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Ovarian Reserve Testing: A Promising Tool for Family Planning and  
Fertility Preservation in the 21<sup>st</sup> Century

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A project submitted in fulfillment of  
NURS 997 Independent Study  
College of Nursing and Professional Disciplines  
University of North Dakota  
Spring 2018

**PERMISSION**

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### Abstract

Advances in contraception over the past several decades have resulted in delayed conception and increased maternal age. Many women are now delaying conception until their fertility has begun to decline. There is a need for healthcare providers to expand family planning services to include those which provide for early identification of fertility decline and promote fertility preservation. A case study explored the utility of fertility screening in a healthy 31-year-old woman with a history of prolonged oral contraceptive use and strong family history of breast cancer who desired conception in the future. A literature review investigated available pro-fertility screening tests which might benefit this patient. This review revealed that *Ovarian Reserve* (OR) testing has been historically used to identify women at risk for subfertility. *Anti-Müllerian Hormone* (AMH) serum testing is the preferred method used to evaluate OR and has been widely used within infertile populations. However, the quality of AMH assays varies greatly and external factors have the potential to influence AMH testing results. Nonetheless, AMH testing may prove to be a useful part of broader fertility assessments. AMH testing has the potential to impact future family planning activities as they relate to fertility assessment, counseling, and the development of informed family planning goals. Patient demand for pro-fertility services, like AMH screening, is rising and further, large-scale studies are needed in healthy populations to improve the fertility screening process.

*Keywords:* ovarian reserve screening, ovarian insufficiency, female fertility, Anti-Müllerian Hormone, hormonal contraception, BRCA, oral contraceptives

## Ovarian Reserve Testing: A Promising Tool for Family Planning and Fertility Preservation in the 21<sup>st</sup> Century

The dynamics of family planning are changing, and it may be time for healthcare providers to expand their family planning toolkits to include services focused on fertility preservation. There have been significant advances in female hormonal contraception over the past 50 years. These advances have provided women with family planning options focused primarily on delayed conception. Many women are now choosing to delay timing of conception until their fertility has already begun to decline. Unfortunately, some women are ultimately unable to conceive without costly assistance, if at all. The trend towards increased maternal age warrants exploration of family planning services which focus on early identification of fertility decline and preservation of female fertility.

### **Background**

Age-related subfertility is an unfortunate reality many women in developed countries may face in the future. Long-term contraceptive use has provided women with the option to pursue increased financial stability and professional attainment prior to childrearing; the natural result has been an observed increase in maternal age over the past few decades (Nelson, Telfer, & Anderson, 2012; O'Brien et al., 2017; Petersen et al., 2017). Postponing parenthood is expected to result in a large increase in the number of pregnancies in older mothers as well as a significant increase in the number of couples seeking reproductive assistance and struggling with infertility (Nelson et al., 2012; Petersen et al., 2017).

The American College of Obstetricians and Gynecologists (ACOG) committee opinion statement regarding female age-related fertility decline references a known decline in female fertility at approximately age 32, with a more rapid decrease after age 37 (Appendix A) (2014).

ACOG supports expedited fertility evaluation and fertility treatment in women older than 35 after six months of failed attempts at conception (2014). According to recent data, 14% of women who delay trying to conceive until the age of 35 will ultimately remain childless (one in seven), while 34% of women who delay conception until age 40 will find themselves faced with this devastating reality (one in three) (O'Brien et al., 2017). Providers should educate, enhance awareness, and counsel patients regarding the negative effect of age on fertility (ACOG, 2014).

Long term contraceptive use is safe, effective, and quite common in developed countries, but long-term hormonal contraceptive use may present unique challenges to fertility preservation. This form of birth control is now quite commonplace in developed societies; 50-89% of women living in Western countries will use hormonal contraception at some point during their life (Alkema et al., 2013; Kushnir, Barad, & Gleicher, 2014). One drawback of long-term hormonal contraception use is that it renders women unaware of menstrual changes indicative of sub-fertility, such as anovulation, amenorrhea, and menstrual changes associated with *Polycystic Ovarian Syndrome* (PCOS) (Hvidman et al., 2015; Kushnir et al., 2014). An estimated 10% of women will quietly develop *Premature Ovarian Insufficiency* (9%) or overt *Ovarian Failure* (1%), which largely remains undetected until a woman stops use of hormonal contraception with the intent to conceive (Kushnir et al, 2014; Tal & Seifer, 2017).

