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Info Medicus

The essence of medical practice

CONTENTS

EDITORIAL

Dear Doctor,

On behalf of the entire editorial board, we are grateful to all our readers for their visible contribution and encouragement that have added to the success of Info Medicus so far. We are confident with your ongoing support and assistance Info Medicus will continue to be an important medium for disseminating new informations in these rapidly evolving areas of medical science.

Today's young generation is increasing in obesity which will eventually lead to diabetes. Therefore, we have selected type 2 diabetes in youth as one of the Patient Handouts. Our hands are the most important weapons of our body. Keeping this in mind, we have selected Examinations of the hand and wrist as our topic in Essential procedure.

Women's mortality is increasing day by day due to cervical cancer. It has become an alarming issue for developed and developing countries. There are many new management techniques of cervical cancer that we have discussed elaborately in review article section. Hope this will be beneficial in your daily practice. Other sections remain as usual.

Thanking you and warm regards

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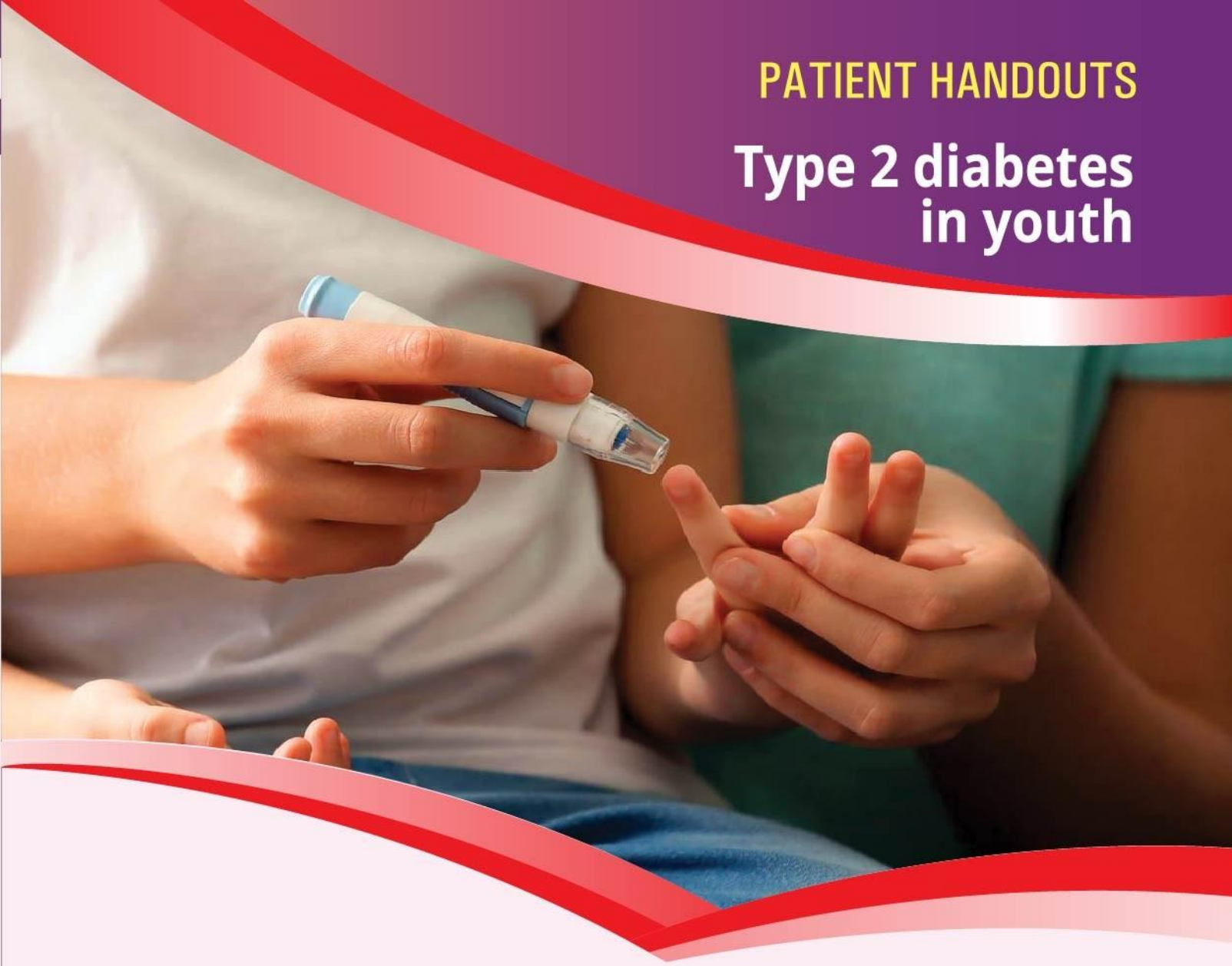
Type 2 diabetes in youth



What is type 2 diabetes?

Diabetes is when the body cannot control the amount of sugar in blood. Usually, a hormone called insulin helps to turn the sugar from food into energy for the body. In diabetes, body does not make enough insulin (type 1 diabetes) or doesn't use it right (type 2 diabetes). Diabetes can cause problems in the heart, blood vessels, eyes, kidneys, and feet. Adults usually get type 2 diabetes, but more and more children and teenagers are getting the disease. This could be because more children are overweight.

How to know if a child is at risk of getting type 2 diabetes?

Children are more likely to get the disease if they are overweight or have a family member who has type 2 diabetes, high blood pressure, or high cholesterol. Children of certain races are more likely to get the disease (for example, American Indians, Blacks, Hispanics or Latinos, Asian Americans and Pacific Islanders).

How to prevent a child from getting type 2 diabetes?

Exercise and eating right can help a child stay a healthy weight and lower the chances of getting the disease. Children should exercise at least one hour almost every day. For example, children could walk, ride a bike, dance, or play sports. Fruits, vegetables, whole grains, lean meats, nuts, and low fat yogurt are healthy food choices. Child should drink water or low fat milk instead of soda and fruit drinks. If the child is overweight, he or she should lose weight to prevent the disease.

How is type 2 diabetes managed?

Diabetes can be managed with diet, exercise, and medicine. Glucose meter can be used to check blood sugar levels during the day. Parents should be aware of their child's blood pressure and cholesterol levels to make sure they stay normal.

How can the parent help their child controlling type 2 diabetes?

Diabetes can be stressful for children and their families. Parents should watch for signs of depression or eating disorders in their child. Parents should talk to their child about not using tobacco, alcohol, and other drugs. Parents should teach their child how to manage his or her diabetes at school. A teacher or school nurse can also help.

Reference: Am. Fam. Phys., 01 September 2007, Vol. 76(5):665-666

Low back pain

What is low back pain?

Low back pain is feeling soreness or discomfort in lower back, buttocks, or hips. It is a common problem.

What causes low back pain?

It is usually caused by muscle strain in lower back. If straining a muscle in the back, it can hurt to move, walk, bend or twist. Another cause of low back pain is a bulging disk. Sometimes, back pain is caused by an infection, cancer, or other diseases.

Who gets low back pain and why?

Three out of four people have low back pain at some time in their lives. People get low back pain from straining to lift heavy objects or by twisting the back. People often hurt their backs when they are moving furniture, playing sports, or gardening.

How long the pain will last?

Most people slowly start to feel better over a few weeks. Nearly all people are completely better within six to eight weeks.

What can patient do to manage the pain?

