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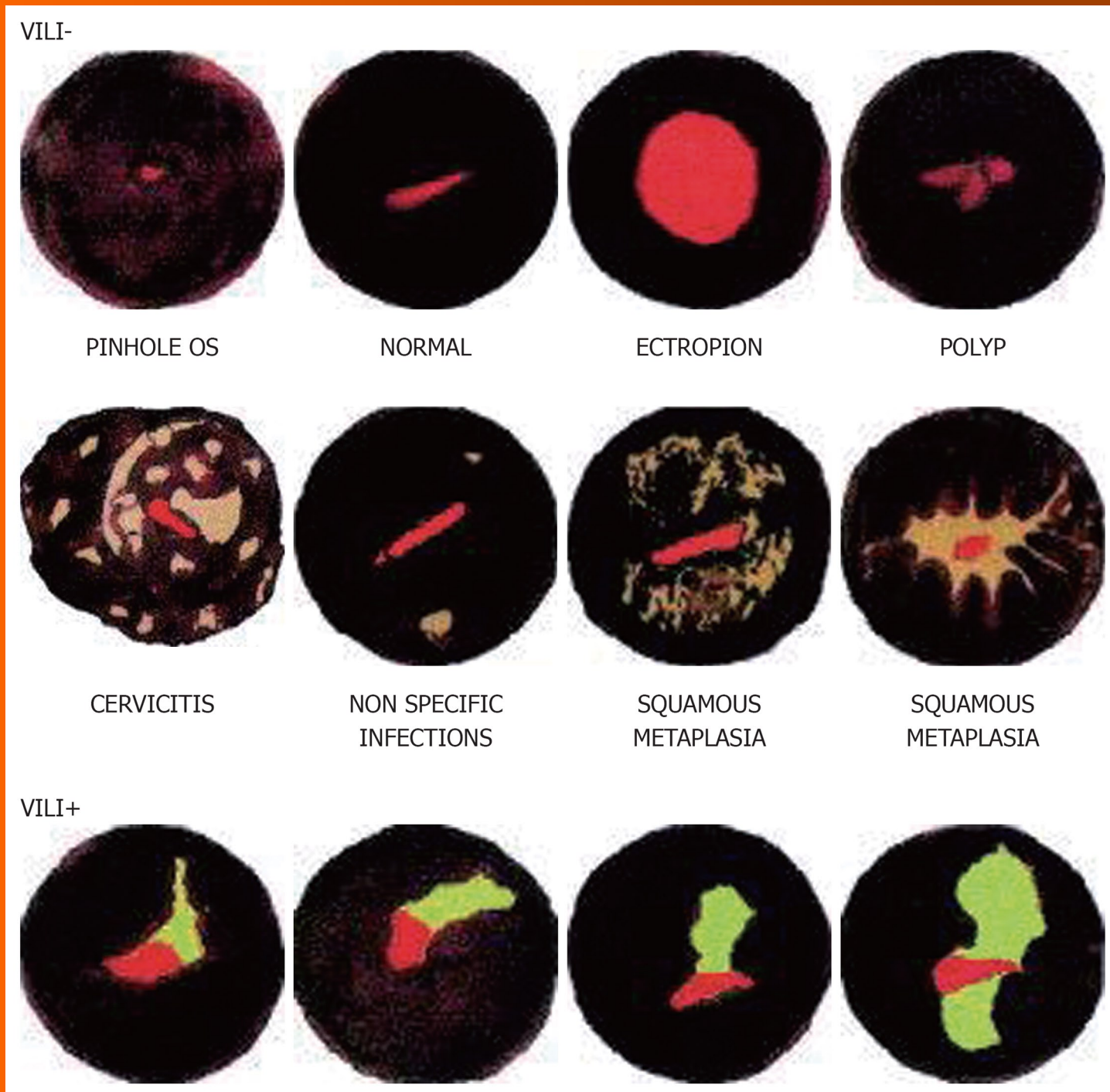

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EDITORIAL

Why hypertension is good new and preeclampsia bad news-demonstrating the failure of prevention

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Abstract

Hypertensive disorders in pregnancy continue to be an intriguing and potentially lethal complication in humans and some other primates. In a simplistic way the current hypothesis is that the genesis of preeclampsia starts at 12 to 14 wk gestation with failure of trophoblast invasion in the spiral arteries, resulting in some degree of hypoxemia in the placenta. The hypoperfused placental tissue starts to secrete variable amounts of angiogenic and antiangiogenic factors which eventually cause endothelial damage all over the pregnant women's body with one of the many signs of preeclampsia as the clinical endpoint. For some incomprehensible reason a major interest has existed for decades concerning the early prediction of preeclampsia, most commonly tested using uterine artery Doppler (the earlier the better) and various serum markers, alone or in combination. Any new model for detection has been welcomed enthusiastically, although nothing has changed in the outcome of women presenting with preeclampsia.

Key words: Hypertensive disorder; Pregnancy; Preeclampsia

Hypertensive disorders in pregnancy continue to be an intriguing and potentially lethal complication in humans and some other primates[1]. In a simplistic way the current hypothesis is that the genesis of preeclampsia starts at 12 to 14 wk gestation with failure of trophoblast invasion in the spiral arteries, resulting in some degree of hypoxemia in the placenta. The hypoperfused placental tissue starts to secrete variable amounts of angiogenic and antiangiogenic factors which eventually cause endothelial damage all over the pregnant women's body with one of the many signs of preeclampsia as the clinical endpoint[2]. For some incomprehensible reason a major interest has existed for decades concerning the early prediction of preeclampsia, most commonly tested by uterine artery Doppler (the earlier the better) and various serum markers, alone or in combination. Any new model for detection has been welcomed enthusiastically, although nothing has changed in the outcome of women presenting with preeclampsia. But is the news really so bad?

We and others have demonstrated that actual birth weight in cases of gestational hypertension, which do not develop into preeclampsia, tends to be higher than in normotensive women[3,4]. One possible explanation for this is that the originally hypoperfused placenta is highly successful in increasing its blood supply by secreting angiogenic factors. Isolated gestational hypertension is good news and it is only when the rescue mechanism activated by the placenta fails, that preeclampsia will develop with

all the well-known detrimental effects including fetal growth retardation, preterm birth, fetal death, and possibly maternal convulsions and death.

If some kind of endothelial damage makes the difference, then almost anything that has a vascular effect (and most drugs, nutritional supplements and physical exercise have been shown to influence blood vessels) can be (and has been) tried as a measure to prevent the development of preeclampsia. Possibilites range from calcium to calcium blockers, from aspirine to NO, any vitamin or food supplement such as arginine, from bed rest to physical training.Both individual studies and meta-analyses are often conflicting. For example, Trivedi *et al*[5] recently concluded that low dose aspirin resulted in a significant reduction of preeclampsia in high risk patients, while another meta-analysis which was published almost simultaneously on the same subject by Rossi *et al*[6] concluded that low dose aspirin does not lead to less preeclampsia in high risk women. At least we all agree that aspirin should not be given to low risk women. Not only does this demonstrate that a disturbing level of subjectivity makes our current model and methods for evidence based medicine fail in providing clinicians a tool to guide their management, but it also shows that we simply have no idea what is really happening in pre-eclampsia. The really bad news is that when one critically considers all preventive measures that have ever been proposed, we are left with nothing to offer our patients except "promising news", as promising as it has been for the last 30 years.

As long as we do not understand why trophoblast invasion fails, and why not all preeclamptic placentae show failed trophoblast invasion, we will continue to be unable to differentiate between the good news of a compensatory hypertension and the bad news of the overshooting reaction that we call preeclampsia.

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EDITORIAL

Mucinous cystadenocarcinoma of ovary: Changing treatment paradigms

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Abstract

Traditionally, all carcinomas arising from the surface epithelial layer of the ovary have been grouped together. This grouping has led to a single therapeutic strategy that is used for all epithelial ovarian cancers. However mucinous cancers appear to be distinct from serous cancers in their clinical behaviour and molecular signatures. In comparison to serous tumours, early stage mucinous tumours tend to be localised at diagnosis with a higher overall survival. But when metastatic at presentation or after recurrence, the outcome of mucinous tumours is far inferior to serous tumours. With standard platinum based chemotherapy the response rate and survival is far worse in mucinous cancers. The precise biological and molecular explanation for this difference remains unanswered. There is urgent need for testing and adoption of therapeutic approaches tailored to molecular characteristics of mucinous carcinomas so that patient survival can be optimised.

