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Case Illustration

Graves Disease: Successful Cesarean Section and Salpingectomy

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A 41-year-old G2P1001 female patient was presented to the emergency department at 37-weeks of gestation with a prior history of non-compliance, uncontrolled hypertension and hyperthyroidism. Upon further questioning in the emergency department, the patient reported for a cesarean section (C-section) and bilateral salpingectomy for permanent sterilization and she was not taking her medications for her comorbid conditions. Diagnostic testing including assessment of thyroid stimulating hormone (TSH) and anti-thyroid peroxidase (anti-TPO) antibodies proved to be inconclusive due to high-levels of fluctuation. Further testing to confirm the degree of hyperthyroidism was then considered. A nuclear medicine thyroid uptake scan was performed after the risks and benefits were discussed with the patient. To reduce the risk for the fetus, the patient was advised to increase fluid intake. Increased fluid intake and increased urine output significantly reduces the risk of fetal exposure to radioactive material.[1] Administration of 302 unique client identifier (UCI) of I-123 Isotope was administered and thyroid uptake was measured. Five-hours after administration, thyroid uptake was 63.8% and at 23-hours was 67.1%, both markedly increased. The normal uptake for these studies is 7-20% at 6-hours and 10-35% at 24-hours. As illustrated in Figure 1, the scan shows uniform isotope uptake evident of the right and left lobes of the thyroid gland with no focal areas of decreased or increased uptake. The radiologic impression significantly increased the isotope uptake at both 5-hours and 23-hours that is consistent with the graves disease. After the detailed discussion about the probable results with the patient, high-risk obstetric surgery was planned. A low transverse C-section was performed along with bilateral salpingectomy. The patient tolerated the procedure well with no anesthetic complications. Upon the birth of the neonate, there were no complications reported after assessment by an in-house neonatologist. Thus, making this high-risk surgery a success. Graves disease affects 1 out of every 1000 women and the unique steps taken during this case has made it successful and noteworthy.[2]

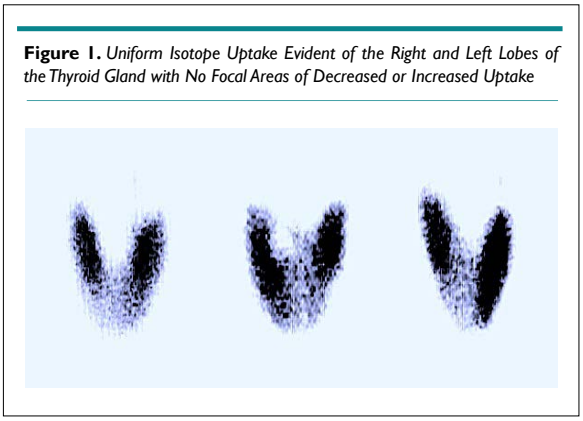

Figure 1. *Uniform Isotope Uptake Evident of the Right and Left Lobes of the Thyroid Gland with No Focal Areas of Decreased or Increased Uptake*

DISCUSSION

It is important to note that the patient was documented as clinically euthyroid and short-term corticosteroids were given. Despite the patient's history of hyperthyroidism disease, she had no reported complications during any previous pregnancies.[3] Given the fact that poorly controlled thyrotoxicosis is related to several maternal and fetal complications, it is crucial to achieve euthyroidism rapidly. Short-term courses of corticosteroids should be considered to attain rapid clinical and biochemical control of thyrotoxicosis.[4] Fluctuating levels of initial diagnostic testing led to consideration of nuclear medicine. In addition to reducing the risk for the fetus being exposed to radioactive material through aggressive hydration of the mother, many studies have suggested pregnant women do not undergo nuclear medicine procedures unless risks outweigh safety.[1] Risk is considered fairly low when used for diagnostic purposes, as highlighted in this case. As fetal surveillance is highly paramount, the patient reported that she had been seeing an obstetrician regularly for prenatal care. Successful high-risk surgery

was completed, and postpartum advice to not breastfeed after the surgery due to exposure of radiation was explained to the patient.

