Clearblue®

CLEARBLUE DIGITAL PREGNANCY TEST WITH WEEKS INDICATOR

The only pregnancy test that also indicates weeks (1–2, 2–3, 3+) since conception

Clearblue Professional Series

PREGNANCY

About Clearblue

Clearblue® is the world's number one selling brand in home pregnancy and fertility tests.[a] Consumers trust the Clearblue brand because it delivers the accurate information they want. The Clearblue product range is built on a strong foundation of peer-reviewed science and consumer understanding. Clearblue is supported by over 30 years of expertise, quality, and innovation in consumer diagnostics.

Revolutionising home pregnancy testing

The Clearblue Digital Pregnancy Test with Weeks Indicator is the latest innovation in pregnancy testing. It is an over-the-counter semi-quantitative urine test for human chorionic gonadotrophin (hCG), which is intended for the detection of pregnancy. It is a simple-to-use product that is unique because it not only informs a woman whether she is pregnant or not, but also estimates the time since conception, in categories of 1–2, 2–3 and 3+ weeks.

- The Clearblue Digital Pregnancy Test with Weeks Indicator is over 99% accurate in detecting pregnancy from the day of the expected period[1]
- The Weeks Indicator feature uses known levels of hCG in urine relative to the day of the luteinising hormone (LH) surge to estimate time since conception
- Agreement between Clearblue Digital Pregnancy Test with Weeks Indicator results and time since conception by LH surge (+/- 1 day) is 93%[2]
- It is also sensitive enough to be used up to 5 days before the missed period (which corresponds to 4 days before the expected period).[1,b]

Innovation using established technology

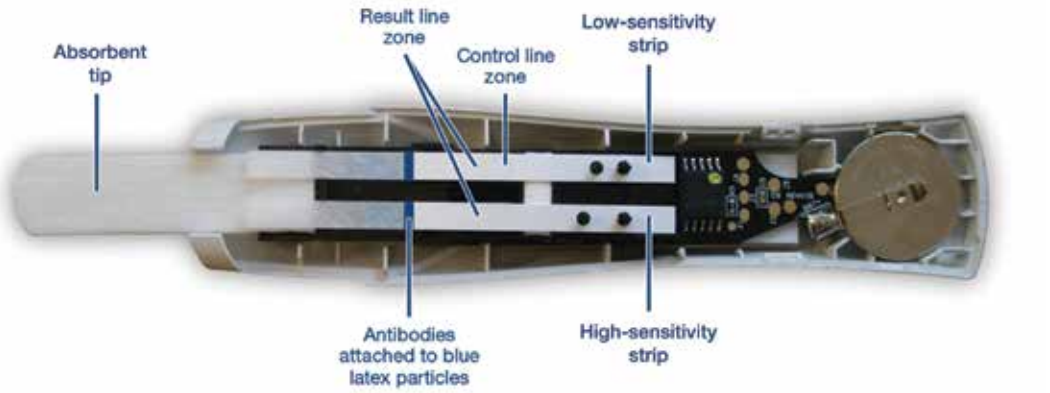
- As with other home pregnancy tests, the Clearblue Digital Pregnancy Test with Weeks Indicator detects hCG, the hormone produced early in pregnancy and excreted in the urine[3]
- The hormone hCG is the marker of choice for detecting pregnancy and has a long and proven history in pregnancy testing[4]
- Uniquely, in addition to detecting hCG, the Clearblue Digital Pregnancy Test with Weeks Indicator also measures the level of hCG, which indicates 1–2, 2–3, 3+ weeks since conception[5]
- The Weeks Indicator feature assumes conception occurred on the day after the urinary LH surge (which stimulates ovulation)[6,7] and works on a threshold basis of urinary hCG levels (Table One).[2] These thresholds are based on extensive research of the urinary hCG rise in early pregnancy.[8,9]

Table One: Urinary hCG threshold levels used in the Clearblue Digital Pregnancy Test with Weeks Indicator to determine time since conception

Weeks since conception	Urinary hCG threshold (mIU/ml)
1–2 weeks	10
2–3 weeks	153
3+ weeks	2753