Key words: Ovary; Carcinoma; Mucinous

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INTRODUCTION

Traditionally, all carcinomas arising from the surface epithelial layer of the ovary have been grouped together. This grouping has led to a single therapeutic strategy that is used for all epithelial ovarian cancers. With the emergence of more robust clinicopathologic, molecular, and genetic data over the past decade, we are clearly in the midst of an exciting paradigm shift that challenges the status quo of treating all women with a diagnosis of epithelial ovarian cancer similarly, regardless of cell type or histological grade. Specifically, mucinous carcinoma appears to have a distinct clinical behaviour and molecular profile[1]. In the year 2004, as noted by Hess *et al*[2] advanced stage mucinous ovarian cancer had a worse outcome than women with non mucinous type, with advanced stage non mucinous living three times longer than those with mucinous pathology. If we are going to preach about tailored oncology care, we need to walk the talk; it is time to get it right. The purpose of this review is to examine the differences between mucinous cystadenocarcinoma of ovary from other histological subtypes, and to discuss strategies for better management of this tumor.

INCIDENCE

Mucinous carcinomas appear to comprise approximately

2%-5% of ovarian epithelial neoplasms[3]. The incidence of mucinous histology in various large trials ranged from 1.6%-4.4%[4,5], and the standard treatment in these tumors was based on these large studies with very limited histological subtype of mucinous tumor. Hence behaviour and natural history of mucinous carcinoma *per se* remained an unresolved issue so long.

PRIMARY *VS* METASTATIC MUCINOUS CARCINOMA OF THE OVARY?

Primary mucinous carcinomas of the ovary are distinct from other ovarian carcinoma types, but they can pose a particular challenge for correct diagnosis from metastases, which most usually originate from the colorectum. The question also arises whether the survival of women with advanced stage primary mucinous carcinoma of the ovary differs significantly from that of women with mucinous carcinoma metastatic to the ovary.

These quandaries were looked into by the Gynaecologic Oncology Group Study conducted by Richard J Zaino[6]. Using the Lee and Young study[7], they classified tumor as metastatic or primary tumor based on 12 parameters.

Metastatic tumors pathologically had a diameter less than 13 cm, were bilateral, and had surface involvement, hilar involvement and nodularity. These tumors were associated with infiltrative patterns of invasion, signet ring cells, small glands/tubules and single neoplastic cells. Primary mucinous carcinoma of the ovary were usually larger, unilateral, had an expansile growth pattern with complex papillae and necrotic luminal debris. Most primary ovarian mucinous tumors are of surface epithelial-stromal origin and exhibit diffuse expression of cytokeratin 7 combined with variable expression of cytokeratin 20 (CK20); this immunoprofile distinguishes them from most lower gastrointestinal tract tumors secondarily involving the ovaries, but this last difference was not used in the above study.

The median survival did not differ significantly between the groups interpreted as primary or metastatic. Longer survival was possibly seen with the absence of- signet ring cells, an infiltrative pattern of invasion, and small neoplastic glands. The study highlighted that the overall survival for women with advanced stage mucinous carcinomas (whether the ovary was the primary or metastatic site) is significantly less than that for women with advanced stage serous carcinoma (median survival of 14 mo *vs* 42 mo, respectively $P < 0.001$).

SEROUS *VS* MUCINOUS CANCERS OF THE OVARY

Natural history

Clinically most primary mucinous carcinoma of ovary are confined to ovary at time of diagnosis; an advanced stage mucinous carcinoma involving the ovary at first diagnosis should be evaluated as possible metastasis from other site, particularly the gastrointestinal tract. In comparison to serous tumors, mucinous tumors of the ovary are usually early stage at diagnosis (early stage: 4% serous *vs* 83% mucinous)[3], with no evidence of occult lymph node metastasis (10% serous *vs* 0% mucinous)[8] and have a higher overall survival (34 mo *vs* 70 mo)[9]. However in advanced stages, the outcome of mucinous tumor is far inferior (Table 1)[2,10].

Table 1 outcome of advanced stage mucinous tumor compared to other histological subtypes

Advanced stage	Mucinous subtype	Other histology
Hess *et al*[2]	Mucinous	Non mucinous
Progression free survival	5.7 mo	14.1 mo
Overall survival	12 mo	36.7 mo
Winter *et al*[10]	Mucinous	Serous
Progression free survival	10.5 mo	16.9 mo
Overall survival	14.8 mo	45.2 mo

OUTCOME WITH TREATMENT

Early stage disease

The primary treatment for early stage mucinous neoplasm is surgical- that is total abdominal hysterectomy, bilateral salpingo-oophorectomy, and surgical staging as with serous tumors. In patients who have undergone a thorough staging laparotomy and in whom there is no evidence of spread beyond the ovary, the uterus and contra lateral ovary can be retained in women who wish to preserve fertility. Early stage mucinous tumors originate from a genetically stable precursor lesion, frequently from a borderline tumor and have an indolent course. In contrast high grade early stage serous tumors arise from a precursor lesion in distal fallopian tube, called STIC (serous tubal intraepithelial carcinoma)[11] and have poorer outcome due to cytogenetic instability[12]. Hence there is a questionable role of adjuvant chemotherapy or radiotherapy in early stage (1A-B) mucinous tumors.

Advanced disease

Response to platinum based chemotherapy-first line setting: In one of the earliest study in 2004 by Hess *et al*[2], where the outcome of advanced mucinous tumor was compared with non mucinous ovarian tumor with standard platinum based chemotherapy, the response rate and survival was far worse in advanced mucinous group. In their study the outcome of eighty-one patients (27 mucinous, 54 non mucinous) treated with platinum-based regimens was analyzed. The response rates for mucinous and non mucinous tumors were 26.3% and 64.9%, respectively. Median progression-free survival was 5.7 mo *vs* 14.1 mo and overall survival was 12.0 mo *vs* 36.7 mo for mucinous and non mucinous tumors, respectively. Other studies also showed poor response rate of mucinous tumors to platinum based chemotherapy, and the response rate was inferior to serous tumors (Shimada *et al*[13]:

mucinous 12.5% *vs* serous 67.7% and Pectasides *et al*[14]: mucinous 38.5% *vs* serous 70%).

Response to platinum in the recurrent setting: The Study of an Ovarian Cancer cohort Recurred After first-line Treatment: a retrospective Survey[15] showed that mucinous ovarian carcinoma have a poorer prognosis compared with other histological subtypes with platinum based chemotherapy in recurrent platinum sensitive setting, with lower response rate (36.4% *vs* 62.6%), median progression free survival (4.5 mo *vs* 8 mo) and overall survival (17.9 mo *vs* 28.8 mo) in recurrent setting. Other studies[16] also showed poor response of mucinous ovarian cancer to chemotherapy both in the first-line and in the recurrence settings. No response was observed to platinum/paclitaxel retreatment in patients with very late recurrence and no response to liposomal doxorubicin or topotecan was observed in platinum-refractory/resistant patients treated as second- or third-line chemotherapy.

MOLECULAR BIOLOGY

The differences in the natural history and outcome with treatment between mucinous and serous cancers may be due to the differences in the molecular biology of the tumors. About 50% of mucinous ovarian carcinomas had *KRAS* mutations, compared to only 5% of serous ovarian carcinomas. *BRCA1* and *BRCA2* mutations are thought to play a significant role in the development of serous ovarian carcinomas but not mucinous ovarian carcinomas. Mutations in *p53* have been found in almost 60% of serous tumors but only 16% of mucinous tumors. With better understanding of molecular pathways, ovarian tumors are classified into two subtypes: type I tumors which typically involve mutation in genes such as *KRAS*, *BRAF*, *PTEN* and *PI3K* pathway and type Ⅱ tumors which involve mutation in genes such as *p53* and *BRAC1* and *BRAC2*. Mucinous tumor and low grade serous tumor are classified under type I tumor, whereas high grade serous tumors are classified under type Ⅱ tumor. These differences are also seen in the immunohistochemical studies where mucinous tumors are more likely to express E-cadherin (62% *vs* 4%) and less likely to stain positive for N-cadherin (8% *vs* 68%). Carcinoembryonic antigen which is a well known marker for gastrointestinal malignancy is expressed as a serum marker in mucinous tumors (CEA: 88% mucinous *vs* 19% non mucinous) whereas CA 125 is less likely to be expressed[3]. Interestingly the KRAS/BRAF pathway which is involved in pathogenesis of mucinous tumors is also involved in pathogenesis of colorectal malignancies.

