ARCHITECT FSH

REF 7K75-25
REF 7K75-20
REF 7K75-35
REF 7K75-30

en

FSH
7K75
G6-5315/R11
B7K750

Read Highlighted Changes: Revised January 2016.

Package insert instructions must be carefully followed. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

NAME

ARCHITECT FSH

INTENDED USE

The ARCHITECT FSH assay is a Chemiluminescent Microparticle Immunoassay (CMIA) for the quantitative determination of follicle stimulating hormone (FSH) in human serum and plasma.

SUMMARY AND EXPLANATION OF THE TEST

Human Follicle Stimulating Hormone (FSH, follitropin) is a glycoprotein of approximately 30,000 daltons which, like luteinizing hormone (LH, lutropin), human chorionic gonadotropin (hCG) and thyroid stimulating hormone (TSH, thyrotropin), consists of two noncovalently associated subunits designated α and β.[1] The α subunit of FSH contains 92 amino acids and is very similar to the α subunits of LH, hCG, and TSH.[1] The β subunit of FSH is unique and confers its immunological and functional specificity.[1]

FSH and LH control growth and reproductive activities of the gonadal tissues.[2, 3] FSH promotes follicular development in the ovary and gametogenesis in the testis.[3, 4] The gonadotroph cells of the anterior pituitary secrete both FSH and LH in response to gonadotropin releasing hormone (LHRH or GnRH) from the medial basal hypothalamus.[5] Both FSH and LH are secreted in a pulsatile manner, with rapid fluctuations over the normal range.[3, 6, 7] The pulsatility of FSH is less pronounced than that of LH. Release of both FSH and LH from the pituitary is under negative feedback control by the gonads.[5]

FSH in mature females acts to stimulate development of the ovarian follicles. Circulating FSH levels vary throughout the menstrual cycle in response to estradiol and progesterone. A small, but significant increase in circulating FSH accompanies the mid-cycle LH surge. However, the physiological significance of this increase is unknown. Circulating levels of FSH decline in the luteal phase in response to estradiol and progesterone production by the developing corpus luteum.[2, 5]

At menopause, ovarian function is diminished with concomitant decrease in estradiol secretion. FSH and LH then increase significantly in response to diminished feedback inhibition of gonadotropin release.[8, 9] In males, FSH, LH, and testosterone regulate spermatogenesis by the Sertoli cells in the seminiferous tubules of the testes. FSH is less sensitive to feedback inhibition by testosterone than is LH and is thought to be regulated independently by the inhibitory peptide inhibin produced by the Sertoli cells.[10, 11]

Because of the negative feedback mechanisms regulating gonadotropin release, elevated concentrations of LH and FSH are indicative of gonadal failure when accompanied by low concentrations of the gonadal steroids. In males, these observations suggest primary testicular failure or anorchia.[4] FSH may also be elevated in Klinefelter's syndrome (seminiferous tubule dysgenesis) or as a consequence of Sertoli cell failure.[4] In females, situations in which FSH is elevated and gonadal steroids are depressed include menopause, premature ovarian failure, and ovariectomy, while with polycystic ovarian syndrome the LH/FSH ratio may be increased.[7]

Abnormal FSH concentrations may also indicate dysfunction of the hypothalamic-pituitary axis. In sexually mature adults, FSH deficiency, together with low concentrations of LH and sex steroids, may indicate panhypopituitarism.[7] This can result either from a decrease in the release of GnRH or from a lack of response of the pituitary to GnRH. Determination of serum FSH, following administration of GnRH, may allow differentiation of these two conditions.[5, 7] The use of oral contraceptives usually results in reduction of gonadotropin levels due to negative feedback by these steroids.[5]

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

The ARCHITECT FSH assay is a two-step immunoassay to determine the presence of FSH in serum and plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex.

