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Prevalence of premature ovarian failure and premature menopause in refugee and immigrant women in the U.S. compared to that of women born in the United States

Deering, Victoria Ann

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Thesis

**PREVALENCE OF PREMATURE OVARIAN FAILURE AND PREMATURE
MENOPAUSE IN REFUGEE AND IMMIGRANT WOMEN IN THE U.S
COMPARED TO THAT OF WOMEN BORN IN THE UNITED STATES**

by

VICTORIA ANN DEERING

B.S., Stony Brook University, 2012

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Approved by

First Reader

Melody Eckardt, M.D.
Director of Women's Refugee Health
Instructor, Obstetrics & Gynecology

Second Reader

R.J Rushmore, Ph.D.
Assistant Professor, Anatomy & Neurobiology

DEDICATION

I would like to dedicate this to all the people who have helped me get where I am today. I would especially like to thank my mother and sister for their unwavering support in everything I do.

ACKNOWLEDGMENTS

I would like to thank Dr. Melody Eckardt for helping me to develop this project and helping me along the way with any obstacles that came up. I would also like to thank Olivera Vragovic and Linda Rosen for her help with data collection and the organization of data for this project. Lastly I would like to thank my advisor, Dr. Jarrett Rushmore, for his help and support.

**PREMATURE OVARIAN FAILURE AND PREMATURE MENOPAUSE IN
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VICTORIA ANN DEERING

ABSTRACT

Objective: Premature ovarian failure is a disease with many far reaching and serious consequences. Little is known about the complete etiology of the disease or what women may be at an increased risk for developing it. We sought to evaluate the prevalence of premature ovarian failure among women born in the United States and women not born in the United States who were patients of Boston Medical Center. We compared the prevalence of POF in these two groups to evaluate any relationships that may exist between birthplace and premature ovarian failure.

Methods: We collected data from the data warehouse of Boston Medical Center. We used data from women who had an FSH test done between the ages of 18 and 40 before June 30, 2013 as the control. We also compiled data of women who had an FSH level over 15mIU/ml as well as those who had diagnoses in SDK and Logician. Birthplaces data was also compiled for those women who had an FSH level > 15mIU/ml.

Results: Women born outside of the U.S had a slightly higher prevalence of POF when compared to women born in the United States. Data analysis showed a significant difference among the two groups with $p < 0.0001$ for each group. When birthplace data was compiled, Haiti had the highest number of women with $FSH > 15 \text{ mIU/ml}$ with Cape Verde and the Dominican Republic having the next highest amounts of women.

Conclusion: Our study highlights the possible relationship that exists between premature ovarian failure and birthplace. This was a preliminary study to gather data that may be used in future, more specific studies to be done on the topic. These future studies should further investigate the reason this relationship exists, other causes that may be associated with premature ovarian failure, and further analysis of the prevalence of POF in various areas of the world.

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LIST OF ABBREVIATIONS

| | |
|------------|---|
| BMC..... | Boston Medical Center |
| CDW..... | Clinical Data Warehouse |
| EMR..... | Electronic Medical Record |
| FSH..... | Follicle Stimulating Hormone |
| ICD-9..... | International Classification of Disease 9 th edition |
| POF..... | Premature Ovarian Failure |

INTRODUCTION

Premature ovarian failure is defined by Arora and Polson (2011) as a loss of ovarian function diagnosed when a woman under 40 years old presents with four months or greater of amenorrhea and two FSH levels that are 30 iu/ml or greater for at least four weeks. According to Mamas and Mamas (2009) this condition affects between 1 and 5 percent of women. In North American women the incidence is 10 per 100,000 for women aged 15-29, 76 per 100,000 for women aged 30-39 and 881 per 100,000 for women aged 40-44 (Davis, 1996). Some common causes of POF include genetic abnormalities, enzymatic defects, autoimmune diseases, hormone or receptor defects, and various environmental as well as physical causes (Rebar, 2005, Schoemaker & Drexhage, 1997). Most cases of POF have no identifiable cause and are thus referred to as idiopathic (Mamas and Mamas, 2009). Patients with premature ovarian failure have been shown to have ovarian function return sporadically after a diagnosis has been made and there is a 5-10% chance of conception after the diagnosis of POF (Kalantaridou, 2012, L.T Shuster et al. 2010). Several authors use the terms premature ovarian failure and premature menopause interchangeably but this has recently begun to be challenged by some authors including Rahman (2009), Kalantaridou (2012), and Nelson et al. (2005).

Menopause is defined by Nelson et al. (2005) as “permanent cessation of menses; termination of menstrual life.” Premature menopause is therefore defined as permanent cessation of ovarian function before the age of 40 (Nelson et al. 2005). The most common age given for natural menopause is 50-52 and studies have shown that the later menopause begins, the greater the life expectancy (Gold et al. 2013). Premature menopause has some of the same risk factors as premature ovarian failure but it is not a reversible condition (Kalantaridou, 2012). Premature menopause and premature ovarian failure are used interchangeably in the clinic when a woman presents with the symptoms and characteristics of premature ovarian failure and thus both terms were used for the same condition while gathering data for this study.

Women with premature ovarian failure have an increased risk of early morbidity, which is due to several factors (S.H Chang et al., 2007). These risk factors include osteoporosis, impaired endothelial function, and cardiovascular disease (Chang et al., 2007). Woman diagnosed with premature ovarian failure have also been reported to have increased anxiety, lower sexual drive, depression, anger, and sensitivity (Shuster et al., 2010). Hormone therapy is the primary treatment offered to patients with POF. This treatment, which replaces some of the estrogen that would normally be produced by the ovaries, helps to alleviate the risks to

the cardiovascular system and keeps bone density from dropping too low (Arora & Polson, 2011). The diagnosis of premature ovarian failure can be very emotional for women as it can mean that their chances of conceiving a child are greatly diminished among other concerns they may have and thus psychological support is also offered as a part of treatment (Singer et al., 2011).

