Clinical Obstetrics, Gynecology and Reproductive Medicine

Review Article ISSN: 2059-4828

HPV induced tongue cancer in pregnancy: Diagnosis and the role of vaccination in management

Panagiotis Tsikouras[1*], Anastasia Bothou[1], Konstantinos Paraskevopoulos[2], Xanthoula Anthoulaki[1], Anna Chalkidou[1], Ioannis Tsirkas[1], Fotini Gaitatzi[1], Michael Koutsogiannis[1], Stavroglou Athanasia[2], Apostolos Lazarou[2], George Dragoutsos[2], Konstantinos Nikolettos[1], Panagiotis Petsidis[3], Stefanos Zervoudis[3], George Iatrakis[3], George Galazios[1], Ioannis Astridis[2], Nikolaos Nikolettos[1] and Konstantinos Vahtsevanos[2]

[1]Department of Obstetrics and Gynecology, Democritus University of Thrace, Greece 1

[2]Department of Oral and Maxillofacial Surgery, Papanikolaou General Hospital, Aristotle University of Thessaloniki Thessaloniki, Greece

[3]Department of Obstetrics and Gynecology, Rea Hospital, 17564 Athens, Greece

Abstract

Oral cancer is frequently a squamous cell carcinoma. In Western countries it is more commonly found on the tongue and consists one of the most common malignancies in the oral mucosa. The exact causes of squamous cell carcinoma are not known. There are many risk factors such as chemical, biological, natural and other related to culture, habits, customs and traditions, religion and environmental influences at the national level and differ in different nations. Biological agents are viruses (such as the herpes simplex virus, HPV, HIV) and mycoses. Human papillomavirus (HPV), especially HPV subtype 16, is on the rise in young people with oral cancer who are not smokers. Epidemiological studies throughout world with the help of molecular techniques undoubtedly show the crucial importance of human papillomavirus (HPV) in growth squamous cell carcinoma. The sensitive anatomical unit of the tongue in cases of malignancy in pregnant women creates significant bioethical concerns that must be addressed with delicacy, discernment and responsibility by the oncology medical team. The contribution of the 9 valent vaccination, which provides protection against this oncogenic subtype of HPV 16 associated with squamous cell carcinoma, is likely to be valuable to young women and men, and may be recommended after future studies during pregnancy.

Introduction

Oral cancer during pregnancy is rare with an incidence of less than 2%, and tongue cancer is the most common location in oral cancer, surpassing lip cancer in frequency over the past two decades [1-3]. For many years, health professionals were unsure about how to deal with this cancer especially during pregnancy. Most women with cancer start or continue treatment during pregnancy so there is more medical information and information about the treatment and course of cancer in pregnant women [4-6]. Cancer during pregnancy can be complicated for both the mother and for the medical staff that has undertaken the treatment and monitoring of her pregnancy. It is important to know that cancer itself rarely directly affects the developing fetus. Until the 1980s, squamous cell carcinoma of the tongue was considered as a predominant disease in men as only approximately 10% was observed in women [7]. In recent years, there has been a significant increase in the incidence of this disease in females, apparently as a result of the influence of many of the harmful habits of men, which were followed also by the female sex [7-12]. The treatment is carefully planned so that both the woman and the unborn baby to be safe. In general, cancer treatment during pregnancy requires close teamwork with an interdisciplinary team of oncologists and obstetricians who specialize in high-risk pregnancies [6-12]. Clear guidelines for dealing with these women are particularly important [6-12]. The purpose of this review is to contribute to the establishment (despite the absence of strict such guidelines) of certain gold standards in order to be followed, such as:

a) the ultimate goal is to save the mother's life,

b) adequate treatment of curable malignancies,

c) attempt to protect the fetus and newborn from the harmful effects of antineoplastic therapy and

d) attempt to maintain the mother's entire reproductive system for future pregnancies. There are three distinct goals in the treatment of tongue cancer: treatment, prolongation of life, and relief from symptoms. This is the aim of this review to help facilitate therapeutic decisions based on the stage of pregnancy, type of location, size and stage of the cancer and the wishes of the woman and her family.

Tongue cancer

Squamous cell carcinoma consists one of the most frequent malignancies and showed up in approximately 90% of the malignant mouth neoplasms.There is a steady upward trend and the annual prevalence ranges from 550-750 new cases [13-14]. Squamous cell carcinoma consists the third leading cause of death after lung and breast cancer in many countries all over the world [15-16]. This may explained by the fact that it is not diagnosed in an early stage and for this reason, sometimes the cancer has already spread to local tissues or metastasized to other organs. Moreover, there is a high risk of developing secondary primary tumors, which may last 5-10 years after the first diagnosis. Oral cancer is on the rise in Greece, Belgium, Denmark, Portugal, Scotland and most of Central and Eastern Europe [12]. The most common

Correspondence to: Panagiotis Tsikouras, Professor Obstetrics and Gynecology, Democritus University of Thrace, Greece, E-mail: ptsikour@med.duth.gr

Received: August 19, 2020; **Accepted:** September 10, 2020; **Published:** September 17, 2020

locations are tongue (30%), lips (20%), mouth (15%), larynx (15%) and pharynx (10%) [12,15]. It is important to note that 85-90% of tongue cancers can be treated if diagnosed early and treated with appropriate treatment interventions [14,16]. Thus, the delay in diagnosis is the most unfavorable prognostic factor. Delayed onset of clinical symptoms, local recurrences, the development of secondary primary tumors, the absence of appropriate indicators for early diagnosis, local lymph node metastases, and failure to respond to chemotherapy for late lesions contribute to poor outcome [17,18].