The Clearblue Digital Pregnancy Test with Weeks Indicator

State-of-the-art micro-semi-quantitation



- The Clearblue Digital Pregnancy Test with Weeks Indicator uses a pioneering new approach and novel algorithm for measuring urinary hCG
- It contains two hCG measurement strips – a low-sensitivity strip and a high-sensitivity strip, to enable the device to detect and analyse the wide dynamic range of hCG concentrations found in urine during pregnancy. The high-sensitivity strip detects low levels of hCG, expected in early pregnancy, and the low-sensitivity strip detects higher levels of hCG, typical when pregnancy is more than 3 weeks since conception
- The test monitors the Control line, which is present on the low-sensitivity strip, and the Result lines, which are present on both strips. Only when a valid Control line is detected will the result be determined
- The Control and Result lines cannot be read by eye. Instead, the test uses an optical system to measure the density of the lines – a red light shines onto the Control and Result line zones, the photodiode detects reflected light and a micro-processor converts this signal into clear results visible on a liquid crystal display (LCD).

Over 99% accurate[c] from the day of the expected period

The Clearblue Digital Pregnancy Test with Weeks Indicator demonstrated over 99% accuracy in detecting pregnancy when compared with a laboratory method (quantitative AutoDELFIA).[1]

The study, using urine samples from 300 women aged 18-45 years across three batches, found overall agreement between the Clearblue Digital Pregnancy Test with Weeks Indicator in detecting pregnancy and quantitative hCG measurement to determine pregnancy to be 99.4%.[1]

Can be used up to 5 days before the missed period[b]

The Clearblue Digital Pregnancy Test with Weeks Indicator is highly sensitive and can be used up to 5 days earlier. In a study, 135 women provided first morning urine samples every day during the cycle in which they became pregnant.

The Clearblue Digital Pregnancy Test with Weeks Indicator detected 65% of pregnancies 5 days before the missed period (which corresponds to 4 days before the expected period) and 90% of pregnancies 4 days before the missed period (which corresponds to 3 days before the expected period) (Table Two).[1]

Table Two: Number of pregnancies detected with the Clearblue Digital Pregnancy Test with Weeks Indicator.[1]

Days before the expected period	4	3	2	1	0
Number of pregnancies detected	65%	90%	97%	98%	99%

Has excellent specificity

Concentrations of hCG in non-pregnant women increase with age, which can potentially result in some peri-or post-menopausal women obtaining inaccurate false-positive results with some types of pregnancy tests. The Clearblue Digital Pregnancy Test with Weeks Indicator is over 99% accurate from the day of the expected period, regardless of whether women are pre-, peri- or post-menopausal.[1]

A total of 301 individual female urine samples were collected from pre-menopausal (n=100), peri-menopausal (n=101) and post-menopausal (n=100) age groups. Qualitative hCG analysis was performed on all samples prior to conducting the study. In this non-pregnant population, all 301 urine samples were tested with three batches of Clearblue Digital Pregnancy Test with Weeks Indicator. All tests conducted on this panel were negative with no false positive results reported.[1]

The 'Weeks Indicator' feature – Background on how the Clearblue Digital Pregnancy Test with Weeks Indicator provides an estimate of time since conception

LH surge – an accurate method for referencing time since conception

The day of fertilisation is the most accurate method for dating pregnancy and this can be estimated from the day of ovulation, as studies have shown that the egg survives for only up to 24 hours,[10] and that a woman's fertile period ends on the day of ovulation.[11–13]

LH is a hormone produced by the anterior pituitary gland. A surge in LH triggers ovulation, and also initiates the conversion of the residual follicle into a corpus luteum that, in turn, produces progesterone to prepare the endometrium for a possible implantation. The World Health Organization (WHO) has defined the rise in circulating LH as the best parameter for impending ovulation, and the day of ovulation is considered a surrogate marker for conception, as conception can only occur within 24 hours of egg release.[14,15] Levels of LH in urine correlate 100% with ultrasound detection of ovulation.[16]

A prospective study using the Clearblue Fertility Monitor found that the LH surge preceded the day of ovulation in 76% of cycles where there was a surge, and was within ±1 day of day of agreement for 97% of these cycles. Therefore, ovulation can be presumed to occur on the day of the LH surge +1 (with a ±1 day range).[17]

Human chorionic gonadotrophin (hCG) – an accurate scientific marker of time since conception

The peptide hormone hCG is produced by the embryo soon after conception, and later by the syncytiotrophoblast (part of the placenta). An important role of hCG is to prevent the disintegration of the corpus luteum and thereby maintain progesterone production, which is critical for pregnancy in humans.