CONSENT

The authors have received written informed consent from the patient.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Case Report

Blighted Ovum: A Case Report

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ABSTRACT

Presenting in her late twenties, this case report examines a G6P2 patient at 11-weeks gestation that was diagnosed with a blighted ovum, as well as the subsequent outcome and methods of additional management. A blighted ovum refers to a fertilized egg that does not develop, despite the formation of a gestational sac. The most common cause of a blighted ovum is of genetic origin. Trisomies account for most first trimester miscarriages, while consanguineous marriages result in recurrent miscarriages due to a blighted ovum. Additionally, a higher percentage of deoxyribonucleic acid (DNA) damage in sperm carries a higher rate of miscarriage. Nutritional factors that may lead to a blighted ovum include low-levels of copper, prostaglandin E2, and anti-oxidative enzymes. High body mass index (BMI), especially in women with a BMI≥30 kg/m^2 has been shown to be linked to a blighted ovum. Globally, it has been shown that a blighted ovum is a serious adverse event related to vaccination against dengue fever.

INTRODUCTION

The case presented is of a 28-year-old female with a blighted ovum, with a focus on outpatient management. With 50% of miscarriages occurring in the first trimester, it is very likely that primary care physicians will encounter a patient with a blighted ovum and will have to properly manage the patient, whether it be expectant or a more invasive approach.

CASE PRESENTATION

A 28-year-old African American patient, G6P2 at 11-weeks gestation by last menstrual period with a past medical history of obesity and iron deficiency anemia presented with hyperemesis, abdominal pain, shortness of breath, urinary frequency, and passage of blood clots through the vaginal canal. A urine β-hCG conducted in the office indicated that the patient was pregnant. An ultrasound performed one-week previous by the patient's primary care provider was unable to establish an intrauterine pregnancy. Transvaginal ultrasound indicated an anteverted uterus measuring 11.6×8.2×7.8 cm. A 2.7 cm fluid collection was noted in the endometrial canal, which may represent an irregular gestational sac. No yolk sac or fetal pole could be seen. Ultrasound findings were concerning for a non-viable intrauterine gestation however, an early ectopic pregnancy or normal early uterine pregnancy could not be excluded. Serial exams and β-hCG measurements were recommended.

Laboratory analysis indicated a β-hCG of 21,457 mIU/mL, and two days later β-hCG levels decreased to 18,198 mIU/mL. Repeat ultrasound was unable to detect an intrauterine pregnancy. Due to the falling levels of β-hCG, it was concluded that the gestation was non-viable, and termination was discussed with the patient. Cytotec (misoprostol), a prostaglandin E1 analog, was considered as one option to induce shedding of the endometrial lining and the endometrial sac. Another option was dilation and curettage, which would be conducted under anesthesia in an inpatient setting. At the next follow-up appointment, the patient indicated that she had spontaneous passage of the gestational tissue, thus no further management was needed for the patient.

Differential Diagnosis

Ectopic pregnancy: Ectopic pregnancies can be attributed to any factor that damages the integrity of the fallopian tube or impairs the function of the fimbriae. Pelvic inflammatory disease is one of the leading causes of ectopic pregnancies. The most common location for an ectopic pregnancy is the fallopian tube but can occur in other areas such as the abdomen, ovary, or cervix, which

are much rarer.[1] Patients with an unruptured ectopic pregnancy usually present with first-trimester bleeding and abdominal pain. A transvaginal ultrasound is recommended over a transabdominal ultrasound to directly visualize the ectopic mass. However, a gestational sac cannot be visualized with ultrasound until β-hCG levels are between 1500 to 2000 mIU/mL.

Gestational trophoblastic disease: Gestational trophoblastic disease, also known as hydatidiform mole or complete mole, is a product of conception that arises in one of two ways: 1) an ovum with no maternal nucleus that is fertilized by a normal sperm, resulting in paternal DNA duplication; or 2) an ovum with no maternal nucleus that is fertilized by two sperm. The result is a diploid karyotype of either 46XX or 46XY, with 46YY being lethal. Fetal tissue is usually absent. A partial mole is also possible, in which the ovum preserves the nucleus and is subsequently fertilized by two sperm. This results in a triploid karyotype of 69XXY, 69XXX, or 69XYY. This type of gestation usually has a fetus, with a chance of viability, and amniotic fluid.[2]

Patients usually present with hyperemesis gravidarum, pelvic pressure, and a rapidly enlarging abdomen. A transvaginal ultrasound would indicate presence of cystic lesions or the classic "snowstorm" appearance. Some patients may experience passage of these cysts or "grape-like" masses through the vaginal canal. As with any other type of pregnancy, serial β-hCG levels should be measured. However, compared to a normal gestation, the β-hCG levels in trophoblastic diseases are magnitudes higher, usually in the hundreds of thousands range.

