ISSN 2218-6220 (online)

World Journal of *Obstetrics and Gynecology*

World J Obstet Gynecol 2013 August 10; 2(3): 37-61

Baishideng Publishing Group
www.wjgnet.com

WJOG World Journal of Obstetrics and Gynecology

A peer-reviewed, online, open-access journal of obstetrics and gynecology

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World Journal of Obstetrics and Gynecology

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Quarterly Volume 2 Number 3 August 10, 2013

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World Journal of Obstetrics and Gynecology
Volume 2 Number 3 August 10, 2013

NAME OF JOURNAL
World Journal of Obstetrics and Gynecology

ISSN
ISSN 2218-6220 (online)

LAUNCH DATE
June 10, 2012

FREQUENCY
Quarterly

World Journal of Obstetrics and Gynecology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
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http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai,
Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PUBLICATION DATE
August 10, 2013

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2218-6220/g_info_20100722175812.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Obstetrics and Gynecology

Online Submissions: http://www.wjgnet.com/esps/
wjog@wjgnet.com
doi:10.5317/wjog.v2.i3.37

World J Obstet Gynecol 2013 August 10; 2(3): 37-41
ISSN 2218-6220 (online)

TOPIC HIGHLIGHT

Chibuike O Chigbu, MD, *Series Editor*

The general surgeon in inter-disciplinary gynaecological cancer care

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Received: September 13, 2012 Revised: April 3, 2013
Accepted: April 9, 2013
Published online: August 10, 2013

Abstract

Gynaecological cancers pose a significant cancer burden globally. In 2008 cancers of the cervix, uterus and ovaries accounted for 529000 (4.2%), 287000 (2.3%) and 225000 (1.8%) cancers, respectively, and together were responsible for 486400 deaths. Inter-disciplinary gynaecological care is an emerging concept aimed at providing more effective care by integrating different disciplines into a team working together to perform the various aspects of management at one time. This model has both advantages and potential shortcomings. In advanced healthcare systems there appears to be little role for the general surgeon. However in developing world, the general surgeon has a valuable, but complementary role in inter-disciplinary gynaecological cancer care. This role depends on the available workforce and includes, but is not limited to, the establishment of a diagnosis and treatment, including the management of complications. There is however little evidence-based research to provide guidance on the general surgeon's role in inter-disciplinary gynecologic cancer care and more research is needed.

Key words: General surgeon; Inter disciplinary; Diagnosis; Treatment; Gynaecological; Cancer

Core tip: Gynaecologic cancers constitute a major cancer burden. The general surgeon's role in inter-disciplinary gynaecological cancer differs between developed and developing countries. The increased sub-specialization in surgery in developed countries has obviated the need for the general surgeon in gynaecologic cancer care. In developing countries the general surgeon plays an essential but variable role, depending on the medical infrastructure and available manpower, which is usually limited in this setting. Interdisciplinary care is an emerging concept aimed at improving outcomes in cancer management and may be useful irrespective of the setting.

Isichei MW, Ismaila BO. The general surgeon in inter-disciplinary gynaecological cancer care. *World J Obstet Gynecol* 2013; 2(3): 37-41 Available from: URL: http://www.wjgnet.com/2218-6220/full/v2/i3/37.htm DOI: http://dx.doi.org/10.5317/wjog.v2.i3.37

INTRODUCTION

Cancers which primarily affect women are a major contribution to the global cancer burden. When breast cancer is excluded, gynaecological cancers still constitute a significant part of the cancer burden worldwide. Gynaecological cancer includes, but is not limited to, cancers of the cervix, uterus, ovary, vulva and vagina. Since cervical, uterine and ovarian cancers are the most common gynaecological cancers, they will be the main ones considered in this review. Of the estimated 12.7 million new cancer cases in 2008, cancers of the cervix uterus and ovaries accounted for 529000 (4.2%), 287000 (2.3%) and 225000 (1.8%), respectively, and these cancers were responsible

for 486400 of the 7.6 million cancer deaths in the same year. These 3 gynaecological cancers alone are among the 10 most common cancers in women[1].

A general surgeon is difficult to define. Trunkey's statement over 25 years ago provides an interesting but adequate description. He stated that a general surgeon is one who can treat the injured, the very sick patient and perform non-cardiac thoracic, general vascular, gut and gland surgery[2]. While there is currently increasing subspecialization within general surgery, we would concern ourselves with those specialists trained in general surgery who can provide competent and high quality care across a broad range of conditions. A general surgeon may be involved in the management of patients with gynaecological cancer for reasons including those related to diagnosis, treatment, and follow-up as well as workforce availability. Traditionally the general surgeon's role in the management of gynaecological cancer depends strongly on the medical infrastructure and varies from country to country and from region to region. There is a major difference in the role of a general surgeon in interdisciplinary gynaecological cancer care between developed and developing countries. While specialists and subspecialists are widely available in the developed world, with technology that aids accurate diagnosis and treatment, the reverse is the case in the developing world[3,4]. This review article will discuss the role of the general surgeon in interdisciplinary gynaecological cancer from these two perspectives.

Modern cancer care may be interdisciplinary or multidisciplinary with different specialties contributing their knowledge and experience to improve patient outcome. It has become important for health workers to collaborate to achieve improved outcomes. They bring knowledge and expertise from their different disciplines which can be effectively channeled into better patient care. The various disciplines working together in a team complement each other[5]. Suitable definitions of interdisciplinary and multidisciplinary teams have been difficult[6]. An interdisciplinary team may be described as that which integrates separate disciplines into a single consultation. This is such that history taking, physical examination, diagnosis and management are conducted with the patient by the combined team at one time[7]. This should be differentiated from multidisciplinary care which also utilizes the skills and experience of individuals from different disciplines but with each discipline approaching the patient from their own perspective. The consultations may be arranged for different times on a single day and the multidisciplinary team meets frequently to discuss the management, but in the absence the patient[8]. It is expected that each member of the interdisciplinary team should be individually knowledgeable, skillful, reliable, experienced, and able to communicate effectively sharing responsibility in teamwork[9]. The general surgeon is no exception.

Advantages of interdisciplinary care are related to the patient, health workers and the health care system. Advantages to the patient include better outcomes, reduced waiting time and greater level of involvement in decision making. For the health worker, advantages are more equal workload distribution, increased learning opportunities and greater work satisfaction. On the whole, there is reduced cost and more efficient utilization of the health care system. Possible disadvantages include role confusion, differing values and interests, and sometimes lack of common purpose[6]. In addition, the views of quieter team member may be neglected. There is a paucity of literature on the role of a general surgeon in an interdisciplinary team.

In developed countries, current recommended management for gynaecogical cancer is multidisciplinary[5]. The team is generally made up of a gynaecological oncologist, a site specialist oncologist, pathologist, gynaecological cancer nurse specialist, radiologist, palliative care specialist and a clinical geneticist. In addition, patient management is aided by advanced medical equipment including those used for imaging, thus pretreatment diagnosis and staging is usually known and treatment planned accordingly.

DIAGNOSIS

Gynaecological malignancies present in various ways. Presentation depends on the type of cancer, site and stage. Classical presentation with vaginal bleeding and other symptoms related to the female reproductive tract are likely to present no difficulty to the primary care physicians or the gynecologists. Cancers detected by screening, like cervical cancer, are also relatively straightforward in terms of diagnosis.

Occasionally a general surgeon may encounter a gynaecological malignancy while managing surgical patients. If this occurs preoperatively it is recommended that the patient be referred to the gynaecological oncology team. However, if this occurs intraoperatively it is more difficult to decide on treatment, but studies have shown that patient outcomes are better when gynaecological cancer surgeries are performed by gynaecogical oncologists[10,11].

In this context, the role of a general surgeon in an interdisciplinary setting may be to contribute in the initial clinical assessment of a patient with a gynaecological tumour which has progressed to involve other organs. This may be the case in a patient with ovarian cancer who has relapsed. However, it may be argued that rather than the general surgeon, the specific sub-specialists associated with the cancer sites should be part of the interdisciplinary team. In this context then, there will be little role if any for the general surgeon. In reality it may be that, in this context, there is little need for the specialist referred to as a general surgeon in any role.

The converse is the situation in the developing world, characterized by the absence of skilled manpower and equipment. The classical presentations of gynaecological malignancies will similarly present no major difficulty in diagnosis for the primary care physicians and gynaecologists but precise diagnosis and staging may be challenging

due to inadequate complementary diagnostic investigations, such as modern imaging. There is greater reliance on the clinical evaluation in this setting, with the attendant difficulty in accurate staging[12]. Patients also tend to present at healthcare facilities later, with more advanced disease and attendant complications[13].

In this setting, the general surgeon as a part of interdisciplinary care may contribute in the process of history taking and examination by helping to determine or exclude involvement of other organs. Advanced gynaecological tumors presenting as intra abdominal masses, gastrointestinal or vascular obstruction, will require input from the general surgeon. Ovarian tumors are well known for their relatively late presentation[14] and complications such as bowel obstruction are common[15]. This type of late presentation is common in less developed countries where there are limited investigation modalities and preoperative diagnosis may be difficult. Sometimes the exact diagnosis is determined during surgery. The general surgeon will provide knowledge and experience that would be useful to the interdisciplinary team in the evaluation of these cases. The presence of metastatic disease at sites remote from the female reproductive tract will be easier for the general surgeon to detect during the interdisciplinary evaluation of the patient. The general surgeon may also play a complementary role in the choice of investigations in the diagnostic work-up, enabling early, relevant and necessary investigations that will influence further management. Involvement of neighboring structures, such as small and large bowel, and ureters are determined early. The presence of remote metastases and how this may affect treatment plans (curative versus palliative) is another area where the general surgeon's expertise will be useful.

