REVIEW ARTICLE

Key Words: infertility, hyperprolactinemia, antipsychotics, women's mental health

Hyperprolactinemia, Clinical Considerations, and Infertility in Women on Antipsychotic Medications

By Amber N. Edinoff, Nancy S. Silverblatt, Hayley E. Vervaeke, Cassidy C. Horton, Eden Girma, Alan D. Kaye, Adam Kaye, Jessica S. Kaye, Andrew J. Garcia, Elisa E. Neuchat, Treniece N. Eubanks, Giustino Varrassi, Omar Viswanath, Ivan Urits

ABSTRACT *~ Infertility, the inability to establish a clinical pregnancy after 12 months of regular unprotected sexual intercourse, is caused by a wide variety of both male and female factors. Infertility is estimated to affect between 8–12% of couples trying to conceive globally. Female factor infertility can be subdivided into the following broad categories: ovulatory dysfunction, fallopian tubal disease, uterine causes, and oocyte quality. Hyperprolactinemia causes ovulary dysfunction along with other hormonal abnormalities, such as decreased estrogen, which can lead to infertility. In this regard, antipsychotics are commonly used for both schizophrenia and bipolar disorder. The use of these medications can be associated with hyperprolactinemia and hyperprolactinemia associated infertility. Antipsychotic-induced hyperprolactinemia occurs through blockade of D_2 receptors on lactotroph cells of the anterior pituitary gland. Discontinuation of the hyperprolactinemia-inducing antipsychotic is an option, but this may worsen the patient's psychosis or mood. If antipsychotics are determined to be the culprit of infertility, the degree of hyperprolactinemia symptoms, length of treatment with the antipsychotic, and risk of relapse should*

Amber N. Edinoff, Nancy S. Silverblatt, Eden Girma, Louisiana State University Health Science Center Shreveport, Department of Psychiatry and Behavioral Medicine. Hayley E. Vervaeke, Cassidy C, Horton, Louisiana State University Shreveport School of Medicine. Alan D. Kaye, Treniece N. Eubanks, Louisiana State University Shreveport, Department of Anesthesiology, Shreveport, LA. Adam Kaye, Jessica S. Kaye, Andrew J. Garcia, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Department of Pharmacy Practice, Stockton, CA. Elisa E. Neuchat, Department of Biological Sciences, Florida International University, Miami, FL. Giustino Varrassi, Paolo Procacci Foundation, Via Tacito 7, Roma, Italy. Omar Viswanath, Louisiana State University Shreveport, Department of Anesthesiology, Shreveport, LA; University of Arizona College of Medicine-Phoenix, Phoenix, AZ; Valley Anesthesiology and Pain Consultants – Envision Physician Services, Phoenix, AZ. Ivan Urits, Louisiana State University Shreveport, Department of Anesthesiology, Shreveport, LA; Southcoast Health, Southcoast Physicians Group Pain Medicine, Wareham, MA.

To whom correspondence should be addressed: Corresponding Author: Dr. Amber Edinoff, Louisiana State University Health Science Center Shreveport, Department of Psychiatry and Behavioral Medicine, Shreveport, LA 71103. Phone: (318) 675-8969; E-mail: aedino@lsuhsc.edu

be assessed prior to discontinuation, reduction, or switching of antipsychotic medications. The treatment of a women's mental health and her desire to have children should always be considered as treatment may influence fertility while on the medication. Psychopharmacology Bulletin. *2021;51(2):131–148.*

Introduction

Infertility, the inability to establish a clinical pregnancy after 12 months of regular unprotected sexual intercourse, is caused by a wide variety of both male and female factors.[1] Infertility is estimated to affect between 8–12% of couples trying to conceive globally. Although male factors account for more than half of the causes of infertility, women still find themselves carrying much of the social stigma.[2] Female factor infertility can be subdivided into the following broad categories: Ovulatory dysfunction, fallopian tubal disease, uterine causes, and oocyte quality. Oocyte quality is primarily the product of a woman's age and the most powerful factor determining fertility. Most causes of non-age related female infertility fall under the umbrella of ovulatory dysfunction – examples include hypogonadotropic hypogonadism, polycystic ovarian syndrome, premature ovarian insufficiency, and hyperprolactinemia.[3] Hyperprolactinemia causes infertility via suppression of the hypothalamic-pituitary-gonadal axis. When prolactin levels are excessively high, the anterior pituitary gland will stop secreting luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This reduction in gonadotropins results in menstrual cycle dysregulation and causes a decrease in ovarian estrogen release, subsequently causing anovulation and infertility.[4] Antipsychotics induce hyperprolactinemia by blocking dopaminergic transmission in the tuberoinfundibular pathway, thus relieving the tonic inhibition of prolactin release.[4,5] One study found that 65.6% of reproductive-aged women taking typical antipsychotics developed hyperprolactinemia, making this a very significant side effect to consider when managing psychotic illness in female patients.[5] The lifetime prevalence of schizophrenia and bipolar I disorder is equal for men and women, with each disorder having a lifetime prevalence of 1%.[6,7] On the other hand, women are more likely to present with bipolar II disorder, mixed mania, and/or rapid cycling.[7] There are many unique considerations for female patients with psychosis that highlight the importance of both hormonal and social influences on disease. For example – women report mood dysfunction that fluctuates with their menstrual cycle, there are significantly increased risks of bipolar recurrence during pregnancy and postpartum, and menopause comes with more agitated depression and psychotic mood episodes.[7] Many women are diagnosed with a psychotic illness or mood disorder and may require

the use of antipsychotic medications that have implications on their fertility. However, given the propensity of typical antipsychotics to induce hyperprolactinemia (a well-described cause of hypogonadotropic hypogonadism and infertility in women) we should also consider the patient's reproductive desires.[4]

Infertility Overview

Epidemiology

The prevalence of infertility in reproductive-aged women has been estimated to be one in every seven couples in the western world and one in every four couples in developing countries.[8] In a study conducted by the National Survey of Family Growth that interviewed 12,000 women in the United States, the prevalence of infertility decreased with the increase in the woman's age.[9] As a woman gets older, her chances of infertility increases. In women aged 15 to 34 years, infertility rates ranged from 7.3 to 9.1%. In women ages 35 to 39 years old, the infertility rates increased to 25%. Lastly, women from ages 40 to 44 years had a 30% chance of infertility.[9] Worldwide, infertility rates are higher in Eastern Europe, North Africa, and the Middle East. Worldwide, 2% of women aged 20 to 44 were never able to have a live birth, and 11% with a previous live birth were unable to have an additional birth.[8] To understand infertility as a whole, the complete pathophysiology should be discussed.

