Since 1993

March 2016 Vol 23 No. 1 ISSN 1681-5552

the SQUARE

Healthcare bulletin

- Sleep Disorder
- Teratogenic Drug
- Zika Virus

Test yourself 40

www.squarepharma.com.bd/medical-periodicals.php

Published as a service to medical professionals by

SQUARE PHARMACEUTICALS LTD. BANGLADESH

AWARDED Superbrands BANGLADESH

the SQUARE
healthcare bulletin

Contents

March 2016 VOL 23 NO.1

ISSN 1681-5552
Key title: The square (Dhaka)
Abbreviated key title: Square (Dhaka)

www.squarepharma.com.bd/medical-periodicals.php

Editorial

Dear Doctor

Welcome to this edition of *"the SQUARE"* healthcare bulletin!

In this issue we bring you the details on "Sleep Disorder", are among the most common clinical problems encountered in medicine and psychiatry. According to the National Institute of Neurological Disorders and Stroke, about 40 million people in the United States suffer from chronic long-term sleep disorders each year and an additional 20 million people experience occasional sleep problems. In February 2016, results of a study released by the U.S. Centers for Disease Control and Prevention (CDC) indicate more than a third of American adults are not getting enough sleep on a regular basis. A topic on "Teratogenic Drug" has been included in this issue. Teratogenic exposures result in a wide variety of effects that range from infertility, prenatal onset growth restriction, structural defects, and functional CNS abnormalities to miscarriage or fetal death. We have also published a feature on "Zika Virus", which was subsequently identified in humans in 1952 in Uganda and the United Republic of Tanzania. On Feb 1, 2016, the World Health Organization (WHO) declared Zika Virus a public health emergency of international concern (PHEIC). On February 8, 2016, CDC elevated its response efforts to a Level 1 activation, the highest response level at the agency. Local transmission has been reported in many other countries and territories. Zika virus likely will continue to spread to new areas. Moreover, our regular features like "Product Profile" and "Test Yourself" have been incorporated in this issue as well.

We hope that you will find this edition of healthcare bulletin both interesting and informative!

On behalf of the management of SQUARE we wish you all healthy, prosperous, safe and blissful lives!

Thank you!

Omar Akramur Rab

Sleep Disorder

Sleep is a period of unconsciousness during which the brain remains highly active. It is a complex biological process that helps people process new information, stay healthy, and rejuvenate. During sleep, the brain will cycle through five distinctive phases: stage 1, 2, 3, 4 and rapid eye movement (REM) sleep. Each phase is important to ensure that the mind and body are completely rested. Certain phases are needed to feel rested and energetic the next day, while other phases help to learn information and form memories. Inadequate sleep contributes, in the short term, to problems with learning and processing information and it can have a harmful effect on long-term health and well-being. Sleep affects performance on daily tasks, mood and health.

Sleep disorders are among the most common clinical problems encountered in medicine and psychiatry. Inadequate or non restorative sleep can markedly impair a patient's quality of life. Sleep disorders may be primary or may result from a variety of psychiatric and medical conditions. Primary sleep disorders result from an endogenous disturbance in sleep-wake generating or timing mechanisms, often complicated by behavioral conditioning. They may be divided into the following 2 broad categories: Parasomnias - These are unusual experiences or behaviors that occur during sleep; they include sleep terror disorder and sleepwalking (which occur during stage 4 sleep) and nightmare disorder (which occurs during rapid eye movement [REM] sleep). Dyssomnias - These are characterized by abnormalities in the amount, quality or timing of sleep; they include primary insomnia and hypersomnia, narcolepsy, breathing-related sleep disorder (sleep apnea) and circadian rhythm sleep disorder. It is important to distinguish these primary sleep disorders from secondary sleep disorders. At times, determining whether anxiety and depression are causing sleep problems or the anxiety and depression are secondary to a primary sleep problem is difficult. Primary insomnia is the general term for difficulty in initiating or maintaining sleep. Because sleep requirements vary from individual to individual, insomnia is considered clinically significant when a patient perceives the loss of sleep as a problem.

Pathophysiology

Sleep is divided into the following 2 categories, each of which is associated with distinct patterns of central nervous system:

REM sleep - This is characterized by muscle atony, episodic REMs, and low-amplitude fast waves on electroencephalography (EEG); dreaming occurs mainly during REM sleep

Non-REM (NREM) sleep - This is further subdivided into 4 progressive categories, termed stages 1-4 sleep; the arousal threshold rises with each stage, and stage 4 (delta), characterized by high-amplitude slow waves, is the sleep state from which arousal is most difficult

Disturbances in the pattern and periodicity of REM and NREM sleep are often found when people admit to experiencing sleep disorders. Sleep-wake cycles are governed by a complex group of biologic processes that serve as internal clocks. The suprachiasmatic nucleus, located in the hypothalamus, is thought to be the body's anatomic timekeeper, responsible for the release of melatonin on a 25-hour cycle. The pineal gland secretes less melatonin when exposed to bright light; therefore, the level of this chemical is lowest during the daytime hours of wakefulness. Multiple neurotransmitters are thought to play a role in sleep. These include serotonin from the dorsal raphe nucleus, norepinephrine contained in neurons with cell bodies in the locus ceruleus and acetylcholine from the pontine reticular formation. Dopamine, on the other hand, is associated with wakefulness.

Abnormalities in the delicate balance of all of these chemical messenger systems may disrupt various physiologic, biologic, behavioral and EEG parameters responsible for REM (active) sleep and NREM (slow-wave) sleep.

Etiology

The major causes of insomnia may be divided into medical conditions, psychological conditions and environmental problems.

Medical conditions

Cardiac conditions that may give rise to disordered sleep include ischemia and congestive heart failure. Neurologic conditions include stroke, degenerative conditions, dementia, peripheral nerve damage, myoclonic jerks, restless leg syndrome, hypnic jerk and central sleep apnea.

Age	Recommended Amount of Sleep
Newborns	16-18 hours a day
Preschool-aged children	11-12 hours a day
School-aged children	At least 10 hours a day
Teens	9-10 hours a day
Adults (including the elderly)	7-8 hours a day

Amount of sleep need everyday

Endocrine conditions affecting sleep are related to hyperthyroidism, menopause, the menstrual cycle, pregnancy, and hypogonadism in elderly men. Pulmonary conditions include chronic obstructive pulmonary disease, asthma, central alveolar hypoventilation (the Ondine curse) and obstructive sleep apnea syndrome (associated with snoring). Gastrointestinal (GI) conditions include gastroesophageal reflux disease. Hematologic conditions include paroxysmal nocturnal hemoglobinuria, which is a rare, acquired, hemolytic anemia associated with brownish-red morning urine. Substances that may result in insomnia include stimulants, opioids, caffeine and alcohol or withdrawal from any of these also may cause insomnia. Medications implicated in insomnia include decongestants, corticosteroids and bronchodilators.

Other conditions that may affect sleep include fever, pain and infection.

Psychiatric conditions

It should be borne in mind that the major psychiatric conditions now are known to have a biologic basis and thus constitute a subset of medical conditions. Depression may cause alterations in REM sleep. As many as 40% of people with depression have insomnia post traumatic stress disorder (PTSD) can produce vivid and terrifying nightmares. Anxiety disorders predispose to insomnia. The most common of these are generalized anxiety disorder, panic disorder and anxiety disorders not otherwise specified. Thought disorders and misperception of sleep state are other potential states that cause insomnia. Psychotropic medications, such as antidepressants, may interfere with normal REM sleep patterns. Rebound insomnia from benzodiazepines or other hypnotic agents is common.

Environmental problems

Stressful or life-threatening events (bereavement or PTSD) may cause insomnia. Shift work may disturb the sleep cycle, as may jet lag or changes in altitude. Sleep deprivation may occur as a result of an overly warm sleeping environment, environmental noise or frequent intrusions such as occur in an intensive care unit (ICU).

Key Sleep Disorders

Sleep-related difficulties affect many people. The following is a description of some of the major sleep disorders. It is important to receive an evaluation by a doctor or, if necessary, a sleep medicine specialist if someone experiencing any of the following-

Insomnia

Insomnia is characterized by an inability to initiate or maintain sleep. It may also take the form of early morning awakening in which the individual awakens several hours early and is unable to resume sleeping. Difficulty initiating or maintaining sleep may often manifest itself as excessive daytime sleepiness, which characteristically results in functional impairment throughout the day. Before arriving at a diagnosis of primary insomnia, the healthcare provider will rule out other potential causes, such as other sleep disorders, side effects of medications,

substance abuse, depression or other previously undetected illness. Chronic psychophysiological insomnia (or "learned" or "conditioned" insomnia) may result from a stressor combined with fear of being unable to sleep. Individuals with this condition may sleep better when not in their own beds. Chronic insomnia may be treated with a combination of use of sedativehypnotic or sedating antidepressant medications, along with behavioral techniques to promote regular sleep.

