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REVIEW

Acceptability of self-collected human papillomavirus specimens in cervical cancer screening: A review

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Abstract

Cervical cancer morbidity and mortality is an important public health problem around the world. Some of the barriers to cervical cancer screening include the embarrassment, discomfort, lack of privacy and time and cost associated with clinician-collected, clinic-based screening with cytology or human papillomavirus tests. Self-collection of a human papillomavirus (HPV) test has been found to be generally more acceptable, less embarrassing, more comfortable, more private and easy to do and preferred to pelvic examination for cervical cytology by many women worldwide. The most commonly reported limitation to self-collection is a woman's lack of confidence in her ability to perform it correctly. Self-collected human papillomavirus tests have been shown to be as or more sensitive than cytology or clinician-collected HPV tests. With confidence-building education about self-collection, it is likely a viable method to extend the reach of screening in high and low-resource areas around the world.

Key words: Cervical cancer; Self-collected; Human papillomavirus; Acceptability

Core tip: Self-collected human papillomavirus specimens using swabs, brushes or lavage devices have been found to be as accurate as clinician-collected specimens. With appropriate education to increase self-efficacy and confid ence in the quality of the collection and the results, self-collected HPV tests may improve cervical cancer detection among unscreened and underscreened women in high and low resource areas.

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INTRODUCTION

Though it is largely preventable, cervical cancer is an important cause of morbidity and mortality throughout the world. The age-adjusted incidence of cervical cancer is 14 cases per 100000 women worldwide. It is as high as 15.7 per 100000 in less developed areas of the world and 9.9 per 100000 in more developed areas. The age-standardized mortality rate for cervical cancer is 8.3 per 100000 for women in less developed regions, with a much lower rate of 3.3 per 100000 women in more developed areas[1]. The much lower rates in more developed areas underscore the importance of effective screening programs. In lesser developed regions with fewer healthcare resources, the lack of a reliable screening test and inadequate screening coverage result in more new cervical cancer cases and ultimately in more cervical cancer deaths[2].

Human papillomavirus (HPV) infection is now known to be a necessary cause of cervical cancer and as a result, testing women for high-risk subtypes of HPV is proving to be an effective method of screening. As the

relative value of HPV testing in cervical cancer screening became more apparent, a variety of self-collection options were developed. Self-sampling options tend to be more acceptable to women because they overcome the previously identified barriers to cervical cancer screening. As a result, self-collection of HPV specimens will extend the reach of cervical cancer screening programs even in low-resource areas.

BARRIERS TO CERVICAL CANCER SCREENING

While every woman is an individual in terms of how personal characteristics and life circumstances affect her health care behaviors, women who are underscreened or unscreened for cervical cancer often experience one or more of a number of common barriers to participation. In a group of primarily urban minority women, the reluctant tended to possess a fatalistic attitude, believing that they are better off not knowing about their cancer or that cancer occurs in those who have bad luck. Additionally they reported a lack of family support and lack of understanding of the risk of cervical cancer[3]. Among 300 women in Botswana who answered questions about their perceptions of barriers to Papanicolau (Pap) testing, 32% found it embarrassing and 52% believed that getting a screen suggested a woman is sexually active. Many (63.3%) of the women who had never been screened and 51.7% of those who had been screened thought lack of information was a barrier for screening for cervical cancer. However, none of the barriers identified by the women was significantly associated with their screening behaviors[4]. In a study of 493 women in Brazil, 36.7% of women had adequate knowledge of cervical cancer, 67.2% had an appropriate attitude (recognized the importance of screening) and 69.6% reported having had a Pap in the past 3 years. The barriers to undergoing Pap testing with the highest scores were a lack of symptoms of cervical cancer and the embarrassment associated with the exam[5]. In a study 345 Appalachian women aged 40-64, questions regarding barriers were grouped according to the PRECEDE-PROCEED model as predisposing factor barriers, enabling factor barriers and reinforcing factor barriers. Barriers that were found among more than half of the women included: (1) worry (78%); (2) fear of cancer (67%); (3) embarrassment (56%); (4) the belief that cervical cancer (52%) and polyps (50%) would have symptoms; (5) unavailability of public transportation (71%); (6) preference for home screen (66%); (7) insurance coverage (65%); and (8) lack of choice of a male or female provider (62%)[6]. Among 21-65 year-old Malaysian women, 70% reported that cervical cancer screening is too embarrassing and almost half found the attitude of clinic staff, the lack of female healthcare providers, the worry associated with the outcome and the fear that she would no longer be a virgin after the test were important barriers[7]. In a review of the literature on cervical cancer screening in Asian women, barriers to screening could be grouped as cognitive, emotional, economic, logistic or social. Barriers to screening identified in each of these categories included a lack of understanding of the reason for or benefits of testing, fear, time away from work, lack of insurance, transportation and childcare issues, wait times in the clinic, and lack of support from family and healthcare clinic staff[8]. Lastly, a study of women with cervical abnormalities who were enrolled in a research program to help them navigate the healthcare system in multiple cities in the United States found that nearly half of the women experienced at least one barrier to care and some experienced as many as seven. Barriers that significantly delayed time to diagnosis included the presence of comorbidities, health insurance issues, minimization of the importance of treatment, out of town travel, and employment demands or healthcare system problems. Interestingly, the time from detection of the cervical abnormality to definitive diagnosis was not affected by fear, attitudes toward providers, perceptions about tests and treatments, quality of communication, ability to read and write, or language[9].

SELF-COLLECTED HUMAN PAPILLOMAVIRUS TEST

Self-collection of cervicovaginal HPV specimens is purported to be a viable alternative to Pap testing or clinician-collected HPV specimens that will overcome some of these barriers and extend the reach of screening in low-resource or underscreened populations. A variety of self-collection methods have been developed and tested around the world to determine their diagnostic accuracy (Figure 1). The available devices today include swabs, brushes, and lavage devices. In addition to the polyester (Dacron) tipped swab, flocked swabs are now available. The flocked swab is a variation on the polyester swab that comprises a solid plastic applicator with short nylon fibers attached perpendicularly to the tip. It is designed to allow the specimen to remain near the surface of the swab for ease of retrieval relative to the traditional cotton or Dacron swab. An additional variation on the swab includes the Fournier device. Its swab is wrapped in a sheath much like a tampon applicator. Upon insertion, the woman pushes the end of it to deploy the swab and after collection the swab retreats back into the sheath to prevent absorption of vaginal secretions when the device is removed. There are also a variety of brushes available including the cervical sampler brush and broom-shaped devices commonly used for clinician-collection of cervical cytology specimens. The Evalyn brush also offers an applicator to ease deployment of the brush. Following collection, the pink cap is snapped back onto the transparent applicator and the specimen is transported dry to the lab. Cervical lavage devices have also been developed. For the lavage, the woman inserts the device as she would a tampon and then pushes and holds a button for three seconds. During that time, a small amount of sterile fluid is released from the end near the proximal vagina and

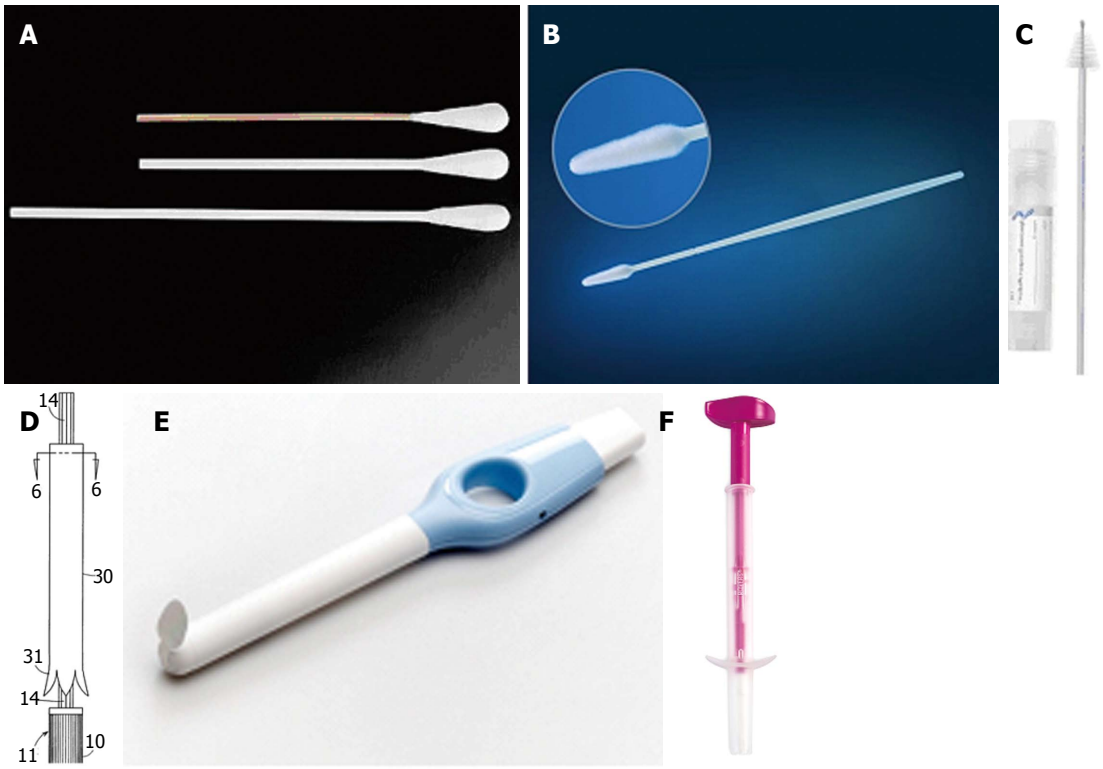

Figure 1 Self-collection device. A: Dacron swab (http://www.danlab.fi/WebRoot/GPL/Shops/16092008-100026/4B75/27BB/C58D/08D9/5A21/0A28/1011/F968/300234.jpg); B: Flocked swab (http://img.bosscdn.com/photo/product/82cda9df62bc1a6f25394c652966adb6/cervical-specimen-collection-flocked-swabs.jpg); C: Cervical sampler brush (http://www.mysynergylab.com/uploads/images//DigeneCervicalBrush.JPG); D: Fournier device (http://patentimages.storage.googleapis.com/US6387058B1/US06387058-20020514-D00000.png); E: Delphi screener (http://www.medicaldevice-network.com/contractor_images/10440/images/140283/large/4-delphi-screener.jpg); F: Evalyn brush (http://www.roversmedicaldevices.com/images/new_images/02_EVALYN%20INGESCHOVEN.jpg).

cervix. When she releases the button, the fluid flows back into the device along with cervical and vaginal cells.

The agreement of HPV self-collected specimens with clinician-collected specimens has been demonstrated to be strong in several studies[10-13]. The sensitivity of the self-collected studies has been consistently as high or higher than that of cervical cytology specimens for the detection of high-grade cervical intraepithelial neoplasia[10]. Self-collected HPV tests are emerging as an alternative to cervical cytology or even clinician-collected HPV tests because their diagnostic accuracy has been favorable and the self-collection kit can be distributed in person or by mail with the collection occurring almost anywhere. If HPV self-collection methods are acceptable to women and they are willing to collect, self-collection has the potential to extend the reach of screening to under- or unscreened women in high or low resource regions.

ACCEPTABILITY OF SELF-COLLECTION

The acceptability of self-collected HPV samples has been examined in a number of different ways. It is usually measured by an interview or a written questionnaire and compared with clinician-collected HPV or Pap test with acceptability parameters determined by the previously reported barriers to cervical cancer screening. Pain, discomfort, degree of embarrassment, level of privacy, ease of use, trust or confidence in the results are commonly measured parameters for acceptability. Other studies focused on women's preferences for self-collection or clinician-collection and the reasons for their preferences.

Swabs

The acceptability of self-collection of HPV samples using some type of soft swab has been examined in various locations internationally. In Ontario, women's responses to self-sampling were stratified by age and in both the younger (< 50 years old) and the older (> 50 years old) groups more than 45% of women preferred self-sampling to a clinician examination or had no preference[14]. A predominantly unscreened sample of women in India was invited to self-collect a HPV test either in the clinic or in their homes. Younger women (< 45 years old) and those invited for home collection were more likely to agree to participate. Among those who lived in remote areas where screening may only be possible once or twice in a lifetime, 71.5% said they would be willing to self-collect at home and 53.8% said they would be willing to go to a clinic to self-collect[15]. The response to self-collection in Uganda was very positive with 93.66% willing to self-collect a sample with no more than 5% of the sample concerned that the self-collection would be embarrassing or painful or too difficult to perform correctly. Most women were willing to either have the swab kit dropped off and picked up by a community health worker or to return the swab to the clinic themselves[16].

In a comparison of self-collection with a clinician collected Pap test, Mexican women reported the overall acceptability of the self-collection to be significantly greater than the Pap. They also reported less pain, less discomfort, less embarrassment and more privacy with self-collection than with the Pap. A majority (68%) preferred self-collection, citing greater comfort and less embarrassment as the primary reasons. Those who did prefer the Pap noted greater confidence in the results as the primary reason[17,18]. Similarly, in Puerto Rico[19] and Nicaragua[20], the overall acceptability of the self-collection was significantly higher. The individual acceptability parameters all scored higher for the self-collection with the exception of "comfort" in Nicaragua, seemingly because the women interpreted the question as comfort with the accuracy of the results rather than a measure of physical comfort. Nonetheless, in both studies more women preferred clinician-collection because they had more confidence in the accuracy of the results. The acceptability of self-collected swabs was also high in Ontario, London and in a predominantly Hispanic sample from New York City. In Ontario, two thirds of the sample found the swab easy and comfortable to self-collect and 87.7% were willing to perform self-collection again in the future[21]. In London the characteristics of the self-collected swab that appealed to most women were the lower levels of embarrassment, discomfort, anxiety and unpleasantness associated with it. Clinician-collection was preferred by some women because they had greater confidence in the results. There were some demographic differences in attitudes toward self-collection in that married women were more positive than single women and Asian women were more negative than women of other ethnicities[22]. One third of women in a New York City study preferred self-collection because they found it easy to use, less painful and more private than clinician collection. Almost two thirds could identify nothing unfavorable about self-collection. Once again, those who preferred the clinician collection did so because they had more confidence in the physician's ability to do it properly. There were statistically significant differences in preference for ethnicity and education with non-Hispanic and more educated women preferring self-collection most[23]. A Cincinnati-based study asked adolescent women about their preferences before and after they performed self-collection. Their impressions of self-collection improved after they tried it themselves but even then more women preferred clinician-collection because they thought the results were more trustworthy[24]. A comparison of a polyester swab (dry transport) to a flocked swab (transported in liquid medium) in Switzerland found no difference between the two in overall acceptability though a few more women thought the wet transport system was slightly more complex[25]. In the northeastern United States, the acceptability of a self-collected swab was compared with that of a tampon with 90% of the respondents reporting they would be willing to self-collect in the future with either device. In a series of open-ended questions, respondents reported concern that the swab may break and that they would still want to have their annual physicals with a provider even if they self-collected their cervical cancer screen. There was a potential for bias in this study in that only 67 of 103 participants completed the questionnaire[26]. A Canadian study (n = 200) compared the acceptability of screening for HPV with vulvar and vaginal swabs as well as a urine specimen. In terms of overall acceptability, 88.2% of participants found a vaginal swab acceptable compared with 79% for the physician exam. In general they ranked the acceptability in order from furthest away to closest to the cervix. Of note the rank order of the sensitivities of the tests was the inverse[27]. In the Cameroon, all subjects agreed to self collect and self-collection scored more favorably than clinician collection for all parameters (embarrassment, pain, anxiety and ease of use) except confidence in the quality of collection, which scored much higher for the clinician collection. Women with a greater understanding of HPV and those who had been screened for cervical cancer in the past were significantly more likely to prefer self-collection[28]. Finally a qualitative study of African American women living in the Mississippi delta comprised focus groups with a total of 87 women exploring their HPV and cervical cancer knowledge as well as their attitudes toward self-collection. Of the 87 participants, 9 returned for a second phase to perform self-collection. Participants were willing to self-collect but had some concerns about accuracy, cost and the possibility of the specimen getting lost in the mail. They liked the privacy associated with home collection and avoiding the wait time associated with clinic appointments. Positive feedback from the nine who self collected included having female study personnel explain the collection and getting to handle a sample device during the explanation[29].

Brushes

The overall acceptability of self-collection with a cervical sampler brush was quite high (mean score 4.33 on 5-point scale) in a study in rural China, though 74% of women preferred clinician collection to self-collection. The primary reason was because they had greater confidence in the accuracy of the results. Among those who did prefer self-collection, there was substantial variation in the primary reason for their preferences including greater convenience, less embarrassment, less cost and greater comfort. There was no association of demographics with preferences[30]. Self-collection with a cytobrush was reviewed positively by a group (n = 435) of women in Munich. Nearly all of them said they were willing to self collect at home in the future and very few of them found the collection difficult to perform. When asked about their preference of self-collection or clinician-collection, 63% preferred them equally and 23% preferred self-collection[31]. Among 134 women in the Netherlands who self-collected with the Evalyn brush, 95% reported the experience, the instructions and the convenience as good, very good or excellent. Nearly all (95%) preferred self-sampling with the primary reasons that is simpler to use and less painful than clinician collection. Reliability of the result was the main reason for 6 of the 7 who preferred

clinician collection[32]. A randomized trial in Holland demonstrated a significantly higher response rate to an invitation to self-collect with the brush kit mailed to their homes (30.8%) than to an invitation to come to the clinic for cytology (6.5%) among a group of Dutch women who had not responded to a reminder for their regular cervical cancer screen. The 29-33 years old age group had the lowest response rate in the self-sampling group[33]. Self-collection with a sampler brush was also reviewed favorably in the Netherlands with 70% of the 135 participants preferring self-collection to clinician-collection for their next exam and 91% reporting that the brush was easy to use[34].

Lavage devices

Lavage devices for self-collection have also been found to be highly acceptable to women. In Italy, 2480 women who had not previously responded to screening invitations were randomized to receive a letter of invitation for a Pap test, a letter of invitation for a clinic-based HPV test, a letter of invitation to request by phone a home HPV kit or a self-collection kit. The self-collection kit had the best response rate and the only rate that was significantly higher than the standard of care (letter of invitation for a Pap). Among the women who completed the questionnaires, 78.4% preferred the self-collection and the most commonly reported reasons were that they could do it themselves and it was more private[35]. A large Dutch study of nonresponders found that though adjusted response rate to an invitation to self collect with a lavage device was only 27.5%, it was significantly higher than the rate (16.6%) in the group receiving the standard Pap reminder letter[36]. In addition, in a pooled analysis of the Dutch brush and lavage studies, ethnicity, age and screening history predicted response rate with native Dutch, older age and previously screened women responding more often than immigrant, younger and underscreened or never-screened women[37]. In a similar study, 31.5% of Finnish nonresponders opted to participate in self-collection either by return-mailing a sample in the kit or presenting to clinic to self-collect a sample. The comparison group, sent a reminder card for clinician collection had a significantly lower response rate (25.9%)[38]. A group of 197 low-income women from New York City successfully self-lavaged a short time after their routine Pap test. A significantly higher percentage (96%) found the self-collection comfortable compared with the Pap (47%). Seventy-nine percent indicated they would prefer the self-collection with the lavage device for their next screening, largely because of the greater level of comfort and the convenience of the self-collection[39]. Among 354 Thai women who self-collected a cervicovaginal sample for cytology with the Kato device, more than 80% found it more convenient and less painful and 78.6% said they prefer it for their next cervical cancer screen. Though 94.3% of women were either satisfied or very satisfied with self-collection with this device, 57.6% thought the clinician collection was likely to produce more accurate results[40]. Though the Kato device was used to collect a cytology specimen, the process and likely the level of acceptability would be the same if the sample had been used to test for HPV. A London-based study involving focus groups (n = 28 total) explored Muslim women's attitudes toward the thought of self-collection with a swab or a lavage device. The women were somewhat reluctant to endorse self-sampling though they all preferred the swab because it was smaller and seemed less messy to use[41]. In a group of 205 Italian women, 111 self-collected with a cervical sampler kit and the others used the self-lavage device. The entire group also underwent a pelvic exam with clinician-collected sample. Both self-collection methods were well accepted in terms of increased comfort and decreased embarrassment compared with clinician collection. However, the scores for overall acceptability and embarrassment were significantly better for the lavage device than for the cervical sampler. Among those in the lavage group, 77.6% preferred self-sampling to clinician-collection and in the cervical sampler group, 60.4% preferred self-sampling[42].

