Healthcare Improvement Scotland | Evidence
Advice, guidance and intelligence

Topic Exploration

PREMAQUICK® for diagnosis of preterm labour

Topic explorations are high-level briefings intended to facilitate the consideration of topics referred to the HIS Evidence directorate for support. Topic explorations may be used to informed decision making around further work, or published as standalone outputs. Published topic explorations include a description of the topic, a summary of the available evidence, and concluding remarks.

Topic	PREMAQUICK®
Date of search	17/18 April 2023
Referrer	BHR PHARMACEUTICALS LTD
Author	Lorna Thompson
Further assessment of topic?	*Publish as stand alone product*

1. What were we asked to look at and why?

The majority (>80%) of women who present with symptoms of threatened preterm labour (TPTL) do not deliver early (<37 weeks gestation). Accurately predicting which women with TPTL will have imminent spontaneous delivery, means that appropriate management can be instituted for those most likely to benefit. Interventions include; hospital admission, tocolytics (labour suppressants), antenatal corticosteroids and in-utero transfer to specialist centres. Extending pregnancy duration may improve infant survival.[1] Identifying which women can safely be reassured and not require intervention can prevent exposure to unnecessary treatments and reduce parental stress. In this scenario, avoiding false negatives is considered more important than avoiding false positives since the harms of overtreatment are likely to be outweighed by the harms of undertreatment.[1]

Current practice in assessing women who present with symptoms of TPTL includes assessment of symptoms of PTL and transvaginal ultrasound measurement of cervical length.[1] Measurement of fetal fibronectin (fFN) (qualitative or quantitative) is an additional test which may be used instead of or alongside cervical length. Vaginal fFN is a marker of disruption of the maternal-foetal interface.[1]

An app called QUiPP is available as a regulated medical device in the UK. The app integrates risk factors, medical and pregnancy history, symptoms, cervical length and quantitative fFN measurements to calculate probability of spontaneous delivery at a range of time points. The app forms part of the British Association of Perinatal Medicine (BAPM) antenatal optimisation toolkit for improvement. The Scottish Perinatal Network has published guidance around in-utero transfer and incorporates probabilities from the QUiPP app within its risk assessments.

We were asked to look at the evidence for PREMAQUICK® to assess if it offers benefits alongside or in addition to current methods. This three point swab test is a rapid (10 minutes) multiparameter lateral flow test for the in vitro detection of IGFBP-1 (Insulin-like Growth Factor-Binding Protein 1), fragmented forms of IGFBP-1 and IL-6 (Interleukin 6) in vaginal secretions.[2] PREMAQUICK® is intended for assessing the risk of imminent birth between 22 and 37 (+6 days) weeks of amenorrhea in women who present with TPTL. IGFBP-1 is a marker of cervical ripening. The presence of fragmented forms of IGFBP-1 indicates a significant local proteolytic activity and fetal stress caused by contractions. The third marker, IL-6, is a marker of inflammation or infection of the amniotic cavity and the cervicovaginal area.