Although most hydatidiform moles are benign and can be managed conservatively with measures such as dilation and curettage or suction evacuation, there is still a possibility of transformation to malignant gestational trophoblastic disease or choriocarcinoma. After evacuation of the mole, patients should be monitored with weekly β-hCG measures until levels normalize.[2] Follow-up for 6-months is recommended while the patient is on a form of contraception to ensure β-hCG measures are not due to another gestation. If β-hCG levels do not normalize, the possibility of choriocarcinoma should be investigated.

DISCUSSION

According to research, there are about 200,000 cases of blighted ovum in the United States annually, and most patients first present to their primary care doctor with chief complaints of missed periods or vaginal spotting, abdominal pain, or nausea/vomiting. A blighted ovum causes 1 out of 2 miscarriages in the first trimester of pregnancy.[3] Evaluation of a patient initially begins with a pregnancy test, which can be conducted using urine or serum. Pregnancies with early embryonic failure have lower-levels of both human chorionic gonadotrophin (β-hCG) and human placental lactogen (HPL).[4] However, in order to confirm the diagnosis an ultrasound has to be conducted. A pregnancy is an embryonic if a transvaginal ultrasound reveals a sac with a mean gestational sac diameter (MGD) greater than 25 mm and no yolk sac, or a MGD>25 mm with no embryo.[3] Once the diagnosis is established, several options for management can be utilized. Expectant management can be employed and can wait for the tissues to pass on its own; Misoprostol is a medical treatment option to induce passage of tissues. Methotrexate has also been used as a modality in cases of ectopic pregnancy to remove non-viable tissue while preserving future fertility. If these options fail, the remaining options are surgical, with a dilation and curettage (D&C). Nonetheless, expectant management is preferred over surgical interventions as it is more safe and has lower pelvic infection rates than a D&C.[5]

CONCLUSION

From an epidemiologic perspective, half of the global population has the potential to undergo a gestation. With consanguineous marriages being prevalent in certain ethnic groups, there is a likelihood of a physician having a patient with a blighted ovum. Physicians should be well-versed in how to manage a blighted ovum and the treatment modalities available.

CONSENT

The authors have received written informed consent from the patient.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Commentary

Measurement of Women's Leg Edema Using Ultrasonography

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Peripheral edema is the swelling of lower legs or hands. Venous edema, which differs from lymphedema, occurs when something disrupts the usual balance of body fluids[1] and involves the accumulation of fluid in the extracellular compartment, which results in an increase in the volume of interstitial fluid.[2] Physiologically, a balance exists between intravascular hydrostatic and oncotic pressures and the interstitial pressure.[3] Transcapillary hydrostatic pressure tends to drain fluid from blood vessels, whereas oncotic pressure (hypoalbuminemia) tends to produce fluid retention in blood vessels. Venous edema consists of excess low-viscosity, protein-poor interstitial fluid resulting from increased capillary filtration that cannot be accommodated by a normal lymphatic system.[4] Thus, fluid movement occurs from the venous system into the extravascular space. Initially, gravity pulls the fluid down into both legs and feet.

Leg edema can occur under both normal and disease conditions. Under normal conditions, it occurs in cases of sitting or standing too long, pregnancy, excessive salt intake, and drug reactions-, just to name a few. Under disease conditions, it occurs in cases of venous insufficiency, deep vein thrombosis (DVT), heart failure, preeclampsia, cirrhosis, pulmonary hypertension, and renal failure, among others.[5]

Pitting edema is a characteristic of leg edema, and is detected when pressure that is applied to the skin leaves a depression when removed. This method of detection of leg edema is a qualitative diagnostic method performed. In brief, there is not a quantitative method to measure leg edema.

Ultrasonography is a quantitative imaging method that is easy to use and produces consistent results between operators. Furthermore, when using a portable ultrasound device, a doctor or nurse can perform this imaging method easily in an outpatient setting. In particular, this approach will also prove useful for the assessment of the effects of treatments for leg edema.

Several attempts to observe skin edema using ultrasonography have been made.