Diagnosis

The most common location of the disease is on the lateral lips of the tongue, while on the dorsal surface it occurs with much lower frequency. On the lateral lips of the tongue the majority of cases are located in the middle third. Carcinoma usually extends submucosally and even more so than is seen on an episcopal basis, while statistically it seems to extend mainly backwards [4,17]. It can also extend to other anatomical structures such as the lower jaw, the floor of the mouth, the oropharynx and the base of the tongue. The infiltration of the muscles of the tongue limits its mobility, so there are disturbances in speech, chewing and swallowing [17]**.** Because the lesion usually appears on the lateral lips of the tongue, the healthy side maintains its normal mobility, while the heterogeneous muscles remain functional when the tumor does not become large. This is the main reason why the language retains a significant degree of functionality despite its significant infiltration by a malignant neoplasm [17-18]. In case that the tumor is located at the base of the tongue, it is frequent extensive when the diagnosis is made. Primarily malignant neoplasms of the posterior third have a worse prognosis than those found in the two anterior third of the tongue. This seems to be due to the difficult access of the area during the clinical examination, and therefore to the untimely diagnosis of cancer, to the more difficult surgical treatment as well as to the proximity of the area with important anatomical structures such as the palate, pharynx, epiglottis. Expanding to adjacent structures makes it more difficult to deal with and more unfavorable for the prognosis. The absence of specific symptoms is often typical, at least until the lesion becomes large. Intolerance is the common symptom that patients complain of. The ulcer, with which cancer usually occurs, causes various ailments. When the primary lesion grows, reduced mobility of the tongue occurs, resulting in difficulty speaking, chewing, and swallowing [21-22]. Taste disturbances may occur depending on the location of the tumor. When the tumor is at the base of the tongue, all the symptoms are more intense and also there is more difficulty. The pain does not often appear in the early stages of the disease, while it is intense in the advanced stages. It mainly concerns the point of localization, while it may also reflect on the ipsilateral. Tongue carcinoma usually metastasizes to the neck early and often. In case that the lesion is located on one side of the lip, the metastases may appear unilaterally or bilaterally. Most commonly, neck metastases occur unilaterally. Bilateral metastases are seen when the unilateral flow of the lymph is obstructed by the tumor, surgery, or fibrosis that occurs after radiotherapy. Subsequent, after any treatment, one-sided metastasis may mean either that the metastases pre-existed but were not clinically and imaginatively apparent, or occurred during or after treatment [21-22]. The lymph nodes that are affected depend on the location of the primary focus. Hypogenic lymph nodes are mostly not affected, however they are always included in cervical cleansing. Tumors on the lateral lips of the tongue metastasize to the submandibular lymph nodes or directly to the deep sphincters. Tumors of the posterior third of the tongue give metastases directly to the deep jugular lymph nodes. In the rare cases of localization in the midline of the tongue, metastases are expected bilaterally, although very often they remain unilateral. The diagnosis of tongue cancer is based on clinical observation, on imaging, but is sealed by histological examination. The appearance of a lesion with the clinical picture mentioned above raises the suspicion of a malignancy. This clinical picture should be combined with the information of a good history [23,24]. Elements such as family history, time of onset and course of the lesion, as well as various habits (smoking, alcohol, previous illnesses or treatments, etc.) could help in the diagnosis. The imaging test for the diagnosis of tongue cancer is basically the MRI and in case of weakness the CT. These imaging in addition to the primary lesion also helps to staging the disease by depicting the cervix. Possible infiltration of lymph nodes, blood vessels, nervous system and other anatomical structures modifies the choice of treatment significantly, but also the prognosis of the disease. Moreover, MRI gives to the doctors more accurate information about the extent and nature of the lesion. On MRI, malignant lesions of the tongue are characterized by blurred lesions, heterogeneity of the lesion signal, infiltration of adjacent anatomical structures, and low signal in the T2 sequence [23,24]. The diagnosis of tongue's squamous cell carcinoma can also be made by cytological examination. The material is usually obtained with the help of a heatsink, while fine needle aspiration (FNA) is used to examine suspicious cervical lymph nodes. In cytological examination there is always a percentage of error, while it is not always possible to determine the type of carcinoma [19-24]. The final diagnosis of tongue cancer is made by histological examination of a portion of the lesion, which is obtained by biopsy. Proper biopsy is considered very important, so that the conclusion of pathologists is reliable. Material should be taken from the most suspicious areas of the lesion, capable in quantity and as far as possible in order to avoid dead areas of the tumor. Recent studies have shown an overexpression of immunohistochemical p16 and FGFR3 (fibroblast growth factor receptor protein) in HPV-positive samples as well as a number of proposals such as IL6 IL8 TNFRSF-19, VEGFA, DLL1, ESM-1 that are positively associated with angiogenesis and hypogenesis [25,26].

How HPV is detected in the oral cavity

No diagnostic test is needed to detect the virus in the oral cavity in asymptomatic patients. This practically means that it is not advisable to encourage asymptomatic oral patients to undergo various and pointless tests to detect possible infection of the oral mucosa, when there are no lesions compatible with those caused by HPV viruses. This also applies to women with HPV in the genitals, as research shows that HPV infection in the prenatal area does not predispose to HPV infection in the oral mucosa, even in cases where there is oral sex [27,28]. Only if there is clinical damage can the dentist document the infection by having a biopsy. Smoking cessation can be linked to a reduction in the rate of HPV-negative cancers, while changes in sexual activity reflect a growing percentage of HPV-positive cancers. Some recent studies indicated that among people who do not drink alcohol or smoke, the leading cause of mouth and throat cancer is HPV infection. Oral infection with the HPV virus precedes the development of HPV - oral cancer. The infection is transmitted through small non-visible wounds of the oral mucosa, which serves as the gateway for the HPV virus and which has very similar characteristics to the lining of the cervix. Oral infection with the HPV virus precedes the development of HPV - oral cancer [29-31].

Infection occurs through small invisible wounds of the oral mucosa, which serves as an entrance gate for the HPV virus and which has very similar characteristics to the mucosa of the cervix. Persistent (an infection that the body cannot eliminate and remains) and this

infection eventually affects the cells that contain the virus and turns them into cancer cells [29-31].

Carcinogenesis begins after persistent infection with oncogenic viruses, high-risk HPVs are first caused by precancerous lesions and tumor suppression mechanisms followed. In the presence of lesions, precancerous lesions do not cause any symptoms except in advanced cancer, so preventive testing is required. The DNA mechanism of the virus mobilizes its genetic mechanism and new HPVs are continuously produced and infect neighboring cells allow in the future its greater integration both in the primary population control and in the sorting and monitoring of precancerous lesions of the neck [29-32].

