

# TOTAL BETA-HUMAN CHORIONIC GONADOTROPIN ( $\beta$ -hCG)

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## Intended Use

The i-STAT® Total Beta-Human Chorionic Gonadotropin ( $\beta$ -hCG) assay is an *in vitro* diagnostic test for the quantitative and qualitative determination of beta-human chorionic gonadotropin in whole blood or plasma samples.  $\beta$ -hCG can be used for the detection of early pregnancy.

## Method Explanation

The i-STAT  $\beta$ -hCG test cartridge uses a two-site enzyme-linked immunosorbant assay (ELISA) method. Antibodies specific for  $\beta$ -hCG are located on an electrochemical sensor fabricated on a silicon chip. Also deposited in another location on the sensor silicon chip is an antibody/alkaline phosphatase enzyme conjugate specific to a separate portion of the human chorionic gonadotropin molecule. The whole blood or plasma sample is brought into contact with the sensors allowing the enzyme conjugate to dissolve into the sample. The hCG within the sample becomes labeled with alkaline phosphatase and is captured onto the surface of the electrochemical sensor during an incubation period of approximately seven minutes. The sample, as well as excess enzyme conjugate, is washed off the sensors. Within the wash fluid is a substrate for the alkaline phosphatase enzyme. The enzyme bound to the antibody/antigen/antibody sandwich cleaves the substrate, releasing an electrochemically detectable product. The electrochemical (amperometric) sensor measures this enzyme product, which is proportional to the concentration of  $\beta$ -hCG within the sample.

## Contents

Each i-STAT  $\beta$ -hCG cartridge provides a sample inlet, sensors to detect the  $\beta$ -hCG as described above, and all the necessary reagents needed to perform the test. The cartridge contains a buffer and preservatives. A list of reactive ingredients is provided below:

| Reactive Ingredient                     | Biological Source             | Minimum Quantity |
|-----------------------------------------|-------------------------------|------------------|
| Antibody/Alkaline Phosphatase Conjugate | Murine IgG : Bovine Intestine | 0.003 $\mu$ g    |
| IgG                                     | Murine IgG                    | 8 $\mu$ g        |
| IgM                                     | Murine IgM                    | 3 $\mu$ g        |
| Sodium Aminophenyl Phosphate            | Not Applicable                | 1.8 mg           |
| Heparin                                 | Porcine Intestine             | 0.45 IU          |

## Metrological Traceability

The i-STAT System test for  $\beta$ -hCG measures hCG amount-of-substance concentration in plasma or the plasma fraction of whole blood (dimension IU/L) for *in vitro* diagnostic use.  $\beta$ -hCG values assigned to Abbott Point of Care's controls and calibration verification materials are traceable to Abbott Point of Care's working calibrators that are traceable to the World Health Organization's 5<sup>th</sup> International Standard (07/364), prepared from pooled plasma and hCG antigen obtained from 3<sup>rd</sup> party sources. i-STAT System controls and calibration verification materials are validated for use only with the i-STAT System and assigned values may not be commutable with other methods. Further information regarding metrological traceability is available from Abbott Point of Care Inc.

## Reportable Range

The i-STAT  $\beta$ -hCG Test will report 5.0 to 2000.0 IU/L. Samples below the reportable range will display "<5.0 IU/L" on the handheld. Samples above the reportable range will display ">2000.0 IU/L" on the handheld.

## Qualitative Interpretation of Results

The default setting on the handheld displays a quantitative  $\beta$ -hCG value as well as a qualitative interpretation of the  $\beta$ -hCG test result. The handheld can be customized to disable or enable the qualitative  $\beta$ -hCG interpretation.

| Quantitative $\beta$ -hCG Result | Qualitative $\beta$ -hCG Interpretation* | Handheld Display |
|----------------------------------|------------------------------------------|------------------|
| $\beta$ -hCG $\leq$ 5.0 IU/L     | Negative                                 | hCG QUAL ( - )   |
| $5.0 < \beta$ -hCG < 25.0 IU/L   | Indeterminate                            | hCG QUAL ( )     |
| $\beta$ -hCG $\geq$ 25.0 IU/L    | Positive                                 | hCG QUAL ( + )   |

If enabled, qualitative interpretations will always be displayed with quantitative values.