1. Sample and anti-β FSH coated paramagnetic microparticles are combined. The FSH present in the sample binds to the anti-β FSH coated microparticles.
2. After washing, anti-α FSH acridinium-labeled conjugate is added to create a reaction mixture.
3. Following another wash cycle, Pre-Trigger and Trigger Solutions are added to the reaction mixture.
4. The resulting chemiluminescent reaction is measured as relative light units (RLUs). There is a direct relationship between the amount of FSH in the sample and the RLUs detected by the ARCHITECT iSystem optics.

For additional information on system and assay technology, refer to the ARCHITECT System Operations Manual, Section 3.

REAGENTS

Kit Contents

ARCHITECT FSH 7K75

NOTE: Some kit sizes are not available in all countries or for use on all ARCHITECT iSystems. Please contact your local distributor.

REF	7K75-25	7K75-20	7K75-35	7K75-30
Σ	100	400	500	2000
MICROPARTICLES	1 x 6.6 mL	4 x 6.6 mL	1 x 27.0 mL	4 x 27.0 mL
CONJUGATE	1 x 5.9 mL	4 x 5.9 mL	1 x 26.3 mL	4 x 26.3 mL

MICROPARTICLES Anti-β FSH (mouse, monoclonal) coated Microparticles in MES buffer with protein (murine and caprine) stabilizers. Minimum concentration: 0.1% solids. Preservative: antimicrobial agents.

CONJUGATE Anti-α FSH (mouse, monoclonal) acridinium-labeled Conjugate in MES buffer with protein (bovine) stabilizers. Minimum concentration: 45 ng/mL. Preservative: antimicrobial agents.

Other Reagents

MULTI-ASSAY MANUAL DILUENT 1 x 100 mL ARCHITECT Multi-Assay Manual Diluent, **REF** 7D82-50, containing phosphate buffered saline solution. Preservative: antimicrobial agent.

PRE-TRIGGER SOLUTION ARCHITECT Pre-Trigger Solution containing 1.32% (w/v) hydrogen peroxide.

TRIGGER SOLUTION ARCHITECT Trigger Solution containing 0.35 N sodium hydroxide.

WASH BUFFER ARCHITECT Wash Buffer containing phosphate buffered saline solution. Preservatives: antimicrobial agents.

NOTE: Bottle and volume varies based on order.

Warnings and Precautions

- **IVD**
- For *In Vitro* Diagnostic Use

Safety Precautions

CAUTION: This product requires the handling of human specimens. It is recommended that all human-sourced materials be considered potentially infectious and handled in accordance with the OSHA Standard on Bloodborne Pathogens. Biosafety Level 2 or other appropriate biosafety practices should be used for materials that contain or are suspected of containing infectious agents.[12-15]

Safety Data Sheets are available at www.abbottdiagnostics.com or contact your local representative.

For a detailed discussion of safety precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 8.

Reagent Handling

- Do not use reagent kits beyond the expiration date.
- **Do not pool reagents within a kit or between kits.**
- Before loading the reagent kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that may have settled during shipment. For microparticle mixing instructions, refer to the **PROCEDURE, Assay Procedure** section of this package insert.
- **Septums MUST be used to prevent reagent evaporation and contamination and to ensure reagent integrity. Reliability of assay results cannot be guaranteed if septums are not used according to the instructions in this package insert.**
  - To avoid contamination, wear clean gloves when placing a septum on an uncapped reagent bottle.
  - Once a septum has been placed on an open reagent bottle, **do not invert the bottle** as this will result in reagent leakage and may compromise assay results.
  - Over time, residual liquids may dry on the septum surface. These are typically dried salts and have no effect on assay efficacy.

For a detailed discussion of handling precautions during system operation, refer to the ARCHITECT System Operations Manual, Section 7.

Reagent Storage

When stored and handled as directed, reagents are stable until the expiration date.

	Storage Temperature	Maximum Storage Time	Additional Storage Instructions
Unopened/ Opened*	2-8°C	Until expiration date	May be used immediately after removal from 2-8°C storage. Store in upright position.
On board	System temperature	30 days	Discard after 30 days. For information on tracking onboard time, refer to the ARCHITECT System Operations Manual, Section 5.

