Environmental Contaminants Influence Gamete Development but not Hormone Profiles of Patients Undergoing IVF

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Introduction

Environmental contaminants, especially endocrine-disrupting chemicals (EDC), profoundly affect human and animal health, including reproduction. Endocrine-disrupting chemicals are defined by the U.S. Environmental Protection Agency (EPA) as any exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are responsible for homeostasis, reproduction, and developmental processes. Endocrine-disrupting chemicals are found throughout modern life; they include plasticizers like bisphenol A (BPA), alternatives to BPA like bisphenol S (BPS), heavy metals like arsenic and mercury, and agrochemicals like pesticides and herbicides. Studies in animals and humans have identified some of the pathways affected by EDCs. Many of these studies were conducted on humans who work directly with these compounds daily or on animals utilizing pharmacologic doses to elicit a response. However, it does not show the effect of living in geographic regions of intense EDC.

Long-term passive exposure to EDCs can occur in many environments; most Americans are exposed to some level of EDCs in food packaging and other household goods. However, there are significant regional differences in EDC use based upon regional economic activities. This phenomenon is seen in the north-western portion of Texas, where economies can change drastically within relatively short distances. The panhandle and western region of Texas include the Texas Panhandle, Texas South Plains Permain Basin, and the Rolling Plains regions comprising of all or part of 90 counties. If the region were an independent State, it would rank 11th in size, just above Idaho (82,643.12 square miles), with a total land area of 88,256.4 square miles.

The region is home to approximately 2 million people, with 65% of the population living in the counties surrounding the seven urban centers in the region, Lubbock, Amarillo, Midland/Odessa, Abilene, Wichita Falls, and San Angelo. The economies of the urban centers and the areas surrounding them vary drastically. The Panhandle and Rolling Plains portions of the regions that center around Amarillo, Abilene, and Wichita Falls are mainly rural with economies based on cattle and grain production, with pockets of oil production. However, Lubbock and the 24 counties surrounding it, collectively called the South Plains region, are the largest cotton-producing region globally, producing an estimated 1.71 billion pounds of cotton per year. The Permian Basin is to the south of the South Plains. It includes Midland/Odessa and is the largest oil-producing region in the U.S., producing approximately 4 million barrels of oil per day in 2020, and cumulative production of 28.9 billion barrels of oil and 75 trillion cubic feet of gas to date (Figure 1).

This diverse economic activity across the region means that patients present with a variety of causes of infertility. In previous preliminary research consisting of 350 men seeking semen analysis, differences were observed in semen parameters depending upon occupation or home environment. Men who lived in urban environments had significantly higher normal morphology than their rural counterparts (P < 0.001; Figure 2). Men who worked using agrochemicals had higher motility than men who did not (P < 0.001; Figure 3 [1]). In a previous phase of this study, 267 couples seeing infertility treatment were compared for various fertility parameters based upon home environment being urban, mostly-urban, mostly-rural or rural. In that study, pre-wash sperm concentration was significantly higher in men who live in urban environments in west Texas (P < 0.034; Figure 4 [2]). Women from rural environments had a lower fertilization rate (P<0.002; Figure 5). Further, women from mostly rural environments had fewer oocytes recovered (P < 0.02; Figure 6), and fewer embryos reach blastocyst (P < 0.039; Figure 7). The possible cause of these observed differences in fertility parameters is EDC in the form of pesticides and herbicides commonly used in agricultural production, specifically cotton production, which relies heavily on using these chemicals for plant health and aid in harvesting. Commonly used chemicals in cotton-production are 2,4-dichlorophenoxyacetic acid (2,4-D), 1,1'-Dimethyl-4,4'-bipyridinium dichloride (Paraquat), and glyphosate (Roundup).

Only a few agrochemicals have been evaluated for EDC properties. Glyphosate is cytotoxic, genotoxic, and impacts steroid production and conversion by aromatase [2]. In contrast, the evidence of endocrine-disrupting characteristics from 2,4-D is mixed. Several agrochemicals have chemical structures similar to steroid hormones; however, it is unknown if the compounds are similar enough to interfere in feedback loops or bind with hormone receptors on reproductive tissues.