CHANGING PARADIGM

Both mucinous carcinomas of the ovary and colorectum have led to the same dilemma. Hence there is an urgent need for considering testing and adoption of therapeutic approaches tailored to molecular characteristics of mucinous carcinomas, irrespective of organ site, so that patient survival can be optimised.

Hess *et al*[2] in his study had highlighted the need for specific alternative therapeutic approaches for mucinous tumors, perhaps involving fluorouracil-based chemotherapy. The role and benefit from 5-flourouracil and its oral analogue has been shown by Sato *et al*[17] in advanced or recurrent mucinous ovarian cancer.

Based on *in vitro* sensitivity of these tumors to irinotecan[18], Shimizu *et al*[19] conducted a phase Ⅱ trial in platinum refractory mucinous carcinoma and showed a response rate of 52% and median overall survival of 15.3 mo with irinotecan and mitomycin.

In a prospective phase Ⅱ study of heavily pretreated patients with ovarian cancer, 5-fluorouracil and oxaliplatin was found to have a clinical efficacy rate of 58% (overall response rate of 29% and stable disease of 29% by Response Evaluation Criteria in Solid Tumors criteria)[20]. This regimen also has been evaluated in ovarian cancer cell lines (MN-1, OMC-1, RMUG-L, RMUG-S, TU-OM-1) and was found to be additive or synergistic[17].

CONCLUSION

In the past the standard treatment for all advanced stage epithelial ovarian cancer was cytoreductive surgery followed by standard postoperative treatment with platinum based chemotherapy.

Unfortunately, recent data have confirmed what many clinicians have long suspected: that mucinous ovarian cancers do not respond to the standard platinum based chemotherapy routinely employed in the malignancy and both progression- free and overall survival are substantially shorter for mucinous subtypes compared to other epithelial ovarian morphologies.

Of interest, the majority of documented mucinous ovarian cancers appear to be localized to the ovary at diagnosis and surgically resectable, but when revealed to be metastatic at presentation, or if recurrence is experienced, the prognosis is very poor. Molecular explanation involving difference in oncogenes and tumor suppressor gene expression and mutation may account for this discrepancy. In advanced mucinous ovarian cancers (metastatic/recurrent), an argument can be made to use a chemotherapy regimen known to be active in colon cancer (e.g., 5 flourouracil with oxaliplatin- or irinotecan), although unfortunately there is currently a paucity of evidence suggesting such an approach will be beneficial in advanced stage mucinous cystadenocarcinoma.

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TOPIC HIGHLIGHT

Chibuike O Chigbu, MD, *Series Editor*

Trends in cervical cancer screening in developing countries

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Abstract

Developing countries suffer the highest burden of cervical cancers but have the lowest resources. Effective cervical cytology screening programme, along with a network of diagnostic and therapeutic colposcopy centres, like developed countries, is almost impossible to be reproduced in developing countries. Visual inspection methods [e.g., Visual inspection with Lugol's iodine (VILI) and Visual Inspection with Acetic Acid (VIA)] which are cheaper, require less expertise and have the advantage of possible treatment in one setting have been shown to be effective alternatives. The sensitivity to detect CIN2+, by VIA and VILI, have been shown to be 80% and 91% respectively, with a specificity rate of 92% and 85% respectively. Screening by human papillomavirus (HPV) testing has high sensitivity (96.4%) but low specificity (94.1%) to detect CIN2+, when compared to Pap Smear (sensitivity, 55.4% and specificity, 96.8%). A single lifetime HPV testing in a large unscreened population has been shown to significantly reduce cervical cancer incidence and mortality when compared to cervical cytology, VIA or no screening. HPV testing of self-collected vaginal specimens also helps to overcome religious and socio-cultural barriers towards pelvic examination amongst women in developing countries. Current HPV testing methods are expensive, skill/infrastructure demanding and takes time to produce results. A cheaper HPV test, called careHPV™, which is able to provide results within 2.5 h and requires minimal skill/infrastructure to operate, was designed for use in developing countries. One stop screen and treat facilities using VIA or rapid HPV testing, and cryotherapy, can overcome non-compliance to follow-up which is a major issue in developing countries. Cure rates of 81.4% for CIN1, 71.4% for CIN2 and 68.0% for CIN3 at 6 mo after treatment have been reported. Incorporating telemedicine with cervicography of VIA or VILI or even telecolposcopy, has great potential in cervical cancer screening, especially in countries with vast geographical areas.

Key words: Cervical cancer; Screening; Cytology; Visual inspection with acetic acid; Visual inspection with Lugol's iodine; Human papillomavirus

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EPIDEMIOLOGY AND GENERAL CONSIDERATIONS

World Bank classifies 145 countries in the world with

Gross National Income per capita ranging from less than USD $1005 to USD $12 275 as developing countries[1]. In 1989, a cut-off of USD $6000 has been set as an explicit benchmark to divide between lower-middle and upper-middle income countries[1]. About 80% or 4.8 billion out of the world's 6 billion people live in the less developed regions[2]. To make the situation worse, the burden of poverty is further compounded by high burden of diseases in the less affluent countries. Amongst others, global figures show that more than 85% of cervical cancer cases occur in the developing world and in these countries it remains as the most common cancer among women as opposed to second or third placing elsewhere[3].

Cervical cancer in the less developed regions of the world has an estimated incidence of 453 000 cases per year and death rate of 242 000 cases per year as opposed to the more developed regions of the world whereby the incident and mortality rates are almost 6-7 times lesser[4]. Age Standardise Incidence Rate for cervical cancer in developing countries range from 15 to 55 per 100 000 people compared to less than 10 per 100 000 people in the developed countries[5]. 88% of mortality caused by cervical cancer in 2008 occurred in the developing countries[4]. Many of these countries have limited facilities for cervical cancer screening and treatment such as surgery, chemotherapy or radiotherapy. Resorting to traditional and alternative treatments or even just "waiting to die" are not uncommon in these places. Early detection and treatment will inevitably reduce the burden of the disease in these resource limited nations. Effective national Papanicalou Smear screening has been shown to reduce cervical cancer incidence by 80% only when it has at least 70% coverage which is unrealistic in many developing countries[6-8]. Stage per stage, morbidity and mortality of cervical cancer is significantly reduced the earlier the treatment is instituted and thus the importance of early and effective screening. The aim of this review is to provide a comprehensive and in-depth overview of the trends in the methods of screening for cervical cancers in developing countries.

CERVICAL CYTOLOGY

History

The basis of cervical cytology methods of screening for cervical cancer was described by Dr. George Papanicolaou[9,10] since the early 19th century and is commonly known nowadays as Pap Smear or less commonly, Papanicolaou Smear. Even though the effectiveness of cervical cytology has never been analysed in randomised controlled trials, sufficient evidence from observational studies has led to its widespread adoption as the main cervical cancer screening strategy across the world[11-14]. From its initial description of using a rubber suction bulb with curved glass pipette onto the posterior vaginal fornix and subsequently ether-alcohol cellular fixation on the microscope slide, the current technique has evolved into using Ayre's spatula or cervical brush directly onto the cervix and cellular fixation on the microscope slide using alcohol/ether-alcohol or newer cellular stabilization agents (e.g., CytoFix®)[15]. It is interesting to note here that a Cochrane Review found no difference in the diagnostic outcome of both the Ayre's spatula and spatula's with extended tips (e.g., Aylesbury) even though the former collected less endocervical cells[16].

