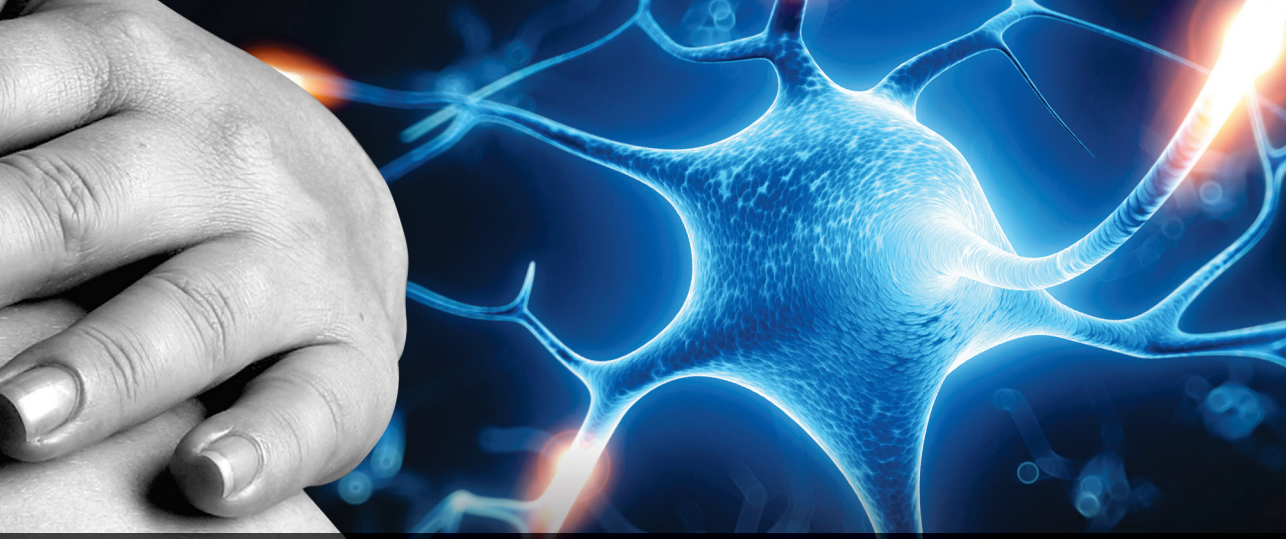

NEUROLOGICAL ILLNESS IN PREGNANCY

PRINCIPLES AND PRACTICE

Edited by

Autumn Klein

M. Angela O'Neal

Christina Scifres

Janet F. R. Waters

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WILEY Blackwell

Neurological illness in pregnancy

Principles and practice

This book is dedicated to Autumn Klein's daughter, Cianna.

Neurological illness in pregnancy

Principles and practice

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Preface

Dr. Autumn Klein

The creation of this textbook was initiated by Dr. Autumn Klein, a pioneer of women's neurology. She developed the format and carefully chose the authors from an elite group of specialists from across the United States and abroad. She unexpectedly passed away on April 17, 2013, before the completion of the book. In her memory, the authors of the book chose to complete the textbook as a legacy to her passion for the field of women's neurology.

Dr. Klein began her education by studying gender and neuroscience at Amherst College where she earned her BA magna cum laude. She went on to obtain a PhD in neuroscience and an MD from Boston University School of Medicine. After an internship in internal medicine at Brown University, she completed her residency in the Harvard Neurology Residency Program at Brigham and Women's Hospital and Massachusetts General Hospital, where she served as chief resident in her final year.

She completed a fellowship in clinical neurophysiology and epilepsy and then went on to establish the Division of Women's Neurology at Brigham and Women's Hospital. She subsequently moved to Pittsburgh where she founded the Division of Women's Neurology within the Departments of Neurology and Obstetrics at the University of Pittsburgh. From its inception, Dr. Klein served as the chief of this unique subspecialty of neurology. The division served and continues to serve as an interdisciplinary program bridging neurology with obstetrics, gynecology, and women's medicine. It focuses on gender differences in medical evaluation, diagnosis, and implementation of treatment and care. In addition to the creation of this division, she created an epilepsy monitoring unit for the treatment of pregnant women with epilepsy.

Autumn is fondly remembered for her selfless devotion to the patients for whom she cared. She made herself available for consultation on obstetrical patients 24/7. It was always

reassuring to have her respond to an unexpected neurologic event. She educated her patients about their neurologic disease and about what to expect during pregnancy and motherhood. She collaborated extensively with obstetricians, anesthesiologists, and epilepsy staff to provide comprehensive patient care. With this first edition of *Neurological Illness in Pregnancy*, we hope that Autumn's vision will be fulfilled and that it will create a legacy that carries on for generations to come.

M. Angela O'Neal
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CHAPTER 1
The history and examination

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Introduction

The focus of this chapter will be on the information most helpful to understand, counsel, and treat female neurology patients in their reproductive years. The key elements of the neurologic history and examination will be systematically reviewed with emphasis on gender differences. It will conclude with a few clinical cases. The goal is to enable neurologists to develop the knowledge and skills to maximize care for their female patients with regard to family planning and pregnancy. The objective of this chapter is to help physicians to perform a history and examination that focuses on and identifies the specific family planning concerns of the female patient and how these concerns relate to their neurologic disease.

Many common neurological diseases preferentially affect young women. How we, as neurologists, approach treatment depends on our patients' needs at that point in her life cycle. This is different for each disease process.

