Ovarian Assessment Report

OAR™ with Egg Supply Score (ESS™)

Patient: Patient, Example
Physician: Clinician Example
Date of Report: 08/03/2017

PRIVATE AND CONFIDENTIAL

ReproSource®
The Source For Fertility Testing & Information™

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ReproSource®
The Source For Fertility Testing & Information™

Ovarian Assessment Report 1.5

Patient: Patient, Example
Gender: F Age: 28 years Date of Birth: 01/01/1989
Specimen: 00297602 Reported: 08/03/2017
Received: 07/24/2017 Time: 15:15
Collected: 07/23/2017 Time: 15:15

Physician: Clinician Example
Phone: 413-555-5555 Fax: 413-555-5556
Address: Example Clinic
123 Example St
Example City, EX 55555

Tests:	FSH	Estradiol	LH	AMH	Inhibin B
Patient Values:	8 mIU/mL	30 pg/mL	2.2 mIU/mL	**0.51** ng/mL **(4% for age)**	30 pg/mL
Ranges: Follicular Day 2,3	3.0 to 14.4	ND to 84	1.1 to 11.6		
Midcycle	5.8 to 21.0	34 to 400	17.0 to 77.0		
Menopausal	21.7 to 153.0	ND to 30			

	AMH	Inhibin B
Low	0.0 to <0.3	
Reduced	0.3 to <0.7	0 to 64
Satisfactory	0.7 to 3.5	>64
High	>3.5	

Note: Ranges calibrated to egg supply defined by ovulatory response during egg retrieval[1].

COMMENTS:

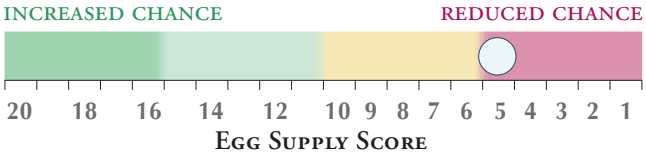
Results suggest a reduced chance of a good egg supply. Age suggests a good chance of good egg quality. Given egg supply and quality diminish with time, women experiencing difficulty with conception or considering egg preservation should discuss treatment options with a fertility specialist. Low age specific 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]

Reviewed by: Benjamin Leader MD PhD

ReproSource is CAP accredited, certified under CLIA '88 to provide high complexity testing, and NY State approved to provide the above testing for clinical use. ReproSource has established, and continues to monitor, the performance characteristics of the above testing. AMH and inhibin B testing has not been cleared or approved by the US FDA and utilizes certain materials labeled "RUO. For Research Use Only." The FDA does not require this testing to go through premarket FDA review. This testing is used for clinical purposes. It should not be regarded as investigational or for research.

Egg Supply Score (ESS)

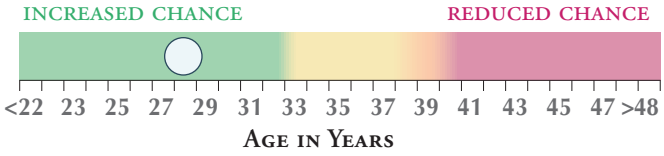
Reduced **5**



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[10,11].

Egg Quality & Your Age

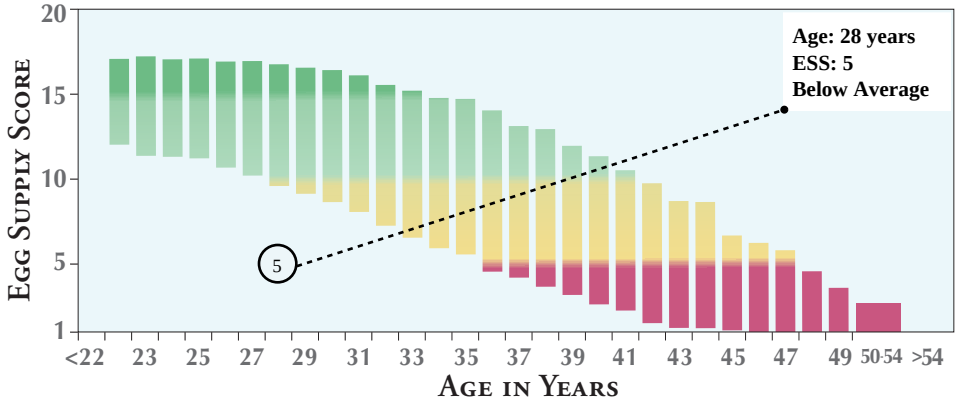
Good **28**



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.