Liquid based cytology

Apart from Pap Smear which is also referred to as the conventional method, liquid based cytology is another method of cervical cytology employing similar method of collecting cervical cells with a cervical brush which is then washed into a liquid fixative solution (e.g., ThinPrep®, SurePath™) and finally vortexed, filtered and monolayer plated in the cytology laboratory[17,18]. Additionally, these liquid based specimens can be utilised further for human papillomavirus (HPV), gonorrhoea and chlamydia testing[19,20]. Generally, despite some conflicting large scale research outcomes, the common opinion is that the liquid based cytology is better than conventional smears in the sense of specimen adequacy, detection of glandular abnormalities, possibility of additional tests and overcoming blood/other contaminants in the smear[21,22]. However, liquid based cytology solutions are patented and additional laboratory facilities are needed to process these samples. Altogether, they add a significant cost to cervical cytology screening programme and thus, liquid based cytology is neither a suitable alternative nor is there any established programme employing this technique among developing countries.

Feasibility

Traditionally, performing cervical cytology screening involves three visits (when abnormality is detected), namely initial cervical smear, colposcopic diagnosis usually with biopsy and finally definitive treatment depending on the biopsy result[23]. At each step, there will also be communication of the test results to the patient. Thus, despite being available in developing countries, cervical cytology screening tend to be an expensive exercise and frequently impractical as it involves a relatively sophisticated infrastructure and system, skilled personnel (colposcopists, cytotechnicians, cytopathologists *etc.*), functional referral and communication system, transportation and loss of wages issue for multiple attendance and consequently non compliance by the patients[24]. A cost-effectiveness analysis of different modalities of cervical screening in developing countries has shown that the most cost-effective strategies were the ones that required least visits, which have shortest linkage to treatment and relied less on laboratory facilities[25]. These criteria are not completely fulfilled by cervical cytology screening. Moreover, cervical cytology by Pap Smear technique showed low sensitivity, even at the lowest cut off of atypical squamous cells of undetermined significance for CIN2+ (57%; 95%CI: 38%-76%) but the specificity was rather high (93%; 95%CI: 89%-97%)[26]. Visual inspection methods described below which are widely advocated for

Figure 1 Visual inspection with Lugol's iodine: staining patterns associated with negative (-) and positive (+) test outcomes[30] (reproduced with permission from John Wiley and Sons).

cervical cancer screening in developing countries, have higher sensitivity rates but lower specificity compared to Pap Smear[27].

VISUAL INSPECTION OF THE CERVIX

Visual inspection with Lugol's iodine

Interestingly, naked eye inspection of the cervix stained with Lugol's iodine, known as the Schiller's test, is historically (since 1930s) the first described method of cervical screening[28,29]. Visual inspection with Lugol's iodine (VILI) is similar to Schiller's test whereby Lugol's iodine solution is applied onto the cervix and visualized with the naked eye to identify mustard-yellow iodine non-uptake areas on the cervix[30]. The abnormal cervical epithelium which contains little or no glycogen will not stain black with Lugol's iodine but remains colourless, pale or stained mustard-yellow[31]. A meta-analysis of 11 cross sectional studies involving over 58 000 women in Africa and India showed VILI to have a sensitivity of 91% (95%CI: 88%-94%) and specificity of 85% (95%CI: 81%-88%) for the detection of CIN2 or worse[26]. Despite these impressive numbers, only few colposcopists employ this technique as Lugol's iodine staining of the cervix is considered to be less refined, tends to obscure finer details and is less acceptable to the woman if it stains her clothes compared to acetic acid. However there is no published data to support this perception. A pilot study amongst field health workers (non-specialists) trained to perform cervicoscopy however reports that it is easier to detect the colour patterns produced by iodine staining rather than acetic acid[30] (Figure 1).

Visual inspection with acetic acid, direct visual inspection, speculoscopy and unaided visual inspection

Another technique of visual inspection with the naked eye is Visual Inspection with Acetic Acid (VIA); also known as Acetic Acid Test (AAT) or Vinegar Acid Test. VIA is often interchangeably used with the term cervicoscopy even though in the strictest sense, cervicoscopy simply means visualizing the cervix with the naked eye after applying a staining solution and should be applicable to VILI as well[32,33]. A task force by the International Academy of Cytology has recommended the usage of the term Direct Visual Inspection (DVI) to mean inspecting the cervix with naked eye after application of 3%-5% acetic acid[34]. DVI with a special chemiluminescent light and using magnification is called speculoscopy[35]. A large trial involving more than 1100 patients in South Africa showed no added benefit in using this technique and the usage of the special light increases its cost[36]. DVI should not be confused with Unaided Visual Inspection (UVI) which is visual inspection of the cervix without using any staining solution, also known as "downstaging", which is

now a discarded stand alone technique due to its unacceptable inaccuracies in detecting cervical disease[37]. The term VIA will be used in this paper in keeping with its more popular usage.

In VIA, acetic acid of 3%-5% concentration, depending on the centre, is applied onto the cervix and the cervix is visualized to identify the acetowhite areas which are concentrated in the abnormal cervical epithelium[38,39]. Abnormal epithelium usually have higher content of precipitated nuclear protein due to hyperchromasia which prevents the reflection of the underlying pink stroma with rich blood vessels and thus appears white[39]. A meta-analysis involving 26 studies where VIA was utilised for primary screening showed that VIA has a sensitivity of 80% (range: 79%-82%), specificity of 92% (range: 91%-92%) and positive predictive value of 10% (range: 9%-10%) for the detection of CIN2 and worse[40]. Despite having less sensitivity than VILI (but higher than cytology), VIA has rapidly gained popularity in many developing countries. An attractive feature of cervical screening by VIA is the short duration of time needed to train non-physician field health workers, ranging from 7 to 21 d which is very useful in resource limited developing countries especially if it has vast geographical areas with large population[30,41]. However, a large trial involving 34 087 women undergoing VIA in India by non-physician field health workers reported issues of declining rates of cervical abnormality detection, implying progressive drop in skills and the need for yearly re-training[42,43].

Frequently, cervical cancer screening facilities in developing countries face the issue of concurrent sexually transmitted diseases amongst the women being screened. A study amongst 2754 women in South Africa has also shown that the efficacy of VIA is not affected by co-existing *Neisseria gonorrhoeae*, *Trichomonas vaginalis* or *Chlamydia trachomatis* infection of the genital tract but the presence of HIV infection significantly decreased its specificity[44]. Due to the wider availability of affordable anti-retroviral therapy, more women with HIV are living longer and cervical cancer screening strategies need to be tailored accordingly[45-47]. Despite its limitations amongst patients with HIV, VIA still seem to perform better than cytology in this group. In a recent cross-sectional study involving 303 HIV-positive women, Sahasrabuddhe *et al*[48] have showed that at CIN2+ disease threshold, the sensitivity, specificity and positive and negative predictive value estimates of VIA were 80.0%, 82.6%, 47.6% and 95.4%, respectively, compared to 60.5%, 59.6%, 22.4% and 88.7% for the atypical squamous cells of undetermined significance or severe (ASCUS+) cut-off on cytology, 60.5%, 64.6%, 24.8% and 89.4% for the low- grade squamous intraepithelial cells or severe (LSIL+) cut-off on cytology and 20.9%, 96.0%, 50.0% and 86.3% for high-grade squamous intraepithelial lesion or severe (HSIL+) cut-off on cytology.

Various other problems are present in visual inspection of the cervix strategies. Squamo-columnar junction where pre-cancerous lesions commonly occur, tend to migrate inward into the endocervical canal with increasing age. Contrary to cytology where shed cells from deep inside the endocervical canal may be picked up; direct visualization can be increasingly difficult in older women in order to obtain adequate view of the transformation zone. Training non-physician health workers to use the endocervical forceps can become more technical even though it is not impossible. Real world performance may differ from the promising figures of controlled research settings. Variations in defining acetowhite or Lugol's non-uptake area will alter efficacy rates amongst centres, issues of training and re-training standards need to be addressed and quality control strategies need to be incorporated (Figure 2).