Agrochemicals are not the only source of concern for EDC exposure in the north-west Texas region. There is evidence compounds associated with fracking and horizontal drilling, practices that have lead to increases in domestic U.S. oil production and revitalization of the petroleum industry worldwide, have EDC properties. More than 130 of the over 1000 compounds utilized in fracking have documented EDC properties include volatile organic compounds (VOCs), such as xylene and benzene, and heavy metals, such as arsenic and lead. Many of the EDCs used in fracking have been shown to have adverse effects on the menstrual cycle, fecundity, and an increased risk of miscarriage and still birth [5]. Further, exposure has been linked to low birth weights, pre-term birth and developmental defects [5].

Infertility practitioners practicing in regions where EDCs are commonly used, such as in areas with intense agricultural or petroleum production, should be aware of the potential impact of various EDCs on their patients. However, there is limited research on the effects of long term passive exposure to EDCs. The purpose of the present study is to examine if there is a possible effect of passive exposure to EDCs in north-west Texas.

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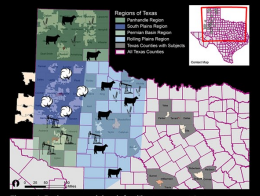

Figure 1: Patients receiving infertility treatment between August 1, 2013 to August 1, 2017 lived across a region larger than Idaho. West Texas is comprised of four geographic regions with economies based in agriculture and petroleum. Two industries with known risk for exposure to endocrine-disrupting compounds.

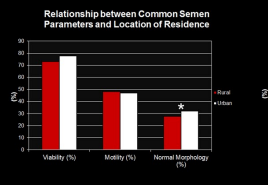

Figure 2: Previous research on men seeking semen analysis. a population at risk for infertility issues, demonstrated that men from urban environments had a higher percent of morphologically normal sperm cells (P< 0.001).

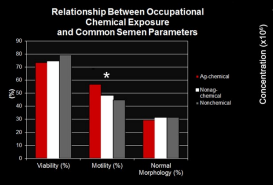

Figure 3: Previous research on men seeking semen analysis a population at risk for infertility issues, demonstrated that men who worked in agricultural professions had higher average motilities that other occupations (P< 0.001).

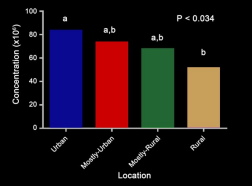

Figure 4: In a previous phase of this study it was observed that men seeking infertility treatment in the form of IUI or IVF, demonstrated those who live in rural environments have lower sperm concentration compared to their urban counterparts (P < 0.034)

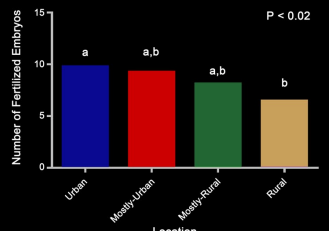

Figure 5: In a previous phase of the present study it was observed that women undergoing ART procedures from rural environments had fewer fertilized embryos than urban women in West Texas (P<0.02).

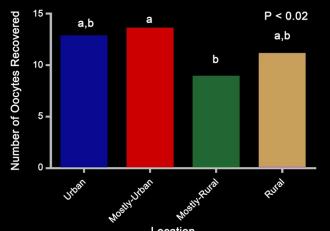

Figure 6: In a previous phase of the present study it was observed that women seeking ART who lived in mostly-rural environments had fewer oocytes recovered at retrieval than their mostly-urban counterparts (P<0.02).

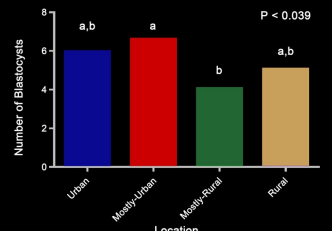

Figure 7: In a previous phase of the present study it was observed that women seek ART from mostly-rural environments had fewer blastocysts than women from mostly-urban environments (P<0.039).

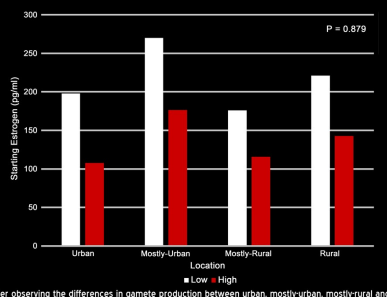

Figure 8: After observing the differences in gamete production between urban, mostly-urban, mostly-rural and rural populations in West Texas it was decided that hormone levels in women undergoing stimulation for IVF should be evaluated. While all hormone tests run were analyzed estrogen is of particular importance to a stimulation cycle and is demonstrated here. There were no differences in starting estrogen levels across the four environments of interest.