Medical advances have made it possible for women to potentially avoid finding themselves unintentionally childless. *Ovarian Reserve* (OR) evaluation can help to identify women at risk for poor reproductive outcomes, and thus potentially aid in both family planning and fertility preservation (Tal & Seifer, 2017). There are quantitative measures available to evaluate OR which include serum measurement of *Follicle Stimulating Hormone* (FSH), ultrasound measurement of *Antral Follicle Count* (AFC), and serum measurement of *Anti-*

*Müllerian Hormone* (AMH) (O'Brien et al., 2017). Exploration of the utility of these tests, as well as consideration of factors with the potential to influence test results, may arm providers and patients with novel tools to detect threats to fertility. The results of such tests may help to direct family planning activities in the future.

### **Case Summary**

To highlight the important practical applications of OR testing, a case study was explored through the lens of fertility preservation (see Appendix B for complete case note). A 31-year-old nulliparous, healthy female with no known medical conditions presented to an outpatient family practice clinic to establish care with a new provider. She had been utilizing oral hormonal contraceptives for several years as her preferred method of family planning, and she expressed interest in having a family of her own at some point in the future. She reported that she had been in a stable relationship with one male partner for greater than one year but was not currently married and did not have any plans to conceive within the next 12 months. Discussion of her family history revealed several cases of breast cancer as well as one case of ovarian cancer. The patient denied knowledge of any genetic testing within the family to identify breast cancer susceptibility (*BRCA*) gene mutations. Her present age, nulliparous status, desire for future conception, and history of long-term oral contraceptive use made her an excellent candidate for evaluation of family planning within the context of fertility preservation. The possibility of hormone-mediated disease led to further exploration of OR testing and female fertility as it relates to *hormonal contraceptive use* and potential genetic *BRCA* fertility risk factors.

## Literature Review

### Search Strategies

A literature search identified current relevant evidence within the scientific literature which examined the utility of OR testing for fertility evaluation and family planning for the selected case patient. To ensure appropriate healthcare related returns, the search was completed within the *Cumulative Index to Nursing and Allied Health Literature (CINAHL)* and *PubMed* databases. *CINAHL* was utilized to obtain greater understanding of OR testing within the context of the family planning environment as well as potential patient education considerations. *PubMed* provided access to large volumes of scientific research data related to OR testing. Key search terms included: *ovarian reserve screening, ovarian insufficiency, female fertility, Anti-Müllerian Hormone, hormonal contraception, BRCA, and oral contraceptives*. Selected terms were similar to those found within recent scientific studies and systemic reviews related to OR testing.

Search limitations were implemented to ensure relevant, reliable, and recent literature returns. Articles explored included peer reviewed articles published within the past five years and written in the English language. These search limitations provided results of high quality that incorporated the most recent research findings applicable to the selected case study patient. The initial literature search yielded 147 articles, of which 12 appropriate sources were selected for final in-depth review.

### Findings

*Ovarian Reserve Testing* has historically been used by fertility specialists to identify women at risk for *Diminished Ovarian Reserve (DOR)*; *Ovarian Reserve (OR)* serves as a general indicator of a woman's reproductive potential and has proven beneficial for those



seeking in vitro fertilization (Petersen et al., 2017; Tal & Seifer, 2017). Three distinct methods are currently utilized to screen for DOR: *Follicle Stimulating Hormone* (FSH), *Antral Follicular Count* (AFC), and *Anti-Müllerian Hormone* (AMH) analysis. FSH is the oldest screening method and is based on feedback inhibition of FSH secretion from the pituitary gland in response to ovarian factors (Tal & Seifer, 2017). Unfortunately, FSH levels vary widely throughout the menstrual cycle, greatly reducing the testing window and reliability of this test (Tal & Seifer, 2017). *Antral Follicular Count* (AFC) is obtained via ultrasound and equates to the sum of follicles in both ovaries observed within the early stage of follicular development (menstrual cycle days 2-4) (Tal & Seifer, 2017). Unfortunately, like FSH, AFC tends to be quite variable, and the reliability of this test is limited as a result (Tal & Seifer, 2017).

