Overview

Useful For

As part of the diagnosis and workup of precocious and delayed puberty in females and, to a lesser degree, males

As part of the diagnosis and workup of suspected disorders of sex steroid metabolism (eg, aromatase deficiency and 17 alpha-hydroxylase deficiency)

As an adjunct to clinical assessment, imaging studies and bone mineral density measurement in the fracture risk assessment of postmenopausal women, and, to a lesser degree, older men

Monitoring low-dose female hormone replacement therapy in postmenopausal women

Monitoring antiestrogen therapy (eg, aromatase inhibitor therapy)

Testing Algorithm

See Steroid Pathways in Special Instructions.

Special Instructions

- Steroid Pathways

Method Name

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

NY State Available

Yes

Specimen

Specimen Type

Serum Red

Specimen Required

Collection Container/Tube: Red top

Submission Container/Tube: Plastic vial

Specimen Volume: 1.2 mL

Collection Instructions:

1. Centrifuge and remove serum from red blood cells within 2 hours of draw.

2. Aliquot serum to submission container.

Additional Information: See Steroid Pathways in Special Instructions.

Specimen Minimum Volume

0.8 mL

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK
Gross icterus	OK
Other	Serum gel or SST tube

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum Red	Refrigerated (preferred)	28 days	
	Ambient	28 days	
	Frozen	28 days	

Clinical and Interpretive

Clinical Information

Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important for many other, nongender-specific processes, including growth, nervous system maturation, bone metabolism/remodeling, and endothelial responsiveness. The 2 major biologically active estrogens in nonpregnant humans are estrone (E1) and estradiol (E2). A third bioactive estrogen, estriol (E3), is the main pregnancy estrogen, but plays no significant role in nonpregnant women or men.

E2 is produced primarily in ovaries and testes by aromatization of testosterone. Small amounts are produced in the adrenal glands and some peripheral tissues, most notably fat. By contrast, most of the circulating E1 is derived from peripheral aromatization of androstenedione (mainly adrenal). E2 and E1 can be converted into each other, and both can be inactivated via hydroxylation and conjugation. E2 demonstrates 1.25-5 times the biological potency of E1. E2 circulates at 1.5-4 times the concentration of E1 in premenopausal, nonpregnant women. E2 levels in men and postmenopausal women are much lower than in nonpregnant women, while E1 levels differ less, resulting in a reversal of the premenopausal E2:E1 ratio. E2 levels in premenopausal women fluctuate during the menstrual cycle. They are lowest during the early follicular phase. E2 levels then rise gradually until 2 to 3 days before ovulation, at which stage they start to increase much more rapidly and peak just before the ovulation-inducing luteinizing hormone/follicle stimulating hormone surge at 5 to 10 times the early follicular levels. This is followed by a modest decline during the ovulatory phase. E2 levels then increase again gradually until the midpoint of the luteal phase and thereafter decline to trough, early follicular levels.

Measurement of serum E2 forms an integral part of the assessment of reproductive function in females, including assessment of infertility, oligo-amenorrhea and menopausal status. In addition, it is widely used for monitoring ovulation induction, as well as during preparation for in vitro fertilization. For these applications E2 measurements with modestly sensitive assays suffice. However, extra sensitive E2 assays or simultaneous measurement of E1, or both are needed in a number of other clinical situations. These include inborn errors of sex steroid metabolism, disorders of puberty, estrogen deficiency in men, fracture risk assessment in menopausal women, and increasingly, therapeutic drug monitoring, either in the context of low-dose female hormone replacement therapy or antiestrogen treatment.

See Steroid Pathways in Special Instructions.

Reference Values

CHILDREN*

1-14 days: Estrone levels in newborns are very elevated at birth but will fall to prepubertal levels within a few days.

Males

Tanner Stages#	Mean Age	Reference Range
Stage I (>14 days and prepubertal)	7.1 years	Undetectable-16 pg/mL
Stage II	11.5 years	Undetectable-22 pg/mL
Stage III	13.6 years	10-25 pg/mL
Stage IV	15.1 years	10-46 pg/mL
Stage V	18 years	10-60 pg/mL

#Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

Females

Tanner Stages#	Mean Age	Reference Range
Stage I (>14 days and prepubertal)	7.1 years	Undetectable-29 pg/mL
Stage II	10.5 years	10-33 pg/mL
Stage III	11.6 years	15-43 pg/mL
Stage IV	12.3 years	16-77 pg/mL
Stage V	14.5 years	17-200 pg/mL

#Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

*The reference ranges for children are based on the published literature(1,2), cross-correlation of our assay with assays used to generate the literature data and on our data for young adults.

ADULTS

Males: 10-60 pg/mL

Females

Premenopausal: 17-200 pg/mL

Postmenopausal: 7-40 pg/mL

Conversion factor

E1: pg/mL x 3.704=pmol/L (molecular weight=270)

For SI unit Reference Values, see https://www.mayocliniclabs.com/order-tests/si-unit-conversion.html

Interpretation

Irregular or absent menstrual periods with normal or high estradiol (E2) levels (and often high estrone: E1 levels) are indicative of possible polycystic ovarian syndrome, androgen producing tumors, or estrogen producing tumors. Further work-up is required and usually includes measurement of total and bioavailable testosterone, androstenedione, dehydroepiandrosterone (sulfate), sex hormone-binding globulin, and possibly imaging.

Estrogen replacement in reproductive age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women, luteinizing hormone/follicle-stimulating hormone (LH/FSH) should be within the normal range, and E2 levels should ideally be higher than E1 levels.

Postmenopausal women and older men in the lowest quartile of E2 levels are at increased risk of osteoporotic fractures. E2 levels are typically less than 5 pg/mL in these patients.