**\*Note:** The Qualitative  $\beta$ -hCG Interpretation displayed on the i-STAT 1 analyzer screen is based on the quantitative  $\beta$ -hCG result **prior** to rounding. Thus, due to rounding, a Quantitative  $\beta$ -hCG result of 5.0 IU/L may be displayed with a Qualitative  $\beta$ -hCG result of either Negative (-) or Indeterminate ( ). Similarly, a Quantitative  $\beta$ -hCG result of 25.0 IU/L may be displayed with a Qualitative  $\beta$ -hCG result of either Indeterminate ( ) or Positive (+).

## Expected Values

Because hCG is normally synthesized and secreted by cells of the placenta or its precursor, levels of the hormone in normal, non-pregnant individuals are low to undetectable.<sup>1</sup> Concentrations of hCG measured in the sera of nonpregnant individuals, as reported in the literature, are <5 IU/L.<sup>2,26</sup> The concentration of hCG rises rapidly during the first weeks of pregnancy, approximately doubling every two days. Therefore, values of total  $\beta$ -hCG between 5 and 25 IU/L may be indicative of early pregnancy.<sup>3</sup> However, these results must always be evaluated in the context of the clinical situation, the date of the last menstrual period, pelvic examination, and other clinical findings or diagnostic modalities.<sup>4</sup> (See Limitations of Procedure section below.) When borderline results between 5 IU/L and 25 IU/L are encountered, or  $\beta$ -hCG results do not match clinical context, re-test  $\beta$ -hCG again 48 hours later.<sup>3,5</sup> Levels of hCG >25 IU/L are indicative of early pregnancy.<sup>2</sup> Values for hCG generally peak during the first trimester and decline slowly throughout the remainder of the pregnancy.

## Summary and Explanation of Test

Human chorionic gonadotropin (hCG) is a glycoprotein hormone that is secreted by the syncytiotrophoblastic cells of the placenta. It is a complex molecule, consisting of two antigenically different glycoprotein subunits, alpha ( $\alpha$ ) and beta ( $\beta$ ). The  $\alpha$  subunit is found in other pituitary glycoprotein hormones (luteinizing hormone [LH], follicle stimulating hormone [FSH] and thyroid stimulating hormone [TSH]), as well as hCG. The  $\beta$  subunit is specific to hCG, yet exhibits considerable

homology with LH. Both the intact hCG molecule and the free subunit are found in early pregnancy. Both  $\beta$  forms (intact and free) are detected by this assay.

Physiologically,  $\beta$ -hCG appears to maintain the corpus luteum, thereby allowing synthesis of progesterone and estrogens that support the endometrium. As uncomplicated pregnancies progress, the placenta assumes the production of these hormones.  $\beta$ -hCG levels increase to a peak concentration, then decrease and plateau.  $\beta$ -hCG circulates as the intact molecule in the serum of women who have an uncomplicated pregnancy. The subunits are cleaved rapidly and cleared by the kidneys.<sup>6</sup> With the availability of sensitive quantitative assays for the measurement of  $\beta$ -hCG, it has been shown that hCG levels can be useful in prediction of spontaneous abortions,<sup>7,8</sup> aiding in the detection of ectopic pregnancy<sup>7,9,10</sup> and multiple gestation.<sup>7</sup>

The rapid and accurate diagnosis of pregnancy is commonly required by clinicians. Females of child-bearing age frequently present to emergency departments (EDs), urgent care centers, physician offices, clinics and other care providers with symptoms of pregnancy or other clinical conditions such as abdominal pain, vaginal bleeding, syncope or shock -- conditions that may be pregnancy-related. During pregnancy, many common medications are contraindicated, and diagnostic imaging is avoided if possible. It is often necessary to determine rapidly whether women are pregnant, and the menstrual history alone is not reliable.<sup>11</sup> For these reasons, clinicians may require a rapid, quantitative  $\beta$ -hCG test at the point of care.