Pathophysiology

Premature Ovarian Failure

Premature ovarian failure (POF), also known as primary ovarian failure, is defined as the depletion of ovarian follicles and cessation of menses before the age of 40. POF is characterized by a decrease in estrogen, lack of folliculogenesis, and loss of oocytes. The causes may be idiopathic, genetic, infectious, environmental toxins, associated with autoimmune conditions, and induced chemotherapy alkylating agents. The most common cause of POF is Turner syndrome, which results from having a single x chromosome instead of two. Spontaneous POF is not an uncommon condition; it is estimated that approximately 0.3% to 1.1% of reproductive-age women experience menopause prematurely.[10] Among women younger than 40, the incidence of POF steadily increases with advancing age. POF is recognized in 0.01% of women younger than 20, 0.1% younger than 30, and about 1% of women younger than 40.[11]

Polycystic Ovary Syndrome

The polycystic ovary syndrome (PCOS), a heterogeneous condition, is the most prevalent endocrine disorder in women, affecting 5–10% of the female population.[12] PCOS can be diagnosed using the Rotterdam criteria, requiring at least two of the following three criteria: oligoovulation or anovulation, clinical signs of hyperandrogenism, and polycystic ovaries demonstrated on ultrasound. Women with PCOS show also markedly raised Anti-Mullerian Hormone (AMH) levels due to both the increased number of small antral follicles and intrinsic characteristics of their granulosa cells, which may contribute to anovulation.[13] Obesity has been associated with exacerbated metabolic and ovulatory dysfunction related to PCOS, and weight loss has been found to restore ovulation and reduce hyperandrogenism.[14]

Endometriosis

Endometriosis is a pathological gynecological disorder defined as endometrial tissue outside of the uterine cavity. The mechanisms involved in endometriosis related infertility include anatomical distortions due to adhesions and fibrosis as well as endocrine abnormalities and immunological disturbances.[15] Of women with endometriosis, 40% to 50% will experience infertility.[16] Endometriosis is categorized into four stages, according to the American Society of Reproductive Medicine, with stage I being minimal and stage IV severe. Endometriosis is known to cause infertility, but the pathophysiology is thought to change according to the stage.[17] The estimated overall prevalence of endometriosis in population-based studies varies from 0.8% to 6%; however, in subfertile women, the prevalence seems to be considerably higher, ranging from 20% to 50%, but with significant variations over time periods and with the age of patients.[15]

Uterine Fibroids

Uterine leiomyomas are the most common benign tumor in the female reproductive tract. The actual role of fibroids on fertility is neither completely known nor understood. Several possible mechanisms have been reported on how leiomyomas may affect fertility, such as anatomical distortion of the endometrial cavity, abnormal uterine contractility, reduced blood supply to the endometrium, and altered endometrial receptivity.[18] Uterine fibroids are more prevalent in black women, and black women may have larger and higher numbers of fibroids.[19]

Pelvic and Tubal Infections

Pelvic and tubal adhesions caused by genital tract infections are most commonly responsible for a large portion of female infertility. The most common infectious process to affect female infertility is Pelvic inflammatory disease (PID). The most common infectious agent causing infertility is Chlamydia trachomatis, with the highest incidence in Hispanic patients (33.3%).[20] Neisseria gonorrhea is another pathogen that may affect the Fallopian tube.[21]

Hyperprolactinemia

Prolactin is a polypeptide hormone composed of 199 amino acids that is secreted by lactotroph cells from the anterior pituitary gland. Prolactin is also produced in adipose cells of subcutaneous, breast, and visceral tissues. Prolactin functions as a growth hormone, activating various signaling pathways upon binding their receptors and resulting in modification of gene transcription. Prolactin receptors are part of the class I cytokine receptor family, located in several organs such as the pancreas, uterus, liver, and prostate. Prolactin secretion is pulsatile, with levels rising and falling in a circadian pattern. Prolactin secretion peaks approximately 4 hours after sleep onset and reaches its nadir approximately 6 hours after waking. Prolactin secretion is also influenced by meals, stress, and sexual activity. Production of prolactin is stimulated by estrogen, while prolactin release is stimulated by serotonin binding to 5-HT_{1A} and 5-HT_2 receptors. Prolactin release is inhibited by dopamine binding to D_2 receptors on pituitary lactotroph cells. Dopamine is produced in the tuberoinfundibular neurons of the hypothalamus and is released in the median eminence. It is then transported to the pituitary via the portal hypophyseal circulation, where it binds to D_2 receptors. Stimulation of D_2 receptors on lactotrophs results in the activation of multiple signaling pathways, culminating in the modification of prolactin gene transcription, synthesis, and release from the pituitary gland. The accepted normal range of prolactin levels in both men and women is 15–25 mg/L.[5] Prolactin serum values of 25–50 ng/mL cause insufficient progesterone release from the corpus luteum, shortening the luteal phase, which may lead to infertility and manifests as hypogonadotropic hypogonadism (HH). Levels above 25 ng/mL are considered to be elevated in women.[22] Prolactin values of 50–100 ng/mL cause abnormal feedback on the hypothalamic-pituitary-ovarian axis, which results in anovulation, corresponding oligomenorrhea, or amenorrhea. Prolactin concentration greater than 100 ng/mL is most commonly

associated with pituitary adenomas. Prolonged hyperprolactinemia can cause hypoestrogenism due to his chronic suppression of GnRH, which can put women at risk for osteoporosis.[22] Physiologically, prolactin functions to facilitate breast enlargement during pregnancy and milk production during lactation.[23]

