9th ANNUAL SUMMER MENTORSHIP IN
REPRODUCTIVE MEDICINE
JUNE 13th – JULY 29th, 2016

AMERICAN CENTER FOR REPRODUCTIVE MEDICINE
CLEVELAND CLINIC

SCIENTIFIC WRITING PROJECT

Ranked No. 2 in the nation for Urology and Nephrology
by U.S. News & World Report, 2015-16

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72. Index of Scientific Writing Project 2016 Summer Mentorship
1. ROLE OF HEALTHY DIET IN SPERM FUNCTION

Background:
Studies suggest that appropriate nutritional modifications can improve the natural conception rate of infertile couples. What you eat may have an impact on the quality of the sperm. Paternal nutrition influences offspring metabolism in mammals. Metabolic gene expression was reported to be altered in offspring generated via in vitro fertilization (IVF) using sperm obtained from animals consuming a control or low-protein diet (19 or 10% protein, respectively). Paternal diet can also affect offspring metabolism via information located in sperm. Higher consumption of a prudent dietary pattern (versus western or mixed diet) was associated with higher sperm concentration and higher level of testosterone. Sperm chromatin structure was inversely related to higher consumption of a prudent dietary pattern. So it makes sense that the food choices could play a significant part in the ability to conceive. A healthy intake of micronutrients—including vitamin C, E, folate, and zinc—can boost sperm DNA quality in older men. Studies show that the more antioxidants and micronutrients that are present in the diet, the smaller the risk for sperm with DNA damage, especially in older men. In fact, men ages 44 and older who ate the most vitamin C had 20 percent less damage compared to men of the same age who consumed very little vitamin C. Sub-fertile men who took zinc sulfates daily reported a 74 percent increase in total normal sperm count after 26 weeks, compared to men who were treated with placebos. Foods rich in omega 3, alpha-linoleic acid (ALA), fatty acid, lycopene may have beneficial effects on sperm quality.
Foods to be avoided are those rich in saturated fats, canned foods, fruits and vegetables laced with pesticides. Increasing evidence indicates that offspring metabolic disorders can result from the father’s diet, but the mechanism remains unclear. Here, in a paternal high-fat diet (HFD) mouse model, show sperm tRNA-derived small RNAs (tsRNAs), mainly from 5’ tRNA halves and ranging in size from 30 to 34 nucleotides, exhibit changes in expression profiles and RNA modifications. This represents a type of
paternal epigenetic factor that may mediate intergenerational inheritance of diet-induced metabolic disorder.

**Significance:**
In this review we will discuss foods to embrace and those to avoid and list other assorted sperm killers to avoid especially for men who may already be at risk of compromised male fertility health.

**Outline:**
1. Paternal diet and offspring metabolism
2. Role of transfer RNAs (tRNA) and small RNAs (sRNA) in sperm maturation
3. sRNA biogenesis and its dietary regulation during posttesticular sperm maturation
4. Role of small RNAs (sRNAs) in epigenetics
5. Effect of low protein diet on sRNAs
6. Healthy intake of vitamins in foods (vitamins A, C, E, B12)
7. Essential mineral in diet and sperm health
8. Foods good for the sperm (foods rich in folic acid, lycopene)
9. Super foods to increase sperm count (eggs, spinach, bananas, chocolate)
10. Foods to avoid (canned foods, saturated fats, pesticide laced fruits and vegetables, processed meat)
11. Drink water and avoid alcohol
12. Diet and declining sperm quality (High fat, low protein diets)
13. Intake of healthy fruit and vegetables and sperm DNA fragmentation

**Literature review:**
Preliminary literature search has been done using resources of Cleveland Clinic Alumni Library. An exhaustive literature review needs to be done before the article.

**Journal:**
To be decided.
Synopsis of Writing Project

Suggested reading:

Resources of Cleveland Clinic Alumni Library


**Intended audience:**
Urologists, Andrologists, Male infertility specialists

**Deadline:**
July 26, 2016
2. IMPACT OF DRUGS ON OOCYTE QUALITY

Background:
The female reproductive function is directly determined by the ovarian life span. Ovary is a metabolically active organ and serves as a germ cell reservoir during reproductive life span of female. Ovary has approximately 0.3 million primordial follicles that contain diplotene arrested oocytes. Pituitary gonadotropins surge induces steroidogenesis, follicular growth, development, maturation and ovulation in most of the mammalian species. Environmental changes, lifestyle changes, pathological conditions or drugs treatment may induce accumulation of ROS leading to OS that may have a negative impact on oocyte physiology by inducing apoptosis.