- Not doing the things that make the pain worse, like sitting for a long time, lifting heavy objects, bending or twisting
- Stick to normal activities as much as possible. Gentle exercise like walking and some pain killer medicines helps to get better faster
- Using heating pads or taking a warm bath or shower may help with the pain
- Exercise, a physical therapist, massage therapist or chiropractor may reduce the pain and make feel better

What can patient do to prevent low back pain?

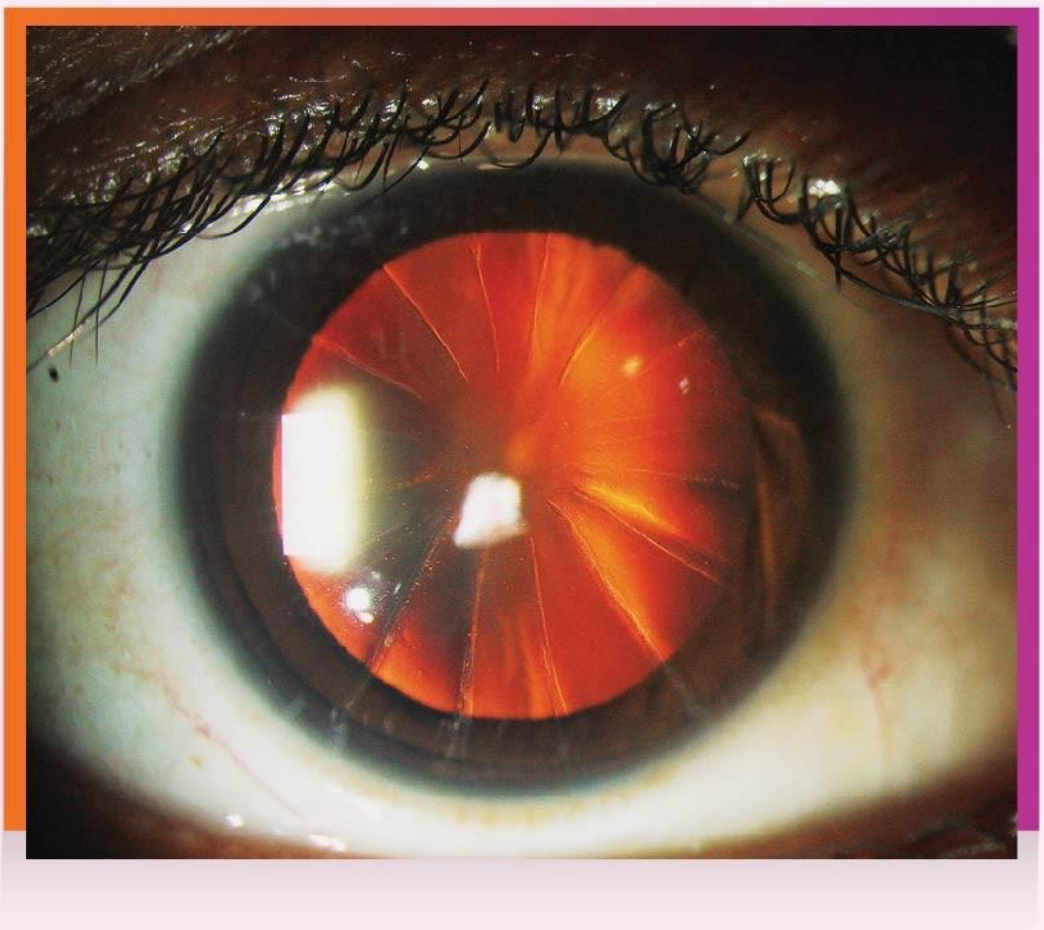
Low back pain can be prevented with physical therapy, exercising and stretching. Regular exercise and weight loss helps if patient is overweight. Regular exercise like walking, swimming or biking is good for the back. Don't twist the body while lifting. If sitting at desk or driving for a long time, take breaks to stretch.

When patient should get medical care right away?

- When patient is older than 50 years
- When the pain was caused by an injury, like a fall or car crash
- When trouble sleeping because of the pain
- When trouble urinating or controlling bowels

Reference: Am. Fam. Phys., 01 October 2018, Vol. 98(7)

Radial keratotomy



A 41 year old woman presented to the ophthalmology clinic with vision that had been deteriorating during the preceding 20 years. Her subjective refraction showed that a hyperopic shift had occurred since her current corrective lenses had been prescribed. Her best corrected visual acuity was 20/25 in both eyes. Slit lamp examination revealed features that suggested that radial keratotomy had been performed: a clear central cornea with 16 corneal incisions extending from the periphery. Because radial keratotomies are performed manually, the incisions are neither perfectly radial nor symmetric. The patient confirmed that she had undergone this surgery for the treatment of myopia 23 years before presentation. At the time of the procedure, she had had no immediate complications.

Radial keratotomy was frequently performed in the 1980s and 1990s to correct myopic refractive errors. However, the procedure is associated with a number of complications. Overlapping or excessively central incisions may lead to reduced visual acuity, and corneal scarring is associated with glare and halos. Patients are at risk for progressive hyperopia and, in rare cases, owing to reduced corneal biomechanical strength, globe rupture with minimal trauma. The Patient received a new prescription for corrective lenses and was advised of the importance of protective eye wear. At a 6-month follow-up visit, her vision had not deteriorated further.

Reference: N. Eng. J. Med., 24 January 2019, Vol. 380(4):e4

Examination of the hand and wrist

Overview

The hand and the wrist are complex. They have a higher concentration of joints than any other part of the body. Here we describe the anatomy of the hand and approaches to the assessment of common diseases of the hand.

Anatomy of the hand

Familiarity with the terms used to describe the anatomy of the hand is important for clinical assessment. The terms "volar" and "palmar" refer to the palm of the hand and the term "dorsal" refers to the back of the hand. The "radial border" refers to the edge of the hand next to the thumb and the "ulnar border" refers to the opposite edge next to the fifth digit. Each finger is composed of three phalangeal bones that articulate at three joints: the metacarpophalangeal joint between the metacarpal bone and the proximal phalanx, the proximal interphalangeal joint between the proximal and intermediate phalanges and the distal interphalangeal joint between the intermediate and distal phalanges. The thumb has only two phalangeal bones and two joints: the metacarpophalangeal joint and the interphalangeal joint.

The anatomical snuffbox is the triangular depression on the dorsal radial aspect of the hand and wrist and is an important surface landmark. The two sides of the isosceles triangle that make up the anatomical snuffbox are formed by the extensor muscles of the thumb. The base of the triangle is formed by the radial styloid process in the wrist and the apex is denoted by the carpometacarpal joint at the base of the thumb. The scaphoid bone which is positioned in the floor of the snuffbox is the carpal bone that is most commonly fractured.

Examination of the hand

A general examination of the hand includes inspection, palpation, assessment of range of motion and assessment of grip strength. Start by observing the dorsal and volar aspects of the hand for signs of trauma and deformity. Next palpation is done by palpating each digit, the dorsal and volar aspects of the palm and the wrist for tenderness or abnormal masses paying close attention to areas of sensitivity to lumps if present. This part of the examination can be performed while taking a history from the patient. To assess range of motion the patient should be asked to make a fist and then to fully extend all digits. Next the patient should ask to extend and flex the hand at the wrist and to bend the wrist towards the thumb (radial deviation) and towards the little finger (ulnar deviation) paying close attention to any stiffness and asymmetry. Finally physician should assess grip strength in both hands by asking the patient to squeeze two of the fingers in each of the hands tightly.

