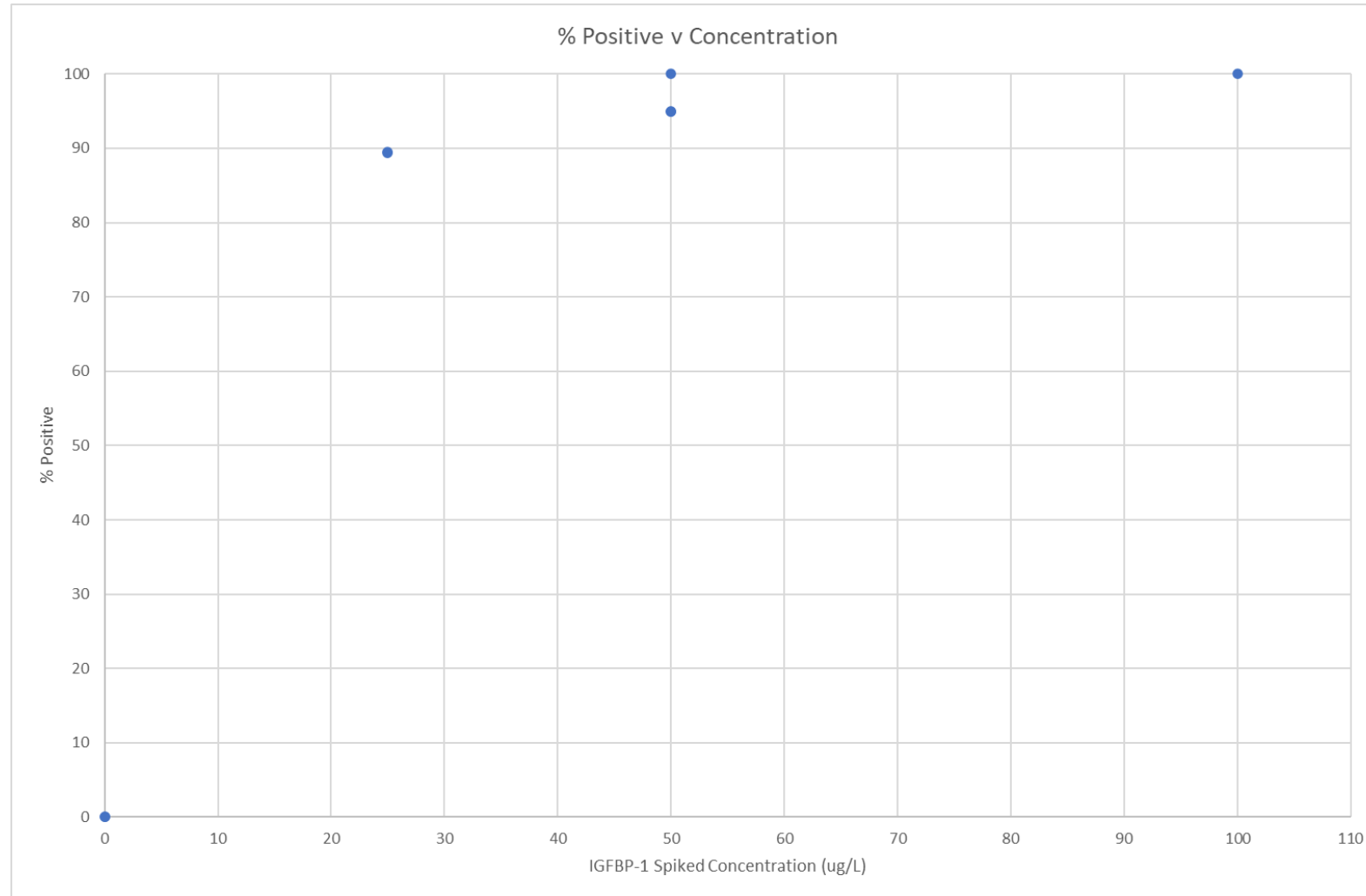
Performance on Weqas ph-IGFBP-1 Programme