Significance:
Reproductive aging is an increasingly pressing problem facing women in modern society, due to delay in child bearing. The postponement of childbearing, which is a demographic trend in all several countries, contributes considerably to the increasing proportion of subfertile couples that require assisted reproductive technology (ART) procedures. Indeed, age of the female partner is one of the most significant factors influencing the clinical outcomes of ART cycles. Our review examines the enzymatic antioxidants such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and glutathione oxidase and non-enzymatic antioxidants such as vitamin C, taurine, hypotaurine, vitamin E, Zn, selenium (Se), betacarotene, and carotene and their beneficial effects on oocyte quality. Oocyte post-ovulatory aging can be overcome by the peri-ovulatory putrescine supplementation which is being investigated as a new intervention. It could act as a possible remedy for reproductive aging. Review also examines the role of calcium channel blockers and anticancer drugs on oocyte quality. This review is significant in reviewing the literature on current interventions to improve overall oocyte quality in women.
Synopsis of Writing Project

Outline:
1. Changes in oocyte quality with reproductive ageing structural changes and underlying mechanisms
2. Impact of Oxidative stress on oocyte quality
3. Antioxidants; N-Acetyl-Cysteine and L-Carnitine do they have protective effects on oocyte
4. Interventions to improve oocyte maturation in older women by overcoming including Loss of chromosome cohesion, mitochondrial dysfunction, defective spindles and insufficient histone deacetylation
5. Periovulatory drug interventions for enhancing oocyte quality
6. Calcium channel blockers: do they prevent premature oocyte ageing
7. Anticancer drugs and their impact on oocytes
8. Conclusions and future research

Literature review:
Preliminary literature search has been done using resources of Cleveland Clinic Alumni Library. An exhaustive literature review needs to be done before the article

Journal:
To be decided.

Suggested Reading:
Resources of Cleveland Clinic Alumni Library


11. Aging and the environment affect gamete and embryo potential: can we intervene? Meldrum DR, Casper RF, Diez-Juan A, Simon C, Domar AD, Frydman R.
Synopsis of Writing Project

**Intended audience:** reproductive endocrinologists, reproductive biologists and gynecologists

**Deadline:**
July 26, 2016
Sezgin Ozgur Gunes, PhD
Associate Professor, Ondokuz Mayis University,
Department of Medical Biology
Samsun, Turkey
Email: sezgingunes@yahoo.com

3. DEFECTS OF MICROTUBULES ASSOCIATED WITH MALE INFERTILITY

Background:
Microtubules are tubulin polymers that have function many essential cellular processes including cell division and migration. In addition, they have roles in sperm head shaping, and sperm motility. Several defects of the different parts of that compose the microtubules have been described and associated to human male infertility.

Significance:
Microtubules are associated dynamic changes in cytoskeleton, organelle movement, mitosis, meiosis and motility during spermatogenesis.

Outline:
1. Background
2. Methods
3. Structure and functions of microtubules
4. Microtubule dynamics
5. Microtubules in Sertoli cells
6. Flagellum formation
7. Conclusions

Literature review:
Preliminary literature searches have been done using resources of Cleveland Clinic Alumni Library. An exhaustive literature review needs to be done before the article is written.

Journal:
Synopsis of Writing Project

Review article. Journal to be decided.

**Suggested readings:**


**Intended audience:**

Andrologist, gynecologists, reproductive endocrinologists, embryologists and basic scientists

**Deadline:**

July 26, 2016
4. IMPACT OF ENDOCRINE DISRUPTING COMPOUNDS ON CAUSING MALE INFERTILITY

Background:
Humans are exposed on a daily basis to a wide array of toxic compounds that interfere with vital functioning of our various biological systems. Endocrine disrupting compounds or commonly called as EDs as well as androgen disruptors play a major role in the malfunctioning of male reproductive system subsequently affecting the male fertility. Extensive work has been carried out on animal model systems on the exposure to these organic compounds. These works were complimented with cell line studies to study the specific effects these metabolites on pathways associated with male reproductive system. The primary targets of EDs as well as androgen disruptors molecules including organochlorinated pesticides, industrial chemicals, and plasticizers with capacity to ligand the androgen receptor are the genes and proteins involved in the reproductive pathways centered around the androgen receptor since it is the key molecule that regulates the major events associated with spermatogenesis. The effect of these compounds have a major impact on the normal male developmental programming during spermiogenesis as well as subsequent events for the processing of the fully functional spermatozoa. The maximum impact of these accumulated compounds is observed in the microenvironment environment of the developing immature as well as the mature spermatoza. The deleterious effects of these compounds are manifested in the form of low sperm counts, malignancies associated with the prostate, as well as testicular dysgenesis syndrome as proved by animal model studies. This review will highlight the evidence for androgen and ED disrupting chemicals that act through interference with the specific receptors that perturbs the normal functioning of the male reproductive system leading to male infertility.