In gravity dependent edema, the echogenicity on ultrasonography was reported to be higher in the lower leg than in the upper leg, without a marked difference between the medial and lateral sides.[6] In addition, the subcutaneous echogenicity of chronically edematous legs prior to sleep was reported to be higher than that of reduced legs in the early morning.[7]

Using high-frequency ultrasound, Volikova et al measured the dermal thickness (between the surface of the epidermis and the interface of the dermis) of the legs of patients with a history of previous DVT and symptoms of post-thrombotic syndrome (PTS) and age-matched healthy controls.[8] The median dermal thickness in the control group was 1.34 mm, while that in the PTS group without ulceration was 2.16 mm (p<0.001), with the PTS group showing thicker skin than the control group.

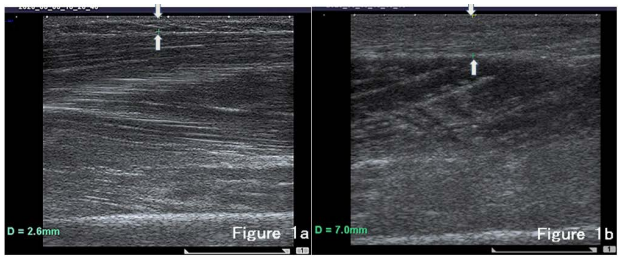
Ciggiati reported the ultrasonographic findings of skin changes in legs with chronic venous disease.[9] In apparently normal skin of C2 class (varicose vein) according to of the clinical-etiology-anatomy-pathophysiology (CEAP) classification, the main ultrasonographic findings were a normal skin appearance, dermal edema or inflammatory infiltration of the cutaneous layer and/or of the subcutaneous layer. In C3 class (edema) of the CEAP classification, by contrast, the findings were homogeneous subcutaneous thickening, presence of anechoic lacunae and presence of dermal edema. These findings are drawn as the same images under both normal and disease conditions.

Of note, the subcutaneous layer, or subdermal layer, consists mainly of adipose tissue and collagen and contains abundant lymphatic and blood vessels, making it a suitable environment for the accumulation of extracellular fluid, much of which is found in the collagen network that surrounds adipocytes.[10] Therefore, venous edema tends to first appear in the subcutaneous layer of the legs and feet.

A previous study evaluated the subcutaneous tissue thickness of the arms, thighs and abdomen in women using ultrasonography.[11] At the arm, the subcutaneous tissue thickness ranged from 3.30 to 18.20 mm; at the thigh, range was 2.70 to 25.20 mm; at the abdomen, the range was 3.40 to 25.20 mm in women. In all cases, the subcutaneous tissue thickness increased as the body mass index (BMI) increased.

We recently measured the skin thickness (including the epidermis, dermis and subcutaneous tissue) in pregnant women with leg edema using B-scan portable ultrasonography as a quantitative method.[12] The skin thickness of the legs in pregnant women with edema was significantly higher than that in pregnant women without edema (6.4±0.3 mm *vs.* 4.6±0.4 mm) (p=0.0001) (Figure 1). The cut-off for the measurement of skin edema compared with non-edema in all legs was 4.7 mm, with a sensitivity of 83.9%, a specificity of 66.7% and an accuracy of 77.6%. However, we faced a problem in that fatty legs showed a thick skin, even in cases without edema.

Figure 1. *Ultrasonographic Measurements of Skin Thickness in Women with and without Leg Edema*



*(**a**) Using ultrasonography (7.5-MHz Linear Array Probe, Siemen), the distance between the skin surface and the fascia was measured as the skin thickness (between the epidermis, dermis, and subcutaneous layers). The skin thickness was 2.6 mm in a woman without edema. (**b**) The skin thickness was 7.0 mm in a woman with edema.*

In the future, we should develop accurate methods for measuring the volume of fluid that accumulates in the leg's skin layer and carefully monitor cases of lower limb skin edema while providing early treatment.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Opinion

Preparing for an *In vitro* Fertilization Cycle

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Pursuing the path to parenthood is a time of life that we should never take for granted. There are many paths to parenthood. For some people, the only way of achieving pregnancy is pursuing an *in vitro* fertilization (IVF) cycle.