## Performance Characteristics

### Precision

The i-STAT  $\beta$ -hCG assay is designed to have a precision of <10% (CV).<sup>\*</sup> A precision study was performed following CLSI EP5-A2.<sup>12</sup> Three levels of control were tested in duplicate, twice a day, for 20 days using three different cartridge lots for a total of 80 results per control level per cartridge lot. The average statistics are presented below:<sup>\*\*</sup>

| Control Level | Mean, IU/L | Within-day, %CV | Between-day, %CV | Total %CV |
|---------------|------------|-----------------|------------------|-----------|
| 1             | 20.8       | 5.3%            | 0.4%             | 5.5%      |
| 2             | 725.3      | 3.0%            | 0.6%             | 3.7%      |
| 3             | 1064.1     | 4.0%            | 0.9%             | 4.2%      |

<sup>\*</sup> The precision at lower levels is limited by a background imprecision designed to be  $\leq 1.4$  IU/L.

<sup>\*\*</sup> Representative data; results in individual laboratories may vary from these data.

### Method Comparison

Method comparison data were collected using CLSI guideline EP9-A2.<sup>13</sup> Commercially available frozen plasma samples containing  $\beta$ -hCG were spiked into venous whole blood samples collected in heparinized evacuated tubes and analyzed in duplicate on the i-STAT System. A portion of the sample was centrifuged and the separated plasma samples were analyzed in duplicate on the i-STAT System and the Architect system within 4 hours of collection.

Deming regression analysis was performed on the first replicate of each sample. In the method comparison table,  $n$  is the number of specimens in the first data set, and  $S_{xx}$  and  $S_{yy}$  refer to estimates of imprecision based on the duplicates of the comparative and the i-STAT methods, respectively.  $S_{y.x}$  is the standard error of the estimate, and  $r$  is the correlation coefficient.<sup>\*\*\*</sup>

Method comparisons will vary from site to site due to differences in sample handling, comparative method calibration and other site-specific variables.

\*\*\*The usual warning relating to the use of regression analysis is summarized here as a reminder. For any analyte, "if the data is a narrow range, the estimate of the regression parameters are relatively imprecise and may be biased. Therefore, predictions made from estimates may be invalid."<sup>13</sup> The correlation coefficient,  $r$ , can be used as a guide to assess the adequacy of the comparative method range in overcoming the problem. As a guide, the range of data can be considered adequate if  $r > 0.975$ .

#### Method Comparison: i-STAT vs Abbott Architect (IU/L)

|                  | i-STAT (Whole Blood) vs<br>Architect (Fresh Plasma) | i-STAT (Fresh Plasma) vs<br>Architect (Fresh Plasma) |
|------------------|-----------------------------------------------------|------------------------------------------------------|
| <b>n</b>         | <b>288</b>                                          | <b>287</b>                                           |
| <b>Slope</b>     | <b>1.01</b>                                         | <b>1.00</b>                                          |
| <b>Intercept</b> | <b>2.40</b>                                         | <b>-3.21</b>                                         |
| <b>Sy.x</b>      | <b>0.0084</b>                                       | <b>0.0044</b>                                        |
| <b>Syy</b>       | <b>5.7%</b>                                         | <b>4.0%</b>                                          |
| <b>Sxx</b>       | <b>N/A</b>                                          | <b>2.4%</b>                                          |
| <b>r</b>         | <b>0.990</b>                                        | <b>0.997</b>                                         |
| <b>Xmin</b>      | <b>8.8</b>                                          | <b>7.9</b>                                           |
| <b>Xmax</b>      | <b>2024.8</b>                                       | <b>1983.6</b>                                        |

#### Analytical Specificity

The  $\beta$ -hCG method is specific for the beta subunit (free and intact) of human chorionic gonadotropin. The following were tested and found to have an insignificant effect on the measured  $\beta$ -hCG.

| <b>Crossreactant</b> | <b>Concentration</b> | <b>Crossreactivity (%)</b> |
|----------------------|----------------------|----------------------------|
| LH                   | 450 IU/L             | <10%                       |
| FSH                  | 300 IU/L             | <10%                       |
| TSH                  | 100 mIU/L            | <10%                       |

#### Limit of Quantitation, Limit of Detection, Limit of Blank

The Limit of Quantitation (LOQ), Limit of Detection (LOD), and Limit of Blank (LOB) were all estimated (as per CLSI guideline EP17-A<sup>14</sup>) to be below the lower end of the reportable range, 5 IU/L.