Significance:
The current study will help to summarize the latest development on the role of endocrine disrupting compounds in affecting male infertility. Toxic compounds, pesticides and EDCs and their effect on spermatogenesis as well as malfunctioning of the male reproductive system will be targeted in the
proposed assignment. This study will help to understand the close association between the various EDCs, which we come in contact, and their effect on the fecundity factor of males in the long run.

Outline:
1. Introduction
2. Prevalence of EDs in the environment
3. Classes of EDs associated with male reproductive function
4. Role of EDs/androgen disruptors in male reproduction
5. Primary targets and localization if EDs in male reproductive system
6. Mechanism of action EDs in the malfunctioning of the male reproductive system
7. Invitro and invivo studies related to EDs and fertility
8. Genetic regulation of EDs in mimicking endocrine function associated with male infertility
9. TOXICO genomics and proteomics studies associated with EDs and male infertility
10. Case studies associated with ED related to male infertility

Literature review:
Preliminary literature search has been done using resources of Cleveland Clinic Alumni Library. An exhaustive literature review needs to be done before the article is prepared.

Journal:
Will be decided later.

Suggested reading:
Synopsis of Writing Project


Intended audience:
Andrologists, male infertility specialists, urologists and basic biologists

Deadline:
July 26, 2016
5. Phthalates, semen quality and male fertility: an evidence based review

Background

Phthalates are esters of phthalic acid and a class of organic chemicals used as plasticizer to increase the flexibility of polyvinylchloride (PVC). These are used in large variety of products such as food packaging, medical devices, medications, toys as well as cosmetics and personal care products (Crinnion, 2010). They are also commonly used in various mediums to maintain the color and scent (Cadogan and Howick, 1996) in perfumes, lotion, nail polish, lipsticks and deodorants (Blouinet et al., 2000). Among the primary phthalate compounds diethyl-hexyl phthalate (DEHP) is most commonly used plasticizer worldwide (Lorz et al., 2003). Other important phthalates products are dibutyl phthalate (DBP), diethyl phthalate (DEP), butylbenzyl phthalate (BBzP), and di-iso and n-butyl phthalate (DiBP, DnBP) (Koch et al., 2003). In the body, phthalates are rapidly metabolized to their respective monoesters (Silva et al., 2006). They undergo a series of phases i.e. phase I hydrolysis and phase II conjugation reactions and are then excreted in feces and urine (Frederiksen et al., 2007). Both primary and secondary metabolites are biologically active (Forster et al., 1981; Gray et al., 1986; Richburg et al., 1996; Stroheker et al., 2005). Phthalates have negative impact on male fertility. The New York Times report (March 21, 2014 1:31 PM). “To study the impact of everyday chemicals on fertility, federal researchers recently spent four years tracking 501 couples as they tried to have children. One of the findings stood out: while both men and women were exposed to known toxic chemicals, men seemed much more likely to suffer fertility problems as a result”. The impact of phthalates starts at testicular level as the hormonal environment is essential for the developing male gonads and male reproductive tract. In utero as well as in adults phthalates exposure can interfere with the production or action of hormones which may partially or completely prevent the masculinization process of the developing fetus and could also compromise the semen quality leading to fertility issue. The adverse effects of phthalates on male development and reproduction might be mediated from reactive oxygen species (ROS), that have been shown to induce DNA damage and may
accelerate the process of germ cell apoptosis, leading to the decline in sperm counts associated with male infertility. This association seems conceivable, since (i) phthalates have been reported to cause peroxisome proliferation, a process also featured by an enhanced production of ROS (ii) ROS mediated female fertility disorders share many pathogenic similarities with the ones on the male.

**Significance**

This article will review the data published on semen characteristics in response to the exposure to phthalates and will contribute in the understanding of the role of phthalates in male fertility.

**Outline**

1. Phthalates as endocrine disrupting chemicals
2. Chemistry of the phthalates metabolites
3. Role of phthalates in testes development
4. Role of phthalates in development of male reproductive tract
5. Phthalates and neonatal exposure
6. Phthalates and semen characteristics
7. Phthalates and male infertility
8. Conclusions
9. Recommendations

**Literature review:**

Preliminary literature search has been done using Google Scholar, PubMed and the keyword search. An exhaustive literature review needs to be done before the article is prepared.

**Journal:**

Will be decided later.

**Suggested readings**

**Intended Audience**

This review is of interest to the fertility specialists, reproductive biologists and toxicologists, andrologists.

**Deadline:**

July 26, 2016