Migraine is a very common disorder with lifetime prevalence in women of up to 25%. Because of hormonal influences, the ratio of affected women over men is 3:1 [1]. The history should include usual triggers, of which menses and ovulation are common. Birth control pills (BCPs) have a variable influence on migraine frequency and in some women may aggravate the disorder [2]. However, many women with menstrual headaches report that cycle suppression (which can be obtained using the subdermal implant, injectable contraception, a pill, patch, or ring) improves their symptoms. The type of migraine is important when discussing contraception. Women with classic migraines should be counseled to avoid estrogen-containing contraceptives (e.g., the pill, patch, or ring), given the increased risk of ischemic stroke. However, common migraine does not preclude use of estrogen-containing contraceptives unless associated with other cerebrovascular risk factors such as an underlying hypercoaguable state. [3] Furthermore, when choosing medications (abortive or prophylactic), you should take into account, whether the woman are trying to get pregnant, or, if not trying to conceive, what birth control they are utilizing. For instance, topiramate in doses above 200 mg/day may reduce the effectiveness of oral contraceptives [4]. Does the patient have regular menses? Could she have polycystic ovarian syndrome? If so, Valproate would not be a good choice as a prophylactic medication [5]. Another concern with patients already predisposed to obesity is that many prophylactic medications can contribute to weight gain.

Multiple sclerosis is another example of a neurologic disease that affects women in their childbearing years [6]. Many of these patients are on an immunomodulatory medication. Interferons are pregnancy class C, copaxone pregnancy class B, and methotrexate a pregnancy class D medication. Because immunomodulatory

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medications are not recommended during pregnancy, birth control should be discussed if the woman is not planning pregnancy. What should we recommend to our patients who would like to become pregnant? [7] They should discontinue their immunomodulatory medication when they discontinue their hormonal or intrauterine contraceptive, as the only contraceptive that typically delays return to fertility is depot medroxyprogesterone acetate. They should be counseled that pregnancy does not worsen overall MS disability [8] Treatment needs to be appropriately adjusted to best address our patient's needs at each particular point in her life cycle.

Past medical history

Patients' medical background allows us to frame a more accurate diagnosis for their current complaints. The disorders from which women suffer are different from those that affect men. A woman's reproductive desire adds an additional layer of complexity. The medical illnesses more common in women influence which is the most probable neurologic disorder. The following is a brief snap shot of some of the disorders that are more prevalent or occur exclusively in women and how that shapes their care.

The psychiatric problems of depression, anxiety, and borderline personality disorder are more frequent in women [9, 10]. Thus, their neurological problems may be a consequence of somatization, conversion, or have an overlay due to these conditions. These women are at risk for over testing and noncompliance, as well as poor maternal weight gain, poor infant bonding, substance abuse, and postpartum depression [11, 12]. The medications we choose need to take these factors into account.

Autoimmune disorders also affect women more frequently. They may have neurologic complications directly due to their rheumatologic problem, like lupus flares [13, 14]. In addition, their neurologic problem may be due to a result of an underlying hypercoaguable state or as a consequence of their immunosuppressant medications. The recommendations and concerns for these women during pregnancy are highly specialized.

Cardiovascular concerns are important though they are uncommon in premenopausal women. Although estrogen before the menopausal transition is likely protective against cardiovascular disease, we cannot ignore women with a strong family history of vascular disease especially if associated with other risk factors such as tobacco use and migraines [15]. These women do suffer from cardiovascular complications and need advice about risk factor modification. Women with congenital or acquired cardiac disease will need specialized care to appropriately manage the physiologic changes that occur during pregnancy and labor.

An obstetrical and lactation history is extraordinarily important. The number of pregnancies, the gestational stage of the current pregnancy, and the history of either planned or spontaneous abortions predict which obstetrical and neurological diseases are most likely. These factors also determine how, if necessary, to image and what medications are appropriate. For instance, the association with antiphospholipid antibody syndrome and spontaneous miscarriages is well established [16]. A history of eclampsia should be sought. There is good evidence that prior eclampsia predicts eclampsia in future pregnancies as well as increases risk of future maternal hypertension [17, 18]. Other obstetrical issues such as preterm premature rupture of membranes and placenta previa should be asked about directly as these patients are predisposed for recurrence in future pregnancies [19]. A woman with a history of recurrent fetal loss needs an obstetrical referral to help planning/monitoring in future pregnancies.

Bone health is often neglected. The medications we choose should reflect this concern [20]. In addition, many neurologic patients' disability may limit weight bearing [21]. It is

Table 1.1 Drugs that may have adverse effects on bone metabolism

Anticoagulants
Warfarin
Cyclosporine
Steroids
Medroxyprogesterone acetate
Vitamin A and synthetic retinoids
Loop diuretics
Antiepileptic drugs
Phenytoin
Carbamazepine
Phenobarbital
Chemotherapeutic drugs
Aromatase inhibitors
Methotrexate
Ifosfamide
Imatinib
Proton pump inhibitors
Antidepressants
Selective serotonin reuptake inhibitors (SSRIs)
Tricyclics
Thiazolidinediones
Antiretroviral therapy

important to be aware of the effects of medication on bone health; as the long-term use of many medications increase the risk of osteoporosis [22] (see Table 1.1). Examples of commonly used medications that promote bone loss include the anticonvulsants, phenytoin, and carbamazepine. Counseling about the benefits of exercise as well as recommending daily calcium and vitamin D intake is helpful to avoid these complications.

A history of an underlying hypercoaguable disorder is an extremely important historical data in pregnancy planning. During pregnancy there is an increase in factors I, II, VII, VIII, IX, and X as well as a decrease in protein S. The net result is that normal pregnancy is a hypercoaguable state. If a woman has a preexisting hypercoaguable disorder, her chance of having a clotting complication is high and anticoagulation during her pregnancy should be recommended [23].

Surgeries such as those involving the lower spine may make epidural anesthesia more challenging or complicated. For example, a lumbar peritoneal shunt depending on the location may preclude an epidural. Other patients with severe scoliosis, obesity, or lumbar fusion may make neuroaxial anesthesia challenging. A personal or family history of anesthetic complications is an additional historical piece to be obtained. A prior history of postdural headache should be inquired about as this increases a patient risk for recurrence [24]. Anything that would make the patient at risk for anesthesia should warrant an early consult to an obstetrical anesthesiologist.