The Weeks Indicator feature of the Clearblue Digital Pregnancy Test uses urinary hCG levels to estimate the time since conception, as hCG levels change predictably with pregnancy duration.

- Levels of hCG in serum and urine rise rapidly during the first days of pregnancy[18,19] and are first detectable 7 days before the missed period (which corresponds to 6 days before the expected period), when this is estimated using the day of ovulation[10]
- In studies, absolute levels of hCG have been used to estimate gestational age[20,21]
- Rigorous trials on approximately 3000 individual samples show there is a consistent pattern to urinary hCG levels during early pregnancy[9]
- Three separate studies conducted in the UK and US over several years have each provided identical evidence that hCG rises consistently in early pregnancy (Figure One)[22,23,24]

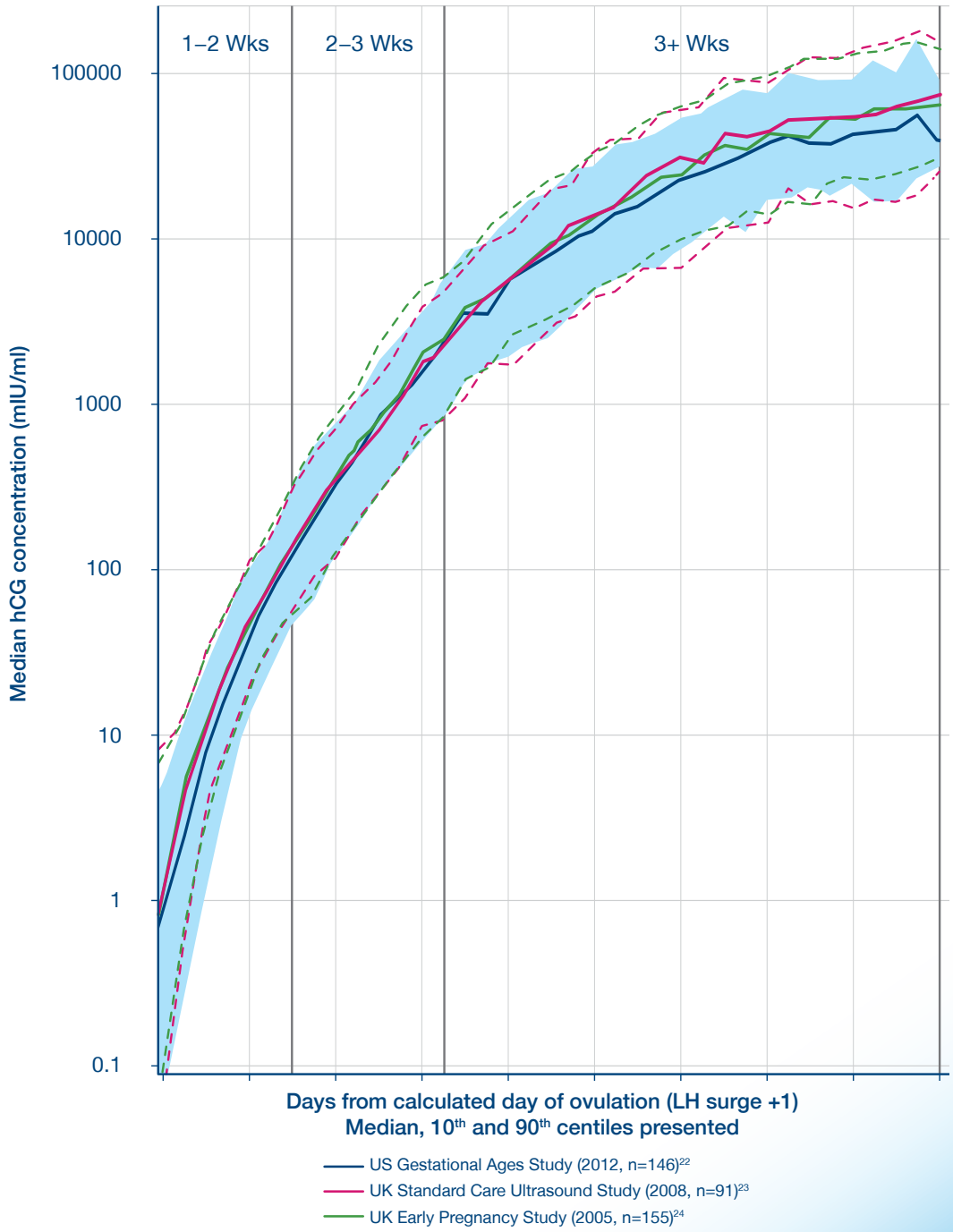


Figure One: The daily rise in urinary hCG detected in early pregnancy in three different studies.

- No differences are observed in daily hCG concentration in early pregnancy between different ethnicities or races[9,25]
- Pregnancy duration has been scientifically validated as being related to absolute quantities of hCG in urine and can be used to give an estimation of time since ovulation in weeks, relative to LH surge (Figure Two).[8,9,18,20,24] Studies have shown that gestational age estimated by hCG concentration (measured by automated immunoassay) agrees with gestational age estimated using the day of ovulation by 96% for 1–2 weeks gestation, 93% for 2–3 weeks and 95% for more than 3 weeks.[9]