BACKGROUND

Causes of Premature Ovarian Failure

There are several known causes of premature ovarian failure, which are listed in Table 1. According to Béranger et al. there is a known cause in only 25% of premature ovarian failure cases, the other 75% are all classified as idiopathic (2012). Most of those cases that have a known cause are genetic in origin (Rebar 2005). Recently a few studies have been published linking environmental chemicals to premature ovarian failure. These chemicals include diesel exhaust (Ogliari et al., 2013) and various chemicals women may be exposed to in their occupations (Béranger et al. 2013). The chemicals associated with premature ovarian failure that may be encountered in various occupations will be listed in Table 2.

Regardless of the cause, premature ovarian failure occurs by one of two main mechanisms. These mechanisms include depletion of the follicular reserves and a malfunction in the maturation of follicles (Arora & Pulson 2011). Turner Syndrome is one of the most common genetic abnormalities that cause premature ovarian failure. It is a 45X chromosomal abnormality, which results in early atresia of the follicles as well as gonadal dysgenesis (Davis 1996). Fragile X permutations are another common chromosomal abnormality that results in premature ovarian failure. It is believed that an increase in FMR-1 transcription leads to premature depletion of the follicular reserve (Arora & Pulson 2011).

Iatrogenic premature ovarian failure is usually the result of chemotherapy and other cancer related treatment (Arora & Pulson 2011). Damage to the ovaries after cancer treatment depends on the age of the patient at treatment and the type of treatment received. Those patients at the highest risk of ovarian failure are those treated after puberty, those exposed to high doses of alkylating agents, and those exposed to high doses of radiation to the ovary (Sklar, 2005).

Environmental factors may also have a role in causing premature ovarian failure. Ogliari et al found that exposure to acceptable levels of diesel exhaust compromised ovarian function of female mice, which

diminished their ovarian reserves. They argue that humans may also be affected in the same way and further studies should be done (2013). Béranger et al. found that several chemicals that women may be exposed to in their occupations can also cause premature ovarian failure (2013). The final list compiled by the authors included 20 chemicals that are damaging to ovarian reserves (Béranger et al., 2013). Other environmental factors such as cigarette smoking have also been shown to increase a woman's risk of developing premature ovarian failure (Chang et al. 2007). Luborsky et al. found a significant association of premature ovarian failure with diabetes, poor health, high BMI, low education level, and low income (2002).

Table 1. Causes of Premature Ovarian Failure

| | |
|------------|--|
| Genetic | Fragile X Permutations (Kasteren et al 1999), Turner Syndrome, FMR1 permutation, 46XY gonadal dysgenesis (Arora & Pulson 2011), Mutations in FOXL2, E1F2B, AIRE, PMM2, or BMP15 genes (Rebar 2005) |
| Immune | Mutations in receptors for FSH and LH (Rebar 2005). Autoimmune adrenal deficiency, APS-1, APS-II, APS-III, thyroid autoimmunity (Dragojevic-Dikic et al., 2010) |
| Iatrogenic | Radiation, chemotherapy (Sklar 2005) |
| Physical | Viral infections, surgical injury (Rebar 2005). |

Table 2, Occupational exposure to chemicals implicated in causing premature ovarian failure. This table shows the various environmental factors that can be a possible cause of POF. These are important to note as they may be very prevalent in various areas of the world. Table taken from Berenger et al., 2013.

| | |
|-----------|--|
| Chemicals | Circumstances of occupational exposure |
| Lead | Exposures are still high among craftsmen (manufacture of enameled pottery, stained glass, crystal), but are generally controlled in industry. Tin-lead welding in the electronics industry generally gives low exposures |

| | |
|----------|---|
| | (unless defective hygiene, nail-biters, etc.). Possible environmental contamination (storage of acid foods in enameled dishes, some North African cosmetics, shooting as a hobby or for sport, old lead water-supply pipes particularly if attacked by soft water, etc.) |
| Chromium | A trace metal essential to the metabolism. Exposure may be high in various circumstances: metalwork (e.g. electrolytic chroming, welding of stainless steels with a mass content of more than 10% Cr), stabilizing and fixing agent for other products (e.g. mordant agent in tanneries, wool dye fixing agent in the textile industry, fixing agent for fungicidal and insecticidal metals on wood), dyes (chromates, Cr (VI), for dyes for plastics, paints, anti-corrosion paints, chromium (III) green oxide, also present in soaps and cosmetics), catalyzer. Also present in cements and refractory materials. Little leaching of chromium to foods stored in stainless steel containers. Possible exposure through dental prostheses, implants, etc. |
| Cadmium | 80% of Cd is used in manufacture of Ni-Cd batteries. Other sources of exposure are zinc metallurgy, cadmium plating to protect metals from corrosion, pigments (yellow-red) used in particular in plastics, ceramics, enamels, glass and materials resistant to high temperatures, some alloys and welding rods with a low melting |

| | |
|---|---|
| | point. As for other metals, tobacco use is a notable source of exposure |
| 2-Bromopropane | Solvent in the electronic industry, intermediate agent in the chemical and pharmaceutical industries, now little used. Unlike 1-bromopropane, we have found no instances of exposure in France (request to anti-poison centers). In the early 1980s, "NIOSH has statistically estimated that about 1600 workers (including 300 female) were potentially exposed to isopropyl bromide in the USA" (HSDB). Occupational exposure to isopropyl bromide may occur through inhalation and dermal contact with this compound at workplaces where it is produced or used |
| 2,5-Hexanedione | Metabolite of n-hexane, which is decreasingly used as it causes polyneuritis. May be present in glues, petrol, degreasers in the automobile industry, solvent in paints, vegetable oils |
| EGME (2-methoxy ethanol, or ethylene glycol methyl ether) | Solvent in water-based paints, resins, inks, dyes, varnishes, cosmetics. May be used in the electronics industry in Asia, in hydraulic fluids, antifreeze in aircraft fuel, or as a degreasing agent. EGME and its acetate are of restricted use since they are now classified as reprotoxic agents (ex: 1-B in EU) |
| Hexachlorobenzene | Formerly used as a fungicide/insecticide. Found as an impurity in synthesis of chlorine derivatives. Persistent organic pollutant. Accumulates in fatty tissue |