Other sampling devices

The acceptability of the Fournier device was examined in home collection in the Little Haiti section of Miami, Florida. More than 90% of women found it easy to use, were comfortable using it at home and said they would recommend it to a friend. Self-collection was preferred by 86.8% of the women who also had a Pap. As is common, the women who did not prefer self-collection expressed concern about having performed the collection correctly[43].

Intent to self sample

In addition to evidence generated through randomized trials and observational studies of self-collection compared with clinician-collection, women who have been educated about cervical cancer screening and HPV, and then surveyed regarding their preference for self-sampling as an alternative to a pelvic examination have responded in favor of self-collection. A large proportion of Kenyan women have stated they would be comfortable with self-collection (82%) and would prefer to collect at home rather than going to a clinic for an examination (84%)[44]. In a similar survey of willingness to self-collect, 80% of Ugandan women responded that they would be willing. An examination of the characteristics that predict a woman's willingness to self-collect revealed that older age and a feeling of embarrassment with home-collection were negative predictors while a willingness to have a health worker deliver the swab to her home and go to a clinic for a pelvic examination if the HPV results were abnormal were positive predictors[45]. A study of personality characteristics predictive of willingness to self collect in college students found that women whose personality profiles ranked highly in extraversion, openness and conscientiousness were less likely to be deterred by the common barriers to self-collection[46].

CONCLUSION

Cervical cancer prevention is an important health priority

around the world. Historically, cytology based screening programs have been effective in reducing morbidity and mortality but there are still significant numbers of unscreened or underscreened women in more developed as well as less developed countries. Barriers to cervical cancer screening range from personal issues such as the embarrassment and discomfort associated with the speculum exam and issues with being examined by a male provider to logistical concerns such as transportation to a clinic, childcare during the visit and the extended clinic wait times keeping women away from a job or family. Human papillomavirus testing, including self-sampling for HPV has been demonstrated to be as or more sensitive than cytology in the detection of high-grade cervical neoplasia. A number of different self-collection instruments including various brushes, swabs and lavage devices have been developed and found to be highly acceptable to women. The number of acceptability studies, conducted on at least five continents, continues to grow and the preponderance of the evidence indicates that women find the various types of self-collection instruments highly acceptable. Most women have indicated a preference for self-collection and willingness to self collect in the future. The most commonly occurring limiting factor to self-collection has been the woman's confidence that she is collecting the specimen correctly. Another reason offered by women who preferred the clinician exam to self-collection despite a higher acceptability for self-collection was their concern that they would lose contact with their physicians. They preferred the clinician-collection because it provided an opportunity for somewhat regular interaction with the provider. These are important concerns that need to be considered in the development and implementation of large scale screening projects designed to draw unscreened or underscreened women by offering self-collection. Simple diagrams and written instructions for literate populations or clear oral instructions by culturally similar women who have used the device are likely to help overcome this barrier. As with any screening program, the systems-related barriers will need to be minimized for the extended reach of the screening program to have a meaningful impact on mortality and quality of life. With these caveats, self-collection of human papillomavirus specimens as a primary screen for cervical cancer seems to be highly acceptable to women and has the potential to extend the reach of screening programs, particularly in previously unscreened or underscreened women.

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REVIEW

Preeclampsia: Definitions, screening tools and diagnostic criteria in the supersonic era

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Abstract

Preeclampsia is still a major risk factor for maternal-fetal health. Therefore, early identification of pregnant women at risk for preeclampsia is a big priority in obstetrics in order to decrease the mortality and morbidity associated with this disease. On the basis of well known and new pathophysiological mechanisms of preeclampsia, different biochemical and ultrasonographic parameters have been investigated in the literature, without finding an ideal marker for early screening. In this brief review, we present the best studied ultrasonographic markers and the most recent genetic factors and promising emerging biomarkers of preeclampsia, to date. We hope that in the future the combination of these tests will allow us to predict which women are at risk of preeclampsia.

Key words: Preeclampsia; Diagnosis of preeclampsia; Screening of preeclampsia; Ultrasonographic markers of preeclampsia

Core tip: Preeclampsia is a very important disease in pregnancy but substandard care has been found in its management. The core content of this paper is the review of the literature to evaluate possible markers for early diagnosis of preeclampsia.

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INTRODUCTION

Preeclampsia is still an important cause of maternal and fetal death. The 8th report of the Confidential Enquiries into Maternal Deaths in the United Kingdom reported that in the triennium 2006-2008, 261 women died from complications directly or indirectly related to pregnancy. Among these, 22 deaths were related to preeclampsia and 20 of 22 cases demonstrated substandard care[1].

Moreover, preeclampsia is an important risk for the health of the baby. The Perinatal Mortality Report of the United Kingdom[2] reports that 5% of stillbirths without congenital abnormality occurred in women with preeclampsia and that half of the women with severe preeclampsia gave birth preterm.

Then a question arises. Is the real problem to find a univocal definition of this complex disease or to find markers for the screening of preeclampsia? Or is the problem in the inadequate treatment?

In this review, we focus our attention on the possibility of screening for preeclampsia based on the data available in the literature.

However, the present report needs to include the definition of preeclampsia.

There has been confusion about the definition of hypertensive disorders in pregnancy for a long time.

In 2001, the International Society for the Study of Hypertension in Pregnancy[3] provided a consensus on classification, adopting the statement of the Australasian

Society for the Study of Hypertension in Pregnancy (ASSHP)[4] and the report of the National High Blood Pressure Education Program (NHBEP)[5].

The definition and classification is the following: hypertension in pregnancy, systolic blood pressure (SBP) ⩾ 140 mmHg and/or diastolic blood pressure (DBP) ⩾ 90 mmHg.

Four categories are identified: (1) preeclampsia: *de novo* hypertension after 20 wk gestation associated with proteinuria. Proteinuria is defined as appearance of urinary protein greater than 300 mg/d or a spot urine protein/creatinine ratio ⩾ 30 mg/mmol; (2) gestational hypertension: de novo hypertension alone after 20 gestational weeks; (3) chronic hypertension: hypertension diagnosed before 20 wk gestation or preconception hypertension; and (4) preeclampsia superimposed on chronic hypertension: in a woman with chronic hypertension, development of proteinuria and/or symptoms associated with preeclampsia after 20 gestational weeks.

In the definition of hypertension, both ASSHP and NHBPEP consider values below 140/90 mmHg as absolute values and do not provide an increase in blood pressure of 15 mmHg and 30 mmHg, respectively, for diastolic and systolic levels.

The ASSHP and NHBPEP agree on the definition and classification of hypertensive disorders during pregnancy with an important difference: the NHBPEP considers only hypertension associated with proteinuria as diagnostic criteria, whereas the ASSHP uses a clinical classification based on the pathophysiology of the disorder[4]. In fact, the definition of preeclampsia includes renal insufficiency, liver disease, neurological problems, hematological disturbances and fetal growth restriction (FGR), along with hypertension and proteinuria.

In 2009, the American Society of Hypertension (ASH) published a position paper that summarized the definitions and clinical features regarding the different forms of hypertension during pregnancy[6] and included the guidelines of the American College of Obstetricians and Gynecologists.

Like other opinions, the ASH position paper considers hypertension as a SBP ⩾ 140 mmHg and/or DBP ⩾ 90 mmHg, avoiding the dated concept of an increase in DBP of 15 mmHg or more and an increase in SBP of 30 mmHg or more. In the definition of preeclampsia, proteinuria is defined by the appearance of urinary protein greater than 300 mg/d, a spot urine protein/creatinine ratio ⩾ 30 mg/mmol or a qualitative dipstick +1. The protein/creatinine ratio is recommended in the ASH position paper because dipsticks have many false-positives and negatives and urine collection may be difficult in pregnancy.

The terminology used is that recommended by NHBPEP: preeclampsia/eclampsia, gestational hypertension, chronic hypertension and preeclampsia superimposed on chronic hypertension.

However, the ASH position paper also introduces new entities: (1) late postpartum hypertension: usually the blood pressure returns to normal in the immediate postpartum in preeclamptic women or in women with hypertensive disorders in pregnancy. However, there is a little known entity in which the hypertension appears after delivery in women with normotensive gestation and regresses within the first post-partum year; (2) late postpartum eclampsia: the eclamptic convulsions occur from 48 h to several weeks after delivery; and (3) early gestational hypertension: a very rare entity in which patients have excessive sensitivity to progesterone due to activating mineralocorticoid reception mutations. These women develop early hypertension concomitantly with the progesterone rise in the first trimester.

Preeclampsia in the ASH position paper is usually defined by hypertension associated with proteinuria, but the American Society of Hypertension suggests the distinction between "Less Severe" and "More Severe" preeclampsia (defined by the American College of Obstetrics and Gynecology as mild and severe preeclampsia) on the basis of symptoms, hypertension level and clinical data. The "more severe preeclampsia" is defined as the presence of severe hypertension (⩾ 110 mmHg diastolic and ⩾ 160 mmHg systolic), nephrotic range proteinuria, oliguria, neurological symptoms, thrombocytopenia (< 100000/μL), hemolysis and abnormal liver function.

Despite this distinction, the American Society of Hypertension recommends that even just a suspicion of preeclampsia is a sufficient reason for hospitalization because all preeclampsia is potentially explosive.

In 2010, the National Institute for Health and Clinical Excellence (NICE)[7] published a guideline, including a classification. The definition and classifications are as follows: (1) chronic hypertension: hypertension that is present at the booking visit or before 20 wk gestation. It can be primary or secondary in etiology; (2) gestational hypertension: a new hypertension presenting after 20 wk gestation without significant proteinuria; (3) preeclampsia: a new hypertension presenting after 20 wk gestation with significant proteinuria. Significant proteinuria is defined as +1 or more in an automated reagent strip or urinary protein/creatinine ratio greater that 30 mg/mmol or greater that 300 mg protein in 24 h urine collections; (4) eclampsia: a convulsive condition associated with preeclampsia; (5) HELLP syndrome: hemolysis, elevated liver enzymes and low platelet count; (6) severe preeclampsia: preeclampsia with severe hypertension and/or with symptoms and/or biochemical and/or hematological impairment. In addition, the Guideline Development Group has defined three different levels of hypertension: mild, moderate and severe; (7) mild hypertension: diastolic BP 90-99 mmHg, systolic blood presure (BP) 140-149 mmHg; (8) moderate hypertension: diastolic BP 100-109 mmHg, systolic BP 150-159 mmHg; and (9) severe hypertension: diastolic BP 110 mmHg or greater, systolic BP 160 mmHg or greater.

In agreement with the ASH position paper, the NICE guidelines recommend hospitalization of preeclamptic women with all degrees of hypertension.

The 2010 guidelines of the Royal College of Obstetrics and Gynecologists (RCOG)[8] regarding the Manage-

Table 1 Uterine artery doppler studies for the prediction of preeclampsia

Ref.	Weeks of evaluation (wk)	Sensitivity	Specificity
Campbell *et al*[10]	16-18	68%	69%
Valensise *et al*[11]	22	74%	97.5%
Jacobson *et al*[12]	24	44%	73%
Arduini *et al*[13]	18-20	64%	94%
Ziemmermann *et al*[14]	21-24	56%	83%
Bower *et al*[15]	18-22	75%	86%
Chan *et al*[16]	20	27%	97%
North *et al*[17]	19-24	27%	90%

ment of Severe Preeclampsia substantially agree with the other definitions of preeclampsia, but there are still differences about the definition of severe preeclampsia compared to the NICE guidelines. The RCOG considers severe preeclampsia as the presence of a DBP ⩾ 110 mmHg on two occasions or a SBP ⩾ 170 mmHg on two measurements with significant proteinuria (at least 1 g/L).

In agreement with the ASH position paper, the RCOG guidelines report the evidence level I b and II b regarding the measurement of blood pressure, referred to below.

The woman should be rested and sitting at a 45 degree angle. The cuff should be an appropriate size and be placed at the level of heart. The diastolic pressure is taken at the 5th Korotkoff phase, therefore the older concept that gravid women show large differences between the 4th and the 5th Korotkoff phase has been abandoned and the 5th Korotkoff has been established as the sound of true diastolic pressure.

SCREENING FOR PREECLAMPSIA

Ultrasounds

Uterine artery Doppler: The increase of impedance to flow in the uterine artery is evidence of impaired trophoblastic invasion of the maternal spiral arteries, a well known mechanism of the pathophysiology of preeclampsia. In fact, several studies have shown a reduction in the maternal uterine resistance index with advancing gestational age in normal pregnancy[9], while the presence of an increased resistance in maternal flow or the presence of a notch as evidence of abnormal uterine flow has been associated with the development of preeclampsia. For many years, the Doppler ultrasound evaluation of uterine arteries has been used to predict an unfavorable pregnancy outcome. However, discrepant results are described among studies in the literature (Table 1) which could be due to the different gestational age at which the women were evaluated, the different populations included, the single or two steps examination, the different cut-off of abnormal resistance index and finally the differences in ultrasound (US) Doppler technique.

In an unselected population, Bower *et al*[15] reported a sensitivity of 75% and specificity of 86% for preeclampsia in women at 18-22 wk gestation with an abnormal resistance index (above the 95th percentile and/or with the presence of a notch within the uterine artery Doppler waveform), with a better prediction for severe conditions. Valensise *et al*[11] found a sensitivity of 74% and specificity of 97.5% for the development of gestational hypertension in primigravidas at 22 wk gestation with increased impedance (resistance index more than 0.58).

Other authors report less favorable results. Chan *et al*[16] found that sensitivity of the test for preeclampsia was 27% and specificity was 97% in women at 20 wk gestation. Similar results from North *et al*[17] found a sensitivity of 27% and specificity of 90% at 19-24 wk gestation.

With the aim of reducing the number of false-positives, Steel *et al*[18] proposed a two step trial for uterine Doppler US with the first evaluation at 18 wk gestation and in the presence of increased impedance (resistance index greater that 0.58), a second Doppler evaluation at 24 wk gestation. The authors reported a sensitivity for preeclampsia of 63%. Also, Bower *et al*[19] reported an increase of positive predictive value (PPV) for preeclampsia from 12% to 28%, reanalyzing women at 24 wk with abnormal Doppler US at 20 wk gestation.

Several studies regarding the application of Doppler uterine evaluation as a screening tool have been conducted in selected populations at risk for preeclampsia. Arduini *et al*[13] evaluated women with previous gestational hypertensive disorders or essential chronic hypertension at 18-20 wk and reported a sensitivity of 64% and a specificity of 94%, but the true value of those data are still questionable. In fact, several biases and criticisms have been levelled at data from this research group. Jacobson *et al*[12] found a sensitivity of 44% and specificity of 73% for preeclampsia in women with chronic hypertension or a history of preeclampsia. Caruso *et al*[20] examined women with chronic hypertension in order to assess the predictivity power of Doppler uterine US and found a sensitivity of 78% and specificity of 45%.

Valensise *et al*[11] observed that the value of Doppler uterine evaluation as a screening test strictly depends on the studied population in his Paramount study. The PPV for hypertension is acceptable for screening in the high risk population, while in low risk pregnant women the correlation seems to be weaker. More recently, Elena Parretti from Florence[21] conducted a cross-sectional (at 24 wk gestation) and a longitudinal (at 16, 20 and 24 wk gestation) study of uterine artery Doppler in normotensive women with risk factors for preeclampsia. In agreement with other investigators, the value of 0.58 as the normal resistance index and a PPV of 44% were confirmed, still inadequate for a screening test. Instead, with a longitudinal approach, the PPV seemed to improve to 72.2% by reducing a number of false-positive results.

To improve the possibility of using the Doppler velocimetry of the uterine arteries as a screening for preeclampsia, several studies have proposed other parameters likely to be integrated with the Doppler evaluation.

Valensise *et al*[22] proposed the combination of Doppler and 24 h automated maternal blood pressure evaluation. This study stated that in the presence of abnormal Doppler and asymptomatic raised blood pressure, pa-

tients had a higher incidence of pregnancy complications with a PPV of 76% for preeclampsia.

With the aim of reducing the number of false-positive patients, other authors have proposed the use of Doppler velocimetry associated with biochemical parameters.

Elevated levels of second trimester β-human chorionic gonadotropin have been found in plasma of patients at risk for hypertensive disorders in pregnancy[23]. A study by Elsandabesee *et al*[24] demonstrated that in the presence of a diastolic notch, the association of serum screening with alpha-fetoprotein and β-human chorionic gonadotropin improves sensitivity and PPV to 91% and 41% respectively.

Initial studies showed a significant decrease in placental protein-13 (PP-13) levels in preeclamptic women[25,26], while recently Stamatopoulou *et al*[27] did not show a relationship between PP-13 levels and preeclampsia. Akolekar *et al*[28] studied PP-13 associated with PAPP-A (pregnancy-associated plasma protein A) and uterine artery Doppler US in the first trimester in 208 preeclamptic patients and in 416 normal pregnancies; a significant reduction of PP-13 level was shown in early preeclampsia but not in late preeclampsia, with a PPV for early preeclampsia of 79% and 49% for late preeclampsia. Although PAPP-A was reduced and uterine velocimetry Doppler was increased in preeclampsia, the combination of these parameters with PP-13 does not appear to improve the sensitivity of PP-13[28].

A systematic review in 2010[29] studied the role of biochemical markers associated with ultrasonographic markers to improve the possibility of prediction for early preeclampsia. The authors included 37 articles within their review in which the most frequently studied biochemical markers were hCG (human chorionic gonadotropin), inhibin A, α-fetoprotein, sFlt-1 (soluble fms-like tyrosine kinase 1), PAPP-A, activin A, placental growth factor (PlGF) and PP-13. In some cases, markers were evaluated in the second trimester as well as the ultrasound velocimetry, in other cases the markers were assessed during the first trimester before ultrasonographic evaluation. The analysis of these papers elucidates that the addition of biochemical markers to uterine artery Doppler ultrasound scan in the second trimester or the combination of first trimester biochemical and second trimester uterine velocimetry improves the predictive performance of ultrasound alone and of markers alone. This review also suggests that the addition of maternal characteristics does improve their predictive power.

Despite these promising results, the heterogeneity between studies regarding gestational age at the study time or the selected populations (high *vs* low risk) led to uncertainty about the combination of ultrasonographic and biochemical markers as a screening procedure for preeclampsia.

Maternal echocardiography: It is well known that important changes occur in pregnancy in the hemodynamic and cardiovascular system, with initial vasodilatation adaptation of the maternal cardiovascular tree that begins in the first trimester as a consequence of invasion of the spiral arteries by trophoblasts. Indeed, the remodeling of the spiral arteries contributes 20% to 26% to the total reduction of systemic vascular resistance in the second trimester[30]. Another important change is the increase in blood volume. A study based on the multifrequency bioelectrical impedance documented that total body, extracellular and intracellular water increased significantly and progressively from the first to the second trimester[31].

Cardiovascular and hemodynamic modifications consist of an increased preload, a decreased afterload, an increased compliance of the vascular tree and a ventricular remodeling at the level of the heart. Therefore, there is an enlargement of the vascular bed and an increase in blood volume to fill the enlarged vascular bed. Conversely, an inadequate placentation and the failure of the hemodynamic adaptation were identified as the basis of the pathological process leading to pregnancy complications. In 1988, Nisell *et al*[32] showed that in preeclamptic women, independently of the cardiac output, a high peripheral resistance can be observed and in those with a low cardiac output generally, a low birth weight could occur. Duvekot *et al*[33] observed that patients with FGR had a smaller left atrial diameter and a failure of cardiac output in early pregnancy.

On this basis, Valensise *et al*[30] designed a different study to evaluate the predictive value of some echocardiographic parameters for maternal and fetal complications, alone or associated with uterine Doppler velocimetry[30,34].