Some patients with gynaecological malignancies have hereditary cancers and may have or be at risk of other tumours outside the female reproductive tract. These include hereditary non-polyposis colorectal cancer syndromes (HNPCC) and BRCA mutations[16]. These are now largely managed by colorectal and breast surgeons as part of the interdisciplinary team in developed countries. However, the general surgeon replaces these sub-specialists in developing countries, and may be able to advise on the possible need for further genetic evaluation.

A possible drawback in the interdisciplinary approach to these patients may be the loss of privacy involved in asking questions about, and evaluation of parts of the body that are normally concealed. Thus the patient may feel uncomfortable divulging information and exposing her body to examination by a group.

TREATMENT

Treatment of gynaecological cancer is multimodal. Options include surgery, radiotherapy, chemotherapy and hormonal therapy. It is not uncommon for patients to undergo extensive pelvic surgery with neoadjuvant or adjuvant chemotherapy as well as chemotherapy. The multimodal treatment of these tumours already encourages multidisciplinary collaboration and has the potential to foster an interdisciplinary approach to patient care. Modern trends suggest that surgical treatment should be done by gynaecological oncologists for more favorable outcomes. However in the interdisciplinary setting, the treatment of the patient is individualized, recognizing the needs, condition and aim of treatment. Treatment with curative intent should be the goal but is not always possible and the interdisciplinary team has the potential to offer the best available form of care when the team brings their collective expertise to bear. For early tumors the gynaecological oncologist in conjunction with the team attempt to achieve a cure, but the radiologist and pathologist aid in determining accurately what constitutes early disease. Tumour involvement of adjacent organs may require the inclusion of other specialists like urologists and colorectal surgeons, especially in more advanced tumors. As previously discussed, the role of the general surgeon is limited in advanced countries.

However in less advanced healthcare settings, as a result of dearth of relevant manpower, the general surgeon can contribute to the decision on the type and extent of surgery and the need for other modalities of treatment. Issues such as the extent of resection, dealing with other involved organs and whether a stoma is required temporarily or permanently, can be resolved preoperatively. The role of surgery in the management of early and advanced gynaecological cancer is established[17-20]. Even intraoperatively, the presence of more extensive disease than anticipated or detected preoperatively poses less of a challenge to the interdisciplinary team. Modifications to the operative technique traditionally out of the purview of the gynecological oncologist can be carried out readily and competently without the need for further surgery. Issues such as bowel involvement and possible need for primary anastomosis or the creation of stoma, are addressed confidently as they arise and vascular involvement by the tumour need not be an indication for limiting the extent of surgery. Intraoperative complications, especially in extensive surgeries, involving bowel, vessels and the urinary tract, can be repaired during a single surgery. Surgical management of advanced gynaecological malignancies poses a major challenge in oncological care[19]. The general surgeon will provide assistance in cytoreductive and palliative surgeries. It is important to note that oncological care in less developed countries at present largely involves management of advanced diseases. Closely related to advanced presentation is the treatment of recurrent disease either as a result of previous suboptimal or inadequate treatment or of disease recurrence even in well treated cases.

Use of multimodal treatment options like radiotherapy for gynaecological malignancies increases the risk of bowel related complications such as fistulae and strictures[21]. Definition of the extent and location of these complications may require the expertise of a general surgeon in the interdisciplinary team.

There have been reports that patients managed by gynaecological oncologists have better outcomes than those treated by general surgeons[10,11]. This may be related more to the working environment rather than surgical skill[22]. However, it is clear that multidisciplinary care results in better outcomes[23-27]. The role of a general surgeon in interdisciplinary care will be complementary and useful even if there are doubts about the outcome when he/she manages the patient alone.

FOLLOW UP

Patients with gynaelogical cancer may undergo multimodal treatment with curative or palliative intent. They may be cured, or symptoms effectively palliated. At the other extreme, they may develop debilitating complications from the cancer or it treatment. Often the outcome falls between these two extremes, therefore consigning the patient to a lifetime of repeated evaluation to determine recurrence, manage symptoms and treat complications. The general surgeon's skill is a useful part of the interdisciplinary management of these patients. Gastrointestinal symptoms and complications can be detected and managed accordingly.

Evaluation of the patient for evidence of recurrence or distant spread may enable earlier detection and appropriate management.

WORKFORCE

In parts of the world where there is inadequate availability of health workers to manage gynaecological cancers, general surgeons may provide a readily available pool that can provide the knowledge and technical skill required to achieve better outcomes in an interdisciplinary setting. They also can be trained to fill any gaps that currently exist in the provision of high quality gynaecological oncology services.

There is little evidence in the literature about the role of general surgeons in interdisciplinary health teams involved in the management of gynecological cancers. Research in this and related areas is required.

CONCLUSION

Interdisciplinary healthcare is an emerging system which challenges the traditional paradigms. It has the potential to improve patient care and change the way gynaecological cancer is managed. The general surgeon's role in an interdisciplinary team for gynaecological care can be viewed from two perspectives; in an advanced healthcare setting in which his/her role is very limited due to the availability of the relevant subspecialists, and in a less advanced setting in which his/her role is complementary but important and useful. The general surgeon may be a valuable resource where there is inadequate manpower and should perhaps be trained in gynaecological oncology to provide optimal care.

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doi:10.5317/wjog.v2.i3.42

World J Obstet Gynecol 2013 August 10; 2(3): 42-46
ISSN 2218-6220 (online)

MINIREVIEW

Intrapartum application of the continuous glucose monitoring system in pregnancies complicated with diabetes: A review and feasibility study

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Received: December 23, 2012 Revised: April 21, 2013
Accepted: May 18, 2013
Published online: August 10, 2013

Abstract

Intrapartum maternal normoglycemia seems to play an important role in the prevention of adverse perinatal, maternal and neonatal outcomes. Several glucose monitoring protocols have been developed, aiming to achieve a tight glucose monitoring and control. Depending on the type of diabetes and the optimal or suboptimal glycemic control, the treatment options include fasting status of the parturient, frequent monitoring of capillary blood glucose, intravenous dextrose infusion and subcutaneous or intravenous use of insulin. Continuous glucose monitoring system (CGMS) is a relatively new technology that measures interstitial glucose at very short time intervals over a specific period of time. The resulting profile provides a more comprehensive measure of glycemic excursions than intermittent home blood glucose monitoring. Results of studies applying the CGMS technology in patients with or without diabetes mellitus (DM) have revealed new insights in glucose metabolism. Moreover, CGMS have a potential role in the improvement of glycemic control during pregnancy and labor, which may lead to a decrease in perinatal morbidity and mortality. In conclusion, the use of CGMS, with its important technical advantages compared to the conventional way of monitoring, may lead into a more etiological intrapartum management of both the mother and her fetus/infant in pregnancies complicated with DM.

Key words: Diabetes mellitus; Pregnancy; Intrapartum management; Glucose monitoring protocols; Continuous glucose monitoring system

Core tip: In pregnancies complicated with diabetes, intrapartum maternal normoglycemia seems to play an important role in the prevention of adverse perinatal outcomes. Several glucose monitoring protocols have been developed, aiming to achieve a tight glucose monitoring and control intrapartum. The continuous glucose monitoring system is a relatively new technology; its intrapartum application in pregnancies complicated with diabetes is feasible, allows for a closer observation of glucose concentrations and is expected to lead to a more etiological management of both the mother and her fetus/infant.

Harizopoulou VC, Tsiartas P, Goulis DG, Vavilis D, Grimbizis G, Theodoridis TD, Tarlatzis BC. Intrapartum application of the continuous glucose monitoring system in pregnancies complicated with diabetes: A review and feasibility study. *World J Obstet Gynecol* 2013; 2(3): 42-46 Available from: URL: http://www.

wjgnet.com/2218-6220/full/v2/i3/42.htm DOI: http://dx.doi.org/10.5317/wjog.v2.i3.42

INTRODUCTION

The incidence of diabetes mellitus (DM) continues to rise worldwide[1,2]. Obviously, this increase affects the incidence of hyperglycemia in pregnancy[3]. The co-existence of DM and pregnancy, commonly encountered in clinical practice, is important both from a pathophysiology and clinical point of view as it is associated with short and long-term morbidity and mortality for the foetus/infant and the mother. Generally, it is accepted that tight glycemic control during pregnancy and labor leads to a decrease in perinatal morbidity and mortality. Pregnancies complicated with DM are treated intrapartum under this principle.

The continuous glucose monitoring system (CGMS) is a relatively new technology that measures interstitial glucose every 1 to 10 min for a maximum of 3 to 6 d, depending on the monitor used. The resulting profile provides a more comprehensive measure of glycemic excursions than intermittent home blood glucose monitoring. Clinical indications for CGMS use include conditions where tight control is crucial[4].

The aim of this review is to present the intrapartum glucose monitoring protocols in pregnancies complicated with DM. The potential role of CGMS as a tool in the achievement of the optimal glycemic control intrapartum is discussed in detail.

SIGNIFICANCE OF INTRAPARTUM NORMOGLYCEMIA

Although the need for normoglycemia during pregnancies complicated with DM has been well established[5-8], the importance and need for intrapartum normoglycemia arise from epidemiological studies only[9-13]. Poor glycemic control intrapartum is associated with adverse maternal (hypoglycemia, ketoacidosis) and neonatal (hypoglycemia, ketoacidosis and respiratory distress syndrome) outcomes[14]. Neonatal hyperglycemia, specifically, has an impact not only on immediate morbidity but also seems to affect long-term neurological development[14].