| | |
|--------------------|---|
| Mancozeb | Fungicide still widely used in agriculture |
| Methoxychlor | Former organochlorine insecticide (prohibited in Europe in 2002, in the USA in 2004) |
| Dicofol | Organochlorine insecticide formerly used in agriculture and building industry (miticide, acaricide). Some preparations have contained DDT residues (or DDT related compounds). Recently prohibited in Europe (2008), Dicofol use has also declined in the USA since 2006, and is in 2011 the last organochlorine pesticide to go through a cancellation process to terminate all its remaining uses in the U.S. (production ceased in 2011, sales and distribution will cease in 2013, and use will be prohibited since 2016) |
| Carbosulfan | Insecticide recently prohibited in Europe (2008) |
| HBCD | Flame retardant, particularly in insulating foams in the building industry, some plastics, or textiles. |
| BMPD | Flame retardant (polyester resins and polyurethane foams) |
| Bisphenol A | Production of epoxy or polycarbonate resins |
| 1,3-Butadiene | Production of resin and polymers, rubber for tyres |
| 4-Vinylcyclohexene | Feedstock in production of organic compounds and polymers. Dimer of 1,3-butadiene. Present in rubber vulcanization fumes. "Consumers may be exposed to 4-vinylcyclohexene from volatiles from carpets based on monitoring data" (HSDB) |

| | |
|----------|--|
| Isoprene | Rubber production (natural rubber is an isoprene polymer) |
| PAHs | Coke, pitch coke, creosote, metallurgy, old tars, heated or recycled neat cutting oils, products of combustion (fires, vehicles). In the environment, tobacco smoke and cooking fumes (fried food, etc.) |

Ethnic Variations in the Diagnosis of Premature Ovarian Failure.

Studies have shown some variation in the prevalence of premature ovarian failure among different ethnicities (Butts & Seifer, 2010). The percentage of women diagnosed with premature ovarian failure in different ethnicities will be listed in table 3. African American and Hispanic women have the highest frequency of premature ovarian failure. Chinese and Japanese women have the lowest frequency (Luborsky et al. 2002). To our knowledge, there have been no studies that have found an explanation for the variation in premature ovarian failure among different ethnicities. Bleil et al. found that African American, Hispanic, and Chinese women may have a lower ovarian reserve than Caucasian women based on anti-mullerian hormone levels, but further research is needed to decide if this has any influence on premature ovarian failure (2014).

Table 3. Variations in prevalence of Premature Ovarian Failure by ethnicity. This table shows that African American and Hispanic women have the highest prevalence of POF and Japanese women have the lowest prevalence. Data taken from Luborsky et al., 2002

| Ethnicity | Prevalence (%) |
|------------------|----------------|
| African American | 1.4 |
| Hispanic | 1.4 |
| Caucasian | 1.0 |
| Chinese | 0.5 |
| Japanese | 0.1 |

Long Term Consequences of Premature Ovarian Failure

Women who are diagnosed with premature ovarian failure face many long-term consequences. These can range from physical issues such as osteoporosis and cardiovascular diseases to psychological effects such as anxiety and depression (Singer et al. 2011). The younger a woman is when premature ovarian failure is diagnosed, the greater the effect these consequences can have (Shuster et al. 2010). It is important that women who are diagnosed with premature ovarian failure are made aware of the risk factors associated with the disease so that proper precautions can be taken.

The physical consequences of premature ovarian failure include: osteoporosis, cardiovascular issues, infertility, sexual dysfunction, and neurological issues (Shuster et al. 2010). Osteoporosis is a disease characterized by low bone density, Shuster et al. found that bone density decreases after menopause and the earlier menopause occurs, the greater the risk of osteoporosis (2010). Yorgun et al. have found that loss of sex steroids increases a woman's chance of having a myocardial infarction or a stroke (2013). There is also increased chance of ischemic heart disease and cardiovascular mortality (Okeke et al., 2013). Infertility is a condition that is faced by women diagnosed with premature ovarian failure. Pregnancy may occur in some women with POF, but oocyte donation is usually the best way for a child to be conceived to affected women (Okeke et al., 2013). The neurological issues that POF patients may face include an increased risk of dementia and parkinsonism (Shuster et al., 2010).

The psychological issues associated with premature ovarian failure include anxiety, depression, and other various emotional issues (Singer et al., 2011). These issues can arise due to the stress of the diagnosis of POF. For many women, a diagnosis of POF may challenge some of the preconceived plans they have for the future (Davis, 1996). The idea that a woman may no longer be able to conceive a child naturally is often hard

to face, as it is something that many women want for themselves. According to Panay and Kulu, the loss of normal reproductive function is often very upsetting to women, regardless of whether they have another child (2009). Women also experience stress about other concerns associated with POF such as weight gain, body image issues, treatment options, management of symptoms, and their overall health (Singer et al. 2011).