The same author[30], in his first study on this topic, evaluated the relationship between cardiac systolic and diastolic function and uteroplacental resistance in a longitudinal observation of 248 patients with a normal pregnancy. He reported a significant reduction in resistance index between first and second trimester in the uterine Doppler velocimetry. The echocardiographic evaluation showed a significant increase in left atrial diameter, stroke volume and cardiac output in normal pregnant women throughout gestation, mainly from the first to the second trimester, according to the fall of the uterine resistance index that contributes to a decrease of the afterload.

Conversely, in a study[35] performed on 21 pregnancies complicated by gestational hypertension, the analysis of systolic and diastolic function associated with morphological left ventricular modifications showed that hypertensive women have an altered geometric pattern with concentric hypertrophy. Functionally, this finding is associated with higher blood pressure, higher total vascular resistance (TVR) and higher uterine resistance index compared to normotensive patients. Therefore, the use of maternal cardiac function evaluation in women presenting with an abnormal uterine Doppler resistance index in the second trimester is recommended to increase the prediction of hypertensive disorders of pregnancy. With the scope to increase the predictive values for gestational hypertension of ultrasound evaluation, Valensise *et al*[36] carried out echocardiography in 36 women with uterine Doppler abnormalities (bilateral notch and RI > 0.58)

at 24 wk gestation, showing a normal ventricular left isovolumic relaxation time (IVRT) in the normotensive women group, evidence of adequate diastolic function; while in patients with pathological outcomes, an elevated IVRT, meaning cardiac diastolic dysfunction and an altered ventricular geometric pattern was found, evidence of abnormal cardiac adaptation to pregnancy. Therefore, he proposed the association of data from maternal cardiovascular adaptation with uterine artery screening to reduce the number of false-positive diagnoses of pathological pregnancy.

In a subsequent study[37], the same research group evaluated the predictive value for maternal and fetal complications of TVR and left ventricular morphology in normotensive high risk primigravidas with a bilateral notch of uterine artery at 24 wk. They reported that the increase of TVR above the cut-off had a sensitivity at 89%, specificity at 94%, PPV at 77% and negative predictive value at 97%. Considering the importance of the assessment of the cardiac function in pregnancy, another study[34] was conducted to evaluate the significance of myocardial function associated with abnormal uterine Doppler velocimetry in women with hypertensive complications and in normal pregnancy. The results showed that in pregnancy with abnormal uterine artery Doppler and complicated outcomes, the myocardial function is impaired prior to the development of complications and remains depressed 6 mo postpartum; in women with normal uterine artery and normal pregnancy, the myocardial function was unchanged compared to the postpartum; in patients with bilateral notching and a normal outcome of pregnancy, an enhanced myocardial function is reported and the authors hypothesize that it is a crucial mechanism to maintain normal hemodynamic parameters.

Echocardiographic parameters of cardiac performance during pregnancy could be an important predictor of pregnancy complications and a predisposition to cardiovascular disease in normotensive women.

Genetic assessment

Preeclampsia is a complex multisystem and multifactorial disorder with an unclear genetic component. However, it can be hypothesized that well known etiological factors may have a genetic implication[38]. In the past, it has been suggested that Mendelian or mitochondrial gene transmission could be a cause of preeclampsia; however, studies conducted on monozygotic twins did not confirm this hypothesis. Fetal genotype was also investigated without demonstrating a clear role in determining an increased risk of preeclampsia[38].

Not only the genotype but also the m-RNA expression of specific genes seems to be associated with the development of preeclampsia[38]. Indeed, Rajakumar *et al*[39] identified 368 genes differentially expressed in preeclamptic women and normotensive patients in a recent study analyzing leukocyte gene expression. Particularly, he observed that this different expression concerns genes that play a central role in functions, such as cell proliferation, inflammation, apoptosis, immune function and angiogenesis that are involved in the pathogenesis of preeclampsia.

Therefore, it appears that preeclampsia is a complex multifactorial and multigenic disease.

In a systematic review, Mütze *et al*[38] reported more than 50 candidate genes as predisposing factors for preeclampsia but only a few genes account for about 70% of research.

Evaluating the current state of the literature regarding the role of gene polymorphisms in preeclampsia, we distinguish different genes on the basis of their pathophysiological role in this disease: endothelial dysfunction, oxidative stress and placental thrombosis.

Genes involved in endothelial dysfunction: Different genes were identified in endothelial remodeling and their polymorphisms have been associated with endothelial dysfunction, although with controversial results.

For example, it is well known that endothelin-1 (ET-1) is an important vasoconstrictor produced by endothelial and smooth muscle cells and that endothelial-1 converting enzyme (ECE-1) is connected with ET-1 concentration. However, one study examined the role of polymorphism Lys198As in the ET-1 in preeclamptic women but found no significant association[40]. Another recent study[41] evaluated the polymorphism Lys198Asn of ET-1 and Thr34IIe of ECE-1 and no statistically significant differences in polymorphic frequencies between hypertensive pregnant women and the control group were found. Moreover, the gene encoding for endothelin-1 receptor was investigated but the polymorphism considered (231G>A) was not found to be related to the risk of preeclampsia[42].

Genes encoding for information regarding blood pressure, hemodynamic changes and vascular remodelling as gene components of the renin-angiotensin systems have been investigated to evaluate the presence of polymorphism candidates for involvement in preeclampsia.

The polymorphism in intron 16 (insertion/deletion) of angiotensin converting-enzyme (*ACE* gene) is associated with changes in ACE activity. A large study by Serrano *et al*[43] in 665 preeclamptic women and 1046 controls did not find a significant association of a deletion form with preeclampsia. Li *et al*[44] investigated polymorphism of the *ACE* gene and the polymorphism A1166C of angiotensin Ⅱ receptor type 1 gene (*AT1R*) in a Chinese population. He found no significant differences in the frequency of genotypes of the *ACE* gene and *AT1R* gene in preeclampsia and normal pregnancy; however, preeclamptic women carrying the deletion form are more susceptible to developing renal dysfunction.

Another recent study investigated the association of both polymorphisms with the risk of preeclampsia[45] and showed that the polymorphisms of the renin angiotensin system could be associated with elevated oxidative stress involved in preeclampsia development. Although is well known that the renin angiotensin system contributes to fetoplacental blood flow regulation, there are still no conclusive studies regarding the association of genetic polymorphisms of this system and preeclampsia.

Nitric oxide is an important regulator of vasodilatation and vascular remodeling and its production by nitric oxide synthase (eNOS) is known to be decreased in preeclampsia.

Häkli *et al*[46] evaluated the polymorphism Glu298Asp of *eNOS* gene in 132 preeclamptic women and 113 controls and found a similar distribution in both populations. A systematic review[38] on genes and preeclampsia regarding the eNOS E298D polymorphism concludes that this polymorphism does not seem to be related to a significantly increased risk of preeclampsia.

The production of vasoactive substances regulating the vascular tone is mediated by estrogen receptors α and β (ER α/β). Polymorphisms for these receptors have been reported to be associated with vascular disorders and the pathogenesis of hypertension[47]. Maruyama *et al*[47] found a similar distribution of polymorphisms in preeclamptic women and the control group when considering the relationship between four SNPs (single nucleotide polymorphisms) in ER β and preeclampsia. Another study[48] investigated two polymorphisms of the *ER α* gene (c.454 -397T>C and c.454 -351A>G) in 119 women with severe preeclampsia and 103 normotensive women and found no association between severe preeclampsia and single gene polymorphism; however, the presence of both polymorphisms (TT/AA genotypes) was significantly more frequent in severe preeclamptic patients than in the normotensive population. However, Zhang[49] did not confirm these data in a study in a Chinese population conducted on 204 preeclamptic subjects and 236 normal women, reporting a similar distribution of combined polymorphisms of *ER α* gene in both groups.

In recent years, the attention has been focused on binding of vascular endothelial growth factor (VEGF) and PlGF and their receptor Fms-like tyrosine kinase-1 receptor (sFlt-1) that stimulates placental vasculogenesis and angiogenesis; this interaction leads to decreased circulating levels of PlGF and in preeclamptic women an increase in sFtl-1 and a corresponding decrease in PlGF is observed. A recent meta-analysis[50] of 11 case-control studies analyzing 1069 preeclamptic women and 1315 normal pregnancies concluded that VEGF polymorphisms +936C/T and -634G/C were associated with preeclampsia and there was no evidence of the association between them. Only one study, to the best of our knowledge, has been published regarding the polymorphisms in Flt-1 receptor, based on the observation that a misregulation of Flt-1 results in over-expression of sFlt-1, and could contribute to pathophysiology of preeclampsia. Kim *et al*[51] did not find a significant difference in frequencies of the dinucleotide repeat polymorphism in preeclamptic women and the normotensive group.

Genes implicated in oxidative stress: It has been reported that oxidative stress plays an important role in the etiology of preeclampsia. Indeed, in an imbalance between reactive oxygen species (ROS) production and antioxidant defence, placental oxidative stress may stimulate syncytiotrophoblast apoptosis resulting in impaired placental function characteristic of preeclampsia[52].

In recent years, the expression of *OLR1* gene encoding for LOX-1 receptor (low-density lipoprotein oxidized) has been investigated in preeclamptic women. Indeed, LOX-1, extensively studied for its role in myocardial ischemia, is a powerful mediator of endothelial dysfunction through generation of superoxide, induction of chemokine expression and inhibition of nitric oxide production leading to cell apoptosis[53]. An immunohistochemical study in preeclamptic placentas showed LOX-1 positive specimens in syncytiotrophoblasts significantly upregulated compared with normal placentas, confirming the elevated apoptotic activity of syncytiotrophoblasts in preeclampsia[53].

The Western blot examination of OLR-1 expression in syncytiotrophoblasts had a higher expression in cases of preeclampsia and other pregnancy diseases[54]. OLR1 is the main scavenger receptor responsible for up-take of LDL-ox within placental cells. The high level of OLR1 expression is evidence of enhanced oxidative stress in preeclamptic placentas, in agreement with previous observations of elevated levels of serum lipid peroxides in preeclampsia[55,56].

Polymorphisms in genes involved in the production of ROS or in the metabolism of these reactive species can also lead to placental dysfunction.

Among anti-oxidant systems, an important role is played by placental glutathione S-transferase (GST) which contributes to placental detoxification. Zusterzeel *et al*[57] reported that homozygous genotype GST 1b/1b was significantly more represented in preeclamptic women than in normotensive controls (OR = 3.4), which could result in a lower detoxification capacity.

Conversely, Kim *et al*[58] showed that *GST* gene polymorphisms, as well as polymorphisms in the oxidative stress related genes, do not seem to be factors of susceptibility to preeclampsia in their study of 214 normotensive pregnant women and 121 preeclamptic patients.

Cytochrome P4501A1 (CYP1A1) was also related to preeclampsia; however, no study demonstrated the association between the single CYP4501A1 and preeclampsia[58].

Although single polymorphism does not seem to increase susceptibility to gestational hypertensive disorders, Zusterzeel *et al*[59] described a significant association between higher ROS production or a lower detoxification pattern and preeclampsia development when studying the simultaneous occurrence of severe genetic polymorphisms (GST, epoxide hydrolase and CYP1A1) in women developing preeclampsia.

Polymorphisms of the gene encoding for superoxide dismutase (SOD) were also investigated, with SOD acting as a cell protector from superoxide radicals. Kim *et al*[58] reported no association between gene polymorphisms and susceptibility for preeclampsia. More recently, two missense polymorphisms of extracellular SOD (Arg-213Gly and Ala40Thr) were investigated in 114 normotensive women and 159 preeclamptic patients and no significant differences were found, but it has been demonstrated that women carrying these polymorphisms do

Table 2 Biochemical markers predicting preeclampsia

Markers	Ref.	Age of testing	Sensitivity	Specificity
hCG	Jauniaux *et al*[73]	2nd trimester	72.7%	90%
	Merviel *et al*[74]	2nd trimester	54.5%	93.5%
Inhibin A	Spencer *et al*[75]	1st or 2nd trimester	68%	95%
	Florio *et al*[76]	2nd trimester	38.9%	92.5%
PP-13	Nicholaides *et al*[77]	1st trimester	90%	90%
AFP	Jauniaux *et al*[73]	2nd trimester	72.7%	70%
	Kuo *et al*[78]	2nd trimester	61.5%	47.3%
Activin A	Florio *et al*[76]	2nd trimester	61.1%	77.5%
	Spencer *et al*[75]	2nd trimester	63%	95%
PAPP-A	Poon *et al*[79]	1st trimester	20.5%	95%
	Spencer *et al*[80]	1st trimester	62.1%	95%

hCG: Human chorionic gonadotrophin; PP-13: Placental protein-13; AFP: α-fetoprotein; PAPP-A: Pregnancy-associated plasma protein A.

present with a higher risk of severe preeclampsia complicated by FGR[60]. Another recent study[61] in Romanian women described that the genotype Val/Val was significantly associated with preeclampsia and a more clinically severe disease.

Inherited thrombophilias: The observation that women developing preeclampsia subsequently have a higher risk of thromboembolism has often suggested the existence of a correlation between inherited thrombophilias and preeclampsia[62,63]. The occurrence of villous thrombosis is also considered an important mechanism in the pathogenesis of preeclampsia. The condition of inherited thrombophilias is generated by specific polymorphisms in genes encoding for specific coagulation factors. These polymorphisms include factor V Leiden mutation (G1691G>A mutation Factor V), methylenetetrahydrofolate reductase (MTHFR) (MTHFR 677C>T), the prothrombin mutation (G20210G>A) and the plasminogen activator inhibitor-1 mutant genotype (PAI-1 4G/4G>5G/5G).

In 1995, Dekker *et al*[64] described an association between inherited thrombophilias and severe preeclampsia. Since then, many studies have followed on the role of thrombophilic mutations in gestational hypertensive disorders, with contradictory results. In a 2005 review, Calderwood *et al*[65] report inconclusive results due to the absence of large scale, randomised controlled studies. However, he did underline a feasible association between placental troubles and factor V Leiden. A large meta-analysis by Kosmas *et al*[66] with almost 3000 women focused on factor V Leiden reports an odds ratio of 2.3, showing the important role of this polymorphism as a risk factor for preeclampsia. The same author reports[67] a moderately increased risk of preeclampsia in carriers of heterozygous and homozygous mutation of MTHFR 667 (OR = 1.3). However, a subsequent review by Pabinger[68] of several interesting studies reports no association between factor V Leiden and prothrombin mutation (G20210G>A) compared to hypertensive gestational disorders.

Our study group analyzed a link between inherited thrombophilias and preeclampsia with preeclamptic and normal pregnant women and no evidence of an association between preeclampsia and factor V Leiden or prothrombin gene mutation[69] was found. Given the low PPV of a single thrombophilia in the detection of preeclamptic risk, we conducted another study considering the association of double inherited thrombophilias and risk of adverse pregnancy outcomes. We found a slight but significant association between the combination of MTHFR C677T with Factor Ⅷ and the combination of factor Ⅱ and factor V mutations and the occurrence of abruptio placentae; however, we did not find an increased incidence of adverse pregnancy outcomes in subjects with a combination of MTHFR C677T and factor V Leiden or in patients with the simultaneous presence of factor Ⅱ mutation and PAI-1 (G5/G5)[70].

A recent review[71] of preeclampsia and inherited thrombophilias reports that mild preeclampsia is unlikely to be associated with thrombophilias, but severe and early onset preeclampsia seems to be significantly related to inherited thrombophilias, and preeclamptic patients carrying gene mutations are at greater risk of developing more severe forms and sequelae.

In agreement with these findings, our study group highlighted that in preeclamptic patients with inherited thrombophilias, a more severe involvement of kidneys and a more severe damage in the course of hypertensive gestational disease might occur[72].

It is therefore clear that there are contradictory results regarding the association between thrombophilic gene mutations and preeclampsia and there are no consistent data to suggest mandatory thrombophilic screening as predictive of preeclampsia.

New biochemical markers

In obstetrical practice, a long-term objective is to identify ideal maternal biomarkers for preeclampsia but it is very difficult because the "ideal marker" requires the coexistence of different characteristics: noninvasiveness, high sensitivity and specificity and a high PPV to predict disease prognosis. We currently have a plethora of studies intended to identify an ideal biomarker; however, differences in the studied populations, the methodologies and the interpretation of results make it difficult to perform a systematic analysis of all the markers (Table 2). Therefore, in this review we only consider markers that have been proposed more recently as potential new biomarkers.

Research of these new emerging biomarkers arises from the new model of pathogenesis of preeclampsia which focuses on the angiogenesis process rather than the vasoconstrictive phenomenon[81].

VEGF and PlGF are among the proangiogenic factors, soluble endoglin (sEng) and soluble fms-like tyrosine kinase 1 receptor(sFlt-1) are among the antiangiogenic factors.

Cells expressing VEGF are located near fenestrated endothelia and the inhibition of VEGF leads to pathological conditions in many organs with fenestrated endothelia (*e.g.*, liver, kidney, choroid plexus, *etc.*), as observed in se-

vere preeclampsia. PlGF is expressed mainly by placental cells and its levels increase from the second to third trimester. Both VEGF and PlGF bind to the VEGF receptor family, named Flt-1 and kinase insert domain receptor (KDR). PlGF binds more actively to Flt-1, while VEGF binds to KDR. It has been suggested that sFlt-1 acts to modulate VEGF availability[82].

This evidence confirms the antiangiogenic role of soluble form of VEGF-PlGF receptor sFlt-1.

sFlt-1 binds these angiogenic factors and inhibits their vasodilatory effect. The other antiangiogenic factor is sEng. In animal studies, it allows the formation of the endothelial tube, increases capillary permeability and could be responsible for hypertension, nephrotic syndrome and liver dysfunction during preeclampsia[83].

A recent review reported significant changes in the levels of sFlt-1, PlGF and sEng in preeclamptic patients with a different time course, the earliest in the first trimester for PlGF and later for sFlt-1 and sEng.

Levine *et al*[84,85], in two studies from 2004 and 2006, demonstrated that levels of sFlt-1 increased 5 wk before the onset of clinical disease and parallel levels of PlGF and VEGF decreased due to the binding by sFlt-1, while the levels of sEng increased 2-3 mo before clinical disease.

More recently, the level of PIGF has been evaluated in pregnancy complicated by hypertension disease[86] and it has been found that a positive PIGF test can predict delivery before 37 wk in over 90% of pregnant women with hypertensive disease. Therefore, a low level of PIGF could be used before 35 wk in hypertensive women to evaluate the risk of pregnancy complications. sEng level also seems to be prognostic and its level appears to be correlated with severe preeclampsia or eclampsia[87]. Despite this evidence, there are no conclusive data yet on their diagnostic capability, the cut-off of normality and the time or strategy to measure these markers.

Regarding diagnostic capability, a recent extensive study conducted on 2200 patients with PlGF and sFlt-1 in the first trimester found a sensitivity of 55% and 57% respectively and a specificity of 43% and 40% respectively[88]; this result does not improve later in pregnancy. It is evident that the predictive positive value is too low to use this marker in the first trimester for screening for preeclampsia. Other strategies in measuring angiogenic factors have been proposed: a longitudinal evaluation and a ratio between two factors.

Indeed, an increase from first to second trimester of sFlt-1, sEng and PlGF[89] has been demonstrated in preeclamptic women. On the other hand, several studies have proposed a ratio between sFlt-1 and PlGF (sFlt-1: PlGF)[90] and between PlGF and sEng (PlGF:sEng)[91] based on the observation that levels of PlGF and sFlt-1 are altered together in preeclampsia, reporting an important improvement in sensitivity (88.5% and 100% respectively) and specificity (88.5% and 98% respectively). Despite these promising results, larger studies are needed to confirm these finding.

Our brief review of the possibility of early screening for preeclampsia analyzed the most recent literature and highlighted the lack of a single certified method able to predict the risk. However, despite the complexity of clinical and pathophysiological behavior of preeclampsia, it is possible that in the future the combination of several tests will allow us to predict women at risk of preeclampsia.

One point needs to be underlined: we started from ultrasonic evaluations (uterine arteries Doppler US) and in a relatively short period we arrived at a supersonic era in which more promising and accurate tests seem to come from the laboratory.