It is generally accepted that the main target of intrapartum management in pregnancies complicated with DM is to achieve optimal glycemic control. On the other hand, the definition of "optimal" remains a matter of debate. In the literature, there is a great variance in the recommended targets for blood glucose control during labor, ranging from 4.0-6.5 mmol/L[15] to 4.0-8.0 mmol/L[16] and 3.88-6.5 mmol/L[17].

INTRAPARTUM GLUCOSE MONITORING PROTOCOLS

Different protocols for glycemic control during labor have been developed worldwide. The controversies in the literature concerning the management of pregnancies complicated with DM in the delivery room led to the adoption of different local policies[18-23]. Depending on the type of DM and the optimal or suboptimal glycemic control, the treatment options include fasting status of the parturient, frequent monitoring of capillary blood glucose, intravenous dextrose infusion and subcutaneous or intravenous use of insulin.

Most of the protocols are based on the intravenous dextrose and insulin infusion when the concentration of blood glucose is not maintained in the desired range. The insulin infusion rate usually depends on capillary blood glucose, which is monitored hourly during labor[17,23-25]. Specific algorithms that include simultaneous adjustment of both dextrose and insulin infusion rates during labor have been published. These are considered as the standard of care since their efficacy and safety in reducing the risk for maternal hypoglycemia or ketoacidosis have been tested in many studies[23,26-28].

Insights into the pathophysiology and the intrapartum management of pregnancies complicated with insulin-requiring DM suggest that the amount of insulin required during the onset of labor is often zero; thus, it seems that the probability of ketoacidosis due to the prolonged fasting status constitutes a real problem[20-29].

CLINICAL INDICATION OF CGMS USE

The main clinical indications of the CGMS include: (1) adjustment of anti-diabetic treatment; (2) quantitative assessment of the effect of anti-diabetic therapy; (3) assessment of the effect of lifestyle changes in glycemic control; (4) situations where strict glycemic control is particularly important; (5) diagnosis and prevention of hypoglycemia, particularly during sleep; and (6) diagnosis and prevention of post-prandial hyperglycemia[4,30,31].

The most common use of CGMS is during the adjustment of anti-diabetic therapy towards a better glycemic control[30]. These adjustments include modification of insulin dosage before meals, change of the type of insulin administered, changes in the composition of the diet in carbohydrates, decrease in the dose of insulin during periods of intense physical exercise and changes in diet or DM treatment during the night in an attempt to avoid the "dawn phenomenon"[4,31]. CGMS have been also used in clinical trials concerning anti-diabetic agents in an attempt to obtain accurate data about their effect on patients' glycemic profile[32]. CGMS have been used to monitor glucose levels not only in patients with DM, but also in other populations with high risk of hyperglycemia or hypoglycemia. Much attention has been paid to patients with cystic fibrosis[33,34] who face an increased risk of developing DM, in patients hospitalized in intensive care units[35] who are at a high risk of hypoglycemia[36,37] or hyperglycemia[35,38] and in patients with glycogen storage diseases[39] who also face an increased risk of hypoglycemia.

The aim of a very recent publication of a task force

of experts appointed by the Endocrine Society was to formulate practice guidelines for determining settings where patients are most likely to benefit from the use of CGMS[40]. Indications and implications of the use of CGMS in the perinatal and intrapartum setting were not evaluated and so still need to be assessed.

USE OF CGMS IN PREGNANCY

Although publications on the use of CGMS in pregnancies with or without DM are scarce, their significance is of great importance due to the proposed changes in the therapeutic approach.

The main research aims concerning the use of CGMS during pregnancy include comparison of CGMS to intermittent blood glucose monitoring (finger prick self-monitoring)[41-44], determination of the ideal time to measure post-prandial glucose concentrations[44-50] and day to day variability of the glycemic profile[41,51-54]. Additionally, some studies have evaluated the reliability, specificity and accuracy of the CGMS's readings. In particular, the ability of CGMS to detect asymptomatic episodes of hypoglycemia and hyperglycemia has been studied in pregnant women with DM type 1[41,42].

INTRAPARTUM APPLICATION OF CGMS

In 2008, two pilot studies concerning intrapartum application of CGMS were published. In a prospective study by Stenninger *et al*[55], a CGMS was used to monitor the glucose profile of fifteen pregnant women with insulin-treated DM in the last 120 min before delivery. The capillary plasma glucose concentrations were checked hourly and rapid-acting insulin analogues were injected subcutaneously if these levels exceeded 7 mmol/L, in an attempt to reduce the frequency of early neonatal hypoglycemia. In their conclusions, researchers state that parturients with insulin-treated DM coped well with CGMS. They also emphasized the correlation between strict normoglycemia and occurrence of postnatal hypoglycemia. Their suggestion was that CGMS is a feasible and valuable method for close glucose monitoring intrapartum. The interpretation emerges from the superiority of CGMS over intermittent blood glucose monitoring when maximal information about glucose fluctuations is vital.

In the second study, Iafusco *et al*[56] used a real time CGMS to monitor the glucose profile of eighteen pregnant women with DM type 1 in two phases: antenatal, during treatment with bethamethasone for fetal lung maturation and intrapartum. The main target in both phases was to achieve normoglycemia by using intravenous administration of insulin and glucose fluctuation monitoring. In their conclusions, the researchers state that no infant experienced hypoglycemia or respiratory distress syndrome at the moment and within the first hours after birth. They also emphasized the importance of strict glycemic control in these two phases in pregnant women with DM type 1, considering the CGMS as an important tool to achieve it.

More recently, our group conducted a feasibility study[57] with the primary aim to assess the feasibility of the CGMS in the deliveries of pregnancies complicated with DM; a secondary aim was to examine CGMS acceptance by the women. The study involved twelve pregnant women with GDM. The minimally invasive microdialysis-based CGMS (Gluco-Day, Menarini Diagnostics) was used to record glucose profile during labor. The device was installed 6 h before delivery for a total of 48 h. As far as the primary aim is concerned, no pain was reported during sensor installation and removal. Subcutaneous application into the abdominal wall did not affect the obstetric interventions. In the case of vaginal delivery, even an operative one, CGMS did not affect the continuous electronic fetal monitoring, the application of epidural analgesia, or the use of ultrasonography, when needed. In the case of caesarean section, the selection of the site for the placement of the sensor (far enough from the incision) and its careful immobilization guaranteed the successful recording. In two cases, the monitoring failed (breaking of the microdialysis fiber, device disconnection). As far as the secondary aim is concerned, the mode of delivery was associated with the acceptance of the device postpartum: all women that gave birth vaginally (n = 6) reported discomfort in contrast to the women that underwent caesarean section (n = 6). This can be attributed to different levels of postpartum mobility between the two groups. All women coped well with the CGMS and reported feeling secure by checking glucose concentrations in real-time.

CONCLUSION

In pregnancies complicated with DM, both perinatal and intrapartum normoglycemia is an important milestone in the ultimate goal of reducing perinatal morbidity and mortality. Once diagnosed with DM, pregnancies receive special obstetric management by intense monitoring and adjustment of therapeutic interventions. Even then, the absolute absence of any complication is not guaranteed. Intrapartum glucose monitoring protocols were developed in the name of strict glucose control, although there is still much to be elucidated in the pathophysiology of DM and its behavior intrapartum. CGMS is a tempting and promising technology, with its reliability, specificity and accuracy being evaluated and tested in recent clinical trials. The intrapartum application of CGMS in pregnancies complicated with DM allows for a closer observation of glucose concentrations and is expected to lead to a more etiological management of both the mother and her foetus/infant. As a future perspective, a large, prospective study is needed to determine the clinical implications of intrapartum application of CGMS.

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World Journal of Obstetrics and Gynecology

Online Submissions: http://www.wjgnet.com/esps/
wjog@wjgnet.com
doi:10.5317/wjog.v2.i3.47

World J Obstet Gynecol 2013 August 10; 2(3): 47-52
ISSN 2218-6220 (online)

MINIREVIEW

Laparoscopic surgical repair of pelvic organ prolapse and female stress urinary incontinence

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Received: March 9, 2013 Revised: April 6, 2013
Accepted: June 8, 2013
Published online: August 10, 2013

Core tip: Laparoscopic approaches in urologic surgery have become over the years very popular. Novel laparoscopic expertise is continuously acquired in many different surgical fields such as pelvic organ prolapse (POP). We summarize the relevant literature upon the laparoscopic surgical repair of POP and female stress urinary incontinence.

Mourmouris PI, Skolarikos A, Mitsogiannis IC, Migdalis V, Papatsoris AG. Laparoscopic surgical repair of pelvic organ prolapse and female stress urinary incontinence. *World J Obstet Gynecol* 2013; 2(3): 47-52 Available from: URL: http://www.wjgnet.com/2218-6220/full/v2/i3/47.htm DOI: http://dx.doi.org/10.5317/wjog.v2.i3.47

Abstract

Pelvic organ prolapse (POP) occurs in a relatively big population of women which is continuously increasing and is associated with a variety of urinary bowel and sexual symptoms. As this problem magnifies, the need for surgical repair is increasing relatively. The main goals of surgical repair for POP include: no anatomic prolapse, no functional symptoms, patient satisfaction and avoidance of complications, goals that cannot always be fully achieved. The decision for the type of surgery depends of various factors such as patient characteristics and prolapsed compartment but also by the surgeon expertise. The laparoscopic approach is already the gold standard procedure for many urologic procedures and can also be used for the treatment of POP and stress urinary incontinence. Herein, we review the literature about the available data concerning laparoscopic surgery techniques for treating POP.