Narcolepsy

Excessive daytime sleepiness (including episodes of irresistible sleepiness) combined with sudden muscle weakness are the hallmark signs of narcolepsy. The sudden muscle weakness seen in narcolepsy may be elicited by strong emotion or surprise.

Episodes of narcolepsy have been described as "sleep attacks" and may occur in unusual circumstances, such as walking and other forms of physical activity. Narcolepsy may be treated with stimulant medications combined with behavioral interventions, such as regularly scheduled naps, to minimize the potential disruptiveness of narcolepsy on the individual's life.

Restless Legs Syndrome (RLS)

RLS is characterized by an unpleasant "creeping" sensation, often feeling like it is originating in the lower legs, but often associated with aches and pains throughout the legs. This often causes difficulty initiating sleep and is relieved by movement of the leg, such as walking or kicking. Abnormalities in the neurotransmitter dopamine have often been associated with RLS. A combination of medications often use that help to correct the underlying dopamine abnormality along with a medicine to promote sleep continuity in the treatment of RLS.

Sleep Apnea

Snoring may be more than just an annoying habit - it may be a sign of sleep apnea. Persons with sleep apnea characteristically make periodic gasping or "snorting" noises, during which their sleep is momentarily interrupted. Those with sleep apnea may also experience excessive daytime sleepiness, as their sleep is commonly interrupted and may not feel restorative. Treatment of sleep apnea is dependent on its cause. If other medical problems are present, such as congestive heart failure or nasal obstruction, sleep apnea may resolve with treatment of these conditions. Gentle air pressure administered during sleep (typically in the form of a nasal continuous positive airway pressure device) may also be effective in the treatment of sleep apnea. As interruption of regular breathing or obstruction of the airway during sleep can pose serious health complications, symptoms of sleep apnea should be taken seriously.

Sleep Studies

Sleep studies are important because untreated sleep disorders can raise risk for heart disease, high blood pressure, stroke and other medical conditions. Sleep disorders also have been linked to an increased risk of injury, such as falling (in the elderly) and car accidents. People usually aren't aware of their breathing and movements while sleeping. They may never think to talk to their doctors about issues that might be related to sleep problems.

Sleep studies can help diagnose :

- ❏ Sleep-related breathing disorders, such as sleep apnea
- ❏ Sleep-related seizure disorders
- ❏ Sleep-related movement disorders, such as periodic limb movement disorder
- ❏ Sleep disorders that cause extreme daytime tiredness, such as narcolepsy

Sleep studies help to diagnose or rule out restless legs syndrome (RLS). However, RLS usually is diagnosed based on signs and symp-toms, medical history and a physical examination.

To diagnose sleep-related problems, one or more of the following sleep studies may done :

- ❏ Polysomnogram or PSG
- ❏ Multiple sleep latency test, or MSLT
- ❏ Maintenance of wakefulness test or MWT
- ❏ Home-based portable monitor

Sleep and Chronic Disease

As chronic diseases have assumed an increasingly common role in premature death and illness, interest in the role of sleep health in the development and management of chronic diseases has grown.

Notably, insufficient sleep has been linked to the development and management of a number of chronic diseases and conditions, including diabetes, cardiovascular disease, obesity, and depression.

Diabetes

Research has found that insufficient sleep is linked to an increased risk for the development of Type 2 diabetes. Specifically, sleep duration and quality have emerged as predictors of levels of Hemoglobin A1c, an important marker of blood sugar control. Recent research suggests that optimizing sleep duration and quality may be important means of improving blood sugar control in persons with Type 2 diabetes.

Cardiovascular Disease

Persons with sleep apnea have been found to be at increased risk for a number of cardiovascular diseases. Notably, hypertension, stroke, coronary heart disease and irregular heartbeats (cardiac arrhythmias) have been found to be more common among those with disordered sleep than their peers without sleep abnormalities. Likewise, sleep apnea and atherosclerosis appear to share some common physiological characteristics, further suggesting that sleep apnea may be an important predictor of cardiovascular disease.

Obesity

Laboratory research has found that short sleep duration results in metabolic changes that may be linked to obesity. Epidemiologic studies conducted in the community have also revealed an association between short sleep duration and excess body weight. This association has been reported in all age groups-but has been particularly pronounced in children. It is believed that sleep in childhood and adolescence is particularly important for brain development and that insufficient sleep in youngsters may adversely affect the function of a region of the brain known as the hypothalamus, which regulates appetite and the expenditure of energy.

Depression

The relationship between sleep and depression is complex. While sleep disturbance has long been held to be an important symptom of depression, recent research has indicated that depressive symptoms may decrease once sleep apnea has been effectively treated and sufficient sleep restored. The interrelatedness of sleep and depression suggests it is important that the sleep sufficiency of persons with depression be assessed and that symptoms of depression be monitored among persons with a sleep disorder.

Treatment

Many agents are useful in treating insomnia. Short-term drug therapy is preferred to restore a normal sleep pattern. Generally, hypnotic drugs are approved for 2 weeks or less of continuous use. In chronic insomnia, longer courses may be indicated, which require long-term monitoring to ensure ongoing appropriate use of the medication.

Barbiturates and chloral hydrate are seldom used now, because of safety concerns related to their undesirably low therapeutic indexes.

Drugs that block the histamine type 1 receptor are used primarily in over-the-counter preparations, which are inexpensive and help some patients. However, in view of the anticholinergic properties of these agents, they should be used cautiously in older patients and in patients who have conditions such as prostatic hypertrophy, cognitive disorders and constipation. In addition, most of these drugs have a long duration of action and their sedative effects may persist well into the following day.

Zolpidem and zaleplon are the newest and arguably, the safest agents that have been approved by the US Food and Drug Administration (FDA) for short-term hypnotic use. Zolpidem is available an extended-release version that lasts slightly longer than the original preparation. In addition, the FDA has approved eszopiclone as the first agent for long-term use in the management of chronic insomnia.

Tasimelteon was approved by the USFDA in January 2014 for treatment of non-24-hour sleep-wake disorder in the totally blind. Approval was based on results of 2 trials: the Safety and Efficacy of Tasimelteon (SET) trial, a 26-week study that included 84 patients and the Randomized Withdrawal study of the Safety and Efficacy of Tasimelteon (RESET), a 19-week trial that included

20 patients, all of whom had been previously screened during the SET trial and entrained during open-label tasimelteon treatment. Entrainment of the circadian rhythm, as measured by urinary 6-hydroxymelatonin sulfate (aMT6s), a main metabolite of melatonin, was the primary efficacy endpoint for SET. Scores on the 24-hour clinical response scale were another defined endpoint for SET. Outcomes for RESET included maintenance of entrainment (aMT6s) and maintenance of clinical response. Study results demonstrated that tasimelteon entrains the master clock (both melatonin and cortisol) and has clinically meaningful effects on the sleep-wake cycle in terms of the timing and amount of sleep and improved measure of global functioning.

Suvorexant was approved by the FDA in August 2014 and is the first orexin receptor antagonist for insomnia. It is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R by suvorexant is thought to suppress wake drive. Approval was based on three clinical trials involving more than 500 participants. The recommended dose is 10 mg for most patients. After taking 20 mg, impairment of next-day driving was observed.

Diet and Activity

No special diet is needed to treat insomnia, but large meals and spicy foods should be avoided in the 3 hours before bedtime. Patients should avoid sleep-disturbing substances such as alcohol, nicotine, and caffeine. Alcohol creates the illusion of good sleep, but it adversely affects sleep architecture. Nicotine and caffeine are stimulating and should be avoided in the second half of the day, from late afternoon on. Consumption of tryptophan-containing foods may help induce sleep; the classic example is warm milk.

Strenuous exercise during the day may promote better sleep, but this same exercise during the 3 hours before bedtime can cause initial insomnia. Stimulating activities should be avoided 3 hours before bedtime. Examples include tense movies, exciting novels, thrilling television shows, arguments, and vigorous physical exercise.

Long-Term Monitoring

Inpatient care is rarely, if ever, required for treatment of insomnia. Only a severe underlying medical, psychiatric, or substance abuse disorder would warrant inpatient care. The numerous possible medical causes of sleep disorders make them difficult to diagnose and necessitate regular appropriate follow-up care until the final diagnosis has been made and successful treatment has been implemented. Several medical specialists may be needed for care and consultations; these may be coordinated by the patient's internist, personal physician or medical sleep specialist. Regular follow-up care, even if infrequent, is necessary once appropriate medication is successfully in use. (However, medication may be unnecessary).

Prognosis

The prognosis varies widely, depending on the cause of the insomnia or other sleep disorder. For example, insomnia due to OSA resolves with successful treatment of the apnea, whereas insomnia due to refractory major depression is itself refractory until a successful treatment can be found for the depression.

Chronic insomnia is associated with an increased risk of depression and accompanying danger of suicide, anxiety, excess disability, reduced quality of life, and increased use of health care resources.