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REVIEW

Role of minimally invasive surgery in complex adnexal tumours and ovarian cancer

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Abstract

Ovarian cancer is one of the most common causes of cancer-related death in women. Adnexal masses are frequently diagnosed during reproductive age and often require surgical removal. The risk of malignancy when dealing with a complex adnexal mass should be defined prior to surgery and several scoring systems may be useful for this purpose. Laparoscopic management of ovarian tumours allows a minimally invasive approach with respect to several oncological assumptions. In the last decade concerns have been raised regarding the risk of cyst rupture and tumour spillage as a consequence of the laparoscopic technique itself both in early and advanced stages of ovarian cancer. Although limited data have been reported in the literature on the use of minimally invasive techniques in ovarian cancer, the clear benefits of this approach must be balanced with the potential hazards in different clinical situations. Laparoscopic staging in borderline tumours and presumed early-stage ovarian cancer performed by a laparoscopic oncologist seems to be safe and effective when compared to laparotomy. The precise role of laparoscopy in patients with more advanced cancer is still to be defined, and the risk of suboptimal surgery should never outweigh the potential benefits of minimally invasive surgery. Thus, a tailored prediction of optimal laparoscopic debulking is mandatory in these patients.

Key words: Ovarian cancer; Laparoscopy; Borderline tumour; Adnexal masses

Core tip: The systematization of laparoscopic techniques and the improvement in technology have provided the basis for the increased use of laparoscopy in oncology in the last decade. Preoperative evaluation of complex adnexal masses and surgical planning are key factors in defining the most appropriate tailored therapy for each patient. Herein, we address the limitations and concerns regarding the use of minimally invasive techniques in the treatment of complex adnexal masses and ovarian cancer, including the clinical scenarios of borderline tumours, and both early and more advanced stages of the disease.

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INTRODUCTION

In the last two decades there has been increasing interest in the use of minimally invasive techniques in the field of gynaecological oncology. The role of laparoscopy

has been widely used in cervical and endometrial cancer due to its known clinical benefits such as magnification of the operative field, reduced intraoperative and postoperative complications, less intraoperative blood loss, and a shorter postoperative recovery. Nevertheless, the laparoscopic approach for the staging of ovarian cancer and management of suspicious adnexal masses has raised several concerns among gynaecological oncologists such as a possible reduction in radical surgical excision, an increased risk of port-site metastases or a higher recurrence rate related to more frequent intra-operative tumour cyst rupture.

Ovarian cancer is the sixth most common cause of cancer-related death among women in Europe[1] . Women have a 1 in 70 lifetime risk of developing ovarian cancer and more than 200000 women worldwide are diagnosed each year with ovarian cancer. Unfortunately, more than 65% of cases are diagnosed at advanced stages, and the five-year overall survival rate is 46%[2]. Of note, ovarian cancer is identified incidentally in up to 13% of cases after oophorectomy for a presumed benign adnexal mass[3]. Early ovarian cancer (EOC) includes cases in which the tumour is limited to the pelvis [Federation of Obstetrics and Gynecology (FIGO) stages Ⅰ-Ⅱb], whilst the term advanced ovarian cancer (AOC) is used for cases with extrapelvic disease or metastasis (FIGO stages Ⅱc or more). The five-year survival of EOC is noted to be over 90%. This figure is in sharp contrast to that of patients affected with more advanced disease, where the 5-year survival rate is poor at approximately 25%.

The laparoscopic approach for surgical staging or restaging of ovarian cancer was first reported in the mid 1990s[4]. When considering a minimally invasive approach it is of utmost importance to perform an accurate preoperative evaluation and to define the rules for surgical management of adnexal masses. As patients with EOC confined to the ovary have a good 5-year survival rate, important considerations including quality of life and fertility preservation should also be taken into account. Finally, the specific clinical features of borderline tumours raise important considerations in the laparoscopic management of these neoplasms.

In this review, we will address the limitations and concerns of the use of minimally invasive techniques in the treatment of complex adnexal masses and ovarian cancer.

EVALUATION AND MANAGEMENT OF COMPLEX ADNEXAL MASSES

Adnexal masses are a worrisome issue for gynaecologists worldwide. They may be symptomatic or incidentally discovered and can be found in females of all ages, even in fetuses. The prevalence of adnexal masses in the premenopausal asymptomatic population is about 8%, and decreases to 2.5% in postmenopausal women. The diagnostic evaluation of the mass is guided by the anatomic location, symptoms, age and reproductive status of the patient. The expertise of the multidisciplinary team in charge of the patient is essential in women with adnexal masses at high risk of malignancy, and therefore, they should be referred to specialized centres, whereas patients at low-risk can be managed at general hospitals[5]. The American College of Obstetricians and Gynecologists has proposed guidelines for the management of adnexal masses and the detection of EOC[6].

Serum markers, such as CA125 or CA 19.9 have been widely used in the diagnostic evaluation of adnexal masses. Unfortunately, the positive predictive value (PPV) for malignancy of these glycoproteins has been shown to be lower than 20% in the best scenarios of postmenopausal asymptomatic women[7]. Another emerging tumour marker that deserves special mention is the human epididymis secretory protein 4 (HE4)[8,9], a protein overexpressed in ovarian and endometrial cancers. That was the rationale for including HE4 in addition to CA125 in the Risk of Ovarian Malignancy Algorithm (ROMA), which has been used over the last five years yielding an improved PPV for the detection of high-risk patients when compared with previous decision-making strategies[10,11]. Another model widely used over the past two decades is the Risk of Malignancy Index (RMI), which is calculated using several ultrasound variables, the menopausal status and the CA125 level. Its relative simplicity makes it easy to use[12,13]. Recently, Van Gorp *et al*[14] compared the diagnostic accuracy of ROMA with the RMI and subjective assessment by ultrasound in 432 women with a pelvic mass who were scheduled to undergo surgery in a single-centre prospective cohort study. Surprisingly, the subjective assessment proved to be more accurate than the other two methods, suggesting that the addition of plasma biomarkers did not only further improve the usefulness of ultrasonography, but in contrast, worsened the diagnostic value.

Laparotomy is still the most widely used approach, particularly in patients with complex masses at ultrasound. In order to increase the rate of the minimally invasive approach in these patients, Canis *et al*[15,16] suggested a reasonable approach for managing adnexal masses under suspicion in specialized centres. Laparoscopy should be the first indication in both premenopausal and postmenopausal patients, excluding tumours exceeding 12 cm or in the presence of obvious advanced disease. In cases in which malignancy is histologically diagnosed intraoperatively, a complete surgical staging should be performed either by laparotomy or laparoscopy, according to the extent of the disease and the surgeon's experience. Under these conditions the need for laparotomy to treat benign neoplasms could be reduced from 42% to 14%. Ghezzi *et al*[17], showed that the availability of a precise diagnosis from a frozen section might favour a laparoscopic approach independently of clinical or ultrasound characteristics or level of tumour markers. They demonstrated that frozen section analysis was 100% sensitive enabling optimal staging in 16.9% of postmenopausal women with a diagnosis of ovarian cancer.

The laparoscopic approach to complex adnexal masses must always maintain the principle that the specimen

Table 1 Operative evaluation of macroscopic characteristics predicting the potential of malignancy in adnexal masses

Multiloculation
Aberrant neovascularization at ovarian surface
Thick cystic wall
Papillary excrescences
Firm adhesions
Ascites
Bilaterallity
Infiltration of surrounding structures

could be malignant. Therefore, special care should be taken while establishing the pneumoperitoneum, in order to avoid rupture of the cystic wall. Systematic examination of the abdominal cavity should be performed and reported after surgery. Peritoneal washings and biopsies of any suspicious areas are also mandatory.

Laparoscopic examination is essential to identify adnexal masses at high-risk of malignancy. Several macroscopic findings must be borne in mind and included in the operative report (Table 1). In the presence of a high-risk suspicious mass at the preoperative evaluation the mass should be mobilized bluntly with gentle traction of the ligamentary structures that support it, therefore, avoiding the possibility that the small and sharp laparoscopic instruments could damage the mass. Laparoscopic trocars should be secured to the abdominal wall to avoid any leakage of CO_2 and gas evacuation must be carried out at the end of the procedure through the trocar sheave and never directly through the wall incision. Under these conditions, the only limitation for the laparoscopic management of adnexal masses is the size of the endoscopic bag, as the whole mass should be contained in this device to permit its safe extraction through the abdominal wall without risk of contamination (Figure 1). To facilitate the manoeuvre of exteriorization, the fascia and the skin incision may be increased to 2-3 cm. As the tumour is being removed, morcellation of large specimens is allowed always inside the bag. Once the extraction has been successfully completed, the trocar can be replaced in its orifice and easily secured using a fascial closure instrument, thus permitting continuation of the procedure if necessary.

BORDERLINE OVARIAN TUMOURS

Borderline ovarian tumours (BOTs) form a separate entity within the group of epithelial ovarian tumours recognized by the World Health Organization (WHO). Three terms are used to clasify these tumours: borderline tumour, tumour of low malignant potential, and atypical proliferative tumour. They represent about 15%-20% of all epithelial ovarian malignancies and have a worldwide incidence of 1.8-4.8 per 100000 women per year. In comparison with ovarian carcinomas, BOTs are diagnosed at a lower FIGO stage, tend to appear in younger women (average 10 years younger), have a higher infertility rate and they are not usually associated with other neoplasms. Although prognosis for patients with BOTs is, in general,

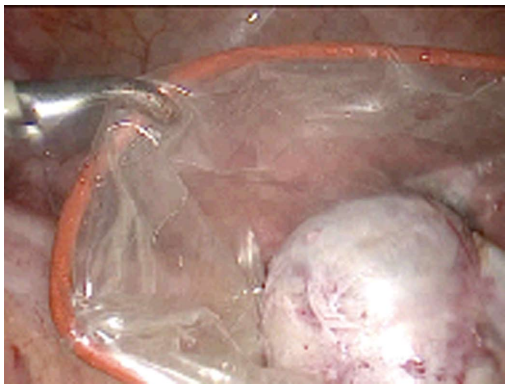

Figure 1 Specimen retrieval.

excellent, a minority will have a more aggressive form and may have long-term recurrence with a global 10-year recurrence rate of 10%-20%[18]. Therefore, the correct management and follow up is essential in these patients.

BOTs are characterized by increased epithelial proliferation accompanied by nuclear atypia (usually mild to moderate) and mildly increased mitotic activity with no stromal invasion. In typical serous BOTs, approximately 35% of patients have implants, which are either invasive (25%) or non-invasive (75%), and an invasive peritoneal implant is an adverse prognostic factor. When a BOT is identified at surgery by intraoperative histology, the recommended treatment is laparoscopic salpingo-oophorectomy (Figure 2). The correct staging surgery includes exploration of the entire abdominal cavity, peritoneal washings, omentectomy, multiple peritoneal biopsies, and complete resection of all macroscopic suspected lesions. For resection of the primary tumour, bilateral salpingo-oophorectomy in combination with hysterectomy is recommended, although some authors suggest that hysterectomy may cause more morbidity without a clear role in overall prognosis. Lymphadenectomy is not indicated. If a mucinous tumour is suspected or intraoperative histologic consultation leads to this diagnosis, appendectomy should be performed.

BOTs are usually diagnosed in women during reproductive age, which implies that therapeutic decisions regarding fertility-sparing surgery, treatment of infertility or premature hormonal deprivation, intra and postoperative morbidity, and adjuvant chemotherapeutic treatments are particularly pertinent. Nevertheless, the risk of recurrence and the risk of progression to invasive disease, which accounts for up to 2%-4% should be taken into consideration. The fertility-sparing options can range from cystectomy to adnexectomy, however, patients who undergo a conservative ovarian cystectomy should be informed that there is a substantial risk of relapse, and recurrence can even develop many years later, therefore, a long-term follow up must be agreed[19].

Laparoscopy is an attractive approach for BOTs supported by lower morbidity and fewer adhesions than laparotomy (both important for fertility). However, in many studies, laparoscopic management of BOTs was

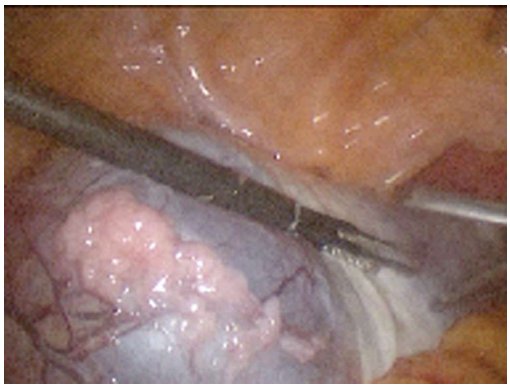

Figure 2 Macroscopic findings in borderline tumour.

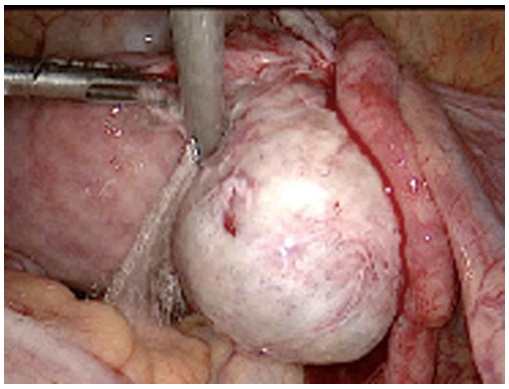

Figure 3 Laparoscopic cystectomy technique.

associated with a higher rate of cyst rupture and incomplete staging, probably due to low experienced surgeons[18,19]. Therefore, a laparoscopic approach for BOTs should always be performed by oncologic surgeons with expertise in extensive laparoscopic procedures in order to obtain both an optimal surgical staging and an optimal prognosis (Figure 3). In each patient affected by a suspicious adnexal mass it is essential to perform a careful and systematic examination of the abdominal cavity in order to detect possible peritoneal invasive implants. Ghezzi *et al*[17] reported a statistically significant difference in the rate of minor postoperative complications, with 6.7% of patients in the laparoscopy group experiencing such an event compared to 42.1% of patients in the laparotomy group. Fanfani *et al*[20] tested the accuracy of narrow band imaging in BOTs in order to increase the sensitivity of laparoscopy in the detection of peritoneal implants. This technology processes the spectral characteristics of the narrow-bind light aiming to enhance visualisation of the subperitoneal vessels. This allows significant improvements in the detection of tumoral implants in the peritoneum, as well as occult lesions, by revealing their characteristic surface staining or vascular pattern. This method has introduced the concept of "optical biopsy", and this principle of precise detection of malignancy has more recently been used in the laparoscopic management of recurrent platinum sensitive ovarian cancer[21] (Figure 4).

Intraoperative rupture is one of the main concerns

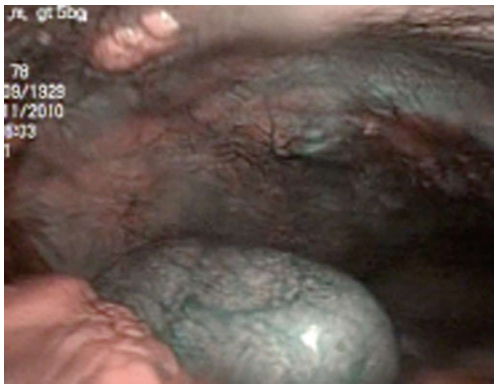

Figure 4 Narrow binding imaging in advanced ovarian cancer.

during the laparoscopic management of adnexal masses. Although the rupture rate is regarded to be higher for laparoscopy than for laparotomy in several studies, it did not affect the recurrence risk of BOTs[22-24]. Moreover, ovarian cyst rupture was not related to the surgical route, but to the implementation of cystectomy instead of adnexectomy[22]. Since the recurrence rate after cystectomy is high, it has been suggested that laparoscopic cystectomy should be considered only in women with one ovary or with bilateral tumours who wish to preserve their childbearing potential[22,23]. Nowadays, there is no evidence that adjuvant treatments improve prognosis or survival, as these tumours have poor response rates to traditional cytotoxic agents[24]. Some studies have shown that treatment with adjuvant platinum-based chemotherapy for invasive serous BOTs improves the prognosis with a relapse rate of less than 22%[25].

Fertility-preserving treatments are often desirable for women of reproductive age who are diagnosed with BOTs. When conservative surgery is indicated, the uterus and at least part of an ovary are preserved. Although data suggest that the rate of recurrence is higher after conservative surgery, this possibility could be offered to those women who wish fertility-sparing surgery due to their personal interests. It should be noted that conservative management should be limited to selected patients with complete resection in the absence of invasive peritoneal implants. Cystectomy should be considered only in bilateral tumours or in patients with one ovary, as oophorectomy has resulted in a lower recurrence rate in the contralateral ovary in comparison to cystectomy. If a relapse in the remaining ovary occurs conservative management may be offered, but this should be reserved for patients without invasive implants who are young (age < 40 years), desire fertility preservation, and engage in long-term follow-up (Figure 5). Cystectomy is not safe in patients undergoing conservative management for mucinous borderline tumours due to an increased risk of recurrence as invasive carcinoma. If the relapse occurs as invasive disease, complete debulking should be performed. If no relapse occurs after childbearing, there is no need to perform restaging surgery as long as the patient accepts a long-term follow up[26-29].

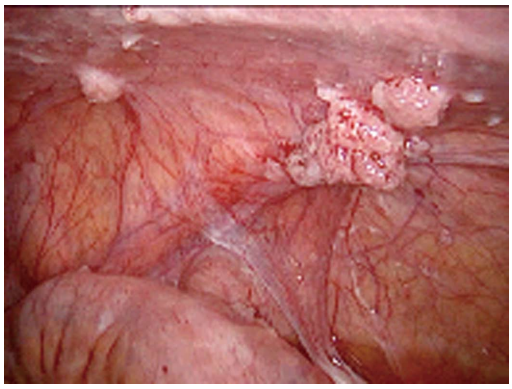

Figure 5 Peritoneal invasive implants in mucinous borderline tumours.

The impact of conservative fertility-sparing surgeries has been compared with more extensive surgical approaches. Yinon *et al*[30] studied the recurrence rate in 40 patients who underwent unilateral salpingo-oophorectomy *vs* 22 patients who were managed conservatively with ovarian cystectomy. Recurrence rates were found to be similar between the two groups (27.5% *vs* 22.7%, respectively, $P = 0.8$). Park *et al*[31] confirmed these results in a group of 360 women with BOT. A radical approach was associated with a similar recurrence rate (5.1%) to conservative management (4.2%), with no differences in disease-free survival rates. Patterns of recurrence also seem to differ between the fertility-sparing and the radical surgery group, where isolated recurrence in the remaining ovary was the most frequent form of relapse in the former and recurrence in the contralateral ovary in the latter. Therefore, a systematic follow-up should be planned in order to detect recurrences and complementary surgery after fulfilling childbearing desires can be agreed with the patient.

EARLY-STAGE OVARIAN CANCER

The extended approach for surgical staging of EOC is usually performed by exploratory laparotomy including hysterectomy and salpingo-oophorectomy, pelvic and paraaortic lymph node dissections, omentectomy, peritoneal washings, and peritoneal biopsies following the recommendations of the International FIGO[32]. Reich published the first report on laparoscopic staging in EOC in the early 1990s[33]. Two decades ago Querleu *et al*[4] published the first report on laparoscopic complete restaging of nine patients with EOC. After these initial reports there has been a progressive improvement in the instrumentation and imaging quality, which has led to more groups considering this approach in selected patients.

The Cochrane Collaboration recently performed a systematic review to evaluate the benefits and risks of laparoscopy compared with laparotomy for the surgical treatment of FIGO stage I ovarian cancer[34]. This meta-analysis did not find any publications that met the inclusion criteria to address this subject. Even with the lack of well-established evidence and the low quality of available survival data, several studies address important issues concerning the role of laparoscopy in this type of tumour. Three different studies[35-37] have analysed the differences in survival rates between patients undergoing laparoscopy *vs* laparotomy for EOC. No statistical difference was observed in survival rates or other oncological parameters. Laparoscopy showed less blood loss and better recovery with a significantly higher operative time, which could be explained by the learning curve in this type of procedure. Other authors[38] found, in short series, that the laparoscopic approach in EOC resulted in significantly worse overall survival in comparison to laparotomy. However, these results are questionable as comprehensive staging was not the purpose of laparoscopy in most of these women. A shorter interval to chemotherapy was demonstrated by Park and colleagues in patients staged by laparoscopy than in patients staged by laparotomy (12.8 ± 4.9 d *vs* 17.6 ± 8.3 d), confirming that a minimally invasive approach does not delay important adjuvant treatment, and may avoid delays due to surgical complications more frequently associated with laparotomy[39].

