

Ovarian Assessment Report

OAR with Egg Supply Score (ESS)

Patient: Example, Patient
Clinician: Clinician Example
Date of report: 03/17/2022

OBGYN Format

ReproSource[®]
Fertility Diagnostics
ILLUMINATING PATHWAYS TO REPRODUCTIVE HEALTH

Ovarian Assessment Report

OBGYN Format

Patient: Example, Patient

Clinician: Clinician Example

Gender: F Age: 29 years Date of birth: 01/01/1993

Telephone: 413-555-5555

Fax: 413-555-5556

Specimen: 90020030 Chart #: Not Provided

Address: Example Clinic

Reported: 03/17/2022

123 Example St

Received: 03/17/2022 Time: 10:00

Example City, EX 55555

Collected: 03/17/2022 Time: 09:00

Tests:		FSH	Estradiol	LH	AMH	^b Inhibin B
Patient Values:		8 mIU/mL	30 pg/mL	2.2 mIU/mL	0.51 ng/mL (6% for age)	<40 pg/mL
RANGES	Follicular Phase	3.5 to 12.5	^a 20.5 to 62.8	2.4 to 12.6	Low 0.0 to <0.3	< 64.0
	Ovulation Phase	4.7 to 21.5	60.4 to 602.0	14.0 to 95.6	Reduced 0.3 to <0.7	64.0-200.0
	Post Menopausal	25.8 to 134.8	<5 to 138.0	7.7 to 58.5	Adequate 0.7 to 3.5	
		^a Reflects early follicular phase range for Elecsys [®] Estradiol			Note: Ranges calibrated to egg supply defined by ovulatory response during egg retrieval. ¹	

COMMENTS:

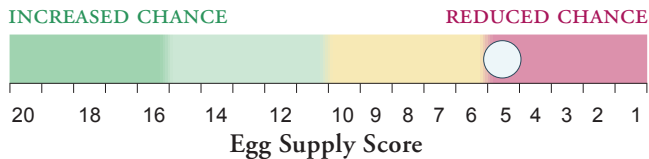
Results suggest a reduced chance of a good egg supply. Age suggests a good chance of good egg quality. Given egg supply and quality diminish with time, women experiencing difficulty with conception or considering egg preservation should discuss treatment options with a fertility specialist. Low age specific AMH is associated with premature ovarian insufficiency, earlier menopause, and autoimmunity, while high AMH is associated with PCOS and later menopause. Hormonal contraceptives may lower AMH within the first 8 weeks of use with increasing AMH observed within 8 weeks after discontinuing use. NOTE: Consider repeat testing to confirm concerning serum AMH results. In some women retested within 1 year AMH can show substantial biological fluctuations. AMH results and ranges are specific to ReproSource. ²⁻⁹

^b The ReproSource Inhibin B test was developed and its analytical performance characteristics have been determined by ReproSource Fertility Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

Egg Supply Score (ESS)

Reduced

5

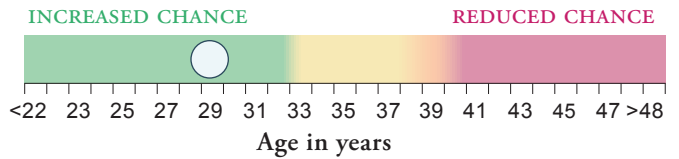


The ESS estimates likelihood of good egg supply (quantity) by optimizing the combination of age with multiple ovary-related hormones such as AMH and FSH.^{12,13}

Egg quality and your age

Good

29

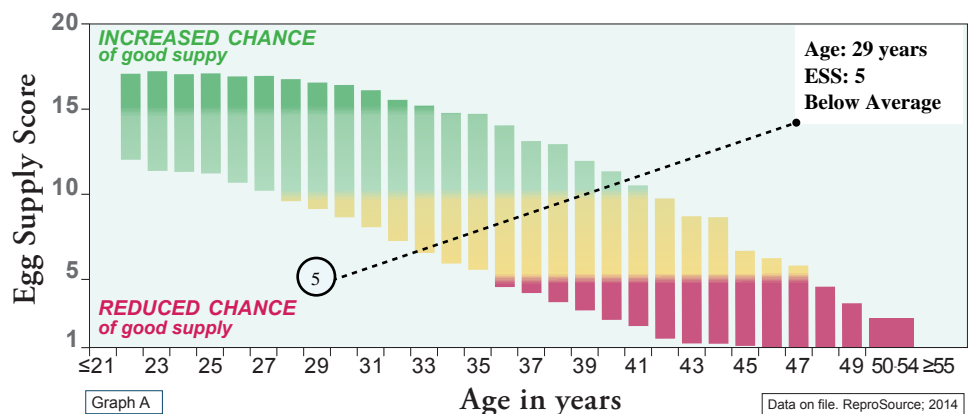


Currently, age is the best predictor of good egg quality. The bar above shows, based upon age alone, how aging decreases the chance of good egg quality.