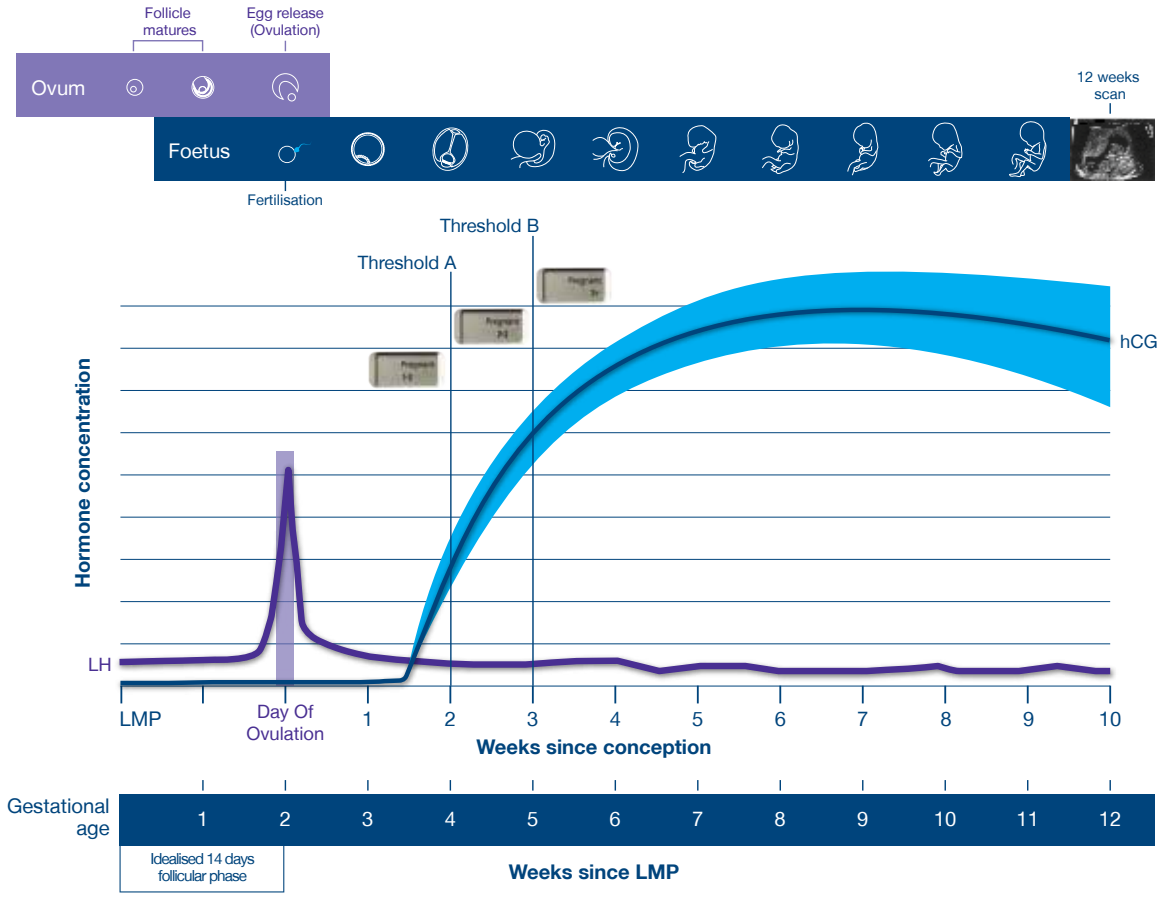


Figure Two: Derivation of Clearblue Digital 'Weeks' indications based on hCG levels relative to the day of ovulation (day following LH surge), in comparison to dating of pregnancy by last menstrual period (LMP).

Comparison of Clearblue Digital Pregnancy Test with Weeks Indicator to standard methods of dating pregnancy

Day of last menstrual period – a frequently inaccurate method

Traditionally the date of the first day of a woman's last menstrual period (LMP) is used to date pregnancy, as this is often the only information available in early pregnancy upon which to base an estimate. LMP is, however, frequently inaccurate due to a variety of reasons:

- Many women do not know, or are uncertain of their LMP:
  - Examination of US birth records found that 16–20% of women have no recorded LMP[26,27] and another study found that 16% of women had an unknown LMP[28]
  - Only 32% of women are truly certain of their LMP[29]
  - The high incidence of 'round number' preference observed when women are asked to recall their LMP supports the uncertainty of many women; 2.5 times more women chose the 15th day of the month as their LMP than would be expected[30]
- Bleeding in early pregnancy can be mistaken for LMP
- Recent contraceptive use or underlying endocrine problems can lead to an inaccurate estimate of LMP
- For those women whose LMP is certain, there is an assumption that the follicular phase is 14 days long; however, the follicular phase can range from 5–24 days[31] resulting in as many as 10% of women who are certain of their LMP date being more than 7 days inaccurate in their estimation of gestational age[32]
- LMP provides a value to the same week in only 46% of women (within +1 week in 78%, within +2 weeks in 87%).[33]

Ultrasound – standard of care for dating pregnancy in many countries