Egg Supply Score Compared to 26,125 Women from Fertility Centers

The graph 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.



Understanding Your Egg Supply Score (ESS)

Egg Supply Score Clinical Ranges:

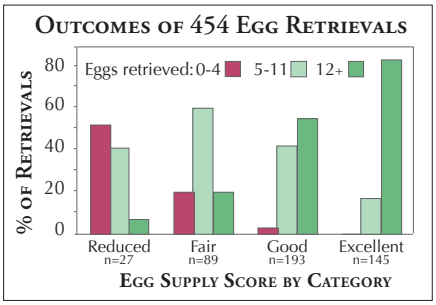
Historically, an accurate egg supply assessment was difficult to obtain. The number of eggs obtained through an IVF egg retrieval procedure is considered to be the gold standard for measuring egg supply, but this procedure is not a practical diagnostic test. Although many studies demonstrate the ability 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[10,11]. 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

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[10,11], 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 (graph to upper right) 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.

Age Specific AMH Percentile and Women's Health

AMH Level Compared to 65,128 Women* Evaluated at Fertility Centers

High AMH

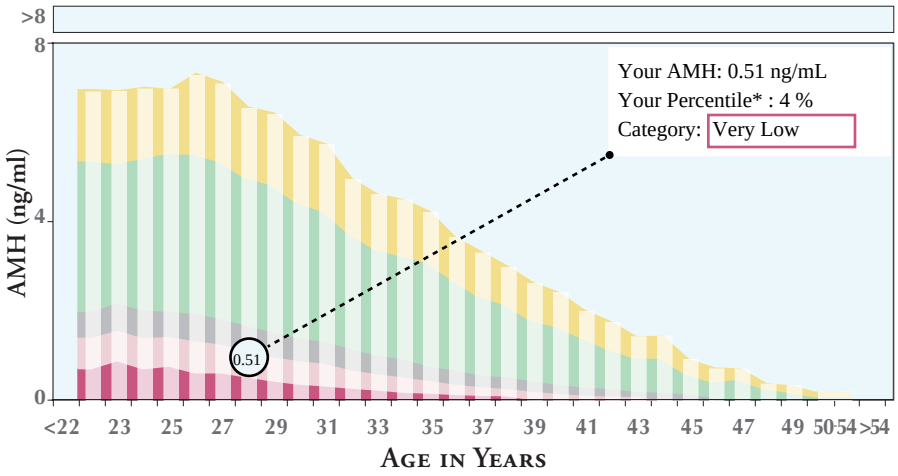
Condition: Polycystic Ovary Syndrome
IVF/ART: excessive response

AMH
Age Specific Average

Menopause: earlier than average
Conditions: POI/POF, autoimmunity
IVF/ART: poor 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:** Women at fertility centers are not randomly selected from the general population but do represent women who are fertile (egg donors), infertile, and randomly selected (partners of infertile men). Thus, percentiles reported may not exactly match the general population.
Graph: Displayed above is the distribution of ReproSource serum AMH values (ng/ml, y-axis) by age (years, x-axis) from 65,128 women evaluated at fertility centers. Color is used to indicate population percentiles, for example, the middle 70% of the population (green) or lowest 5th percentile (red).

AMH and Women's Health

If appropriately calibrated to clinical outcomes, age specific serum AMH testing can provide helpful information for a number of conditions in women's health[2,3]. Although the population average AMH level declines steadily from 25 years of age until undetectable[12], individual AMH levels vary considerably among women of the same age (graph, above right). The more elevated the age-specific AMH, the higher the likelihood of polycystic ovary syndrome (PCOS)[6,7] and later menopause[4,5]. Conversely, lower age-specific AMH values are associated with premature ovarian insufficiency/failure (POI/POF) and earlier menopause. Although not a screening test for autoimmunity, lower serum AMH is observed in conditions such as systemic lupus erythematosus and Crohn's disease[2]. Importantly, clinical studies now conclude that hormonal contraceptives can lower AMH values as can ovarian related surgery and chemotherapy[2,8,9].

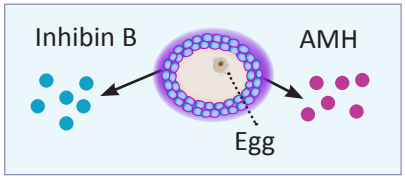
Note: AMH levels are not standardized across laboratories[2,3]. Thus, AMH results from different laboratories cannot be compared. Secondly, while there is clear clinical benefit from AMH testing, especially as values approach the extremes of high and low, definitive cut points for the general population 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.