Graph A to the right displays bars with the ESS range containing the middle 70% of women ("average") by year of age in 26,125 women evaluated at fertility centers. Women with an ESS in the lowest 15% are defined as "below average" while those with an ESS in the highest 15% are "above average." Bar color indicates chance of good egg supply based upon ESS.

Note: Women from fertility centers are not randomly selected from the general population but are comprised of both fertile and infertile women with low, intermediate, and high egg supply.

Egg Supply Score compared to 26,125 women from fertility centers ^{12,13}



Understanding your egg supply score (ESS)

Egg Supply Score clinical ranges:

Historically, an accurate egg supply assessment was difficult to obtain. The number of eggs obtained through an IVF egg retrieval procedure is considered to be the gold standard for measuring egg supply, but this procedure is not a practical diagnostic test. Although many studies demonstrate the ability of various blood tests to correlate with eggs retrieved, general clinical testing laboratories do not calibrate their test results to this clinical outcome.

The Egg Supply Score (ESS) calibrates age and blood test results from ovary related hormones including AMH and FSH to the number of eggs obtained in an egg retrieval.^{12,13} The ESS ranges from 1 to 20, with likelihood of good egg supply increasing as the score increases.

ESS	Category
1 to 5	Reduced
6 to 10	Fair
11 to 15	Good
16 to 20	Excellent

Chart A

Note: No single test can predict a woman's ability to have a child and the ESS does not assess egg quality.

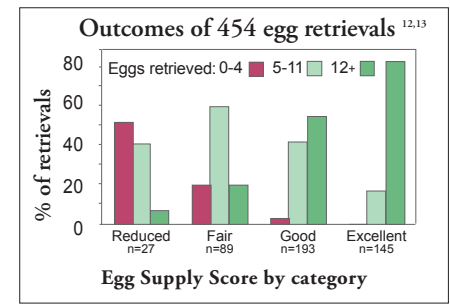
Study calibrating ESS to egg supply:

Objective: To provide the most accurate and easily interpreted assessment of a woman's current egg supply from a blood test.

Methods: In a blinded study,^{12,13} blood samples from women undergoing a total of 454 egg retrievals were tested by ReproSource, and included women with likely excellent egg supply (79 egg donors and 26 female partners of infertile men) and with likely poor egg supply (139 infertile women). ReproSource conducted testing for ovary related hormones, such as AMH and FSH, and for calculation of the ESS. A third party unblinded and analyzed results.

Results: The results (see Graph B) showed that women with lower ESS values were more likely to have a low egg supply (0 to 4 eggs retrieved, red bars) and women with higher ESS values were more likely to have a good egg supply (12 or more eggs retrieved, dark green bars).

Conclusions: The Egg Supply Score (ESS) is highly correlated with the gold standard measurement of a woman's egg supply: the number of eggs obtained in an egg retrieval procedure. The ESS can be a useful tool to help clinicians and patients better understand a woman's likely egg supply.