Hyperprolactinemia results in inhibition of the hypothalamic-pituitary-gonadal (HPG) axis at many levels. Prolactin inhibits both the release of GnRH from the hypothalamus and its effects at the anterior pituitary. In women, prolactin also inhibits the positive feedback mechanism of estradiol on LH release. Decreased GnRH secretion leads to diminished LH and FSH release from the anterior pituitary, ultimately resulting in decreased estrogen and testosterone secretion.

Schizophrenia

Overview

Schizophrenia is a psychiatric disorder affecting approximately 1 percent of the population. It is characterized by positive symptoms, negative symptoms, and cognitive impairment. Positive symptoms of schizophrenia include delusions and hallucinations. Negative symptoms of schizophrenia include flattening of affect, alogia, anhedonia, and avolition. Schizophrenia is also associated with social or occupational dysfunction.[24] Lasting effects of schizophrenia include chronic symptoms and disability, higher rates of unemployment, and reduced life expectancy.[25]

Epidemiology

The prevalence of schizophrenia is an estimated average of 5/1,000 in the population, based on ranges of 2.7/1,000 to 8.3/1,000. The incidence of schizophrenia is an estimated average of 0.20/1,000/year, based on ranges of 0.11/1,000/year to 0.70/1,000/year.[26] Schizophrenia occurs equally among men and women, but disease presentation is often earlier in men. Several studies are being conducted on possible risk factors for schizophrenia, including maternal stress and infection during pregnancy, socioeconomic factors, childhood adversity, immigration, cannabis use in adolescence, head injury, epilepsy, and autoimmune diseases.[25]

Presentation

Schizophrenia is associated with episodes of psychosis, often presenting in late adolescence or young adulthood. Disease onset can be acute

or preceded by a long prodromal period. This prodromal period is associated with impairments in cognition and social functioning such as social withdrawal, loss of interest in activities, abnormal behavior, and poor hygiene and grooming. Disease onset differs between males and females, with a peak onset in males between 15 and 25 years of age and a peak onset in females between 25 and 35 years of age.[27] During the disease course, the positive symptoms often relapse and remit, while negative and cognitive symptoms are more chronic and impair social functioning.[25]

Assessment

Schizophrenia is a clinical diagnosis based on a thorough history and physical and mental examination. The DSM-5 criteria for diagnosis of schizophrenia require two or more of the following symptoms present for a significant portion of time in a 1-month period: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. Other criteria for diagnosis include social or occupational dysfunction, minimum disease duration of 6 months, and exclusion of other disorders.[28] Several other disease processes can present similarly to schizophrenia, including brief psychotic disorder, delirium, delusional disorder, medical illnesses, medication-induced disorder, mood disorders with psychotic features, schizophreniform disorder, schizotypal personality disorder, and substance abuse.[24] Further assessment of schizophrenia includes neuropsychological assessment, brain imaging, genetic testing, assessment of positive and negative symptoms, assessment of suicide risk, assessment of the risk of aggression, and assessment of substance use. Schizophrenia is managed with antipsychotics, which are used to control positive symptoms and prevent relapses of psychotic symptoms.[25] Schizophrenia can be further managed with cognitive-behavioral therapy as well.

Bipolar Disorder

Overview

Bipolar disorder is a psychiatric disorder associated with mood dysregulation, especially episodes of depression and mania or hypomania. Bipolar disorder can be further characterized as type I or type II. Type I bipolar disorder is associated with at least one manic episode, while type II bipolar disorder is associated with at least one hypomanic episode and one major depressive episode. Bipolar disorder can lead to impaired functioning in relationships, a decline in cognitive abilities, and poor

performance.[29] Bipolar disorder is associated with an increased risk of death from suicide, physical illness, homicide, and accidents.[30]

Epidemiology

The prevalence of type I bipolar disorder is estimated to be 1.0%, and the prevalence of type II bipolar disorder is estimated to be 1.1%. Bipolar disorder occurs equally among men and women, but a higher prevalence of type I bipolar disorder in men and a higher prevalence of type II bipolar disorder in women has been noted. The peak onset of bipolar disorder is between 20 and 30 years of age but may present earlier or later in life. Possible risk factors for bipolar disorder include genetic factors, prenatal *Toxoplasma gondii* infection, childhood maltreatment, psychosocial stressors, and substance misuse.[31]

Presentation/ Assessment

Type I bipolar disorder is associated with episodes of mania, a period of a week or longer of an abnormally elevated or irritable mood. It can manifest as a decreased need for sleep, grandiosity, racing thoughts, risk-taking behavior, and impulsivity. Manic episodes may also present with psychotic features. Manic episodes can lead to impairment in social or occupational functioning and often requires hospitalization to manage symptoms.[30] Type II bipolar disorder is associated with episodes of hypomania, a period of approximately four days of persistently elevated, expansive, or irritable mood. Hypomania can also manifest as a decreased need for sleep, inflated self-esteem, racing thoughts, increased psychomotor activity, and increased impulsivity. Hypomanic episodes do not usually result in an impairment of social or occupational functioning and do not present with psychotic features. Type II bipolar disorder is also associated with major depressive symptoms, including sadness, hopelessness, apathy, irritability, increased sleep, hyperphagia, and psychomotor slowing. Patients with bipolar disorder often present to clinicians with symptoms of depression, which must be distinguished from major depressive disorder. Patients with bipolar disorder often have an earlier age of onset of depressive symptoms, may display mood reactivity, and may also present with increased motor activity, rapid or pressured speech, grandiosity, and delusions during depressive episodes.[32]