HPV Infection

The types of HPV virus that cause the vast majority of cancers in the organs mentioned (procto-genital area in women, especially the vagina, the cervix, the vulva and anus) above are type 16 (mainly) and type 18, just like in cervical cancer [35,36]. HPV-16 in particular is the most common type and is associated with a wide range of oral cavity lesions, both benign and precancerous and malignant. The incubation period ranges approximately from 6 weeks to 8 months and the time between infection and clinical manifestation of the disease is up to 10 years [37-38]. HPV infection does not necessarily mean the onset of the disease. The manifestation or not of the infection depends on the relationship of the viral action-load of the HPV type and the immune response of the organism. In most cases, the immune system does not allow infection to develop. So, if the infection is caused by oncogenic types of HPV and the immune system is not working, there will be precancerous lesions. In fact, when the body's defenses coexist and other factors (such as smoking, immunosuppressive drugs) contribute, precancerous lesions develop into cancer [37-38]. Although it is not clear exactly what the limit of clinically significant persistent infection is, it appears that infections lasting more than two years represent high-risk cases. Infections with high-risk types (about 10% of infections) that persist for years are the main risk group for developing precancerous lesions. The infection is characterized as persistent when detected in two or more visits to the gynecologist (more than two years). Infections with high-risk types tend to last longer than those with low-risk strains, and HPV 16 infection is usually more persistent. HPV genotypes differ in their ability to cause oncogenic transformation. Based on this criterion, they are distinguished into: Low risk HPV types such as HPV 6,11,42,43,44,54 etc., which are detected mainly in exophytic acute warts (condylomataacuminata), in flat warts (condylomaplanum) and in intraepithelial lesions of the squamous epithelium (LSIL). High risk HPV types such as HPV 16,18,26,45,56,58 etc., which are detected in high-grade intraepithelial lesions (HSIL) as well as in the majority of invasive carcinomas. Due to the fact that HPV vaccination protects against these two types of virus, the prospect of vaccination is now seriously considered not only by women, but also by boys and men. Although in some countries, e.g. Australia have already made positive decisions and are starting mass vaccination of 11-13 year old boys in schools, according to the annual report of the US National Cancer Institute, it remains to calculate the economic figures on national scales [35,36]. In the next future the international community will have to face in a new light the importance of the HPV and the effects of its presence on both boys and girls. Vaccination is the only solution with a good chance of success at the youngest age of both sexes [35,36]. The best age for the vaccination against HPV is between 11 and 14 years old, because the children are still under the control of the parents and moreover, because they have not yet started their sexual activity. At the age of 15-17, approximately 48% of adolescents in our country begin their sexual activity and this, together with the lack of formal sexual education and information, is responsible for the development of high-risk behaviors such as unprotected sex [35,36].

Anyone who has or has had sex in the past is potentially at risk [39-42]. This infection is enough common and as a result almost all sexually active men and women have passed the HPV infection at some point in their lives. This is also true even for people who have had a single sexual partner. It has been shown that a young woman is more likely to be infected with HPV compared to those who drink alcohol more than four times a month and have regular (at least 2-6 week) sexual intercourse and an increase depending on the number of recent sexual partners and similar with the number of sexual partners their partner had in the past. Most often the infection is transmitted through sexual contact. HPV can be transmitted after genital contact alone or oral sex. Interestingly, someone can have HPV infection without the presence of signs and symptoms few years after the contact with an infected person. The transmission is possible due to the virus settling in an injured epithelium. Often the sites of location in women are the posterior dome of the vagina, the cervix (transition zone), while in men the primary sites are the bridle, the crown and the inner petal of the foreskin. Thus, the various types are transmitted by rubbing infected epithelium and while condoms can reduce the risk of infection with the virus, they do not fully protect. The risk of contracting a new infection peaks around the age of 20, then decreases to the age of 35, increases slightly to the age of 45, and then declines steadily [40-42].

The overall risk of new infection within a year was estimated by studies at 17% for the women aged 15-19 years old, 9% for the women aged 20-24 years old, 4% for the women aged 30-44 years old and 1% for the women over 45 years. Pregnant women can also become infected with HPV. Usually, HPV infection does not cause any problems [40-43]. Cellular changes that are detected by the Pap test can be developed. It is therefore very important doctors to check the cervix with a Pap test in all pregnant women who have not checked with the Pap test in the previous year before pregnancy [40-43].

Vaccination with vaccines currently available is done in 3 doses. For Gar-dasil® 9 valent vaccine: 1st dose 0 day, 2nd dose: 2 months after the 1st dose, 3rd dose: 6 months after the 1st dose. All 3 doses should be given within one year. If the exact schedule is not followed, the doctor may continue the vaccination without losing the previous doses [44-46].

Full protection is provided 1 month after the administration of the 3rd dose. Until now, we do not know whether an extra dose of the vaccine will be needed in the future. HPV vaccines are very safe and without an increased incidence of adverse reactions or side effects compared to other vaccines [44-48]. It is noteworthy that the claim that someone who is vaccinated get cancer is not valid because the vaccine does not contain cancer cells but is a recombinant protein that causes antibodies to form.

However, it is recommended that for girl or woman to be in a sitting or lying position during the vaccination, as well as to stay in the doctor's office for 15 minutes after the vaccination.

To date, after the ~ 140,000,000 dose of the vaccine, according to the World Health Organization, because data on the effect of the vaccine on pregnancy are limited, its use in pregnancy should be avoided. Prevalence-induced HPV vaccination is not an indication for termination of pregnancy. If pregnancy is detected after the 1st or 2nd dose of vaccination, the regimen will continue after the end of pregnancy [44-48]. Breastfeeding mothers can be vaccinated. People

with severe allergic predisposition or allergic reactions to the vaccine's ingredients are best advised not to be vaccinated. Vaccination should also be postponed in people with high fever. It is clear that HPV vaccines continue to be intensively monitored by the authorities for the possible occurrence of serious adverse reactions in the future [44-49].