Laboratory Director: (CLIA) Kathryn Go, PhD (New York State) Benjamin Leader, MD, PhD

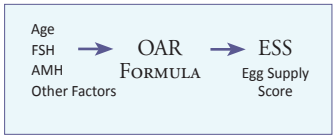
Why Fertility Experts Use ReproSource and the Ovarian Assessment Report (OAR)

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, which is secreted from the granulosa cells surrounding each egg, has emerged as a more accurate blood test[1,2]. ReproSource has demonstrated AMH is more accurate than other hormones in assessing egg supply[1], declines gradually with age[12], 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)[13].



② Mathematical Formula Calibrates Results to Egg Supply for Easier Interpretation



Clinical reference laboratories report a variety of tests related to egg supply but generally do not calibrate to egg supply[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.[10,11]

Example Performance Detecting Low Egg Supply

Test	≤4 eggs		≤6 eggs	
	AUROC	*vs ESS*	AUROC	*vs ESS*
ESS	0.833	*n/a*	0.792	*n/a*
AMH	0.806	*P=0.02*	0.762	*P=0.03*
FSH	0.688	*P<0.01*	0.651	*P<0.01*

The ESS demonstrated higher accuracy (P<0.05) 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[10,11].

③ Continuous Improvement of Clinical Information Through Clinical Research

The field of fertility medicine 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 fertility focused laboratory which calibrates to clinical outcome, and maintains the link between the reported test result and new clinical information[14]. ReproSource provides this service.

Recent advancements in egg supply testing, especially related to AMH, have important consequences to women's health. The biggest barrier to the clinical utility of this testing is the frequently changing test methodology, and cut points not calibrated to egg supply[2,3]. 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 appropriately calibrated ovarian reserve and other fertility testing used by hundreds of fertility specialists.

References (** ReproSource Publications)

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** 3. **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.**

4. **Prediction of age at menopause from assessment of ovarian reserve may be improved by using body mass index and smoking status.** La Marca A, Sighinolfi G, Papaleo E, Cagnacci A, Volpe A, Faddy MJ. *PLOS One*. **2013**;8(3):e57005.

** 5. **The relationship between anti-Müllerian hormone in women receiving fertility assessments and age at menopause in subfertile women: evidence from large population studies.** Dolleman M, Faddy MJ, van Disseldorp J, van der Schouw YT, Messow CM, Leader B, et al. *The Journal of Clinical Endocrinology and Metabolism* **2013** May;98(5):1946-53.

6. **Can anti-Mullerian hormone predict the diagnosis of polycystic ovary syndrome? A systematic review and meta-analysis of extracted data.** Iliodromiti S, Kelsey TW, Anderson RA, Nelson SM. *The Journal of Clinical Endocrinology and Metabolism*. **2013** Aug;98(8):3332-40.

** 7. **Characterization of women with elevated antimüllerian hormone levels (AMH): correlation of AMH with polycystic ovarian syndrome phenotypes and assisted reproductive technology outcomes.** Tal R, Seifer DB, Khanimov M, Malter HE, Grazi RV, Leader B. *American Journal of Obstetrics and Gynecology*. Epub **2014** Mar 2.

8. **Antimüllerian hormone levels decrease in women using combined contraception independently of administration route.** Kallio S, Puurunen J, Ruokonen A, Vaskivuo T, Piltonen T, Tapanainen JS. *Fertility Sterility*. **2013** Apr;99(5):1305-10.

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** 10. **Index predicts number of oocytes at retrieval in fertile and infertile women.** Leader, B, Baca QJ, Stadtmauer L, Riggs R, Rivnay B, L Yin. *Human Reproduction* **2008** Jul; 23(Sup1);i80.

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** 12. **Age-specific serum anti-Mullerian hormone values for 17,120 women presenting to fertility centers within the United States.** Seifer DB, Baker VL, Leader B. *Fertility and Sterility* **2011** Feb;95(2):747-50.

** 13. **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.** Leader B, Hegde A, Baca Q, Stone K, Lannon B, Seifer DB, et al. *Fertility and Sterility* **2012** Oct;98(4):1037-42.

14. **Testing and interpreting measures of ovarian reserve: a committee opinion.** Practice Committee of the American Society for Reproductive Medicine. *Fertility and Sterility* **2012** Dec;98(6):1407-15.

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