Key words: Pelvic organ prolapse; Laparoscopic; Minimal invasive; Repair

INTRODUCTION

Pelvic organ prolapse (POP) is defined as the descent of one or more of the following: anterior vaginal wall, posterior vaginal wall and apex of the vagina (cervix/uterus) or vault (cuff) after hysterectomy. Absence of prolapse is defined as POP stage 0, while POP can be staged from stage I to stage Ⅳ. POP occurs in up to 50% of parous women and may be associated with a variety of urinary bowel and sexual symptoms[1]. The prevalence of POP is currently increasing and the lifetime risk of requiring surgery for POP is more than 10%[1]. The main goals of surgical repair for POP is to achieve no anatomic prolapse, no functional symptoms, patient satisfaction and avoidance of complications, goals that usually cannot be fully established[2]. The available surgical techniques in correlation with the relevant anatomical compartments are listed in Table 1.

Laparoscopic approach is the gold standard operation for many urological clinical entities. In POP the laparoscopic approach has the advantage of allowing a very good view of the anterior and posterior compartments so that an overall approach for POP is possible by the

same surgical route[3]. There have been described over 100 different approaches for the repair of the POP. The decision for the type of surgery depends on the compartments that are affected and the patient characteristics. The laparoscopic approach for the surgical treatment of POP was introduced to treat the three compartment defects with the objectives of being less invasive than open surgery, of easier magnified access to the pelvis with less blood and shorter postoperative convalescence.

We performed a search at PubMed and Cochrane databases for articles concerning surgery repair of POP and laparoscopic approaches published between 1970 and 2013. We used as key words the terms: POP, laparoscopic, minimal invasive techniques and robotic assisted laparoscopic techniques. We studied all the relevant articles and we analyzed the ones with the biggest series.

LAPAROSCOPIC RETROPUBIC SUSPENSION

Laparoscopic techniques for retropubic suspension were introduced by Vancaillie and Schuessler in 1991. They performed a Marshall Marchetti-Krantz urethropexy laparoscopically and since then laparoscopic techniques have been applied to both the Burch procedure and the paravaginal repair. Proposed advantages of the laparoscopic approach include improved intraoperative visualization, less postoperative pain, shorter hospitalization and quicker recover times[4]. Disadvantages include greater technical difficulty, longer operative times and higher operative costs[5]. The procedure may be performed extraperitoneally or transperitoneally and each approach has its proponents. Although extraperitoneal technique may be associated with shorter operating times, easier dissection and fewer bladder injuries[6] the transperitoneal approach provides a larger operating space and the ability to perform concomitant intraperitoneal procedures and apical prolapsed repair[5].

Paraiso *et al*[5] reviewed 13 studies of laparoscopic retropubic suspensions, reported success rates from 69% to 100% with follow up of 1 to 36 mo and these rates are comparable to the outcomes of open procedures. Both retrospective[7] and randomized prospective trials[8] between open and laparoscopic techniques have demonstrated similar short term success rates. However when following patients for a longer time, laparoscopic suspensions tend to fail in comparison with open surgery. McDougall *et al*[9] reported only 30% recovery of stress urinary incontinence (SUI) and 50% cure with a laparoscopic Burch procedure after 45 mo of follow up.

Five trials summarized in a Cochrane review compared laparoscopic with open colposuspension[8,10-13]. Overall, there was a significantly higher success rate after open colposuspension (RR = 0.89; 95%CI: 0.82-0.98) equivalent to an absolute difference of an additional 9% risk of failure after laparoscopic surgery. No significant differences between the two groups were observed for postoperative urgency, voiding dysfunction, or *de novo* detrusor overactivity. A trend was shown toward a higher complication rate, less postoperative pain, shorter hospital stay, and more rapid return to normal function for laparoscopic colposuspension. The operating time tended to be longer, the intraoperative blood loss less, and the duration of catheterization shorter for laparoscopic compared with open colposuspension. Carey *et al*[12] published a randomized trial upon 200 women during 1997 and 1998, with 2-year follow-up available for 83% of participants. The authors found no difference in urodynamic studies outcome, incidence of detrusor overactivity, or patient satisfaction at 6 mo, with an overall objective cure rate of 75%. Detrusor overactivity was recorded in 12% of the women. The overall satisfaction rate was 87%. At 24 mo after surgery there were no significant differences between the two treatment groups with respect to reporting SUI, urgency, and urgency incontinence and a satisfaction score of greater than or equal to 80. Although follow-up information was only available on approximately 80% of all patients by 24 mo, a sensitivity analysis was performed assuming that all women who did not complete the 24-mo follow-up had either occasional or frequent SUI. With these assumptions, cure rates decreased to 61% for open colposuspension and 50% for laparoscopic colposuspension. There were no significant differences between the two treatment groups at 3 to 5 years after surgery. Mean operating time was approximately twice as long for laparoscopic colposuspension, but surgeon's estimates of blood loss and patient's estimates of immediate postoperative pain at rest were significantly less after the laparoscopic procedure with a return to normal activities, 5 d earlier ($P = 0.01$). Kitchener *et al*[14] also found no difference in the objective cure rate (79% for laparoscopic *vs* 70% for open) or subjective cure rate (55% *vs* 54%) between the study arms. The intention-to-treat analysis indicated no significant difference in cure rates between open and laparoscopic surgery.

In a meta-analysis of all of the comparative studies published between 1995 and 2006 of laparoscopic *vs* open colposuspension, 16 studies matched the selection criteria of 1807 patients, of whom 861 (47.6%) underwent laparoscopic and 946 (52.4%) underwent open colposuspension[15]. The length of hospital stay and return to normal life were significantly reduced after laparoscopic surgery. These findings remained consistent on sensitivity analysis. Bladder injuries occurred more often in the laparoscopic group, but only with a marginal statistical significance. Comparable bladder injury rates were found when studies were matched for quality, year, and randomized trials. Cure rates were similar between the two procedures at 2 years follow-up. Table 2 summarizes the available data in laparoscopic retropubic suspension.

The current evidence suggests that in adequately experienced hands there is no difference in overall safety and efficacy between laparoscopic and open colposuspension. Laparoscopic colposuspension shows comparable subjective outcome, but poorer objective outcome

Table 1 Surgical repair of pelvic organ prolapse

Compartment	Prolapsed organ	Vaginal wall site	Abdominal repair
Anterior	Urethra	Distal anterior vaginal wall	Retropubic urethropexy
Anterior	Bladder (cystocele)	Proximal and distal anterior vaginal wall	Paravaginal repair
Middle	Cervix	Cervix	Abdominal sacrocolpopexy
Middle	Small bowel (enterocele)	Ureterosacral scar	Halban culdoplasty
Posterior	Small bowel AP (enterocele)	Proximal posterior vaginal wall	Colpoperineopexy
Posterior	RectumBp (rectocele)	Proximal and distal posterior vaginal wall	NA
Posterior	Perineal body	Perineal Body	NA

NA: Not available.

Table 2 Laparoscopic retropubic suspension overview

Ref.	*n*	Follow up (mo)	Objective cure rate (%)	Satisfaction rate (%)
Paraiso *et al*[5]	150	1-36	69-100	NA
McDougall *et al*[9]		45	30	NA
Carey *et al*[12]	200	24-60	50	87
Kitchener *et al*[14]	291	24	79	NA
Tan *et al*[15]	861	24	NA	NA

NA: Not available.

Table 3 Laparoscopic promontofixation overview

Ref.	*n*	Mean follow up (mo)	Objective cure rate (%)	Recurrence rate (%)
Bacle *et al*[18]	501	20.7	NA	11.5
Ganatra *et al*[19]	1197	24.6	NA	10
Sabbagh *et al*[20]	186	60	92.4	NA
Rivoire *et al*[21]	138	33.7	64	NA
Maher *et al*[23]	108	24	77	5

NA: Not available.

than both open colposuspension and tension-free vaginal tape procedure in the short to medium term follow.

LAPAROSCOPIC PROMONTOFIXATION

The wide spectrum of open and laparoscopic surgical approaches used to treat POP represented the complexity of managing this medical condition[16]. Irrespective of the route or repair chosen by the surgeon, a sound surgical judgment, complete understanding of the pelvic anatomy and the mechanisms involved in POP are required for a successful outcome[17].

Recently, Bacle *et al*[18] studied prospectively 501 consecutive patients that underwent laparoscopic promontofixation (LP) for POP. They reported a 1.7% intraoperative compilations rate and after a mean follow up of 20.7 mo the complications rate was 17.8% and the recurrence rate was 11.5%. Risk factors for recurrence were the prolypropylene mesh when compared with the polyester mesh ($P < 0.0001$), intra-operative hysterectomy ($P = 0.02$) and bleeding ($P = 0.0049$). The authors concluded in a statistically significant improvement in most of the symptoms ($P < 0.001$). Ganatra *et al*[19] reviewed 11 laparoscopic studies that included 1197 patients and reported a 10% recurrence rate for POP. In this study the mean incidence of vaginal erosion was 2.7%. Sabbagh *et al*[20] performed a retrospective study of 186 consecutive women who underwent LP for POP. The median follow up was 60 mo with a success rate of 92.4%, complications rate up to 6% and satisfaction rate up to 91.1%.

Rivoire *et al*[21] performed LP in 138 patients with POP. The follow up was 33.7 mo with a recurrence rate at 11%, while 98% of patients were satisfied with the operation but the postoperative SUI rate was 46%. White *et al*[22] in their study of 30 patients concluded that there was no significant difference with respect to the operative time, blood loss, pain score and duration of hospitalization between laparoscopic and robotic assisted approaches. They concluded that laparoscopic and robotic assisted sacral colpopexy offered comparable efficacy and superior cosmetic results compared to open approaches.