Interestingly, a woman, despite being vaccinated, may be infected with another type of HPV type and thus be at risk for pre-cancerous lesions in various organs. At this point, of course, it is worth noting that the ongoing studies show an expansion of the vaccine protection provided to some other oncogenic HPV types, due to their molecular affinity for types 16 and 18. This means that the protection provided by vaccination ultimately seems to exceed 70% and possibly up to 85-93% [50].

Who should be vaccinated and when?

Vaccines have no therapeutic effect and are therefore not used to treat precancerous lesions or cervical or wart cancer. Ideally, vaccination should be provided before sexual intercourse, because by then the body has not yet been exposed to the virus. In addition, the body's response to vaccination (ie the creation of antibodies) is much greater at a young age. According to the above, and after a decision of the competent Ministries, HPV-vaccination was introduced in our country since the beginning of 2008 in the National Vaccination Program, with a recommendation to vaccinate girls aged 12-15, as well as girls and young women aged 15-26 years who were not vaccinated at a younger age [44,47-52].

Results of similar studies, of course, show that older women (up to 45 years old) with a previous HPV infection or a history of cervical cone resection can also benefit from HPV vaccination. A woman who has already had sex can do the vaccine. It's just that a woman who has sex may be already infected with some type of HPV, and therefore the protection provided by the vaccine in this case - compared to a 12-year-old girl - is likely to be reduced [44,47-52].

So, for example, if she has already been infected with one of the types of the virus that covers the vaccine, vaccination will protect her from other types, but not from the type she is already carrying. Therefore, it is possible that in the future there will be some damage due to this strain of the virus. A woman should check if she has been infected with HPV before getting the vaccine [47-52].

It's not necessary for a woman to have an HPV DNA test before getting vaccinated because the probability, of a concomitant infection with both the oncogenic types of the virus (16 & 18), which covers the vaccine, is minimal (<1%) [47-52]. Nowadays, there have been no reliable tests for antibodies to HPV in the blood showing if a previous HPV infection has occurred. It has been estimated that >70% of women who have sex come in contact with some type of HPV virus. It is worth noting that approximately 90% of them will be cured automatically.

The frequency of infection with the types of viruses contained in vaccines is clearly lower. Vaccination of all women aged 12 to 26 will provide protection against the types of viruses included in vaccines. Girls who are positive for one of the types of vaccine are protected from the other types that the vaccine contains. HPV infection is reversed once the immune system is activated. However, there is a possibility of recurrence and effects of the same HPV infection [53-56].

Vaccination leaves long-term immunity to given virus types and to some extent to other types of virus. Many studies have shown that a vaccinated woman have a lower risk of developing secondary damage after a cone resection than non-vaccinated. This means that a vaccinated woman who develops a lesion other than the vaccine and has a cone resection is less possible to develop a new lesion and undergo again a cone resection than a woman who has never been vaccinated [53-56].

A woman can catch the virus at any time and for as long as she is sexually active. The incidence of infection is lower in older women, but it establishes a long-term infection and makes it more difficult to reverse. According to the European Medicines Agency, which is responsible for the approvement of the HPV vaccine, its effectiveness and efficiency in women between 26 and 45 years old is confirmed. Based on the scientific data that are available until now, the need for a memory dose has not been proven. HPV vaccines are expected to provide long-term protection. There is insufficient data to confirm the safety of HPV vaccines during pregnancy. According to the scientific results from the vaccine in pregnant women show that it does not increase the risk of miscarriage or teratogenesis. However, because the number of women is limited, vaccination during pregnancy is not recommended. If the vaccine is given to a pregnant woman who is not yet aware of the pregnancy, then the vaccination is continued after childbirth and lactation and the pregnancy proceeds normally. Vaccination effectively protects against the diseases caused by the types included in vaccines does not fully protect against all oncogenic types, so the woman should continue to be examined after vaccination, just as she has done to date [53-56].

Discussion

HPV infection usually does not pose a major medical risk, but it often has social implications. So, we need to understand that the majority of the population is at some point in life the carriers of the virus, since it is very easily transmitted. It is by no means a sign of infidelity if in a couple the only partner is a carrier, because may has been infected even decades ago [57-58].

So, patients should not panic, but have frequent clinical preventive check-ups, if necessary, and timely treatment of suspected lesions, if they are found in the oral cavity. The incidence of head and neck cancers has increased significantly in the last decade, including tumors in the oral cavity, tongue, oropharynx, hypopharynx and larynx. International data show that their frequency has increased sevenfold in the last 10 years and now affects 15-20 people per 100,000 people, making it the sixth most common cancer in men and women combined [57-58].

At European level, 150,000 new cases of head and neck cancer are recorded in both sexes each year. Most patients are ≥50 years old. Male sufferers from HPV are at least three times more likely in risk than women. The predominant histological type of tongue and laryngeal malignancies is squamous cell carcinoma [59-60].

Epidemiological data show some changes in recent years due to lifestyle changes that have a direct impact on the epidemiology of laryngeal malignancies. Possible predisposing factors include smoking, increased alcohol consumption, exposure to radiation/ harmful chemicals and HPV infection [60-64].

Scientific data suggest that the HPV virus is also involved in the development of cancers, mainly in the area of the oral cavity and oropharynx (usually at the base of the tongue and tonsils), but also in the pharynx and larynx, albeit to a lesser extent [60-64].

This difference is according to the fact that the oral mucosa at the back differs from the anterior one and facilitates the entry of the virus into the basal layer of the epithelium. Infection of the oral cavity with

the HPV 16 virus at least doubles the risk of developing oral cancer, according to current already published literature [65,66]. It is observed mainly in younger patients and non-smokers, where it plays a special role. The oral cavity includes many anatomical molecules, the lips, a thin lining inside the lips and cheeks called the parietal mucosa, the teeth, the floor of the mouth under the tongue, the anterior 2/3 of the tongue, the palate (hard palate), gums, and a small area behind the wisdom tooth (pen or third molar). The oral part of the pharynx includes the tonsils, the posterior third of the tongue, the posterior wall of the pharynx and soft palate. Sebaceous glands are found throughout the oral cavity and produce saliva that keeps mouth moist and helps digest food [64-66].