In contrast, *Anti-Müllerian Hormone* (AMH) is expressed early within follicular development and remains largely unaffected by circulating gonadotropins. AMH presents in utero at roughly 36 weeks gestation, increases throughout adolescence, peaks at roughly age 25, and then gradually declines until it is no longer detected a few years prior to menopause (Tal & Seifer, 2017). This inverse correlation with chronological age has helped researchers to develop age-specific AMH ranges which have been widely utilized in infertile populations to assess potential ovarian response to assisted reproductive technology (Kushnir et al., 2014; Tal & Seifer, 2017). Serum AMH evaluation has been found to be a more reliable measure of OR than both FSH and AFC, and AMH testing has become the screening test of choice in evaluation for DOR (Bentzen et al., 2012; Grossman et al., 2017; Kushnir et al., 2014; Tal & Seifer, 2017). Abnormally high levels of AMH have been linked to *PCOS* as well, so this tool offers the potential added benefit of early detection and treatment of *PCOS* (which is known to be linked to sub-fertility) (Kushnir et al., 2014; Tall & Seifer, 2017).

Unfortunately, serum AMH testing has some significant limitations. No standardized international assay presently exists; different tests provide different results measured in different units and patients can even purchase unvalidated AMH testing kits online (Hvidman et al., 2015; Kushnir et al., 2014; Tal & Seifer, 2017). Low AMH cut off points from various assays have been found to have sensitivities ranging from 44% - 97% and specificities ranging between 41% - 100% for prediction of poor ovarian response to stimulation with gonadotropins (Tal & Seifer, 2017). Additionally, research regarding AMH testing has been conducted largely on patients seeking fertility treatments and current data regarding AMH testing in fertile populations is lacking (Grossman et al., 2017; Hvidman et al., 2015; Tal & Seifer, 2017). However, the quality of AMH testing continues to improve, and newer Automated AMH assay platforms have enhanced the precision, sensitivity, and turn-around time of these tests when compared to older enzyme-linked immunosorbent assay-based assays (Kushnir et al., 2014). These improved assays are now being actively utilized in Europe and Asia, and one new Automated AMH test was recently approved by the Food and Drug Administration (FDA) for evaluation of OR within the United States (Tal & Seifer, 2017).

Even though the quality of AMH testing continues to improve, several external factors impact serum AMH levels, potentially influencing the utility of this test. No strong association exists between AMH and fertility in younger women as AMH represents the number of remaining primordial follicles which is more reflective of reproductive lifespan (Kushnir et al., 2014; Nelson et al., 2012). Ethnicity also has potential to influence AMH testing as white women tend to have higher AMH levels than black, Chinese, and Latina patients (Kushnir et al., 2014; Tal & Seifer, 2017). Biological factors specifically associated with decreased AMH are *BRCA-1* gene mutations and the presence of systemic illnesses (such as Type I diabetes, Lupus, and

Crohn's Disease) (Nelson et al., 2013; Tal & Seifer, 2017). Additionally, environmental factors, such as smoking and Vitamin D deficiency, must be considered as they have been shown to suppress AMH levels (Grossman et al., 2017; Nelsen et al., 2013; Tal & Seifer, 2017). Another factor providers must consider when evaluating AMH is the use of hormonal forms of contraception. Combined *oral contraceptive* use has been associated with decreased AMH levels and reduced AFC follicle size (Bentzen et al., 2012; D'Arpe et al., 2016). This reduction in AMH is thought to reverse after stopping hormonal contraceptives, but data suggests there may be a negative linear association between the duration of hormonal contraceptive use and serum AMH concentrations (Bentzen et al., 2012; D'Arpe et al., 2016).