Management

Bipolar disorder is managed with several different medications, including mood stabilizers, antipsychotics, antidepressants, and antianxiety

medications. Mood stabilizers are used to control manic or hypomanic episodes. Mood stabilizers, however, are associated with congenital abnormalities. The use of these medications in reproductive-age females needs to weigh what the reproductive choices are at the time of treatment and any time during treatment. Documentation of the discussion of a reliable form of birth control should be noted in the chart. Antipsychotics can also be used to control episodes of mania, hypomania, or psychosis. Atypical antipsychotics are not usually related to the risk of congenital abnormalities; as such, often the decision to use these medications is based on this in reproductive-age females.[33]

Antipsychotics

Classification of Antipsychotics

Antipsychotic medications are categorized as either typical or atypical, a classic delineation based on their propensity to cause extrapyramidal side effects (EPS), i.e., drug-induced movement disorders.[34] This delineation can be attributed to each class's affinity for dopamine D_2 receptors—the widely accepted target associated with therapeutic effect and precipitation of both EPS and hyperprolactinemia.[35] Both antipsychotic classes are FDA-approved for the management of chronic psychotic disorders, such as schizophrenia, as well as the treatment of bipolar mania and acute agitation. Many considerations are made when selecting which antipsychotic is best, including efficacy in treating the patient's condition, tolerance of the side effect profile, cost, and availability.[36] Given the unique challenges faced by women with psychotic disorders, it is also prudent to consider how these medications influence menstrual cycles, hormone levels, and fertility.[6,7]

Typical Antipsychotics (TAPs)

Collectively, the TAPs (e.g., haloperidol and chlorpromazine) are high-affinity antagonists of dopamine D_2 receptors designed to treat psychosis by reducing dopaminergic transmission in the mesolimbic pathway.[35] These drugs are notably efficacious in reducing positive symptoms. Additionally, since these drugs have been on the market since the 1950s, they are considerably cheaper than the newer atypical drugs. However, their clinical efficacy and cost-benefit must be carefully weighed against their propensity to cause EPS; this includes the feared complication tardive dyskinesia, which can be irreversible.[37] These drug-induced movement disorders are mediated by a reduction in dopamine signaling in the nigrostriatal pathway and present with acute dystonia,

bradykinesia, tremor, etc.[38] Other CNS effects include sedation, slowed cognition, and neuroleptic malignant syndrome.[39] Another important consideration is the possible worsening of negative symptoms in patients with schizophrenia. Worsening apathy, anhedonia, and flat affect can be attributed to strong D_2 antagonism resulting in decreased dopaminergic signaling in the prefrontal cortex.[40] TAPs have a wide array of other unwanted side effects resulting not only from their D_2 receptor antagonism but also from their affinity for muscarinic, histaminergic, and norepinephrine receptors. Autonomic and cardiovascular effects include orthostatic hypotension, tachycardia, risk of torsade de pointes arrhythmia, dry mouth, and constipation. Hyperprolactinemia, a very common side effect attributed to D_2 receptor blockade, causes galactorrhea, amenorrhea, and anovulatory cycles in women. Antipsychotic-induced hyperprolactinemia has also been linked to decreased bone mineral density and an increased risk of breast cancer.[5] One study found that 65.6% of reproductive-aged women and 45.1% of postmenopausal women taking typical antipsychotics developed hyperprolactinemia.[5] Other special considerations for women taking TAPs include decreased libido, orgasmic dysfunction, first-trimester teratogenicity, and the ability of TAPs to be secreted in breastmilk.[39,41] Due to the possibility of EPS, atypical antipsychotics are often preferred unless the patient has a history of tolerating the side effect profile of typical antipsychotics.[35]

Atypical Antipsychotics (AAPs)

Most AAPs (e.g., clozapine, risperidone, and olanzapine) are alike in their increased affinity for serotonin $5HT_{2A}$ receptors with a relatively decreased affinity for D_2 receptors.[34] Other AAPs (e.g., cariprazine) achieve therapeutic effects via D_2/D_3 receptor antagonism along with varying degrees of serotonergic effects.[34] Evidence suggests that AAPs are more efficacious than their TAP counterparts in controlling negative symptoms, alleviating cognitive impairment, and preventing relapse, all while still maintaining a low incidence of EPS and hyperprolactinemia.[40] The unique efficacy and side effect profiles of each AAP can, in part, be explained through their pharmacokinetic properties and receptor affinities. The serotonin-dopamine antagonist theory suggests that the degree of $5HT_{2A}$ receptor affinity relative to the dopamine D_2 receptor affinity predicts each drug's tendency to cause EPS. Serotonin $5HT_{2A}$ antagonism may act to attenuate the effects of D_2 blockade in the striatum that result in EPS.[42] A more recent study concludes that, along with the degree of $5HT_{2A}$ antagonism, D_2 receptor association rate determines a drug's propensity for inducing EPS. Drugs with a fast D_2 association rate (e.g., the TAP haloperidol) are more likely to