Medication considerations

Contraception is a topic that neurologists tend to neglect. It is important to provide patients with recommendations on which contraception options are most appropriate. The most effective contraceptives are the subdermal implant and intrauterine contraceptives, which have been estimated to be 20 times as effective as oral contraceptives and surgical sterilization. There is a myriad of contraceptive choices and they are generally chosen due to personal preference, efficacy, and safety. In our patients, efficacy may be affected by medication interactions (e.g., topiramate) or at times disability. For instance, young women whose disability involves the spinal cord may not be good candidates for certain barrier methods of contraception due to difficulty in positioning or with peroneal sensory loss. In other women, certain types of contraception are contraindicated by safety concerns. For women who have had a stroke, significant cardiovascular risk factors, an underlying hypercoaguable state, and migraine with aura, combined estrogen-containing pills, patch, or ring are not recommended [3]. However, progestin-only methods including the subdermal implant, intrauterine contraceptive, the injectable contraceptive,

or progestin-only pills (e.g., Micronor) are safe.

When choosing to prescribe medications to women of childbearing age, it is important counsel the patient on risks and benefits of treatment. We are prescribing medications to young women who may or may not be planning on pregnancy at the time of consultation. Knowledge of the pregnancy class of the medication prescribed and what that means to your patient is essential in order to counsel them on the risks of taking that medication during pregnancy and what to do with the medication if they get pregnant. The Mother to Baby website (www.mothertobaby.org) and hotline is a useful source for information on medication use during pregnancy; free information on medication use during lactation is available from Lactmed (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT). Is there any influence of the medication on their method of birth control? Should they be taking higher doses of folate (e.g., 5 mg/day)? The potential effect of *in vitro* fertilization on the underlying neurological disease may need to be discussed especially for women with migraines [25]. The effects of medication on the long-term gender-specific health issues such as weight and bone health should also be considered.

The issues around fertility are complex. What are the potential risks of fertility treatment? Are there alternatives? The available options for these women require discussion, planning, and individualization for best care. A number of medications may affect fertility. The mechanisms are diverse, but weight gain is the most common. Additional weight contributes to the metabolic syndrome and polycystic ovarian syndrome. In addition, to weight gain, valproate may also influence androgen levels making contraception more problematic [26]. It has also been associated with neural tube defects. Therefore, if there is a reasonable alternative medication that controls the neurological disorder in women of childbearing age that would be preferred.

Family history and genetics

Family history is a critical component to the history. It tells us which disease processes are likely, so we can appropriately screen and counsel patients to minimize risk. Women with a strong family history of coronary artery disease, hypertension, or diabetes need to be made aware of increased risk of vascular disease associated with obesity, sedentary life style, smoking, and estrogen. Pregnancy may add to risk factors.

Do they have a genetic disorder? What is the mode of inheritance? Is there a reliable genetic test? These are important factors to help women make informed decisions about pregnancy. The more information the patients have the better equipped they are to make appropriate choices. It is a mistake to assume a patient understands the disease, simply because it runs in their family. For example, a young woman presented to clinic with a family history of maternal Huntington's disease. Her mother had tested negative. She did not understand that she was not at risk for inheriting the disorder. Knowledge is a powerful tool.

Habits

The habits (good and bad) that women employ before and during pregnancy affect their cardiovascular risk. During pregnancy, these risks are magnified. Moreover, it is hard to over emphasize the benefits of exercise on managing stress, weight, depression, and sleep. The effects on heart and brain health are well documented. Barriers for routine monitoring including health screening like mammograms and Pap smears need to be recognized. These may be cultural, socioeconomic, or driven by the patient's disability. For example, consider a patient with multiple sclerosis who attempted to obtain a gynecologic examination. If she is paraplegic, she may be unable to transfer onto her internist's examination table.

Review of systems

A review of systems there should include special attention to a number of issues for female patients. Are they at their ideal weight? Has there been weight loss or gain? Their weight influences their risks, as well as what medications should be chosen or avoided. Obesity increases the risk for gestational diabetes, hypertension, and eclampsia [27–29]. Irregular menses may indicate an underlying hormonal imbalance, influence fertility, and determine which medications are most appropriately employed. Menorrhagia and iron deficiency are common problems in young women that can be effectively treated with use of the levonorgestrel-containing intrauterine system. Iron deficiency is often compounded during pregnancy exacerbating conditions such as restless leg syndrome. Breast masses or discharge are key elements/components that deserve to direct query of our female patients.

Examination

Gender does not affect the neurologic examination. The areas on which to focus are determined by the patient's history. The history of the present illness, medical background, and physiologic state of the woman allows the physician to generate a list of the most likely possibilities. The findings on examination help to narrow and/or confirm this differential. The most important elements of the medical examination include blood pressure and weight. The other necessary pieces of the medical examination are patient-specific and dependent on the history.

Cases studies

Below are vignettes that demonstrate the importance of a gender-based history and how this will guide a therapeutic approach. These cases are based on actual patients.

Case 1

A 24-year-old woman comes in for evaluation of her headaches. She has two kinds of headaches. The first is a daily constant aching headache worst at the end of the day. It is aggravated by stress and is associated with bilateral neck pain. This headache has been present for past 1 year, but worse over the last several months. She takes acetaminophen or ibuprofen about six tablets of either everyday for this headache.

The second headache is hemicranial throbbing and much more severe. She has nausea, rare vomiting, and light sensitivity with this headache. She denies any other symptoms. During this headache she has to lie down. The frequency varies from one to three times a month. It occurs always 1–2 days prior to her menses. She has noted that red wine can trigger it. The headache lasts usually 1 day. These headaches began in her teens. Her mother and sister have similar headaches. She has never been treated for her headaches.

Her past medical and surgical history is unremarkable.

Medications include: acetaminophen prn, ibuprofen prn

She drinks four to six caffeinated beverages a day.

She recently stopped her oral contraceptives as she wants to become pregnant.

Pertinent social history is that she is engaged to be married in 2 months. They are planning on starting a family as soon as possible. She has no history of tobacco use, alcohol use, or illicit drugs, but she does not exercise on a regular basis.

Her family history is positive for migraine in mother and sister. In addition, her mother and an aunt had breast cancer.