Laparoscopy also seems to have more advantages when fertility-sparing treatment is indicated in well-differentiated FIGO I a stages in women wishing to conceive. In these cases, laparoscopic staging should include a complete pelvic and paraaortic lymph node dissection, omentectomy, and unilateral salpingo-oophorectomy with preservation of the uterus as well as the contralateral ovary and tube after careful checking for the absence of suspicious areas, and if detected, directed biopsies should be performed. Patients should be advised that several studies have reported an increased recurrence rate with fertility-sparing techniques[40,41]. Therefore, it is advisable to proceed with a strict follow-up and complete restaging, which can be performed also by laparoscopy after delivery. Muzii *et al*[42] reported two pregnancies with term deliveries and two miscarriages out of 27 unexpected ovarian cancer patients who underwent fertility-saving laparoscopy and a follow up of 20 mo.

Port-site metastasis is one of the main concerns among gynaecological oncologists while managing ovarian cancer in either early or advanced stages. The positive CO_2 pressure with changes in peritoneal ambient pressure and the possible facilitation of tumoral cell implantation at the trocar sites due to gas leakage are considered to be the possible mechanisms of this complication. Initial reports showed a very high rate up to 20% in patients with ascites, affected by recurrent or advanced disease or undergoing multiple laparoscopic procedures. More recent series have shown a prevalence of port-site metastasis lower than 2%, which is similar to traditional laparotomy[43,44]. There are several manoeuvres that can be adopted in order to prevent this complication, although none have been clearly demonstrated to be effective in well-designed trials[45,46] (Table 2). The laparoscopic surgeon has to take into account this possible complication in cancer managed by laparoscopy irrespective of the dis-

Table 2 Surgical manoeuvres in order to decrease port-site metastasis in the laparoscopic management of complex adnexal masses

Using wound protectors
Minimizing tumour manipulation
Anchoring ports to prevent dislodgment
Avoiding carbon dioxide leakage and sudden desufflations
Using gasless laparoscopy
Irrigating and suctioning the abdomen, instruments and ports before removal
Using heparin or 0.25%-1% povidone-iodine solution to irrigate wounds and the abdomen
Excising trocar sites and deliberate closure of all abdominal layers including the peritoneum after laparoscopy; or postoperative port-site radiation
Resuming definitive surgery or chemotherapy early
Using 5-fluorouracil, topical taurolidine or intraperitoneal endotoxin

ease stage.

Another concern with the laparoscopic approach is the feared possibility of an increase in the risk of rupture of malignant masses in comparison to laparotomy. However, various studies have shown that this risk is similar to that observed following laparotomy, which ranges from 11.4%-30.3%[47-51]. Vergote *et al*[48] performed a review of a large series of 1545 patients with different stages of ovarian cancer in which reduced progression-free survival was associated with increased cystic rupture. In contrast, Sjövall and colleagues[52] showed that tumour rupture during surgery did not have an impact on survival in 394 patients.

Finally, a recent systematic review of 11 observational studies[53] showed that the laparoscopic approach for EOC had less blood loss with an overall conversion to laparotomy of 3.7%. The overall rate of recurrence in studies with a median follow-up period of 19 mo was 9.9% concluding that the operative outcomes of the laparoscopic approach in patients with EOC was comparable with those of laparotomy.

Taking into consideration the lack of high-grade evidence, the laparoscopic approach in the early stages of ovarian cancer seems safe and effective in terms of oncologic outcomes. In addition, early recovery and initiation of adjuvant therapy may be beneficial for patient outcome, however, oncological manoeuvres adopted during surgery should be similar to those performed during laparotomy.

ADVANCED-STAGE OVARIAN CANCER

The standard treatment of AOC includes upfront surgery with intent to accurately diagnose and stage the disease and to perform maximal cytoreduction, followed by chemotherapy in most cases. Rosenoff *et al*[54] reported the use peritoneoscopy for pretreatment evaluation in ovarian cancer four decades ago. In the early 1990s, pioneers in laparoscopic surgery used minimally invasive techniques to treat gynaecologic cancers, including laparoscopic staging of EOC and primary and secondary cytoreduction in advanced and recurrent disease in selected cases[55,56]. The potential role of minimally invasive surgery in the treatment of AOC is warranted for the following: (1) laparoscopic assessment of the feasibility of upfront surgical cytoreduction by laparotomy in patients with advanced ovarian cancer; (2) laparoscopic debulking of advanced disease; (3) laparoscopic reassessment in patients with complete remission after primary treatment; and (4) laparoscopic assessment and cytoreduction of recurrent disease[55].

Different indications for the laparoscopic approach in advanced ovarian cancer have been described including triage for resectability, second-look assessment, and in select cases, primary or secondary cytoreduction (Figures 6 and 7). Laparoscopy offers multiple advantages over traditional laparotomy including smaller incisions, improved visualization, less blood loss, reduction in the need for analgesics, decreased morbidity and a more rapid recovery. An additional advantage for patients with ovarian cancer requiring adjuvant therapy includes a shorter interval before initiation of adjuvant therapy[56].

Gallotta *et al*[57] reported the outcome of laparoscopic secondary cytoreduction in patients with localized recurrence of ovarian cancer. Twenty-nine patients with localized recurrent ovarian cancer were selected for laparoscopic cytoreduction. A complete debulking was achieved in 96.2% of cases with a median disease-free survival time of 14 mo. The median operating time was 188 min with a median estimated blood loss of 150 mL and a median hospital stay of 4 d. No intraoperative complications occurred and two conversions to laparotomy occurred due to technical difficulties.

Fagotti *et al*[58] retrospectively evaluated ovarian cancer patients with isolated platinum sensitive relapse, defined as the presence of a single nodule in a single anatomic site. In every case the presence of isolated relapse was assessed at preoperative positron emission tomography-computed tomography (PET/CT) scan and confirmed by cytoreductive laparoscopy followed by Hyperthermic Intraperitoneal Chemotherapy (HIPEC). Out of 84 women with platinum sensitive relapse, 10 cases showed isolated relapse and were treated with laparoscopic/robotic cytoreduction and HIPEC. In all cases, a complete debulking was achieved. The median operative time was 122 min (95-140 min), with an estimated blood loss of 50 cm^3 (50-100 cm^3) and a median length of hospital stay of 4 d (3-7 d). The interval from surgery to adjuvant chemotherapy was 21 d (19-32 d). No grade 3/4 surgical, metabolic, or haematologic complications occurred. In all cases, postoperative PET/CT scan was negative and no recurrence was observed after a median time of 10 mo.

More recently, another report[59] evaluated the prognostic impact of routine use of staging laparoscopy (S-LPS) in patients with AOC. All women were submitted to S-LPS before primary debulking surgery (PDS) or neoadjuvant treatment (NACT) and interval debulking surgery (IDS). The surgical and survival outcomes were evaluated in 300 consecutive patients submitted to S-LPS. One hundred forty-eight (49.3%) women were considered suitable for PDS and the remaining 152 (50.7%)

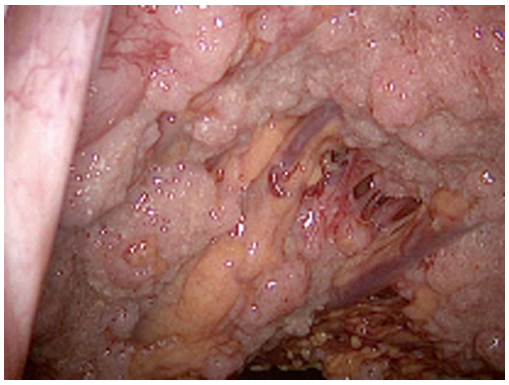

Figure 6 Extensive bowel infiltration in advanced-stage ovarian cancer.

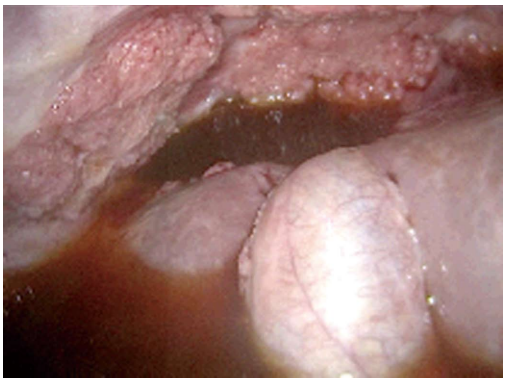

Figure 7 Liver and diaphragmatic infiltration in stage III ovarian cancer.

received NACT. The percentages of complete (residual tumour, RT = 0) and optimal (RT < 1 cm) cytoreduction following PDS and IDS were 62.1% and 57.5%, 22.5% and 27.7%, respectively. The number of post-operative complications in the NACT/IDS group were lower than that in the PDS group with a median disease-free survival interval in women with RT = 0 at PDS of 25 mo (95%CI: 15.1-34.8), which was longer than that in all other patients, irrespective of the type of treatment they received. At multivariate analysis, residual disease and performance status maintained an independent association with PFS (60).

Nezhat *et al*[60] described their preliminary experience with laparoscopic total primary or interval cytoreduction in 32 women with presumed advanced (FIGO stage ⅡC or greater) ovarian, fallopian tube, or primary peritoneal cancers. Seventeen patients underwent total laparoscopic primary or interval cytoreduction, and 88.2% had optimal cytoreduction. Eleven underwent diagnostic laparoscopy and conversion to laparotomy for cytoreduction, and 72.7% had optimal cytoreduction. Four patients had biopsies, limited cytoreduction or both. In the laparoscopy group, 9 patients have no evidence of disease (NED), 6 are alive with disease (AWD), and 2 have died of disease (DOD), with a mean follow-up time of 19.7 mo. In the laparotomy group, 3 patients have NED, 5 are AWD, and 3 have DOD, with a mean follow-up of 25.8 mo. Estimated blood loss and length of hospital stay were less for the laparoscopy group, while operating time and complication rates were not different. Median time to recurrence was 31.7 mo in the laparoscopy group and 21.5 mo in the laparotomy group. The authors concluded that laparoscopy is an effective tool in advanced ovarian cancer in order to predict optimal debulking.

Interestingly, a prospective study[61] reported the accuracy of laparoscopy performed to describe intraabdominal extent of the disease in AOC. One hundred sixty-eight cases were considered eligible for the study. A per-protocol analysis was performed on 120 cases. The worst laparoscopic assessable feature was mesenteric retraction, whereas the remaining variables ranged from 99.2% (peritoneal carcinomatosis) to 90% (bowel infiltration). The accuracy rate was over 80% for both single parameters and overall score. The parameters used to predict the resectability of the tumour by laparoscopy should be chosen according to the experience of the surgical team in order to minimize the rate of suboptimal surgery (Table 2).

There is still controversy in defining the exact role of laparoscopy in advanced disease. Prediction of resectability is one of the most valuable tools in patient management and might facilitate a better selection of patient candidates for neoadjuvant chemotherapy.

CONCLUSION

In conclusion, although limited data has been reported on the use of minimally invasive techniques in ovarian cancer, the clear benefits of this approach must be balanced with the potential hazards in different situations. Laparoscopic staging in borderline tumours and presumed early-stage ovarian cancer should be performed by a trained laparoscopic oncologist and seems to be safe and effective in comparison to laparotomy. Early recovery and reduced intraoperative complications and blood loss leads to a short period before initiation of adjuvant therapy. In addition, fertility-sparing management in well selected patients managed by laparoscopy could have additional benefits in terms of pregnancy rates. There is still insufficient data supporting the role of laparoscopy for advanced ovarian cancer, but the minimally invasive approach permits selection of candidates for primary optimal cytoreduction resulting in a lower rate of suboptimal surgeries.

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REVIEW

Unwanted pregnancies, unwanted births, consequences and unmet needs

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Abstract

Worldwide women have to cope up with heavy burden of unwanted pregnancies, mistimed, unplanned, with risk to their health. Their children and families also suffer. Such pregnancies are root cause of induced abortions (safe/unsafe) and grave consequences. Women, their partners can, for most part, prevent unwanted pregnancies by using contraceptives. However many women either do not use any contraceptive or use methods, with high failure rates. These women account for 82% of pregnancies that are not desired. Remaining unintended pregnancies occur among women who use modern contraceptive, either because they had difficulty using method consistently or because of failure. Helping women, their partner use modern contraceptives effectively is essential in achieving Millennium Development Goals for improving women's health, reducing poverty. If all women in developing countries use modern contraceptives, there would be 22 million less unplanned births, 25 million fewer induced, 15 million fewer unsafe abortions, 90000 less maternal deaths and 390000 less children losing their mothers. Also making abortion services broadly legal, by understanding size, type of unmet needs, most important by creating awareness in communities can surely help tackle this problem to a large extent.

Key words: Contraception; Induced abortion; Pregnancy; Unmet need; Unsafe abortion

Core tip: Unintended pregnancies are the root cause of induced abortions, both safe and unsafe, and their grave consequences all over the world. The high rates of unintended pregnancies all over the world are due to many reasons, including unmet needs of modern contraceptives. This article throws light on issues of unmet needs of contraception, unintended births their consequences and rates of unsafe abortions and their reasons all over the world.

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INTRODUCTION

In 2008, two hundred and eight million pregnancies occurred worldwide, out of which 102 million resulted in intended births (49%), 42 in induced abortions (20%) (22 legal and 20 unsafe)[1], 33 (16%) in unintended births and 31 (15%) in miscarriages[2]. Singh[3] reports, around 86 million unintended pregnancies occurring each year with grave consequences, unsafe abortions which lead to disabilities and deaths, stillbirths, neonatal deaths[4,5] affecting families, nations, particularly in low/middle income countries[1,6]. Such pregnancies slow the progress towards socioeconomic development, lead to population growth, difficulties in providing education for all and eradication

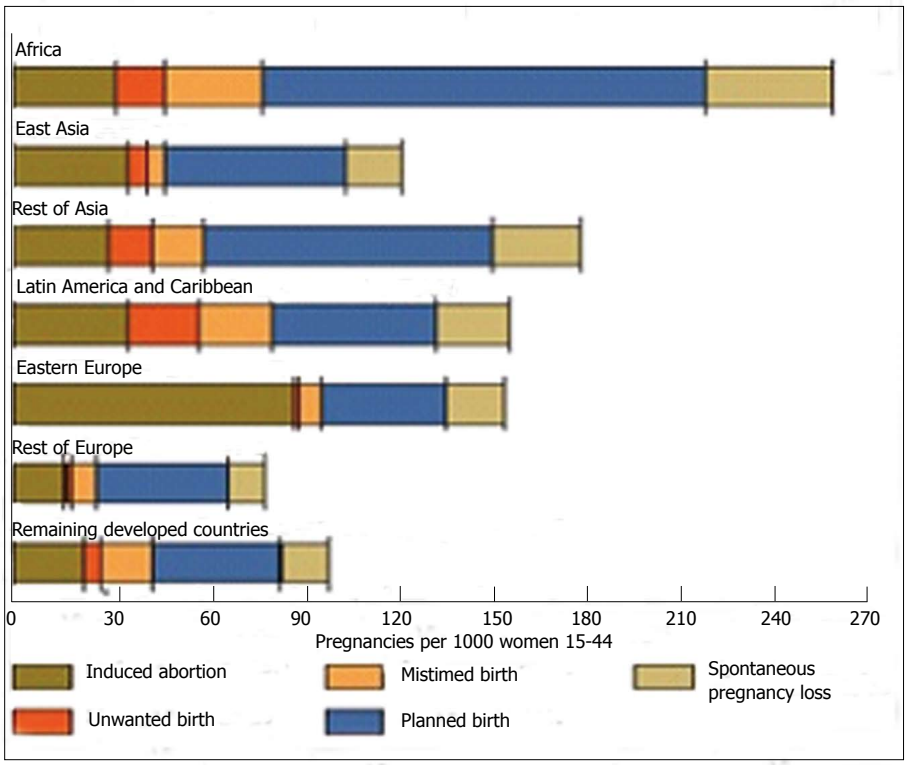

Figure 1 The regional pregnancy levels worldwide.

of extreme poverty and hunger.

GLOBAL STATUS

Of developed countries, the United States has the highest unintended pregnancy rates, including in teens[7]. Worldwide 40% of pregnancies among white women, 67% blacks, 53% Hispanics[8] and 48% among Southeast Asian are unintended[9]. Each year, 2.7 million unintended pregnancies occur in young women in Southeast Asia[9]. Worldwide between 1995-2003, the overall abortion rate dropped from 35 to 29, but remained virtually unchanged at 28, in 2008[1]. Overall, pregnancy rates are higher in developing world than in developed countries[3,10] (Figure 1). In India annually 78% conceptions are unplanned and 25 % unwanted. The abortion rates are strikingly similar for developed and developing countries, however close to half of abortions are unsafe, (98% from developing countries)[11]. Indian Council of Medical Research, reported 13.5 illegal abortions per 1000 pregnancies[12]. Given that abortions taking place at registered facilities are grossly under-reported in India[13-17], figures represent only tip of the iceberg. Many studies reveal 3.4-14.0 induced abortions per 100 live births[14,18]. According to NFHS-3, India has 13.2% unmet need for contraception, 50 % for spacing methods[19].

Worldwide, 60% of women of reproductive age (15-44) live in countries where abortion is broadly legal[20] and remaining 40%, almost entirely in the developing world where abortion is highly restricted[21]. Globally, laws are varied based on grounds for which abortion is permitted, range from no grounds or to save a woman's life, to preserve physical health or mental health or rape or incest, in cases with fetal impairment or even for economic or social reasons, and without restriction. In 32 countries, abortion is not legally permitted on any grounds and in 36 countries, it is permitted when a woman's life is threatened. A further 59 countries allow abortion to save a woman's life, to preserve her physical health, and to protect her mental health. Fourteen countries, including India, permit on all the above and also socioeconomic grounds. A total of 56 countries and territories allow it without restriction[22] (Figure 2). There has been effect of issues like Global Gag, under which agencies receiving USAID funds are prohibited from performing or campaigning for abortion. Contrary to its stated intentions, the global gag rule resulted in more unwanted pregnancies, unsafe abortions, and female deaths[23]. Moreover, some laws seek to protect or otherwise recognize the fetus as human. The American Convention on Human Rights, a treaty signed by 24 Latin American countries states that from the moment of conception, human beings have rights[24].

REASONS FOR SEEKING ABORTION

The reasons cited for choosing abortion are broadly similar globally. Although official records in India show

Figure 2 World abortion map, 2013. Source: www.eorldabortion.com.

Table 1 Contraceptive failure rates and unintended pregnancies, 2007

Contraceptive method	Number of contraceptive users 000 s	Estimated failure rate (typical use) %	Number of women with accidental pregnancies (typical use) 000 s
Female sterilization	232564	0.50	1163
Male sterilization	32078	0.15	48
Injectables	42389	0.30	127
IUD	162680	0.80	1301
Pill	100816	5.00	5041
Male condom	69884	14.00	9784
Vaginal barrier	2291	20.00	458
Periodic abstinence	37806	25.00	9452
Withdrawal	32078	19.00	6095
Total	712586	4.70	3369

Available from[31]. IUD: Intra-uterine device.

contraceptive failure and risk to mother's health as leading reasons[25], reliability of these records, for obvious reasons can be questioned. Where effective contraceptive methods are available and widely used, the rates decline sharply, but nowhere to zero[26].