Common conditions of the hand and wrist

Carpal tunnel syndrome: The carpal tunnel is a passageway for the median nerve, tendons and connective tissue on the palmar side of the wrist residing just below the transverse carpal ligament when the palm is facing upward. Swelling of any of the nine tendons within the carpal tunnel can increase compartmental pressure and compress the median nerve causing the symptoms that are characteristic of carpal tunnel syndrome including tingling and pain in the fingers or hand and numbness in the thumb, the second and third digits and the radial half of the fourth digit. To assess for carpal tunnel syndrome, first physician should assess for sensation to light

touch at the terminal pads of the fingers. Although assessment of two point discrimination or the ability to discern two distinct points on the skin is more sensitive assessment for an asymmetric or abnormal response to light touch may also be useful. Next to determine whether there is nerve irritation, the patient should assess for Tinel's sign by firmly percussing the median nerve.

Durkan's test is done by using thumb to compress the carpal tunnel for up to 30 seconds (Figure-1). The onset of pain, tingling or any abnormal sensation in the median nerve distribution constitutes a positive test result.

Figure-1: Durkan's carpal tunnel compression test

Next, Phalen's maneuver should be performed by asking the patient to hold the wrist in forced flexion for 30 to 60 seconds (Figure-2). This maneuver can increase pressure on the carpal tunnel and further irritate the median nerve causing abnormal sensations that include burning, tingling or numbness in the thumb or in the second or third digits.

Figure-2: Phalen's maneuver

Carpal tunnel syndrome is caused by ischemia of the median nerve. A decrease in cardiac output during sleep can exacerbate the ischemia, resulting in pain that may cause the patient to wake during the night. Splinting which minimizes wrist flexion and extension, can alleviate symptoms by decreasing external compression of the carpal tunnel. However, unrelenting symptoms may be an indication for surgical release. Prolonged compression or ischemia of the median nerve can lead to irreversible damage.

Injuries of the digital flexor: Each finger has two tendons. One is the flexor digitorum profundus tendon which is assessed by having the patient flex the distal interphalangeal joint. The other tendon is the flexor digitorum superficialis which is assessed by having the patient flex the proximal interphalangeal joint of the affected finger while holding the other fingers in an extended position. By blocking flexion of the other digits the work done by the flexor digitorum superficialis can be isolated from the work done by the flexor digitorum profundus, thus allowing a more specific evaluation of the former (Figure-3).

Figure-3: Assessment of the flexor digitorum superficialis

Finkelstein's test can be used to assess for de Quervain's disease. The test is done by placing the patient's thumb against the hand and closing the fingers to form a fist. Deviate the wrist in the ulnar direction (Figure-4). If the result is positive the patient will feel a sharp pain. A positive result in the Finkelstein's test may be an indication of de Quervain's disease.

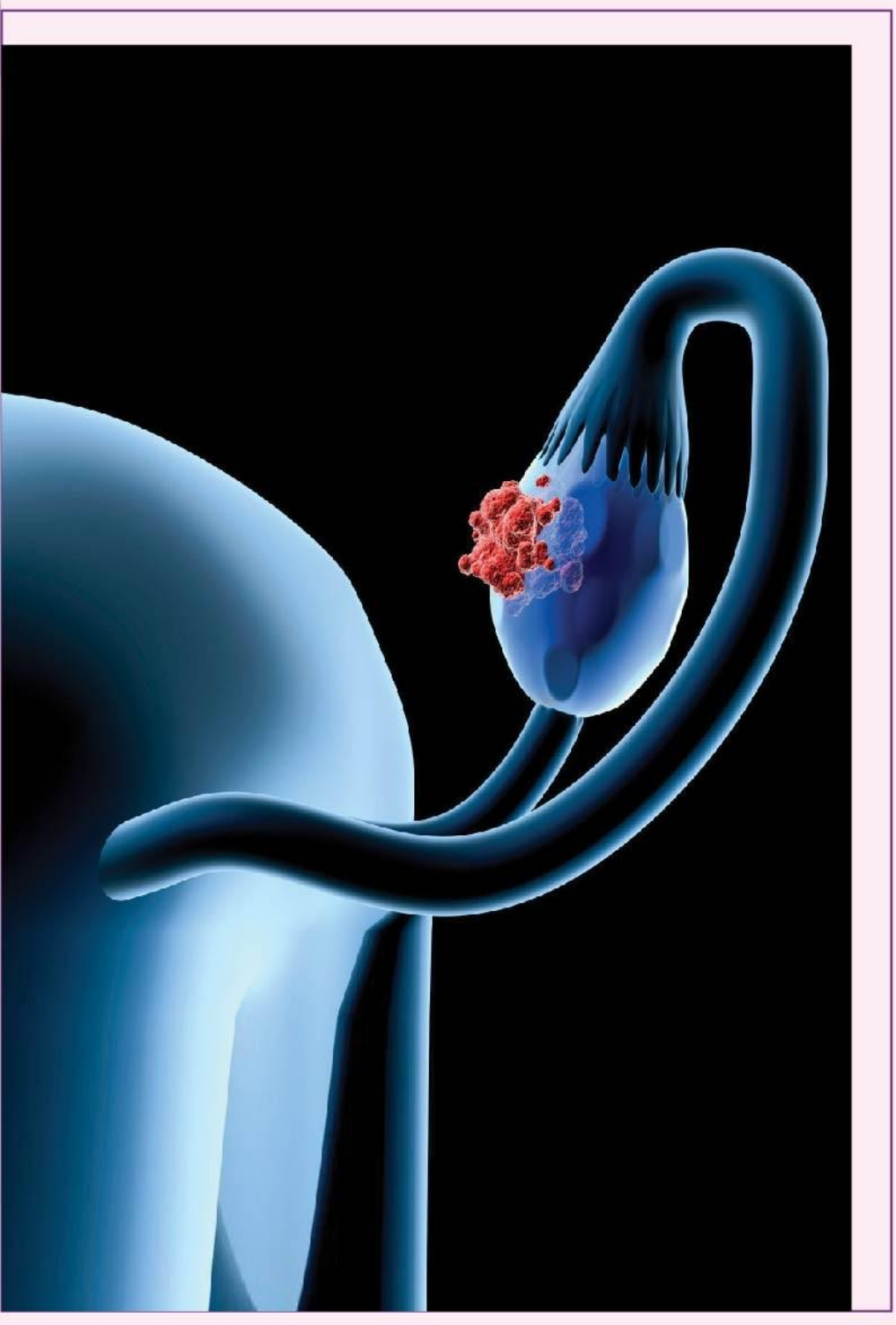
Figure-4: Finkelstein's test

Summary

Proper clinical evaluation of the wrist requires the clinician to obtain a patient's medical history and to inspect and palpate the site of injury. Depending on the circumstance, a radiograph can be helpful and surgical consultation may be necessary.

Reference: N. Engl. J. Med., 21 March 2019, Vol. 380;12:e15 (1-6)

Carcinosarcoma: A rare tumour of the ovary



Introduction

Primary ovarian carcinosarcoma is a rare tumour. It accounts for 1-3% of ovarian malignancies. In this tumour both epithelial and stromal components are malignant. It is also known as malignant mixed mesodermal tumour or Malignant Mixed Mullerian Tumour (MMMT). They are further sub-classified as "heterologous" or "homologous." This categorization is based on the presence or absence of astromal component containing mesenchymal tissue not normally found at the primary tumour site. Usually there is the extra-ovarian intra-abdominal spread at the time of diagnosis in the majority of the cases. The primary treatment has traditionally been surgical cytoreduction followed by radiotherapy and chemotherapy or chemotherapy alone. These tumors are aggressive in nature with poor prognosis.

