NICE advice

Proov Confirm for ovulation confirmation

Medtech innovation briefing
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www.nice.org.uk/guidance/mib322

Overview

NICE has developed a medtech innovation briefing (MIB) on Proov Confirm for ovulation confirmation.

The information provided includes a description of the technology, how it's used and its potential role in the treatment pathway. A MIB also includes a review of relevant published evidence and the likely costs of using the technologies, but they are not NICE guidance and do not make any recommendations on the value of using the technologies.

Summary

- The **technology** described in this briefing is Proov Confirm. It is a lateral flow test designed to confirm ovulation by detecting pregnanediol-3a-glucuronide (PdG), the major metabolite of progesterone, in the first morning urine during the luteal phase of the monthly reproductive cycle.

- The **innovative aspects** are that Proov Confirm is a non-invasive home test that tracks a progesterone marker to confirm ovulation quality. Compared with standard care, which is a single blood test, Proov Confirm provides an overview of PdG hormone levels over a 4-day period with instant results. The company says it is designed to help pregnancy happen faster.
- The intended **place in therapy** would be as an alternative to a blood test for confirming ovulation.
- The **main points from the evidence** summarised in this briefing are from 3 studies, including 2 prospective observational studies (1 of which was a pilot study) and 1 retrospective pilot study, including a total of 226 people. The studies suggest that Proov Confirm may be an effective technology for confirming ovulation.
- **Key uncertainties** around the evidence or technology are that there is limited evidence and none of the published studies were based in the UK. There is also no randomised study comparing the technology to standard care or to a similar technology.
- **Experts advised** that Proov Confirm is a novel technology that is less invasive and convenient for people to self-test at home without the need for clinic visits, and it provides an immediate result for confirming ovulation. They noted that evidence is limited, and they advised that large-scale studies are needed on its accuracy, efficacy and validity before routine adoption in the NHS.
- The **cost** of Proov Confirm is £24.99 per pack of 5 tests (excluding VAT) per month of testing. The cost of a standard care blood test is £1.85.

The technology

Proov Confirm (MFB Fertility) is designed to confirm ovulation across the implantation window. It measures pregnanediol-3a-glucuronide (PdG) in the first morning urine during the luteal phase of the menstrual cycle. PdG is a hormone marker released after ovulation that supports implantation.

Proov Confirm is a disposable lateral flow test strip, which has a test area and a control area. The urine sample is applied to the strip by dipping. The sample moves by lateral flow into the test area, and then into the control area. The test area contains PdG-specific reagents on it which detect hormone metabolites in urine. The control area contains

antibodies that are an internal control for proper assay function. The technology is intended for use outside the body (in vitro diagnostic use) and provides qualitative results, with a single red line indicating a positive result and 2 red lines indicating a negative result for PdG in urine.

A Proov Confirm test result can be read by eye or paired with an optional smartphone application that provides quantitative results of the test. The smartphone application is used as a logging tool that provides test reminders, results, and an ovulation insight report at the end of the testing period. A Proov Confirm pack contains 5 tests. The first test is used early in the menstrual cycle to establish a baseline, and the result is expected to be negative. The remaining 4 tests are used during the key implantation window, which takes place on days 7 to 10 after peak fertility. Users track their peak fertility either by using a luteinising hormone (LH) test, a fertility tracking device, or cervical mucus production.

Innovations

The technology provides non-invasive monitoring of luteal phase health in natural cycles. It is an over-the-counter product that does not need a GP or hospital visit. The company says that Proov Confirm detects elevated PdG levels across the full implantation window to confirm that hormone levels are sustained, indicating successful ovulation and promoting the highest chance of pregnancy. The company also claims that Proov Confirm can help prevent early miscarriages caused by low progesterone levels, through detection of a luteal phase defect. There is no published evidence to support this claim.

Current care pathway

Standard care involves offering people having investigations for infertility a blood test to measure serum progesterone in the mid-luteal phase of their cycle to confirm ovulation. In the case of an irregular menstrual cycle, blood tests may need to be done later in the cycle and repeated weekly thereafter until the next cycle. A clinical expert noted that in certain instances, ovulation detection could include repeated examination for an LH peak, and repeated ultrasound examination.

The following publication has been identified as relevant to this care pathway: NICE's guideline on fertility problems: assessment and treatment.

Population, setting and intended user

Proov Confirm is intended to be used to confirm ovulation for people who are trying to conceive. Proov Confirm can be used at home and in primary care settings, including GPs.

Costs

Technology costs

The cost of Proov Confirm is £24.99 per pack (excluding VAT) per month of testing. A Proov Confirm pack contains 5 tests. The smartphone application is free to download.

Costs of standard care

Based on the national schedule of NHS costs for 2020 to 2021, the average cost of a clinical biochemistry (progesterone blood test category) pathology service is £1.85.