There are clearly several limitations to consider prior to utilizing AMH serum testing to evaluate OR. However, despite these limitations, AMH testing is still considered the best available marker of OR and research data supports its expanded use (Grossman et al., 2017; Tal & Seifer, 2017). Literature supports expanded OR testing in a wide variety of patients, including women considering elective oocyte cryopreservation, those seeking fertility preservation prior to gonadotoxic treatments, women with *PCOS*, peri-menopausal women, and those with known *BRCA-1* mutations (Kushnir et al., 2014; O'Brien et al., 2017; Tal & Seifer, 2017). ACOG acknowledges the usefulness of this screening test for women at high risk of DOR; results outside of the patient's expected range can be useful for patient encouragement to pursue more aggressive conception treatment options (2015). Examining both AMH and AFC data simultaneously has been utilized in some populations and may provide a clearer picture of ovarian function; this provides for estimation of OR as it relates to biological age compared with chronological age (Hvidman et al., 2014; Petersen et al., 2017).

Several recent studies have found women to be quite open to the idea of OR testing for non-medical reasons to help them to avoid becoming unintentionally childless (O'Brien et al., 2017). AMH testing could be used as part of a broader fertility assessment which would provide clinicians with a useful tool to counsel women on family planning options; results would also assist providers to identify high risk individuals in need of medically assisted reproductive technology (Nelson et al., 2013; Petersen et al., 2016). The recent development of fertility assessment clinics, and the increasing demand for pro-fertility counseling and education, further highlights the important role fertility screening modalities, like AMH testing, will likely play in family planning of the future (Hvidman et al., 2015; O'Brien et al., 2017; Petersen et al., 2106).

### **Case Application**

Serum AMH testing could be quite useful to the selected case study patient for several reasons. First, this individual presented for family planning services one year prior to her anticipated fertility decline (ACOG, 2014). Early identification of fertility decline could be of great value to her as she continues to develop family planning goals. She had also been utilizing *oral contraceptive* pills for several years which is associated with decreased AMH levels (Bentzen et al., 2012; D'Arpe et al., 2016). Prolonged *hormonal contraceptive* use may also have rendered this patient unaware of menstrual changes that would signal a decline in her fertility (Hvidman et al., 2015; Kushnir et al., 2014). Additionally, this patient's strong family history of breast cancer may also place her at increased risk for sub-fertility as *BRCA* gene mutations have been linked to diminished OR and infertility (Tal & Seifer, 2017). This possibility further illustrates the potential value AMH serum analysis may have for this patient.

Choosing to proceed with AMH testing could serve an important role in this patient's future family planning activities. *Ovarian reserve* testing would allow her to become more

informed regarding her present fertility status, estimated reproductive lifespan, and options available to help her to achieve her desired childbearing outcomes (Grossman et al., 2017; Hvidman et al., 2014). This clinical discussion could result in a change in her reproductive goals, including an earlier attempt at conception, revision of family planning goals, or even cryopreservation of oocytes (Grossman et al., 2017; Hvidman et al., 2014; O'Brien et al., 2017). If this patient was found to be at risk for sub-fertility related to DOR, she might also choose to proceed with non-hormonal forms of contraception or schedule interruptions in contraceptive schedules; these breaks from *hormonal contraception* would permit AMH levels to normalize and allow for proper ongoing evaluation of her OR in the critical years ahead (Kushnir et al., 2014; Grossman et al., 2017). Should she choose to pursue AMH testing, she would join a growing number of other women worldwide seeking pro-fertility assessment and counseling (Hvidman et al., 2015; Petersen et al., 2017).