Case report

A 60 year old postmenopausal female presented with pain and distension of abdomen since 15 days. She came with complaints of white discharge per vagina on and off, breathlessness and increased frequency of micturition and loss of appetite since 10 days. She had no history of bleeding per vagina, loss of weight. There was no past history of any medical or surgical illness.

On examination, she was averagely built with pallor present. Her pulse, blood pressure, respiratory and cardiovascular system were normal. Her abdomen was distended. She had a suprapubic mass of 24 weeks uterine size, cystic in nature, non-tender. Per speculum examination revealed cervix flushed with vagina and vagina was pale. Cervix was flushed with vagina as revealed by per vaginal

examination. Uterine size could not be made out as there was a tense cystic mass felt through all fornices. Per rectal examination revealed a diffuse cystic mass felt anteriorly and the rectal mucosa was free.

The contrast enhanced Computerised Tomography (CT) of the abdomen showed a well defined hypodense lesion of approximately 13.6 x 14.3 x 15.3 cm noted in the lower abdomen, arising probably from the ovary. Both the ovaries not visualised separately. Uterus appears atrophic. Multiple heterogenous enhancing lymph nodes seen in the pre and para aortic region and pelvis, largest of size 1.2 x 1.2 cm. The ascites was moderate. The cytological examination of the peritoneal fluid was positive for malignant cells.

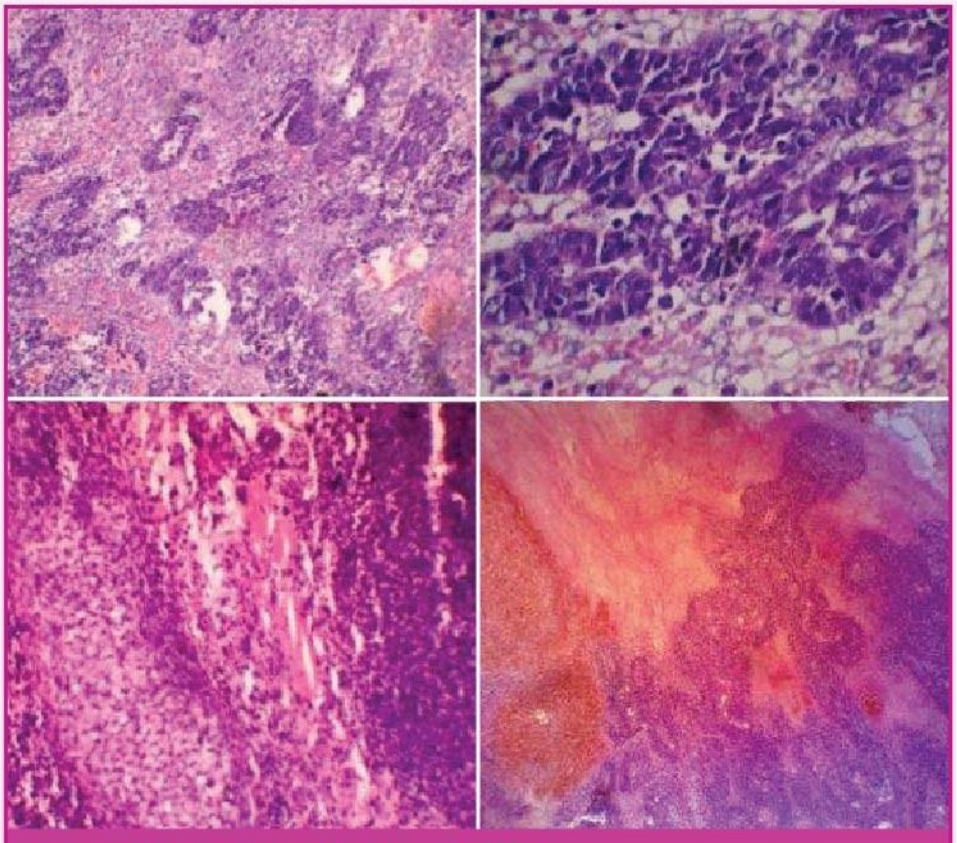


Figure-1: Histopathologic findings of MMMT

The level of cancer antigen (CA)-125 was elevated (281.3 IU/ml, normal < 35 IU/ml). The routine haematological and biochemical investigations were within the normal limits. A staging laparotomy was done. Peritoneal fluid was haemorrhagic. Peritoneum was thin, vascular and adherent to the bladder on the lower half. Intra operatively there was a large irregular friable mass present just below the peritoneum, occupying the space below the umbilicus, adherent to the small and large intestine. The uterus was small and atrophic, both adnexa was oedematous and vascular. Left ovary was totally replaced by growth. Right ovary was atrophic. Maximum debulking surgery was done followed by total abdominal hysterectomy with bilateral salpingo-oophorectomy, along with infra colic omentectomy. There were 5-6 pre and para-aortic, non-mobile, enlarged lymph nodes. Peritoneal biopsies were taken. All specimens and peritoneal fluid sent for histopathological and cytological examination.

Cut section of the malignant ovarian mass showed areas of necrosis, cystic areas, whitish nodules and brownish areas with necrosis. Microscopically, there were solid sheets of plump spindle cells with ovoid hyperchromatic nuclei and high mitotic activity. There is moderate pleomorphism and anisonucleosis with many foci of poorly differentiated cells. Ocassional bizzare and multinucleolated cells are also seen. Few fragments show islands of chondroid differentiation, multinucleate and rhabdoid differentiation. Occasional focus shows squamous differentiation. At places plump spindles cells arranged in interlacing fasciles and whorl like pattern are seen. Extensive areas of haemorrhage and necrosis are seen. Atypical mitotic figures are plenty. Cervix showed chronic cervicitis with extensive squamous metaplasia and mild dysplasia. There was no evidence of metastatic deposits. Based on the histopathological findings, the final diagnosis was given as malignant mixed mullerian tumour (Carcinosarcoma) of the ovary. The patient had an uneventful post-operative period. She was discharged and advised medical oncology consultation following surgery.

Summary

To summarize, malignant mixed mullerian tumors of the ovary are very aggressive tumors that were usually diagnosed at an older age compared to women with epithelial ovarian cancer. MMMT are usually at an advanced stage at the time of diagnosis and survival after diagnosis varies by stage of disease and histological type. Despite aggressive treatment that includes surgery and chemotherapy, women with these tumors have a significant increased risk of death compared to women with epithelial ovarian cancer and very poor prognosis. The poor prognosis associated with this rare disease emphasizes the need for collaborative prospective studies targeted to better understand the molecular changes of MMMT and the need to design new therapeutic regimens to improve patients' survival.