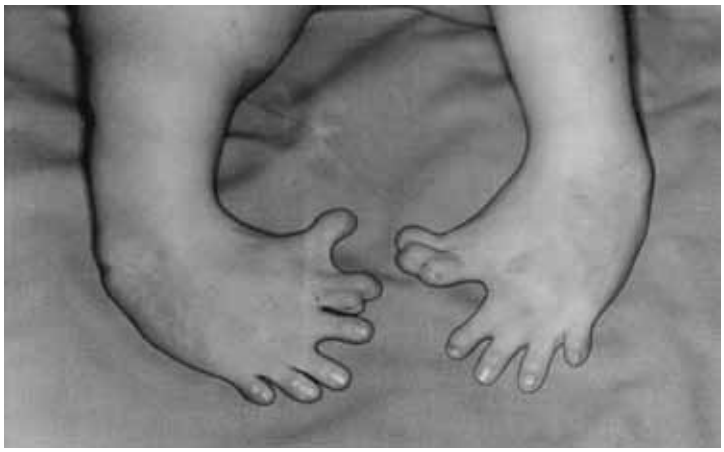
Insufficient sleep can result in industrial and motor vehicle crashes, somatic symptoms, cognitive dysfunction, depression and decrements in daytime work performance owing to fatigue or sleepiness.

Older women with sleep-disordered breathing (characterized by recurrent arousals from sleep and intermittent hypoxemia) have an increased risk of developing cognitive impairment compared with those without sleep-disordered breathing.

References :

- Emedicine.medscape.com
- WWW.cdc.gov
- WWW.nhlbi.nih.gov

Teratogenicity or reproductive toxicity broadly refers to the occurrence of biologically adverse effects on the reproductive system that may result from chemical exposure to several environmental agents which is characterized by alterations to the female or male reproductive organs related to endocrine system or pregnancy outcomes.



Teratogenesis signifies the structural malformations during fetal development, in distinction from other kinds of drug induced fetal damage such as growth retardation, dysplasia (Iodine deficiency related goitre) or the asymmetrical limb reduction. The exposure of teratogenic chemical prior to conception, during prenatal or postnatal development leads to manifestations of developmental toxicity including the death of the developing organism, structural abnormality, altered growth and functional deficiency.

It is estimated that approximately 10%-15% of congenital structural anomalies are the result of the adverse effect of environmental factors on prenatal development. The human teratogen is a chemical drug, metabolic state, physical agent or psychological alteration during development that produce a permanent pathologic or pathopsychologic alteration in the offspring at exposures or circumstances that commonly occur. Birth defects, together with deformation and chromosomal abnormalities are leading causes of neonatal and postneonatal deaths and carry a high social and economic impact. Defects in the development of the heart is the most common birth defects and are recognized in about 15% of infants with birth defects.

Other common abnormalities include extra fingers and toes (polydactyly), especially on the outer aspect of the hands, webbing between fingers and toes (syndactyly), defects in closure of the developing spine (myelomeningocele), club foot (talipes equinovarus and calcaneovalgus), cleft lip, cleft palate and incomplete closure of the urethra of the male (hypospadias).

The result of teratogenesis is determined by its site of action and the stage of development of the target organ. These congenital abnormalities are caused by defected genes or exogenous agents. In genetic defects, the scheme indicates the site and stage of development at which the mutant gene is expressed.

In nongenetic defects the site and stage refer to exposure to an exogenous teratogen. The four main sites of action of a defective gene or an exogenous teratogen are illustrated in Figure 1.

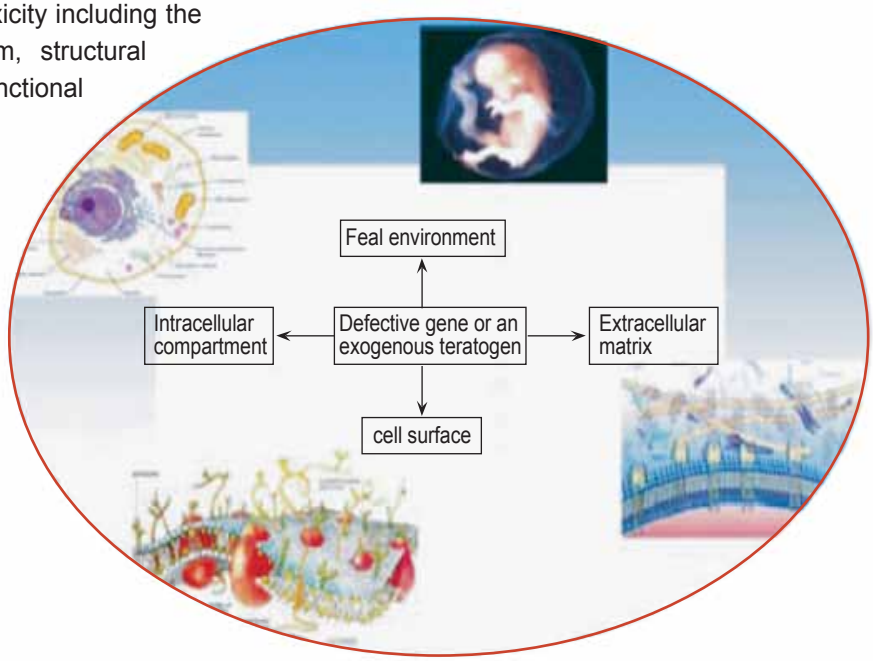


Figure 1. Major sites of action of defective gene or teratogen.

Table 1: Common human teratogens

Category	Examples
Drugs	ACE inhibitors-benazepril, enalapril, captopril Acid nonsteroidal anti-inflammatory agent-diclofenac Androgen hormones-oestrogen Antiepileptics-phenytoin, valproic acid, carbamazepine, trimethadione Antineoplastic-folic acid antagonists-methotrexate, amiopterine Retinoids-isotretinoin Penicillamine Thalidomide Warfarin Xanthine alcoloids-caffeine Pesticides-organophosphates
Unnecessary chemicals	Alcohol Cocaine
Physical agents	Cigarette smoke Ionising radiations-high doses at least >5 rad
Other chemicals	Methyl mercury

General mode of action of teratogen: The timing of the teratogenic insult in relation to fetal development is critical in determining the type and extent of damage. Mammalian fetal development passes through three main phases: blastocyst formation, organogenesis, histogenesis and maturation of function. Many teratogens have ability to inhibit cell division and kill embryo during cell division, which was involved in blastocyst formation. But most of time the embryo survives; its subsequent development does not generally seem to be compromised. Ethanol is one of the causes of teratogen which affects development at this very early stage. Administration of teratogen during the period of organogenesis (Day 17-60) leads to gross malformations. The type of malformation produced by teratogen depends on the time of exposure to organisation of the embryo includes eye and brain, skeleton and limbs, heart and major vessels, palate and genitouri-nary system. The cellular mechanisms of teratogens and teratogenic effects are not at all well understood and may produce mutagenic effect, e.g. vitamin A derivatives (retinoids), which are involved in morphogenesis and are potent teratogens. Drugs like methotrexate and phenytoin do not react directly with

Table 2: US FDA Pregnancy categories

Pregnancy Category	Description
A	No risk in controlled human studies: Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	No risk in other studies: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
C	Risk not ruled out: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	Positive evidence of risk: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Contraindicated in Pregnancy: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits
N	FDA has not yet classified the drug into a specified pregnancy category.

DNA but influence folate metabolism. The foetal develop-ment depends on an adequate supply of nutrients during the final stage of histogenesis and functional maturation and development is regulated by a variety of hormones.

Gross structural malformations do not arise from exposure to mutagens at this stage but teratogens that interfere with the supply of nutrients or the hormonal milieu may have deleterious effects on its growth and development.

A female fetus exposure to androgens can cause masculinisation. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists cause oligohydramnios and renal failure if administered during later stages of pregnancy because of selective inhibition of angio-tensin II which plays an important role in the later stages of fetal development and in renal function in the fetus.

Drugs:

ACE inhibitors: captopril

The ACE inhibitors are competitive inhibitors of kininase II. They affect both the angiotensin/aldosterone and bradykinin/ prostaglandin systems. Administration of ACE inhibitors during pregnancy leads to fetal wastage. The fetotoxic effects of ACE inhibitors include fetal hypotension, renal tubular dysplasia, anuria & oligohydramnios, growth restriction, hypocalvaria and death when used in the second and third trimesters of pregnancy. The administration of these drugs during the second and third trimesters of pregnancy causes high fetal and perinatal mortality.

This unfavorable outcome may be related to the reduction in systemic blood pressure and uterine blood flow secondary to the significant vasodilatory effect, possibly caused by a decrease in angiotensin-II production and reduced degradation of bradykinin and prostaglandins mediated by these agents. The reduction in amniotic fluid can also be observed in 30-32 weeks of gestation which might be due to decrease in fetal renal function and urine output.