* Reagents may be stored on or off the ARCHITECT iSystem. If reagents are removed from the system, store them at 2-8°C (with septums and replacement caps) in an upright position. For reagents stored off the system, it is recommended that they be stored in their original trays and boxes to ensure they remain upright. **If the microparticle bottle does not remain upright (with a septum installed) while in refrigerated storage off the system, the reagent kit must be discarded.** For information on unloading reagents, refer to the ARCHITECT System Operations Manual, Section 5.

Indications of Reagent Deterioration

When a control value is out of the specified range, it may indicate deterioration of the reagents or errors in technique. Associated test results are invalid, and samples must be retested. Assay recalibration may be necessary. For troubleshooting information, refer to the ARCHITECT System Operations Manual, Section 10.

INSTRUMENT PROCEDURE

The ARCHITECT FSH assay file must be installed on the ARCHITECT iSystem from an ARCHITECT iSystem Assay CD-ROM prior to performing the assay.

For detailed information on assay file installation and viewing and editing assay parameters, refer to the ARCHITECT System Operations Manual, Section 2.

For information on printing assay parameters, refer to the ARCHITECT System Operations Manual, Section 5.

For a detailed description of system procedures, refer to the ARCHITECT System Operations Manual.

Alternate Result Units

Edit assay parameter "Result concentration units" to select an alternate unit.

Conversion formula:

(Concentration in Default result unit) x (Conversion factor) = (Concentration in Alternate result unit)

Default result unit	Conversion factor	Alternate result unit
mIU/mL	1	IU/L

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Specimen Types

Verified specimen types to be used with this assay:

Specimen Types	Collection Tubes
Human serum	Serum
	Serum separator tubes
Human plasma	Lithium heparin
	Sodium heparin
	Potassium EDTA

- Other anticoagulants have not been validated for use with the ARCHITECT FSH assay.
- The instrument does not provide the capability to verify specimen type. It is the responsibility of the operator to verify that the correct specimen types are used in the assay.

Specimen Conditions

- For optimal results, serum and plasma specimens should be free of fibrin, red blood cells or other particulate matter.
- Ensure that complete clot formation in serum specimens has taken place prior to centrifugation. Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting time. If the specimen is centrifuged before a complete clot forms, the presence of fibrin may cause erroneous results.
- To prevent cross contamination, use of disposable pipettes or pipette tips is recommended.

Preparation for Analysis

- Follow the tube manufacturer's processing instructions for specimen collection tubes.
- Specimens must be mixed THOROUGHLY after thawing, by LOW speed vortexing or by gently inverting, and centrifuged prior to use to remove red blood cells or particulate matter to ensure consistency in the results.
- Inspect all specimens for bubbles. Remove bubbles with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.

Specimen Storage

Specimen Type	Storage Temperature	Maximum Storage Time
Serum/Plasma	2-8°C	≤ 7 days

If testing will be delayed more than 24 hours, remove serum or plasma from the clot, serum separator or red blood cells. Specimens may be stored for up to 7 days at 2-8°C prior to being tested.

If testing will be delayed more than 7 days, specimens should be frozen at -10°C or colder. Specimens stored frozen at -10°C or colder for 12 months showed no performance difference.

Avoid multiple freeze/thaw cycles.

Specimen Shipping

- Package and label specimens in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances.
- Do not exceed the storage limitations listed above.

PROCEDURE

Materials Provided

7K75 ARCHITECT FSH Reagent Kit

Materials Required but not Provided

- ARCHITECT FSH Assay file obtained from the ARCHITECT iSystem e-Assay CD-ROM found on www.abbottdiagnostics.com.
- 7K75-01 ARCHITECT FSH Calibrators
- 7K75-10 ARCHITECT FSH Controls
- 7D82-50 ARCHITECT Multi-Assay Manual Diluent
- ARCHITECT Pre-Trigger Solution
- ARCHITECT Trigger Solution
- ARCHITECT Wash Buffer
- ARCHITECT Reaction Vessels
- ARCHITECT Sample Cups
- ARCHITECT Septum
- ARCHITECT Replacement Caps
- Pipettes or pipette tips (optional) to deliver the volumes specified on the patient or control order screen.