cause EPS. Furthermore, drugs with a slow D_2 dissociation rate (e.g., the TAP chlorpromazine) are more likely to cause hyperprolactinemia. Based on this model, AAPs like clozapine exhibit a low incidence of EPS and hyperprolactinemia due to their slow D_2 association rate and fast D_2 dissociation rate, respectively.[38] However, not all AAPs have the same pharmacokinetic profile for D_2 receptors. For example, risperidone can elevate serum prolactin levels, even more than any of the TAPs.[5] Risperidone's predilection for causing hyperprolactinemia, as well as its slight risk of EPS, can be explained by its relatively high affinity for D_2 receptors compared to other atypicals.[38] Clozapine is recognized for its remarkable efficacy in reducing positive symptoms of patients with treatment-resistant schizophrenia and carrying a low risk of EPS.[34,43] The partial $5HT_{1A}$ agonism of clozapine has been linked to increased efficacy against anxiety, depression, and negative symptoms of schizophrenia with improved cognition, attributed to enhanced dopamine release in the prefrontal cortex.[42] It is also unique in its ability to decrease suicide risk in patients with schizophrenia, schizoaffective disorder, or a history of suicide attempts. However, this unique AAP also comes with a burdensome side effect profile—an increased risk of agranulocytosis necessitating frequent hematological monitoring.[34] As a group, the most common adverse effects of AAPs are weight gain, hyperglycemia, and dyslipidemia.[42] These three side effects exist on a spectrum with clozapine and olanzapine carrying the greatest risk and newer AAPs, such as ziprasidone, carrying minimal risk.[40] Unlike the TAPs, atypical drugs are non-teratogenic, and multiple studies have exhibited no increased risk of major congenital malformations.[44,45] For this reason, AAPs are preferred in reproductive-aged women. This preference should also be given over the use of lithium, carbamazepine, and valproate as mood stabilizing agents in women with bipolar disorder as they are all associated with an increased risk of major congenital malformations.[46]

Antipsychotics and Hyperprolactinemia-associated Infertility

Typical antipsychotics have been demonstrated to affect endocrine function.[47] Antipsychotic-induced hyperprolactinemia occurs through blockade of D_2 receptors on lactotroph cells of the anterior pituitary gland.[5] Increased levels of prolactin can cause decreased production and secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, resulting in decreased release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary.[5] With antipsychotic use, hyperprolactinemia can lead to reduced estrogen

levels in women and gonadal dysfunction. The resulting hypogonadotropic hypogonadism in women on antipsychotics can lead to amenorrhea, menstrual irregularities, and infertility.

Evaluation of Infertility

Prior to the discussion of hyperprolactinemia, a discussion should be had on the general workup of infertility. The evaluation of female infertility is complex, often involving assessment of ovulatory function, cervical mucus, reproductive anatomy, and peritoneal factors. A thorough menstrual and reproductive history should be obtained during the evaluation of infertility.[48] All sources of infertility should be assessed; in some women time may be of the essence to be able to make decisions regarding their reproductive health.

Evaluation of ovulatory function includes serial measurement of urinary LH and measurement of mid-luteal serum progesterone, which both assess luteal function. Urinary LH should peak at least 12 days before the onset of menses in a normal luteal phase. A serum progesterone level greater than 5 ng/mL often indicates ovulatory function, and levels ranging from 5 to 40 ng/mL are observed in a normal luteal phase. Measurement of FSH, TSH, and prolactin levels should be attained to assess for ovulatory function. An elevated FSH typically reflects primary ovarian insufficiency. An elevated TSH level suggests hypothyroidism as a potential etiology of anovulation and amenorrhea. In hypothyroidism, negative feedback to the hypothalamic-pituitary axis is lost, resulting in increased TRH release. TRH consequently stimulates the release of TSH and prolactin, which can result in hyperprolactinemia and anovulation. An elevated prolactin level reflects hyperprolactinemia and is associated with decreased levels of FSH and LH. If hyperprolactinemia is discovered, an assessment for possible hypothalamic or pituitary causes should be performed. Measurement of early follicular FSH and estradiol is used to assess the ovarian reserve of a patient. Ultrasound can be used to assess the antral follicle count and the presence of polycystic ovaries. If polycystic ovaries are observed on ultrasound, an assessment of polycystic ovarian syndrome (PCOS) should be performed. Evaluation of PCOS includes measurement of free testosterone levels, a two-hour glucose tolerance test, fasting lipid and lipoprotein levels, and the ratio of LH to FSH. A progestin challenge may be used to assess causes of amenorrhea, including PCOS, idiopathic anovulation, uterine abnormalities, or estrogen deficiency.[48]

Evaluation of cervical mucus must occur immediately prior to the preovulatory phase, on days 12 to 14 of a normal 28-day cycle. The amount of mucus and its consistency is assessed, along with its ability

to stretch. The stretch of cervical mucus is tested by touching the mucus with pH paper and lifting vertically. The mucus should stretch at least 6 cm to be considered normal. The pH of the cervical mucus is also evaluated, with normal values of 6.5 or greater. A Pap smear should be performed to assess for cellular abnormalities of the cervix, along with a wet prep to assess for cervical infections.[48]

Evaluation of reproductive anatomy includes an assessment of the uterus and fallopian tubes. The uterus is assessed through transvaginal and/or abdominal ultrasound and hysteroscopy. Uterine abnormalities contributing to infertility include large submucosal fibroids and endometrial polyps. The fallopian tubes are assessed via hysterosalpingography (HSG) or laparoscopy. The primary tubal abnormality contributing to infertility is tubal occlusion, often occurring after infection or surgery.[48]

Evaluation of the peritoneum is used to assess for endometriosis, along with any other adhesions of the reproductive system. Peritoneal evaluation occurs via laparoscopy, looking for endometrial implants, endometriomas, and adhesions. Endometriosis can impair tubal motility, obstruct the fallopian tubes, and disrupt oocyte transport to the fimbriae.[48]