On review of systems she endorses the following: She has lost ten pounds over the last 2 months. She has regular menses and normal breasts; she has not had an obstetrics and gynecology (OB/GYN) examination for 2 years. Her sleep is poor with difficulty falling asleep. She says she has been quite anxious about her upcoming wedding.

The history is consistent with a diagnosis of chronic daily headaches of the tension type and common migraine. Her triggers, factors that are provoking her headaches, and her desire to conceive all frame the therapeutic approach. In this case, education about analgesic rebound, overuse of caffeine, and poor sleep will need to be addressed. Stress management including a regular exercise program and its importance and relation to headache and sleep. She needs education on which medications are considered safe in pregnancy and the importance for women with a family history of breast cancer to have regular examinations. Prophylactic medication is less appropriate as she is actively trying to conceive. Abortive therapy may be an option, providing the medication is not contraindicated during pregnancy, it is also important to avoid the potential pitfall of analgesic rebound.

Case 2

A 28-year-old woman gravida 7 para 3, 24 weeks pregnant with chronic hypertension comes in for evaluation of headaches. The headache began 3 weeks ago. They were initially intermittent, but over the last 10 days they have become constant. They are worse in the morning or if she coughs. She has no clear relieving factors. Her blood pressure has not been well controlled with systolic pressures recorded as high as 220. Her labetalol was increased and her blood pressures have improved. They have been running around 140–150/90. Over the last week, she has been having blurred vision and worsening headache. Over the last 2 days, she has noted some double vision with the images side by side. The diplopia is worse when she looks far away and while watching television. She denies any other neurologic problems. She does not usually suffer from headaches. She underwent a 24-hour urine protein which was normal, suggesting that preeclampsia was not the source of her headache. CBC including platelet count was normal. Liver enzymes were also normal. She had a brain MRI and MR venogram 10 days ago which were normal.

Her past medical history is remarkable for hypertension, renal stone, history of requiring a nephrostomy tube during her last pregnancy, and a history of herpes simplex virus

She is taking multivitamins and labetalol only.

Her review of systems is notable for weight gain of 30 pounds since the start of the pregnancy. She has no diabetes and no sleep problems.

The history is concerning for elevated intracranial pressure causing a sixth nerve palsy in the second trimester of pregnancy with a 30 lb. weight gain. Of note is that she had recent normal imaging. She had gained a significant amount of weight which makes idiopathic intracranial hypertension (IIH) a concern. The hypercoaguability associated with pregnancy causing cerebral venous thrombosis is also in this differential, but less likely given her normal venogram. Neurologic consequences of hypertension such as stroke (ischemic or hemorrhagic) are unlikely given her history and normal imaging studies. Posterior reversible encephalopathy syndrome would also be less likely given her history of worsening headache with improved blood pressure control. On examination, her blood pressure was 120/90. Her weight was 205 lbs. and height 61 inches. The neurological examination confirmed a left sixth nerve palsy and papilledema. A repeat brain MRI and MR venogram was done. The MR venogram was normal. The repeat brain MRI showed dilatation of the subarachnoid space around the optic nerve sheath a finding seen in IIH (Figure 1.1) Her CSF opening pressure was 550 mm. The testing confirms a diagnosis of IIH.

These cases illustrate how to individualize the history in order to consider gender differences and allow us to better treat our female patients. It is important to anticipate our patient's risks for disease based on their genetic makeup, lifestyle choices, and preexisting medical conditions. In this setting, clinicians must also be aware of the patient's desires for conception present and future. This will allow our patients to achieve their life goals with minimal health risk.

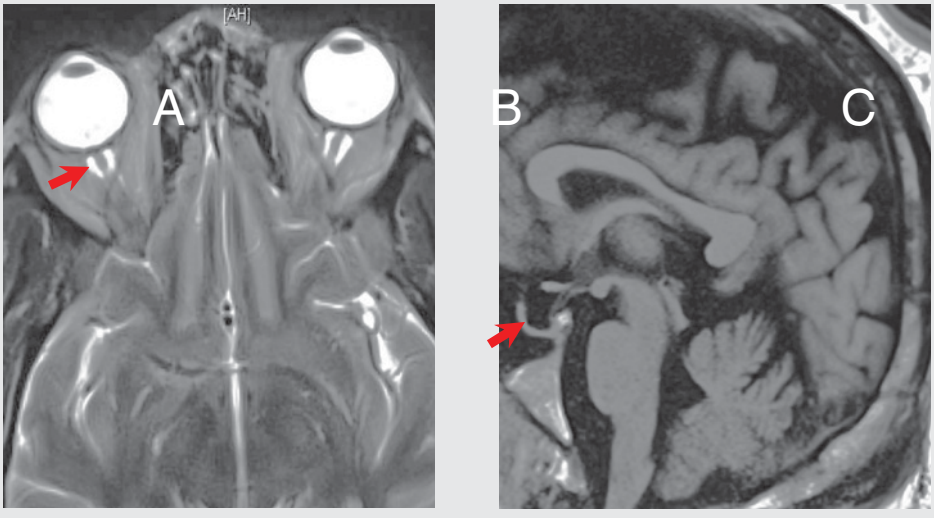

Figure 1.1 The axial T_2 image on the left shows dilatation of the subarachnoid space around the optic nerves. On the right is a sagittal T_1 image depicting an empty sella.

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CHAPTER 2

Hormonal and physiologic changes in pregnancy

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Physiologic and endocrine changes are necessary to support the growth and health of the fetus during pregnancy and to assure the health of the mother up to and beyond delivery. Copious production of polypeptide and steroid hormones by the fetal/placental unit produces physiologic adaptations of virtually every maternal organ system [1]. This chapter will review what is currently understood about the flood of hormonal changes that occur in the various phases of pregnancy.