### **Learning Points**

- Advances in contraceptive options have enabled women to delay conception, resulting in increased maternal age and a need for family planning services that focus on preservation of fertility and early identification of fertility decline.
- Evaluation of *Ovarian Reserve* (OR) has been successfully used to assist providers in identifying women at risk for reduced reproductive potential.
- *Anti-Müllerian Hormone* (AMH) is the preferred method used to evaluate OR, but a lack of standardized assays and the impacts of various external variables must be considered for appropriate interpretation and utilization of test results.
- Further large-scale studies of AMH testing in healthy populations are needed to enhance the utility of this tool and allow for expanded use within the realm of family planning.

- Utilization of AMH testing as part of a broader fertility assessment can provide women with increased knowledge about their fertility and reproductive lifespan, empowering them to achieve individual family planning goals and helping them to avoid unintentional childlessness.

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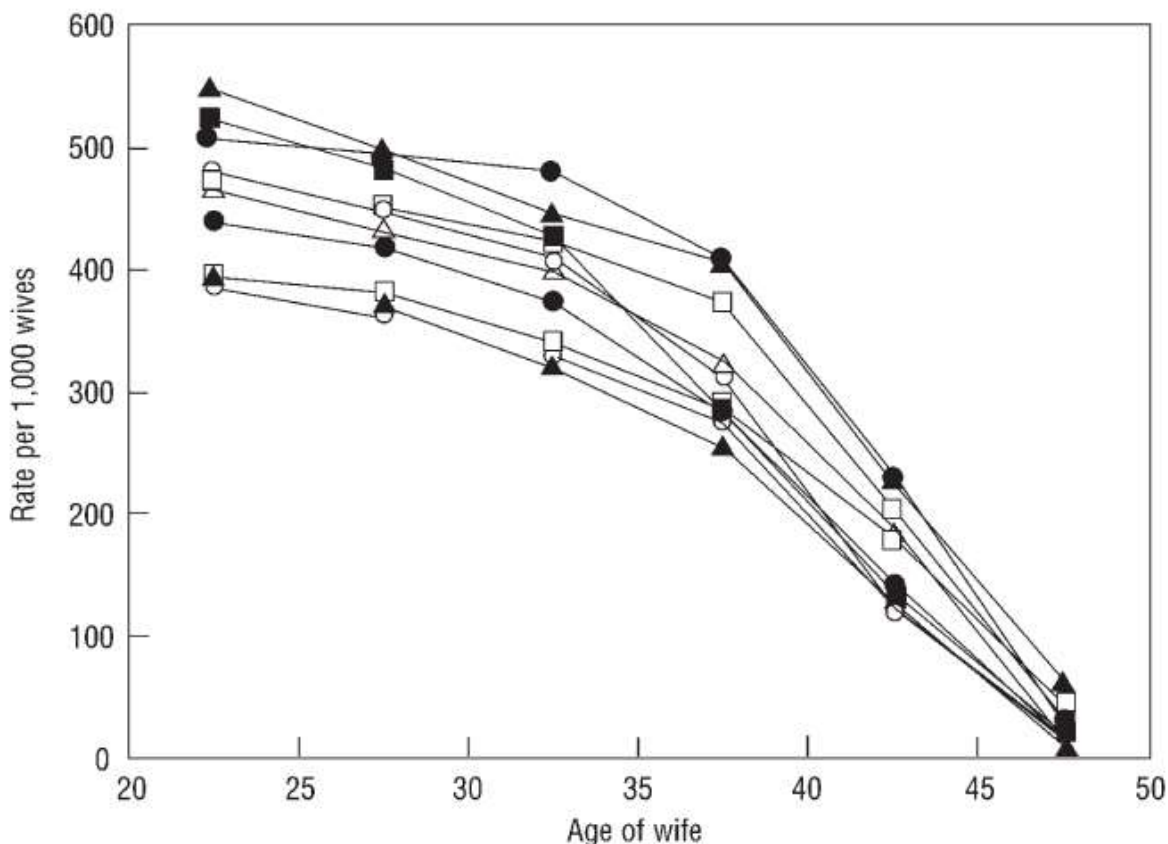
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Appendix A