Tongue cancer in the oral cavity due to HPV infection metastasizes usually through the lymphatic system, even in the early stages T1 / T2 is already in N2 / N3 regarding lymph nodes in the cervical spine [65-66]. Cancer cells that enter the lymphatic system move through it with the lymph, which is an almost transparent aqueous substance and contains cells that help fight infection and disease. Along the lymphatics there are groups of lymph nodes. When oral cancer metastasizes, it is usually to the lymph nodes in the cervix. It can even metastasize to other parts of the body [65-67].

It is important to diagnose tongue cancer in the oral cavity as early as possible, because treatment works best before the disease progresses. Periodic dental check-ups involving control of the entire oral cavity are very important for the early diagnosis of oral cancer or a precancerous condition [65-68].

Usually, oral cancer occurs in people > 40 years old, but can also affect people of any age. Some of the warning signs are as following: a wound in the mouth that does not heal, difficulty in chewing or swallowing, numbness of the tongue, pain or feeling that something is stuck in the pharynx, swelling in the jaw that prevents the denture from applying to its position or making it uncomfortable, swelling or thickening on the lips or cheeks, difficulty moving the lower jaw or tongue, white or red spot on the gums, tongue, or oral mucosa [65-67].

'Pain is usually not one of the early symptoms of oral cancer. It is important to see a dentist or doctor if any of the above symptoms last for more > 2 weeks. Special tests help the doctor assess whether the cancer has spread and which parts of the body have been affected [65-67].

These tests include dental x-rays and x-rays of the head and neck. The doctor may even ask for a computed tomography (CT) scan. CT consists of a series of x-rays that are analyzed by a computer to form a detailed picture of the area being tested.

Ultrasound is another test. High-frequency sound waves (ultrasound) that humans cannot hear reflect on organs and tissues. The echo created by this reflection creates an image called an ultrasound [65-67].

Sometimes an MRI will be useful. Also, the doctor palpates the neck lymph nodes to check for swelling or other changes. Oral cancer treatment depends on a number of factors such as: the location, the size, the type, the extent of the tumor, and the stage of the disease. Early diagnosis and treatment of leukoplakia and erythroplakia are important because cancer can develop in these spots [65-67].

Pregnancy is a condition that causes significant endocrine changes in the female body, on the one hand disrupting the microbial flora of the mouth and on the other hand affecting the immune mechanism of the oral cavity [7,9,60,63].

Perhaps, the most characteristic alteration of pregnancy in the oral cavity is the volume of pregnancy. Pregnancy can be a nuisance for pregnant women because it increases rapidly and can be very large, causing bleeding in some cases. It usually appears during the 3rd and 4th month of pregnancy, while it has an extremely good prognosis, as after childbirth it reverses and often disappears completely within 1-3 months. However, if the damage persists, surgical removal after childbirth or even better after weaning is recommended. Of course, in cases where the damage is quite large and causes bleeding, it may be necessary to remove it during pregnancy [7,9,60,63].

Another condition that can occur in a pregnant woman's oral cavity is fungal stomatitis. The condition is caused by the fungus Candida Albicans, which is normally present in the microbial flora of the mouth, without causing discomfort. However, from the endocrine changes that occur during pregnancy, the fungus can become pathogenic and cause stomatitis. Gingivitis is common in pregnant women and is not only due to endocrine changes, but also to changes in dietary habits during pregnancy.

The symptoms are redness, swelling and bleeding of the gums, especially in the area of the front teeth. It usually occurs after the 2nd month and may become more severe after the 8th month. It resolves automatically after childbirth, but even in this case surgery is needed in cases of severe injury or significant bleeding of the gums [7,9,60,63].

Gestures of adamantine or tooth decay are often seen in pregnant women. This is not due, as previously thought, to the reduction of calcium in the blood, but to the change in the quality and quantity of meals, the sometimes poor dental care and the effect of acidic gastric fluid on the teeth due to frequent vomiting. In any case, the pregnant woman is exposed to diseases that affect both the teeth and the mucosa and other organs of the oral cavity. These conditions, although most of them are extremely benign and have a good prognosis, do not cease to be unpleasant.

Of crucial importance is the prognosis, the oral hygiene and of course the regular monitoring and cooperation with both the dentist and the other specialties that deal with the oral cavity. Oral ulcers are the most common disease of the oral cavity during pregnancy [7,9,60,63].

Oral ulcers cause severe pain and stinging, as they occur in an area of the human body that is particularly sensitive to pain. During pregnancy, it is important to use topical treatment that soothes the pain and speeds up the healing process of injuries [7,9,60,63].

Oral ulcers cause severe pain and stinging, as they occur in an area of the human body that is particularly sensitive to pain. During pregnancy there is a physiological decline in the immune system that can lead to inflammation and vertical transmission with HPV as well as other HIV viruses, herpes zoster group b streptococcus with negative consequences for mother and fetus [68-72]. In many cases vaccination is recommended. Passive immunization is not recommended. In cases such as HPV immunization, it is not recommended as a precaution, but if it has been initiated, it is not recommended to terminate a pregnancy but to continue and complete the immunization regimen because HPVs contain inactive virus-like elements that cause antibodies [73-82].

Oral epithelium and tongue epithelium is similar to that of the vaginal cavity. Tongue and cervical cancer, however, can be treated with prophylaxis in primary cervical cancer prevention programs [73-82]. Especially in pregnant women after treatment of tongue cancer despite the existing dilemmas of embolism for possible reduction of recurrences and therefore conduct multicenter studies in the future to eliminate the above problem.