Reference: Ind. J. Obs. Gyn., Jan-Mar 2019, Vol. 7, N. 1:112-116

Scientists have created synthetic DNA with 4 extra letters

Scientists have recently molded a new kind of DNA into its elegant double helix structure and found it had properties that could support life. The researchers from U.S.A. crafted the synthetic DNA using four additional molecules so that the resulting product had a code made up from eight letters rather than four. With the increase in letters this DNA had a much greater capacity to store information. Scientists called the new DNA "hachimoji" meaning "eight letters" in Japanese, expanding on the previous work from different groups that had created similar DNA using six letters. Natural DNA is composed of four molecules called nitrogenous bases that pair up with each other to form the code for life on Earth. A binds with T, G binds with C. The hachimoji DNA includes these four natural bases, plus four more synthetically made nucleotide bases: P, B, Z and S. The research group included several different teams across the U.S. They created hundreds of these hachimoji double helixes with different combinations of the natural and synthetic nucleotide base pairs. Then they conducted a series of experiments to see if the various double helixes had properties needed to support life. Natural DNA has a hallmark property that no other genetic molecule seems to have. It's stable and predictable.

Senior author Steven Benner, a distinguished fellow at the foundation for applied molecular evolution in Florida agreed that if life is also coded in DNA it's not going to be exactly like what we have here on earth. Benner noted that DNA that stores information isn't enough. It also has to have the ability to transfer that information to its sister molecule RNA so that RNA can then instruct proteins to carry out all the business in an organism. With that in mind the researchers developed synthetic enzyme proteins that facilitate a reaction that successfully copied hachimoji DNA into hachimoji RNA. Furthermore, they found that the RNA molecule was able to fold into a sort of L shape that would be necessary for it to further transfer information. The team created three crystal structures of hachimoji DNA, each with different sequences of the eight base pairs and found that indeed each formed the classic double helix. In order for the hachimoji DNA to support life there's a fifth requirement. However the researchers stopped short of investigating this step in order to prevent the molecule from becoming a biohazard that could one day work its way into the genomes of organisms on earth.

Reference: www.livescience.com

Overview of cervical cancer

Introduction

Cancer is increasingly growing as a major public health problem in both developed and developing countries amongst the chronic diseases. Cancer can impose health, heavy economic and social burden. It is a global pandemic affecting both developed and developing regions, but it is rapidly increasing in low and middle income countries where resources for prevention, diagnosis and treatment are limited or non-existent. Cervical cancer has become a major public health issue in the developing countries. The burden of the disease is considerable with associated morbidity and mortality among women in their productive years. The most important risk factor for cervical cancer is infection by the Human Papilloma Virus (HPV). HPV is a group of more than 150 related viruses, some of which cause a type of growth called papilloma's which are more commonly known as warts. These HPVs are grouped into low and high risk HPVs respectively. The low risk types of HPV are those types which hardly cause cancer but may cause warts on or around the female and male genital organs and in the anal area (such as HPV 6 and 11) while the high risk are those HPV which are linked to cancers most especially HPV 16 and 18 which causes about two-thirds of all cervical cancers.

Epidemiology

Cervical cancer is the fourth most common type of cancer in women in the world and in some low income countries it is the most common cancer in women. Persistent infection with oncogenic genotypes of the sexually transmitted human papilloma virus is a necessary, although not sufficient, factor in the development of this cancer. Globally, there are 528,000 new cases of cervical cancer per year, 85% of which occur in low income countries; highlighting the significant inequities that exist in global health. Annually, 266,000 women die of cervical cancer which is as high a death toll as that of maternal deaths. Although there is effective screening for cervical cancer, it continues to be a healthcare problem in developing countries where effective screening programs are limited. Cervical cancer is the second leading malignancy in terms of both incidence and mortality among Bangladeshi women. While incidence and treatment modalities for cervical cancer have been previously investigated in Bangladeshi populations there is virtually no published information regarding outcomes among those treated from cervical cancer. Data collection in resource limited countries has been challenging and new options using low tech applications have been suggested.

Anatomical considerations

The cervix which is the lowermost part of the uterus is a cylindrical shaped structure composed of stroma and epithelium. The intravaginal part, the ectocervix, projects into the vagina and is lined by squamous epithelium. The endocervical canal extends from the internal os at the junction with the uterus to the external os which opens into the vagina and is lined by columnar epithelium. Almost all cases of cervical carcinoma originate in the transformation zone from the ecto cervical or endocervical mucosa. The transformation zone is the area of the cervix between the old and new squamocolumnar junction.

Risk factors

Several risk factors increases the chance of developing cervical cancer. Women without any of these risk factors rarely develop cervical cancer. Although these risk factors increase the odds of developing cervical cancer, many women with these risks do not develop this disease. When a woman develops cervical cancer or pre-cancerous changes, it might not be possible to say that a particular risk factor was the cause. Cervical cancer risk factors include:

- Human papillomavirus (HPV): Almost all (99.7%) cervical cancer cases are result of persistent infection with high risk type HPV. There are 15 high risk (oncogenic) HPV, with just two, 16 and 18 responsible for 70% of all cervical cancers. HPV commonly spreads through sexual contact; it can spread without sex, by skin to skin contact with an infected area of body. Most of these infections are transient and 90% resolve spontaneously within 2 to 5 years. On an average, a newly diagnosed HPV infection in young women lasts from 8 to13 months
- Sexual activity: Most common route of spread of HPV infection is through sexual contact especially early onset sexual activity, multiple partners, high risk sexual partners and failure to use condoms
- Compromised immune system: A weak immune system, as a result of HIV or by drugs causing suppression of immune response places women at high risk for HPV infection and cervical cancer
- Teenage pregnancy: A first term pregnancy in women < 17 years of age doubles risk of cervical cancer later in life as compared to women with first term pregnancy at age 25 and older
- Multiple pregnancies: Women with 3 or more pregnancies are at an increased risk due to hormonal changes or weak immune system during pregnancy
- Family history: Woman with mother or sister having cervical cancer has 2 to 3 times risk of developing cervical cancer than women without family history
- Oral contraceptives: Long term use (> - 5 years) increases risk of cervical cancer
- Smoking: Smoking also increases risk of squamous cell cancer by exposing body to cancer causing chemicals and also by weakening immune system
- Dietary habits: A diet deficient in fruits, vegetables, as well as being overweight, increases risk of cervical cancer
- Diethylstilbestrol (DES): DES increases risk of adenocarcinoma in cervix, especially in women whose mothers took DES when pregnant

Classification

According to gross pathology

- Exophytic lesions: Most common form and arises on ectocervix. Grows to form large, friable, polypoidal masses that bleed profusely
- Infiltrating lesions: Presents as stony hard cervix with minimal or invisible lesion on cervix
- Ulcerative lesions: Presents as an ulcer over cervix often replacing whole of cervix

According to histopathology

- Squamous cell carcinoma (66%): Arises in squamous epithelial cells of cervix
- Adenocarcinoma (28%): Arises from mucus-producing glandular cells of endocervix
- Rarer types (6%): Adenosquamous carcinoma, neuroendorine carcinoma

Staging

There are two types of staging, the TNM staging system and FIGO staging of cancer of the cervix uteri (Table-1).

The TNM staging system

TNM stands for Tumour, Node and Metastasis. This system describes the size of the initial cancer (the primary tumour), whether the cancer has spread to the lymph nodes and whether it has spread to a different part of the body (metastasized). The system uses numbers to describe the cancer.