This path can be filled with a mix of emotions that can be overwhelming and stressful creating feelings of fear of the unknown. Patients who seek emotional support early in treatment are often better prepared for their experiences and find it significantly less stressful than patients who do not, according to Dr. Ali Domar, founder of mind/body programs for women's health".[1]

There are ways to prepare for an IVF cycle that can aid in managing these emotions making this an exciting time while enhancing positive outcomes. Education of the IVF process and understanding the procedures, self-care and nurturing support systems are key action steps when making the IVF decision.

EDUCATION AND UNDERSTANDING OF THE IVF PLAN AND PROCESS

Prior to meeting with your physician and starting your IVF cycle, please follow the below steps:

- Read through the materials provided by your clinic.
- Write down all questions prior to your appointment you may have, bring to your appointment.
- Bring along your schedule for work, vacation and personal dates so you can coordinate the treatment with the clinic.
what to expect from your appointments?
- The first appointment with the doctor usually covers the required pre-testing prior to treatment, procedures, medications, complications, protocols statistics and your personal possible outcomes.
- A second meeting may be with the IVF coordinator who will educate you on the treatment plan, review and execute consents, order medications, schedule blood and ultrasound appointments
- In the U.S, a meeting with the financial advisor will review possible insurance coverage, authorizations and out of pocket expenses.

SELF CARE

Prepare to be Your Best Self

Preparing for an IVF cycle when dealt with an emphasis on self care, the experience will feel more positive and enabling. This is a challenging time. It is extremely important for men and women to practice self-care. Making changes to diet, exercise and managing stress levels are all key, fertility nurse consultant guides patients towards 5 areas to enhance fertility wellness[2]:

Mind/Mindset: Be aware of your thoughts. Let positive thoughts dominate the negative. Prepare your mind to accept a positive outcome throughout your IVF cycle, do not prepare for the "*What if it does not work?*"

Physical Self: Proper nutrition, exercise, supplements, and sleep provide a healthy environment and give the best support during the IVF cycle. Nicotine, caffeine and alcohol have negative effects on outcomes.

Emotional Self: Recognize feelings of excitement, love, nervousness, stress, loss, grief and other emotions. When stressed with negative feelings such as fear, sadness, anxiety, the stress hormone cortisol increases which impacts the entire body. Take time to relax and practice stress management techniques, such as – gentle ex-

ercise, journaling, social activities, naps, relaxation techniques and talking through your emotions.

Social Self: It is difficult to initiate or participate in social activities, especially if babies and children are included. This is natural and understandable. Social activities can help your emotions, de-stress, lift your mood or act as a distraction.[3]

Financial Self: The financial side of treatments can be overwhelming. Plan and work out finances beforehand and perhaps a new job, additional insurance, extra savings.

SUPPORT SYSTEMS

During the fertility journey support systems are very important. Leaning on family and friends to support social and interpersonal needs. Doctors and nurses educate and guide throughout the process and offer advice and support. Personalized fertility coaching focuses on support and strategies that enhance preconception health.[4] Choosing a coach with fertility expertise ensures guided support to focus on all 5 points to enhance wellness and a journey that feels like you're never alone. Joining an in person or online support group is another option that may validate and support personal experiences. The coach should have fertility expertise to ensure you have the guided support needed to never feel alone during the fertility journey.

It is believed and witnessed that "*Success happens for those who are willing to make every day changes and embrace every opportunity to enhance their fertility. Understanding how the mind and body respond to a temporary crisis like infertility and having the ability to fully prepare for the next step impacts positive outcomes.*"[5]

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Mini Review

Endometrial Cancer in the United States: A Review of the Current Literature

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ABSTRACT

Background

Endometrial cancer is cancer of, or from, the endometrium of the uterus. According to the ACS, it is estimated that, in the United States, about 61,880 cases of cancers of the body of the uterus will be diagnosed in 2019 alone, while about 12,160 women will die from the disease. There are several types and classifications of endometrial cancer based on basic histological or clinical features, or a combination of both. Most of the current interventions have been focused on early detection especially in high-risk women. This is a review of the epidemiology and risk factors, public health actions, and latest interventions in the management of endometrial cancer in the United States.

Keywords

Endometrial cancer; the United States; Review.