Conclusion

HPV infection usually does not pose a major medical risk, but often social outbreaks should not cause panic, but frequent clinical screening should be considered, if necessary, and early treatment of suspected lesions, if found in the oral cavity. Moreover, HPV vaccine should be encouraged to both sexes in order to protect them not only from cancer of genital organs, but also from tongue cancer.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, et al. (2008) CA Cancer statistics, 2008. *Cancer J Clin* 58: 71-96. [Crossref]
2. Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics, 2010. *CA Cancer J Clin* 60: 277-300. [Crossref]
3. Scully C, Bagan J (2009) Oral squamous cell carcinoma overview. *Oral Oncol* 45: 301-308. [Crossref]
4. Mhallem Gziri M, Han SN, Van Calsteren K, Heyns L, Delaere P, et al. (2013) Tongue cancers during pregnancy: Case reports and review of literature. *Head Neck* 35: E102-E108.
5. Sato K, Shimamoto H, Mochizuki Y, Hirai H, Tomioka H, et al. (2019) Treatment of oral cancers during pregnancy: a case-based discussion. *J Otolaryngol Head Neck Surg* 48: 9. [Crossref]
6. Chow VLY, Chan JYW, Man Ng RW, Wei WI (2008) Management of head and neck tumours during pregnancy: case report and literature review. *Asian J Surg* 31: 199-203. [Crossref]
7. Layton SA, Rintoul M, Avery BS (1992) Oral carcinoma in pregnancy. *Br J Oral Maxillofac Surg* 30: 161-164.
8. Yokoshima K, Nakamizo M, Sakanushi A, Ozu R, Yamaguchi S, et al. (2012) Surgical management of tongue cancer during pregnancy. *Auris Nasus Larynx* 39: 428-430.
9. N Lasaridis, I Tilaveridis, D Karakasis (1996) Management of a carcinoma of the tongue during pregnancy: report of case. *J Oral Maxillofac Surg* 54: 221-224.
10. Simard EP, Torre LA, Jemal A (2014) International trends in head and neck cancer incidence rates: differences by country, sex and anatomic site. *Oral Oncol* 50: 387-403. [Crossref]
11. Tota JE, Anderson WF, Coffey C, Califano J, Cozen W, et al. (2017) Rising incidence of oral tongue cancer among white men and women in the United States, 1973-2012. *Oral Oncol* 67: 146-152. [Crossref]
12. Abogunrin S, Di Tanna GL, Keeping S, Carroll S, Iheanacho I (2014) Prevalence of human papillomavirus in head and neck cancers in European populations: a meta-analysis. *BMC Cancer* 14: 968. [Crossref]
13. Romanitan M, Näsman A, Ramqvist T, Dahlstrand H, Polykretis L, et al. (2008) Human papillomavirus frequency in oral and oropharyngeal cancer in Greece. *Anticancer Res* 28: 2077-2080.
14. Zavras AI, Laskaris C, Kittas C, Laskaris G (2003) Leukoplakia and intraoral malignancies: female cases increase in Greece. *J Eur Acad Dermatol Venereol* 17: 25-27. [Crossref]
15. Li R, Koch WM, Fakhry C, Gourin CG (2013) Distinct epidemiologic characteristics of oral tongue cancer patients. *Otolaryngol Head Neck Surg* 148: 792-796.
16. Jaber MA, Porter SR, Speight P, Eveson JW, Scully C (2003) Oral epithelial dysplasia: clinical characteristics of western European residents. *Oral Oncol* 39: 589-596. [Crossref]
17. Berrino F, Gatta G (1998) Variation in survival of patients with head and neck cancer in Europe by the site of origin of the tumours. EUROCARE Working Group. *Eur J Cancer* 34: 2154-2161.
18. Gatta G, Botta L, Sánchez MJ, Anderson LA, Pierannunzio D, et al. (2015) Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study. *Eur J Cancer* 51: 2130-2143.
19. Najeeb T (2006) Clinicopathological presentation of tongue cancers and early cancer treatment. *J Coll Physicians Surg Pak* 16: 179-182. [Crossref]
20. Murphy J, Berman DR, Edwards SP, Prisciandaro J, Eisbruch A, et al. (2016) Squamous cell carcinoma of the tongue during pregnancy: a case report and review of the literature. *J Oral Maxillofac Surg* 74: 2557-2566. [Crossref]
21. Atabo A, Bradley PJ (2008) Management principles of head and neck cancers during pregnancy: a review and case series. *Oral Oncol* 44: 236-241. [Crossref]
22. Chin D, Boyle GM, Porceddu S, Theile DR, Parsons PG, et al. (2006) Head and neck cancer: past, present and future. *Expert Rev Anticancer Ther* 6: 1111-1118. [Crossref]
23. Bahadur S, Bindra GS, Bhatia R, Rath GK (1986) Pregnancy and head and neck malignancy. *Indian J Cancer* 23: 64-68.
24. Kiciński K, Skorek A, Stankiewicz C (2011) Managment of head and neck cancers during pregnancy. *Otolaryngol Pol* 65: 326-332.
25. Busquets JM, García HA, Trinidad-Pinedo J, Baez A (2003) Clinicopathologic characteristics of head and neck squamous cell carcinoma in Puerto Ricans. *P R Health Sci J* 22: 259-264. [Crossref]
26. Troeltzsch M, Knösel T, Eichinger C, Probst F, Troeltzsch M (2014) Clinicopathologic features of oral squamous cell carcinoma: do they vary in different age groups? *J Oral Maxillofac Surg* 72: 1291-1300.
27. Fu TC, Hughes JP, Feng Q, Hulbert A, Hawes SE, et al. (2015) Epidemiology of human papillomavirus detected in the oral cavity and fingernails of mid-adult women. *Sex Transm Dis* 42: 677-685. [Crossref]
28. Han YW, Houcken W, Loos BG, Schenkein HA, Tezal M (2014) Periodontal disease, atherosclerosis, adverse pregnancy outcomes, and head-and-neck cancer. *Adv Dent Res* 26: 47-55. [Crossref]
29. Tapisiz OL, Gungor T, Ustunyurt E, Ozdal B, Bilge U, et al. (2008) An unusual case of lingual alveolar soft part sarcoma during pregnancy. *Taiwan J Obstet Gynecol* 47: 212-214. [Crossref]
30. Daponte A, Pournaras S, Tsakris A (2014) Self-sampling for high-risk human papillomavirus detection: future cervical cancer screening? *Womens Health (Lond)* 10: 115-118.
31. Read TR, Hocking JS, Vodstrcil LA, Tabrizi SN, McCullough MJ, et al. (2012) Oral human papillomavirus in men having sex with men: risk-factors and sampling. *PLoS One* 7: e49324. [Crossref]
32. Paaso AE, Louvanto K, Syrjänen KJ, Waterboer T, Grénman SE, et al. (2011) Lack of type-specific concordance between human papillomavirus (HPV) serology and HPV DNA detection in the uterine cervix and oral mucosa. *J Gen Virol* 92: 2034-2046.
33. Iype EM, Pandey M, Mathew A, Thomas G, Sebastian P, et al. (2001) Oral cancer among patients under the age of 35 years. *J Postgrad Med* 47: 171-176.
34. Iype EM, Pandey M, Mathew A, Thomas G, Nair MK (2004) Squamous cell cancer of the buccal mucosa in young adults. *Br J Oral Maxillofac Surg* 42: 185-189.
35. Mayeaux EJ Jr, Khan MJ (2013) Nongenital human papillomavirus disease. *Obstet Gynecol Clin North Am* 40: 317-337.
36. Andrews E, Seaman WT, Webster-Cyriaque (2009) Oropharyngeal carcinoma in non-smokers and non-drinkers: a role for HPV. *J Oral Oncol* 45: 486-491.
37. Beutner KR (2000) Nongenital human papillomavirus infections. *Clin Lab Med* 20: 423-430.
38. Zandberg DP, Bhargava R, Badin S, Cullen KJ (2013) The role of human papillomavirus in nongenital cancers. *CA Cancer J Clin* 63: 57-81. [Crossref]
39. Gillison ML, Shah KV (2003) Chapter 9: Role of mucosal human papillomavirus in nongenital cancers. *J Natl Cancer Inst Monogr* 31: 57-65. [Crossref]
40. Beutner KR (2005) Human papillomavirus (HPV) in head and neck cancer. *J Clin Virol* 32 Suppl 1: S59-S66.
41. Attner P, Du J, Näsman A, Hammarstedt L, Ramqvist T, et al. (2010) The role of human papillomavirus in the increased incidence of base of tongue cancer. *Int J Cancer* 126: 2879-2884.
42. Eliassen AM, Hauff SJ, Tang AL, Thomas DH, McHugh JB, et al. (2013) Head and neck squamous cell carcinoma in pregnant women. *Head Neck* 35: 335-342. [Crossref]
43. Pandey D, Solleti V, Jain G, Das A, Shama Prasada K, et al. (2019) Human Papillomavirus (HPV) infection in early pregnancy: Prevalence and implications. *Infect Dis Obstet Gynecol* 2019: 4376902. [Crossref]
44. Agorastos T, Chatzistamatiou K, Katsamagkas T, Koliopoulos G, Daponte A, et al. (2015) Primary screening for cervical cancer based on high-risk human papillomavirus (HPV) detection and HPV 16 and HPV 18 genotyping, in comparison to cytology. *PLoS One* 10: e0119755. [Crossref]