Recently, Maher *et al*[23] compared laparoscopic sacral colpopexy to total mesh placement for vaginal vault prolapsed. In this randomized study of 108 patients the laparoscopic group had a shorter hospitalization period and quicker return to work while the follow up of 2 years showed a 77% success rate at all vaginal site for laparoscopic sacral colpopexy as compared with 43% for total vaginal mesh ($P < 0.001$). The re-operation rate was significantly higher after the vaginal mesh surgery (22%) as compared to the laparoscopic sacral colpopexy (5%) ($P = 0.006$). The authors concluded that laparoscopic sacral colpopexy provided higher success rates and lower perioperative morbidity and re-operation rates in comparison with the total vaginal mesh procedure. The overview of the above results are summarized in Table 3.

LAPAROSCOPIC PLACEMENT OF THE ARTIFICIAL URINARY SPHINCTER FOR SUI

The first clinical report of laparoscopic transperitoneal artificial urinary sphincter (AUS) implantation in women was published by Ngninkeu *et al*[24]. In this study the authors reported their preliminary results (mean follow up 6 mo) of treating four women with SUI due intrinsic sphincter deficiency (ISD) with implantation of the

AMS 800 AUS. The aim was to evaluate the efficacy and safety of the AMS 800 implanted by the transperitoneal laparoscopic approach. The primary inclusion criterion for this study was a negative Marshall test (urine leakage on straining or coughing not corrected with vaginal elevation)[25]. Patients in whom bladder overactivity was diagnosed were excluded from the study. The age of the patients was 50 to 79 years old, while the same surgeon performed all the procedures. Three trocars were inserted into the left iliac fossa, at midline halfway between the umbilicus and the pubis and into the right iliac fossa. The first step was the anterior approach to the bladder followed by dissection of the periurethral fascia and of the bladder neck from the vagina. The next step was the placement of the cuff and the pump. Finally, the balloon was introduced at the left lateral space of the bladder. The connections were performed and the device was deactivated. The activation of the device took place after 6 to 8 wk. All the cases were successfully completed within 2-2.5 h except from one. The urethral catheter remained for 7 d, while in one patient the symptoms persisted and the AUS balloon was replaced. All the patients had functioning devices at the end of the study. None of the patients experienced any preoperative or postoperative complications.

Hoda *et al*[26] used an extraperitoneal laparoscopic approach for the implantation of the AMS 800 sphincter in two women with high body mass index (BMI) and significant co-morbidities. The technique of the surgeon involved the placement of balloon trocars in the preperitoneal space, complete mobilization of the bladder neck, placement of the cuff at the bladder neck, insertion from the same port of the AUS balloon and placement of the pump in a pocket in the right labia major. The urethral catheter remained 2 d but one patient after the catheter removal experienced urinary retention and for 1 wk he performed intermittent self catheterization. The mean operating time was 117 min and patients were discharged after 5-6 d. The activation of the AUS occurred 6 wk after surgery. One patient developed an abdominal wall hematoma which resulted in protrusion of the tubes from the suprapubic incision and secondary healing. Nearly 5 to 8 mo postoperatively both patients were continent. The authors concluded that the laparoscopic AUS implantation is a feasible and safe method but in order to achieve optimal results a careful patient selection must occur.

Rouprêt *et al*[27] reported their preliminary results with the laparoscopic approach for AUS implantation in 12 women with SUI due to ISD. The inclusive criterion for this study was a negative Marshall test associated with a low urethral closure pressure. Nine cases underwent laparoscopic extraperitoneal implantation of AUS and three of them the transperitoneal approach. Three procedures were converted to open and one was abandoned. Eleven patients out of 12 had a history of an anti-incontinence surgery. The extraperitoneal approach was performed with two trocars placed medially to the anterior superior iliac spines and one trocar placed at the midpoint between the pubis and umbilicus. After identifying the bladder neck the surgeon entered the endopelvic fascia on both sides. The next step was the dissection of the bladder neck below the periurethral fascia and the cuff was positioned and pressurized. The balloon was introduced through the iliac fossa mini incision and placed at the right of the bladder and after that the pump was placed into the labia major. The last step was to make the connections and deactivate the device. The mean operative time was 181 min with no significant blood loss. The mean hospital stay was 7 d. The AUS activation was done at a mean period of 40.6 d. During the mean follow up of 12 mo 11 patients had a functioning device and the SUI was resolved in 10 patients. The remaining woman improved, but had a persistent degree of SUI (1 pad/d). Urinary retention occurred in 5 out of 12 patients (45%) and in 3 patients the authors encountered intra-operative injuries (25%). No postoperative erosion or device malfunctions during the follow up. The authors concluded that the laparoscopic implantation of AUS in women appeared to be technically feasible and that the results were promising.

Recently, Mandron *et al*[28] published the results in 25 patients that underwent laparoscopic implantation of AUS for SUI with ISD. This study is the largest in terms of patients (25 patients) and follow up (26.1 mo). The mean BMI was 26.8 and all patients had a negative Marshall test. All patients had a history of anti-incontinence and or pelvic surgery. All operations started with the placement of one 10 mm trocar for the laparoscope followed by a 10 mm trocar midway between the umbilicus and the pubic symphysis, and two 5 mm trocars 2 cm medially to each superior iliac crest. The next step was the incision of the peritoneum and the dissection of the lateral attachments of the bladder neck. Next were the dissection of the urethra from the vaginal wall and the placement of the AUS measuring tape and cuff. After the placement of the cuff around the urethra the AUS balloon reservoir with the relevant volume of fluid was inserted. Finally, after progressive dilatation (up to 14 F) the AUS control pump was pocketed in the major labia and after the connection were made and placed in the Retzius place, the device was deactivated. The authors significantly reduced the operative time (mean 92 min) and hospital stay (mean 4 d). The urethral catheter remained for 2 d and the success rate (92%) was comparable to the open AUS implantation. There were no perioperative complications except for one vaginal perforation which was repaired during the operation in two layers with absorbable sutures. The device was activated 6 wk after the surgery. Five out of 25 patients (20%) developed urinary retention and after surgery four patients were diagnosed with a urinary tract infection. Vaginal erosion was diagnosed in two patients during the first appointment. There was no need for blood transfusion. Out of 25 patients, 23 reported continence and functional devices, 19 of which had no need for pads per day and 4 needed 1 pad/d.

The results of the above mentioned studies upon the

Table 4 Results of the studies upon laparoscopic implantation of the artificial urinary sphincter

Ref.	*n*	Mean follow up (mo)	Success rate (%)	Operative duration (min)	Hospital stay (d)
Ngninkeu *et al*[24]	4	6	80	150	8
Hoda *et al*[26]	2	6	100	120	6
Rouprêt *et al*[27]	12	12.1	88	180	7
Mandron *et al*[28]	25	26.1	92	92	4

laparoscopic implantation of the AUS are summarized in Table 4.

LAPAROSCOPIC AND ROBOTIC ASSISTED LAPAROSCOPIC SACROCOLPOPEXY

Since sacral colpopexy is considered to be the most effective operation for the treatment of vaginal vault prolapse it was inevitable that laparoscopic approach would be attempted in order to minimize morbidity and reach higher cure rates. The largest series on this approach was reported by Stepanian *et al*[29] who studied 446 patients. They formed 2 groups, one with patients undergoing concominant hysterectomy and one with history of hysterectomy. The risk for mesh related complications was 1, while no differences were found between the two groups. The median follow up was 12 mo. Although the study was the largest in this type of procedure it was a cohort study that used questionnaires and chart reviews[29].

Robotic assisted laparoscopic procedures for the treatment of POP are relatively novel procedures. Although this type of procedure is performed transabdominally with increased morbidity compared with the vaginal repairs the complication and recurrence rates are low. Elliott *et al*[30] reported low complication rates and only one patient with recurrent grade 3 rectocele but the mean follow up was relatively short (5 mo). Di Marco *et al*[31] followed 5 patients for 4 mo and found no relapse in any of the 3 compartments and no complications except one patient that experienced vaginal bleeding. They concluded that robotic assisted techniques may provide the same long term durability with open sacroclpopexy[31]. The need for largest randomized studies is important in order to reach safe results.

CONCLUSION

Laparoscopic surgical repair of POP is safe and efficient and it can be used from surgeons that are familiar with the anatomy of the pelvic floor. Many different laparoscopic techniques have been published with relatively good results that are equal with open surgery. However, the number of patients is these studies are still small and better studies with bigger number of patients are warranted.

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P- Reviewers D Moore R, Sacco E, Wang PH
S- Editor Wang JL **L- Editor** A **E- Editor** Zheng XM

World Journal of Obstetrics and Gynecology

Online Submissions: http://www.wjgnet.com/esps/
wjog@wjgnet.com
doi:10.5317/wjog.v2.i3.53

World J Obstet Gynecol 2013 August 10; 2(3): 53-61
ISSN 2218-6220 (online)

BRIEF ARTICLE

Smoking and genital human papilloma virus infection in women attending cervical cancer screening in Greece

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Author contributions: Agorastos T conceived and co-ordinated the study; Chatzistamatiou K drafted the manuscript; Zafrakas M, Konstantinidis TC and Agorastos T revised the manuscript critically for important intellectual content; all authors contributed in data acquisition, analysis and interpretation, as well as in drafting the article; all authors have read and approved the final version of the manuscript.
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Received: March 20, 2013 Revised: April 9, 2013
Accepted: May 16, 2013
Published online: August 10, 2013

Abstract

AIM: To investigate whether smoking is associated with human papilloma virus (HPV) infection.