Graph B

Age specific AMH percentile and women's health

AMH associations
AMH results alone do not establish a diagnosis

High AMH

Condition: Polycystic Ovary Syndrome
IVF/ART: greater response

AMH
Age Specific Average

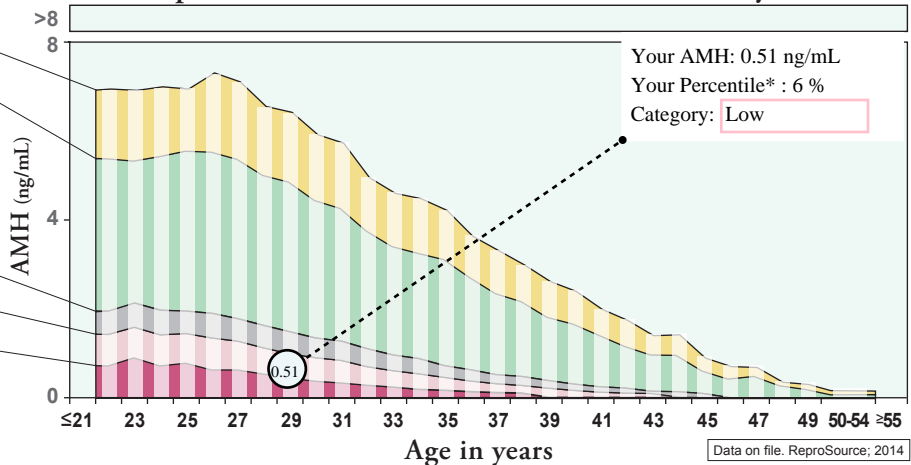
Menopause: earlier than average
Conditions: POI/POF, autoimmunity
IVF/ART: reduced response possible decreased egg quality
Exposures: contraceptive hormones, chemotherapy, ovarian surgery

Low AMH

LEGEND:	Category	Percentile
	Borderline high	76% to 85%
	Average	26% to 75%
	Borderline low	16% to 25%
	Low	6% to 15%
	Very low	0 to 5%

NOTE: Although elevated or reduced AMH values relative for a given age have associations with the above conditions, AMH percentiles alone should NOT be used to establish a diagnosis of any of the above conditions.

Comparison to 65,128 women^c evaluated at fertility centers



Data on file. ReproSource; 2014

AMH and women's health

If appropriately linked to clinical outcomes in women's health, AMH testing provides a wide range of helpful information^{2,3} independently from FSH.⁴ Population average AMH levels decline steadily from 25 years of age until undetectable,⁵ however within individuals of the same age, AMH levels vary considerably (above graph) as may the rate of decline.³ Elevated, age-specific AMH, is associated with higher likelihood of polycystic ovary syndrome (PCOS).^{6,7} Lower age-specific AMH is associated with premature ovarian insufficiency/failure (POI/POF), earlier menopause, and is observed in autoimmune diseases such as systemic lupus erythematosus and Crohn's disease.^{3,8} Importantly, studies now conclude that hormonal contraceptives can lower AMH values as can ovarian related surgery and chemotherapy.^{3,9}

In Graph C above, the y-axis represents ReproSource serum AMH (ng/mL). The x-axis indicates age (in years) from 65,128 women evaluated at fertility centers. Color indicates population percentiles (e.g. green=middle 70% of population and red= lowest 5th%).

^c Note: Women at fertility centers are not the general population but do include fertile (egg donors), infertile, and randomly selected (partners of infertile men) women. Thus, percentiles may not exactly match the general population.

Note: Comparing AMH and FSH from different sources is not advised as levels differ widely amongst laboratories.^{2,3,10} While AMH testing provides clear clinical benefit, especially with extreme high and low values, definitive cut points for the general population are still the subject of active research. Therefore, interpretation of AMH results in the general population should be directional rather than definitive, prompting further investigation rather than establishing diagnoses or current fertility status.^{2,3,11}

Why fertility experts use ReproSource and the OAR

① Most up-to-date ovarian reserve testing for clinical use

ReproSource provides the latest testing related to egg supply and ovarian reserve. Historically FSH has been the blood test most frequently used as a marker of egg supply, but it has a high frequency of falsely reassuring results. AMH (see Figure A) which is secreted from the granulosa cells surrounding each egg, has emerged as a more accurate blood test.^{1,3,6} ReproSource has demonstrated AMH is more accurate than other hormones in assessing egg supply,¹

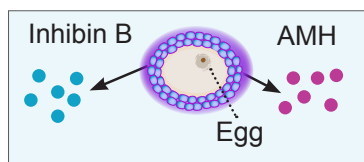


Figure A © ReproSource 2009

declines gradually with age,^{1,5} and identifies many women at risk for poor egg supply missed by FSH testing (1 in 11 women tested under age 35 are missed which rises to 1 in 3 women above 39 years of age).⁴

③ Continuous improvement of clinical information through clinical research

The field of Reproductive Health is complex and rapidly evolving with hundreds of studies published each year, many of which rely upon diagnostic testing to categorize patients. Therefore, clinicians need a laboratory focused on Reproductive Health which calibrates to clinical outcome and maintains the link between the reported test result and new clinical information.^{2,3,14} ReproSource provides this service.