Hyperprolactinemia

Physiologic causes of hyperprolactinemia include pregnancy, lactation, nipple stimulation, orgasm, and stress. Pathologic causes of hyperprolactinemia include hypothalamic and pituitary disease, drug use, and systemic diseases. Disease states associated with hyperprolactinemia include prolactin-secreting pituitary adenomas, hypothyroidism, chronic renal failure, Cushing's disease, and cirrhosis. Several medications are associated with hyperprolactinemia, including antipsychotics, antidepressants, antihypertensives, serotonergic medications, antiandrogens, estrogens, opiates, and cocaine.[5] First-generation antipsychotics are notably associated with hyperprolactinemia, but some second-generation antipsychotics also induce elevations in prolactin levels. Of the second-generation antipsychotics, risperidone and paliperidone have demonstrated evidence of inducing hyperprolactinemia.[5]

Hyperprolactinemia-associated Infertility

Hyperprolactinemia causes infertility through inhibition of GnRH release from the hypothalamus. With the loss of GnRH secretion, FSH and LH are not released from the anterior pituitary. As a result of decreased FSH, ovarian follicular development does not occur during

the follicular phase of the menstrual cycle. This also results in decreased estrogen production by the developing follicles. In the absence of an LH surge, the ovarian follicle does not rupture and release a mature ovum, resulting in anovulation. The absence of LH also results in a poorly developed endometrium that cannot support the implantation of an embryo.[49]

Antipsychotic-induced Hyperprolactinemia

Antipsychotic medications function through blockade of D_2 receptors, including those located in the mesolimbic and mesocortical areas, the striatum, and tuberoinfundibular pathway. Blockade of D_2 receptors in the mesolimbic and mesocortical regions is associated with the antipsychotic effects of these drugs, while blockade of D_2 receptors in the striatum has been demonstrated to result in drug-induced Parkinsonism. Blockade of D_2 receptors of the tuberoinfundibular pathway, especially lactotroph cells, results in the disinhibition of dopamine on prolactin secretion, which results in the increased release of prolactin from the anterior pituitary.[47]

The prevalence of hyperprolactinemia in females taking first-generation antipsychotics has been reported as 47.6%.[23] The prevalence of hyperprolactinemia in females taking risperidone, a second-generation antipsychotic, is significantly higher, reported as 88%.[23] Hyperprolactinemia has been correlated with the potency of antipsychotic medications, relative to the degree of D_2 receptor blockade achieved.[50]

Risperidone has also been demonstrated in a patient to induce pituitary hyperplasia and the development of a prolactinoma.[51] On cranial MRI, evidence of a microadenoma was visualized, with no compression of the optic chiasm or the cavernous sinus. In this patient, prolactin levels were measured to be 100.1 mg/L while on risperidone therapy. The transition from risperidone to ziprasidone therapy was initiated, resulting in a drop in prolactin level to 41.7 mg/L and regression of the prolactinoma on follow-up MRI.[51]

Antipsychotic-induced hyperprolactinemia has been demonstrated to produce estradiol levels normally found in postmenopausal women in women of reproductive age.[23] With decreased gonadotropin levels and decreased release of estrogen and progesterone from the ovaries, menstrual irregularities are common in patients with antipsychotic-induced hyperprolactinemia.[23] These irregularities include oligomenorrhea and secondary amenorrhea. This is a result of the loss of estrogen's effect on the proliferation of the endometrium, which can lead to no menses since the lining is thin. Anovulation, as a result of decreased FSH and LH levels, can result in oligomenorrhea or amenorrhea. Anovulation is

the absence of the release of an egg from an ovary. With anovulation, progesterone is not produced as there is no corpus luteum, which is produced when an egg is released from the ovary. Continued anovulation in patients with antipsychotic-induced hyperprolactinemia results in infertility since there is no egg to fertilize. The loss of estrogen also results in a thin endometrium, so even if ovulation occurs and the egg is fertilized, the lining may not support implantation. The effects of hyperprolactinemia can be multiple in its effects on female fertility.

Evaluation of Antipsychotic-induced Hyperprolactinemia

The evaluation of hyperprolactinemia begins with the measurement of prolactin levels from a fasting blood sample 2 hours after waking.[50] The evidence of a single prolactin level above the upper limit of normal, which is 25 mg/L in women, confirms a diagnosis of hyperprolactinemia.[52] Other causes of hyperprolactinemia must be excluded from the differential, including prolactinomas, hypothyroidism, chronic renal failure, and other medication use. A brain MRI should be obtained to rule out a pituitary or hypothalamic mass. Thyroid function panels should be obtained to assess for hypothyroidism, as thyrotropin-releasing hormone (TRH) can stimulate prolactin release. Renal function panels should also be obtained, as impaired renal function can lead to decreased prolactin degradation and clearance. Studies have demonstrated antipsychotic-induced hyperprolactinemia is associated with serum prolactin levels ranging from 25 mg/L to 100 mg/L, along with levels exceeding 200 mg/L with risperidone use.[52] If possible, prolactin levels measured prior to the initiation of antipsychotic therapy can establish a baseline prolactin level and be used to evaluate for changes with treatment.

Management of Antipsychotic-induced Hyperprolactinemia and Infertility

Management of diagnosed antipsychotic-induced hyperprolactinemia and subsequent infertility involves assessment of several factors, including the degree of hyperprolactinemia symptoms, duration of secondary amenorrhea in premenopausal patients, length of treatment with the antipsychotic, degree of benefit gained from the antipsychotic, and risk of relapse if the antipsychotic is discontinued, reduced, or switched.[23] Discontinuation of the hyperprolactinemia-inducing antipsychotic is an option, but this may worsen the patient's psychosis or mood. If discontinuation of the antipsychotic is not feasible, reduction in the dose can be attempted. The antipsychotic can also be changed to a prolactin-sparing antipsychotic, such as olanzapine, quetiapine, ziprasidone, aripiprazole,

and clozapine.[50] The addition of a hormonal contraceptive can be used to replace estrogen, regulate menstrual cycles, and prevent osteoporosis. The risks associated with hormonal contraceptive use include thromboembolism and breast cancer. Contraindications to the use of hormonal contraceptives include cigarette smoking in women over 35 years of age, history of thromboembolic events, and migraine with aura though the risks must be weighed with expected benefits.[53] A dopamine agonist, such as cabergoline and bromocriptine, may be initiated to reduce the prolactin level directly. The use of dopamine agonists must be weighed against the risk of worsening psychosis in these patients.[5] The worsening of psychosis stems from the increase of dopamine. It is important to continually monitor the prolactin level during the transition to alternative treatment options to assess for improvement.[5]