METHODS: HPV infection is considered to be a necessary condition for cervical cancer development. The study population included 1291 women, aged 25-55 years, attending cervical cancer screening. All women had a Papanicolaou (Pap) test, with liquid-based cytology (Thinprep®), an HPV-DNA test and an evaluation of smoking habits. The COBAS® 4800 system was used for HPV-DNA testing, enabling identification of the following high-risk HPV (hrHPV)-types: each of HPVs 16 and 18 separately, and HPVs 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 as a cocktail. The evaluation of smoking habits was assessed using the smoking intensity index (SII), a variable formed as the product of cigarettes consumed per day by the days (years × 365) that a woman was a smoker, divided by 1000.

RESULTS: There were 136 smokers among 238 women tested positive for hrHPV-types (HPVs 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and/or 68), and 463 smokers among 1053 hrHPV-negative women (OR = 1.7, $P < 0.001$). This association was attributed to the youngest age group of women, aged 25-34 years (OR = 2.3, $P < 0.001$), while there was no association in other age groups. The intensity of smoking (increasing SII) showed no statistically significant association with hrHPV infection. Cervical infection with HPV 16 and/or HPV 18 was also not associated with age or smoking habits. Finally, no association was found between Pap test status and smoking habits or smoking intensity.

CONCLUSION: Smoking appears to be associated with hrHPV infection of the uterine cervix, particularly in younger women. Further studies should investigate whether this association is based on causality and evaluate the role of other possible co-factors.

Key words: Human papilloma virus; High-risk human papilloma virus; Human papilloma virus-DNA test; Smoking; Cervical cancer; Screening

Core tip: Human papilloma virus (HPV) infection is a prerequisite for cervical cancer development. We investigated whether smoking can influence the course of HPV infection, in 1291 women attending cervical cancer screening. Smoking appeared to be associated with high-risk HPV (hrHPV) infection of the uterine cervix, particularly in younger women, aged 25-34 years. In addition, women in this younger age group with a negative Pap test were more likely to have hrHPV infection if they were smokers than if they did not smoke. Further studies should investigate whether this association is based on causality and evaluate the role of other possible co-factors.

Chatzistamatiou K, Katsamagas T, Zafrakas M, Zachou K, Orologa A, Fitsiou F, Theodoridis T, Konstantinidis T, Konstantinidis TC, Agorastos T. Smoking and genital human papilloma virus infection in women attending cervical cancer screening in Greece. *World J Obstet Gynecol* 2013; 2(3): 53-61 Available from: URL: http://www.wjgnet.com/2218-6220/full/v2/i3/53.htm DOI: http://dx.doi.org/10.5317/wjog.v2.i3.53

INTRODUCTION

Genital infection by human papilloma virus (HPV) is considered to be a *sine qua non* condition for development of cervical cancer[1]. In general, HPVs are divided into two groups, according to their oncogenic potential: The first group consists of the so-called low-risk and the second of the high-risk HPV (hrHPV)-types. Specific types of hrHPV can cause cervical cancer, and more than 95% of cervical cancer biopsies contain DNA from hrHPV genomes[2].

There are, however, certain other factors that may influence the probability of hrHPV infection or accelerate the carcinogenic processes leading to cervical cancer[3]. Transmission of HPV between sexual partners is influenced by the age of a woman and her partner, the number of sexual partners, the age at first sexual intercourse, use of barrier contraceptive methods, co-infections, male sexual behaviour, and male circumcision[4]. In some studies however, age at first sexual intercourse was not identified as an independent risk factor in multivariate analysis[5-7]. Other factors that have similar impact on disease progression include high parity, long-term oral contraceptive use, and smoking[8-10].

Many studies have shown that cigarette and tobacco smoking in general have a moderate and statistically significant association with cervical cancer and cervical intraepithelial neoplasia (CIN)[10-19], although the latter is not supported by other studies[20]. In detail, Syrjänen *et al*[20], by using multivariate analysis, found that cigarette smoking was not an independent risk factor for CIN2 or more advanced lesions; however, there is evidence that suggests a potential role of passive smoking on invasive cervical cancer[21,22]. There is also evidence suggesting an association between smoking and an increased risk of high grade vaginal intraepithelial neoplasia (high grade VAIN)[23].

It is not quite clear though, if tobacco smoking, apart from increasing the risk for invasive cervical cancer and its precursors, may also influence HPV infection, particularly persistent HPV infection. Recent research focusing on the possible association between tobacco smoking and HPV infection has shown a positive association in women[18,24,25], as well as in men[26]. In the present study, this possible association has been investigated in an urban population of women participating in cervical cancer screening in Greece.

MATERIALS AND METHODS

Participants and specimen collection

Women attending cervical cancer screening in two outpatient clinics of the Hippokrateio Hospital in Thessaloniki, Greece, were recruited for the present study, as well as for an ongoing multi-center study dealing with screening for cervical cancer based on hrHPV-DNA detection as primary test, using the Cobas® 4800 HPV Test. In total, 1291 women were recruited for the present study between August 2011 and January 2013. Participants were 25-55 years old, living in the urban area of Thessaloniki. The following exclusion criteria were used: pregnancy, treatment for CIN during the previous 5 years, history of hysterectomy, and use of conventional cytology.

Every woman was informed about all aspects and the rationale of the study, and signed a consent-form in order to participate. After recruitment, women answered certain questions about their smoking habits; if they smoked, and if yes, how many cigarettes per day and for how many years. According to this information, the number of cigarettes per day, multiplied by years of smoking [n (cig/d) × 365 × n (years) divided by 1000] was calculated, creating a new variable, the smoking intensity index (SII), by which the sample was stratified. Following completion of the questionnaire, all women were examined by a specially trained healthcare professional (either a gynecologist or a midwife), who took cell samples from both the ecto- and the endocervix, using the Cervex brush® (Rovers® Medical Devices, B.V. Oss, The Netherlands). Brushes were inserted in Thinprep® vials containing PreservCyt® Solution (Hologic, Inc, Marlborough, MA, United States), and were discarded after handling according to the instructions of the manufacturer.

Cytology

Papanicolaou (Pap) smears were prepared using the Thinprep® liquid-based methodology, as previously described[27] and examined by a specially trained cytologist. The cytological assessment was performed according to the Bethesda 2001 classification[28]. The remaining liquid sample was then sent to the Peripheral Laboratory of Public Health of the Hellenic Center for Disease Control and Prevention and Laboratory of Hygiene and Environmental Protection/Laboratory of Microbiology of the Democritus University of Thrace in Alexandroupoli, Greece, where it was tested for HPV-DNA, using the

Cobas® 4800 system (Roche® Molecular Diagnostics, CA, United States).

HPV-DNA detection

The Cobas® 4800 HPV Test is based on two main procedures[29]: (1) automated isolation of viral and human nucleic acids from clinical samples; and (2) enhancement and detection with real-time-polymerase chain reaction of 22 target-DNA sequences. Specifically, the Cobas® 4800 HPV Test employs primers for the determination of a sequence of approximately 200 nucleotides within the L1 polymorphic region of the HPV genome. The HPV primer concentration that exists in the Main Compound has been designed for the DNA enhancement of 14 hrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). The oligonucleotide fluorescent tracers are bound to the polymorphic regions within the sequence determined by those primers. An additional primer couple and an additional tracer target the β-globulin human genome -clone (amplicon) 330 bp- in order to supply a control serum. Simultaneous infusion, enhancement and detection of human β-globulin genome and viral sequences using Cobas® 4800 HPV Test gives the user the added advantage of control during all stages of the examination. The HPV primer concentration in the main compound reagent for the Cobas® 4800 HPV Test has been designed for the DNA enhancement of 14 hrHPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. The enhanced signals from HPV 16 and 18 are each detected with a separate special fluorescent stain, while the other twelve hrHPV types are detected using the same fluorescent stain[29].

Statistical analysis

The association between HPV infection and smoking was evaluated using the χ^2 test and Fisher's exact test. The influence of smoking and smoking intensity on hrHPV infection as well as on cytology status was evaluated with the use of cross-tabulation matrices associating age. Frequencies and relative frequencies, as well as their corresponding *P*-values of the χ^2 test and the ORs are calculated. *P*-values < 0.05 were considered statistically significant. Analyses were performed using the SPSS 20.0 statistical software (IBM Co., New York, United States).

RESULTS

Recruited women (n = 1291) were divided into two groups: (1) hrHPV-positive women, *i.e.*, women positive for any of the 14 hrHPV types (n = 238); and (2) hrHPV-negative women, *i.e.*, women negative for all 14 hrHPV types (n = 1053).

Smoking and HPV status

In the younger group of women, aged 25-34 years, 95 out of 158 hrHPV-positive women were smokers, as compared with 125 out of 316 hrHPV-negative women (60.1% *vs* 39.6%, $P < 0.001$). Hence, in this age group, smokers were 2.3 times more likely to have a hrHPV infection than non-smokers. There was no statistically significant difference between hrHPV-positive and hrHPV-negative women in the 35-44 years old (46.7% *vs* 45.4%) and the 45-55 years old age groups (57.1% *vs* 46.3%). Regardless of age, a significantly higher proportion of hrHPV-positive women were smokers, as compared with hrHPV-negative women (57.1% *vs* 43.8%, $P < 0.001$). The OR for smokers to be hrHPV-positive in all age groups, *i.e.,* for ages between 25 and 55, was 1.7 ($P < 0.001$). An overview of these results is presented in Table 1.