Resource consequences

The technology is not currently used in the NHS. It would be used as an alternative to standard care in a primary care setting or at home. The technology costs more than standard care but if adopted could result in earlier or more accurate detection of ovulation disorders. The company claims that providing the product for use in the NHS will reduce healthcare costs by diagnosing ovulation disorders that lead to infertility and early miscarriages, reducing the need for fertility treatments such as in vitro fertilisation (IVF). There is very limited published evidence to support these claims.

Regulatory information

Proov Confirm is a CE-marked in vitro diagnostic self-test class I medical device.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination, and fostering good relations between people with particular protected

characteristics and others.

The technology is not suitable for people who are using birth control, in menopause or using hormone replacement therapy. It is also not relevant for people without fallopian tubes or who do not have a uterus and cannot conceive naturally.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement for medtech innovation briefings. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

There are 3 studies summarised in this briefing, including a total of 226 people. The evidence includes 2 prospective observational studies (1 of which was a pilot study) and 1 retrospective pilot study. The clinical evidence and its strengths and limitations are summarised in the overall assessment of the evidence.

Overall assessment of the evidence

The evidence base for Proov Confirm is limited and comes from pilot and observational studies. All 3 studies had no comparators and relatively small sample sizes. All studies tracked pregnanediol-3a-glucuronide (PdG) hormone for a short duration of approximately 1 cycle. None of the studies were done in the UK.

Overall, the results suggest that Proov Confirm has the potential to accurately confirm ovulation. One study associated positive PdG cycles with increased pregnancy rates and lower odds of a first-trimester pregnancy loss.

To improve the evidence base, further research with larger sample sizes across multiple sites, ideally in the UK, is needed. Also, studies comparing the technology to standard care in the NHS can help evaluate the impact on changes to clinical management.

Beckley et al. (2022)

Study size, design and location

Prospective observational study of 185 people in the US actively trying to conceive or not actively trying to avoid pregnancy.

Intervention and comparator

Proov Confirm with mobile application diagnostic device, no comparator.

Key outcomes

Of the total 185 people, 172 enrolled in the study had a complete cycle, and 54 (31.4%) of those with complete cycles reported pregnancies. Of these pregnancies, 35 (64.8%) resulted from a PdG-positive cycle, with a miscarriage rate of 14.3% (5 out of 35). Nineteen pregnancies (35.2%) resulted from PdG-negative cycles, with a miscarriage rate of 89.5% (17 out of 19). The association of a negative or positive cycle with pregnancy outcome was significant (2-sided p=0.0001).

Strengths and limitations

A main limitation of the study is that 45% of people with a complete cycle were reported to be on 1 or more fertility medications for ovarian stimulation, ovarian induction, or luteal phase support. People were recruited on the basis that they were established users of the app and had also already completed 1 cycle using Proov Confirm. The study was funded and carried out by the company.

Leiva et al. (2019)

Study size, design and location

Pilot observational prospective cohort study of 28 people in Canada.

Intervention and comparator

Proov Confirm, no comparator.

Key outcomes

Of the 28 people recruited to the study, 22 contributed 1 cycle each for analysis. Ages ranged from 18 to 42 years with a recorded median luteal phase of 12 days. Peak fertility was determined either by using luteinising hormone (LH) test strips or by tracking cervical mucus production. The specificity of the PdG test for confirming ovulation was 100%. The sensitivity varied depending on whether a peak-fertility mucus day or a positive LH test was seen during the cycle. Sensitivity was 85% if a positive LH test was followed by 3 consecutive positive PdG tests. Sensitivity was 88% if a peak-fertility mucus day was followed by 3 consecutive positive PdG tests. Fifty percent of users found the test results easy to understand.

Strengths and limitations

The study measured serum progesterone levels as an additional approach to confirm ovulation and determine the specificity of the tests. It also provided an estimate of the number of ultrasound-monitored cycles that will be needed to expect a narrow confidence interval range between 95% and 100% in future studies. The main limitation of the study was the small sample size from a single centre, which limits its generalisability.

Bouchard et al. (2019)

Study size, design and location

Retrospective pilot study of 13 people in the US to confirm ovulation.

Intervention and comparator

Proov Confirm, no comparator.

Key outcomes

People in the study had a mean age of 33.6 years and produced 34 menstrual cycles of data with the luteal phase ranging from 10 to 16 days. There were 17 menstrual cycles of data using PdG test sticks for each of the 7 microgram/ml and 5 microgram/ml thresholds. When the 7 microgram/ml test strips were used, 59% (10 out of 17) of menstrual cycles had a positive confirmation of ovulation. When the 5 microgram/ml test strips were used, 82.4% (14 out of 17) had a positive confirmation of ovulation. The positive PdG tests

happened 2 to 10 days after the second peak reading of LH on the monitor, with the most frequent positive results on days 4 and 5 past the surge. But all 14 of the menstrual cycles that had a positive PdG with the 5 microgram/ml test strips had a narrower window, happening 2 to 5 days past the LH surge, with the positive test happening most frequently on days 4 and 5. The 95% confidence intervals were 0.64 to 1.00 for the 5 microgram/ml test and 0.36 to 0.82 for the 7 microgram/ml test.