45. Faust H, Artemchuk H, Oštrbenk A, Triglav T, Poljak M, et al. (2019) Seropositivity to Multiple Anogenital Human Papillomavirus (HPV) types is associated with current anogenital HPV infection, abnormal cytology, and seropositivity for nongenital HPVs. *J Infect Dis* 219: 489-496. [Crossref]

46. Louvanto K, Rautava J, Syrjänen K, Grénman S, Syrjänen S (2014) The clearance of oral high-risk human papillomavirus infection is impaired by long-term persistence of cervical human papillomavirus infection. *Clin Microbiol Infect* 20: 1167-1172. [Crossref]

47. Schwartz SM, Daling JR, Doody DR, Wipf GC, Carter JJ, et al. (1998) Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. *J Natl Cancer Inst* 90: 1626-1636.

48. Cook RL, Thompson EL, Kelso NE, Friary J, Hosford J, et al. (2014) Sexual behaviors and other risk factors for oral human papillomavirus infections in young women. *Sex Transm Dis* 41: 486-492. [Crossref]

49. Leddy MA, Anderson BL, Gall S, Schulkin J (2009) Obstetrician-gynecologists and the HPV vaccine: practice patterns, beliefs, and knowledge. *J Pediatr Adolesc Gynecol* 22: 239-246

50. Louvanto K, Eriksson T, Gray P, Apter D, Baussano I, et al. (2020) Baseline findings and safety of infrequent vs. frequent screening of human papillomavirus vaccinated women. *Int J Cancer* 147: 440-447. [Crossref]

51. Stillo M, Carrillo Santisteve P, Lopalco PL (2015) Safety of human papillomavirus vaccines: a review. *Expert Opin Drug Saf* 14: 697-712.

52. Macartney KK, Chiu C, Georgousakis M, Brotherton JM (2013) Safety of human papillomavirus vaccines: a review. *Drug Saf* 36: 393-412. [Crossref]

53. Mammas NI, Sourvinos G, Zaravinos A, Spandidos DA (2011) Vaccination against human papilloma virus (HPV): epidemiological evidence of HPV in non-genital cancers. *Pathol Oncol Res* 17: 103-119. [Crossref]

54. Bharti AC, Singh T, Bhat A, Pande D, Jadli M (2018) Therapeutic startegies for human papillomavirus infection and associated cancers. *Front Biosci (Elite Ed)* 10: 15-73. [Crossref]

55. Craig SG, Anderson LA, Schache AG, Moran M, Graham L, et al. (2019) Recommendations for determining HPV status in patients with oropharyngeal cancers under TNM8 guidelines: a two-tier approach. *Br J Cancer* 120: 827-833.