Embryology

At 3–4 weeks gestation, in the absence of a Y chromosome, the gonad begins to form an ovary. Primordial germ cells proliferate and migrate through the dorsal mesentery reaching the gonadal ridge at 6 weeks gestation. These premiotic cells continue to proliferate and are referred to as oogonia. At 10–12 weeks, some oogonia begin meiosis and arrest in prophase I and become primary oocytes. By 16 weeks, primordial follicles develop and by 20 weeks a peak of 6–7 million germ cells are formed. During the second half of gestation, atresia leads to reduction in the number of oocytes to 1–2 million at birth. No further oocytes develop after birth and follicular atresia continues throughout childhood. Most girls will enter puberty with 300,000 to 400,000 oocytes in their ovaries [1].

Menstrual cycle

The menstrual cycle is produced through complex hormonal feedback loops involving the ovary and the hypothalamic–pituitary axis. There are two phases that occur in the ovary during the menstrual cycle: the follicular phase and the luteal phase. The endometrium undergoes three phases that are triggered by hormones produced in the ovary. These phases include the proliferative phase, secretive phase, and degenerative phase. During the ovarian follicular phase, the ovary secretes estradiol that stimulates proliferation of the endometrium, which lines the uterus. At the beginning of the menstrual cycle, the endometrium is thin but as ovulation nears, estrogen stimulates growth and enhanced blood supply. After ovulation, the ovary secretes progesterone which inhibits further endometrial proliferation. During the luteal phase, progesterone stimulates endometrial changes that cause it to be more edematous as a result of increased capillary permeability. Endometrial cells enlarge and produce prostaglandins that play an important role in implantation, pregnancy, and menstruation. This endometrial stage is known as the secretory phase. If implantation does not occur, the endometrium enters the degenerative phase. Estrogen and progesterone withdrawal leads to prostaglandin production leading to endometrial ischemia and reperfusion

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injury. The endometrium becomes necrotic and sloughs away. Blood loss can vary from 25 to 60 mL [1].

If conception occurs, implantation takes place in the mid-portion of the secretary phase of the endometrium, and the luteal phase of the ovary. The embryo invades the uterus 8 to 10 days after ovulation and fertilization. The syncytiotrophoblast secretes human chorionic gonadotropin (hCG) which preserves the corpus luteum and maintains production of progesterone and other hormones to allow the development of the decidua, the endometrium of pregnancy.

Hormonal changes in pregnancy

Ovarian hormones of the corpus luteum

The corpus luteum produces several hormones that are crucial to maintaining pregnancy in the first 6 weeks of gestation. Hormones produced include estradiol, progesterone, 17-hydroxy progesterone, and relaxin. Removal of the corpus luteum in the first trimester of pregnancy leads to a drop in progesterone and estradiol which could induce abortion. Primate studies have shown that relaxin plays several roles in maintaining pregnancy. It increases vascularization of the endometrium and stimulates differentiation of endometrial stromal cells into predecidual cells. Its presence also stimulates insulin-like growth factor-binding protein and prolactin which in turn promotes the development of the decidua [2]. It also softens the pubic symphysis and acts in synergy with progesterone to inhibit contractions.

Polypeptide hormones

A role of the placenta is to facilitate communication between the mother and the developing fetus while maintaining the immune and genetic integrity of both. Initially, the placenta alone provides endocrine function. As the fetus matures, it begins to contribute and by the end of the first trimester, it will provide hormonal precursors to the placenta [3].

Human chorionic gonadotropin

In the first 6 weeks of gestation, hCG levels double every 1.7 to 2 days. Its plasma half-life is 24 hours and can be detected in the maternal peripheral circulation within 24 hours of implantation. Maternal plasma hCG concentration peaks in the 10th week of pregnancy and then declines gradually in the third trimester. hCG is a glycoprotein consisting of 237 amino acids and has two chains, an alpha chain and a beta chain. The alpha chain is identical to the alpha chain of TSH, FSH, and LH. The beta chain is similar to the beta chain found in luteal hormone (LH) but has an additional 30 proteins. It plays a role in the establishment of maternal blood flow in the intervillous space.

Human placental lactogen

Human placental lactogen (HPL) is produced by early trophoblasts and is detectable in maternal circulation at 4–5 weeks gestation. It is a protein of 190 amino acids and is structured similarly to growth hormone and prolactin. HPL alters maternal glucose metabolism and mobilizes free fatty acids. It contributes to the peripheral insulin resistance of pregnancy. It has not been shown to promote lactation.

Other placental peptide hormones

A number of peptides have been isolated from placental tissues. Placental growth factor and vascular endothelial growth factor play a role in placental angiogenesis and fetal growth and may be involved in the cascade of events that lead to preeclampsia and eclampsia. Activin, inhibin, corticotropin-releasing hormone, fibroblast growth factor, epidermal growth factor, platelet-derived growth factor, all have been identified in placental tissue but the mechanism of their function has yet to be elucidated.

Steroid hormones

Steroid hormones are crucial to the establishment and maintenance of pregnancy. Included in this group are estrogens, progestins, glucocorticoids, mineral corticoids, and androgens. The precursor for all steroids is the 27 carbon-containing cholesterol molecule, a lipid composed of four fused rings with associated side chains [4]. Modification of the side chains, and at locations along the steroid back bone alters bioactivity. The placenta is unable to synthesize steroid hormones *de novo*, but it is able to convert steroids derived from fetal and maternal precursors [3].

Progesterone

Progesterone is necessary for the maintenance of pregnancy. It is produced by the corpus luteum during the first 6–8 weeks of pregnancy in response to the stimulus LH, and later in response to the stimulus of placental hCG. Following involution of the corpus luteum, the placenta is the major site of synthesis of progesterone from cholesterol precursors. The principle source of precursors is maternally derived circulating low-density lipoprotein (LDL). The LDL can also be synthesized *de novo* in the fetal liver and adrenal glands [5]. Enzymes in the placenta cleave the cholesterol side chain to produce pregnenolone which is subsequently isomerized to create progesterone. In total, 250–350 mg of progesterone are produced daily by the placenta in the third trimester [3]. Progesterone has a number of important roles including preparation of the endometrium for implantation and preparation of the breasts for lactation. Progesterone in conjunction with relaxin and nitrous oxide prevents uterine contraction during pregnancy. Progesterone causes hyperpolarization of myometrial cells decreasing the amplitude of action potentials. Progesterone also inhibits T-cell-mediated allograft reduction and may play a role in immunologic tolerance in the uterus. Insufficient progesterone production can lead to preterm labor and spontaneous abortion [6].