Management of Premature Ovarian Failure

According to Panay and Kalu (2009), the management of premature ovarian failure should involve professionals from various specialties including doctors, counselors that specialize in premature ovarian failure, and nutritionists so that every need of diagnosed women can be met. Seeing different professionals is important for these women, as there are many different facets to this disease. Counselors provide emotional support that a woman may need after she is told having children may be harder than she imagined, or when she starts having symptoms of menopause well before she had originally expected (Okeke et al. 2013). Reproductive health care specialists can help a women understand her options if she wants to have a child (Panay & Kulu, 2009). Hormone replacement therapy is the most common treatment for

premature ovarian failure (Davis, 1996). Replacement of estrogen is necessary in women with premature ovarian failure; the disease leaves them with levels of estrogen that are pathologically low (Panay & Kulu, 2009). The replacement of estrogen reduces a woman's risk of osteoporosis, cardiovascular issues, and some neurologic diseases (Panay & Kulu, 2009). Mamas and Mamas (2009) found that treatment using DHEA has been successful in helping women conceive a child naturally after diagnosis. Oocyte donation is also used when women with premature ovarian failure are ready to have a child (Okeke et al., 2013).

Justification for this study

This study aims to address the prevalence of premature ovarian failure in refugee and immigrant populations compared to that of women who were born in the United States. Premature ovarian failure is a disease with many consequences, both physical and emotional, there is a clear need for studies to be done that will help us to better understand this disease. As was previously discussed, there is some variation in the prevalence of premature ovarian failure among different ethnicities. There is very little information available that can explain this variation.

It is our hope that we may find some connection between premature ovarian failure and refugee or immigrant status. If there is in fact a correlation, more research can be done to not only understand why the connection exists, but also to discover new ways to prevent the disease.

SPECIFIC AIMS

The objective of this study is to explore and describe the relationship between premature ovarian failure and refugee and immigrant status of women in the United States. The first goal of this thesis is to determine the prevalence of premature ovarian failure among the women born in the United States and those not born in the United States from the population of women treated at Boston Medical Center before June 30, 2013. The second goal is to determine if the group of women born outside of the United States had a higher prevalence of premature ovarian failure than those who were born in the United States. The last goal is to compare the birthplaces of women born outside of the United States who have an FSH level over 15mIU/ml to see if there was one area that had a higher amount of cases than others. The results of this thesis will be used to formulate future study ideas on the topic of premature ovarian failure among women born outside of the United States.

It has been suspected by BMC providers that a higher prevalence of premature ovarian failure may exist among refugee and immigrant populations compared to women born in the United States that are patients at Boston Medical center. We hope this study will shed light on

this relationship and open the door for further research to be done on the subject.

MATERIALS AND METHODS

This is a descriptive study that is designed to describe the prevalence of premature ovarian failure among women seen at Boston Medical Center before June 30, 2013. The study population consists of women who were born in the United States and those who were not. The women who were not born in the United States are immigrants and refugees from other countries. The data we have used has been collected from the Clinical data warehouse database of Boston Medical Center. This database contains the various diagnoses, tests, personal information, and other pertinent details of patients at Boston Medical Center. The data in this warehouse is all originally from SDK and Logician. SDK is the billing and registration software application of Boston Medical Center. Logician, also known as centricity, is Boston Medical Center's outpatient EMR software application. All of this information can be searched electronically and compiled for further analysis. We searched the database for information from women aged 18 to 40 who had an FSH test done at the clinic before June 30, 2013. Women with the diagnosis of premature menopause using ICD-9 code 256.31 or menopause status

using ICD-9 code V49.81 in SDK or Logician were also included in this inquiry.

Once data was collected based on the above criteria, we stratified the data using several indicators. These indicators included FSH level and the diagnosis recorded in charts. After the initial collection, the data we collected were separated into three separate groups. These groups included women with an FSH level over 15, those with a diagnosis in SDK and Logician of ICD-9 code 256.31 or V49.81 before age 40, and those with either an FSH level greater than 15 or a diagnosis in SDK or Logician using the unique ICD-9 codes. The breakdowns by SDK vs. Logician diagnoses were also counted. The separation of the data into groups was completed in order to facilitate comparisons of the prevalence of premature ovarian failure between the two different groups of women. For the purposes of this study, women between 18 and 40 years old who had an FSH test done before June 30, 2013 were counted as the control group for comparison with the other groups. In these groups, including the control group, the data was broken up into three further groups. These groups included: women born in the United States, women not born in the United States, and women who had no birthplace listed in their charts. All data collected was then roughly compared using percentages before further statistical analysis was completed.

In addition to the other data collected, we recorded the birthplace of women seen at the clinic of Boston Medical Center that had an FSH test done. We also recorded the birthplace of the women who had an FSH level over 15mIU/ml. A list was made that included all of these birthplaces and the number of patients born in each place was recorded. For those women with an FSH level was over 15mIU/ml, birthplace was noted and compared to the control group birthplaces. For privacy reasons, only countries that had more than 6 women with an FSH test over 15mIU/ml were counted with exact numbers. Any other country with 6 or fewer women was simply noted and compiled into a list. This was done to understand if there was a particular part of the world outside of the United States that had a higher prevalence of premature ovarian failure than the others. It is important to note that all birthplaces recorded are self reported by the patient and thus may be misspelled or incorrect. As there is no way for us to correct for this, all birthplaces recorded, misspelled or otherwise, will be used in this study.

Data Analyses

Before statistical analysis was done on the data the number of women in each group was compared to the control to find the percentage of women tested in both U.S and non-U.S born groups had an FSH level over 15mIU/ml. The same procedure was done to test the groups of women who had either an FSH level over 15mIU/ml or a diagnosis in SDK or Logician using the respective ICD-9 codes. Once the initial comparison was complete, statistical analysis was preformed. We analyzed the data using SAS (Version 9.2, SAS Institute, Inc., Cary, NC). We performed a chi square test in order to check if there was a significant difference between proportions of the two groups (U.S born Vs. not U.S born). A p value of $p < 0.05$ was considered to be significant.

RESULTS

There were 8104 unique women with an FSH test done between the ages of 18 and 40 before June 30, 2013 listed in the main database that had registration information. Of these 8104 women, 42% were born in the United States, 48% were born outside of the United States, and 10% had no birthplace listed. Table 4 shows the exact number of women in each sub group.