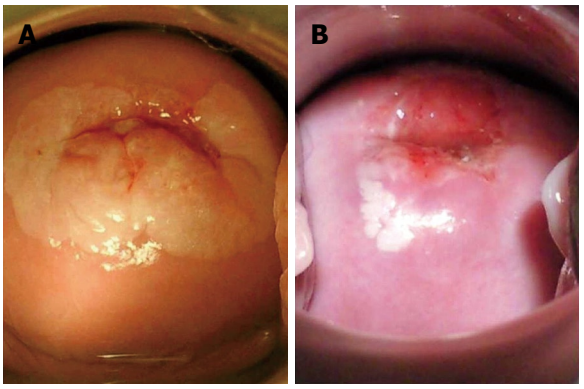

Figure 2 Positive acetowhite lesions (A = transient acetowhite area; B = dense acetowhite lesion) after Visual Inspection With Acetic Acid with the application of 4% acetic acid to the cervix for 3 min[73] (reproduced with permission "Copyright (2011) Royal Society of Medicine Press, United Kingdom").

VIAM

Low level magnification (2-4.5 ×) using hand held devices (e.g., Gynoscope, AVIscope or just ordinary magnifying lense) in conjunction with VIA, also known as VIA with magnification or VIAM, has been trialled in India, South Africa, Mexico, Peru, Costa Rica and a few other developing countries with the hope of increasing the efficacy of VIA[45,49-53]. However, these trials have shown that low level magnification did not give any added benefit to VIA. A meta-analysis of 3 studies involving over 18 000 patients has shown that VIA has a pooled sensitivity and specificity of 60.3% (95%CI: 53.6%-66.7%) and 86.8% (95%CI: 86.3%-87.3%) respectively, in detecting high-grade squamous intraepithelial lesions (HSIL)[49]. VIAM on the other hand, showed a sensitivity of 64.2% (95%CI: 57.6%-70.4%) and specificity of 86.8% (95%CI: 86.2%-87.3%)[49]. There are no reported trials of magnification techniques using VILI.

Cervicography

Taking digital or 35-mm photographs of the cervix after the application of acetic acid which is referred to as cervicography producing cervicographs/cervicograms/cervigrams has also been trialled in developing countries. It

was first introduced by Adolph Stafl in 1982[54]. There are no published studies assessing the usage of cervicography after the application of Lugol's iodine even though technically it utilises the same principles. It has been evaluated both as a primary screening tool and as an addition to other screening methods. A large trial involving 8640 women in Costa Rica showed that cervicography has an overall sensitivity of 49.3% and specificity of 95.0% in detecting high-grade squamous epithelial lesions or cancer, as opposed to 77.2% sensitivity with 94.2% specificity for cytology in the same study[55]. Cervicography was particularly not recommended for postmenopausal women in this study as it only had a sensitivity of 26.9% for women 50 years of age and older[55].

HUMAN PAPILLOMAVIRUS TESTING

Human papillomavirus tests

Since the establishment of persistent high risk HPV infection as a precursor for cervical cancer, various techniques of detecting them either for triaging, co-testing, test of cure or primary screening have been developed. Currently, the following tests which detects presence/absence of or identifies specific types of high risk HPV (DNA or E6/E7 viral messenger RNA) in cervical specimen, have been approved by the United States Food and Drug Administration; Hybrid Capture® 2 (HC2; detects DNA presence/absence of 13 HPV types), Cervista™ HPV HR test (detects DNA presence/absence of 14 HPV types), Cervista™ HPV 16/18 (specifically detects DNA presence/absence of HPV 16/18), cobas HPV test (identifies specific HPV16 and HPV18 DNA and a pooled result of DNA presence/absence of 12 other HPV types) and Aptima® mRNA test (identifies messenger RNA of 14 HPV types)[56]. The Canadian Cervical Cancer Screening Trial involving 10154 women has shown that the sensitivity of HPV testing for detecting CIN2+ was 94.6% (95%CI: 84.2%-100.0%) and the specificity was 94.1% (95%CI: 93.4%-94.8%) compared to 55.4% (95%CI: 33.6%-77.2%) sensitivity and 96.8% (95%CI: 96.3%-97.3%) specificity for Pap Smear[57]. Despite its high sensitivity being offset by reduced specificity, HPV testing has been repeatedly trialled as a primary screening tool both in developing and developed countries especially since an Italian study showed an overall reduction of cervical cancer incidence through HPV screening[58]. A study among 2900 women in South Africa has shown that the specificity of HPV testing to detect CIN2+ can be increased to 90% but at the expense of reducing sensitivity to 79% by increasing the positivity threshold (expressed as relative light units per positive control specimen, RLU/PC) from > 1 RLU/PC to > 8 RLU/PC[59].

Single lifetime HPV screening

A large trial involving 131 746 women was performed in India, to compare HPV testing using HC2 as a single lifetime screening strategy *vs* cervical cytology, VIA or standard care which is the control group (i.e., no screening at all which is standard for that population group and geographical area)[43]. The HPV testing group has shown a significantly reduced incidence of cervical cancer and cervical cancer mortality rate compared to cervical cytology and VIA[43]. Cumulative data over 8 years revealed that compared to the control group, hazard ratio for the incidence of cervical cancer was 1.05 (95%CI: 0.77%-1.43%) for HPV testing, 1.34 (95%CI: 0.99%-1.82%) for cervical cytology and 1.30 (95%CI: 0.95%-1.78%) for VIA[43]. Hazard ratio for death due to cervical cancer was 0.52 (95%CI: 0.33%-0.83%) for HPV testing, 0.89 (95%CI: 0.62-1.27) for cervical cytology and 0.86 (95%CI: 0.60%-1.25%) for VIA[43]. The authors also emphasized that the drawback to widespread usage of HPV testing in developing countries is high cost (USD $20-$30 per test), requiring at least 24-48 h to provide the results and need for sophisticated laboratory infrastructure[43].

CareHPV™

A cheap HPV test called careHPV™ (Qiagen, Gaithersburg, USA), which costs around USD $5 per test and able to provide results (detecting 14 high risk HPV types) within 2.5 h, has been developed specifically for usage in low-resource public-health settings to screen women 30 years of age and older[60,61]. It is yet to be marketed commercially. A cross sectional study involving 2388 women in China tested with careHPV™ showed that it had significantly better sensitivity at 90.0% (95%CI: 83.0%-97.0%) and specificity at 84.2% (95%CI: 82.7%-85.7%) for detecting CIN2+ from cervical specimens compared to VIA which showed sensitivity of 41. 4% (95%CI: 29.9%-53.0%) and specificity of 94.5% (95%CI: 93.6%-95.4%)[61]. careHPV™ performed comparably to HC2 and cervical specimens yielded better results compared to self-collected vaginal specimens; all of which were also tested concurrently[61]. A cost-effectiveness analysis from this study results also showed that for a 70% participation rate, once a lifetime screening at the age of 35 years would reduce cancer mortality by 8% (for VIA) to 12% (for careHPV™) over the long term, with a cost-effectiveness ratio of USD $557 (for VIA) to USD $959 (for careHPV™) per life year saved compared to no intervention; referenced to a 2008 GDP per capita in Shanxi Province of USD $2975[62]. Lower cost, easy and shorter learning curve to learn to use the technique, good cost-effectiveness and rapid results make careHPV™ an attractive option for developing countries[63].

HPV test and self-sampling

HPV testing also paves the way for analysing self-collected specimen from the vagina by the women using various methods such as tampon, swab, cytobrush, vaginal lavage or custom made device[64]. No good evidence is available to compare between self-sampling methods. Cultural, re-

ligious and even socio-economic barriers among women (which are particularly prevalent in developing countries) may hinder participation in cervical cancer screening programmes which traditionally requires speculum aided collection of cervical specimen. This was studied in a randomised controlled trial comparing conventional cervical cytology and cytobrush for self-sampling among 25061 Mexican women[65]. This study revealed higher acceptability for self-sampling among women at 98% compared to 89% among women who underwent conventional cytology[65]. It also showed that HPV analysis of self-sampled cervical specimen displayed higher sensitivity, lower specificity and lower positive predictive value compared to cervical cytology for detecting CIN2 or worse[65]. Analysis of 2530 self-collected vaginal specimen using careHPV™ in China showed a sensitivity of 81.4% (95%CI: 72.3%-90.5%) and specificity of 82.4% (95%CI: 80.8%-83.9%) for the detection of CIN2 or worse[61].