Estrogen

Estrogens oppose many of the actions of progesterone. It has a role in softening the cervix in advance of delivery. Estrogen also promotes uterine contractility. It increases the number of uterine oxytocin receptors and myometrial gap junctions to produce effective contractions during labor. Estrogen also stimulates an increase in lactotrophs in the pituitary and raises the prolactin level to its peak just prior to delivery. Estrogen is produced by the placenta primarily by converting fetal dehydroepiandrosterone (DHEA) sulfate to estriol. 16a-hydroxy-DHEA sulfate is produced in the fetal adrenal and liver. In the placenta, this substrate undergoes desulfation and aromatization to produce the weak estrogen, estriol. During pregnancy, levels of estriol increase 1000-fold. Fetal DHEA sulfate is also a precursor to estrone and estradiol. In the placenta, fetal DHEA sulfatase is converted by placental sulfatase to free DHEA and then is enzymatically converted to the androgens, androstenedione, and testosterone. They are aromatized in the placenta to estrone and estradiol, respectively [3]. Estrone is 10 times more potent than estriol and estradiol is 100 times more potent. Levels of estrone and estriol increase during pregnancy by 50-fold.

Endocrine changes during pregnancy

Pituitary gland

The pituitary gland increases in size during pregnancy by approximately one-third. This increase is due primarily to the increase in lactotrophs for the production of prolactin. Prolactin rises progressively during pregnancy and increases following meals and at night. Increased pituitary size and elevation in prolactin persists in breast-feeding mothers. In non-lactating women, pituitary size and prolactin levels return to baseline 3 months after delivery. Serum FSH and LSH drop to near undetectable levels during pregnancy. Growth hormone, ACTH, and TSH secretion remain unchanged.

Pancreas

The role of insulin and glucagon is to expedite intracellular transport of glucose, amino acids, and fatty acids. In early pregnancy, insulin levels remain unchanged or drop into the low range of normal. As the pregnancy progresses, secreting beta cells undergo hyperplasia and pancreatic islets increase in size. In the second trimester, insulin levels rise due to increased secretion. Insulin secretion in response to meals is accelerated. Pregnancy becomes a hyperinsulinemic state, with resistance to its peripheral metabolic state. Fasting glucose levels are maintained at low-normal levels and excess carbohydrates are converted to fat [3].

Adrenal cortex

Cortisol levels increase throughout pregnancy reaching a threefold increase by the third trimester. Elevated cortisol levels likely contribute to insulin resistance during pregnancy and may also contribute to the development of striae. Despite the rise of cortisol levels to that seen in Cushing's syndrome, no other manifestations of Cushing's syndrome are seen. High levels of progesterone may be exercising antagonist actions to minimize the glucocorticoid effects.

Estrogen stimulates increased hepatic synthesis of renin. Renin is then converted to aldosterone resulting in an eightfold increase in aldosterone production in the zona glomerulosa. Renin, aldosterone, and angiotensin all become elevated during pregnancy. Nevertheless, no blood pressure elevation, hypokalemia, or hypernatremia occurs. Progesterone is a competitive inhibitor of mineral corticoids and likely mitigates the response to higher levels.

Thyroid gland

The thyroid gland enlarges during the first trimester of pregnancy. Estrogen stimulates an increase in thyroid-binding globulin that results in an elevation in total serum thyroxin. Free thyroxin and triiodothyronine remain in the normal range. The polypeptide hormone hCG has weak TSH-like activity and can produce transient biochemical hyperthyroidism in early gestation.

Parathyroid gland

Fetal skeletal development requires on average 30 g of calcium prior to delivery at term. To facilitate this, the maternal parathyroid becomes hyperplastic and serum PTH levels become elevated. Maternal serum calcium levels decline between 28 and 32 weeks gestation due to fetal bone formation as well as hypoalbuminemia of pregnancy. Ionized calcium is maintained at normal serum levels throughout pregnancy.

Physiologic changes in pregnancy

The prodigious output of polypeptide and steroid hormones by the fetal–placental unit results in physiologic alteration of virtually every maternal organ system [3]. Some of these striking changes are summarized below.

Weight

There is wide variation in total weight gain in women during pregnancy. On average, a gain of 25 pounds occurs, but in some individuals, weight gain is considerably greater. Obesity during pregnancy has increased dramatically in the past 20 years in the United States and is associated with increased risk of a number of adverse outcomes including gestational diabetes, venous thromboembolism, congenital defects, fetal demise, and surgical morbidity [3]. In the neurologic setting, obesity in pregnancy is associated with increased risk of preeclampsia and eclampsia and idiopathic increased intracranial pressure (pseudotumor cerebri). These complications will be discussed in detail in subsequent chapters.

Blood

Blood volume increases dramatically during pregnancy. During the second trimester, blood

volume reaches a level of 150% of prepregnancy volume. Because the plasma volume expands faster than does the red cell mass, a relative anemia of pregnancy is seen. A 20% drop in hematocrit is not uncommon. Similarly, a drop in platelet count occurs but the overall mass of platelets increases. Fibrinogen increases by up to 40%. All coagulation factors increase during pregnancy except for Factors 11 and 13 and there is a decrease in Protein C and S. With all of these changes, in the last trimester, a relatively hypercoaguable state exists. As such, there is an increased risk of thrombotic events in the last trimester and peripartum period, particularly in women with a preexisting propensity for thrombosis.

Cardiovascular

In the pregnant woman, blood pressure gradually declines until 34 weeks gestation where it drops by 10% of prepregnancy levels. It gradually increases in the last month of pregnancy to its baseline level. Heart rate increases during pregnancy by 20%. Cardiac output rises rapidly in the first trimester by 20% and continues to increase by an additional 10% by the 28th week of pregnancy. Peripheral vascular resistance declines throughout pregnancy and peripheral venous distention increases until delivery.