- **T** refers to the size of the cancer and how far it has spread into nearby tissue - it can be 1, 2, 3 or 4, with 1 being small and 4 large
- **N** refers to whether the cancer has spread to the lymph nodes - it can be between 0 (no lymph nodes containing cancer cells) and 3 (lots of lymph nodes containing cancer cells)
- **M** refers to whether the cancer has spread to another part of the body - it can either be 0 (the cancer hasn't spread) or 1 (the cancer has spread)

FIGO staging

The FIGO staging was based mainly on clinical examination with the addition of certain procedures that were allowed by FIGO to change the staging.

Table-1: FIGO staging of cancer of the cervix uteri (2018)

Stage	Description
I	**The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)**
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion < 5 mm[a]
- IA1	Measured stromal invasion < 3 mm in depth
- IA2	Measured stromal invasion ≥ 3 mm and < 5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥ 5 mm (greater than Stage IA), lesion limited to the cervix uteri[b]
- IB1	Invasive carcinoma ≥ 5 mm depth of stromal invasion and < 2 cm in greatest dimension
- IB2	Invasive carcinoma ≥ 2 cm and < 4 cm in greatest dimension
- IB3	Invasive carcinoma ≥ 4 cm in greatest dimension
II	**The carcinoma invades beyond the uterus but has not extended onto the lower third of the vagina or to the pelvic wall**
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
- IIA1	Invasive carcinoma < 4 cm in greatest dimension
- IIA2	Invasive carcinoma ≥ 4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	**The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes[c]**
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent
- IIIC1	Pelvic lymph node metastasis only
- IIIC2	Para-aortic lymph node metastasis
IV	**The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous edema as such, does not permit a case to be allotted to Stage IV)**
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

When in doubt, the lower staging should be assigned.

[a]Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumor size and extent, in all stages.

[b]The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.

[c]Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. Example: If imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r, and if confirmed by pathologic findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented.

Dissemination and spread

Direct local extension and lymphatic spread are main routes of spread of cervical cancer. Hematogenous dissemination is rare and occurs commonly with more advanced disease or unusual types, such as adenosquamous or neuroendocrine tumors.

Direct extension: Involves uterine body, vaginal walls, parametrium, peritoneal cavity, bladder or rectum. Ovarian involvement by direct extension is very rare; ovarian metastases occur in 0.5% of squamous and 1.7% of adenocarcinomas. Lateral spread of cervical cancer may involve ureters. It may spread posteriorly to involve rectum or uterosacral ligaments. Anteriorly it spreads to involve bladder, but this is rare in absence of large volume tumors.

Lymphatic embolization: Lymphatic spaces involvement causes lymphatic embolization to regional lymph nodes. It is commonly seen with large volume tumors and/or if many lymphatic spaces are involved. Lymphatics from cervix drain into external iliac, hypogastric, obturator and common iliac nodes. Anterior channels pass behind bladder and drain in external iliac nodes. Posterior channels drain directly into common iliac and para-aortic nodes and superior rectal nodes.

Hematogenous spread: Poorly differentiated, aggressive types are more likely to spread by hematogenous route. Hematogenous spread usually occurs through invasion of veins rather than arteries. About 1% to 2% of women with cervical carcinomas show lung metastases, and 5% to 35% develop pulmonary metastases. Other common sites of hematogenous metastases are liver (3%), bone (16%) and bowel.

Clinical features

In its early stages, cervical cancer usually has no symptoms. The only way to know if there are abnormal cells in the cervix which may develop into cervical cancer, is to have a cervical screening test. If symptoms are present, they usually include:

Early symptoms

- Profuse, thin, watery, blood tinged discharge
- Intermittent, painless metrorrhagia or spotting
- Postcoital or post-douching bleeding or spotting

Symptoms of advanced disease

- Bleeding episodes become heavier, frequent and last longer
- Post-menopausal bleeding
- Referring pain to flanks or legs due to involvement of ureters, pelvic wall, sciatic nerve routes
- Dysuria, hematuria - due to bladder involvement
- Rectal bleeding, obstipation - due to rectum involvement
- Edema lower extremities (one or both) due to lymphatic and venous blockage by pelvic wall disease
- In severe cases uremia as a result of bilateral ureteric compression and damage of kidney due to back pressure

Prevention

The most common form of cervical cancer starts with pre-cancerous changes and there are ways to stop this disease from developing. The first way is to find and treat pre-cancers before they become true cancers, and the second is to prevent the pre cancers. A well-proven way to prevent cervix cancer is to have testing (screening) to find pre-cancers before they can turn into invasive cancer. The Pap test (or Pap smear) and the human papilloma virus test are used for this.

Primary prevention

This is aimed at protecting uninfected individual women from being exposed to human papilloma virus and it can be achieved through:

Vaccination: HPV vaccination helps to reduce the chances of getting cervical cancer. It works by building natural immunity against specific types of HPV targeted by the vaccines. The vaccine is recommended for every woman as from the ages of 9 years and above so as to build immunity against HPV 16 and 18 which have been identified to be the prime cause of cervical cancer.

Delayed onset of sexual intercourse: Delaying the onset of sexual intercourse to at least 20 years will allow full maturation of the transformation zone making it less vulnerable to human papilloma virus.

Secondary prevention

This is aimed at increasing the health seeking behaviour of those at risk for early detection and management. This can be achieved through:

PAP smears screening: This is recommended to every woman starting from 3 years of post coital exposure and/or from 20 years of age and above. The frequency of the screening is directly proportional to the increasing risk of the cervical cancer.

Intensified awareness creation: This is targeted at informing almost every woman on the existence of Pap smear as well as inculcates the consciousness in them. This can be achieved through the use of I.E.C (information, education and communication) materials, mass media, news headlines and health education.

Screening

Cervical cancer screening is the systematic application of a test to identify cervical abnormalities in an asymptomatic population. Women targeted for screening may actually feel perfectly healthy and see no reason to visit health facilities. Key facts about cervical cancer screening are:

- Cervical cancer screening is the testing for pre-cancer and cancer of women at risk, most of whom will be without symptoms
- At a minimum, screening is recommended for every woman 30 to 49 years of age at least once in a life time
- Three different types of tests are currently available:
  - Conventional (Pap) and liquid based cytology (LBC)
  - Visual inspection with acetic acid (VIA)
  - HPV testing for high risk HPV types (e.g. types 16 and 18)

Criteria for the age and frequency of cervical cancer screening

- Women younger than 30 years of age should not undergo screening except for women known to be HIV infected or living in a high HIV prevalence area
- At a minimum, a national programme should prioritize women who are between 30 to 49 years old for screening
- The screening interval (frequency) should not be less than 5 years (and not less than 10 years, if using an HPV test)
- Priority should be given to maximizing coverage within the at risk target age group and assuring complete follow up of those women with abnormal screening test results rather than maximizing the number of tests performed in a woman's lifetime
- In high HIV prevalence countries, women who screen positive for cervical cancer should be offered HIV testing and counselling

Diagnosis and evaluation

Microinvasive disease

Diagnosis of Stage IA1 and IA2 is made on microscopic examination of a LEEP (loop electrosurgical excision procedure) or cone biopsy specimen, which includes the entire lesion. It can also

be made on a trachelectomy or hysterectomy specimen. The depth of invasion should not be greater than 3 mm or 5 mm respectively from the base of the epithelium, either squamous or glandular, from which it originates. Note must be made of lymphovascular space involvement which does not alter the stage, but may affect the treatment plan. The margins should be reported to be negative for disease. If the margins of the cone biopsy are positive for invasive cancer, the patient is allocated to Stage IB1.