Female Age- Related Fertility Decline



**Fig. 1.** Marital fertility rates by 5-year age groups. The ten populations (in descending order at age 20–24 years) are Hutterites, marriages in 1921–1930 (▲); Geneva bourgeoisie, husbands born in 1600–1649 (■); Canada, marriages in 1700–1730 (●); Normandy marriages in 1760–90 (○); Hutterites, marriages before 1921 (□); Tunis, marriages of Europeans 1840–1859 (△); Normandy, marriages in 1674–1742 (●); Norway, marriages in 1874–1876 (□); Iran, village marriages in 1940–1950 (▲); Geneva bourgeoisie, husbands born before 1600 (○). From Menken J, Trussell J, Larsen U. Age and fertility. *Science* 1986;233:1389–94. Reprinted with permission from AAAS. ↵

(ACOG, 2014)

## Appendix B

## Case Study SOAP Note

**Patient Identifying Data:**

Age: 31  
Race: Caucasian  
Gender: Female  
Marital Status: Single

**Subjective (S):**

**Chief Complaint (CC):** Patient presents to establish care as a new patient.

**History of Present Illness (HPI):** Patient is a 31-year-old female who moved to the area one year ago and is currently in need of a primary care provider. She denies any recent illness or specific health concern today and denies the need for any prescription refills at this visit.

**Past Medical History (PMH):**

**Active Problems:** N/A

**Allergies:** Penicillins (hives)

**Current medications:**

Oral Contraceptive (name and dose unknown)

Daily Multivitamin (off and on)

**Age/health status:** 31 years in good health

**Appropriate immunization status:** Up to date on all vaccines; Flu shot fall 2017

**Dates of major illnesses during childhood:** N/A

**Major adult illnesses:** N/A

**Injuries:** N/A

**Hospitalizations:** No recent hospitalizations

**Surgeries:** Appendectomy in grade school without complications

**Prior Diagnostic Tests:** Normal PAP in 2016 and no recent screening labwork

**Family History (FH):** Patient's father alive and well with no known medical problems. Mother deceased with a diagnosis of breast cancer at age 40. Maternal grandmother with history of ovarian cancer and Maternal aunt and cousin both with breast cancer diagnoses. No knowledge of BRCA testing among family members with cancer diagnoses.

**Social History (SH):** Patient is an elementary teacher who reports that she enjoys working with children and has a strong social support system. She does not exercise regularly but reports that she is active and enjoys walking and being outdoors. She tries to eat a healthy diet and she denies any alcohol, tobacco, or drug use. She has had a steady boyfriend for greater than one year and he is her only sexual partner. She denies any concerns regarding sexually transmitted diseases. She denies any known ill contacts or recent international travel.

**Review of Systems (ROS):**

**Constitutional symptoms-** Denies fatigue, malaise, recent illness, fever, recent weight change, or sleeping difficulties.

**HEENT-** Obtains regular eye exams and denies recent vision changes or eye discomfort. She denies any hearing changes or ear discomfort, upper respiratory symptoms, sore throat, voice change, swallowing difficulty or enlarged lymph nodes.

**Cardiovascular-** Negative for chest pain, activity intolerance, swelling.

**Respiratory-** Negative for shortness of breath, wheezing, cough, or recent respiratory infection. No prior history of pulmonary embolism.

**Breasts –** Negative for breast pain, lumps, changes in skin texture, nipple discharge. She does not complete monthly self-breast exams. She has never had a mammogram and it has been greater than one year since her last well-woman examination.

**Gastrointestinal-** Denies change in stool habits, reflux, or food intolerance. No abdominal discomfort reported.

**Genitourinary-** Negative for dysuria, incontinence, hematuria. Negative for irregular menses or breakthrough bleeding. Menses are generally 4-5 days in length with 2 days of moderate flow and 2-3 days of light flow. Denies PMS symptoms and reports she is happy with her current oral contraceptive pill, which she has been taking for “several years”. She is not interested in alternative forms of contraception today. She had a normal PAP in 2016 but does not recall if HPV co-testing was completed. She has no prior history of abnormal PAP, sexually transmitted infections, or gynecological disorders. She has no interest in sexually transmitted disease testing today. She would like to conceive in the future but does not have plans to start a family within the next 12 months.