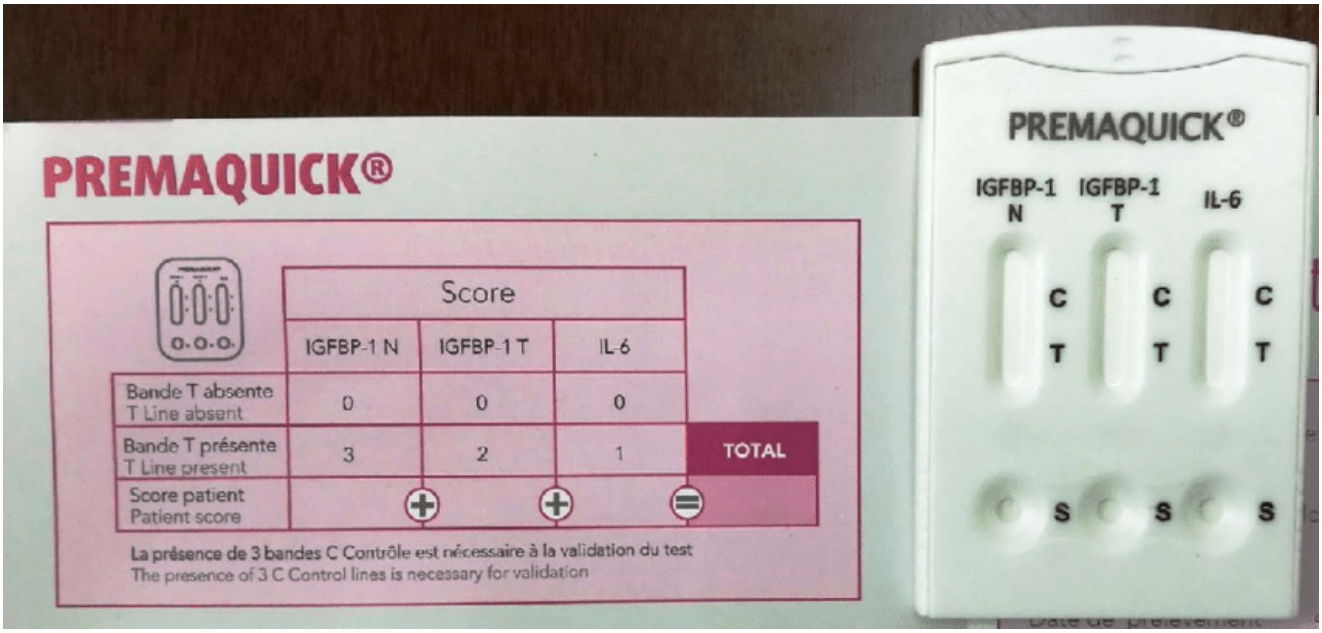

Image source: Abu-Faza M, Abdelazim IA, Svetlana S, Nusair B, Farag RH, Nair SR. Diagnostic accuracy of PremaQuick versus actim partus in prediction of preterm labor in symptomatic women within 14 days. Open Journal of Obstetrics and Gynecology. 2018 Jul 27;8(08):741.

2. The importance of this topic

In Scotland, being born too soon is the main reason babies require admission to neonatal care and the single biggest cause of death in early infancy.[3] Preterm delivery is associated with lifelong health repercussions.[4]

In 2021/22, 6.5% of live singleton babies and 69.3% of live babies from a multiple pregnancy were born preterm. Approximately two thirds of preterm deliveries are spontaneous with the remainder being iatrogenic.[3]

3. The methodological approach we took

We sought single gate diagnostic accuracy studies on PREMAQUICK® which compared test accuracy metrics with fFN and cervical length measurements in the same population. Reference standard of interest was delivery within two to seven days.[5] We also sought any intervention studies which compared clinical and resource outcomes following use of the test.

4. Timeframe requested

Referrer has requested support as soon as possible.

5. Summary of the evidence

- **Secondary evidence**

The NICE guideline on preterm labour and birth (NG25, 2015) examined the diagnostic accuracy of biochemical testing for markers of preterm labour in women with intact membranes. Diagnostic accuracy was examined for the tests alone and in combination with clinical assessment (symptoms and findings on vaginal examination) and cervical ultrasound features including cervical length and funnelling. Two biochemical tests were included; Cervicovaginal fetal fibronectin and IGFBP-1. The 2015 guideline committee noted that "pIGFBP1 plus cervical length was […] not found to be a clinical relevant tool for diagnosis of preterm labour and […] this combination was of no more use than the use of cervical length measurements alone."[1]

An exceptional surveillance was carried out in 2022 and highlighted the QUantitative Innovation in Predicting Preterm birth app (QUiPP app) which has been recommended by NHS England and the British Association of Perinatal Medicine. It also focused on the QUIDS decision tool (quantitative fetal fibronectin to improve decision making in women with symptoms of preterm birth). An ongoing guideline update will incorporate examination of the effectiveness of these tools.