Pulmonary

While respiratory rate remains stable, tidal volume and respiratory minute volume increase by 40%. Expiratory reserve gradually declines by 40%. Vital capacity remains unchanged.

Renal

Due to blood volume expansion, renal flow increases 25–50%. Glomerular filtration rate increases early in pregnancy then plateaus at 40% above prepregnancy levels.

Gastrointestinal

Gastric emptying time slows progressively throughout pregnancy, reaching a low of 50% below baseline by 36 weeks. Heartburn in the third trimester is not uncommon. Esophageal sphincter tone decreases during pregnancy.

Endocrine control of parturition

The precise factors that trigger parturition in humans remain elusive. In animal models, there is a drop in progesterone levels at the onset of labor. This interrupts the quiescence of the uterus and onset of labor takes place. A drop in progesterone levels at the onset of parturition has not been demonstrated in human studies [7]. It has been postulated that progesterone function may be diminished through decreases in functional progesterone receptors, sequestration by a circulating progesterone-binding protein, inactivation of local progesterone activity by myometrial cells, or production of an endogenous progesterone antagonist. In humans, circulating estrogen increases at mid-gestation and continues to rise until birth [8–10]. Decrease in progesterone function releases myometrial inhibition allowing it to become more responsive to the effects of circulating estrogen. Sporadic, painless uterine contractions begin to occur and the lower uterine segment and cervix become softer and thinner, known as effacement [3]. An increase in the estrogen/progesterone ratio increases the number of oxytocin receptors and myometrial gap junctions. This leads to coordinated, effective contractions resulting in labor and delivery.

Endocrinology and physiology of the postpartum patient

Endocrine changes

Twenty-four hours after delivery, progesterone levels drop to luteal phase levels and after several days, return to follicular phase levels. Twenty-four to seventy-two hours after delivery, estradiol declines to follicular phase levels. Both FSH and LH remain low during the first few

weeks of the puerperum. In the non-lactating female, FSH and LH return to follicular phase levels 3–4 weeks after delivery.

Physiologic changes

Blood volume declines to 80% of the predelivery levels by the third postpartum day. Cardiovascular changes influence liver and renal function including clearance of hormones. Hypertrophic myometrial cells decrease in size and the uterus gradually returns to a prepregnant size over a 6-week period after delivery. The endometrium which was sloughed at delivery regenerates by the seventh postpartum day.

Lactation

Prolactin is released by the pituitary gland and increases throughout pregnancy. Prolactin in conjunction with estrogen, progesterone, growth hormone, and glucocorticoids each play a role in the development of breast alveolar lobules. Delivery is associated with a surge in prolactin levels. Although prolactin reaches high levels in the third trimester, lactopoesis does not occur until unconjugated estrogens drop to prepregnancy levels 36–48 hours after delivery [3]. During breastfeeding, suckling leads to the release of oxytocin which results in contraction of the smooth muscle fibers surrounding the alveolar gland ductules. Suckling also leads to increased release of prolactin from the pituitary which supports lactogenesis. Surges of prolactin are believed to inhibit the release of gonadotropin-releasing hormone by the hypothalamus preventing ovulation. If breastfeeding does not occur, prolactin levels drop, lactogenesis ceases, and breasts development returns to a nonpregnant state. Gonadatropin-releasing hormone levels rise and the normal menstrual cycle is initiated.

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CHAPTER 3
Neuroimaging

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Introduction

Throughout pregnancy and the puerperium, hormonal, physiologic, and potentially pathologic changes may result in a variety of neurologic symptoms and clinical findings. Pregnancy-related changes may also influence preexisting medical conditions or bring previously unknown neurologic conditions to clinical attention. When a pregnant patient presents with a neurologic complaint or clinical sign, a physician must consider broad diagnostic categories in order to expedite diagnosis and management of treatable causes as neurologic pathology contributes to up to 20% of maternal deaths [1]. Neuroradiologic imaging is frequently utilized as part of this diagnostic evaluation. This chapter will review the physiologic changes most germane to the imaging of neurologic conditions, safety issues related to diagnostic imaging during pregnancy, and the imaging findings of a spectrum of neurologic conditions with common clinical presentations.

KEY POINTS

1. The health of the mother is the single most important factor in safeguarding the health of the fetus.
2. Radiation and intravenous contrast concerns, though important, should not delay the execution of critical imaging examinations.
3. Careful selection of an imaging workup when evaluating the pregnant patient can minimize potential adverse effects to the fetus without sacrificing diagnostic power.
4. The potential radiation dose associated with diagnostic imaging should be minimized whenever possible, following As Low As Reasonably Achievable (ALARA) principles.
5. Fetal radiation doses of less than 5 rad (50 mGy) have not been shown to increase rates of fetal abnormality or pregnancy loss.
6. Both iodinated and gadolinium-based contrast agents may be administered during pregnancy or the puerperium in appropriate clinical circumstances.
7. Recognition of the imaging features of pregnancy-associated conditions may allow for rapid initiation of therapy, minimizing potential adverse effects for both mother and fetus.

Anatomic and physiologic changes of pregnancy

The following is a review of the specific physiologic, hormonal, immunologic, and hemodynamic physiologic changes in pregnancy to which many anatomic and pathologic processes are generally attributed, and thus most pertinent to neuroimaging (Table 3.1). Many of these changes may influence the imaging appearance

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Table 3.1 Physiologic changes in pregnancy

Hormonal	Metabolic	Immunologic	Hemodynamic	Hematologic
↑ hCG, prolactin; ↑ Estrogen and progesterone precursors and products; ↑ ACTH	↑ Cholesterol turnover; ↑ circulating triglycerides (Weeks 20–40): ↑ insulin resistance; ↑ glycogen synthesis and storage	↑ Cortisol; ↑ progesterone-induced T-cell inhibitors	↑ Heart rate and stroke volume with ↑ cardiac output 40–60%; ↑ blood volume (50% plasma and 10–30% red cell mass resulting in pseudo-anemia of pregnancy)	↑ Levels of coagulations factors (VII, IV, V, fibrinogen; ↑ platelet aggregability; ↑ heparin neutralization; ↑ protein C inhibitors
↓ LH and FSH	(Weeks 1–20): ↓ insulin resistance; ↓ glycogen synthesis and storage		↓ Systemic vascular resistance and ↓ blood pressure	↓ Fibrinolytic activity, antithrombin III levels; ↓ protein S inhibitor