IINTRODUCTION AND SIGNIFICANCE

In its simplest description, endometrial cancer is cancer of, or from, the endometrium of the uterus-the innermost of the three major layers of the womb. It is worthy of note that there are a few semantic distinctions among recognized expert bodies, for which one should be aware, in consideration of the literature. For example, the Centers for Disease Control and Prevention (CDC) distinguishes between cervical cancer and uterine cancer, of which endometrial cancer is the most common type of uterine cancer.[1] However, by definition, the cervix ('cervix uteri') is part of the uterus,[2] hence the potential confusion in the CDC's classification should be avoided. Further, the International Federation of Gynecology and Obstetrics (FIGO) has described cancer of the body of the uterus ('corpus uteri') as what is typically referred to as endometrial cancer.[3] However, the American Cancer Society (ACS) states that up to 10% of cancers of the body of the uterus are not endometrial cancers; rather, these 10% are sarcomas of the body of the uterus.[4]

According to the ACS, it is estimated that, in the United States, about 61,880 cases of cancers of the body of the uterus will be diagnosed in 2019 alone, while about 12,160 women will die from the disease. This is worth comparing to the estimated 320,000 new cases of endometrial cancers diagnosed globally every year.[3] Further, it was estimated that the total cost of care for cancers of the body of the uterus, in the United States, for the year 2018, will be about $4 billion.[5]

There are several types and classifications of endometrial cancer. Some are based on basic histological features of the cancer tissue, while others are based on a combination of both histological and clinical features of the disease. The ACS recognizesthe following histological types of endometrial cancers: (i) adenocarcinoma; (ii) uterine carcinosarcoma; (iii) squamous cell carcinoma; (iv) small cell carcinoma; (v) transitional carcinoma; and (vi) serous carcinoma. Most endometrial cancers are adenocarcinomas, and these adenocarcinomas comprise a very diverse group. The less common types of endometrial adenocarcinomas are clear-cell carcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, de-differentiated carcinoma, and serous adenocarcinoma. Most endometrial adenocarcinomas, however, are called endometroid cancers. Further, endometroid cancers can be further subdivided into

the following variants: adenocarcinoma (with squamous differentiation), adenoacanthoma, adenosquamous (or mixed cell), secretory carcinoma, ciliated carcinoma, and villoglandularadenocarcinoma.[6]

The ascertainment of the stage of endometrial cancer usually follows a diagnosis, in order to assess the extent of cancer, in terms of amount and spread. FIGO has described a comprehensive staging system for cancers of the body of the uterus, and this has benefitted research and practice, for many years. This staging system is reproduced as Table 1.[7]

The grading of endometrial cancer is a description of the amount of the cancer's cellular architecture that are built into glandular structures, as comparable to a non-cancerous endometrium. Grade 1 cancers are those that have at least 95% of the cancer tissue forming glands. Grade 2 has between 50% and 94%. Grade 3 has less than 50% of the cancer tissue forming glands; these types of endometrial cancers tend to have the worst prognoses, relative to those of Grades 1 and 2.[6]

DESCRIPTIVE EPIDEMIOLOGY AND RISK FACTORS

Endometrial cancer is the sixth most common cancer worldwide,[7] with high-income countries reported to have a higher incidence (5.9%), compared to poorer countries (4.0%). In the United States, by the year 2016, cancers of the uterus ranked fourth highest (among all cancers) in terms of incident cancer cases among women, while also ranking sixth highest (among all cancers) in terms of deaths of women.[8] Other United States data show an increase in age-adjusted uterine cancer incidence rates, since about 2003, to current levels of 27.5 per 100,000 women per year.[9] These current levels of incidence have been accompanied by a death rate of 4.7 per 100,000 women per year, based on measures spanning 2012-2016. The 2016 prevalence of uterine cancer is reported by the National Cancer Institute as 772,245, spread across the United States. The following states reported higher age-adjusted incidence rates compared to others: Minnesota, Iowa, Illinois, Wisconsin, Ohio, West Virginia, Pennsylvania, New York, etc. Further, it has been documented that African-American women suffer worse prognoses of endometrial cancer, compared to non-Hispanic White women.[10]