Table 4. Women with an FSH test preformed before June 30, 2013

| Born in the United States | Number |
|---------------------------|--------|
| Yes | 3406 |
| No | 3907 |
| No birthplace listed | 791 |

There were 600 women in the group who had an FSH level over 15 mIU/ml. Of the 600, 594 had birthplaces listed. Of the 600 when compared with the total, 5.3% were in the group born in the United States 8.8% were in the group born outside of the United States, and 9.6% were in the group that had no birthplace listed. These percentages are based on comparison with the original 8104 women using the

breakdown into U.S and not U.S born. Table 5 shows the exact number of women in each group.

Table 5. Women with FSH>15mIU/ml

| Born in the United States | Number |
|---------------------------|--------|
| Yes | 180 |
| No | 344 |
| No birthplace listed | 76 |

There were 200 unique women with SDK and Logician diagnoses using ICD-9 codes 256.31 or V49.81 before the age of 40. When compared to the control group, 2.8% were in the not U.S born group, 2.0% were in the group born in the U.S, and 2.8% were in the group with no birthplace listed.

Table 6. SDK + Logician DX(256.31 or V49.81 before age 40)

| Born in the United States | Number |
|---------------------------|--------|
| Yes | 67 |
| No | 111 |
| No birthplace listed | 22 |

There were 639 women who had either an FSH>15mIU/ml or a diagnosis in SDK or Logician using ICD-9 codes 256.31 or V49.81. Of these

women, 6.1% were in the group born in the United States, 9.67% were in the group not born in the United States, and 6.7% were in the group with no birthplace listed.

Table 7. Women with either FSH>15mIU/ml or dx in SDK or Logician

| Born in the United States | Number |
|---------------------------|--------|
| Yes | 208 |
| No | 378 |
| No birthplace listed | 53 |

The breakdown of women by diagnosis in SDK versus Logician was also done. No further comparisons will be made with this data but it is listed here for completeness. There were 169 women with a diagnosis in SDK before age 40. There were 97 women with a diagnosis in Logician before age 40.

Table 8. Breakdown by SDK vs. Logician

| | U.S born | Not U.S born | No birthplace listed |
|----------|----------|--------------|----------------------|
| SDK | 50 | 99 | 20 |
| Logician | 57 | 32 | 8 |

Data Analysis of those with FSH>15mIU/ml and those with either FSH>15mIU/ml or a DX in SDK or Logician

The numbers below were used to perform a chi square analysis to test the differences between the two groups: U. S born Vs. Not U.S born.

FSH>15mIU/ml

% U.S Born(180/3406): 5.3%

% Not U.S Born (344/3907): 8.8%

Either FSH>15mIU/ml or DX in SDK or Logician

% U.S Born (208/3406): 6.1%

% Not U.S Born (378/3907): 9.67%

There was a significant difference in both comparisons with $p < 0.0001$ in both groups. Table 9 contains the breakdown of data from each group. Group 1 contains those women with an FSH value over 15mIU/ml. The mean age of women born in the United States in this group is 34.8, the mean age of those not born in the United States is 35.86. Group 2 contains those women who had either an FSH value over 15mIU/ml or a diagnosis of either premature menopause using ICD-9 code 256.3 or menopause status using ICD-9 code V49.81 in SDK or Logician. The mean age of those women born in the United States in this group is 34.27, the mean age of those not born in the United States is

35.74. The numbers of women in each group that are not born in the United States were used as n in the table and chi square analysis.

Table 9. Comparison of differences in POF prevalence between women born in the United States and those that were born outside of the United States.

| | P value | Percent of group | Born in the US | Total in group | Women excluded from group criteria who had an FSH test done |
|--|---------|------------------|----------------|----------------|---|
| Group 1 (FSH>15mI U.ml) n=344 | <0.0001 | 4.70 | 180 | 524 | 6789 |
| Group 2 (FSH>15mI U/ml or dx in SDK or Logician) n=378 | <0.0001 | 5.17 | 208 | 586 | 6727 |
| | | | | | |
| Total sample size in each group | | | | | 7313 |

Table 10. Women with no birthplace listed who were not included in the chi square analysis

| | |
|---------|----|
| Group 1 | 76 |
| Group 2 | 53 |

| | |
|---------|-----|
| Control | 791 |
|---------|-----|

Birthplace Data

Birthplace data was collected from the women who had an FSH test done between the ages of 18 and 40 before June 30, 2013. The birthplaces of women with an FSH test done who were not born in the United States are listed in the pages below Table 11. The countries that were the birthplace of more than 15 women are listed with the exact number in Table 11.

Table 11. Areas outside of the United States with more than 15 women who had an FSH test done

| Birthplace | Number of Women |
|-------------|-----------------|
| Antigua | 17 |
| Bangladesh | 29 |
| Brazil | 77 |
| Cameroon | 18 |
| Cape Verde | 338 |
| D.R | 244 |
| El Salvador | 56 |
| Eritrea | 18 |
| Ethiopia | 76 |
| Guatemala | >57 |
| Guyana | 18 |
| Guinea | 24 |
| Honduras | 50 |
| Haiti | 874 |
| Jamaica | 145 |
| Lebanon | 16 |
| Liberia | 21 |
| Morocco | 53 |
| Montserrat | 41 |
| Nigeria | 129 |
| Puerto Rico | 245 |

| | |
|--------------|----|
| Pakistan | 20 |
| Philippines | 24 |
| Portugal | 19 |
| St. Thomas | 16 |
| San Domingo | 29 |
| Sierra Leone | 37 |
| Somalia | 56 |
| Trinidad | 44 |
| Uganda | 17 |
| Venezuela | 20 |
| Vietnam | 37 |