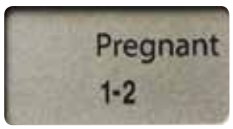
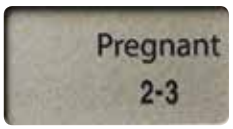
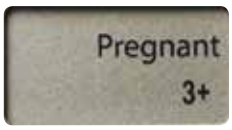
First trimester ultrasound is a more accurate method for dating pregnancy than LMP. Ultrasound at approximately 11^{+0} to 13^{+6} weeks after LMP is the standard of care for dating pregnancy in many countries. This method estimates gestational age based on crown rump length (CRL) converted using validated formulae,[34-36] which include an idealised 14-day follicular phase, to align the result to LMP dating. Dating using ultrasound CRL is typically quoted as providing an accurate estimation of gestational age ±5 days.[37-40]

How the Clearblue Digital Pregnancy Test with Weeks Indicator results relate to clinical care

The Clearblue Digital Pregnancy Test with Weeks Indicator is not intended to be a replacement for clinical care, but rather provides information that a woman is immediately interested in once she has received a pregnant result, i.e., “How long is it since I conceived?”, and knowing the answer to this question can help her when speaking with healthcare professionals (HCPs). The instruction leaflet makes it clear that the woman should seek guidance from a HCP on receipt of a pregnant result, and also helps her to put the results into context with other methods of pregnancy dating; i.e., this test estimates time since conception, which can be related to the way a doctor dates pregnancy if an idealised follicular phase (14 days) is added to the Weeks Indicator result.

The table below is included in the instruction leaflet to help women understand how the result from their Clearblue Digital Pregnancy Test with Weeks Indicator relates to pregnancy dating by HCPs (Table Three).

Table Three: How the Clearblue Digital Pregnancy Test with Weeks Indicator result relates to doctors’ pregnancy dating using LMP.