NICE developed diagnostics guidance (DG33, July 2018) on biomarker tests to help diagnose preterm labour in women with intact membranes. There were three tests examined; Actim Partus, PartoSure and the Rapid fetal fibronectin (fFN) 10Q Cassette Kit (at thresholds other than 50 nanograms/millilitre). NICE concluded that there was insufficient evidence to recommend any of the three tests for routine use.

- **Primary evidence**

Four primary diagnostic studies were identified by the topic referrers. Two were case-control studies which would normally be excluded from systematic reviews of diagnostic studies since they have potential to inflate accuracy. Two were conducted in Nigera. This healthcare context may be of limited applicability to NHS Scotland. None of the studies examined the outcomes of change in management based on PREMAQUICK® compared with standard of care.

- Abdelazim (2022)[6] examined the diagnostic accuracy of PREMAQUICK® in a group of women (n=122) admitted with threatened pre-term labour and compared this test with measurement of cervical length <25mm. This study compared a group of women entering pre-term labour (no true negative or false positive findings) with a control group not at risk of pre-term labour (no true positive or false negative findings). It may be considered an exploratory case-control study rather than a diagnostic accuracy trial in a clinically relevant population.
- Abu-Faza (2018)[7] compared the diagnostic accuracy of PREMQUICK and Actim Partus (bedside immuno-enzymatic test relying on the monoclonal antibodies specific for phosphorylated IGFBP1). This study compared a group of women entering pre-term labour (no true negative or false positive findings) with a control group not at risk of pre-term labour (no true positive or false negative findings). It may be considered an exploratory case-control study rather than a diagnostic accuracy trial in a clinically relevant population.
- Asiegbu (2020)[8] [full study not accessed] compared the diagnostic accuracy of PREMAQUICK® with fFN tests in women (n=175) attending a Federal Medical Centre in Nigeria (described as low income setting) with threatened pre-term labour. Follow up was 14 days. PREMAQUICK® had higher sensitivity for preterm delivery 96.3% versus 51.9%. The abstract did not mention measurement of cervical length. This study may have limited applicability to the Scottish healthcare context.
- Eleje (2017)[9] conducted a diagnostic accuracy study of PREMAQUICK® in a low income setting in Nigeria. There were 97 women (mean gestational age 33.1) in the study. PREMAQUICK® (with two out of three biomarkers reading positive) had PPV of 84.4%(95%CI 67.2 to 94.7) and NPV of 93.9% (95%CI 85.0 to 98.3) for predicting preterm delivery within 7 days of study enrolment. In the full study group the rate of delivery within 7 days was 34%. Of the 40 participants who were enrolled at <35 weeks gestation, 8 (20%) had delivery within 7 days. The PPV was 70.5% (95%CI 34.9 to 96.8), NPV was 100% (95%CI 89.1 to 100). This study does not compare with fFN and although cervical length was measured it is unclear how this information was used. The study population and clinical setting may have limited applicability to the Scottish healthcare context particularly around women having different risk factor profiles for preterm delivery.

- Economic studies
  - No relevant economic analyses were identified

- Planned and ongoing work (including research projects, evidence reviews and implementation projects)
  - Two ongoing comparative studies were identified.

6. Exploration summary and conclusions

Four primary diagnostic accuracy studies of PREMAQUICK® were identified. Two of the studies were conducted in low income settings with populations of women likely to have a very different risk factor profiles for premature labour when compared with the Scottish context. The remaining two studies were case-control studies which would not meet quality thresholds for inclusion in systematic reviews. The evidence base is insufficient in applicability and methodological quality to form the basis of a full evidence assessment. Two ongoing studies were identified.

7. Next steps and further HIS: Evidence support

Suggested next step	☐ Directed to SAPG ☐ Directed to SHTG ☐ Directed to SIGN ☐ Directed to S&I ☐ Directed to SMC ■ Published as stand alone product
Rationale for decision	Insufficient evidence to support systematic evidence review.