**Musculoskeletal-** Negative for muscle pain, joint pain, swelling, limitations or changes in range of motion.

**Neurologic-** Denies syncope, weakness, numbness, tingling, seizures, or headaches.

**Hematologic/lymphatic-** Negative for bleeding, clotting, enlarged lymph nodes.

**Allergic/immunologic-** Penicillin allergy. No environmental or food or allergies.

**Objective (O):****Constitutional-**

VS: BP-110/66, HR- 82 Height- 5’5”, Weight- 155 lbs. BMI 25.8

General Appearance: healthy, well-developed/well-nourished in no acute distress.

**Skin-** Skin color appropriate for race, warm, and dry. No lesions, rashes, open areas noted.

**HEENT - Head:** Skull normocephalic and free from injury. *Eyes:* Sclera white and conjunctiva moist and pink. *Ears:* Hearing appropriate to spoken voice. Bilateral auditory canals free of debris and tympanic membranes without abnormalities. Bony landmarks clearly visible *Nose:* Nasal septum midline. Nasal turbinates free of edema and no drainage noted. *Throat and mouth:* No tonsillar or soft palate abnormality. Tongue midline. Teeth in good repair.

**Thorax and Lungs-** Chest shape within normal limits with symmetric expansion. Lung sounds vesicular and lung fields clear to auscultation.

**Breast -** Examination deferred.

**Cardiovascular-** Heart rate with regular rate and rhythm. Heart sounds S1, S2 and free from murmurs.

**Gastrointestinal-** Normoactive bowels sounds in all four quadrants. No hepatomegaly or splenomegaly noted. Abdomen soft and nontender to palpation.

**Genitourinary-** G0T0P0A0L0. Physical examination deferred.

**Musculoskeletal-** Gait steady, strength symmetrical, no pain noted.

**Neurologic-** No gross focal, motor, or sensory deficits.

**Psychiatric-** Calm and cooperative with intact judgment and insight. Normal and logical rate of thought and speech.

**Hematologic/Lymphatic/Immunologic-** No indication of anemia and no history of deep vein thrombosis, pulmonary embolism, or clotting disorders. No joint deformity or swelling.

#### **Assessment (A):**

1. **Z30.09** – Encounter for other general counseling and advice on contraception
2. **Z80.3** – Family history of malignant neoplasm of breast

#### **Plan (P):**

**Diagnostics:** Screening Mammogram and fasting labwork (CBC, CMP, Lipid Panel and TSH) to be completed prior to annual well woman examination appointment.

#### **Medications:**

- Continue with present oral contraceptive and multivitamin.

#### **Patient education:**

- Patient's family history of breast cancer and the early onset of her mother's disease place her at increased risk for development of breast cancer. She is within 10 years of her mother's diagnosis and has multiple family members with breast and ovarian cancer diagnoses. It is reasonable to pursue screening mammography at this time. An order has been placed for this mammogram to be completed at her convenience. She is also encouraged to complete monthly self-breast exams and to obtain annual clinical breast exams.
- Patient was instructed to call with the name of her present oral contraceptive, so it can be accurately recorded in her chart. She is not currently in need of a medication refill. She was encouraged to call if she desires conception so that pre-conception counseling can be provided. Information on various forms of contraception was provided to her and she was encouraged to continue to practice safe sexual habits.
- Patient was encouraged to schedule her annual well woman exam with fasting labwork. Lab orders were entered so results can be reviewed during this well-woman visit. She has no prior history of abnormal PAP testing and her most recent PAP was one year ago. Therefore, she is not due for a PAP this year. Her next PAP will be due in 2019 and HPV co-testing can be completed at that time. She was advised that a pelvic examination is still recommended during her annual well woman examination.

#### **Referrals:**

- Referral was placed for genetic counseling. Patient will consider BRCA testing and will discuss this further with her genetic counselor at this consultation.