Result	 Pregnant 1–2	 Pregnant 2–3	 Pregnant 3+
What does this mean?	Pregnant and conceived approximately 1–2 weeks ago	Pregnant and conceived approximately 2–3 weeks ago	Pregnant and conceived more than 3 weeks ago
How your doctor will date your pregnancy (weeks pregnant)	3–4 weeks	4–5 weeks	5+ weeks

Clearblue Digital Pregnancy Test with Weeks Indicator compared with reference methods for determining gestational age

A multi-centre, prospective study was conducted to compare the Weeks Indicator results with reference methods for determining gestational age. Women were recruited pre-conception, providing 153 pregnancies for analysis. Urine samples were collected by participants throughout their cycle and for 4 weeks from the date their period was due if pregnancy occurred. Quantitative measurement of urine LH was used to determine the LH surge (with LH surge +1 day defined as the day of ovulation), and ultrasound dating scans were conducted at 11^{+0}–13^{+6} weeks' gestation following Fetal Medical Foundation (FMF) guidelines.[41] Clearblue Digital Pregnancy Test with Weeks Indicator was tested on a random set of urine samples, from 4 days prior to the day the period was due until 4 weeks later, ensuring equal representation per volunteer and per week, and that analysis accounted for within-woman variation.

In this study, agreement between Clearblue Digital Pregnancy Test with Weeks Indicator results and time since conception (ovulation) by LH surge (+/- 1 day) was 93%. If the +/-1 day variation in timing of ovulation from surge is not accounted for, agreement was 87%. The breakdown by weeks category is shown in Table Four.[2]

Table Four: Accuracy of the Clearblue Digital Pregnancy Test with Weeks Indicator compared with ovulation day.[2]

Time since ovulation	Accuracy allowing for measurement error (without allowance for measurement error)
1–2 weeks	96.0% (92.0%)
2–3 weeks	84.0% (72.0%)
3+ weeks	97.0% (94.0%)
Overall	93.0% (87.0%)

When comparing Clearblue Digital Pregnancy Test with Weeks Indicator results to the CRL measurement taken later in the same pregnancy, consideration has to be given to the formula used to convert this CRL measurement into gestational age. Formula choice can have a profound influence on agreement analysis due to the systematic bias evident with some formulae. In addition, CRL measurement has a measurement error associated within it; therefore, in cases of disagreement between methods, it can be unclear whether this is due to the CRL measurement or the Clearblue Weeks Indicator device. Typically, for scans conducted in early pregnancy, a ±5-day leeway is applied to any measurement. Therefore, analysis of the multi-centre prospective study results was conducted applying this clinical practice. Table Five summarises the agreements found between the Clearblue Digital Pregnancy Test with Weeks Indicator and ultrasound, using different formulae and allowing or not allowing for ultrasound measurement error.

Table Five: Agreement between Clearblue Digital Pregnancy Test with Weeks Indicator result and ultrasound estimate using different methods with or without allowing for ultrasound error.[39]

Reference method and method of comparison	Weeks Indicator result			
	1–2	2–3	3+	Overall
Robinson[34] with adjustment for ultrasound error (without adjustment)	95.5% (49.5%)[42]	94.6% (63.7%)[42]	100.0% (98.8%)[42]	98.0% (82.5%)[42]
Hadlock[35] with Pexsters[43] adjustment for bias with adjustment for ultrasound error (without adjustment)	99.1% (76.5%)	97.4% (71.1%)	99.9% (96.2%)	98.9% (86.0%)

Notes on formulae: The Hadlock formula is frequently used in clinical care and is a pre-set formula for most ultrasound equipment. Recent evidence shows that this formula has a systematic bias of +2 days,[43] which has no consequence in clinical practice, but when used as a reference method can provide a low agreement. The Pexsters adjustment removes this bias, indicating that the low level of agreement at 1–2 weeks was algorithm dependent.