SEE AND TREAT (OR REFER)

Detecting cervical pre-cancerous lesions by VIA or presence of high risk HPV by rapid testing methods will enable the provision of immediate treatment or further referral if frank cancer or larger lesions are detected[66]. This is an attractive modality in developing countries where "one stop centres" are useful to overcome issues of communication, recall system failure or unavailability and non-compliance or non-feasibility of multiple visits by the women[67]. The preferred treatment method in this strategy is cryotherapy as it has been shown to have lower and milder complication rates, requires less skill than electrical excision, can be performed by trained non-physician health worker and is cheaper than laser ablation[68-70]. A large trial involving 6555 women in South Africa showed that the prevalence of CIN2+ after 6 and 12 mo, was significantly lower in the VIA and cryotherapy arm, 2.23% (95%CI: 1.57%-2.89%) at 6 mo and 2.91% (95%CI: 2.12%-3.69%) at 12 mo compared to the control group (delayed evaluation), 3.55% (95%CI: 2.71%-4.39%) at 6 mo and 5.41% (95%CI: 4.32%-6.50%) at 12 mo[71]. A study in India where 1026 women underwent VIA and cryotherapy, cure rates of 81.4% for CIN 1, 71.4% for CIN 2 and 68.0 for CIN 3 were reported at 6 mo follow-up[69]. With the availability of rapid HPV testing such as careHPV™ or utilising VIA, along with cryotherapy, "see and treat (or refer)" is a promising avenue for developing countries.

TELECOMMUNICATION

With the aid of modern digital technology, tele-VILI, tele-VIA, tele-cervicography or even tele-colposcopy, either as still digital images or even real-time teleconference images is a reality of the modern era. Utilisation of digital cameras linked to the internet *via* laptop or even multimedia messaging system (MMS) *via* mobile phones, especially modern smartphones, will enable non-physician health workers in remote areas to capture cervical images and transmit them to experts in centralised secondary or tertiary centres for further opinion. This method is adopted in a centre in Zambia and named eC$_3$ (Electronic Cervical Cancer Control)[72]. Limitations of this approach are loss of stereoscopic view and depth perception as the images are 2 dimensional, potential distortions of the images (due to factors such as technique, lighting and camera battery which in turn can cause wrong diagnosis and decisions) and cost of infrastructure, maintenance and repair that can be forbidding in certain countries[72].

CONCLUSION

Large numbers of the world's population live in developing countries where cervical cancer is at endemic proportions and causes most mortality. The successes of developed countries to inhibit cervical cancer rates to very low levels by high intensity cervical cancer screening programmes could not be emulated in low and middle income countries. This is mainly due to economic factors leading to limited health resources, lack of technical expertise and competing interests from more pressing health issues (such as maternal and infant health, infectious diseases like tuberculosis, malaria and HIV/AIDS). Socio-political barriers such as low literacy/education rates, poor access to health facilities, religious taboos, poverty, war and civil unrest, also contribute to this problem. Large proportions of the developing countries' population who are unscreened or under-screened and usually being the ones with higher risk factors for cervical cancer is a huge public health challenge.

Primary prevention of cervical cancer with HPV vaccine is still beyond reach for many poorer countries. Efforts from the GAVI Alliance (formerly the "Global Alliance for Vaccines and Immunisation") and other similar organisations to provide subsidised and even free HPV vaccines in poorer countries will inevitably suppress cervical cancer rates in these countries. In the continuum, the importance of secondary prevention by utilising the most cost-effective cervical cancer screening strategy could not be over emphasized. There is no one technique which will meet the needs of all developing countries and each health authority would need to work in collaboration with the local medical fraternity to determine the best option. Single lifetime HPV testing, careHPV™, VIA, one stop screen and treat centres, self-collecting of vaginal specimen and tele-cervicography seem to offer promising avenues in cervical cancer screening in the developing countries.

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REVIEW

Advanced ovarian cancer: Neoadjuvant chemotherapy plus surgery and HIPEC as up-front treatment

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Abstract

Epithelial ovarian cancer (EOC) is one of the most common malignancies and one of the principal causes of death in gynecological neoplasms. The majority of EOC patients present with an advanced International Federation of Gynecology and Obstetrics stage disease. The current standard treatment for these patients consists of complete cytoreduction and combined systemic chemotherapy of a platinum agent and paclitaxel. Even if the majority of patients with EOC respond to first-line platinum based chemotherapy, almost 20% of them are resistant or refractory. According to these data, the main risk is for a certain number of patients to have undergone cytoreductive surgery (CRS) and subsequent hyperthermic intraoperative peritoneal chemotherapy (HIPEC) in a useful way. Radical surgery, especially in advanced cases, is associated with a high incidence of postoperative morbidity and mortality, which could be increased by the HIPEC. Every effort should be made for previously selected patients to improve outcome and optimize resources. Over the last decade, new options have been introduced to prolong survival. Improved long-term results can be achieved using CRS in combination with intraoperative HIPEC. This combination has also been used in an up-front setting. Controversial outcomes have been reported for neoadjuvant platinum-based chemotherapy. Different papers have been published reporting discordant results. Further studies are needed.

Key words: Epithelian ovarian cancer; Hyperthermic intraoperative peritoneal chemotherapy; Up-front; Neoadjuvant; Treatment; Oncology; Cytoreductive surgery; Chemotherapy

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EDITORIAL

Epithelial ovarian cancer (EOC) is one of the most common malignancies and one of the principal causes of death in gynecological neoplasms. The majority of EOC patients (about 70%) present with an advanced International Federation of Gynecology and Obstetrics (FIGO) stage disease (i.e., Ⅲ or Ⅳ)[1-4]. The current standard treatment for these patients consists of complete cytoreduction and combined systemic chemotherapy of a platinum agent and paclitaxel[5]. The extent of cytoreduction has a direct impact on survival and maximal cytoreduc-

tion was found to be one of the most powerful determinants of survival among patients with stage Ⅲ or Ⅳ EOC in a meta-analysis of almost 7000 patients[6] and in other studies[7-8]. The aim of cytoreductive surgery (CRS) is to remove all the macroscopic disease. Optimal cytoreduction is usually defined as a residual disease of less than 0.5-2 cm. However, it has been demonstrated that the achievement of an optimal cytoreduction, mainly in advanced EOC, is not always possible. Factors which mainly influence suboptimal cytoreduction are: the extent of the disease at the presentation, medical co-morbidities and the surgeon's expertise[9-11]. Sub-optimal and incomplete CRS results in losing the chance to improve survival. In our opinion, however, optimal cytoreduction should no longer be defined as a variable (0.5-2 cm) residual tumor but should be started to be considered as the complete absence of macroscopic residual disease. For this reason, patients should receive treatment only at centers able to undertake complex cytoreductive procedures[12]. Furthermore, phase Ⅲ randomised controlled trials have established the superiority [i.e., improved progression-free survival (PFS) and overall survival (OS) rates] of intraperitoneal cisplatin-based chemotherapy compared to the systemic delivery of the agent for the treatment of small-volume residual advanced EOC[13-15]. Less evidence is available for either medical[16] or surgical[17,18] management of recurrent EOC. Over the last decade, new options have been introduced to prolong survival.

A meta-analysis from Bristow *et al*[18] demonstrated poor outcomes for using neoadjuvant platinum-based chemotherapy instead of primary surgery in advanced EOC. However, this meta-analysis also demonstrated the increase of survival with debulking surgery with a better interval and the negative survival effect of increasing the number of chemotherapy cycles prior to interval surgery. Chua *et al*[19] suggested that the treatment of this malignancy should primarily involve a massive surgical effort for complete cytoreduction and neo-adjuvant chemotherapy (NAC) may be considered in situations where the extension of the disease provokes big limitations to the possibility of achieving a complete cytoreduction[19]. They also excluded the possibility of using the NAC to select a favourable prognostic group of chemo-responsive patients to undergo aggressive surgical cytoreduction[19]. Another meta-analysis by Kang and Nam[20] stated that NAC helps to obtain an increased rate of optimal cytoreduction in patients at a high risk for suboptimal debulking and/or unfavorable general conditions. However, it is not likely that the increased optimal debulking rate with NAC will result in improved survival outcome of patients with advanced EOC. The last meta-analysis by Tangjitgamol stated that no conclusive evidence could be obtained to determine whether NAC would improve or decrease survival rate[9].