#### Recovery

The dilution linearity of the i-STAT  $\beta$ -hCG test was investigated using heparinized whole blood and plasma samples derived from three separate donors. For each donor, the original  $\beta$ -hCG negative sample and a  $\beta$ -hCG spiked sample were prepared. This process yielded three  $\beta$ -hCG positive whole blood samples that were then assayed in 10 cartridges for each of the three separate i-STAT  $\beta$ -hCG cartridge lots. These whole blood samples were then diluted using an equal volume of the original unspiked whole blood and assayed in 10 cartridges from each of three separate i-STAT  $\beta$ -hCG cartridge lots. From this whole blood data, the  $\beta$ -hCG recovery was calculated.

The plasma derived from these three donors was combined in equal volumes and all pairwise combinations. These combinations were then assayed on 10 cartridges for each of three separate i-STAT  $\beta$ -hCG cartridges. The  $\beta$ -hCG recovery was calculated using the average of the 30 results. The % recoveries are listed in the tables below.

## Whole blood

| Sample | Concentration (IU/L) | Diluted Concentration IU/L | % Recovery |
|--------|----------------------|----------------------------|------------|
| A      | 104.1                | 52.9                       | 101.8%     |
| B      | 288.9                | 132.0                      | 91.4%      |
| C      | 899.8                | 467.2                      | 103.8%     |

## Plasma

| Sample | Concentration (IU/L) | Diluted Concentration IU/L | % Recovery |
|--------|----------------------|----------------------------|------------|
| A      | 88.8                 | -                          | -          |
| B      | 298.0                | -                          | -          |
| C      | 971.6                | -                          | -          |
| A+B    | -                    | 203.4                      | 105.2%     |
| B+C    | -                    | 655.3                      | 103.2%     |
| A+C    | -                    | 532.2                      | 100.4%     |

## Test Limitations

This assay is capable of detecting whole molecule (intact) hCG as well as free  $\beta$ -hCG subunits.

The i-STAT Total  $\beta$ -hCG assay is intended for use in the early detection of pregnancy only and should not be performed for any other purpose.

Elevated hCG levels have been associated with some abnormal physiological states such as gestational trophoblastic disease and nontrophoblastic neoplasms, including transitional cell carcinoma of the bladder and urinary tract, renal cancer, prostate cancer, cancers of the gastrointestinal system, neuroendocrine tumors, lung cancer, breast cancer, gynecological cancers, and hematological cancers.<sup>15,16</sup> Results of this test should not be used in the diagnosis of these abnormal states. Persistent low levels of hCG (e.g., <50 IU/L) may be present one to five years preceding malignant gestational trophoblastic disease.<sup>17</sup> There have been reports of people receiving unnecessary medical treatment and surgery, including chemotherapy and hysterectomy, when hCG results were used in the diagnosis of abnormal states.

For diagnostic purposes, hCG results should always be used in conjunction with other data, e.g., patient's medical history, symptoms, results of other tests, clinical impressions, etc.  $\beta$ -hCG cannot be used alone to establish the diagnosis of ectopic pregnancy.<sup>9,10</sup> The i-STAT total  $\beta$ -hCG results should always be used and interpreted only in the context of the overall clinical picture.

Detection of very low levels of hCG does not rule out pregnancy.<sup>18</sup> Low levels of hCG can occur in apparently healthy, nonpregnant subjects.<sup>19,20</sup> Because hCG values double approximately every 48 hours in a normal pregnancy,<sup>18</sup> patients with very low levels of hCG should be resampled and retested after 48 hours.

Specimens from post-menopausal women may elicit weak positive results due to low hCG levels unrelated to pregnancy. With a weak positive result, it is good laboratory practice to resample and retest after 48 hours.

Because of the high degree of sensitivity of the assay, positive results during the initial days after conception may later be negative due to natural termination of the pregnancy. Natural termination occurs in 22% of clinically unrecognized pregnancies and 31% of pregnancies overall.<sup>21</sup> It is good laboratory practice to resample and retest weak positive results after an additional 48 hours.