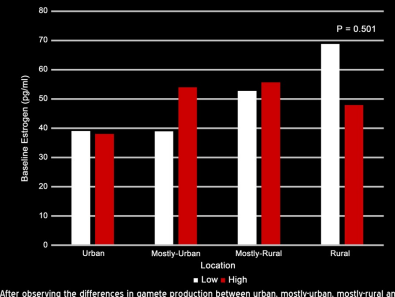

Figure 9: After observing the differences in gamete production between urban, mostly-urban, mostly-rural and rural populations in West Texas it was decided that hormone levels in women undergoing stimulation for IVF should be evaluated. While all hormone tests run were analyzed estrogen is of particular importance to a stimulation cycle and is demonstrated here. There were no differences in baseline estrogen levels across the four environments of interest.

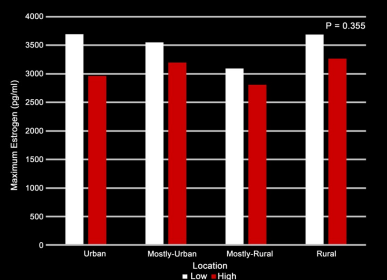

Figure 10: After observing the differences in gamete production between urban, mostly-urban, mostly-rural and rural populations in West Texas it was decided that hormone levels in women undergoing stimulation for IVF should be evaluated. While all hormone tests run were analyzed, estrogen is of particular importance to a stimulation cycle and is demonstrated here. There were no differences in maximum estrogen levels across the four environments of interest.

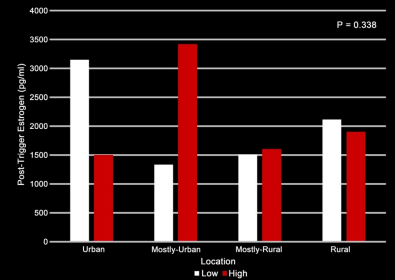

Figure 11: After observing the differences in gamete production between urban, mostly-urban, mostly-rural and rural populations in West Texas it was decided that hormone levels in women undergoing stimulation for IVF should be evaluated. While all hormone tests run were analyzed estrogen is of particular importance to a stimulation cycle and is demonstrated here. There were no differences in post-trigger estrogen levels across the four environments of interest.

Materials & Methods

Hormone profiles of 163 ART procedures that took place between August 1, 2013 and December 31, 2017 were analyzed. Patients were categorized into urban, mainly urban, mainly rural, and rural populations based on zip-code. Data included precycle profiles, down-regulation, maximum estrogen levels, and pregnancy outcomes. Data were then recategorized between different types of environmental regions (heavy versus limited agrochemical use). Finally, the data were then grouped to correspond to periods of heavy agrochemical use, such as during the growing season for regional crops, and analyzed for each hormone. Data were compared by ANOVA, independent Student's t-test, or Chi-square

Results

No differences were found between the hormonal profiles of patients for any of the hormones reviewed regardless of the environment of their home residence (P = 0.118). Further, there appeared to be no difference between the hormonal profile of patients from different agricultural regions where agrochemical used varied from intense to minimal (P = 0.077). Finally, there were no differences seen in the hormonal profiles of patients undergoing treatment cycles during periods of intense versus minimal agrochemical use (p = 0.127). This is demonstrated best by looking at estradiol levels acrosee the cycle (beginning, dow regulated, maximum, and post hCG) were no differencies were seen between the two groups (Figures 8-11).

Conclusions

Previous research from this laboratory has demonstrated a difference in the number of embryos and embryo quality in patients from rural versus urban areas in a region with heavy use of agrochemicals and fracking chemicals. The current data suggests the changes in oocyte and embryo quality are independent of hormonal profile. However, it is unclear if this is due to the effects of the pharmaceutical doses of hormones used to induce follicular development masking differences, or if the early changes reported are truly hormone independent.

In addition, while it did not reach statistical significance, there continues to be a seasonal variability between seasons of intense agricultural production and seasons when fewer agrochemicals are used; this mirrors trends observed in previous data. It is unclear if these observations not reaching statistical significance is due to a lack of power or if there is genuinely no seasonal issue. Due to this uncertainty, continuing research has expanded the population by looking at all patients from August 1, 2013 to August 1, 2023.

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