A randomized trial comparing primary debulking surgery with NAC in EOC showed that similar OS and PFS may be achieved compared to standard primary debulking and with lower complication and post-operative mortality rate[21,22].

Improved long-term results can be achieved in highly selected patients using CRS, including parietal and visceral peritonectomy procedures, in combination with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC)[23-31]. Recent data from a multi-center phase Ⅱ trial using CRS and HIPEC with cisplatin and doxorubicin in up-front treatment of EOC reported good results[31]. The authors accrued 26 patients over 6 years in 4 different centers, achieving macroscopically complete cytoreduction in 15 patients and only minimal residual disease ($\leqslant$ 2.5 mm) in the remaining 11. Although major complications occurred in four patients, including one postoperative death, 25 of the 26 patients started systemic chemotherapy within a median of 46 d after surgery. A five year OS of 60.7% and a PFS of 15.2% were obtained. Another pilot experience reported good results in using CRS + HIPEC in an up-front setting[30,32]. Literature results are encouraging. In any case, as stated by different authors[18,33], the absence of phase-Ⅲ trials suggests a few considerations before validating CRS + HIPEC as a strategy for up-front treatment of advanced EOC.

Even if the majority of patients with EOC (up to 80%) respond to the first-line platinum based chemotherapy, almost 20% of them are resistant or refractory[17]. According to these data, the main risk is for a certain number of patients to have undergone CRS and subsequent HIPEC in a useful way. Radical surgery, especially in advanced cases, is associated with a high incidence of postoperative morbidity and mortality[34-36], which could even be increased by the HIPEC. HIPEC remains a burdensome procedure: every effort is needed to select patients who will achieve the maximum benefit from it. NAC brings, as a marginal effect, the "*ex-iuvantibus*" determination of chemo-sensitivity of the tumor. This could have a few advantages: for those patients who will certainly not benefit from HIPEC, not to have it. Even if NAC followed by CRS + HIPEC does not show better results in terms of PFS and OS[21,22], valuing the patients' response to NAC could be a strategy to select the patients who showed a chemo-sensitivity to platinum and taxanes for HIPEC only. NAC, by reducing the surgical load, should allow surgery to result in no residual tumor in the vast majority of this set of patients; less required radical surgery is associated with lesser peri-operative complications, permitting a shorter recovery before starting adjuvant chemotherapy; and lastly, this strategy could be offered to a high proportion of women with advanced EOC[2,5].

There are a few studies reporting a total of 334 patients with primary EOC treated with CRS and HIPEC in an up-front setting[1,16,24-30,37-41]. All these phase Ⅱ observational studies included patients where in most cases a great surgical effort has been necessary and the chemo-sensitivity state was unknown: in only 107 cases (36.3%) the patients had undergone NAC to test *in vivo* chemo-sensitivity before CRS + HIPEC.

Bearing in mind the advantages of HIPEC associated with CRS, randomized controlled trials (RCTs) testing its

efficacy have been requested by many clinicians at all time points of the natural history of advanced EOC, especially in up-front settings[6,13,14], as already has been done for colon and gastric cancer[42,43].

Actually, there are five ongoing RCTs evaluating the effectiveness of CRS and/or HIPEC in primary or recurrent EOC[15,44-46]. The one proposed by The Netherlands Cancer Institute (OVHIPEC trial) is intended to evaluate the efficacy of secondary cytoreduction with or without HIPEC[46]. In this study, HIPEC is used in an up-front setting after primary chemotherapy. In our center, a RCT called CHORINE (Cytoreduction and Hipec in the treatment of OvaRIaNcancEr) is starting. This study is a multicenter phase Ⅲ prospective RCT, comparing CRS + HIPEC (cisplatin + paclitaxel) *vs* CRS alone in Stage ⅢC unresectable EOC with partial or complete response after 3 systemic cycles of carboplatin + paclitaxel (NAC), followed by a further 3 cycles of carboplatin + paclitaxel (adjuvant chemotherapy). The primary outcome is two year disease-free survival. Only patients with complete or partial clinical response after the 3 cycles of neoadjuvant therapy are eligible for the study and, after signing the informed consent form, are submitted to CRS with radical intent. The randomization (HIPEC *vs* no HIPEC) will be applied after adequate CRS (residual tumor ⩽ 2.5 mm): patients with suboptimal cytoreduction (residual tumor > 2.5 mm) are not suitable for randomization and will be excluded.

Paclitaxel has been demonstrated to be effective and safe in intraperitoneal hyperthermic use. Different *in vitro* and *in vivo* studies showed that hyperthermia enhances the cytostatic and cytotoxic effect of paclitaxel[47-50]. This drug's characteristics make it a very good candidate to be administered intraperitoneally[51]. Some authors suggest a lower complication rate when paclitaxel is administered in a mono-therapy regimen[52].

On one hand, the advantages of the CHORINE study would be the following: firstly, NAC selects only patients for inclusion in the study in whom there is a clinical response (test of *in vivo* chemosensitivity) and then a response to HIPEC is expected; secondly, the response to NAC should reduce the cytoreductive effort, increasing the occurrence of complete CRS and presumably lowering the morbidity. The reduction of the surgery load after the NAC has been demonstrated to reduce the morbidity but to not influence the OS and the DFS. This probably happens because the macroscopic disease reduced by the NAC is not completely healed. The remnant microscopic disease could be the main cause of disease early progression. The HIPEC treatment has the precise role to reach the diffuse microscopic disease to complete the surgery effort. This is the reason platinum-paclitaxel based chemotherapy is administered. No study has used this combination before; thirdly, the only variable in the study is HIPEC, making it possible to evaluate its effectiveness regardless of CRS, because a radical and complete cytoreduction would be required in either the experimental arm or the control group, as suggested by many authors in the literature[6].

On the other hand, the major limitation of the study is that the control group is not the recognized standard treatment for advanced EOC, namely maximal CRS followed by systemic platinum-based adjuvant chemotherapy. The CHORINE study has already been approved by our review board and we are in the process of completing the administrative requirements and recruiting other participating centers.

CONCLUSION

In conclusion, few studies point out the favorable results in terms of survival after up-front CRS and HIPEC for advanced EOC, but we believe that in the up-front setting, NAC can better select chemoresponsive patients, thus reducing the surgical stress and perioperative complications. Furthermore, by reducing the disease diffusion in responsive patients, NAC could facilitate the dissection and reaching of a real completeness of cytoreduction, evaluated as no macroscopic residual of disease.

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MINIREVIEW

Ethnic disparities: Genetics *vs* (social) environment

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Abstract

To define "ethnicity" in the context of perinatal care is a tough job. The word makes us think: "racial, social, cultural, national…". An ethnic group is generally considered a group of people with a common history, usually (but not always) a common religion and language, sharing aspects of culture such as nutrition and traditions concerning pregnancy, childbirth, the way they care for children. As procreation occurs mostly in-group, every ethnic group will demonstrate a higher prevalence of, more or less well-known, genes and their connected diseases. For some populations, such as Ashkenazi Jewish people, the prevalence and associated risks of these autosomal diseases are well known, as in the case of "Jewish genetic disease", and specific screening programs are available.

Key words: Ethnicity; Perinatal care; Genetic disease; Tradition; Vitamin D

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To define "ethnicity" in the context of perinatal care is a tough job. The word makes us think: "racial, social, cultural, national…". An ethnic group is generally considered a group of people with a common history, usually (but not always) a common religion and language, sharing aspects of culture such as nutrition and traditions concerning pregnancy, childbirth, the way they care for children. As procreation occurs mostly in-group, every ethnic group will demonstrate a higher prevalence of, more or less well-known, genes and their connected diseases. For some populations, such as Ashkenazi Jewish people, the prevalence and associated risks of these autosomal diseases are well known, as in the case of "Jewish genetic disease", and specific screening programs are available. Sometimes health risks during pregnancy, such as vitamin D deficiency in dark skinned women wearing a veil and living in Western Europe[1], are easy to predict. However, it can be extremely difficult unraveling genetics from risk exposure to external stimuli or differences in reporting in different ethnic populations[2].