Recent advancements in egg supply testing, especially related to AMH, have important consequences to women's health. The biggest barriers to benefiting from the clinical utility of this testing are widely varying results from clinical laboratories and assays and cut points or ranges not linked to clinical outcome data. For example, laboratories that provide results for routine tests such as FSH or newer tests such as AMH, generally do not use the same testing methodologies employed in the clinical studies that reported the interpretative ranges of clinical utility. By both conducting clinical outcomes research and providing testing for clinical use, ReproSource provides a reliable source for information and clinical testing related to egg supply and other conditions affecting Reproductive Health.

② Mathematical formula calibrates results to egg supply for easier interpretation



Figure B © ReproSource 2009

Clinical reference laboratories report a variety of tests related to egg supply but generally do not calibrate to egg supply.^{2,3,14} Thus, it is often unclear how reported results link to clinical outcomes or how to weight the results of individual tests together. By conducting clinical outcomes research in egg supply testing, ReproSource is able to directly calibrate testing results to egg supply and mathematically optimize the combination of results to provide the Egg Supply Score: a single, easy to use assessment of egg supply. See Figure B above.^{12,13}

Test	≤4 eggs		≤6 eggs	
	AUROC	vs ESS	AUROC	vs RE
ESS	0.833	n/a	0.792	n/a
AMH	0.806	P=.02	0.762	P=.03
FSH	0.688	P<.01	0.651	P<.01

The ESS demonstrated higher accuracy (P<.05) when compared to single tests such as AMH and FSH for predicting very low (≤4 egg retrieved) or low (≤6 egg retrieved) egg supply when using Area Under the Receiver Operator Characteristic (AUROC) curve comparison.

Chart B © ReproSource 2009

References (★ ReproSource publications)