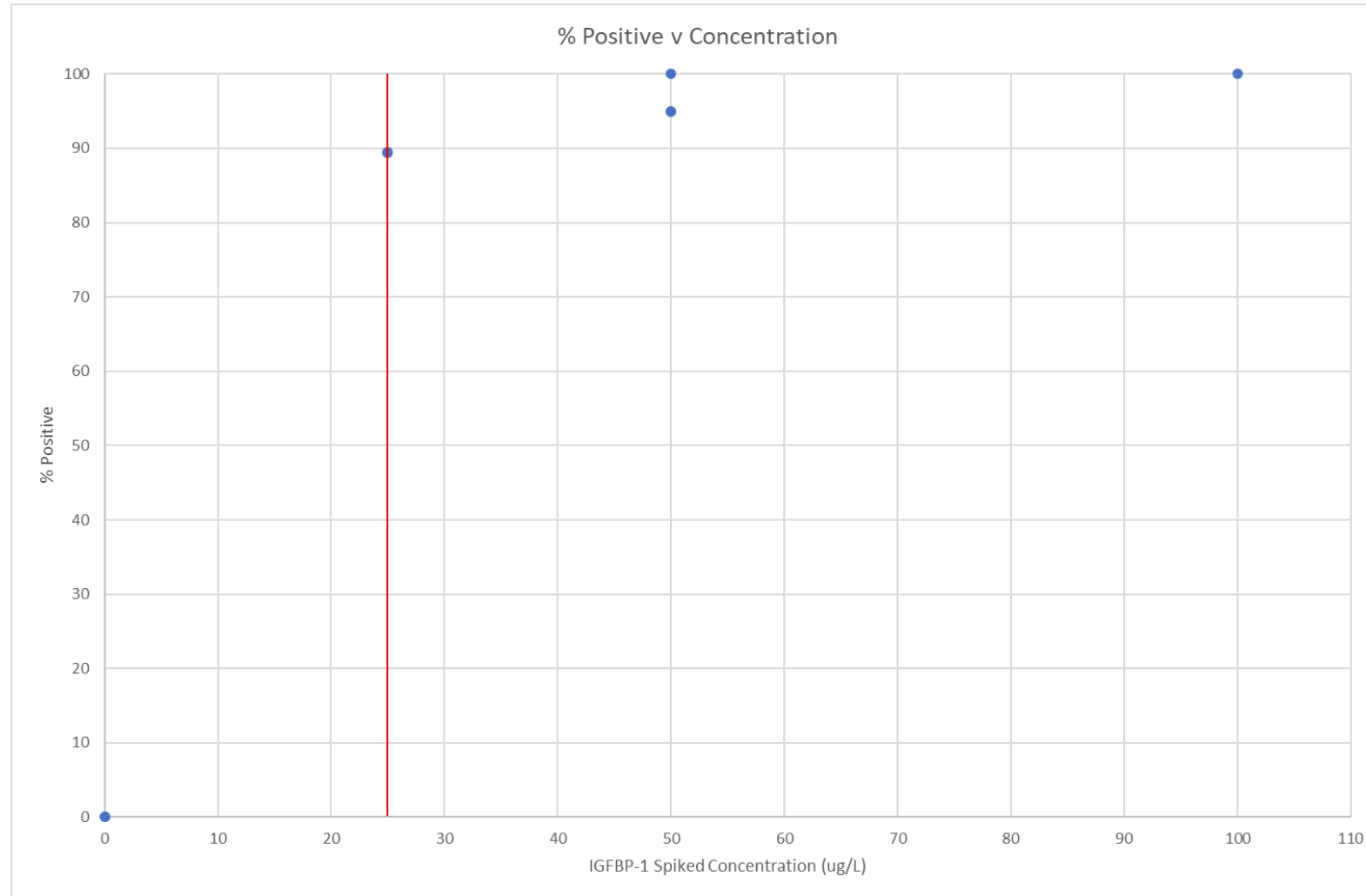
Performance on Weqas ph-IGFBP-1 Programme