Table 1 Association between smoking and high-risk human papilloma virus status, stratified according to age *n* (%)

Age (yr)	Smoking	HPV (+)	HPV (-)	Total	*P*	OR
25-34	Yes	95 (43.2)	125 (56.8)	220	< 0.001	2.3 (1.6-3.4)
	No	63 (24.8)	191 (75.2)	254		
	Total	158	316	474		
35-44	Yes	21 (12.1)	152 (87.9)	173	NS	1.1 (0.6-2.0)
	No	24 (11.6)	183 (88.4)	207		
	Total	45	335	380		
45-55	Yes	20 (9.7)	186 (90.3)	206	NS	1.5 (0.8-3.1)
	No	15 (6.5)	216 (93.5)	231		
	Total	35	402	437		
Total	Yes	136 (22.7)	463 (77.3)	599	< 0.001	1.7 (1.3-2.3)
	No	102 (14.7)	590 (85.3)	692		
	Total	238	1053	1291		

P-value of χ^2 test and corresponding OR (95%CI). NS: Not significant; HPV: Human papilloma virus.

Table 2 Association between smoking intensity and high-risk human papilloma virus status stratified according to age *n* (%)

Age (yr)	Smoking	HPV (+)	HPV (-)	Total	*P*
25-34	< 50	58 (41.4)	82 (58.6)	140	NS
	50-100	23 (44.2)	29 (55.8)	52	
	100-150	10 (50.0)	10 (50.0)	20	
	150-200	1 (33.3)	2 (66.7)	3	
	> 200	3 (60.0)	2 (40.0)	5	
	Total	95	125	220	
35-44	< 50	5 (9.6)	47 (90.4)	52	NS
	50-100	5 (11.6)	38 (88.4)	43	
	100-150	6 (11.1)	48 (88.9)	54	
	150-200	0 (0.0)	5 (100.0)	5	
	> 200	5 (26.3)	14 (73.7)	19	
	Total	21	152	173	
45-55	< 50	2 (4.3)	44 (95.7)	46	NS
	50-100	2 (6.5)	29 (93.5)	31	
	100-150	5 (9.4)	48 (90.6)	53	
	150-200	3 (11.5)	23 (88.5)	26	
	> 200	8 (16.0)	42 (84.0)	50	
	Total	20	186	206	
Total	< 50	65 (27.3)	173 (72.7)	238	NS
	50-100	30 (23.8)	96 (76.2)	126	
	100-150	21 (16.5)	106 (83.5)	127	
	150-200	4 (11.8)	30 (88.2)	34	
	> 200	16 (21.6)	58 (78.4)	74	
	Total	136	463	599	

P-value of χ^2 test. NS: Not significant; HPV: Human papilloma virus.

Table 3 Association between smoking and human papilloma virus-16, human papilloma virus-18 status stratified according to age *n* (%)

Age (yr)	Smoking	HPV-16					HPV-18				
		(+)	(-)	Total	*P*	OR	(+)	(-)	Total	*P*	OR
25-34	Yes	24 (10.9)	196 (89.1)	220	NS	1.5 (0.8-2.8)	8 (3.6)	212 (96.4)	220	NS	1.3 (0.5-3.7)
	No	19 (7.5)	235 (92.5)	254			7 (2.8)	247 (97.2)	254		
	Total	43	431	474			15	459	474		
35-44	Yes	4 (2.3)	169 (97.7)	173	NS	0.8 (0.2-2.9)	1 (0.6)	172 (99.4)	173	NS	0.4 (0.1-3.8)
	No	6 (2.9)	201 (97.1)	207			3 (1.4)	204 (98.6)	207		
	Total	10	370	380			4	376	380		
45-55	Yes	-	206 (100)	206		-	-	206 (100.0)	206		
	No	-	231 (100)	231			-	231 (100.0)	231		
	Total		437	437			-	437	437		
Total	Yes	28 (4.7)	571 (95.3)	599	NS	1.3 (0.8-2.3)	9 (1.5)	590 (98.5)	599	NS	1.0 (0.4-2.6)
	No	25 (3.6)	667 (96.4)	692			10 (1.4)	682 (98.6)	692		
	Total	53	1238	1291			19 (1.5)	1272 (98.5)	1291		

P-value of χ^2 test and corresponding OR (95%CI). NS: Not significant; HPV: Human papilloma virus.

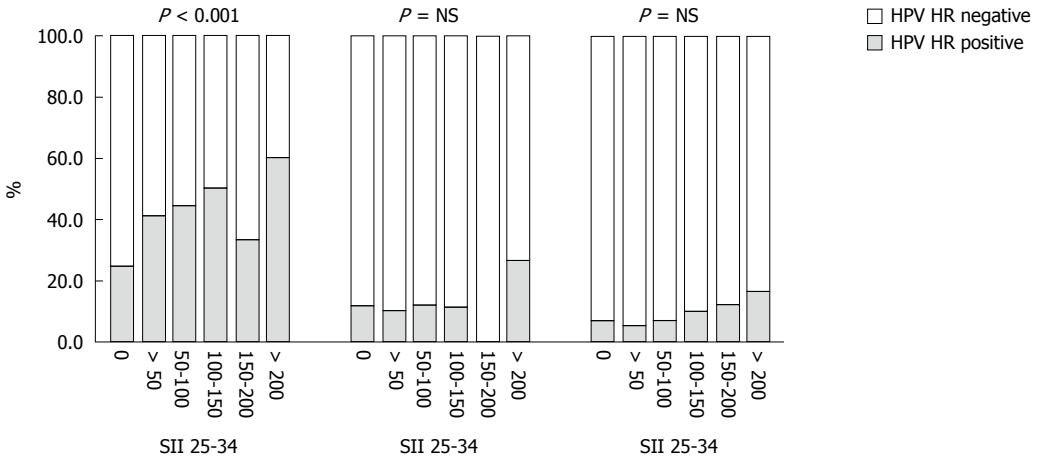

Figure 1 Stratification of human papilloma virus-positive and human papilloma virus-negative women according to age and smoking intensity. There was no statistically significant association between smoking intensity and (h) human papilloma virus (HPV) status. SII: Smoking intensity index. HR: High risk; NS: Not significant.

No association was found between smoking intensity and hrHPV status. These results are presented in detail in Table 2. Figure 1 shows an overview of hrHPV-positive women stratified according to age and smoking intensity. The latter is defined according to the calculated smoking intensity index (SII = cigarettes/d × 365 × years of smoking divided by 1000), and a woman is classified as non-smoker if she had never smoked or if she had stopped smoking at least 1 year earlier. Smokers were classified into one of the following categories according to the previously described variable: SII < 50, if she had smoked less than 50000 cigarettes during her life as a smoker, SII = 50-100, if she had smoked between 50000 and 100000 cigarettes, SII = 100-150 if she had smoked between 100000 and 150000 cigarettes, SII = 150-200 if she had smoked between 150000 and 200000 cigarettes, and SII > 200 if she had smoked more than 200000 cigarettes.

There was no statistically significant association between smoking habits (*i.e.,* smokers *vs* non-smokers) or smoking intensity (increasing SII) and infection from HPV types 16 or 18 in any age group. Table 3 show an overview of the association between smoking and HPV-16 and HPV-18 status, respectively, stratified according to age.

Smoking and cervical cytology results

Regarding cervical cytology results, women were divided into two groups: (1) Women with a negative (normal) Pap-smear (n = 1246); and (2) women with abnormal Pap smear [atypical squamous cells of uncertain significance (ASCUS) or worse] (n = 45). Comparisons according to smoking habits (smokers *vs* non smokers) or smoking intensity between women with normal and women with abnormal cytology results, using the χ^2 test, did not show any statistically significant differences between different age groups (data not shown).

Smoking, HPV status and cervical cytology results

Comparisons according to smoking habits between the two groups of women regarding cervical cytology and the two groups regarding hrHPV status showed that women with a negative Pap test were more likely to have hrHPV infection if they were smokers than if they did

Table 4 Association between smoking habits and high-risk human papilloma virus status according to Papanicolaou test results *n* (%)

Cytology	Smoking	HPV (+)	HPV (-)	Total	*P*	OR
Pap (+)	Yes	18 (69.2)	8 (30.8)	26	NS	1.6 (0.5-5.6)
	No	11 (57.9)	9 (42.1)	19		
	Total	29	16	45		
Pap (-)	Yes	118 (20.6)	455 (79.4)	573	0.001	1.7 (1.2-2.2)
	No	91 (13.5)	582 (86.5)	673		
	Total	209	1037	1246		
Total	Yes	136 (22.7)	463 (77.3)	599	< 0.001	1.7 (1.3-2.3)
	No	102 (14.7)	590 (85.3)	692		
	Total	238	1053	1291		

P-value of χ^2 test and corresponding OR (95%CI). Papanicolaou (Pap) test (+) = atypical squamous cells of uncertain significance or worse; Pap test (-) = Normal. NS: Not significant; HPV: Human papilloma virus.

Table 5 Association between smoking intensity and high-risk human papilloma virus status according to Papanicolaou test results *n* (%)

Cytology	Smoking	HPV (+)	HPV (-)	Total	*P*
Pap (+)	< 50	8 (66.7)	4 (33.3)	12	0.045
	50-100	4 (80.0)	1 (20.0)	5	
	100-150	5 (100.0)	0 (0.0)	5	
	150-200	0 (0.0)	3 (100.0)	3	
	> 200	1 (100.0)	0 (0.0)	1	
	Total	18	8	26	
Pap (-)	< 50	57 (25.2)	169 (74.8)	226	NS
	50-100	26 (21.5)	95 (78.5)	121	
	100-150	16 (13.1)	106 (86.9)	122	
	150-200	4 (12.9)	27 (87.1)	31	
	> 200	15 (20.5)	58 (79.5)	73	
	Total	118	455	573	
Total	< 50	65 (27.3)	173 (72.7)	238	NS
	50-100	30 (23.8)	96 (76.2)	126	
	100-150	21 (16.5)	106 (83.5)	127	
	150-200	4 (11.8)	30 (88.2)	34	
	> 200	16 (21.6)	58 (78.4)	74	
	Total	136	463	599	

P-value of χ^2 test and corresponding OR (95%CI). Papanicolaou (Pap) test (+) = atypical squamous cells of uncertain significance or worse; Pap test (-) = Normal. NS: Not significant; HPV: Human papilloma virus.

not smoke (OR = 1.7, $P = 0.001$). This was not the case if cervical cytology showed ASCUS or worse; however the number of these women was rather low, given that the study was conducted among women attending screening. These findings are presented in Table 4.