Invasive disease

In the case of visible lesions, a punch biopsy may generally suffice, but if not satisfactory a small loop biopsy or cone may be required. Clinical assessment is the first step in allocation of staging. The revised staging permits the use of any of the imaging modalities according to available resources, i.e. ultrasound, CT, MRI, positron emission tomography (PET), to provide information on tumor size, nodal status, and local or systemic spread. The modality used in assigning staging should be noted for future evaluation. Imaging has the advantage of the ability to identify additional prognostic factors which can guide the choice of treatment modality. The goal is to identify the most appropriate method and to avoid dual therapy with surgery and radiation as this has the potential to greatly augment morbidity.

Management

Management of cervical cancer is primarily by surgery or radiation therapy, with chemotherapy a valuable adjunct.

Surgical management

Surgery is suitable for early stages where cervical conization, total simple hysterectomy or radical hysterectomy may be selected according to the stage of disease and extent of spread of cervical cancer.

Microinvasive cervical carcinoma: FIGO Stage IA

Stage IA1: The treatment is completed with cervical conization unless there is lymphovascular space invasion (LVSI) or tumor cells are present at the surgical margin. In women who have completed childbearing or elderly women, total extrafascial hysterectomy may also be recommended. When LVSI is evident, pelvic lymphadenectomy should be considered, along with modified radical hysterectomy. If fertility is desired, cervical conization with close follow up will be adequate.

Stage IA2: Since there is a small risk of lymph node metastases in these cases, pelvic lymphadenectomy is performed in addition to type B radical hysterectomy or more radical surgery. When the patient desires fertility, she may be offered a choice of the following: (1) cervical conization with laparoscopic (or extraperitoneal) pelvic lymphadenectomy; or (2) radical abdominal, vaginal or laparoscopic trachelectomy with pelvic lymphadenectomy.

Post-treatment follow up: Follow up with 3 monthly Pap smears for 2 years, then 6 monthly for the next 3 years is recommended after treatment of microinvasive carcinoma. With normal follow up at 5 years, the patient can return to the routine screening schedule according to the national guidelines.

Invasive cervical carcinoma: FIGO Stage IB1, IB2, IIA1

Surgical treatment is the preferred modality for the treatment of Stage IB1, IB2, and IIA1 lesions. It would usually consist of type C radical hysterectomy with pelvic lymphadenectomy.

FIGO Stage IB1: FIGO Stage IB1 is considered as low risk with the following criteria: largest tumor diameter less than 2 cm, cervical stromal invasion less than 50% and no suspicious lymph nodes on imaging. The standard management is a type C radical hysterectomy but modified radical hysterectomy may be considered in these cases. Pelvic lymphadenectomy should always be included on account of the high frequency of lymph node involvement. In young women desiring fertility sparing, a radical trachelectomy may be performed, indicated for Stage IA2 - IB1 tumors measuring less than or equal to 2 cm in largest diameter.

FIGO Stage IB2 and IIA1: In FIGO Stage IB2 and IIA1 cervical cancer, surgery or radiotherapy can be chosen as the primary treatment depending on other patient factors and local resources, as both have similar outcomes. The advantages of surgical treatment are:

- Feasible to determine the postoperative stage precisely on the basis of histopathologic findings, thereby enabling individualization of postoperative treatment for each patient
- Possible to treat cancers that are likely to be resistant to radiotherapy
- Possible to conserve ovarian function

FIGO Stage IB3 and IIA2

In Stage IB3 and IIA2, the tumors are larger and the likelihood of high risk factors such as positive lymph nodes, positive parametria, or positive surgical margins that increase the risk of recurrence and require adjuvant radiation after surgery are high. In such cases, adjuvant whole pelvic irradiation reduces the local failure rate and improves progression free survival compared with patients treated with surgery alone.

Concurrent platinum-based chemoradiation (CCRT) is the preferred treatment option for Stage IB3 to IIA2 lesions. In areas where radiotherapy facilities are scarce, neoadjuvant chemotherapy (NACT) has been used with the goal of:

- Down staging of the tumor to improve the radical curability and safety of surgery
- Inhibition of micro metastasis and distant metastasis

FIGO Stage IVA or recurrence

Rarely, patients with Stage IVA disease may have only central disease without involvement to the pelvic sidewall or distant

spread. In case of such a recurrence, pelvic exenteration can be considered but usually has a poor prognosis.

Radiation management

Radiation therapy for early stage disease (FIGO Stage IA, IB1, IB2, and IIA1)

Although surgery is preferred for early stage disease, in cases with contraindications for surgery or anesthesia, radiotherapy provides equally good results in terms of local control and survival. Patients with microinvasive disease have been treated by intracavitary radiation therapy (ICRT) alone with good results if surgery is contraindicated owing to medical problems. Both surgery and radiotherapy remain viable options for early stage disease. Definitive radiotherapy or Concurrent Chemoradiation (CCRT) is preferred in patients likely to require postoperative radiotherapy to avoid compounding treatment related morbidity.

Radiation therapy for FIGO Stage IB3 and IIA2

Although feasible, surgery as initial treatment is not encouraged for patients with Stage IB3 and IIA2 disease since 80% of them require Postoperative Radiotherapy (PORT) or Concurrent Chemoradiation (CCRT). CCRT is the standard of care for Stage IB3 and IIA2 disease. CCRT includes external radiation and intracavitary brachytherapy.

Radiation therapy for FIGO Stage IIB-IVA

Concurrent chemoradiation is considered the standard treatment for patients with Locally Advanced Cervical Cancer (LACC). The chemotherapy regimen is intravenous administration of weekly cisplatin during the course of External Beam Radiation Therapy (EBRT).

FIGO Stage IVB or distant metastases

Presentation with distant metastatic disease is rare, reported in about 2% of cases. A management plan should consider that the median duration of survival with distant metastatic disease is approximately 7 months. Concurrent chemoradiation may have better response than systemic chemotherapy with overall and disease-free survivals of 69% and 57% respectively, reported in patients with positive para-aortic and supraclavicular lymph nodes. When para-aortic nodes are involved, Extended Field Radiotherapy (EFRT) with concurrent chemotherapy should be used. Intensity Modulated Radiotherapy (IMRT) may be used in such patients to reduce the toxicity.

Radiation therapy after inadvertent incomplete surgery

Invasive cervical cancer may be found during pathologic evaluation of the specimen of a simple hysterectomy for an apparent benign condition. Inadvertent simple hysterectomy is considered inadequate surgery for invasive cervical carcinoma and subsequent therapy is required for all such cases. In such a situation, the extent of the disease should be assessed by a PET or CT scan if available, or a pelvic and abdominal CT or MRI scan, and chest imaging. The subsequent treatment plan is formulated based on the histologic and radiologic findings.

Post-treatment follow up

In a systematic review of 17 retrospective studies that followed up women treated for cervical cancer the median time to recurrence ranged from 7 to 36 months after primary treatment. Therefore, closer clinical follow up in the 2 to 3 years after treatment may be important. Routine follow up visits are recommended every 3 to 4 months for the first 2 to 3 years, then 6 monthly until 5 years and then annually for life.

Recurrent disease

Recurrences may occur locally in the pelvic or para-aortic, the patient may develop distant metastases, or there may be a combination thereof. Most recurrences are seen within 3 years and the prognosis is poor, as most patients die from progressive disease with uremia being the most common terminal event. The treatment plan depends on the patient's performance status, site and extent of recurrence and/or metastases and prior treatment received.