Interfering substances (such as heterophilic antibodies, non-specific proteins, or hCG-like substances) may falsely depress or falsely elevate results.<sup>18,27,28</sup> These interfering substances may cause false results over the entire range of the assay, not just at low levels. While this product contains reagents that minimize the effect of these interferents and QC algorithms designed to detect their effects, the possibility of interference causing erroneous results should be evaluated carefully in cases where test results are inconsistent with clinical information. In these cases results should be confirmed by an alternate hCG method.<sup>22</sup>

Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may demonstrate either falsely elevated or falsely depressed results when tested with assay kits which employ mouse monoclonal antibodies.<sup>23,24</sup> These specimens should not be tested with the i-STAT  $\beta$ -hCG assay.

Unknown interferences from medications may affect results.

Hook effect: no significant hook effect detected in samples up to 300,000 IU/L.

Partially clotted samples can result in elevated hCG results as well as quality check codes. To prevent clotting in samples collected in heparinized tubes, the sample should be inverted gently at least 10 times to ensure even dissolution of the heparin anticoagulant.

Grossly hemolyzed samples can cause a decreased alkaline phosphatase activity, resulting in decreased detection of hCG or quality check codes.

The  $\beta$ -hCG assay has been characterized in whole blood samples with hematocrit levels up to 55% PCV. Imprecision exceeding 10% (CV) has been observed for samples with hematocrit levels above 50% PCV.

The handheld must remain on a level surface with the display facing up during testing. Motion of the handheld during testing can increase the frequency of suppressed results or quality check codes. A level surface includes running the handheld in the downloader/recharger.

The frequency of suppressed results is affected by atmospheric pressure. Suppressed result rates may increase with higher elevations (decreased barometric pressure) and may become persistent if testing is performed at more than 7500 feet (2286 meters) above sea level. Where unavailability of results is unacceptable, Abbott Point of Care recommends having an alternate test method available.

Prior to filling the i-STAT  $\beta$ -hCG cartridge, invert the blood collection tube and inspect for red cell sedimentation. If sedimentation is observed, continue mixing by repeated inversion until the sedimentation is no longer apparent. Samples from  $\beta$ -hCG positive patients or patients undergoing hormone therapy may have higher erythrocyte sedimentation rates (ESR) which, if not tested immediately, could cause visible red cell sedimentation at the bottom of the collection tube.<sup>29,30</sup>

## Interference Testing

Interference studies were based on CLSI guideline EP7-A2.<sup>25</sup> The following substances were found to have no significant effect (less than 10%) on the  $\beta$ -hCG method when added to a plasma pool containing approximately 40 IU/L of  $\beta$ -hCG at the concentrations indicated:

| Compound              | Test Level ( $\mu$ mol/L unless otherwise indicated) |
|-----------------------|------------------------------------------------------|
| Acetyl Salicylic Acid | 3620                                                 |
| Acetaminophen         | 1660                                                 |
| Allopurinol           | 294                                                  |
| Ampicillin            | 152                                                  |
| Ascorbic Acid         | 342                                                  |
| Atenolol              | 37.6                                                 |
| Caffeine              | 308                                                  |
| Captopril             | 23                                                   |
| Chloramphenicol       | 155                                                  |
| Diclofenac            | 169                                                  |
| Digoxin               | 6.53                                                 |
| Dopamine              | 5.87                                                 |
| Enalaprilat           | 0.86                                                 |
| Erythromycin          | 81.6                                                 |
| Furosemide            | 181                                                  |
| Ibuprofen             | 2425                                                 |
| Isosorbide dinitrate  | 636                                                  |
| Nicotine              | 6.2                                                  |
| Nifedipine            | 1156                                                 |
| Phenytoin             | 198                                                  |
| Propranolol           | 7.71                                                 |
| Salicylic acid        | 4340                                                 |
| Sodium Heparin        | 90 U/mL                                              |
| Theophylline          | 222                                                  |
| Verapamil             | 4.4                                                  |
| Warfarin              | 65.2                                                 |

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