For information on materials required for maintenance procedures, refer to the ARCHITECT System Operations Manual, Section 9.

Assay Procedure

- Before loading the reagent kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that may have settled during shipment. After the first time the microparticles have been loaded, no further mixing is required.
  - **Invert the microparticle bottle 30 times.**
  - Visually inspect the bottle to ensure microparticles are resuspended. If microparticles are still adhered to the bottle, continue to invert the bottle until the microparticles have been completely resuspended.
  - **If the microparticles do not resuspend, DO NOT USE. Contact your local Abbott representative.**
  - Once the microparticles have been resuspended, place a septum on the bottle. For instructions about placing septums on bottles, refer to the **Reagent Handling** section of this package insert.
- Load the reagent kit on the ARCHITECT iSystem.
  - Verify that all necessary reagents are present.
  - Ensure that septums are present on all reagent bottles.
- Order calibration, if necessary.
  - For information on ordering calibrations, refer to the ARCHITECT System Operations Manual, Section 6.
- Order tests.
  - For information on ordering patient specimens and controls and for general operating procedures, refer to the ARCHITECT System Operations Manual, Section 5.
- Minimum sample cup volume is calculated by the system and printed on the Orderlist report. To minimize the effects of evaporation, verify adequate sample cup volume is present prior to running the test.

  Maximum number of replicates sampled from the same sample cup: 10
  - Priority:

    Sample volume for first test: 75 µL

    Sample volume for each additional test from same sample cup: 25 µL
  - ≤ 3 hours on board:

    Sample volume for first test: 150 µL

    Sample volume for each additional test from same sample cup: 25 µL
  - > 3 hours on board: Additional sample volume is required. Refer to the ARCHITECT System Operations Manual, Section 5 for information on sample evaporation and volumes.
  - If using primary or aliquot tubes, use the sample gauge to ensure sufficient patient specimen is present.
- Prepare ARCHITECT FSH Calibrators and Controls.
  - Mix calibrator(s) and controls by gentle inversion before use.
  - Hold bottles **vertically** and dispense recommended volumes into each respective sample cup.
  - Recommended volumes:

    for each calibrator: 4 drops

    for each control: 3 drops
- Load samples.
  - For information on loading samples, refer to the ARCHITECT System Operations Manual, Section 5.
- Press RUN.
- For additional information on principles of operation, refer to the ARCHITECT System Operations Manual, Section 3.
- For optimal performance, it is important to perform routine maintenance as described in the ARCHITECT System Operations Manual, Section 9. Perform maintenance more frequently when required by laboratory procedures.

Specimen Dilution Procedures

Specimens with an FSH value exceeding 150.00 mIU/mL are flagged with the code " >150.00" and may be diluted using either the Automated Dilution Protocol or the Manual Dilution Procedure.

Automated Dilution Protocol

The system performs a 1:5 dilution of the specimen and automatically calculates the concentration of the specimen before dilution and reports the result.

Manual Dilution Procedure

Suggested dilution: 1:5

It is recommended that dilutions not exceed 1:5.

1. Add 20 µL of the patient specimen to 80 µL of ARCHITECT Multi-Assay Manual Diluent (7D82-50).
2. The operator must enter the dilution factor in the Patient or Control order screen. The system will use this dilution factor to automatically calculate the concentration of the sample before dilution and report the result. The result should be > 0.25 mIU/mL before the dilution factor is applied.
3. If the operator does not enter the dilution factor, the reported result will be that of the diluted sample. This result should be > 0.25 mIU/mL.

For detailed information on ordering dilutions, refer to the ARCHITECT System Operations Manual, Section 5.

Calibration

- Test Calibrators 1 and 2 in duplicate. The calibrators should be priority loaded.

  A single sample of each control level must be tested to evaluate the assay calibration. Ensure that assay control values are within the ranges specified in the respective control package insert.
- Calibration Range: 0.00 - 150.00 mIU/mL.
- Once an ARCHITECT FSH calibration is accepted and stored, all subsequent samples may be tested without further calibration unless:
  - A reagent kit with a new lot number is used or
  - Controls are out of range.
- For detailed information on how to perform an assay calibration, refer to the ARCHITECT System Operations Manual, Section 6.