List of Birthplaces outside of the United States of women with an FSH test done

| | | | | |
|----------------------|-------------------|-------------------|--------------------|-------------------|
| Abana, Cuba | Eitrea | Northern Ireland | AR | Georgia Russia |
| Albania | Ekitrai | Norway | Arab | Germany |
| Abudabi, UAE | El Salvador | Nottingham | Arabia | Gernada |
| Accra, ghana | Elaine ar | Nova Scotia | ARECIBO PR | Ghana |
| Acores, Portugal | England | Novacia | Argentina | Glascow, Scotland |
| Addis Ababa, ethopia | Seoul Korea | Novi sad | Argaria | Goiania Brazil |
| Africa | Ecuador | Obausi Ghana | Aritrea | Gonaives Haiti |
| Afghanistan | Eretreal, Africa | Odessa Ukraine | Armania | Granada |
| Ghana | Erita, Asamara | Oman | Aruba | Greece |
| Sierraleone | Eritrea | Ontario | Asmara, Eritrea | Granada |
| Somalia | ERU | Oran Algreria | Asamara, ethopia | Guadalupe |
| Angola | Estonia | Ordu | Ascot, England | Guatamala |
| Bongo | Europe | Osaka | Aserbajgan | Guam |
| Cameroon | Fajardo, PR | Ottawa | Asia | Guyana |
| Nigeria | Filipine | Owerri | Athens, Greece | Guinea Biffau |
| Agadir | Finland | Oxford England | Antigua | Gujarat |
| Agana, Guam | Fogo cape verde | Puerto Rico | Atina, italy | Gulipmala |
| Ahiti | France | P.R China | Augburg, germany | Gunhaes |
| El Salvador | Frankfurt Germany | Pacific Islands | Aukland, NZ | Guyama |
| Alamagordo NW Mexico | Freetown | Pakistan | Australia | Honduras |
| Alexandria, Egypt | Fuggia Italy | Palestine | Austria | Ha Nai |
| Algeria | Fuzhou China | Palermo | AZ | Haifa |
| Aman | Gabon | Palma de mallorca | Azores | Haiti |
| amgola | Gaeta Italy | Panama | Badgab, iraq | Halifax |
| aneho | Gahna | Paraguay | Badhdad | Hamilton Bermuda |
| angora | Galway Ireland | Paria, Cape verde | Bafuta, Africa | Hamilton Canada |
| Anguilla | Gambia | Paris | Bagandash | Pemea Zanzibar |
| Ankra | Gana | Patiala india | Guyana | PERU |
| Antigua | Ganda | P.A.P Haiti | Geneva Switzerland | Peshwar |

| | | | | |
|-------------------|------------------|--------------------|--------------|---------------------|
| Anturo | Gautamala | PEI Canada | Peixotocardo | Philippines |
| Bamberg, Germany | Hait | Republic Dominica | Baghdad | Suriname |
| Bangkok, Thailand | Halifax | Republic of China | Bahamas | Stockholm |
| Bani, DR | Hamilton Bermuda | Republic of Congo | | Bahrain |
| Banju, Africa | Hamilton Canada | Republic of Zambia | | Bainet, Haiti |
| Barbabos | Honduras | Republique du Mali | | Honduras |
| Barbados | Havana | Reykjavik | | Ha Nai |
| barbaro | Holland | Riga | | Haifa |
| Barbbados | Hong kong | Rio | | Pineda-Toribo |
| Barbedos | Hungary | Rio Piedras | | Pingapore |
| Barbobos | Iceland | Rioberde | | Plovdiv |
| Barbosa | Illah | Rivera Soto Maria | | Poland |
| Barcelona | Inchon | Rivera Uruguay | | Portugal |
| Bardados | India | Rotan Honduras | | Prague |
| Brazil | Indian reserve | Romania | | Praia CV |
| Bejing | Indonesia | Rome | | Prezza Italy |
| Beirut | Iraq | Rwanda | | Prince ed island |
| Belarouse | Iran | Russia | | Progresso Guatemala |
| Belarus | Ireland | Ryadh Saudi Arabia | | Punjab India |
| Beleise | Isabela PR | S. Africa | | Purma |
| Beleze | Israel | S. America | | Pusan |
| Belfast | Italy | S. Korea | | Qatar |
| Belgium | Ivory coast | S. Vietnam | | Quamala |
| Belise | Jamaica | Saigon | | Quantana |
| Belize | Japan | St. Martin | | Quatamalea |
| Bengaldesh | Jauco PR | St. Thomas | | Quawat |
| Benin | Jeddah | St. Vincent | | Quebec |
| Berat | Jerusalem | Saipan | | Quwait |
| Berlin | Jimenez Alberto | Salvador | | Rabat |
| Bermuda | Jinja | Salvakia | | Romania |
| Bern | Jling, China | Somali | | Rangoon Burma |
| Beruit | Johannesburg SA | Samara | | Rawanda |