Nonsteroidal anti-inflammatory agents: diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug and commonly used by reproductive age women for the treatment of variety of conditions. Because of its low molecular weight, diclofenac can readily crosses the human placenta during the first trimester. It is also reported that diclofenac accumulates in fetal tissue. Drugs of this category could increase post-implantation loss, decrease fetal number, induce skeletal and heart defects as well as fetal growth retardation. Pregnant women treated with high toxic doses of non-selective cyclooxygenase inhibitors show bone developmental variations in fetus.

Androgen hormones: oestrogen

In humans, androgen levels are far higher in male than female fetuses. Increased level of androgenic hormones during pregnancy causes masculinization of a female fetus. Administration of 17alpha-methyltestosterone, androgenic hormones, produces masculinization and pseudohermaphroditism in pregnant mother. The androgenic progestin administered to the mother is converted to an oestrogen that does not protect the foetus from the masculinization effect and causes cornification of the vagina.

Testicular testosterone produced during a critical perinatal period is thought to masculinize and defeminize the male brain from the inherent feminization program and induce male-typical behaviors in the adult. These actions of testosterone appear to be exerted not through its androgenic activity, but rather through its conversion by brain aromatase into oestrogen, with the consequent activation of oestrogen receptor mediated signaling.

Antiepileptics: phenytoin

Phenytoin is one of the most commonly used antiepileptic medications. It stabilizes voltage-gated sodium channels thereby suppressing abnormal brain activity. Phenytoin is also frequently used in trigeminal neuralgia. The developing stages of central nervous system (CNS) in the neo natal period have been found to be more vulnerable to the neurotoxic effects of phenytoin because of its higher brain concentration.

Exposure during pregnancy has been associated with a constellation of abnormalities sometimes called the fetal hydantoin syndrome that includes abnormalities like short nose, low or broad nasal bridge, epicanthic folds, hypertelorism, microe-phaly, abnormal ears, wide mouth, oral clefts, hypo-plasia of distal phalanges, short/webbed neck, low hairline, abnormal mental development and abnor-mal motor development. The prevalence of major and minor malformations was found among the off-spring of women taking phenytoin during pregnancy.

Polytherapy with anti-epileptic drugs is associated with higher neurotoxic fetal adverse effects than monotherapy.

Sodium valproate

The teratogenicity of the widely popular antiepileptic drug (AED) and mood stabiliser sodium valproate (also known as valproate, VPA) has been evidenced by research; however, the findings have often limited by a small population sample of exposed women and a retrospective study design. Many factors contribute to the teratogenicity of VPA. These include the number of drugs that are co-administered, drug dosage, differences in maternal and/or infant metabolism, the gestational age of the fetus at exposure and hereditary susceptibility. VPA has been associated with a variety of major and minor malformations, including a 20-fold increase in neural tube defects, cleft lip and palate, cardiovascular abnormalities, genitourinary defects, developmental delay, endocrinological disorders, limb defects and autism. It has been suggested that polytherapy treatment in epileptic pregnant women increases the risk of teratogenicity in offspring. Furthermore, there is an established relationship between VPA dose and adverse outcome. Large single doses of VPA potentially cause high peak levels in the fetal serum resulting in deleterious effects.

Antineoplastic: methotrexate

Methotrexate is a synthetic analogue of dihydrofolate and acts as competitive inhibitors of dihydrofolate reductase (DHFR) enzyme. Inhibition of DHFR blocks the conversion of DHFR to tetrahydrofolate, which is essential cofactor in the biosynthesis of purines, thymidylate, and some amino acids. The depletion of pool of tetrahydrofolate methotrexate disrupts DNA synthesis and causes rapidly dividing cells to arrest and die. Methotrexate causes disturbance in folate metabolism and may have a teratogenic effect through inhibition of the folate methylation cycle. More likely, intracellular accumulation of homocysteine leads to increased levels of S-adenosylhomocysteine, which is a competitive inhibitor of many methyltransferases, through which gene expression, protein function and the lipid and neurotransmitter metabolisms might be dysregulated. As a result, neurulation is disturbed by inadequate gene and amino acid methylation.

Methylation steps also play an important role in the metabolism of lipids and neurotransmitters and in detoxification of exogenous substances. This stresses the crucial role of the folate metabolism. These effects of methotrexate contribute to potent teratogenicity in humans. Birth defects in children born to women who have been treated with methotrexate include skeletal defects, low birth weight and a wide range of developmental abnormalities.

Retinoids: isotretinoin

The isotretinoin (13-cisretinoic acid), a synthetic retinoid, is the drug of choice in the management of severe treatment-resistant acne and is widely used for a range of dermatological conditions. The severe teratogenic effect contains serious craniofacial, cardiovascular, thymic and central nervous system malformations. It has a wide spectrum of side effects, including reproductive, cutaneous, ocular, neurological, musculoskeletal and hepatic side effects. The pregnant women exposed to isotretinoin during the first trimester of pregnancy are at high risk level of malformations. It has ability to inhibit the differentiation of sebaceous glands, corrects the keratinisation defect in the follicle and has also some anti-inflammatory activity.

However, along with its wide usage, there are growing incidences of its side effects and the most important side effect is the teratogenicity. A thoracomphalopagus conjoined twin is the most common malformation associated with isotretinoin. It also produces craniofacial abnormalities including ear defects, dysmorphism, cleft palate, depressed nasal bridge and hypertelorism.

CNS abnormalities comprise hydrocephalus, microcephaly, facial nerve palsy, cortical and cerebellar defects. The abnormalities of cardiovascular system consist of tetralogy of fallot, transposition of the great vessels, septal defects and aortic arch hypoplasia. Thymic abnormalities include ectopic, hypoplasia and aplasia. The drug also produces spina bifida and limb reduction.

Penicillamine

D-penicillamine (DPA) (dimethylcysteine) is a sulfhydrylcontaining amino acid and has ability to chelate metals, particularly copper and increase their rate of excretion in the urine. As dose increased, it decreases concentra-tion of tissue copper level. In many studies it was observed that pregnant women treated with DPA showed fetal malformations. The correlation between low copper levels and a high frequency of fetal malformations and death suggested that copper could be a mediating factor in the expression of fetal abnormalities. DPA has ability to cross placental barrier which could be the reason behind its teratogenic potential. Pregnant women treated with DPA showed severe connective tissue defects in infants. It is a drug of choice in diseases like cystinuria, rheumatoid arthritis and Wilson's disease and pregnant patients with these diseases are prone to such severe teratogenic effect.

The copper dependent enzyme lysyl oxidase is required for the cross-linkage of elastic and collagen fibers in the dermis. The indirect inhibition of the enzyme activity by removal of copper from the tissues by penicillamine causes abnormal elastic fiber accumulation. Also the inhibition of the deamination of the lysine residues by the drug is necessary for elastin and collagen maturation contributing in abnormal elastic fiber accumulation.

Thalidomide

Thalidomide is the worst teratogen known in the history of medicine. Consumption of even very less amount of thalidomide leads to severe limb deformities of the fetus. The limb deformities produced by thalidomide is known as phocomelia and amelia that are characterized by severe shortening or complete absence of legs and or arms, whereas the ear malformations include anotia, microtia and hearing loss. Thalidomide has capability to induce reactive oxygen species and oxidative stress which upregulates expression of bone morphogenic proteins through aberrant nuclear Factor-kB activity. This alteration results in blocking fibroblast growth factor (Fgf8/Fgf10), protein kinase B and signaling proteins pathways known to be important for cell survival and proliferation.

Consumption of thalidomide during the first trimester of pregnancy induces dysgenesis of fetal organs. The antiangiogenic effect of thalidomide causes blunting of the growth of long bones in fetal body and leads to cell death and down regulation of growth factors including Fgf8 or Fgf10. The disruption of growth factor signaling pathways is one of the reasons for cell death. This sequence of events produce mesenchymal loss and result in limb deformities. It generates free radicals which cause oxidative damage to the embryonic cellular macromolecules and lead to teratogenic effect. Recently, thalidomide-binding protein, cereblon is identified. Thalidomide binds to cereblon and decreases its activity which is supposed to be the primary target of thalidomide teratogenicity.

Warfarin

It is a potent naturally occurring coumarin and acts as rodenticide, induces internal hemorrhage in rats and mice. It is also adopted in clinical medicine. Advantages of warfarin are water solubility, oral bioavailability and reversibility by the administration of vitamin. Warfarin is associated with fetal abnormalities. It produces embryotoxicity between 6 and 9 weeks of gestation. Warfarin therapy during pregnancy has been associated with spontaneous abortion, stillbirth, nasal hypoplasia, stippled epiphyses, distal limb hypoplasia and malformations of the CNS, eye, jaw and urinary tract.

Microhemorrhages in neuronal tissue due to low stores of vitamin K and low levels of vitamin K dependent procoagulant factors in the fetus are the major factors contributed to CNS defects and neurological abnormalities in children and adults born to women who use warfarin during pregnancy. Discontinuation of warfarin from 6 weeks of gestation until the end of first trimester reduces risk of warfarin embryopathy.