On the other hand, similar comparisons for smoking intensity between the two groups of women regarding cervical cytology and the two groups regarding hrHPV status showed, based on very low numbers, that smoking intensity (increasing SII) was associated with a higher probability of a positive ($P = 0.045$), but not a negative Pap test (Table 5).

Finally, stratification of all these associations between smoking habits, Pap smear results and hrHPV status according to age showed that only younger women (25-34 years old) with a negative Pap test were more likely to have hrHPV infection if they were smokers than if they did not smoke (OR = 2.3, $P = 0.001$). These findings are presented in Table 6.

DISCUSSION

In the present study, smokers were more likely to be tested positive for hrHPV types among women 25-55 years of age in an urban area of Greece. Similar results were found in a population of young women in Brazil: certain HPV types were significantly more frequent in current smokers than non-smokers[30]. Likewise, in a study conducted in Portugal, the CLEOPATRE study group showed that smoking was associated with an increased risk of HPV infection[25]. The association between HPV infection and smoking has also been a consistent finding in other studies, conducted in various countries, including Russia, Belarus and Latvia[20], Germany[31], Costa Rica[7], and Canada[32].

With respect to smoking intensity, the International Agency for Research on Cancer (IARC), in a pooled analysis demonstrated that smoking intensity played a significant role in HPV infection risk[24]. Furthermore, similar results to the IARC study were found in a cohort of Tuscan women[33]. In contrast, Collins *et al*[12] found no evidence linking the risk of acquiring an HPV infection with the intensity of smoking. Likewise, in the present study, there was no association between smoking intensity (expressed by a Smoking Intensity Index) and hrHPV infection of the uterine cervix. These contradictory findings may be due to geographic variations in the prevalence of HPV-types[34], as well as due to differences in study design and methods used.

Despite the fact that smoking is a well established risk factor for cervical cancer, there are still contradicting reports regarding the association between tobacco use and hrHPV infection. In a study conducted in Denmark, current smokers were found to have similar HPV prevalence as compared with women who had never smoked, whereas past smokers had a decreased prevalence of HPV[35]. A significant association between HPV prevalence and smoking was found for HIV positive but not for HIV negative women, in a study comparing these two groups[36]. In a nested case control study, smoking was associated with CIN3, but not with HPV infection[37]. In, a study conducted in the United States and Venezuela, risk factors for cervical cancer development appeared to vary

Table 6 Association between smoking habits and high-risk human papilloma virus status according to Papanicolaou test result and stratified according to age *n* (%)

Age (yr)	HPV (cytology)	Smoking	HPV (+)	HPV (-)	Total	*P*	OR
25-34	Pap (+)	Yes	13 (76.5)	4 (23.5)	17	NS	
		No	9 (64.3)	5 (35.7)	14		
		Total	22	9	31		
	Pap (-)	Yes	82 (40.4)	121 (59.6)	203	< 0.001	2.3 (1.5-3.5)
		No	54 (22.5)	186 (77.5)	240		
		Total	136	307	443		
	Total	Yes	95 (43.2)	125 (56.8)	220	< 0.001	2.3 (1.6-3.4)
		No	63 (24.8)	191 (75.2)	254		
		Total	158 (33.3)	316 (66.7	474		
35-44	Pap (+)	Yes	3 (75.0)	1 (25.0)	4	NS	
		No	1 (100.0)	0 (0.0)	1		
		Total	4	1	5		
	Pap (-)	Yes	18 (10.7)	151 (89.3)	169	NS	
		No	23 (11.2)	183 (88.8)	206		
		Total	41	334	375		
	Total	Yes	21 (12.1)	152 (87.9)	173	NS	
		No	24 (11.6)	183 (88.4)	207		
		Total	45 (11.8)	335 (88.2)	380		
45-55	Pap (+)	Yes	2 (40.0)	3 (60.0)	5	NS	
		No	1 (25.0)	3 (75.0)	4		
		Total	3	6	9		
	Pap (-)	Yes	18 (9.0)	183 (91.0)	201	NS	
		No	14 (6.2)	213 (93.8)	227		
		Total	32	396	428		
	Total	Yes	20 (9.7)	186 (90.3)	206	NS	
		No	15 (6.5)	216 (93.5)	231		
		Total	35	402	437		
All ages	Pap (+)	Yes	18 (69.2)	8 (30.8)	26	NS	
		No	11 (57.9)	8 (42.1)	19		
		Total	29	16	45		
	Pap (-)	Yes	118 (20.6)	455 (79.4)	573	0.001	1.7 (1.3-2.3)
		No	91 (13.5)	582 (86.5)	673		
		Total	209	1037	1246		
	Total	Yes	136 (22.7)	463 (77.3)	599	NS	
		No	102 (14.7)	590 (85.3)	692		
		Total	238	1053	1291		

P-value of χ^2 test and corresponding OR (95%CI). Papanicolaou (Pap) test (+) = atypical squamous cells of uncertain significance or worse; Pap test (-) = Normal. NS: Not significant; HPV: Human papilloma virus.

between the two countries[38], and this might be possible for HPV infection as well. Therefore, studies evaluating risk factors for HPV infection should be conducted in various places around the world. An interesting finding in the present study was that younger women (25-34 years old) with a negative Pap test were more likely to have hrHPV infection if they were smokers as compared with non-smokers. This finding may suggest that smoking might enhance HPV-infection in its early stages, before development of pre-invasive lesions. On the other hand, it might be argued that this is a casual rather than a causal association, since younger women are more likely to smoke, as well as to be HPV-positive.

The exact biological mechanisms by which tobacco use is associated with HPV infection, are not clearly understood yet. Persistence of an HPV infection might have been enhanced, leading to an increased risk of progression to cancer, coupled by the carcinogenic effect of polycyclic aromatic hydrocarbons contained in tobacco smoke[21]. These known carcinogens exert a transformation effect on the epithelium of the cervix uteri[21,39,40]. Smoking may also act by increasing cell-turnover in the transformation zone of the cervix[41]. Finally, another possible mechanism might be aberrant, HPV-induced DNA methylation[42].

HPV infections are usually transient. On the other hand, persistence of HPV infection and progression to high grade lesion are probably facilitated by smoking, due to a local immunosuppression that it causes[21,38,43]. This local immune dysfunction results in prolonged duration of oncogenic HPV infections, as well as a decreased probability of clearing the oncogenic infection[44,45]. Furthermore, smoking appears to decrease the capability of the immune system to develop HPV-16/18 antibodies or maintain HPV-16/18 antibody positivity over time, after a natural HPV infection[46]. In addition, smoking has been also associated with a higher baseline HPV-16 and HPV-18 DNA load[47]. In our study, however, smoking did not seem to be associated with cervical HPV-16 and/or HPV-18 infection. Finally, another possible factor that appears to play a role in the persistence of HPV in-

fection, as well as in its progression to high-grade lesions and invasive cervical cancer, is the interaction between smoking and the genetic background of an individual, which determines her susceptibility to infection and disease progression[43].

A limitation of the present study, as well as of most relevant publications, is that HPV-DNA-testing was done only once for each woman. Sequential HPV genotyping of all participants, at certain intervals, could possibly show if smoking might also influence the course of HPV infection. Another limitation of the present study and most relevant publications is that possible co-factors including age at first intercourse, number of sexual partners and oral contraceptive use have not been considered, and thus the possibility of bias cannot be ruled out.

In conclusion, smoking has a well-documented synergistic role with HPV infection, leading to cervical cancer development[48,49]. Furthermore, smoking seems to be associated with an increased prevalence of HPV, a finding confirmed by the present study. Further studies should investigate whether this association is based on causality and evaluate the role of other possible co-factors. In any case, current smokers with either HPV infection or CIN lesion should be managed cautiously, and they should be advised to quit smoking.

COMMENTS

Background

Human papilloma virus (HPV) infection is considered to be a necessary condition for cervical cancer development. High-risk HPV (hrHPV) types can cause cervical cancer, and more than 95% of tumour samples contain DNA from hrHPV genomes. Many studies have shown that smoking is associated with cervical cancer and its precursors.

Research frontiers

Several studies in various countries, including Brazil, Portugal, Russia, Belarus, Latvia, Germany, Costa Rica, and Canada, have shown that smoking is associated with an increased risk of HPV infection. Regarding smoking intensity, results have been contradictory.

Innovations and breakthroughs

In the present study, smokers were more likely to be tested positive for hrHPV types, among women 25-55 years of age, in an urban area of Greece. In respect to smoking intensity, no association with hrHPV infection of the uterine cervix was found in the present study.

Applications

The association between smoking and hrHPV infection is useful for planning cervical cancer prevention strategies. Furthermore, this association may help to clarify or identify new mechanisms of carcinogenesis.

Terminology

HPVs are divided into two groups, according to their oncogenic potential: low-risk HPVs, usually leading to genital warts or low-grade intraepithelial lesions, and hrHPV types, with high oncogenic potential.

Peer review

The paper is interesting and well written. The reviewers encourage authors to continue to explore this issue, improving their analysis with information on general habits of investigated young women and to discover the further correlations with HPV infection/co-infections and other factors, a part smoking.

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World J Obstet Gynecol 2013 August 10; 2(3): I-V
ISSN 2218-6220 (online)

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World Journal of Obstetrics and Gynecology

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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