| | | | |
|------------------------|-----------------------|--------------------|---------------------|
| Berzil | Jordan | Sambia | Razil |
| Bhudan | Kampala Africa | San Domingo | Republic of Georgia |
| Bhusawal | Kanya | San Jose | Bulgaria |
| Bhutan | Karachi | San Juan | Buraundi |
| Bein Hoa | Kazakhstan | San Salvador | Burma |
| Bissau | Kata India | Sao Tome | Burundi |
| Bissiu | Kathmandy | Saudi Arabia | Busnia |
| Bitburg | Kawait | Sicily | C.R |
| Blaise | Kenema Africa | Scotland | C. Verde |
| Boastwana | Kenya | Sierra Leone | Cabral Maria |
| Bogaria | Kent England | Senegal | Cabrera Franceca |
| Bogata | Khartoum | Seoul | Caguaas, PR |
| Bolgaria | Kiev | Serbia | Cairo |
| BOLIVIA | Kindia Guinee | Shahrood | Calcutta |
| Bolton | Kinshsa, Africa | Shakia | Calgary, CA |
| Bombay | Kiruna Sweden | Shanghai | Cali, Colombia |
| Bosnia | Kitchner Canada | Sheffield England | Cameroon |
| Bowtown, Sierra Leone | Kolkata, India | Shinkolobwe Congo | Cambodia |
| Botswana | Kolwezi Zaire, Africa | Shiraz Iran | Canaa |
| Br Virgin Is | Kongo Africa | Shrilaka | Canada |
| Brazil | Kora | Sialkot, Pakistan | Caneroon |
| Brava | Korca Albania | Sidney Nova Scotia | Canton china |
| Brighton UK | Korea | Sinegal Portugal | Cape verde |
| Britain | Kosko | Singapore | Cape haitien hti |
| British Guyana | Kosovo | Sri Lanka | Caracas |
| British Honduras | Kozmaqi feriz | Sirvia | Cardiff uk |
| British virgin islands | Kuaite | Skopje | Cardona margarito |
| British west indies | Kumasi | Slovakia | Caribbean |
| Brussels | Kurdish | Slovenia | Casa Blanca |
| Bucharest, Romania | Kushtia | Smiguel, Azores | Cantania italy |
| Budapest | Kuwait | Somalia | Cayes Haiti |
| Bulawayo, Zimbabwe | Kyrgystan | Soukahras, Algeria | Cayman islands |

| | | | |
|-----------------------------|--------------------|---------------------|--------------------|
| Ceylon | Magog Canada | Suttles Veronica | Ceech republic |
| Chandigarh | Makapi, Phi | Switzerland | Central Africa |
| Changchun china | Malaysia | Sweden | Kyzakstan |
| Chechnya | Malawi, Africa | Sydney, Canada | La Paz Bolivia |
| Checkoslovakia | Mali | Sydney, AU | La Tronche France |
| Chengdu | Malta | Sydney, Nova Scotia | Labana |
| Chennai | Managua | Syria | Lebanon |
| Chicoutmi Quebec | Manati | Taiwan | Lagos |
| Chile | Manchester England | Thailand | Lahore Pakistan |
| China | Mangalore India | Taipei | Lancashire England |
| Cobo Verde | Manila | Tamworth, Aut | Langley BC |
| Columbia | Mannheim | Tanzania | Laos |
| Colon Germany | Maecella | Tappita | Lares PR |
| Combodia | Mardan | Tbilisi Georgia | Latvia |
| Commenwealth of Dominica | Margao | Teheran | Leeds UK |
| Congo | Marshal Islands | Tel Aviv | Lehoee Pakistan |
| Cork Ireland | Martinique | Thaka | Leicester UK |
| Corydoniol IA | Mauritania | Tiber | Liberia |
| Costa Rica | Myanmar | Tibet | Libya |
| Couris Rep | Mengo | Tirana | Ligeria |
| Croatia | Mexico | Trinidad | Lima |
| Cuba | Middle east | Tobago | Limbe |
| Culebra PR | Milano | Tocoos | Lipya |
| Curaco | Minsk Belarus | Togo | Lisbon |
| Curacoa | Mogadishu | Tokyo | Lithuania |
| Curaso | Moldova | Toronto | Loas |
| Cypress | Moncton Canada | Tortola | Loiza PR |
| Czech republic | Montserrat | Tripoli | Lome |
| D.R | Mongolia | Tunisia | London |
| Dakar | Monrovia | Turkey | Lucknow India |
| Damascus | Montserrat | Turnhout | Lushnje Albania |

| | | | |
|----------------------|-----------------|--------------------|--------------------|
| Darka Sengel Africa | Montenegro | Tuxapan | Morocco |
| Delft | Montevideo | UAE | Macu |
| Delhi India | Montreal | Uaxaca, Mexico | Macedonia |
| DR Congo | Moscow | Uganda | South Arabia |
| Demaskus | Mozambique | Yugoslavia | Soviet Union |
| Dhaka Bangladesh | Mp/india | UK | SP Honduras |
| Djibouti | Mpundu | Ukraine | Spain |
| Dominic, west indies | Multan | Umdirman | Sparta Greece |
| DOR | Mumbai | Uruguay | St. Croix |
| Douala | Mwense, Zambia | US Samoa | St. Davids |
| Dublin | Myanmar | US Virgin Is | St. James, Jamaica |
| Dubai | Mysore India | USSR | St. Jerome |
| E. Africa | Nabha India | Uthaihani | St. Johns |
| Ecquador | Naibo Kenya | Uzbekistan | St. Kitts |
| Edmonton Alberta | Nairobi | Vancouver Canada | St. Lucia |
| Egypt | Nanjing | Venezuela | St. Michael |
| Ethiopia | Nepal | Vietnam | St. Miguel |
| Niberia | Netherlands | Vienna | St. Paolo |
| Nicaragua | Nevis | Victoria, Cameroon | St. Petersburg |
| Nice France | New Delhi | Victoria BC Canada | St. Ann Jamaica |
| Nigeria | Newfoundland | Vilnius | St. Elizabeth |
| Niguanda | New Glasglow | W Africa | St. John |
| Nogales Mexico | New Guanda | W Germany | St. Kitts |
| North Iraq | New Zealand | WI | St. Lucia |
| Wallingford | West Bank | Yaoundé Cameroon | St. Michael |
| Warangal | Western Europe | Yemen | St. Miguel |
| Warsaw | Whales UK | Zaire | St. Paolo |
| Watemala | Windsor Ontario | Zambia | St. Petersburg |
| Zanzibar | Winnipeg | Zimbabwe | St. Ann Jamaica |
| Ceech republic | Sudan | Zaire | St. Elizabeth |
| Central Africa | Seychelles | | St. John |

Of the 600 women who had an FSH level over 15mIU/ml, 594 had a birthplace recorded. There were 180 women born in the United States that had an FSH>15mIU/ml, the rest of the 594 women were born outside of the United States. The birthplaces outside of the United States with six or more women associated with them are listed in table 12 below. The number of women from each place is also listed in the table. The country with the highest number of women who had an FSH>15mIU/ml was Haiti. Cape Verde had the second highest amount and the Dominican Republic the third. The country with the highest percentage of women with FSH>15mIU/ml is Somalia. Liberia had the second highest percentage, and Ethiopia the third.