When gestational age estimated by LMP was compared in this study with gestational age estimates based on ultrasound and day of ovulation, it was found to agree in 78% and 82% of cases, respectively (when CRL was converted using the Hadlock formula, with bias adjustment). This is significantly lower than the agreements observed between the Clearblue Digital Pregnancy Test with Weeks Indicator and these reference methods ($P<0.05$).[2]

Comparison with standard-of-care ultrasound

In a study conducted in the UK, the Clearblue Digital Pregnancy Test with Weeks Indicator was compared with standard-of-care ultrasound, for assessing pregnancy duration in a real-life observational setting. Data was available from 52 pregnant women and this study reported an 82% agreement between the two methods. However, when a ±5-day range was applied to the ultrasound reading (as per routine UK clinical practice), the level of agreement increased to 98%.[23]

Comparison with ultrasound assessment in combined data from the US Gestational Ages[22] and UK Standard Care Ultrasound[23] studies

Two separate studies have examined the agreement between Clearblue Digital Pregnancy Test with Weeks Indicator and ultrasound; both studies found a high level of agreement (98%) despite being conducted in different geographies and using slightly different analysis methods.[22,23] To provide a consistent, consolidated agreement figure between Clearblue Digital Pregnancy Test with Weeks Indicator and ultrasound, a new analysis on all the available ultrasound data, using the same methodology was conducted. Data from 143 women from the US Gestational Ages[22] and 44 women from the UK Standard Care Ultrasound[23] studies were combined. Analysis of this combined dataset confirmed a high level of agreement (97%) between the Clearblue Digital Pregnancy Test with Weeks Indicator result and gestational age

based on estimates using dating ultrasound scan, thus indicating that the Clearblue Digital Pregnancy Test with Weeks Indicator results are comparable to an ultrasound dating scan.[44]

Comparison with delivery date

A prospective study was conducted to compare the Clearblue Digital Pregnancy Test with Weeks Indicator results with the ultrasound CRL measurement for the prediction of final delivery date. Urine samples were collected pre-conception until approximately 8 weeks gestational age from 46 women with a natural delivery from the US Gestational Ages[22] and UK Standard Care Ultrasound[23] studies. The mean time from the Weeks Indicator result (time since ovulation) to delivery was 37.47 weeks, while the mean time from ovulation to delivery date based on ultrasound CRL measurement was 37.40 weeks. The Clearblue Digital Pregnancy Test with Weeks Indicator provides a prediction of delivery date comparable to ultrasound CRL measurement, and the mean duration of time from ovulation to delivery is also consistent with the typically-reported 38 weeks.[45]

Comparison with serum levels of hCG

Results of the Clearblue Digital Pregnancy Test with Weeks Indicator have also been compared with serum levels of hCG (Figure Three). It can be seen that there is little overlap between the Clearblue Digital Pregnancy Test with Weeks Indicator result and the serum hCG concentrations.[46]

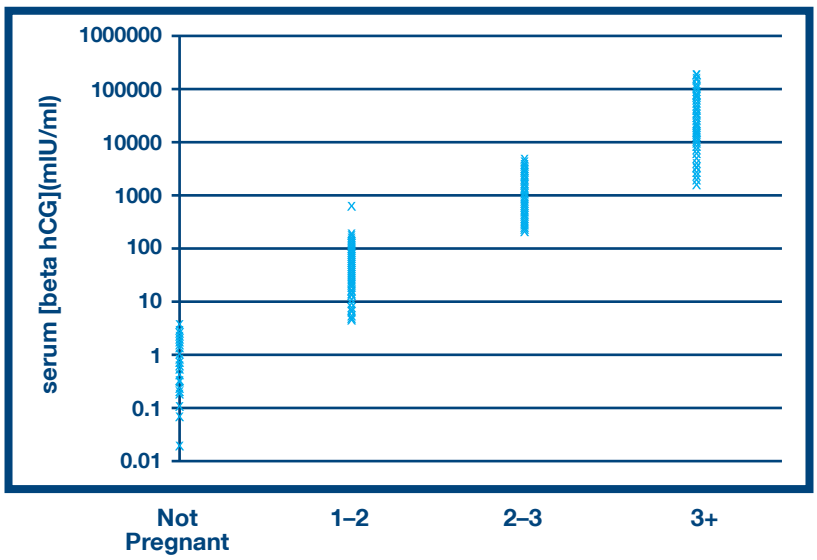


Figure Three: Comparison of Clearblue Digital Pregnancy Test with Weeks Indicator result with serum beta hCG concentration in 500 urine samples from 200 pregnant women[46]

What do consumers think?