Quality Control Procedures

The recommended control requirement for the ARCHITECT FSH assay is that a single sample of each control level be tested once every 24 hours each day of use. If the quality control procedures in your laboratory require more frequent use of controls to verify test results, follow your laboratory-specific procedures.

Ensure that assay control values are within the concentration ranges specified in the package insert.

Verification of Assay Claims

For protocols to verify package insert claims, refer to the ARCHITECT System Operations Manual, Appendix B.

The ARCHITECT FSH assay belongs to method group 1.

RESULTS

The ARCHITECT FSH assay utilizes a 4 Parameter Logistic Curve fit data reduction method (4PLC, Y-weighted) to generate a calibration curve.

For information on alternate result units, refer to the **INSTRUMENT PROCEDURE, Alternate Result Units** section of this package insert.

Flags

Some results may contain information in the Flags field. For a description of the flags that may appear in this field, refer to the ARCHITECT System Operations Manual, Section 5.

LIMITATIONS OF THE PROCEDURE

- For diagnostic purposes, results should be used in conjunction with other data; e.g., symptoms, results of other tests, clinical impressions, etc.
- If the FSH results are inconsistent with clinical evidence, additional testing is suggested to confirm the result.
- 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 show either falsely elevated or depressed values when tested with assay kits such as ARCHITECT FSH that employ mouse monoclonal antibodies. Additional information may be required for diagnosis.[16, 17]
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays. Patients routinely exposed to animals or to animal serum products can be prone to this interference, and anomalous values may be observed. Additional information may be required for diagnosis.[18]

EXPECTED VALUES

The suggested normal range for the ARCHITECT FSH assay represents the FSH values obtained from 150 normal males, 34 post-menopausal females (not on hormone replacement therapy) and 44 normal cycling females. For this study, the follicular phase was defined as the period of time from 10 to 4 days prior to the mid-cycle peak. The luteal phase was defined as the period of time from 4 to 10 days following the mid-cycle peak. Cycle days were synchronized to the mid-cycle peak (the day when LH values are most elevated). The results are presented in the following table. (NOTE: 44 women participated in the study for serial blood draws. At the time of testing for ARCHITECT FSH, only 42 of the mid-cycle samples were available for testing. Samples from all 44 women were included in the Follicular and Luteal Phase expected values testing.)

		FSH Value (mIU/mL)	
	n	Mean	Range (central 95 %)
Males	150	3.37	0.95 - 11.95
Normally Menstruating Females			
Follicular Phase	144	4.95	3.03 - 8.08
Mid-Cycle Peak	42	9.62	2.55 - 16.69
Luteal Phase	138	2.75	1.38 - 5.47
Post-menopausal Females	34	59.71	26.72 - 133.41

It is recommended that each laboratory establish its own reference range that is appropriate for the laboratory's patient population (i.e., a normal range that reflects the type of specimen and demographic variables such as age and sex, as applicable).

SPECIFIC PERFORMANCE CHARACTERISTICS

Precision

The ARCHITECT FSH Assay is designed to have a total CV of ≤ 10% for concentrations in the range of the Low, Medium and High Controls. Precision was determined as described in Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) Protocol EP5-T2.[19] A three member calf serum based panel was assayed, using two lots of reagents, on two instruments, in replicates of two at two separate times per day for 20 days. Data from this study are summarized in the following table.