CONTRACEPTION AND ABORTION

Many women and men either do not have access to appropriate contraceptive methods, or lack adequate information and support to use them effectively. Studies have examined the reasons why some women do not use contraception, though they do not want to become pregnant, referred to as unmet need for family planning[27-29]. Study by Alan Guttmacher Institute[30] reveals that 54% women who had abortion had used contraception during the month they became pregnant, however 76% pill users, 49% condom users reported having used methods improperly, 13% pill users, 14% condom users reported correct use, 46% of women had not used any contraceptive during the months they became pregnant. Of these, 33% had perceived themselves to be at low risk for pregnancy, 32% had concerns about methods, 26% had unexpected sex and 1% had been forced to have sex. Trussell and United Nations Population Division have also reported contraceptive failure rates with estimated unintended pregnancies (Table 1)[31].

Studies reveal that unwanted pregnancies and induced abortions due to contraceptive failure were 48% and 54% in United States[32] and 65% unwanted pregnancies in France respectively[33]. Proportions are more in countries with higher levels of contraceptive use.

COMPLICATIONS OF UNSAFE ABORTIONS AND CARE

About one third of women who undergo abortion, experience serious complications, but less than half receive appropriate medical care. Currently, about 8.5 million women globally suffer from complications of unsafe abortions annually and 3 million remain without treatment[3]. World Health Organization[21] reports that 47000 women died worldwide in 2008 and around 13% pregnancy related deaths were due to unsafe abortions[34]. Annually in Asia, 12% maternal deaths are due to unsafe abortions[21]. Mortality represents only a fraction of abortion related complications, as many more experience life threatening and other morbidities[35,36]. An estimated 7.4 million disability-adjusted life years are lost annually as a result of unsafe abortion[6]. Each year 1.6 million women have secondary infertility and 3-5 million suffer from chron-

Table 2 Demographic and health survey 2000-2009 for unmet need and demand for family planning

Region/Country	Unmet need for spacing A	Unmet need for limiting B	Unmet need Total C = (A + B)	Met need (CPR) D	Total demand for family planning E = (C + D)	Percentage of demand satisfied F = (D/E)
East Asia and Pacific	6	8	14	57	71	79
Europe and Central Asia	4	9	13	60	73	83
Latin America and Caribbean	7	10	17	63	80	77
Middle East and North Africa	4	7	11	57	68	84
South Asia	8	12	20	47	67	70
Sub-Saharan Africa	17	9	26	25	51	45

Available from[28]. CRP: Contraceptive prevalence rate.

ic reproductive tract infections. Rarely bowel injuries can also occur. Agarwal *et al*[37] has reported an unusual case of bowel injury 52 d after induced abortion.

Though most of morbidity and mortality are preventable, yet millions of women suffer due to unavailability of treatment in health care system. So the concept of Post Abortion Care has become visible, a global approach for prevention. The essential elements include: emergency treatment of potentially life-threatening complications, contraceptive counseling services and linkage to other emergency services[38].

UNMET NEEDS

Unmet needs are global, which look at issues related to the family planning needs of reproductive population in a quantifiable mode for prevention of pregnancy or birth or consequences, in currently married women who do not want any more children or who want to postpone their next birth, but are not using any form of family planning[28]. Conventional estimates of unmet need include only married women, but sexually active unmarried, especially teenagers, those with postpartum amenorrhea, using a less effective contraceptive method or using an effective method incorrectly, or dissatisfied, or with contraindications to its use, with unwanted births without access to safe and affordable abortion services; and those with related reproductive health problems, also need to be included.

A recent study revealed that in 2010 worldwide, 146 million (130-166 million) women aged 15-49 years who were married or in a union had an unmet need for family planning. The absolute number is projected to grow from 900 million (876-922 million) in 2010 to 962 million (927-992 million) in 2015, and will increase in most developing countries[39]. The uptake of modern contraceptive methods worldwide has slowed in recent years, from an increase of 0.6% points per year in 1990-1999 to an increase of only 0.1% points per year in 2000-2009. In Africa, the annual increase in modern contraceptive use fell from 0.8% points in 1990-1999 to 0.2% points in 2000-2009[40]. Demographic Health survey (2000-2009) has revealed unmet need, met need and total demand for family planning (Table 2).

CAUSES

The causes of unmet needs are complex. Surveys and other indepth research from 1990s[41,42] reveal a range of obstacles and constraints that can undermine a woman's ability to act on her childbearing preferences. In the developing world, her reasons for not using contraceptives most commonly include concerns about possible side-effects, the belief that they are not at risk of getting pregnant, poor access to family planning, their partner's opposition to contraception or their own opposition because of religious or personal reasons. Other less common reasons are lack of knowledge about contraceptive methods or health concerns. Thirteen surveys completed in 1999 and 2000 by DHS revealed similar findings[43].

WOMEN'S EDUCATION

Education is an important determinant of unmet need for contraception. Both husband's and wife's education affect unmet need for spacing. As per a study in Ethopia[44] about one in five women (18.9% in 2000 and, 20.5% in 2005) with no education had unmet need for spacing, while 11.6% in 2000 and 14.8% in 2005 had unmet need for limiting. Unmet need progressively declined with higher levels of women's education.

RELIGION, CONTRACEPTION AND ABORTION

Religion has a strong influence on sexuality and abortion practices. A study revealed that most Buddists believe that conception occurs when the egg is fertilized, emergency contraception could prevent a fertilized egg from implantation. It therefore is against religion as they see abortion as an act of killing[45]. Catholics believe in using natural methods of contraception rather than modern and are strictly against abortion. According to them "Human life must be respected and protected absolutely from the moment of conception….. Abortion is gravely contrary to the moral law…."[46]. In Hinduism contraception and abortion are not strictly prohibited, there are varying views. In Islam all forms of contraception are acceptable in special circumstances and abortion is permitted if mother's life is at risk. Jewish law prohibits use of contraceptives in males, but there is no mention of females. In Sikhism there are no hard and fast rules for use of contraceptives and abortion. They can have it as and when required.

THE WAY FORWARD

In each country, broader education and communication programs can help address social, cultural barriers and misconceptions. From a policy perspective, reducing unmet need is important for achieving both demographic goals and enhancing individual rights.

It is essential for nations to adopt a continuum of care, access to family planning, emergency contraception, and other reproductive-health services. It is essential to know why women choose abortion and how to reduce morbidity and mortality. Making abortion legal is an essential prerequisite in making it safe. Under the current scenario of high mortality and morbidity, medical means offer great potential for improving access and safety as it does not require extensive infrastructure and is non-invasive.

Not only treatment of complications of unsafe abortion should be extended throughout the health care system, family planning advice and assistance should be offered after treatment of complications; designed with women's preferences in mind. Those wanting to prevent or postpone conception, using an ineffective method, those using an effective method incorrectly and those using an unsafe or unsuitable method[13,47]. Reducing unmet need is an effective way to prevent unintended pregnancies, abortions and births.

A key argument is that meeting unmet needs, saves lives, but to what extent does society value women's lives?

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MINIREVIEWS

Retained placenta: Do we have any option?

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Abstract

Retained placenta is a known cause of post-partum haemorrhage and maternal mortality. A recent systemic review has confirmed that the incidence of retained placenta had increased all over the world, which is more common in developed countries. Failure of retroplacental myometrium contraction is the main cause of retained placenta. Maternal age greater than 35 years, grandmultipara, preterm labor, history of previous retained placenta, and caesarean section were the risk factors for retained placenta. Manual removal of the placenta has been the treatment of choice. Attempts had been made by clinician and researchers to find a safe, effective and reliable method to avoid the need for surgical intervention. The efficacy and safety of prostaglandin, nitroglycerin or acupuncture in the management of retained placenta are yet to be further evaluated. Nonetheless, till date only intra-umbilical vein oxytocin has been studied extensively but with varied success. More randomized clinical trials are needed to address this issue. However, if immediate manual placenta removal service is unavailable, a trial of intra-umbilical vein oxytocin 100 IU at a total volume of at least 40 mL while preparing for transfer to a tertiary center or theatre may result in spontaneous expulsion of the placenta.

Key words: Retained placenta; Manual removal of the placenta; Intra-umbilical vein; Oxytocin; Prostaglandin; Misoprostol; Carboprost; Acupuncture

Core tip: Retained placenta is a known cause of post-partum haemorrhage and maternal mortality. The incidence of retained placenta had increased all over the world, which is more common in developed countries. Manual removal of the placenta has been the treatment of choice. However, it is a surgical intervention requiring anaesthesia with potential risk and complication. This manuscript reviews various methods that had been reported in the management of retained placenta.

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INCIDENCE OF RETAINED PLACENTA

Retained placenta (RP) is a known cause of post-partum haemorrhage (PPH) and maternal mortality. Although this is such an important event, it is often under-reported as the after-event consequences are much more focused and attract a more appealing report. In veterinary reports RP appears more in the dairy farms where cows are reported with this problem[1]. However, RP in women varies between regions of the world and also according to

how it is defined. The reported data may not truly give the exact number of events especially from those countries with lower resources and also as a result of its retrospective reporting. All types of previous uterine surgeries had been shown in early days to increase the incidence rate of RP. In fact it was three times higher with induced labour[2]. Although it was reported that RP was significantly higher in United Kingdom compared to Uganda[3], it is unclear whether or not this is a result of under-reporting. A recent systemic review[4] has confirmed that the incidence of RP had increased all over the world, which is more common in developed countries. In India, Chhabra[5] reported that RP occurred in 0.008% of childbearing women. Titiz *et al*[6] reported an incidence of 3.0% in Australia while Belachew *et al*[7] reported an incidence of 2.1% in Sweden. The median rate of RP at 30 min (2.67% *vs* 1.46%, $P < 0.02$) and median manual removal rate (2.24% *vs* 0.45%, $P < 0.001$) were found to be higher in developed countries. It was also found that the overall rate of manual removal in the United Kingdom has risen (mean of 0.66% in 1920s *vs* 2.34% in 1980s, $P < 0.0001$).

DEFINITION

To date, there is no consensus as to the duration of the third stage of labour, *i.e.*, when placenta should be delivered. Traditionally, interventions are advised if the placenta remains undelivered between 20 to 60 min at the third stage[8]. Studies[9,10] showed that the risk of PPH increased after 30 min elapsed of the third stage of labour, although any delay in active intervention would increase the chance of spontaneous placenta delivery. Hence, the placenta being labeled as "retained" largely depends on balance between the risk of PPH and likelihood of spontaneous placenta delivery. Availability of local facilities such as operating theater, blood bank, and trained medical personnel should be taken into consideration. Hence, National Institue for Health and Clinical Excellence guidelines suggested 30 min, while WHO recommended 60 min elapsed of the third stage to be defined as RP[11].

PATHOPHYSIOLOGY

Back in 1933, Brandt[12] had described the physiology of uterine contraction for placenta detachment from decidual bed in the third stage of labour. He divided the third stage into four phases: latent, contraction, detachment and expulsion phase. The latent phase is immediately after delivery of fetus, where all parts of the myometrium contract except the myometrium behind the placenta that remains relaxed. The retro-placental myometrium contracts during contraction phase, leading to placental detachment. Further contractions of the myometrium expel the placenta from the uterus.

Failure of retro-placental myometrium contraction is the main cause of RP. An observational study also revealed that retro-placental myometrium contraction in dysfunctional labour was lesser than in normal labour[13]. Hence, it is likely that retro-placental contractility fails to occur throughout the process of labour as RP and dysfunctional labour were found to be closely related[9]. A recent study using ultrasonography had confirmed this theory and further improved the understanding of normal and abnormal third stage of labour[14].

RISK FACTORS

Maternal age greater than 35 years and grandmultipara are associated with a seven-fold increase in risk of RP[15]. Fibrous tissue in the uterus of grandmultipara women results in a reduction of contractility power, which is more pronounced in women at an advanced maternal age. Increased abnormality of placenta implantation in grandmultipara also plays a major factor in the pathogenesis of RP.

A history of previous RP increases 2.4-fold the risk of recurrence in subsequent pregnancy[16]. This risk can be as high as 29-fold as demonstrated by another study conducted in Saudi Arabia[2], while a recent study also showed an OR of 12.6 to have recurrent RP[17]. Uterine surgeries such as Caesarean section (OR = 12) and dilatation curettage (OR = 4.4) are significantly associated with RP[18]. These procedures inadvertently cause injury to the endometrium, thus facilitating abnormal placenta implantation and further leading to morbidly adherent placenta.

RP is found strongly in association with preterm labour, particularly less than 27 wk of gestational age with a relative risk of 6 to 13[9,19]. It is believed that risk factors such as infarction or fibrinoid degeneration of decidual arterioles that frequently cause preterm labour lead to abnormal adherence of the placenta[20].

Uterine abnormalities are also associated with a certain degree of RP. Golan *et al*[21] found incomplete uterine septum at hysteroscopic examination in 15% of women who underwent manual removal of the placenta (MRP). Other documented risk factors include induction of labour (3-fold rise) and analgesia such as pethidine (3.5-fold rise)[2].

VARIOUS TREATMENT MODALITIES

Surgical intervention

Traditionally MRP is the treatment of choice for RP. MRP requires insertion of the operator's hand into the uterus through the vagina[22]. The operator's hand follows the umbilical cord to identify the interface between the uterus and maternal surface of the placenta. Dissection of the uterine-myometrium plane is achieved by using fingers in a side-to-side motion. The other hand should be placed at the uterine fundus over the abdomen to minimise risk of uterine perforation[23].

Regional anaesthesia such as spinal anaesthesia is recommended for MRP if epidural anaesthesia is not in place earlier during labour. Use of regional anaesthesia is preferred in obstetric cases to avoid the risk of general anaesthesia such as failed intubation and Mendelsons Syndrome from gastric content aspiration[24]. In the presence of rapid blood loss or haemodynamic instability, general

Table 1 Comparison of various trials[33].

Study	Number of patients	Oxytocin dose (IU)	Total volume infused (mL)	Manual removal of placenta rate (%)
Makkonen *et al*[31]	109	50	20	72.1
Frappell *et al*[40]	41	10	20	63.0
Weeks *et al*[23]	577	50	30	61.3
Selinger *et al*[36]	30	10	20	60.0
Caroli *et al*[37]	286	20	40	58.2
Gazvani *et al*[38]	81	20	20	53.8
Kristiansen *et al*[34]	51	10	10	52.6
Sivalingam *et al*[35]	35	30	30	47.0
Huber *et al*[39]	200	10	20	38.0
Wilken-Jensen *et al*[32]	37	100	30	27.8
Lim *et al*[33]	61	100	40	30.0

anaesthesia is required[25]. The availability of anaesthetist during the procedure would facilitate the performance of further interventions in the occurrence of complications associated with MRP such as haemorrhage, uterine perforation and occasionally morbidly adherent placenta.

An aseptic technique is essential to minimize the risk of haemorrhage and endometritis[23]. The time elapse "accepted" by many obstetricians to removal of the placenta varies between 30-60 min in the absence of haemorrhage[26]. As MRP is also associated with endometritis, the use of prophylactic broad-spectrum antibiotics is recommended[27]. Administration of glyceryl trinitrate (intravenous or sublingual) to relax the uterus in the presence of a tightly closed cervix and avoidance of using sharp curette reduce the risk of uterine perforation[28,29].

Pharmacological interventions

Intra-umbilical vein oxytocin injection: The use of oxytocin in the management of the third stage and RP had been reported in various studies. It is based on the finding of failure of retro-placental contraction, which resulted in RP. However, intra-umbilical vein oxytocin injection in the management of RP had been shown to have various degrees of success mainly due to different techniques, doses of oxytocin, volumes of fluid and timings of injection.

According to the injection method proposed by Pipingas *et al*[30], using size-10 infant feeding tube directly into the umbilical vein 5 cm before the insertion of cord into the placenta, delivery of oxytocin into the retro-placental myometrium has improved.

The dosage of oxytocin used ranges from 10 IU to 100 IU with a greater chance of success found at a higher dosage (Table 1). As reported by Makkonen *et al*[31], there was no significant change in the MRP rate when 50 IU oxytocin was used. This is consistent with a larger double-blind, randomized controlled trial (Release Study) using 50 IU oxytocin, which demonstrates no statistical difference in the MRP rate between oxytocin and placebo groups[3]. Nonetheless, two studies by Wilken-Jensen *et al*[32] and Lim *et al*[33] had achieved the lowest rate of MRP (< 30%) by advocating dosage 100 IU of oxytocin.

The total volume of fluid being injected into the umbilical vein also differs between trials[34-36]. Most of the studies used 10 to 30 mL except two studies by Caroli *et al*[37] and Lim *et al*[33] which used 40 mL. The reported MRP rate by Caroli *et al*[37] was higher than that by Lim *et al*[33] (58.2% *vs* 30.0%), but the disparity may be due to difference in the dosage of oxytocin used (20 IU *vs* 100 IU).

The interval from oxytocin administration to decision for MRP varies from 15 to 45 min or depending on clinical judgment of the obstetrician[31,34-40]. There is always a concern of the increasing risk of PPH with increment of this interval, especially more than 30 min, which had been shown in several studies[9,10].

A Cochrane review including 15 trials with 1704 women that compared the use of intra-umbilical vein oxytocin injection with saline solution had shown a reduction in MRP rate although there was no statistical difference (OR = 0.9). The authors concluded that the use of oxytocin *via* umbilical vein injection is simple and inexpensive but further research is required to ascertain the optimal timing for MRP[41].

Prostaglandin: Prostaglandin is an effective uterotonic agent and has a role in the management of PPH. It has a combination of pharmacodynamic properties with myometrial stimulation, vasoactive mechanism and reduction in platelet function. The use of prostaglandin in management of RP is based on the mechanism that retro-placental myometrium contracts during the contraction phase and leads to placental detachment[14].

The study to evaluate the efficacy of prostaglandin is limited. Prostaglandin resulted in a statistically significant reduction in MRP when compared with oxytocin (RR = 0.43; 95%CI: 0.25-0.75), with a shorter time interval from drug administration to delivery of the placenta (mean difference -6.00; 95%CI: -8.78--3.22)[39]. However, the meta-analysis only analysed two small trials[41], thus intra-umbilical vein injection of prostaglandin needs further evaluation.

Misoprostol: Van Stralen *et al*[42] review the usage of sublingual misoprostol 800 μg among 95 patients with RP in a low resource setting. The trial failed to show any benefit of using misoprostol in the management of RP. MRP was required in 40% of the treatment group patients compared to 33% in the placebo group.

Carboprost: Carboprost tromethamine, a methylated analogue of PGF2-α, is a uterotonic agent which is more potent and has a longer duration of action.

Lately, the use of carboprost has been extended for RP. According to Habek, intra-umbilical vein injection of 0.5 mg carboprost suspended in 20 mL of 0.9% saline yielded the highest therapeutic success rate of 85.7% as compared to two other groups of oxytocin (76.9%) and methylergometrine (64.2%)[43].

Nitroglycerine: Studies with regards to the use of nitroglycerine (NTG) in management of RP has been described and reported in several clinical trials using dif-

ferent dosages, routes of administration, alone or in combination with other agents. Various degrees of success were reported. However, most were observational studies with a small number of patients.

Chedraui and Insuasti[44] in 2003 reported successful deliveries of all RPs in 30 patients, which was in contrary to a 15% success rate in a study by Visalyaputra *et al*[45]. They were given intravenous NTG 50 μg, which was increased by 50 μg every 2 min until a maximum dose of 200 μg[44]. There were five patients who complained of short-duration headaches but no other significant clinical adverse events. The mean duration to achieve delivery of the placenta was 5.3 ± 1.1 min.

Bullarbo *et al*[46] in a small study of 24 patients demonstrated a success rate of 100% by administering subcutaneous NTG 1 mg after intravenous oxytocin compared to only 8.3% in the placebo group. Similarly, Ekerhovd *et al*[47] successfully delivered 21 out of total 24 RPs without significant side effects.

This is consistent with a Cochrane review[48], which then concluded that subcutaneous NTG appeared to be effective and safe but its routine use is not yet recommended due to small sample size.

Acupuncture

The use of acupuncture in the management of RP involves stimulation of certain acupoints to promote uterine contractions. Chauhan *et al*[49] in their retrospective review of 45 patients who required MRP found that 30 of them had acupuncture to expel the placenta. Twenty-five out of 30 patients who had acupuncture delivered the placenta within 20 min. Four of the remainder required MRP for placenta accreta. There were significantly fewer patients in the acupuncture group experiencing PPH (13% *vs* 47%).