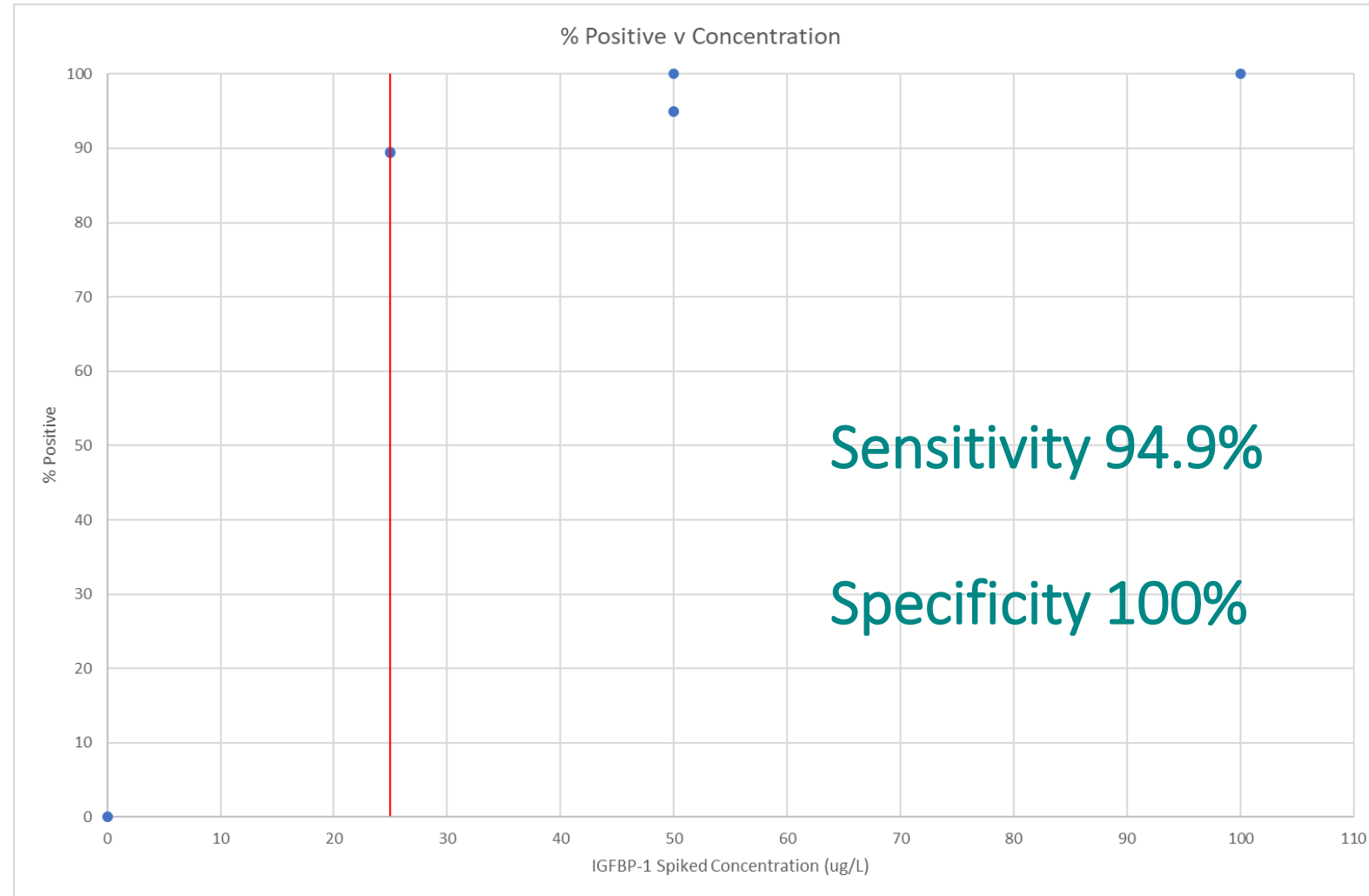
Performance on Weqas POCT PROM Programme



Performance on Weqas POCT PROM Programme



Performance on Weqas POCT PROM Programme



PAMG-1 Programme - Pilot

2 samples per month
Partosure and Amnisure
Qualitative reporting
Samples at appropriate cut-offs for both tests

References

Premature labour and birth, <https://www.nhs.uk/pregnancy/labour-and-birth>

NICE guideline on preterm labour and birth {NG25}

NICE Diagnostic guidance [DG33] Biomarker tests to help diagnose preterm labour in women with intact membranes

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Thank you

Any questions?