Panel	Reagent			Mean Conc.	Within Run		Total	
Member	Lot	Instrument	n	(mIU/mL)	SD	%CV	SD	%CV
1	1	1	80	5.08	0.143	2.8	0.181	3.6
1	1	2	80	5.16	0.171	3.3	0.217	4.2
1	2	1	80	5.55	0.156	2.8	0.204	3.7
1	2	2	80	5.64	0.239	4.2	0.262	4.6
2	1	1	80	25.09	0.686	2.7	0.965	3.8
2	1	2	80	24.95	0.715	2.9	0.895	3.6
2	2	1	80	26.83	0.727	2.7	0.868	3.2
2	2	2	80	26.98	0.767	2.8	1.103	4.1
3	1	1	80	74.72	2.080	2.8	3.027	4.1
3	1	2	80	72.35	1.864	2.6	2.419	3.3
3	2	1	80	78.12	2.554	3.3	3.211	4.1
3	2	2	80	76.54	2.311	3.0	2.582	3.4

Accuracy by Recovery

Accuracy by recovery of this assay was designed to be ± 15% of spike level. Known concentrations of World Health Organization (WHO) 1st International Standard (IS) FSH 92/510 were added to 11 aliquots of human serum at 2 concentration levels (20 mIU/mL and 40 mIU/mL). The concentration of FSH was determined using the ARCHITECT FSH assay. The mean recovery of WHO 1st IS FSH is 96.05%.

Analytical Sensitivity

The analytical sensitivity of the ARCHITECT FSH assay was calculated to be better than 0.05 mIU/mL (n = 36 runs). Analytical sensitivity is defined as the concentration at two standard deviations from the ARCHITECT FSH MasterCheck Level 0 (0.00 mIU/mL), and represents the lowest measurable concentration of FSH that can be distinguished from zero.

Specificity

The specificity of the ARCHITECT FSH assay was determined by studying the cross-reactivity of LH, TSH, and hCG. Aliquots of processed bovine serum were supplemented with 250 mIU/mL LH, 100 µIU/mL TSH, and 200,000 mIU/mL hCG and assayed for FSH. The cross-reactivity was calculated as a percent cross-reactivity and was shown to be 0.002% for LH, 0.043% for TSH and 0.001% for hCG.

Interference

Potential interference from hemoglobin, bilirubin, triglycerides, and protein was studied in the ARCHITECT FSH assay. The ARCHITECT FSH assay demonstrated the following interferences.

- Hemoglobin ≤ 10% at 500 mg/dL
- Bilirubin ≤ 10% at 20 mg/dL
- Triglycerides ≤ 10% at 3000 mg/dL
- Protein ≤ 10% at 2 g/dL and 12 g/dL

Correlation

The ARCHITECT FSH assay was compared to the AxSYM FSH assay. The result of the specimen testing is shown in the following table.**

Abbott ARCHITECT FSH vs. Abbott AxSYM FSH

Method	Number of Specimens	Intercept	Slope	Correlation Coefficient
Least Squares Linear Regression	627	-0.09	1.02	0.99
Passing-Bablok Linear Regression*	627	-0.12	1.03	0.99

In this evaluation, serum specimens ranged from 0.46 to 120.45 mIU/mL with the ARCHITECT FSH assay.

* A linear regression method with no special assumptions regarding the distribution of the samples and measurement errors.[20]

** Representative data; variables such as differences in sampling size and sample population may impact the correlation of the assay; therefore, results in individual laboratories may vary from these data.

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Key to Symbols

	Consult instructions for use
	Manufacturer
	Sufficient for
	Temperature limitation
	Use by/Expiration date
CONJUGATE	Conjugate
CONTROL NO.	Control Number
DISTRIBUTED IN THE USA BY	Distributed in the USA by
INFORMATION FOR USA ONLY	Information needed for United States of America only
IVD	*In Vitro* Diagnostic Medical Device
LOT	Lot Number
MICROPARTICLES	Microparticles
MULTI-ASSAY MANUAL DILUENT	Multi-Assay Manual Diluent
PRODUCT OF IRELAND	Product of Ireland
PRE-TRIGGER SOLUTION	Pre-Trigger Solution
REACTION VESSELS	Reaction Vessels
REAGENT LOT	Reagent Lot
REF	List Number
REPLACEMENT CAPS	Replacement Caps
SAMPLE CUPS	Sample Cups
SEPTUM	Septum
SN	Serial number
TRIGGER SOLUTION	Trigger Solution
WASH BUFFER	Wash Buffer

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