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hCG, human chorionic gonadotropin; ACTH, adrenocorticotropic hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

of normal structures outside the pelvis. For instance, hemodynamic and cellular changes related to hormonal influences may affect organ size including an increasing size of the heart, kidneys, and thyroid [3]. In addition, a decrease in brain size has been observed *in vivo*, both with the administration of high dose exogenous steroids as well as in both healthy and preeclamptic patients over the course of pregnancy, with return to baseline by 6-month postpartum [4, 5].

Fluctuations in pituitary gland function throughout the course of pregnancy may influence its anatomic appearance. Adenohypophyseal enlargement is attributed to lactotroph hypertrophy and may account for up to 30% increase in gland weight and mean volume increase of 120%, as seen in Figure 3.1 [6]. The degree of craniocaudal enlargement may reach 9 mm in the third trimester, and up to 12 mm in the immediate postpartum period. Pituitary enlargement often resolves by 6 months postpartum [7].

Changes in circulating adrenocorticotropic hormone (ACTH), prolactin, and estrogen products have been associated with a trophic effect on neoplasms such as pituitary adenomas, hemangioblastomas, schwannomas, and meningiomas, as well as malignancies such as choriocarcinoma, melanoma, and breast carcinoma, all of which may present with intracranial metastases [8, 9]. Meningiomas, one of the most frequently encountered intracranial

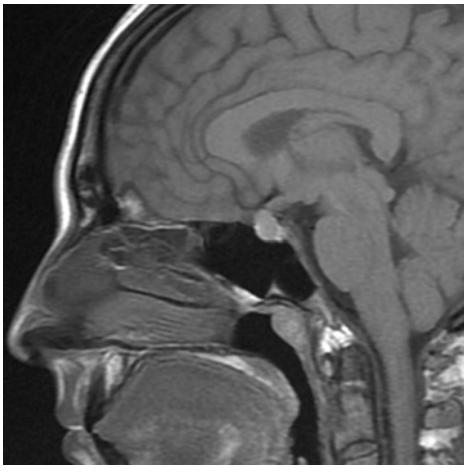

Figure 3.1 34 y/o female, 1-week postpartum, with severe headache. Physiologic hypertrophy with a sagittal T_1-weighted image demonstrating a homogenous, enlarged pituitary gland with convex superior margin, measuring 1.0 cm in height. Reproduced from Reference 2 with permission of Elsevier.

masses, have been shown to express numerous growth factor receptors including those for sex hormones, as have schwannomas [10–14]. In meningiomas, the presence of estrogen receptors has been associated with a more aggressive clinical course, recurrence, and clinical progression [12]. Changes in meningioma size have been reported following modulation of hormonal replacement therapy, further validating the potential hormonal trophic effect [15]. However, regarding schwannomas, recent work examining immunohistochemical stains for growth factor receptors has raised questions regarding the veracity of the widely reported potential hormonal trophic effect on these lesions [16–19].

Selective immunosuppression during pregnancy, primarily from increased levels of circulating cortisol, as well as progesterone-induced T-cell inhibition, may have an inhibitory effect on autoimmune disorders such as multiple sclerosis, discussed in detail elsewhere in this volume.

The hypercoagulable state during pregnancy, due in part to increased circulating fibrinogen and other clotting factor levels, as well as increased platelet aggregability, is compounded by the reduction in fibrinolytic activity due to decreased endogenous anticoagulants such as protein S and antithrombin III [8, 9, 20]. Surprisingly, randomized studies have shown that there is not an increased risk of stroke during pregnancy, however, a significantly increased risk is evident in the peri- and postpartum periods (Figure 3.2) [9, 21], especially in the setting of hypertension, diabetes, hyperlipidemia, and premature atherosclerosis formation. The risk of arterial dissection or deep venous thrombosis during a prolonged or difficult labor also increases the risk of embolic infarction.

Hormonal and hemodynamic changes may also be involved in the growth or development of intracranial aneurysms. Increased levels of relaxin, upregulation of collagenase, and collagen remodeling may affect vessel wall integrity. The risk of subarachnoid hemorrhage (SAH), a leading cause of maternal mortality, has been reported up to five times greater during pregnancy than in a nonpregnant woman [8, 22]. Despite a potential underlying physiologic mechanism, this reported increased risk may be the subject of some controversy as other authors have not shown such a difference in risk [23,24]. Aneurysm rupture has been widely reported as a leading cause of SAH, but some studies suggest that hypertensive disorders may be just as likely an underlying cause [22, 24].

Imaging the pregnant patient

There are up to six million pregnancies in the United States annually, with up to two million ending in pregnancy loss [25]. Physicians across many disciplines encounter pregnant patients in both acute and more chronic care settings, including those presenting with neurologic signs or symptoms. While many conditions may be benign and self-limited, the exclusion of potentially serious conditions often involves diagnostic neuroimaging. In choosing the most appropriate imaging study, diagnostic utility must be weighed against any potential adverse effects to the mother or fetus. With modern imaging techniques and the utilization of available guidelines, both diagnostic efficacy and patient safety can be maximized.

The American College of Radiology (ACR), the European Society of Urogenital Radiology (ESUR), and the American Congress of Obstetricians and Gynecologists (ACOG) have published guidelines regarding imaging of the pregnant patient [26–28]. For both the optimization of patient care and management of potential medico-legal issues, hospitals and radiology departments should formalize their own policies regarding the imaging of pregnant patients, incorporating the available practice guidelines generated by consensus expert panels. In many cases, a well-documented risk–benefit analysis should be performed and informed consent