- **Easy to use** – The Clearblue Digital Pregnancy Test with Weeks Indicator is easy to use and understand. Women prefer its midstream test stick format over other formats such as cassette or strip based pregnancy tests. In a study, more than 95% of women stated that they preferred the midstream test stick format, stating hygiene and ease of use as some of the reasons for this preference.[47]
- **Trusted by women** – Women feel great confidence in the results obtained with the Clearblue Digital Pregnancy Test with Weeks Indicator.[48] It displays a digital test result that is easy to read, giving women reassurance, confidence and trust in the accuracy of the result. In studies 98% of women were confident of the results of a pregnancy test when the results were displayed in words, compared with less than 50% for some traditional line-based tests, and less than 30% of women were confident in reading the results of strip- or cassette-based tests.[47] Furthermore, it has been shown that one in four women can misread traditional line pregnancy test results.[49]
- **Test women most favour** – A pregnancy test with a 'Weeks Indicator' feature is preferred by women.[50]

Points to remember

- The manufacturer's instructions regarding any medication being taken should be read before conducting the test
- When testing before the day of the expected period, an early-morning urine sample should always be used. This is not necessary when testing on or after the day of the expected period
- Testing within 14 days after administration of a fertility drug containing hCG can give a false pregnant result
- Excessive fluid intake should be avoided before testing, as a urine sample that is too dilute may give a false negative (non-pregnant) result
- Ectopic pregnancy can give misleading results[51]
- Elevated levels of hCG that are caused by an increase of pituitary hCG production in perimenopause and chemotherapy-induced suppression of gonadal function, or gestational trophoblastic disease, can give misleading results[51]
- A recent pregnancy, miscarriage or termination can give misleading results, as hCG can be found in the body for several weeks after giving birth[52] and after a miscarriage or termination[53]
- If a positive (pregnant) result is obtained and the woman later obtains a non-pregnant result, or her period starts, it may be due to natural loss during the early stage of pregnancy, which is not uncommon, as around one in four pregnancies end in early pregnancy loss[54,55]
- Women should be encouraged to discuss any unexpected results with their healthcare professional.

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44. Data on file: Analysis of a combined dataset from 143 women from the US Gestational Ages[22] and 44 women from the UK Standard of Care[23] studies reported high level agreement (97%) between Clearblue Digital Pregnancy Test with Weeks Indicator and ultrasound dating scan results.
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48. Data on file: In a study of 114 consumers, 93.8% rated their confidence in the result of the Clearblue Digital Pregnancy Test with Conception Indicator as scale points 1–3 on a 7 point scale (1=very confident; 7=not very confident).
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The Clearblue Digital Pregnancy Test with Weeks Indicator:

Accurate - over 99% accurate in detecting pregnancy from the day of the expected period

Unique - the first and only digital pregnancy test that also indicates weeks since conception (1-2, 2-3, 3+ weeks)

Clinically proven - 97% agreement with estimation of gestational aging by ultrasound[d]

Sensitive - can be used up to 5 days before the missed period[b]

Unmistakably clear - results displayed in words and numbers on a digital screen

Reliable - based on established technology

Simple to use - convenient and easy to interpret

Trustworthy - from Clearblue, the world's number one selling brand in home pregnancy and fertility tests[a]

[a] Based on international sales in nearly 20 countries compiled using independent market research data.

[b] Can be used 5 days before the missed period (which corresponds to 4 days before the expected period). In laboratory testing, 98% of pregnant results were detected on the day before the expected period, 97% were detected 2 days before, 90% were detected 3 days before and 65% were detected 4 days before the expected period (5 days before the missed period).

[c] Data on file. Clearblue Digital Pregnancy Test with Weeks Indicator has been shown to be over 99% accurate from the day of the expected period when compared to a reference method in laboratory studies using urine samples supplied for pregnancy testing.

[d] Based on studies of 187 women comparing ultrasound dating to weeks result (up to 3+ weeks).[22]

[e] The Clearblue Digital Pregnancy Test with Weeks Indicator result does not replace the need for a pregnant woman to attend routine ultrasound examinations.

Clearblue®

For more information about the Clearblue Digital Pregnancy Test, please visit our website:

www.clearblue.com

SPD Swiss Precision Diagnostics GmbH

www.swissprecisiondiagnostics.com

SPD Swiss Precision Diagnostics GmbH, 1213 Petit Lancy, Geneva, Switzerland

Clearblue Professional Series: HCP-0018.4