Conclusion

Infertility is associated with several pathologies, and although antipsychotics may play a role, it is important to work up infertility appropriately and investigate thoroughly to determine the etiology. As mentioned before, antipsychotics are approved therapies for the management of chronic psychotic disorders, such as schizophrenia, bipolar mania, as well as acute agitation. The decision to use antipsychotics in the treatment of bipolar disorder could stem from the fact that most mood stabilizers have teratogenic effects. While treating these disorders, it is important to determine the best antipsychotic and also taking into consideration the patient's tolerance to the different side effect profiles, especially if one is considering conception. While antipsychotics provide its therapeutic effect by primarily targeting D_2 receptors, these medications may consequently block similar receptors on lactotroph cells of the anterior pituitary gland, causing hyperprolactinemia. This increase in prolactin inhibits the production of estrogen and testosterone, ultimately resulting in hypogonadotropic hypogonadism. Women taking antipsychotics are at risk for amenorrhea, menstrual irregularities, and infertility, while men with antipsychotic use may lead to gonadal dysfunction and infertility. If antipsychotics are determined to be the culprit of infertility, the degree of hyperprolactinemia symptoms, length of treatment with the antipsychotic, and risk of relapse should be assessed prior to discontinuation, reduction, or substitution of the antipsychotic medication. If infertility is of utmost concern, discontinuation of the hyperprolactinemia-inducing antipsychotic medication may be an option, although there is a risk of relapsing psychosis. If there is a concern for worsening psychosis, reduction of the antipsychotic dose may be attempted or can also be changed to a prolactin-sparing antipsychotic. Although antipsychotics

have a known tendency to cause hyperprolactinemia, possibly leading to infertility, it is important to discuss the patient's reproductive desires to provide the most efficacious antipsychotic without a side effect profile that may affect their fertility. ✤

References

1. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The International Glossary on Infertility and Fertility Care, 2017. *Fertil Steril*. Elsevier Inc.; 2017;108:393–406.
2. Inhorn MC, Patrizio P. Infertility around the globe: New thinking on gender, reproductive technologies and global movements in the 21st century. *Hum Reprod Update*. 2014;21:411–426.
3. Hart RJ. Physiological aspects of female fertility: Role of the environment, modern lifestyle, and genetics. *Physiol Rev*. American Physiological Society; 2016;96:873–909.
4. Kaiser UB. Hyperprolactinemia and infertility: New insights. *J Clin Invest*. 2012;122:3467–3468.
5. Bostwick JR, Pharm D, Guthrie SK, Pharm D, Ellingrod VL, Pharm D. Antipsychotic-Induced Hyperprolactinemia. *Pharmacotherapy*. 2009;29:64–73.
6. Seeman M V. Women and psychosis. Women's Heal. 2012. p. 215–24.
7. Sit D. Women and bipolar disorder across the life span. *J Am Med Womens Assoc*. 2004. p. 91–100.
8. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. *PLoS Med*. 2012;9.
9. Infertility and impaired fecundity in the United States, 1982–2010: data from the National Survey of Family Growth—PubMed.
10. Luborsky JL, Meyer P, Sowers MF, Gold EB, Santoro N. Premature menopause in a multi-ethnic population study of the menopause transition. *Hum Reprod*. Oxford University Press; 2003;18:199–206.
11. Incidence of premature ovarian failure—PubMed.
12. Franks S. Polycystic ovary syndrome in adolescents. *Int J Obes (Lond);* 2008. p. 1035–1041.
13. Dewailly D. Diagnostic criteria for PCOS: Is there a need for a rethink? *Best Pract Res Clin Obstet Gynaecol*. Bailliere Tindall Ltd; 2016. p. 5–11.
14. Crosignani PG, Colombo M, Vegetti W, Somigliana E, Gessati A, Ragni G. Overweight and obese anovulatory patients with polycystic ovaries: Parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. *Hum Reprod*. Oxford University Press; 2003;18:1928–1932.
15. Tanbo T, Fedorcsak P. Endometriosis-associated infertility: aspects of pathophysiological mechanisms and treatment options. *Acta Obstet Gynecol Scand*. Wiley-Blackwell; 2017. p. 659–667.
16. Prescott J, Farland L V., Tobias DK, Gaskins AJ, Spiegelman D, Chavarro JE, et al. A prospective cohort study of endometriosis and subsequent risk of infertility. *Hum Reprod*. Oxford University Press; 2016;31:1475–1482.
17. Macer ML, Taylor HS. Endometriosis and Infertility. A Review of the Pathogenesis and Treatment of Endometriosis-associated Infertility. *Obstet Gynecol Clin North Am*. 2012. p. 535–549.
18. Leiomyomas and infertility—PubMed.
19. Jacoby VL, Fujimoto VY, Giudice LC, Kuppermann M, Washington AE. Racial and ethnic disparities in benign gynecologic conditions and associated surgeries. *Am J Obstet Gynecol*. 2010. p. 514–521.
20. Smith PB, Phillips LE, Faro S, McGill L, Wait RB. Predominant sexually transmitted diseases among different age and ethnic group of indigent sexually active adolescents attending a family planning clinic. *J Adolesc Heal Care*. Elsevier; 1988;9:291–295.
21. Mitchell C, Prabhu M. Pelvic inflammatory disease: Current concepts in pathogenesis, diagnosis and treatment. Infect. *Dis Clin North Am Infect Dis Clin North Am*; 2013. p. 793–809.
22. Majumdar A, Mangal NS. Hyperprolactinemia. *J Hum Reprod Sci*. Wolters Kluwer—Medknow Publications; 2013. p. 168–175.
23. Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: Mechanisms, clinical features and management. *Drugs*. Springer; 2004. p. 2291–314.
24. Schultz SH, North SW, Shields CG. Schizophrenia: A Review Am Fam Physician. 2007 Jun.
25. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. *Lancet*. Lancet Publishing Group; 2016. p. 86–97.
26. Messias EL, Chen CY, Eaton WW. Epidemiology of Schizophrenia: Review of Findings and Myths. *Psychiatr Clin North Am*. 2007. p. 323–338.
27. Mura G, Petretto DR, Bhat KM, Carta MG. Schizophrenia: from Epidemiology to Rehabilitation. *Clin Pract Epidemiol Ment Heal*. Bentham Science Publishers Ltd.; 2012;8:52–66.
28. Gaebel W, Zielasek J. Schizophrenia in 2020: Trends in diagnosis and therapy. *Psychiatry Clin Neurosci*. 2015;69:661–673.