Xanthine alkaloids: caffeine

Caffeine is a white crystalline xanthine alkaloid. It is recognized as a stimulant of the CNS because of its ability to enhance alertness. It also produces diuresis, increases heart rate and blood pressure. Caffeine can be easily transferred into the embryo from the external environment and accumulate in the fetal brain that disrupts the normal processes of neuronal development. These characters of caffeine are responsible for its teratogenic effects.

Caffeine also causes thickening of cephalic mesenchymal tissue. In humans, as such caffeine does not cause teratogenicity. However it has ability to potentiate the teratogenic effect of other substances such as tobacco, and alcohol and acts synergistically with ergotamine and propranolol to induce maternofetal vasoconstrictions leading to malformations induced by ischemia.

Pesticides: organophosphates

Organophosphorus compounds (OPC) is a wide group of compounds that differs structurally and functionally. Each compound has a unique toxicological profile. Exposure during pregnancy causes malformation in fetus, neural tube defect and shortening of pregnancy. Main teratotoxicity includes decreasing in gestational duration, baby birth weight, body length and head circumference.

Exposure to OPC increases risk of neural tube defects and anencephaly or spina bifida. The exposure of OPC to pregnancy is an important entity because of its effect on two organisms, a mother and a fetus. OPC selectively inhibits brain cholinesterase but the effect of it is more pronounced in maternal brain as comp-ared to fetal brain may be due to placental and fetal detoxification of anti-cholinesterase.

Unnecessary Chemicals:

Alcohol

The study report related to teratogenic effects of alcohol was firstly identified and published as fetal alcohol syndrome (FAS) in 1973. FAS refers to pattern of birth defects in children born to women who are heavy drinkers. FAS is characterised by mainly brain, craniofacial and limb abnormalities in children and high risk of mental deficiencies. Teratogenicity of alcohol was dominantly observed in offspring of mothers who have consumed large quantities of alcohol during pregnancy. Several parameters like genetic factors inherited maternally or paternally, can contribute to the fetal susceptibility to alcohol damage. It is considered that alcohol consumption by father may alter his genetic material inherited by the fetus and provide another source of variability and severity in FAS.

Alcohol has ability to freely cross placental barrier. The ability of alcohol and one or more of its metabolite like acetaldehyde to cross placenta is the primary cause of FAS. As result of the kinetics of amniotic fluid circulation and absences or very less of enzymes necessary for drug biotransformation during fetal development, alcohol accumulates in amniotic fluid and acts as reservoir for unchanged alcohol and acetaldehyde. Thus, the embryo fetus is exposed to both compounds long after they have been cleared from the maternal organism.

Cocaine

Cocaine is a one of potent psychoactive substance. It has potential to inhibit the post-synaptic re-uptake of catecholamines, dopamine and tryptophan and blocks sodium ion permeability, resulting in an anesthetic effect. The potent vasoconstrictive effects of cocaine when exposed during the first trimester may increase the risk of structural abnormalities.

The women treated with cocaine showed placental abruption (premature separation of a normally implanted placenta) which is one of significant causes of maternal morbidity and fetal mortality. This effect may be due to maternal hypertension caused by the drug. Cocaine exposure increases fetal cardiovascular effects like heart rate, mean arterial pressure as a result of accompanying fetal hypoxaemia and the production of fetal catecholamines.

Physical Agents:

Cigarette smoking

Cigarette smoking by the mother is one of major reasons of general developmental abnormalities. Reduced growth in fetus is observed. The array of chemicals like nicotine, carbon monoxide and cyanide released during tobacco smoking interfere with the transport of amino acids across the placenta. Several mechanisms have been proposed like placental necrosis, inhibition of placental exchange and activation of metabolic enzyme based toxic reactive metabolites that produce teratogenic effect, but exact mechanism responsible for teratogenic effects in human is unclear.

Carbon monoxide produced during smoking crosses placenta and increases carboxyhemoglobin levels in blood which has longer half-life in fetal blood than in maternal blood. Nicotine released during cigarette smoking has vasoconstriction effect that results in uterine vascular constriction and intrauterine growth retardation because of decreased perfusion of fetal tissues. It also increases the risk of perinatal mortality and morbidity. The perinatal mortality is attributed to abruption placentae, placenta previa, spontaneous abortion, prematurity and intrauterine growth retardation, preterm delivery, perinatal mortality, subfertility, abnormal placentation, childhood morbidity and mortality, congenital malformations, gastroschisis, cardiac defects, chromosomal anomalies and central nervous system defects.

Ionizing radiation

The cell death or chromosome injury is the common reasons of embryo injury by ionizing radiation. Exposure of radiations 8-15 weeks after fertilization is the most critical exposure period leading to toxicity. Before implantation exposure to radiation causes teratogenic and growth retarding effects. The exposure leads to several effects such as human embryos abortion, malformations, intrauterine growth retardation and has early- or late-stage onset genetic disease of which permanent growth retardation is more severe. The CNS is predominantly affected by radiation exposure and leads to CNS abnormalities like early microcephaly, mental retardation and later increases incidence of hematopoietic malignancies and leukaemia. In early 19th century, X-ray radiation was used to induce abortions. A single dose of 360 rads is enough to kill a fetus before the 14th week of gestation.

The common teratogenic effects of radiation exposure are defects in the brain and eyes like microcephaly, hydrocephaly, microphthalmia, optic atrophy and cataracts. Skeletal, visceral and genital abnormalities are less frequent. Small doses of radiation may induce mutations of germ cells. Excessive exposure to radiation causes chromosomal fragmentation and alters DNA structure leading to mutations. It also impairs cell division and produces cell death and malignancy. Even a small dose of radiation (10 rads) will kill preimplantation embryos.

Conclusion

Pregnancy is a unique physiological condition where drug treatment plays a major role. Most women take a medicine at some point during pregnancy and especially more than 80% of this includes at least one prescribed medication. Some women enter pregnancy with medical conditions like asthma, epilepsy, schizophrenia, hypertension, etc., that requires treatment. But every drug administered or taken by pregnant women may affect the health of both the mother and fetus. Various drugs like antiepileptic, antipsychotics, vitamin A, purine derivatives, antidepressants with benzodiazepines, flavonoids, caffeine, alcohol consumption, smoking and substance abuse causes significant congenital malformations and other perinatal complications.

Teratogenicity or reproductive and developmental toxicity has increasingly been recognized as a most important part of overall toxicology. Each compound has its own unique toxicological profile and mechanism of teratogenicity. The present view-point is to explore and review the teratogenic mechanism and common teratogenic effects of the teratogenic compounds and physical agents. Preconception counseling may play an important role to increase women's knowledge related to the teratogenic drug use and its effects during pregnancy that helps to protect the unwanted birth defects.

References :

- www.elsevier.com/locate/apjtd
- www.wjpps.com
- www.wikipedia/Pregnancy category.htm
- www.fda.org/Pregnancyc ategories.htm

Zika Virus

Zika virus (ZIKV) was first isolated and identified in in rhesus monkeys in the Zika Forest of Uganda in 1947. Studies suggest that humans in that area of Africa could also have been infected with the virus. It was subsequently identified in humans in 1952 in Uganda and the United Republic of Tanzania. From blood tests showed evidence of Zika virus infections in many other African countries and Indonesia (Egypt, Sierra Leone, Malaysia, Thailand, and the Philippines, for example), and researchers found that transmission of the virus to humans was done by mosquitoes (*Aedes aegypti*). In 2007, the virus was detected in Yap Island, the first report that the virus spread outside of Africa and Indonesia to Pacific Islands. The virus has continued to spread to North and South America (Mexico, Columbia, Brazil and into the Caribbean islands).

Virology

Zika virus (ZIKV) is a member of the Flaviviridae virus family and the Flavivirus genus, transmitted by Aedes mosquitoes. Along with other viruses in this family, Zika virus is enveloped and icosahedral with a nonsegmented, single-stranded, positive-sense RNA genome. It is most closely related to the Spondweni virus and is one of the two viruses in the Spondweni virus clade.

Epidemiology

Serological surveys in Africa and Asia indicate a most likely silent ZIKV circulation with detection of specific antibodies in various animal species (large mammals such as orangutans, zebra, elephants, water buffaloes) and rodents.