Local recurrence

The pelvis is the most common site of recurrence and patients who have only locally recurrent disease after definitive therapy whether surgery or radiotherapy, are in a more favorable situation as the disease is potentially curable. Good prognostic factors are the presence of an isolated central pelvic recurrence with no involvement of the pelvic sidewall, a long disease-free interval from previous therapy and the largest diameter of the recurrent tumor is less than 3 cm. When the pelvic relapse follows primary surgery, it may be treated by either radical chemoradiation or pelvic exenteration.

Para-aortic nodal recurrence

The second most common site of recurrence is in the para-aortic lymph nodes. Where there is isolated para-aortic nodal recurrence, curative-intent radiation therapy or chemoradiation, can achieve long-term survival in approximately 30% of cases.

Palliative radiotherapy

Common symptoms in patients with advanced incurable disease include vaginal bleeding, pelvic pain, malodorous discharge and symptoms related to metastatic disease, which may be distressing to the patient. Short course radiotherapy is very effective in palliation of such symptoms. In patients with pain arising from enlarged para-aortic or supraclavicular nodes, skeletal metastases and symptoms associated with cerebral metastases, palliative radiotherapy should be given via larger fractions over shorter periods of time.

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The safety of omeprazole during pregnancy

Introduction

Gastro esophageal reflux disease is one of the most troublesome gastrointestinal disorders during pregnancy. Heartburn is estimated to affect 30% to 50% of all pregnant women and together with regurgitation presents the predominant symptoms, worsening as pregnancy advances. Treatment is sometimes difficult because the disease can be resistant to most of the common recommended means such as lifestyle modifications, antacids and histamine blockers. Omeprazole has been shown to be efficacious in the treatment of conditions in which suppression of gastric acid secretion is required. Most documented exposures to Proton Pump Inhibitors (PPIs) during pregnancy have occurred with omeprazole. However, the available human data to support the safety of omeprazole in pregnancy are described below.

Study on omeprazole

A total 955 infants were identified (944 deliveries) where the mother had reported the use of omeprazole during pregnancy. Among them 815 mother (824 infants) reported the use of

omeprazole only during the first trimester, 91 mother (92 infants) only after the first trimester and 38 mother (39 infants) during both the first trimester and later. Among infants exposed to omeprazole during first trimester, five died. All five dead infants were stillborn without any congenital malformation. In total 950 live birth, 28 malformed infants were identified (whose mother exposed to omeprazole at first trimester) which are divided into relatively major conditions (16) and less severe conditions (12). There were eight cardiac defects and all but one (tetralogy of Fallot with an eye malformation) were mild or unspecified. The other major malformations occurs only in single instances. Among 28 malformed infant's mother, 16 mothers used different drugs simultaneously with omeprazole during pregnancy. Other factors also involved in this malformations were maternal age, parity and maternal smoking.

In another study, a total of 113 women exposed to omeprazole during pregnancy. Exposure during organogenesis was reported by 101 women (89%). A minority of patients (15%) reported omeprazole use throughout pregnancy. The most common indication was reflux esophagitis and heartburn, followed in prevalence by peptic ulcer and gastritis. Each woman exposed to omeprazole during pregnancy was subsequently matched to 2 controls selected from the Motherisk database: (1) a disease control (e.g., women with similar conditions for which omeprazole was taken but who took histamine blockers during pregnancy and (2) a nonteratogenic control, which included women who contacted Motherisk in a similar manner but who were exposed to a nonteratogenic agent (e.g., dental radiation, acetaminophen).

Among live born infants exposed to omeprazole during organogenesis, the incidence of major malformations did not differ from the other two groups. The major defects among omeprazole exposed fetuses were ventricular septal defect, polycystic kidneys, ureteropelvic junction stenosis, and patent ductus arteriosus (1 child each). Major defects among disease paired controls exposed infants were atrial septal defect and ventricular septal defect (1 child and 2 children, respectively). Defects among nonteratogenic controls were atrial septal defect with pulmonary stenosis and develop mental delay (1 child each). No differences were found among the groups for rates of elective abortions and preterm delivery, mean birth weight, and gestational age at delivery or method of delivery. All three groups had malformation rates consistent with the baseline of 1-3%. Cardiac defects were common in all three groups.

Healthy 20 women with an uncomplicated pregnancy of 36 weeks gestation or more and who were to be delivered by elective caesarean section under general anesthesia were selected for the study. They were given on the evening before surgery, 80 mg omeprazole orally. General anesthesia was induced, using a standard technique, 12-16 hours after omeprazole administration.

Blood samples were collected before and 7 days after omeprazole administration for full blood count and biochemical profile. Further blood samples were obtained at delivery for plasma omeprazole estimation, from the umbilical vein and umbilical artery of the infant and also from a maternal vein in the non-infused arm. All infants were examined at birth by a neonatologist and Apgar scores given at one and 5 minutes. The general well being of the infant was assessed daily for 7 days post-partum. No side effects of omeprazole treatment were reported during the pre-operative period and the induction, maintenance and emergence from anesthesia were free of incidents which could be related to its use.

The average Apgar scores at one and 5 minutes were 7.1 and 8.8 respectively. None of the 20 infants required transfer to the intensive care unit and their 7 day follow up revealed normal progress. The electrolyte and liver function screen showed no abnormal variations between pre and post-treatment values. Omeprazole treatment was well tolerated by the women and Apgar scores and subsequent progress of the babies were acceptable. These results indicate that gastric acidity and volume were acceptable in the majority of women after omeprazole treatment.

A cohort study of live births between 1996 and 2008 assessed the prevalence of major birth defects after exposure to PPIs during early pregnancy. 1,800 live born infants were exposed to omeprazole in the first trimester. No significant association was found between exposure to omeprazole during the first trimester and risk of major birth defects was found (2.9%).

Conclusion

Uses of omeprazole during pregnancy found no association between the drug and increased risk of major malformations, spontaneous abortions, decreased birth weight or preterm delivery. The UK National Teratology Information Service (UKTIS) recommends that if a PPI is required during pregnancy, omeprazole should be first choice, as the majority of available data concern this agent and are reassuring. No ill effects on offspring were seen. And according to BNF 75 omeprazole is not known to be harmful in pregnancy. However, a rule of thumb during pregnancy is to choose an older agent in a pharmacologic class for which there are more fetal safety data that indicate the medication is effective. Applying this rule to PPIs makes omeprazole the drug of choice for now.

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WORLD RABIES DAY

28th September 2019

Rabies: Vaccinate to Eliminate

HISTORY OF WORLD RABIES DAY

The first World Rabies Day (WRD) was organized by the two founding partner's Alliance for Rabies Control (ARC) and Centre for Disease Control and Prevention, Atlanta (CDC). On 8 September 2007 with the co-sponsorship of the World Health Organization (WHO), the world organization for animal health and the Pan American Health Organization (PAHO) had organized rabies day. Activities organized by WHO Headquarters (HQ), regional offices and its many rabies Collaborating Centres (CCs) were contributing to the overall aim of the WRD raising awareness about the impact of human and animal rabies, its easy prevention and how to control and to eliminate the disease in animals and humans. During the 25th International Congress for Pediatrics in Athens, 25-30 August 2007, Dr. Pronczuk, from the Department of Public Health and Environment (PHE), WHO/HQ, announced the first WRD and WHO's sponsorship. A special announcement was published in the WHO/UNEP children's environmental health newsletter.

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