29. Young AS, Fristad MA. Bipolar Disorder. *Encycl Ment Heal Second Ed*. Elsevier Inc.; 2016. p. 178–82.
30. Hirschfeld RMA. Screening for bipolar disorder. *Am J Manag Care*. 2007;13:164–169.
31. Rowland TA, Marwaha S. Epidemiology and risk factors for bipolar disorder. *Ther Adv Psychopharmacol*. SAGE Publications; 2018;8:251–269.
32. Hirschfeld RM. Differential diagnosis of bipolar disorder and major depressive disorder. *J Affect Disord*. Elsevier B.V.; 2014. p. S12–S16.
33. Ayano G. Bipolar Disorder: A Concise Overview of Etiology, Epidemiology Diagnosis and Management: Review of Literatures. *SOJ Psychol*. Symbiosis Group; 2016;1–8.
34. Meltzer HY. Update on typical and atypical antipsychotic drugs. *Annu. Rev. Med*. 2013. p. 393–406.
35. Miyamoto S, Miyake N, Jarskog LF, Fleischhacker WW, Lieberman JA. Pharmacological treatment of schizophrenia: A critical review of the pharmacology and clinical effects of current and future therapeutic agents. *Mol. Psychiatry*. Nature Publishing Group; 2012. p. 1206–1227.
36. Mortimer AM. How do we choose between atypical antipsychotics? The advantages of amisulpride. *Int J Neuropsychopharmacol*. 2004.
37. Lieberman JA, Scott Stroup T, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1209–1223.
38. Sykes DA, Moore H, Stott L, Holliday N, Javitch JA, Robert Lane J, et al. Extrapyramidal side effects of antipsychotics are linked to their association kinetics at dopamine D_2 receptors. *Nat Commun*. 2017;8.
39. Casey DE. The relationship of pharmacology to side effects. *J Clin Psychiatry*. Physicians Postgraduate Press, Inc.; 1997;58:55–62.
40. Aringhieri S, Carli M, Kolachalam S, Verdesca V, Cini E, Rossi M, et al. Molecular targets of atypical antipsychotics: From mechanism of action to clinical differences. *Pharmacol Ther*. Elsevier Inc.; 2018. p. 20–41.
41. Arana GW. An overview of side effects caused by typical antipsychotics. *J Clin Psychiatry*. Physicians Postgraduate Press, Inc.; 2000. p. 5–13.
42. Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for schizophrenia: A critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Mol Psychiatry*. Nature Publishing Group; 2005. p. 79–104.
43. Kane J, Honigfeld G, Singer ; Jack, Meltzer H. Clozapine for the Treatment-Resistant Schizophrenic A Double-blind Comparison With Chlorpromazine. *Arch Gen Psychiatry*. 1988;789–796.
44. Cohen LS, Viguera AC, Mcinerney KA, Freeman MP, Sosinsky AZ, Moustafa D, et al. Reproductive Safety of Second-Generation Antipsychotics: Current Data From the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. *Am J Psychiatry*. 2016;173:263–270.
45. Huybrechts KF, Hernández-Díaz S, Patorno E, Desai RJ, Mogun H, Dejene SZ, et al. Antipsychotic use in pregnancy and the risk for congenital malformations. *JAMA Psychiatry*. 2016;73:938–946.
46. Clark CT, Wisner KL. Treatment of Peripartum Bipolar Disorder. *Obstet Gynecol Clin North Am*. W.B. Saunders; 2018. p. 403–417.
47. Smith S. Effects of antipsychotics on sexual and endocrine function in women: Implications for clinical practice. *J Clin Psychopharmacol*. 2003;23:27–32.
48. Hacker N, Gambone J, Hobel C. Hacker & Moore's Essentials of Obstetrics & Gynecology. 6th ed. Philadelphia: Elsevier; 2016.
49. Shibli-Rahhal A, Schlechte J. Hyperprolactinemia and infertility. *Endocrinol Metab Clin North Am*. Elsevier Inc; 2011;40:837–846.
50. Halbreich UM, Kahn LS. Hyperprolactinemia and Schizophrenia: REGULATION. *J Psychiatr Pract*. 2003;9:344–353.
51. Arcari G, Mendes A, Sothern R. A Risperidone-Induced Prolactinoma Resolved when a Woman with Schizoaffective Disorder Switched to Ziprasidone: A Case Report. *Innov Clin*. Neurosci. 2012.
52. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and treatment of hyperprolactinemia: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2011. p. 273–288.
53. Joffe H. Reproductive Biology and Psychotropic Treatments in Premenopausal Women With Bipolar Disorder. *J Clin Psychiatry*. Physicians Postgraduate Press, Inc.; 2007 Aug.