Elevated estrogen levels, the postmenopausal state and obesity are high-ranking risk factors for endometrial cancer.[11] The ACS also identifies the following risk factors: a history of endometrial hyperplasia, family history of endometrial or colorectal cancer, type II diabetes mellitus, use of an intra-uterine device, and any situation that alters the normal hormone balance in a woman - for example, Tamoxifen (a drug used to treat breast cancer), pregnancy, ovarian tumors, polycystic ovarian syndrome, etc. Overall, the risk of endometrial cancer in a woman increases with age.[12] Lynch syndrome (the most common form of the hereditary colon cancer syndromes) accounts for 2% to 3% of all endometrial cancers in the United States.[13]

PUBLIC HEALTH ACTIONS AND INTERVENTIONS

The most far-reaching public health interventions deployed to mitigate the morbidity and mortality of endometrial cancer in the United States have mainly revolved around early detection of the disease, especially in at-risk women. Building on the Gynecological Cancer Education and Awareness Act of 2005,[14] the United States CDC promotes the Inside Knowledge About Gynecological Cancer Campaign, encouraging women, their families/friends, and their healthcare providers to pay close attention to women's bodies and to identify early warning signs.[15] These messages, from the Inside Knowledge campaign, have made at least 7 billion audience impressions since roll-out in the year 2010.

While the ACS provides (on its website) an important summary of treatment options, it appears that, in the United States, patients are left to seek and attain treatments based on their capacity, or the capacity of their friends and families. Throughout the literature, there did not appear to be a national coverage or subsidized care plan that was specific to endometrial cancers.

NEW INTERVENTIONS

A new approach worth considering in endometrial cancer management is the combination of Lenvatinib (a multi-kinase inhibitor) and Pembrolizumab (an antibody targeting programmed cell death protein 1). In a recent, much-cited study,[16] it was demonstrated that when Lenvatinib and Pembrolizumab are combined, they showed anti-tumor activity in advanced, recurrent endometrial cancer, with comparable safety profiles to the monotherapies of each drug, separately. A limitation of this new combined therapy, however, was an increased risk for hypothyroidism. This study was an open-label, single-arm, phase 2 clinical trial that was building on an earlier phase 1b study. The exposures and outcomes were very clearly elucidated in this trial, even though it was an interim analysis of a longer-duration study. In terms of efficacy and effectiveness of this combination therapy, there was documented anti-tumor activity by 24-weeks of initiation of treatment, even though treatment-related adverse events included hypertension, diarrhea, and hypothyroidism. As for generalizability, it is worthy of note that this analysis occurred based on a study that involved patients from at least 11 centers in the United States. For patients with advanced endometrial cancer with a history of recurrence, the results of this study are moderately generalizable.

POLICY IMPLICATIONS AND RECOMMENDATIONS

These policy recommendations are specific to the United States, given the scope of this review. It is highly recommended that more research studies be supported to uncover more insights about the racial disparities in endometrial cancer incidence and mortality rates. Further, strong potentials for collaboration exists between the United States Government and private biological and pharmaceutical companies, in order to subsidize screening methods, including genetic tests for Lynch syndrome. It will be worthwhile for the United States to maximize these potentials as much as possible, and to roll-out in partnership with states with documented high age-adjusted incidence rates. Other important policy implications include providing incentives to pharmaceutical companies interested in research and development for newer, safer and more effective drugs for the treatment of endometrial cancers in the

United States. Such incentives can go a long way to fast track the innovation pipeline, and advance the reach of life-saving drugs to the much-deserving population of American women.

CONCLUSION

More research is required in exploring the racial disparities in endometrial cancer incidence and mortality rates in the United States, as well as new therapies for treatments that are affordable.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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APPENDIX

Table 1: Cancer of the Corpusuteri

FIGO	Stage
I[a]	Tumor confined to the corpus uteri
IA[a]	No or less than half myometrial invasion
IB[a]	Invasion equal to or more than half of the myometrium
II[a]	Tumor invades cervical stroma, but does not extend beyond the uterusb
III[a]	Localand/orregional spread of the tumor
IIIA[a]	Tumor invades the serosa of the corpus uteri and/oradnexae'
IIIB[a]	Vaginal involvement and/or parametrial involvement'
IIIC'	Metastases to pelvic and/or para-aortic lymph nodes'
IIIC1[a]	Positive pelvic nodes
IIIC2[a]	Positive para-aortic nodes with or without positive pelviclymph nodes
IV[a]	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA[a]	Tumor invasion of bladderand/or bowel mucosa
IVB[a]	Distant metastasis,including intra-abdominalmetastases and/or inguinal nodes)