In general it is ethnic minorities that are considered to be at high risk for complications, although this is probably due to a mistaken way of thinking, as we always tend to compare the minority (as the problematic exception) to the "standard" majority. The contrary can actually be the case: we have demonstrated in the past that it is the autochthonous group in Belgium that has a higher risk for preeclampsia and interventions such as induction of labour resulting in (iatrogenic) secondary cesarean section[3] than minorities from Mediterranean and African origin. The same is true for cardiovascular disease.

In demographic studies, genetic and socio-economic factors can often be associated with central variables of interest, such as stillbirth rate, sex ratio at birth, twinning rate, *etc*. Which exogenous factors influence these variables? Is it the genetic or the socio-economic factors

which are the dominant ones? In heterogeneous populations there are often strong association between genetic, socio-economic and geographic factors. Consequently, it is difficult to identify the primary factor. Superficial analyses may erroneously identify a factor which is not the dominant and most important one.

Not only can the condition itself be more or less prevalent depending on the ethnic group, but the expression and way of presentation can also differ. It has long been known that hypertensive complications of pregnancy occur more often in women of African descent, but what is less known, especially to western gynaecologists lacking experience with tropical medicine, is that in these women the classic complications seen in white western women, such as hemolysis, elevated liver test and low platelets (HELLP syndrome), seldom occur. This misunderstanding can result in under-treatment of these women and a worse outcome[4].

Ethnic minorities often demonstrate a higher preterm birth rate, although this is not always the case. Both Moroccan and Turkish migrants in Belgium demonstrate a lower preterm birth rate than the autochthonous population[3], a finding that is in contradiction with data from other countries such as Germany[5]. The causes of these differences are still not clear, whether they are purely socioeconomic or environmental, due to a different immune response and genetically determined inflammatory reaction or any combination of these factors. Our knowledge is as fuzzy as the definition of "ethnic", one should not be surprised that no clear conclusions can be drawn from unclear concepts.

The most disturbing conclusion of most studies on the obstetric outcome of ethnic minorities, is that in the western world these minorities almost always show an increased infant mortality. It is hoped that these differences will disappear with increasing integration of different ethnic groups, and we have noted the disappearance of the increased rate of perinatal mortality in Belgium for Turkish women. Unfortunately this observation can not be generalized as, for instance, Moroccan women in Belgium continue to loose their baby twice as often as autochthonous or Turkish women[3]. The disparities in infant mortality are due to more than just ethnic differences. As noted by Hauck *et al*[6], the greater incidence in minorities is related to a complex interaction of behavioral, social, political, genetic, medical, and health care access factors. Recently it has become clear that there is no real border between genetics and environment, and the further development of our understanding of epigenetics will teach us more about ethnicity and pregnancy complications[7,8].

In the near future countless studies on ethnicity will continue to be carried out. However important these are in increasing our understanding and helping us to deliver health care that is appropriate and fit for those receiving it, we must never forget how transient these findings will continue to be, the more so as ethnicity has never been and will never be a solid concept, but constitutes an ever shifting and sliding part of our evolution as a society.

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Events Calendar 2012

January 26-30, 2012
55th All India Congress of Obstertrics and Gynaecology -2012
Banaras Hindu University, Varanasi, India

March 27-31, 2012
2012 American College of Medical Genetics Annual Clinical Genetics Meeting
Charlotte, NC, United States

May 3-5, 2012
Breast 2012 - IMPAKT
Brussels, Belgium

May 9-11, 2012
III Regional Conference of the Society of Obstetrics and Gynecology
Merida, Venezuela

May 9-12, 2012
EBCOG 2012 - 22nd European Congress of Obstetrics and Gynaecology
Tallinn, Estonia

May 9-12, 2012
19th European Congress on Obesity
ECO2012
Lyon, France

May 10-12, 2012
ESSIC Annual Meeting
Porto, Portugal

May 17-19, 2012
Advances in Health Care for Women Over 40
Las Vegas, NV, United States

May 17-20, 2012
CPP 2012 - The 2nd International Meeting on Cardiac Problems in Pregnancy
Berlin, Germany

May 24-26, 2012
7th Brasilian Congress on Menopause and Climacteric
Sao Paulo, Brazil

June 5-8, 2012
10th RCOG International Scientific Congress (Royal College of Obstetricians and Gynaecologits)
Kuching, Sarawak, Malaysia

June 7-9, 2012
11th European Meeting Days of the French Society of Ginecology
Paris, France

June 13-16, 2012
XXIII European Congress of Perinatal Medicine
Paris, France

June 20-23, 2012
12th ESC Congress- Myths and misconceptions versus evidence on contraception
Athens, Greece

July 1-4, 2012
28th Annual Meeting of the European Society of Human Reproduction and Embriology
Istanbul, Turkey

July 5-6, 2012
British Gynaecological Cancer Society Annual Meeting
Londres, Cuba

July 7-14, 2012
33rd World Medical and Health Games - Antalya 2012
Antalya, Turkey

July 19-22, 2012
16th World Congress on Controversies in Obstetrics, Gynecology & Infertility (COGI)
Singapore, Singapore

August 5-8, 2012
Office Gynecology
Snowmass, CO, United States

August 6-10, 2012
XXXIX Ob Gyn national congress
Guatemala, Guatemala

September 5-8, 2012
21st Society of Laparoendoscopic Surgeon Annual Meeting and Endo Expo 2012
Boston, MA, United States

September 11-14, 2012
21st Annual Congress ESGE (European Society for Gynaecological Endoscopy)
Paris, France

September 19-21, 2012
3rd Congress of Neonatology and 1st Congress of Reproductive Medicine
Ciudad de Panama, Panama

September 20-22, 2012
11th Congress of the European Federation of Sexology
Madrid, Spain

September 24, 2012
Recent Updates in the Reproductive Endocrinology and Infertility International Symposium & Workshop
Riyadh, Saudi Arabia

October 3-6, 2012
23rd Annual Meeting the North American Menopase Society (NAMS)
Orlando, FL, United States

October 5-7, 2012
2012 International Conference on Stillbirth, SIDS/SUID and Infant Survival
Baltimore, Maryland

October 7-12, 2012
XX FIGO World Congress of Gynecology and Obstetrics
Rome, Italy

December 10-13, 2012
National Association of Nurse Practitioners in Women's Health 15th Annual Conference
Orlando, FL, United States

October 11-14, 2012
The 15th congress on Controversies in Obstetrics, Gynecology and Infertility (COGI) congress on Building Consensus in Gynecology, Infertility and Per
Barcelona, Spain

October 12-13, 2012
1st International Medical Congress Woman and Man. Healthy Aging
Warsaw, Poland

October 13-16, 2012
IGCS 2012 - 14th Biennial Meeting of the International Gynecologic Cancer Society
Vancouver, Canada

October 17-20, 2012
Central Association of Obstetricians and Gynecologists 2012 Annual Meeting
Chicago, IL, United States

October 17-20, 2012
International Convention Of Pan-American Medical Women´s Alliance.
Guadalajara, Mexico

November 7-9, 2012
Controversies in Obstetrics, Gynaecology and Sterility International Congress
Valencia, Spain

November 8-11, 2012
17th World Congress on Controversies in Obstetrics, Gynecology and Infertility
Lisboa, Portugal

November 15-18, 2012
The 3rd World Congress on Building Consensus in Gynecology, Infertility and Perinatology (BCGIP): Controversies in Obstetrics, Gynecology and Infertility (COGI)
Delhi NCR, India

November 28-30, 2012
13th Annual Congress of the Asia Pacific Association for Gynecological Endoscopy and Minimally Invasive Therapy
Pattaya, Thailand

December 12-14, 2012
5th International Symposium on Assisted Reproduction
Madrid, Spain

December 14-15, 2012
18th Annual Conference on Challenges in Gynecology
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November 14-16, 2012
19th International Council on Women's Health Issue Congress
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GENERAL INFORMATION

World Journal of Obstetrics and Gynecology (*World J Obstet Gynecol*, *WJOG*, online ISSN 2218-6220, DOI: 10.5317) is a bimonthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 100 experts in obstetrics and gynecology from 33 countries.

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Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJOG* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJOG* is an OA journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJOG* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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

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