UNDIAGNOSED MORBIDLY ADHERENT PLACENTA

Morbidly adherent placenta implies abnormal invasion of the placenta tissue into the inner or outer myometrium or through the serosa of the uterus (termed accrete, increta or percreta, respectively)[50]. It could be one of the reasons for RP, which is also associated with significant maternal morbidity and mortality. Over the last decades, there has been a steady rise in the incidence of morbidly adherent placenta as reflected by the rising number of caesarean deliveries. It is estimated the incidence of morbidly adherent placenta to be 1.7 per 10000 women[50]. In most cases, there were always established risk factors whereby at least one risk factor was identified in 94% of cases[51]. The risk of having morbidly adherent placenta increased in women with previous caesarean scar, previous uterine surgeries, *in vitro* fertilization pregnancy and placenta praevia[52]. Advanced maternal age, even without any previous caesarean delivery, has been found to be associated with morbidly adherent placenta[50].

A high index of clinical suspicion should be exercised in women who are at risk. The use of ultrasonography with Doppler studies and magnetic resonance imaging (MRI) may be of use in reaching the diagnosis antenatally, thus assisting in the delivery care[53]. Till date, there is difficulty in identifying cases of morbidly adherent placenta in those without any risk factor. In such cases, diagnosis is only made after unsuccessful removal of the placenta at delivery.

Traditionally, hysterectomy has been advocated for such cases. However, it is associated with various morbidities such as PPH, massive blood transfusion, intensive care unit admission, ureteric/bladder injury, infection and prolonged hospitalisation. Alternatively other conservative strategies have been implemented to minimise these complications and preserve fertility. Uterine devascularisation *via* embolisation, uterine compression sutures, uterine tamponade and administration of methotrexate during the post-partum period have all been used to manage morbidly adherent placenta conservatively[54]. However, these conservative approaches are very much dependent on the amount of bleeding, haemodynamic status, surgical expertise, facilities available and the desire for fertility preservation.

CONCLUSION

MRP remains the mainstay of treatment for RP. Clinicians and researchers had been trying hard to find a safe, effective, simple and reliable method to manage RP without the need for surgical intervention. The efficacy and safety of prostaglandin, NTG or acupuncture in the management of RP are yet to be further evaluated. Till date, only intra-umbilical vein oxytocin has been studied extensively but with varied success. More randomized clinical trials are needed to address this issue. However, if immediate MRP service is unavailable, a trial of intra-umbilical vein oxytocin 100 IU at a total volume of at least 40 mL while preparing for transfer to a tertiary center or theatre may result in spontaneous expulsion of the placenta.

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CLINICAL TRIALS STUDY

Utility of a hemoglobin A1C obtained at the first prenatal visit

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Abstract

AIM: To evaluate the utility of the hemoglobin A1C (HbA1C) at the first prenatal visit as a triaging tool in patients at high risk for gestational diabetes (GDM).

METHODS: The HbA1C was obtained at the first prenatal visit prior to 20 wk. Women with a HbA1C ⩾ 6.5% (group one) were instructed on diet and daily self-monitoring of blood glucose. Women with a HbA1C between 5.7%-6.4% (group two) were offered testing or daily self-monitoring of blood glucose. Women with a HbA1C < 5.7% (group three) were tested at 24-28 wk. Patients were tested for GDM using the two step testing and Carpenter and Coustan values as cutoffs. Medication was started if patients failed to meet glycemic goals of fasting ⩽ 95 mg/dL (5.3 mmol/L) and 2 h postprandial ⩽ 120 mg/dL (6.7 mmol/L).

RESULTS: In group one (n = 16), 15/16 (95%) required medication to achieve euglycemia. The mean gestational age at which medication was required was early at 14 ± 6 wk. Postpartum, 14/16 patients (87%) remained diabetic. Group two contained 82 patients. Sixty-sixpatients (80%) were given a diagnosis of GDM and 52 patients (64%) required medication. The mean gestational age at which medication was started in group two was 20 ± 7.8 wk. There were 205 patients in group three, 18 patients (8.7%) were diagnosed with GDM and 13 patients (6%) required medication. In comparison to group three, patients in group one were 220 times more likely to require medication (95%CI: 26.9- > 999, P < 0.0001). Patients in group two were 26 times more likely to require medication (95%CI: 12.5-54.3, P < 0.0001).

CONCLUSION: A HbA1C obtained at the first prenatal visit can be used to triage patients based on the level of glucose intolerance found.

Key words: Gestational diabetes; Pregnancy; Hemoglobin A1C; Glycosylated hemoglobin

Core tip: Hemoglobin A1C (HbA1C) has been endorsed by the World Health Organization for use in diagnosing diabetes and also for identifying degrees of glucose intolerance. This has not been validated in pregnancy. This study looks at a cohort of patients who received a HbA1C at the begining of pregnancy to see if the HbA1C can be used as a triaging tool for identifying patients with undiagnosed diabetes and for identifying a degree of glucose intolerance that would benefit from early intervention. HbA1C ⩾ 6.5% is consistent with preexisting diabetes. HbA1C between 5.7% and 6.4% demonstrates a level of glucose intolerance associated with risk of Gestational Diabetes which may benefit from early intervention.

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INTRODUCTION

Gestational diabetes (GDM) is carbohydrate intolerance with onset or first recognition during pregnancy. A major limitation of this definition is the inclusion of women with undiagnosed preexisting diabetes who are at risk for complications different from women with diabetes occurring only during pregnancy.

Treatment of gestational diabetes is geared towards reducing glucose concentrations in order to reduce the risks to mothers and infants. The Hyperglycemia and Pregnancy Outcome (HAPO) study demonstrated that maternal hyperglycemia at levels lower than those diagnostic of diabetes were associated with increased birth weight and cord-blood serum C-peptide levels[1]. Other studies have shown that the offspring of diabetic mothers may be programmed to develop obesity and type 2 diabetes by the intrauterine environment[2,3].

Measurement of Hemoglobin A1C (HbA1C) has been endorsed by the American Diabetes Association (ADA) as a diagnostic and screening tool for diabetes but not for GDM[4]. The World Health Organization (WHO) has concluded that HbA1C can be used as a diagnostic test for diabetes if standardized assays are used[5].

Advantages of HbA1C are that it does not require fasting and is less prone to day to day variations. Disadvantages are possible racial differences and interference by anemia, hemoglobinopathies, and some medications. HbA1C reflects the average glucose over 2 to 3 mo.

The ADA and WHO recommend using HbA1C $\geqslant$ 6.5% as a cut point for the diagnosis of diabetes. Using the ADA guidelines, patients with HbA1C between 5.7%-6.4% are at an increased risk for diabetes and microvascular complications and are designated as having impaired glucose tolerance[4]. The WHO expert group made no formal recommendations on the interpretation of HbA1C levels below 6.5%[5]. However, as the HbA1C rises, the risk of diabetes increases disproportionately in a curvilinear fashion.

It is not known whether HbA1C between 5.7% and 6.4% confers an increased risk of GDM as it does for type 2 diabetes. The use of HbA1C $\geqslant$ 6.5% for the diagnosis of diabetes has not been validated during pregnancy.

We sought to determine if a HbA1C at the first prenatal visit, in women at high risk for GDM, was useful in identifying women with undiagnosed diabetes or impaired glucose tolerance who may benefit from early testing and intervention for gestational diabetes.

MATERIALS AND METHODS

All patients received a HbA1C as part of routine prenatal labs at the first prenatal visit. Patients with a HbA1C $\geqslant$ 6.5% were counseled on diet, exercise and daily self-monitoring of blood glucose and were referred to the diabetes in pregnancy clinic. Patients with HbA1C between 5.7%-6.4% were given the choice of immediate testing for GDM or to begin daily self-monitoring of blood glucose. Additionally, they were counseled on diet and exercise and tested for GDM at 24-28 wk if necessary. Patients with a HbA1C < 5.7% were tested for gestational diabetes at 24-28 wk. Testing for GDM was performed using the standard two step testing and Carpenter and Coustan values were used as cutoffs. Patients with GDM performed self-monitoring of blood glucose four times a day: fasting and two hours after each meal. Glycemic goals were fasting $\leqslant$ 95mg/dL (5.3 mmol/L) and two hour postprandials $\leqslant$ 120 mg/dL (6.7 mmol/L). Medication was started if 20% of values over a two week period exceeded these goals. Medications used included insulin and oral antidiabetic agents. All patients with the first prenatal visit prior to 20 wk were eligible for inclusion. Determination of HbA1C values was done using the TOSOH G8 AutoHPLC (High Performance Liquid Chromatograph). This method is approved by the National Glycohemoglobin Standardization Program (NGSP) and is not affected by the presence of hemoglobinopathies or anemia. This method is subject to interference from the presence of haemoglobin E (HbE). HbE is a hemoglobin variant most common in persons of Thai, Cambodian, Vietnamese or Laotian descent. The enrollment period was from October 2011 to March 2012. Patients with known diabetes were excluded. Data was collected by chart review after delivery. This study was approved by the Institutional Review Board at the University of New Mexico as a retrospective cohort study.

Statistical analysis

Statistical analysis was performed using the SAS package version 9.3. Sample size was chosen assuming that the incidence of GDM in patients with HbA1C $\geqslant$ 5.7 was 15%. In patients with HbA1C < 5.7% the incidence of GDM was assumed to be 5%. A 2:1 ratio of patients with HbA1C < 5.7% to patients with HbA1C $\geqslant$ 5.7% was used to compensate for the comparatively low incidence of GDM in the former group. Desired enrollment numbers were 98 patients with HbA1C $\geqslant$ 5.7 % and 196 patients with HbA1C < 5.7%. The study was powered to have an 80% probability of detecting a difference in the incidence of GDM between patients with HbA1C < 5.7% compared to patients with HbA1C $\geqslant$ 5.7% at a significance level of 0.05. Logistic Regression was used to calculate odds ratios and ANOVA was used to determine the effect of group on the use of medication and the week medication was started.

RESULTS

Three-hundred-three patients had sufficient data for analysis. This included 98 patients with HbA1C $\geqslant$ 5.7% and 205 patients with HbA1C < 5.7% Ethnicity was determined by patient self-reporting; 78% were Hispanic of Mexican descent, 15% Caucasian, 3% Native American, 1% Asian, 1% African American and 0.68% other. Patient demographics including age, parity, BMI and ethnicity are shown in Table 1.

Patients were assigned to groups based on HbA1C.

Table 1 Patient demographics

	A1C ⩾ 6.5% (*n* = 16)	A1C = 5.7%-6.4% (*n* = 82)	A1C < 5 .7% (*n* = 205)
Age	32 ± 6.6 yr	28 ± 4.7 yr	25 ± 4.4 yr
Parity	2.9 ± 1.7	1.7±1.1	0.86 ±. 0.78
BMI	37.3 ± 6.9	32.1 ± 7.7	28.8 ± 6.1
Ethnicity	Hispanic = 14	Hispanic = 61	Hispanic = 162
	Caucasian = 0	Caucasian = 8	Caucasian = 38
	Native Am. = 2	Native Am. = 6	Native Am. = 2
	African Am. = 0	African Am. = 4	African Am. = 0
	Asian = 0	Asian = 3	Asian = 1
	Other = 0	Other = 0	Other = 2

All values are ± SD.

Table 2 Diagnosis of gestational diabetes and medication use by group

	GDM diagnosis *n*%	Required meds *n*%[1] %[2]	Mean gestation at initiation of medication
Group 1[3] (*n* = 16)	16 (100)	15 (95) (95)	14 ± 6 wk
Group 2[4] (*n* = 82)	66 (80)	52 (64) (80)	20 ± 7.8 wk
Group 3[5] (*n* = 205)	18 (8.7)	13 (6) (72)	31 ± 4.3 wk

[3]HbA1C ⩾ 6.5%; [4]HbA1C: 5.7%-6.4%; [5]HbA1C < 5.7%; [1]Percentage of the group that required medication; [2]Percentage of patients in the group with a diagnosis of gestational diabetes (GDM) that required medication. HbA1C: Hemoglobin A1C.

Group one (n = 16) had a HbA1C ⩾ 6.5%. Group two (n = 82) had a HbA1C between 5.7% and 6.4%. Group three (n = 205) had a HbA1C < 5.7%.

We identified 16/303 patients (5.4%) who met criteria for overt diabetes diagnosed during pregnancy. Ninety-five percent or 15/16 patients with a HbA1C ⩾ 6.5% (group one) required medication to achieve euglycemia during pregnancy. Postpartum, 14/16 patients in group one (87%) were diagnosed with type 2 diabetes based on a 75 g two hour challenge test.

Fifty-one patients in group two were diagnosed based on testing. An additional 15 patients in group two were given the diagnosis of GDM because daily self-monitoring of glucose demonstrated a need for medication to achieve glycemic goals.

All patients in group one, 66 patients (80%) in group two, and 18 patients (8.7%) in group three were given a diagnosis of GDM. To achieve glycemic goals, 94% of patients in group one, 64% of the patients in group two and 6% of the patients in group three required medication. Within each group, of the patients who required medication, the mean gestational age at which medication was started was 14 ± 6.0 wk in group one (range 6-28 wk), 20 ± 7.8 wk in group two (range 8-35 wk) and 31 ± 4.3 wk in group three (range 19-36 wk) as shown in Table 2.

Based on group alone, the odds of requiring medication to control blood glucose in comparison to group thee patients who had normal HbA1C values, was 220 times higher in group one (95%CI: 26.9- >999, P < 0.0001) and 26 times higher in group two (95%CI: 12.5-54.3, P < 0.0001).

DISCUSSION

An A1C drawn at the first prenatal visit is convenient for the both the patient and provider. The test can be done as part of routine prenatal labs and does not require the time commitment of the standard two step testing and does not require fasting. Our data indicates that the HbA1C performed at this time will also provide useful information for the management of the patient who is at high risk for gestational diabetes.

In patients with overt diabetes, HbA1C has been correlated with average glucose concentration as measured by daily evaluation of capillary blood glucose levels. However, during pregnancy HbA1C levels have not been used to manage patients because HbA1C levels perform poorly in differentiating women with normal pregnancies from those with GDM. A secondary analysis of the HAPO data was undertaken to determine if HbA1C measurement could provide an alternative to the oral glucose tolerance test in pregnant women[6]. HbA1C measurements were taken at the time of the oral glucose tolerance test (OGTT). Birthweight > 90th percentile, primary cesarean section and clinical neonatal hypoglycemia, preterm delivery, preeclampsia and cord C-peptide > 90th percentile were evaluated. The authors concluded that HbA1C was not a useful alternative to the OGTT because it was not predictive of these adverse outcomes. Our data suggests that the HbA1C at the first prenatal visit, if prior to 20 wk, rather than at the time of the OGTT, can be used to identify women with a level of glucose intolerance that will benefit from early modification of diet and exercise and early testing or self-monitoring of blood glucose. In support of the previous statement, the mean gestational age of medication initiation in groups one and two of our study, was lower than the gestational age at which routine testing for GDM is performed.

In our study we divided patients into three groups based on the recommendations of the ADA for diagnosis: patients with overt diabetes of pregnancy (HbA1C > 6.5%); patients with impaired glucose tolerance (HbA1C between 5.7%-6.4%) and normal glucose tolerance (HbA1C < 5.7%). Our study appears to support the clinical relevance of these categories in pregnancy. Ninety-five percent of patients with HbA1C of 6.5% or greater and 64% of patients with a HbA1C between 5.7 and 6.4 required medication to achieve euglycemia. This is consistent with a study by Balaji looking at 255 Asian women at risk for GDM reported that high (> 6.1%) and intermediate (5.3%-6%) HbA1C in the first trimester was associated with an elevated risk of GDM[7]. In that study 100% of patients with HbA1C > 6% and 23% of the patients with intermediate range HbA1C developed GDM. González-Quintero *et al*[8] found that HbA1C of 6% at the time of diagnosis of GDM was associated with a 61% increase in the odds of insulin use.

One limitation of the study is its retrospective design.

Retrospective studies in general are subject to selection bias. We attempted to ameliorate this effect by including all patients who met inclusion criteria and for whom there was sufficient data for analysis. A second limitation is that 15 patients in group 2, who were labeled as gestational diabetic, did not receive an oral glucose tolerance test. These patients performed daily monitoring of blood glucose and despite counseling on diet and exercise failed to meet glycemic goals and required medication indicating a degree of glucose intolerance consistent with the diagnosis.

The HbA1C $\geqslant$ 6.5% identifies women with a degree of hyperglycemia consistent with preexisting diabetes who have a high risk of requiring medication to achieve euglycemia and who may benefit from dietary counseling and daily monitoring of blood glucose. HbA1C between 5.7%-6.4% identifies women with a degree of glucose intolerance who may benefit from early testing. These women are also at high risk of requiring medication to achieve euglycemia if diagnosed with GDM. HbA1C < 5.7% is associated with minimal risk of GDM.

COMMENTS

Background

Gestational Diabetes and preexisting diabetes in pregnancy are becoming increasingly more common. Early identification allows intervention with resultant improved outcomes.

Research frontiers

There is current controversy on the best method of screening for and diagnosing gestational diabetes and preexisting diabetes in pregnancy. In this study the authors evaluate a hemoglobin A1C (HbA1C) obtained at the first prenatal visit as a tool for identification of patients who may benefit from early intervention for glucose intolerance.

Innovations and breakthroughs

This is the first study to look at the use of the HbA1C specifically in pregnant patients and to use the HbA1C to determine a course of management.

Applications

Data from this study can be used to create protocols for the management of patients based on the value of the HbA1C obtained at the first prenatal visit.

Terminology

Gestational diabetes: Glucose intolerance with onset or first recognition during pregnancy. HbA1C: a measure of the amount of glycated hemoglobin. HbA1C gives a picture of glycemic control over the preceeding 3 mo.

Peer review

The manuscript studied the utility of HbA1C at the first prenatal visit to detect the gestational diabetes (GDM) in local population. The study used the ADA and WHO cutoff to divide over 300 subjects based on HbA1C levels and determine the risk of GDM and subsequent management. The study identified significant high detection rate of GDM with high Hb1AC group with over 200 time more likely to require medication. The results are interesting.

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RANDOMIZED CONTROLLED TRIAL

Effect of vaginal speculum lubrication on cervical cytology and discomfort during smear examination

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Abstract

AIM: To evaluate the role of lubricant gel in the cytology of a Pap smear and whether it results in an improvement in the discomfort experienced by women while undergoing Pap smear screening.

METHODS: A total of 151 women were analyzed in the study. After screening for inclusion criteria, a Pap smear was taken with no lubricant in all the women and the discomfort experienced was rated on a visual analogue scale. The women underwent a second Pap smear on the next visit using a lubricant gel and were again rated on a visual analogue scale for the discomfort felt. The pathologist was blinded to the fact of whether the lubricating gel was used.

RESULTS: The number of unsatisfactory smears in the no gel group was 3 *vs* 5 in the gel group, $P < 0.05$. However, a significant difference ($P = 0.00$) was observed in the visual analogue pain score in both groups, suggesting that application of lubricant gel over the speculum improves the pain experienced by women.

CONCLUSION: Using a small amount of lubricant over the speculum does not impair cervical cytology but significantly improves the discomfort experienced by women while undergoing a Pap smear.

Key words: Lubrication; Cytology; Pain scoring; Pap smear; Discomfort

Core tip: Vaginal speculum lubrication has no effect on cervical cytology and improves the discomfort experienced in Pap smear screening.

Madaan M, Singh A, Puri M, Kaur H, Trivedi SS. Effect of vaginal speculum lubrication on cervical cytology and discomfort during smear examination. *World J Obstet Gynecol* 2014; 3(3): 134-137 Available from: URL: http://www.wjgnet.com/2218-6220/full/v3/i3/134.htm DOI: http://dx.doi.org/10.5317/wjog.v3.i3.134

INTRODUCTION

Worldwide, cervical cancer is the third most common cancer in women. In 2008, there were an estimated 529000 new cases of cervical cancer, of which over 85% occurred in developing countries[1]. Although these numbers are staggering, there has been a marked improvement in early detection of cervical carcinoma with the advent of Pap smears as a screening test. Despite this, there are many women who do not get regular screening with Pap smears. The reasons could be lack of health education, lack of health insurance, cultural barriers, discomfort[2] or anxiety regarding the procedure. Health care providers can address this issue by minimizing the patient's discomfort while performing a Pap smear. Lubricating the speculum can reduce the patient's discomfort and improve the woman's compliance with a Pap smear examination.