Table 12. Number of women with an FSH>15mIU/ml born in areas outside of the United States.

| Birthplace | Number of Women with FSH>15mIU/ml | Total Number of Women with FSH test done | % of women in area with FSH>15mIU/ml |
|--------------------|-----------------------------------|--|--------------------------------------|
| Liberia | 7 | 21 | 33.3 |
| Brazil | 8 | 77 | 10.4 |
| Jamaica | 9 | 145 | 6.2 |
| Morocco | 10 | 53 | 18.9 |
| Nigeria | 15 | 129 | 11.6 |
| Puerto Rico | 18 | 245 | 7.3 |
| Somalia | 21 | 56 | 37.5 |
| Ethiopia | 22 | 76 | 28.9 |
| Dominican Republic | 28 | 244 | 11.5 |
| Cape Verde | 29 | 338 | 8.6 |
| Haiti | 75 | 874 | 8.6 |

DISCUSSION

Prevalence of POF in women born in the U.S vs those NOT born in the U.S

As the results above show, there is a slightly higher prevalence of premature ovarian failure in the group of women born outside of the United States. Of the control group, 8.8% of women with an FSH>15mIU/ml were born outside of the United States and 9.67% of women with an FSH>15mIU/ml or a diagnosis in SDK or Logician were also born outside of the United States. This agrees with our original hypothesis. The chi square analysis that was done on the data shows a significant difference exists between the two groups of women with a p value <0.0001 in both groups, this is a good indication that future studies should be conducted to further investigate the matter.

Birthplaces

Current literature gives the prevalence of premature ovarian failure by various ethnicities, but no study has given the prevalence by specific birthplace. The prevalence by ethnicity is as follows: African American (1.4%), Hispanic (1.4%), Caucasian(1.0%), Chinese(0.5%) and Japanese(0.1%) (Luborsky et al., 2002). In this study, we did not record

the ethnicities of the women in both groups. We have compiled a list of prevalence by birthplace as was shown in the results above.

Of the 594 women with FSH>15mIU/ml, only 180 were born in the United States. Of the women born outside of the United States, Haiti had the highest amount of women with premature ovarian failure. Haiti had over two times the amount of women with POF than the areas with the second and third highest amounts. Cape Verde and the Dominican Republic had the second and third highest amount of women with premature ovarian failure respectively. When compared to the number of women in each respective area that had an FSH test done, Somalia had the highest percentage of women with FSH>15mIU/ml. The percentages are of greater use when comparing birthplace data and will be used in further studies on the subject.

Future Investigations into POF

This study has provided sufficient evidence that warrants future investigations of the topic. Very few studies exist that compare the prevalence of premature ovarian failure between groups of women born in the United States and those that are not. The results of this study only scratch the surface of our hypothesis. We have significant data that proves there is in fact a higher prevalence of premature ovarian failure among the population of women not born in the United States. Future

studies should be done to attempt to identify the cause of the higher prevalence. The higher prevalence in certain areas may be associated with some of the chemicals associated with premature ovarian failure studied by Berenger et al. in 2013. There may also be other causes that are not associated with occupation. These may include: history of trauma, genetics, history of chemical exposure, socioeconomic status, smoking, and nutrition. Further studies should also be conducted to further stratify the birthplaces of women with premature ovarian failure. We have only done a preliminary analysis of this data and a more detailed study would be beneficial for future research. These studies should focus on these factors using a multivariate analysis.

Limitations of this Study

There are a few factors that were not analyzed in this study that may influence its results. There is quite a large percentage of women for which we have no country of origin recorded. Knowing the birthplaces of these women would give more accurate results. The average age of the two groups of women is different by about a year and some other factors were not controlled for. There also may be inaccuracies in the data that come from using such a large database as well as human error in the initial recording of data into this database. Some physicians may not record diagnoses the same way other physicians do so there also may be

some discrepancies with diagnostic data. Any future studies done by our group will control for certain factors to get the most accurate results possible.

Conclusion

As was previously discussed, premature ovarian failure is a disease that has many serious consequences. There are some known causes of premature ovarian failure but a majority of cases are idiopathic (Dragojevic-Dikic et al., 2010). More research should be done to shed light on any possible correlations between premature ovarian failure and various factors such as ethnicity, birthplace, occupation, and psychological issues. This study has provided sufficient evidence that there may be a relationship between premature ovarian failure and birthplace. Once more is known about possible causes of premature ovarian failure, steps can be taken to try to prevent it in women who may be at greater risk of its development.

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VITA

VICTORIA DEERING

Born 1990

vdeering@bu.edu

749 Revere Ave
Bronx NY 10465

Education: **Boston University School of Medicine: Graduate Medical Sciences**
September 2012-May 2014
Masters in Medical Sciences

Stony Brook University

August 2008-May 2012

Bachelor of Science, Biology, May 2012

International Academic Programs: Tanzania

June 2010

Experience: **Stony Brook University Hospital**

Research Assistant in Maternal and Fetal Medicine

April 2010-May 2012

Office of the Vice President of Research-Stony Brook University

Office Assistant

June 2011-May 2012

Worked in various areas of the office scanning and organizing files and answering phone calls. I also worked in the IRB section of the office entering and sorting CITI and HIPPA training certifications for the members of research labs associated with Stony Brook University.

Melville Library-Stony Brook University

Student Assistant

February 2011- August 2011

Helped catalogue books for the library and match authors with their authorities.