56. ESHRI Capri Workshop Group (2014) Simultaneous prevention of unintended pregnancy and STIs: a challenging compromise. *Hum Reprod Update* 20: 952-963. [Crossref]

57. Pampena E, Vanucci R, Johnson LB, Bind MA, Tamayo I, et al. (2020) Educational interventions on human papillomavirus for oral health providers. *J Cancer Educ* 35: 689-695. [Crossref]

58. Skoczyński M, Goździcka-Józefiak A, Kwaśniewska A (2011) Prevalence of human papillomavirus in spontaneously aborted products of conception. *Acta Obstet Gynecol Scand* 90: 1402-1405. [Crossref]

59. Tagliabue M, Elrefaey SH, Peccatori F, Favia G, Navach V, et al. (2016) Tongue cancer during pregnancy: Surgery and more, a multidisciplinary challenge. *Crit Rev Oncol Hematol* 98: 1-11.

60. Triunfo S, Scambia G (2014) Cancer in pregnancy: diagnosis, treatment and neonatal outcome. *Minerva Ginecol* 66: 325-334. [Crossref]

61. Bradley PJ, Raghavan U (2004) Cancers presenting in the head and neck during pregnancy. *Curr Opin Otolaryngol Head Neck Surg* 12: 76-81.

62. Omura K (2014) Current status of oral cancer treatment strategies: surgical treatments for oral squamous cell carcinoma. *Int J Clin Oncol* 19: 423-430. [Crossref]

63. Murphy J, Berman DR, Edwards SP, Prisciandaro J, Eisbruch A, et al. (2016) Squamous cell carcinoma of the tongue during pregnancy: a case report and review of the literature. *J Oral Maxillofac Surg* 74: 2557-2566. [Crossref]

64. Papageorge MB (2007) Etiology of oral cancer in the young patient: is tongue cancer becoming the other cancer in women? *Oral Maxillofac Surg Clin North Am* 19: 163-171.

65. Machin J, Shaw C (1998) A multidisciplinary approach to head and neck cancer. *Eur J Cancer Care (Engl)* 7: 93-96.

66. Tota JE, Best AF, Zumsteg ZS, Gillison ML, Rosenberg PS, et al. (2019) Evolution of the oropharynx cancer epidemic in the United States: moderation of increasing incidence in younger individuals and shift in the burden to older individuals. *J Clin Oncol* 37: 1538-1546. [Crossref]

67. Owosho AA, Velez M 3rd, Tyburski A, Hofheins J, Wiley R, et al. (2019) Epidemiological trends of oropharyngeal and oral cavity squamous cell carcinomas in Northern New England, 2000-2013. *Cancer Causes Control* 30: 291-299.

68. Chaitanya NC, Allam NS, Gandhi Babu DB, Waghray S, Badam RK, et al. (2016) Systematic meta-analysis on association of human papilloma virus and oral cancer. *J Cancer Res Ther* 12: 969-974. [Crossref]

69. Lerman MA, Almazrooa S, Lindeman N, Hall D, Villa A, et al. (2017) HPV-16 in a distinct subset of oral epithelial dysplasia. *Mod Pathol* 30: 1646-1654. [Crossref]

70. Shukla A, Nyambose J, Vanucci R, Johnson LB, Welch K, et al. (2019) Evaluating the effectiveness of human papillomavirus educational intervention among oral health professionals. *J Cancer Educ* 34: 890-896. [Crossref]

71. D'Souza G, McNeel TS, Fakhry C (2017) Understanding personal risk of oropharyngeal cancer: risk-groups for oncogenic oral HPV infection and oropharyngeal cancer. *Ann Oncol* 28: 3065-3069.

72. Valls-Ontañón A, Hernández-Losa J, Somoza Lopez de Haro R, Bellosillo-Paricio B, Ramón Y, et al. (2019) Impact of human papilloma virus in patients with oral and oropharyngeal squamous cell carcinomas. *Med Clin (Barc)* 152: 174-180.

73. Huwiler SS, Spaar A (2016) HPV vaccination. *Ther Umsch* 73: 241-246. [Crossref]

74. Bollen LJ, Chuachoowong R, Kilmarx PH, Mock PA, Culnane M, et al. (2006) Human papillomavirus (HPV) detection among human immunodeficiency virus-infected pregnant Thai women: implications for future HPV immunization. *Sex Transm Dis* 3: 259-264. [Crossref]

75. Phillips A, Patel C, Pillsbury A, Brotherton J, Macartney K (2018) Safety of Human Papillomavirus vaccines: an updated review. *Drug Saf* 41: 329-346. [Crossref]

76. Näsman A, Du J, Dalianis T (2020) A global epidemic increase of an HPV-induced tonsil and tongue base cancer - potential benefit from a pan-gender use of HPV vaccine. *J Intern Med* 287: 134-152. [Crossref]

77. Dilley S, Miller KM, Huh WK (2020) Human papillomavirus vaccination: Ongoing challenges and future directions. *Gynecol Oncol* 156: 498-502.

78. Walhart T, Isaacson-Wechsler E, Ang KH, Arkin M, Tugizov S, et al. (2020) A cell-based renilla luminescence reporter plasmid assay for high-throughput screening to identify novel FDA-approved drug inhibitors of HPV-16 infection. *SLAS Discov* 25: 79-86. [Crossref]

79. Bonde U, Joergensen JS, Lamont RF, Mogensen O (2016) Is HPV vaccination in pregnancy safe? *Hum Vaccin Immunother* 12: 1960-1964. [Crossref]

80. Bonanni P, Zanella B, Santomauro F, Lorini C, Bechini A, et al. (2018) Safety and perception: What are the greatest enemies of HPV vaccination programmes? *Vaccine* 36: 5424-5429.

81. Velentzis LS, Brotherton JML, Canfell K (2019) Recurrent disease after treatment for cervical pre-cancer: determining whether prophylactic HPV vaccination could play a role in prevention of secondary lesions. *Climacteric* 22: 596-602. [Crossref]

82. Rambout L, Hopkins L, Hutton B, Fergusson D (2007) Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. *CMAJ* 177: 469-479. [Crossref]