Strengths and limitations

The main limitation of the study was the small sample size.

Sustainability

The company claims the technology reduces the environmental impact (for example, through less travel and better use of NHS resources) and minimises waste by reducing single-use plastic. There is no published evidence to support these claims.

Recent and ongoing studies

- Ovulation double check (Proov) verification and usability testing. ClinicalTrials.gov identifier: NCT03924440. Status: enrolling by invitation, interim results published. Indication: ovulation disorder. Device: Proov Confirm. Date: December 2022. Country: US.
- Relationship between fertility hormone patterns and pregnancy rates. ClinicalTrials.gov identifier: NCT05033366. Status: enrolling by invitation, interim results published. Indication: pregnancy-related hormone deficiency. Device: Proov Confirm. Date: April 2024. Country: US.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Four experts commented on this briefing. All experts were familiar with similar lateral flow tests. None of the experts had used Proov Confirm before.

Level of innovation

The experts agreed that Proov Confirm is novel and innovative, especially with the convenience for people to test at home, the non-invasive nature of the technology and the ability to provide an immediate result on ovulation occurrence. They noted that it uses simple technology in a new way to provide clinical information without the need to visit the hospital for a blood test. One expert said that the possibility of testing over a 4-day period rather than a snapshot single blood test allows for better detection of progesterone and therefore improves accuracy.

Potential patient impact

The experts said that the potential benefits of Proov Confirm include:

- fewer hospital visits
- less invasive treatment
- quicker diagnosis of an anovulatory cycle
- immediate treatment adjustments
- signposting to relevant fertility services.

One expert said Proov Confirm can provide repeated reassurance for people that they are ovulating.

Two experts said that in addition to Proov Confirm being used to confirm ovulation, it also provides invaluable information about luteal phase health. One expert highlighted the importance of this for in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) treatment cycles. The expert said that there is the potential for people to have progesterone treatment when a luteal phase defect has been identified, which may increase IVF success rate.

Potential system impact

All experts believed that Proov Confirm could replace standard care to confirm ovulation. One expert noted that serum progesterone results received a couple of days after the blood draw, as is the case in most NHS hospitals, are no longer useful. Another expert said

that Proov Confirm represents a significant improvement on current NHS testing. Two experts agreed that Proov Confirm is likely to cost less in terms of staff, equipment and care setting needed. One expert noted that it is difficult to estimate the cost savings without a health economic evaluation.

General comments

The clinical experts said that, overall, there were no potential issues or adverse events related to using Proov Confirm. All clinical experts agreed that Proov Confirm could benefit most of its target population, including people with delayed conception, people requiring assessment of ovulation as part of fertility investigation, and people having IVF, particularly those with frozen embryo transfers.

One expert noted that the use of first morning urine to measure progesterone levels limits the effect of the diurnal variation and pulsatile release of progesterone, potentially making Proov Confirm more accurate than a serum progesterone blood test. One expert identified that the technology could be of interest to other specialists such as endocrinologists and physiologists.

Two experts said that the current level of evidence cannot verify the claims that Proov Confirm could help people to get pregnant faster, prevent early miscarriage and increase the chances of successful implantation. Three experts said that further larger-scale research is needed, including research on its accuracy, efficacy and validity. One expert noted that research is needed in people not currently being treated with ovulation-inducing agents. One expert found it difficult to consider the results as robust.

Patient organisation comments

A representative from Fertility UK commented that Proov Confirm would benefit people wanting to confirm that ovulation had occurred in a cycle, which is valuable information when there have been delays in conception. They said that standard care is a single progesterone reading, which does not give the full width of the fertile period. They also said that Proov Confirm is helpful if a person has an unpredictable lifestyle (such as getting up at different times each day) and cannot sufficiently rely on their waking temperature readings to detect ovulation.

The representative raised concerns about people accessing information on their hormonal

status without having access to a healthcare professional to put the result into context. They noted that home testing can give false assurance and that professional help may be more appropriate and timelier.

Expert commentators

The following clinicians contributed to this briefing:

- Claudia Raperport, senior registrar and PhD student in obstetrics and gynaecology and reproductive medicine, Queen Mary University of London and London North West University Healthcare NHS Trust. Has a non-financial professional interest and a future research-study planning partnership with the company.
- Matthew Prior, consultant gynaecologist and subspecialist in reproductive medicine, Newcastle Fertility Centre. Did not declare any interests.
- Roy Homburg, professor and director of research, Hewitt Fertility Centre, Liverpool Women's Hospital. Did not declare any interests.
- Stuart Lavery, consultant gynaecologist, University College London Hospitals NHS Foundation Trust. Did not declare any interests.

A representative from Fertility UK contributed to this briefing.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement for medtech innovation briefings sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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