8. Brief literature search results

Resource	Results
HIS projects *Check if any team within HIS has conducted/ is conducting work on this topic.*	Preterm perinatal package
UK guidelines and guidance	
SIGN	Nil identified
NICE	NICE NG25 Preterm labour and birth. 2015 NICE NG25 Exceptional surveillance 2022 NICE DG 33 Biomarker tests to help diagnose preterm labour in women with intact membranes 2018
Guidelines International Network (GIN) *Check for UK guidelines e.g. Royal College Physicians*	Nil RCOG refers to NICE GL
Secondary literature and economic evaluations	
Cochrane library *Check for Cochrane reviews*	Berghella V, Saccone G. Fetal fibronectin testing for reducing the risk of preterm birth. Cochrane Database of Systematic Reviews 2019, Issue 7. (Intervention study).
Dynamed	New South Wales Health (NSWH) guideline on management of threatened preterm labor. Queensland Maternity and Neonatal Clinical Guidelines Program guideline on preterm labour and birth.
TRIP database *Check for guidelines/ reviews*	Nil additional
BMJ Best Practice	https://bestpractice-bmj-com.knowledge.idm.oclc.org/topics/en-gb/1002/pdf/1002/Premature%20labour.pdf
HTA database *(https://database.inahta.org/)*	Varley-Campbell J, Mújica-Mota R, Coelho H, Ocean N, Barnish M, Packman D, *et al.* Three biomarker tests to help diagnose preterm labour: a systematic review and economic evaluation. *Health Technol Assess* 2019;23(13)
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Check for systematic reviews, meta-analyses, economic evaluations. Use the SIGN search filters for these study designs.	
Medline *Check for systematic reviews, meta-analyses, economic evaluations. Use the SIGN search filters for these study designs.*	Huang W, Ural S, Zhu Y. Preterm labor tests: current status and future directions. Crit Rev Clin Lab Sci. 2022 Jun;59(4):278-296. Dehaene I, Lorthe E, Gurney L, Turtiainen P, Schwickert A, Svenvik M, Care A, Bergman L; from the International Spontaneous Preterm birth Young investigators (I-SPY) group. Accuracy of the combination of commercially available biomarkers and cervical length measurement to predict preterm birth in symptomatic women: A systematic review. Eur J Obstet Gynecol Reprod Biol. 2021 Oskovi Kaplan ZA, Ozgu-Erdinc AS. Prediction of Preterm Birth: Maternal Characteristics, Ultrasound Markers, and Biomarkers: An Updated Overview. Journal of pregnancy. 2018 Oct 10.
Google Scholar	Giouleka S, Tsakiridis I, Kostakis N, Koutsouki G, Kalogiannidis I, Mamopoulos A, Athanasiadis A, Dagklis T. Preterm Labor: A Comprehensive Review of Guidelines on Diagnosis, Management, Prediction and Prevention. Obstet Gynecol Surv. 2022 May;77(5):302-317.
Primary studies (only if insufficient secondary evidence found)	
Primary studies identified by topic referrer	Eleje GU, Ezugwu EC, Eke AC, Eleje LI, Ikechebelu JI, Ezebialu IU, Obiora CC, Nwosu BO, Ezeama CO, Udigwe GO, Okafor CI. Accuracy of a combined insulin-like growth factor-binding protein-1/interleukin-6 test (Premaquick) in predicting delivery in women with threatened preterm labor. Journal of Perinatal Medicine. 2017 Nov 1;45(8):915-24. Abu-Faza M, Abdelazim IA, Svetlana S, Nusair B, Farag RH, Nair SR. Diagnostic accuracy of PremaQuick versus actim partus in prediction of preterm labor in symptomatic women within 14 days. Open Journal of Obstetrics and Gynecology. 2018 Jul 27;8(08):741. Asiegbu AC, Eleje GU, Ibeneme EM, Onyegbule OA, Chukwu LC, Egwim AV, Okonko CO, Eze SC, Eke AC. Combined insulin-like growth factor binding protein-1/interleukin-6 (Premaquick) versus fetal fibronectin for predicting preterm delivery among women with preterm contractions. International Journal of Gynecology & Obstetrics. 2020 May;149(2):171-7.