- Riggs RM, Duran EH, Baker MW, et al. Assessment of ovarian reserve with anti-Müllerian hormone: a comparison of the predictive value of anti-Müllerian hormone, follicle-stimulating hormone, inhibin B, and age. *Am J Obstet Gynecol.* 2008;199(2):202.e1-202.e2028. doi:10.1016/j.ajog.2008.05.004
- Practice Committee of the American Society for Reproductive Medicine. Testing and interpreting measures of ovarian reserve: a committee opinion. *Fertil Steril.* 2015;103(3):e9-e17. doi:10.1016/j.fertnstert.2014.12.093
- Leader B, Baker VL. Maximizing the clinical utility of antimüllerian hormone testing in women's health. *Curr Opin Obstet Gynecol.* 2014;26(4):226-236. doi:10.1097/GCO.0000000000000087
- Leader B, Hegde A, Baca Q, et al. High frequency of discordance between antimüllerian hormone and follicle-stimulating hormone levels in serum from estradiol-confirmed days 2 to 4 of the menstrual cycle from 5,354 women in U.S. fertility centers. *Fertil Steril.* 2012;98(4):1037-1042. doi:10.1016/j.fertnstert.2012.06.006
- Seifer DB, Baker VL, Leader B. Age-specific serum anti-Müllerian hormone values for 17,120 women presenting to fertility centers within the United States. *Fertil Steril.* 2011;95(2):747-750. doi:10.1016/j.fertnstert.2010.10.011
- Tal R, Seifer DB, Khanimov M, Malter HE, Grazi RV, Leader B. Characterization of women with elevated antimüllerian hormone levels (AMH): correlation of AMH with polycystic ovarian syndrome phenotypes and assisted reproductive technology outcomes. *Am J Obstet Gynecol.* 2014;211(1):59.e1-59.e598. doi:10.1016/j.ajog.2014.02.026
- Quinn MM, Kao CN, Ahmad AK, et al. Age-stratified thresholds of anti-Müllerian hormone improve prediction of polycystic ovary syndrome over a population-based threshold. *Clin Endocrinol (Oxf).* 2017;87(6):733-740. doi:10.1111/cen.13415
- Kim C, Slaughter JC, Wang ET, et al. Anti-Müllerian hormone, follicle stimulating hormone, antral follicle count, and risk of menopause within 5 years. *Maturitas.* 2017;102:18-25. doi:10.1016/j.maturitas.2017.04.018
- Kallio S, Puurunen J, Ruokonen A, Vaskivuo T, Piltonen T, Tapanainen JS. Antimüllerian hormone levels decrease in women using combined contraception independently of administration route. *Fertil Steril.* 2013;99(5):1305-1310. doi:10.1016/j.fertnstert.2012.11.034
- College of American Pathologists. Surveys and Anatomic Pathology Education Programs. Educational Discussion: AMH & FSH Proficiency Testing 2017. Accessed May 26, 2021. <https://documents.cap.org/documents/2017-b-antimullerian-hormone.pdf>
- Steiner AZ, Pritchard D, Stanczyk FZ, et al. Association Between Biomarkers of Ovarian Reserve and Infertility Among Older Women of Reproductive Age. *JAMA.* 2017;318(14):1367-1376. doi:10.1001/jama.2017.14588
- Leader B, Baca QJ, Stadtmayer L, et al. Ovarian reserve index predicts number of oocytes at retrieval in fertile and infertile women. *Hum Reprod.* 2008;23(suppl 1):i80-i81. Accessed May 26, 2021. <https://doi.org/10.1093/humrep/den1051>
- Leader B, Quinn E, Sullivan, et al. Ovarian reserve index outperforms AMH, inhibin B, and FSH in predicting poor egg supply. *Fertil Steril.* 2008 Sep;90(1):S263-S264. Accessed May 26, 2021. <https://doi.org/10.1016/j.fertnstert.2008.07.1239>
- A practical approach to recent advances in ovarian reserve testing. Leader B, Baker V. In: Biennial Reviews of Infertility 3rd edition. Editors: Schlegel PN, Fauser BC, Carrell, DT, Racowsky C. Springer, Inc; 2013.
- La Marca A, Sighinolfi G, Papaleo E, et al. Prediction of age at menopause from assessment of ovarian reserve may be improved by using body mass index and smoking status. *PLoS One.* 2013;8(3):e57005. doi:10.1371/journal.pone.0057005
- Dölleman M, Faddy MJ, van Disseldorp J, et al. The relationship between anti-Müllerian hormone in women receiving fertility assessments and age at menopause in subfertile women: evidence from large population studies. *J Clin Endocrinol Metab.* 2013;98(5):1946-1953. doi:10.1210/jc.2013-3105
- van den Berg MH, van Dulmen-den Broeder E, Overbeek A, et al. Comparison of ovarian function markers in users of hormonal contraceptives during the hormone-free interval and subsequent natural early follicular phases. *Hum Reprod.* 2010;25(6):1520-1527. doi:10.1093/humrep/deq071
- Gustin SL, Ding VY, Desai M, et al. Evidence of an age-related correlation of ovarian reserve and FMR1 repeat number among women with "normal" CGG repeat status [published correction appears in J Assist Reprod Genet. 2016 Jan;33(1):137]. *J Assist Reprod Genet.* 2015;32(11):1669-1676. doi:10.1007/s10815-015-0577-0

Elecsys® AMH reference values measured in healthy population^d Reference range established for AMH in 718 healthy females between ages 20-44 years.

Estimated Quantiles of Elecsys AMH						
Healthy Women	N	2.5%-q ng/mL (95%CI)	5%-q ng/mL (95%CI)	Median ng/mL (95%CI)	95%-q ng/mL (95%CI)	97.5%-q ng/mL (95%CI)
20-24 yrs	150	1.22 (0.4781-1.67)	1.52 (0.758-1.81)	4.00 (3.60-4.44)	9.95 (7.87-13.6)	11.7 (9.11-15.7)
25-29 yrs	150	0.890 (0.493-1.21)	1.20 (0.797-1.75)	3.31 (3.00-3.89)	9.05 (7.59-10.3)	9.85 (8.91-11.3)
30-34 yrs	138	0.576 (0.256-0.958)	0.711 (0.256-1.12)	2.81 (2.35-3.47)	7.59 (6.84-9.52)	8.13 (7.27-9.72)
35-39 yrs	138	0.147 (0.052-0.474)	0.405 (0.053-0.496)	2.00 (1.73-2.36)	6.96 (5.31-9.37)	7.49 (6.49-10.9)
40-44 yrs	142	0.030 (0.030-0.063)	0.059 (0.726-1.13)	0.882 (0.726-1.13)	4.44 (2.9405.56)	5.47 (3.93-6.76)

^dElecsys® [package insert]. Roche; 2020.