The routine teaching in gynecology over the years has

discouraged the use of gel lubricant because of concerns that the lubricant might interfere with the cytology results[3]. A few studies in the literature have addressed this issue and others have also raised some concerns.

We designed this study to formally investigate whether gel interferes with cervical cytology and whether it has any effect on the pain perception of the woman.

MATERIALS AND METHODS

The study was conducted at Lady Hardinge Medical College and Smt Sucheta Kriplani Hospital, New Delhi from November 2010 to July 2011. The study was approved by the Institutional Review Board of the hospital. Women aged 18 to 50 years attending the gynecology outpatient clinic were enrolled in the study. Women presenting with infectious gynecological complaints, genital bleeding or with history of cervical cancer, chronic pelvic pain, hysterectomy or allergy to gel lubricant were excluded from the study. Prior informed consent was taken from the participants. Information regarding age, parity, duration of married life, contraceptive use and history of abnormal Pap smears was obtained from all the women.

All women recruited for the study underwent a Pap smear twice using an appropriate size metal Cusco's speculum. In the first visit, the Pap smear was taken using a dry speculum, with no water or gel, as per the usual practice. The second smear was taken 3-4 d later after applying xylocaine jelly over the outer surfaces of the superior and inferior blades of the Cusco's speculum. The xylocaine jelly contained lignocaine hydrochloride 20 milligram as the active ingredient, hypromellose, methyl hydroxybenzoate, propyl hydroxybenzoate, sodium hydroxide, purified water and hydrochloric acid for pH adjustment.

The smear was taken using an Ayre's spatula and endocervical brush, spread on a glass slide and fixed in 95% isopropyl alcohol for 10 min. The glass slides from the no gel and the gel group were kept in separate containers to prevent contamination of the slides. After drying, the slides were sent to the cytopathologists who were blinded to the group assignments of the smear. The Pap smears were analyzed and classified according to the revised Bethesda scoring 2001. The smear was considered unsatisfactory if 75% of the epithelial cells were covered by blood, inflammation or artifacts.

After each Pap smear, the women were asked to rate their discomfort on a visual analogue scale (VAS) ranging from 0 (no discomfort) to 10 (most discomfort).

In the present study, each woman served as her own control. The Pap smears were collected by one of the three gynecologists at the level of consultant. It was a double blinded trial as both the patients and the cytopathologists were unaware of the method used in collecting the Pap smear.

Statistical analysis

Past studies have indicated the incidence of unsatisfactory smears to be 1.5%-4%. So taking the average incidence as 2.5% and the margin of error as 2.5%, the minimum sample size was calculated to be 150. A χ^2 test and unpaired *t*-test were used for different statistical calculations.

RESULTS

A total of 210 women were enrolled in the present study. The first Pap smear without gel was taken in 180 women who met the inclusion criteria. Out of these 180 women, 29 were lost to follow up. A repeat Pap smear with gel was taken in 151 women who reported for the second visit as per the protocol. Thus, our final sample size was 151. Figure 1 shows the consort flow diagram of the study.

The mean age of women in the study population was 34.6 ± 8.6 years. The mean duration of married life was 12.8 ± 8.1 years and mean parity was 2.0 ± 1.3 (Table 1).

There was no significant difference in the percentage of unsatisfactory smears, low grade squamous intraepithelial lesions or high grade squamous intraepithelial lesions in the gel versus no gel group (Table 2). There were no cases of invasive cancer in the study population.

However, a significant difference (P = 0.0) was observed in the visual analogue pain score between the gel group (mean VAS: 1.2 ± 1.5) and no gel group (mean VAS: 2.1 ± 1.8), as shown in Figure 2.

DISCUSSION

Our study showed that using a small amount of lubricant on the outer side of superior and inferior blades of speculum does not affect the cytology of Pap smears. Thus, speculum lubrication may be performed as a routine practice during Pap smear collection to minimize discomfort to the woman. This is in accordance with earlier studies[4-7] where the same observation was made. In the majority of these studies, subjects were randomized into two groups, while in our study the same woman served as her own control.

A study by Charoenkwan *et al*[8] found a higher incidence of unsatisfactory smears (12.1% *vs* 1.7%) in gel contaminated smears. It should be noted that in their study they applied gel directly over the external cervical os in contrast to our study where we applied the gel over the outer aspects of speculum to facilitate the entry of the speculum. Köşüş *et al*[9] also reported significantly increased rates of unsatisfactory smears in the gel applied group.

The present study also showed that applying gel over the speculum significantly improves the pain score of the women, thus reflecting a reduction in the discomfort associated with undergoing a Pap smear. The majority of studies found in the literature comment on the effect of gel on cervical cytology and only a few studies have evaluated the effect on minimizing the pain for the woman. Gilson *et al*[7] found no significant alteration in patient discomfort with speculum gel lubrication in their study on 40 patients. In a study by Hill *et al*[10], lower pain scores were observed in the gel group compared to speculum

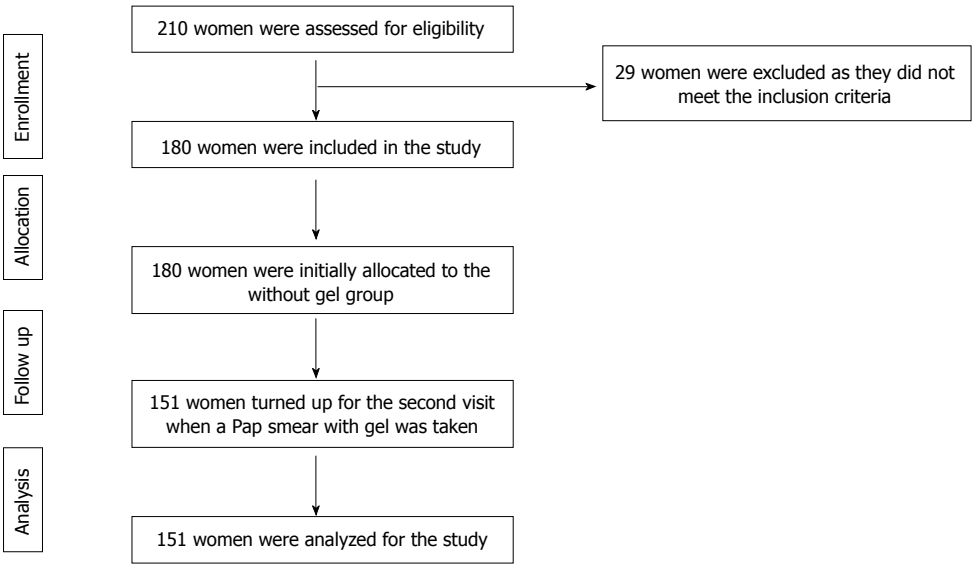

Figure 1 Consort flow diagram.

Table 1 Age distribution of study population *n* (%)

Age interval (yr)	Frequency
< 30	63 (41.7)
30-40	48 (31.8)
40-50	35 (23.2)
50-60	5 (3.3)
Total	151

Table 2 Comparison of Pap cytology results in both groups *n* (%)

Cytology results	Without gel	With gel	*P* value
Unsatisfactory	3 (1.9)	5 (3.3)	0.2
NILM	146 (96.7)	142 (94.0)	0.1
Granulomatous cervicitis	0 (0)	1 (0.7)	0.2
LSIL	0 (0)	1 (0.7)	0.2
HSIL	2 (1.3)	2 (1.3)	0.5

NILM: Negative for intraepithelial lesion or malignancy; LSIL: Low grade squamous intraepithelial lesion; HSIL: High grade squamous intraepithelial lesion.

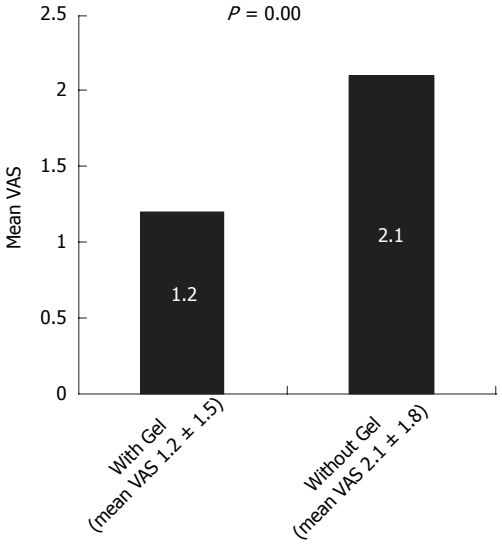

Figure 2 Comparison of mean visual analogue score in both groups. VAS: Visual analogue score.

lubrication with water ($P < 0.01$).

The strength of our study lies in the fact that we evaluated both the parameters simultaneously, *i.e.*, the effect of gel on cervical cytology and pain scoring. The low overall pain scores observed in both groups could be due to experienced gynecologists performing the test.

However, our study is not without limitations. We repeated the procedure with gel on the same woman and this could have resulted in less anxiety due to preexisting increased awareness of the procedure and lower pain scores. However, this protocol was planned so that all women underwent their first smear without gel as per routine protocol so that the diagnoses was not missed in case gel obscured smear cytology or if the woman did not return for repeat testing. Postmenopausal women and women with infective etiology were intentionally excluded from the study as the discomfort caused by a speculum is more in these women. Women with epithelial cell abnormalities were too few in the study to be able to evaluate whether there is an increase in false negative rates with gel. We would recommend doing the same study on larger subset of population using liquid cytology.

The use of gel for vaginal speculum lubrication in the collection of Pap smears had no adverse effect on cervical cytology results and it significantly decreased the level of discomfort in women undergoing Pap smear screening.

COMMENTS

Background

Cervical cancer is still one of the most common cancers in females despite the

application of widespread screening. The common reason cited for noncompliance among women for cervical cancer screening is the discomfort associated with speculum insertion.

Research frontiers

This study was conducted to evaluate whether lubrication of the vaginal speculum improves the discomfort for women as well as its effect on cervical cytology.

Innovations and breakthroughs

Contrary to the old dictum that no speculum lubrication should be used while taking a Pap smear, a few studies have been conducted in the recent past that show that speculum lubrication improves the discomfort during smear examination. However, the effect of speculum lubrication on cervical cytology is conflicting.

Applications

The study shows that speculum lubrication improves the discomfort for women and that it does not affect cervical cytology. However, there is further scope to do a larger study using liquid cytology.

Terminology

A visual analogue score is an objective means of assessing pain felt by a person who marks the intensity of pain experienced on a scale ranging from 0 to 10.

Peer review

This article evaluated the effect of vaginal speculum lubrication with xylocaine gel on cervical cytology and pain scoring in Pap smear screening and concluded that vaginal speculum lubrication with xylocaine gel did not influence the Pap smear screening.

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CASE REPORT

Leiomyoma of the umbilical cord artery: A case report

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Author contributions: Rovas L designed the study, analyzed the data, and wrote the manuscript; Dauksas R performed histologic analysis; Simavicius A collected the patient's clinical data.
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Key words: Umbilical cord; Leiomyoma; Non-trophoblastic tumor; Pregnancy

Core tip: Leiomyoma is a benign tumor originating from non-striated muscle that is rare in tissues outside of the uterus. This article presents an extremely rare case of umbilical cord artery subendothelial leiomyoma.

Rovas L, Dauksas R, Simavicius A. Leiomyoma of the umbilical cord artery: A case report. *World J Obstet Gynecol* 2014; 3(3): 138-140 Available from: URL: http://www.wjgnet.com/2218-6220/full/v3/i3/138.htm DOI: http://dx.doi.org/10.5317/wjog.v3.i3.138

Abstract

A leiomyoma is a benign tumor originating from non-striated muscle that is typically found in the uterus. Intravenous leiomyomatosis is a rare form found within the veins, usually associated with uterine fibroids, and tends to recur. These masses can spread from the uterus throughout the venous system. A rare case involving a subendothelial leiomyoma found in an umbilical cord artery is presented in this article. A 21-year-old patient presented with symptoms of preterm labor, which resulted in the premature birth of a female below the 10th percentile for 24-wk gestational age. The newborn died three days later, and microscopic analysis of the umbilical cord revealed occlusion of the artery by nodular structures. The antepartum diagnosis of intravascular leiomyoma was identified by immunohistochemistry showing that approximately 70% of all tumor cells were diffusely positive for smooth muscle markers, including desmin and smooth muscle actin. These findings indicate the possibility of a pathologic association between the umbilical cord leiomyoma, restriction of fetal growth and preterm delivery due to impaired circulation of blood in the umbilical cord.

INTRODUCTION

Intravenous leiomyomatosis (IVL) is a rare smooth muscle tumor found within the veins of the uterus. The masses are benign-appearing but can exit the uterus and spread throughout the venous system[1]. This condition is related to benign metastasizing leiomyoma, in which the masses appear in distant locations such as the lung, heart and kidneys.

Tumors of the umbilical cord are rare, and cases of subendothelial leiomyoma are even more infrequent. To our knowledge, there are no published reports concerning umbilical cord leiomyomas. However, we recently encountered a case of an unusual non-trophoblastic tumor in an umbilical cord that was diagnosed during histochemical examination after childbirth.

CASE REPORT

A healthy, 21-year-old multiparous pregnant woman presented at Siauliai Hospital at 24 wk of gestation because of bleeding and uterine contractions. The patient had no significant medical history except for a miscarriage at 13 gestational weeks one year before. The current pregnancy was spontaneous without any problems to date.

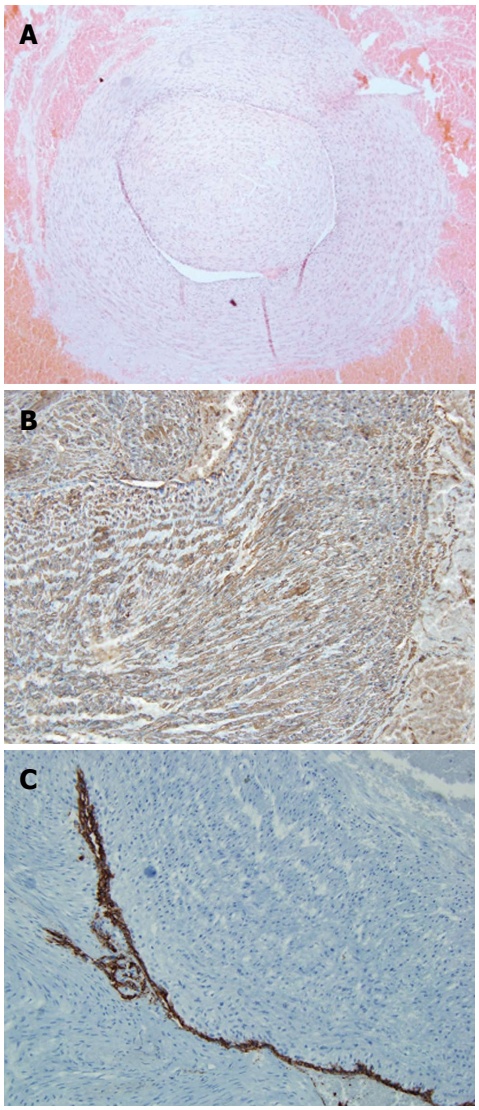

Figure 1 Photographs. A: Circumscribed intravascular tumor. Micrograph showing the intravascular tumor lined with endothelium (hematoxylin-eosin staining, magnification × 20); B: Smooth muscle actin immunohistochemistry. Micrograph showing tumor cells immunoreactive for smooth muscle actin (magnification × 20); C: $CD34^+$ immunoreactivity in tumor cells. Immunohistochemistry revealed the presence of $CD34^+$ tumor cells beneath the endothelium (magnification × 20).

Transvaginal and transabdominal ultrasound did not detect any lesions within the fetus, placenta or umbilical cord. The estimated weight of the fetus was less than the 10^{th} percentile. A blood analysis did not indicate the presence of any inflammatory processes. Regular contractions were detected during cardiotocography. Despite treatment with nifedipine, a selective calcium channel inhibitor used to stop premature uterine contractions, a spontaneous preterm birth occurred. The extremely premature newborn died after three days, and no anomalies were found at autopsy. The maternal surface and membranes of the placenta were unremarkable.

The umbilical cord measured 50 cm in length and was inserted centrally. Microscopic examination of an umbilical cord specimen revealed that arteries were occluded by polyploid nodular structures consisting of oblong, mitotic non-active cells, which formed patches in some places. Further analysis revealed a lesion lined with endothelium (Figure 1A). A diagnosis of intravascular leiomyoma was confirmed by immunohistochemistry that showed that the tumor cells were diffusely positive for smooth muscle markers, including desmin and smooth muscle actin (Figure 1B). Approximately 70% of the tumor cells showed cytoplasmic actin immunoreactivity. Tumor cells were also immunoreactive for antibodies against CD34 (Figure 1C).

DISCUSSION

The histogenesis of primary neoplastic alterations of placenta and umbilical cord are divided into two main groups[2]. They can be of a trophoblastic origin, including placental trophoblastic tumors, choriocarcinomas and hydatidiform moles, or non-trophoblastic, such as in chorioangioma and teratomas. Leiomyomas are of the second group of non-trophoblastic origin, which are extremely rare in the umbilical cord[3]. However, non-trophoblastic tumors are asymptomatic, and can remain undetected during examination of secundines, only being detected incidentally[2].

IVL is a nonmalignant tumor usually confined to the pelvic venous system and histologically characterized as a smooth muscle tumor mass growing within the uterus[4,5]. The cardinal microscopic feature is the protrusion of a smooth muscle endothelium-covered tumor into the vessels. Vascular leiomyomas may be difficult to distinguish from hemangiomas, which are more commonly found in the umbilical cord, and are cavernous[6]. Although IVL are typically confined to the uterine veins, they can progress along the veins into the inferior vena cava, and have been described within intracaval, intracardiac, intrarenal and pulmonary arteries[7,8]. Of the reported cases of IVL[4], none were detected in umbilical cord.

The case described in this article is the first known report of IVL in an umbilical cord artery. There were no suspicions concerning an umbilical cord tumor before delivery, and the leiomyoma was detected only during microscopic examination after birth. It is not clear how the leiomyoma extended in to umbilical cord artery. The umbilical cord forms within the body stalk of the developing embryo from the omphalomesenteric duct, yolk sac and the allantoic duct at around 6 wk into the gestational period[9]. IVL grows in the uterine vascular tree and can presumably metastasize into the fetal-maternal circulation. Although the cause of the fetal growth restriction and preterm delivery in this case is unknown, it is possible that the umbilical cord artery pathology and impaired blood circulation resulting from the leiomyoma contributed.

COMMENTS

Case characteristics

A healthy 21-year-old pregnant women presented with symptoms of preterm labor.

Clinical diagnosis

Premature labor, intrauterine growth restriction.

Differential diagnosis

Premature labor, abruptio placenta.

Laboratory diagnosis

Blood analysis did not reveal any sign of inflammatory processes.

Imaging diagnosis

Pregnancy: 24 wk gestation with normal anatomic development of the fetus. Cervix: 3 cm; normal placenta and umbilical cord. Intrauterine growth restriction.

Pathological diagnosis

Leiomyoma.

Treatment

The patient was treated with nifedipine (calcium channel blocker).

Term explanation

The CD34 protein is a member of a family of single-pass transmembrane proteins expressed in early hematopoietic and vascular-associated tissue.

Experiences and lessons

This case report not only describes the extremely rare intravenous locations of leiomyomas, but also suggests that all available methods should be used to ascertain causes of poor pregnancy outcomes.

Peer review

This article presents the first known report of an intravenous leiomyoma within the umbilical cord. The tumor was diagnosed after immunohistochemical analysis to confirm the origin.

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Patent (list all authors)

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

Statistical data
Write as mean ± SD or mean ± SE.

Statistical expression
Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units
Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics
Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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