	Abdelazim IA, Amer OO, Shikanova S, Karimova B. Diagnostic accuracy of PremaQuick in detection of preterm labor in symptomatic women. Ginekologia Polska. 2022;93(2):121-5.
Medline *Use the SIGN search filters for these study designs.*	Nil additional
Cochrane library *Check for RCTs in the trials database*	Nil additional
Ongoing secondary research	
PROSPERO database *Check for recent systematic review protocols.*	
Ongoing research (only if insufficient secondary evidence and primary studies found)	
Clinicaltrials.gov *Check for ongoing studies that have recently closed or are due to complete in the next 6-12 months.*	Diagnostic Tests in the Context of Threatened Preterm Labour (PREMAQUICK) NCT03608995 Evaluation of a New Predictive Test of Preterm Birth in Case of Threatened Preterm Labor (PREMAQUICK) NCT04374916
Unpublished research	

Concepts used: preterm labour/labor, Premaquick, biomarkers, insulin-like growth factor-binding protein-1.

Appendix 1 Communication with topic referrer/stakeholders

Discussion (18/4/23) with Joanna Kelly who has recent contacts with the SG maternal and infant health policy team and with the Scottish perinatal health network. We agreed not to contact these collaborators at this stage given the limited evidence base identified.

Contacted researchers of ongoing studies – no responses.

1. NICE. Preterm labour and birh. 2015 [cited; Available from: https://www.nice.org.uk/guidance/ng25/chapter/Recommendations#diagnosing-preterm-labour-for-women-with-intact-membranes.
2. BIOSYNEX. PREMAQUICK® RAPID TEST FOR THE PREDICTION OF IMMINENT DELIVERY 2020 [cited; Available from: https://rhogen.es/wp-content/uploads/2021/08/IFU-PREMAQUICK-INGLE%CC%81S.pdf.
3. Public Health Scotland. Births in Scotland. 2022.
4. Watson HA, Carlisle N, Seed PT, Carter J, Kuhrt K, Tribe RM*, et al.* Evaluating the use of the QUiPP app and its impact on the management of threatened preterm labour: A cluster randomised trial. PLoS Med. 2021;18(7):e1003689. Epub 20210706. 10.1371/journal.pmed.1003689
5. Varley-Campbell J, Mujica-Mota R, Coelho H, Ocean N, Barnish M, Packman D*, et al.* Three biomarker tests to help diagnose preterm labour: a systematic review and economic evaluation. Health Technol Assess. 2019;23(13):1-226. 10.3310/hta23130
6. Abdelazim IA, Amer OO, Shikanova S, Karimova B. Diagnostic accuracy of PremaQuick in detection of preterm labor in symptomatic women. Ginekologia Polska. 2022;93(2):121-5.
7. Abu-Faza M, Abdelazim IA, Svetlana S, Nusair B, Farag RH, Nair SR. Diagnostic accuracy of PremaQuick versus actim partus in prediction of preterm labor in symptomatic women within 14 days. Open Journal of Obstetrics and Gynecology. 2018;8(08):741.
8. Asiegbu AC, Eleje GU, Ibeneme EM, Onyegbule OA, Chukwu LC, Egwim AV*, et al.* Combined insulin-like growth factor binding protein-1/interleukin-6 (Premaquick) versus fetal fibronectin for predicting preterm delivery among women with preterm contractions. International Journal of Gynecology & Obstetrics. 2020;149(2):171-7.
9. Eleje GU, Ezugwu EC, Eke AC, Eleje LI, Ikechebelu JI, Ezebialu IU*, et al.* Accuracy of a combined insulin-like growth factor-binding protein-1/interleukin-6 test (Premaquick) in predicting delivery in women with threatened preterm labor. Journal of Perinatal Medicine. 2017;45(8):915-24.