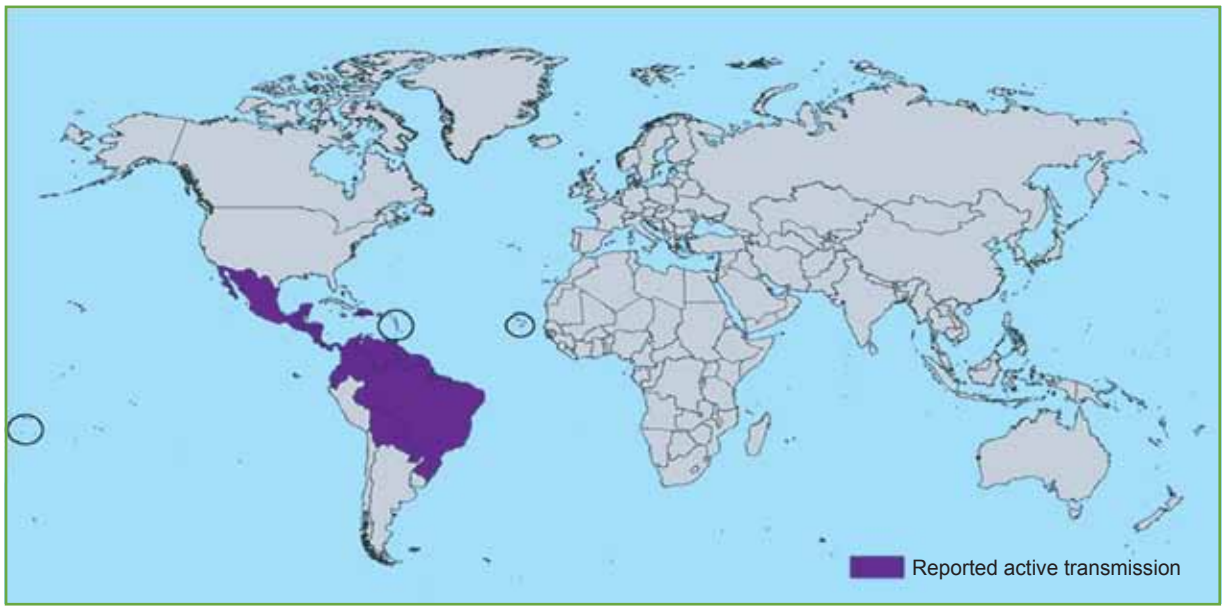


Figure 1: Countries and territories with active Zika virus transmission

The most recent outbreaks have been noted in Puerto Rico, Cape Verde Islands, and a large ongoing outbreak is occurring in Brazil that started in May 2015 and is ongoing. The first isolation of Zika virus in the U.S. occurred in January 2016 in Harris County (Houston), Texas, from an individual who became infected in El Salvador in November and returned to Texas. Although there have not been documented mosquito transmissions in the U.S., Texas and other states have two mosquito strains that could be capable of transmitting the viruses.

The knowledge of geographical distribution of ZIKV is based on results of serosurveys and viral isolation in mosquitoes and humans, and with reports of travel-associated cases and very few published outbreaks. Before 2007, the areas with reported ZIKV circulation included tropical Africa and Southeast Asia.

An outbreak was reported on Yap Island, Federated States of Micronesia (FSM) from April to July 2007. This was the first outbreak of ZIKV identified outside of Africa and Asia.

Between 2013 and 2015, several significant outbreaks were notified on islands and archipelagos from the Pacific region including a large outbreak in French Polynesia. In 2015, ZIKV emerged in South America with widespread outbreaks reported in Brazil and Columbia.

Geographic Distribution

Prior to 2015, Zika virus outbreaks have occurred in areas of Africa, Southeast Asia, and the Pacific Islands. In May 2015, the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed Zika virus infections in Brazil. Currently, outbreaks are occurring in many countries. Zika virus will continue to spread and it will be difficult to determine how the virus will spread over time.

Countries and territories with active Zika virus transmission (upto January 2015)

Americas: Barbados, Bolivia, Brazil, Colombia, Commonwealth of Puerto Rico-US territory, Costa Rica, Curacao, Dominican Republic, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Jamaica, Martinique, Mexico, Nicaragua, Panama, Paraguay, Saint Martin, Suriname, U.S. Virgin Islands, Venezuela.

Oceania/Pacific islands: American Samoa, Samoa, Tonga

Africa: Cape Verde

Modes of Transmission

Zika virus is transmitted to humans primarily through the bite of an infected *Aedes* species mosquito, mainly *Aedes aegypti* in tropical regions. This is the same mosquito that transmits dengue, chikungunya and yellow fever. Other *Aedes* mosquito species (notably *Ae. africanus, Ae. albopictus, Ae. polynesiensis, Ae. unilineatus, Ae. vittatus and Ae*. hensilli) are considered as potential vectors of ZIKV. The mosquito vectors typically breed in domestic water-holding containers; they are aggressive daytime biters (especially in midmorning and between late afternoon and twilight) and feed both indoors and outdoors near dwellings. Nonhuman and human primates are likely the main reservoirs of the virus, and anthroponotic (human-to-vector-to-human) transmission occurs during outbreaks.

Perinatal, in utero, and possible sexual and transfusion transmission events have also been reported. Zika virus RNA has been identified in asymptomatic blood donors during an ongoing outbreak.

Clinical Signs & Symptoms

The incubation period ranges between approximately 3 to 12 days after the bite of an infected mosquito. About 1 in 5 people infected with Zika virus become symptomatic. Characteristic clinical findings are acute onset of fever with maculopapular rash, arthralgia, or conjunctivitis. Other commonly reported symptoms include myalgia and headache. Clinical illness is usually mild with symptoms lasting for several days to a week. Severe disease requiring hospitalization is uncommon and case fatality is low. However, there have been cases of Guillain-Barre syndrome reported in patients following suspected Zika virus infection. The Brazil Ministry of Health is also investigating the possible association between Zika virus and a reported increase in the number of babies born with microcephaly. Due to concerns of microcephaly associated with maternal Zika virus infection, fetuses and infants of women infected with Zika virus during pregnancy should be evaluated for possible congenital infection and neurologic abnormalities. Further evidence is needed to establish a causal link between these neurological/ neurodevelopmental impairments and infections with ZIKV.

Diagnosis

Based on the typical clinical features, the differential diagnosis for Zika virus infection is broad. In addition to dengue, other considerations include leptospirosis, malaria, rickettsia, group A streptococcus, rubella, measles and parvovirus, enterovirus, adenovirus, and alphavirus infections (e.g., Chikungunya, Mayaro, Ross River, Barmah Forest, O'nyong-nyong, and Sindbis viruses). Preliminary diagnosis is based on the patient's clinical features, places and dates of travel, and activities. ZIKV disease diagnostics is primarily based on detection of viral RNA from clinical specimens in acutely ill patients. The viraemic period appears to be short, allowing for direct virus detection during the first 3-5 days after the onset of symptoms.

ZIKV RNA has been detected in urine up to 10 days after onset of the disease. From day five post onset of fever, serological investigations can be conducted by detection of Zika-specific IgM antibodies and confirmation by neutralisation, seroconversion or four-fold antibody titer increase of Zika-specific antibodies in paired serum samples. Serological results should be interpreted according to the vaccination status and previous exposure to other flaviviral infections.

Treatment

No specific antiviral treatment is available for Zika virus disease. Treatment is generally supportive and can include rest, fluids and use of analgesics and antipyretics. Because of similar geographic distribution and symptoms, patients with suspected Zika virus infections also should be evaluated and managed for possible dengue or chikungunya virus infection. The treatment is symptomatic and mainly based on pain relief, fever reduction and antihistamines for pruritic rash. Treatment with acetylsalicylic acid, aspirin and nosteroidal ant-inflammatory drugs (NSAID) is discouraged because of a potential increased risk of hemorrhagic syndrome reported with other flaviviruses as well as the risk of Reye's syndrome after viral infection in children and teenagers. People infected with Zika, chikungunya, or dengue virus should be protected from further mosquito exposure during the first few days of illness to prevent other mosquitoes from becoming infected and reduce the risk of local transmission.

Prevention

Public health control measures

- ❏ No vaccine or prophylactic drug is available.
- ❏ Integrated vector management program aiming to reduce mosquito vector density in a sustainable manner is of primary importance. Intersectoral collaboration and efficient public communication strategy to ensure community participation are required for sustainable vector control program.
- ❏ Activities supporting the reduction of mosquito breeding sites in outdoor/indoor areas by draining or discarding sources of standing water at the community level include:
  - → removal of all open containers with stagnant water in and surrounding houses on a regular basis (flower plates and pots, used tires, tree-holes and rock pools) or if that is not possible, treatment with larvicides)
  - → tight coverage of water containers, barrels, wells and water storage tanks,
  - → wide use of window/door screens by the population.
- ❏ Measures aiming to control larvae and adult mosquito vector population can be applied in an outbreak situation.
- ❏ In affected outbreak areas, elimination of adult mosquitoes through aerial spraying with insecticides can be considered.