The current recommendations for postmenopausal female hormone replacement are to administer therapy in the smallest beneficial doses for as briefly as possible. Ideally, E2 and E1 levels should be held below, or near, the lower limit of the premenopausal female reference range.

Antiestrogen therapy with central or peripheral acting agents that are not pure receptor antagonists usually aims for complete suppression of E2 production, and in the case of aromatase inhibitors, complete E1 and E2 suppression.

Gynecomastia or other signs of feminization in males may be due to an absolute or relative (in relation to androgens) surplus of estrogens. Gynecomastia is common during puberty in boys. Unless E1, E2, or testosterone levels exceed the adult male reference range, the condition is usually not due to hormonal disease (though it sometimes may still result in persistent breast tissue, which later needs to be surgically removed). For adults with gynecomastia, the work-up should include testosterone and adrenal androgen measurements, in addition to E2 and E1 measurements. Causes for increased E1 or E2 levels include:

-High androgen levels caused by tumors or androgen therapy (medical or sport performance enhancing), with secondary elevations in E1 and E2 due to aromatization

-Obesity with increased tissue production of E1

-Decreased E1 and E2 clearance in liver disease

-Estrogen producing tumors

-Estrogen ingestion

Normal male E1 and E2 levels also may be associated with feminization or gynecomastia if bioavailable testosterone levels are low due to primary/secondary testicular failure. This may occur, for example, when patients are receiving antiandrogen therapy or other drugs with antiandrogenic effects (eg, spironolactone, digitalis preparations).

The gonadotrophin-releasing hormone stimulation test remains the central part of the work-up for precocious puberty. However, baseline sex steroid and gonadotrophin measurements also are important. Prepubertal girls have E2 levels less than 10 pg/mL (most <5 pg/mL). Levels in prepubertal boys are less than half the levels seen in girls. LH/FSH are very low or undetectable. E1 levels also are low, but may rise slightly in obese children after onset of

adrenarche. E2, which is produced in the gonads, should remain low in these children. In true precocious puberty, both E2 and LH/FSH levels are elevated above the prepubertal range. Elevation of E2 or E1 alone suggests pseudo precocious puberty, possibly due to a sex steroid-producing tumor.

In delayed puberty, estrogens and gonadotrophins are in the prepubertal range. A rise over time predicts the spontaneous onset of puberty. Persistently low estrogens and elevated gonadotrophins suggest primary ovarian failure, while low gonadotrophins suggest hypogonadotrophic hypogonadism. In this latter case, Kallman syndrome (or related disorders) or hypothalamic/pituitary tumors should be excluded in well-nourished children.

Inherited disorders of sex steroid metabolism are usually associated with production abnormalities of other steroids, most notably a lack of cortisol. Aromatase deficiency is not associated with cortisol abnormalities and usually results in some degree of masculinization in affected females, as well as primary failure of puberty. Males may show delayed puberty and delayed epiphyseal closure, as well as low bone-density. E2 and E1 levels are very low or undetectable. Various forms of testicular feminization are due to problems in androgen signaling pathways and are associated with female (or feminized) phenotypes in genetic males. E2 and E1 levels are above the male reference range, usually within the female reference range, and testosterone levels are very high.

See Steroid Pathways in Special Instructions.

Cautions

No significant cautionary statements.

Clinical Reference

1. Bidlingmaier F, Wagner-Barnack M, Butenandt O, Knorr D: Plasma estrogens in childhood and puberty under physiologic and pathologic conditions. Pediatr Res 1973;7(11):901-907

2. Elmlinger MW, Kuhnel W, Ranke MB: Reference ranges for serum concentrations of lutropin (LH), follitropin (FSH), estradiol (E2), prolactin, progesterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), cortisol and ferritin in neonates, children and young adults. Clin Chem Lab Med 2002;40(11):1151-1160

3. Cummings SR, Browner WS, Bauer D, et al: Endogenous hormones and the risk of hip and vertebral fractures among older women. N Engl J Med 1998;339:733-738

4. Iughetti L, Predieri B, Ferrari M, et al: Diagnosis of central precocious puberty: endocrine assessment. J Pediatr Endocrinol Metab 2000;13 Suppl 1:709-715

5. Ismail AA, Barth JH: Endocrinology of gynaecomastia. Ann Clin Biochem 2001;38:596-607

6. Kligman I, Rosenwaks Z: Differentiating clinical profiles: predicting good responders, poor responders, and hyperresponders. Fertil Steril 2001;76:1185-1190

7. Traggiai C, Stanhope R: Delayed puberty. Best Pract Res Clin Endocrinol Metab 2002;16:139-151

Performance

Method Description

Estrone is extracted from 0.5 mL of serum with the organic solvent methylene chloride. Deuterated 17 beta-estradiol-d5 and estrone-d4 are added to each specimen before the liquid extraction and serve as internal standards. After derivatization with dansyl chloride, HPLC is used prior to introduction of the derivatized sample extract into the tandem mass spectrometer.(1) The calibration utilizes an 8 point standard curve over a concentration range of 0 to

600 pg/mL.(Anari MR, Bakhtiar R, Zhu B, et al: Derivatization of ethynylestradiol with dansyl chloride to enhance electrospray ionization: application in trace analysis of ethynylestradiol in Rhesus monkey plasma. Anal Chem 2002;74:4136-4144)

PDF Report

No

Day(s) and Time(s) Test Performed

Monday through Friday

Analytic Time

2 days

Maximum Laboratory Time

4 days

Specimen Retention Time

2 weeks

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

82679

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
E1	Estrone, S	2258-2

Result ID	Test Result Name	Result LOINC Value
81418	Estrone, S	2258-2