Infection control, personal protection and prevention

- ❏ Prevention is also based on protection against mosquito bites. Aedes mosquitoes have diurnal biting activities in both indoor and outdoor environments. Therefore personal protection measures should be applied all day long and especially during the hours of highest mosquito activity (mid-morning, late afternoon to twilight).
- ❏ Personal protection measures to avoid mosquito bites should be applied when staying in risk areas by:
  - → using repellents and wearing long-sleeved shirts and long pants especially during the hours of highest mosquito activity,
  - → using long-lasting insecticidal treated mosquito bed nets which are essential in providing protection from mosquitos bites if the accommodations are not adequately screened or air conditioned,
  - → removing mosquito breeding sites in close outdoor/indoor premises.
- ❏ Repellent use must be strictly done in accordance with the instructions indicated on the product label. For newborn children under three months of age, repellents are not recommended.
- ❏ Travelers, especially children, pregnant women, and people with immune disorders or severe chronic illnesses, should consult their doctor or seek advice from a travel clinic to receive personalised recommendations on use of repellents and protection before travelling;

- Similar protective measures apply to a symptomatic patient in order to prevent transmitting the disease to non-infected mosquitoes.

Zika and Pregnancy

According to CDC, it is expected that the course of Zika virus disease is similar to that in the general population. No evidence exists to suggest that pregnant women are more susceptible or experience more severe disease during pregnancy. It is not known if pregnant women are more susceptible to Guillain-Barré syndrome they said.

There have been reports of congenital microcephaly in babies of mothers who were infected with Zika virus while pregnant. Zika virus infections have been confirmed in several infants with microcephaly; it is not known how many of the microcephaly cases are associated with Zika virus infection.

Studies are under way to investigate the association of Zika virus infection and microcephaly, including the role of other contributory factors (e.g., prior or concurrent infection with other organisms, nutrition, and environment).

The full spectrum outcomes that might be associated with Zika virus infections during pregnancy is unknown and requires further investigation.

CDC recommends that pregnant women in any trimester should consider postponing travel to an area where Zika virus transmission is ongoing. If a pregnant women is considering travel to one of these areas, she should talk to her healthcare provider. If she travels, she should strictly follow steps to avoid mosquito bites during the trip.

Women trying to become pregnant who are considering travel to an area with Zika virus transmission should consult with their healthcare provider before traveling to these areas and strictly follow steps to prevent mosquito bites during the trip.

Obstetrical providers should obtain a travel history from all pregnant women and use recent travel history to guide decisions about testing. Testing is not indicated for pregnant women without a travel history to an area with Zika virus transmission. Pregnant women with a history of travel to an area with Zika virus transmission and who report two or more symptoms consistent with Zika virus disease (including acute onset of fever, maculopapular rash, arthralgia or conjunctivitis) during or within two weeks of travel should be tested. In addition, pregnant women with a history of travel to an area with Zika virus transmission and who have ultrasound findings of fetal microcephaly or intracranial calcifications should also be tested for Zika virus infection.

Zika virus RT-PCR and serology assays can be performed on maternal serum or plasma. Zika virus RT-PCR can also be performed on amniotic fluid. Other testing that can performed includes the following:

1) Histopathologic examination and immunohistochemical staining of the placenta and umbilical cord
2) Zika virus testing of frozen placental tissue and cord tissue and
3) IgM and neutralizing antibody testing of cord blood.

Amniocentesis should be offered to pregnant women with recent travel to an area with Zika virus transmission, reporting 2 or more symptoms within two weeks of travel and a positive or inconclusive maternal serum test. For pregnant women with recent travel to an area with Zika virus transmission and ultrasound findings of microcephaly or intracranial calcifications, amniocentesis may also be considered. Consultation with a maternal-fetal medicine specialist should be considered.

While amniocentesis is a relatively safe test, risk and benefits of amniocentesis should always be considered. An amniocentesis can be used to provide additional clinical information. For example, a positive RT-PCR result on amniotic fluid would be suggestive of intrauterine infection and potentially useful to pregnant women and their healthcare providers to guide decisions about timing of delivery and the level of neonatal care at delivery sites.

Timing of amniocentesis should be individualized based on the patient's clinical circumstances.

Amniocentesis is not recommended until after 15 weeks of gestation. Amniocentesis performed ≥15 weeks of gestation is associated with lower rates of complications than those performed at earlier gestational ages (≤14 weeks of gestation).

However, the exact timing of amniocentesis should be individualized based on the patient's clinical circumstances. Referral to maternal-fetal medicine or infectious disease specialist with expertise in pregnancy management may be warranted. Risk and benefits of performing the amniocentesis should be discussed with the patient.

A positive Zika virus RT-PCR result from amniotic fluid would be suggestive of intrauterine infection. This information would be useful for pregnant women and their healthcare providers to assist in determining clinical management (e.g., antepartum testing, delivery planning). A negative Zika virus RT-PCR result from amniotic fluid may prompt a work up for other causes of microcephaly (e.g., other infections, genetic disorders).

The accuracy of ultrasound to detect microcephaly in the setting of maternal Zika virus is not known and will depend on many factors such as the timing of maternal infection relative to the timing of screening, severity of microcephaly, patient factors (e.g., obesity), gestational age, the equipment used and the expertise of the person performing the ultrasound.

Because the absence of fetal microcephaly and intracranial calcifications on ultrasound at one point in pregnancy does not exclude future microcephaly, serial ultrasounds may be considered. As more information is obtained day by day specifically related to Zika virus infection and microcephaly, it is expected that more specific guidance for women and their healthcare providers will be developed.

Zika Virus Infection and Congenital Microcephaly

According to CDC Zika virus infections have been confirmed in several infants with microcephaly from Brazil. The time frame and geographic location of reports of infants with microcephaly coincides with the outbreak of Zika virus infections in Brazil. The baseline prevalence of congenital microcephaly is difficult to determine because of underreporting, and the inconsistency of clinical criteria used to define microcephaly. Although population-based estimates of congenital microcephaly in Brazil vary, the number of infants with microcephaly currently being reported in Brazil is greater than would be expected.

Brain abnormalities reported in infants with microcephaly and laboratory-confirmed congenital Zika infection include microcephaly and disrupted brain growth. Some infants with possible Zika virus infection have been found to have intracranial calcifications and abnormal eye findings. It is not known if Zika virus infection caused any of these abnormalities.

A report of 35 infants with microcephaly who were born during an outbreak of Zikus virus infection in Brazil in 2015 described the following brain abnormalities: intracranial calcifications, ventriculomegaly, and neuronal migration disorders (lissencephaly and pachygyria). Other anomalies included congenital contractures and clubfoot. An important distinction is that neither these infants nor their mothers had laboratory-confirmed Zika virus; however, most of the mothers (~75%) reported symptoms consistent with Zika virus.

No treatment is currently available for Zika virus infection. Care for these infants is focused on diagnosing and managing conditions that are present, monitoring the child's development over time, and addressing problems as they arise. The prognosis for infants with congenital Zika virus infection is not known. In infants with severe microcephaly from other causes, a range of neurologic sequelae have been reported (e.g., intellectual disability, hearing loss, vision loss and seizures). These problems can range from mild to severe, are often life long and in some cases can be life threatening. Testing for Zika virus infection is recommended for infants born to women who traveled to or resided in an area with ongoing Zika virus transmission during pregnancy who were 1) diagnosed with microcephaly or intracranial calcifications detected prenatally or at birth or 2) who have mothers with positive or inconclusive test results for Zika virus infection.

Zika virus infection can be diagnosed by performing reverse transcriptase-polymerase chain reaction (RT-PCR) on infant serum. Serology assays can also be used to detect Zika virus-specific IgM and neutralizing antibodies. However, since it has not been established which test is most reliable for a diagnosis in infants, RT-PCR and IgM tests should both be performed.

Plaque-reduction neutralization testing (PRNT) can also be performed to measure virus-specific neutralizing antibodies and differentiate from other flaviviruses.

Zika virus RT-PCR and serology assays can be performed on infant serum or serum or plasma collected from the umbilical cord. If cerebrospinal fluid (CSF) specimens are available, Zika virus RT-PCR should be performed; however, CSF specimens should not be collected for the sole purpose of Zika virus testing. Other specimens that can be tested include the placenta and the umbilical cord. Histopathologic examination and immunohistochemical staining can be performed. Zika virus RT-PCR on fixed and frozen tissue should also be considered.

A newborn is considered to be congenitally infected if 1) Zika virus RNA is detected in any newborn specimen or during testing of amniotic fluid or the placenta or 2) Zika virus IgM antibodies are detected along with confirmatory neutralizing antibody tiers that are ≥4-fold higher than dengue virus neutralizing antibody titers in the infant serum or cerebrospinal fluid (CSF). Testing for congenital infection is considered inconclusive if Zika virus IgM antibodies are detected but Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titers.

Zika virus testing in newborns has several challenges. RT-PCR tests may not detect Zika virus RNA in a newborn who had Zika virus infection in utero if the period of viremia has passed. Serologic tests for Zika virus can often be falsely positive because of cross-reacting antibodies against related flaviviruses (e.g., dengue and yellow fever viruses). Plaque-reduction neutralization testing (PRNT) can be performed to measure virus-specific neutralizing antibodies to Zika virus, but neutralizing antibodies may still yield cross-reactive results in newborns due to maternal antibodies that were transferred to the infant. It is important to work closely with state or territorial health departments to ensure the appropriate test is ordered and interpreted correctly.

A thorough physical examination should be performed, including careful measurement of the head circumference, length, weight and assessment of gestational age. Cranial ultrasound is recommended unless it was performed as part of prenatal screening in the third trimester and clearly showed no abnormalities of the brain. Ophthalmologic evaluation is recommended as well as repeat hearing screen at six months of age. Continued evaluation of developmental characteristics and milestones, including head circumference, is recommended through the first year of life.

Consultations are recommended with a clinical geneticist or dysmorphologist, a pediatric neurologist and a pediatric infectious disease specialist. A complete blood count, platelet count, and liver function tests should also be conducted. If any additional congenital anomalies are identified through clinical examination and imaging studies, genetic and other teratogenic causes should be considered.

For infant without suspected abnormalities, health care providers should continue with routine pediatric care. If the infant has microcephaly or intracranial calcifications, health care providers should continue to evaluate and treat for other possible etiologies.

If the newborn does not have abnormal findings on examination, the infant should receive routine pediatric care including measurement of growth and development and appropriate evaluation and follow-up for any clinical findings that arise. If the newborn has abnormal findings on examination, diagnostic testing for other causes of the newborn's conditions should be performed including testing for other congenital viral infections if indicated.

Although Zika virus RNA has been detected in breast milk, transmission of Zika infection through breastfeeding has not been documented. Based on available evidence, the benefits of breastfeeding infants outweigh any theoretical risk related to Zika virus infection.

(This article has been edited last on 25 February 2016)

References :

- http://www.cdc.gov/zika/
- http://ecdc.europa.eu/
- http://www.medicinenet.com/zika_virus/
- http://www.who.int/mediacentre/factsheets/zika/en/

Test Yourself - 39

Correct Answers :

1.	c	2.	d	3.	a	4.	d	5.	c	6.	b

CONGRATULATIONS!

WINNERS

Dr. Afroza Khatun
MBBS, MS (Obs & Gyn)
Jr. Consultant
Shibganj, Chapai Nawabganj

Dr. MM Himel
D. Card, Jr. Consultant
Labaid Cardiac Hospital
Dhaka

Dr. Md. Raihan Ali
MBBS, BCS, MO
Parbotipur UHC, Dinajpur

Dr. Enamul Haque
MBBS, DCH, Jr. Consultant
Nilphamari Sadar Hospital

Dr. Md. Mainul Islam Mohim
MBBS (Intern)
SBMCH, Barisal

Dr. D. G. M. Akaiduzzaman
FCPS, MS (ENT), Associate Prof.
SSMCMH, Dhaka

Dr. Helal Uddin
MBBS
Homna UHC, Comilla

Dr. Syed Md. Tanjidul Islam
MBBS, BCS, MO
Feni 250 Bedded District Sadar Hospital
Feni

Dr. Lutfun Nahar
FCPS (Obs & Gyn), Consultant,
General Hospital, Faridpur

Dr. Sheikh Md. Arafat Rahman
FCPS (Ophthalmology), Consultant
Community eye care & research center
Rangpur

Test Yourself - 40

1. The followings are true for "Teratogenic Drug" except:

a. Cigarette smoking by the mother is one of the major reasons of general developmental abnormalities.
b. Thalidomide is the worst teratogen known in the history of medicine.
c. No prevalence of major or minor malformation was found among the offspring of women taking phenytoin during pregnancy.
d. The pregnant women exposed to isotretinoin during the first trimester are at high risk levels of malformations.

2. All the followings are correct for "Zika Virus" except:

a. The virus may be detected in the blood during the first 3 - 5 days after the onset of symptoms.
b. Treatment of Zika Virus disease is generally supportive, no specific antiviral treatment is available till now.
c. Zika Virus infections have been confirmed in several infants with microcephaly.
d. Reverse transcriptase-polymerase chain reaction has no role for diagnosing this infection in children.

3. All the below are true for "Sleep Disorder" except:

a. Primary sleep disorders result from an endogenous disturbance in sleep-wake generating or timing mechanisms.
b. Parasomnias are characterized by abnormalities in the amount, qualities or timing of sleep.
c. Dreaming occurs mainly during REM sleep.
d. Non-REM sleep is subdivided into four progressive categories.

4. All the followings are correct for "Zika Virus" except:

a. This virus was first isolated and identified in the rhesus monkeys in the Zika forest of Uganda.
b. The first outbreak of Zika Virus outside Africa and Asia identified in July 2008.
c. Before 2015, the outbreaks of this virus have occurred in areas of Africa, Southeast Asia and the Pacific Islands.
d. The incubation period ranges between about 3 - 12 days after the bite of an infected mosquito.

5. The followings are right for "Sleep Disorder" except:

a. Major causes of insomnia may be divided into medical, psychological and environmental problem.
b. Around 40% of the people with depression have insomnia.
c. Zolpidem and Zaleplon are the safest agents for long term use.
d. Suvorexant is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

6. All the followings are correct for "Teratogenic drug" except:

a. Defects in the development of the heart are the least common birth defects.
b. Administration of teratogen during the period of organogenesis leads to gross malformations.
c. ACE inhibitors and Angiotensin receptor antagonists cause oligohydramnions and renal failure if administered during later stages of pregnancy.
d. The pregnant women exposed to isotretinoin during the first trimester of pregnancy are at high risk level of malformations.

Soon our officials will be visiting you with a token of our appreciation

Composition

Grastim™ : Each 0.5 ml Pre-filled syringe contains sterile solution of Filgrastim BP (rG-CSF) 30 MU (300 mcg).

Description

Filgrastim is a recombinant methionyl human granulocyte colony stimulating factor (Filgrastim). Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology using Escherichia coli as an expression host. The protein has an amino acid sequence similar to the natural sequence predicted from the human DNA sequence analysis, except for the addition of an N-terminal methionine.

Indications and Usage

a. Cancer patients receiving myelosuppressive chemotherapy

b. Patients with Acute Myeloid Leukemia, receiving Induction or consolidation chemotherapy

c. Cancer patients receiving bone marrow transplant

d. Patients undergoing peripheral blood Progenitor cell collection and therapy

e. Patients with severe chronic neutropenia

Administration

Filgrastim should not be administered within 24 hours before or after chemotherapy. Filgrastim is administered by subcutaneous injection or i.v. infusion

Adverse Effects

Neutropenia, vomiting, leukopenia, anaemia, thrombocytopenia, pyrexia, back pain, abdominal pain, diarrhoea, cough, pain, nausea, pain in extremity, headache, constipation, stomatitis, asthenia, mucosal inflammation, alopecia.

Contraindications

Filgrastim is contraindicated in patients hypersensitive to the drug, any ingredient in the formulation, or proteins derived from Escherichia coli.

Pediatric Precautions

Filgrastim has been used in children 3 months to 18 years of age without unusual adverse effect. However, safety and efficacy of the drug in neonates or patients with autoimmune neutropenia of infancy have not been established

Pregnancy and Lactation

Pregnancy category : C. although there are no adequate and controlled studies to date in humans, Filgrastim has been shown to adversely affect pregnancy and the fetus in animals. Filgrastim should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. It is not known whether Filgrastim is distributed into milk. Because many drugs are distributed into milk, Filgrastim should be used with caution in nursing women.

Drug Interaction

a. The safety and efficacy of concomitant administration of doses of Filgrastim with doses of myelosuppressive antineoplastic agents have not been established.

b. Because transient decreases in platelet counts have been reported in some patients receiving Filgrastim, it is recommended that the drug should be used with caution in patients receiving other drugs known to decrease the platelet count.

Overdose

Limited information is available on the acute toxicity of Filgrastim in humans.

Storage

Grastim™ should be stored between 2˚C- 8˚C in a refrigerator. Do not freeze. Avoid shaking

Presentation

Grastim™ : Each box contains 1 Pre filled Syringe of 300 mcg (30 MU) Filgrastim in Alu-Alu blister pack.

SQUARE PHARMACEUTICALS LTD. BANGLADESH

Bisocor®

2.5 mg
5 mg

Bisoprolol Fumarate Tablet

Ensures controlled Blood pressure in smokers

Anclog®

Clopidogrel 75 mg Tablet

Prevents smoking induced platelet aggregation

Since 1958

SQUARE
PHARMACEUTICALS LTD.
BANGLADESH

Heart for Life™

www.squarepharma.com.bd

SQUARE

March 2016 Vol 23 No. 1 ISSN 1681-5552

Healthcare bulletin the SQUARE

Medical services department, SQUARE PHARMACEUTICALS LTD. Corporate headquarters, Square centre
48, Mohakhali Commercial Area, Dhaka- 1212, Tel: 8833047-56, 880-2-9859007 (10 lines) Fax: 880-2 882 8608 / 882 8609
Email: infosquaregroup.com, Web page; http//www.squarepharma.com.bd, Omar Akramur Rab <oar@squaregroup.com>

Designed by Creative services, PMD
SQUARE PHARMACEUTICALS LTD.