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REVIEW

Care of survivors of gynecologic cancers

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Abstract

The number of cancer survivors is increasing and most healthcare providers will manage patients who have completed therapy for malignancy at some point. The care of survivors of gynecologic malignancies may seem daunting in a busy general gynecology practice. This paper intends to review the literature and suggest management of these women for the general gynecologist.

Key words: Survivorship; Gynecologic cancer; Cancer surveillance; Female reproductive malignancy; Cancer survivor

Core tip: As the number of cancer survivors increases, the gynecologist will increasingly care for women with a history of cancers of the reproductive tract. This paper will review survivorship care of gynecologic cancer survivors in the benign gynecologist's office.

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INTRODUCTION

Advances in cancer diagnosis and treatment have led to a steady increase in the number of cancer survivors, a population with unique physical, psychosocial and economic needs. In recent decades, coordinated efforts have focused on understanding this population and on enhancing the length and quality of life of survivors. In 1996 the National Cancer Institute created the Office of Cancer Survivorship, and in recent decades increasing research has investigated diverse aspects of survivorship[1-3].

An individual is considered a survivor from the time of cancer diagnosis for the remainder of his or her life.

The survivorship experience can be divided into phases including an acute treatment phase, an intermediate survivor phase, and a long-term survivor phase. Caregivers are also included as survivors, as their lives may be affected significantly by others' cancer diagnoses. General survivorship care encompasses surveillance of the primary malignancy, managing complications of the cancer or its treatment, risk reduction and screening for second malignancies, and assessment of overall quality of life and psychosocial well-being[1,3].

The number of gynecologic cancer survivors has grown substantially in recent decades, most notably amongst those diagnosed with early stage disease. In the United States there are currently an estimated 625000 survivors of endometrial cancer, 244000 survivors of cervical cancer, and nearly 200000 survivors of ovarian cancer, in total accounting for about 15% of all female cancer survivors[1]. As the number of cancer survivors increases, the general gynecologist can expect to care for women with a history of female genital cancers. Herein we will review literature relevant to gynecologic cancer survivors and offer practical guidance to the non-oncologist caring for these patients. After all, gynecologic cancers combined are the fourth most common cancer type amongst survivors after breast, prostate and colorectal cancers, and the second most common amongst women.

EFFECTS OF GYNECOLOGICAL CANCER AND TREATMENT

Psychosocial issues

Attempting to understand and address the psychosocial challenges faced by cancer survivors is an established and important aspect of survivorship care and research[3]. Proceeding with life after cancer can be a complicated, life-altering process. The psychological evolution that occurs during this process can result potentially in both positive and negative outcomes amongst survivors[4].

Struggles commonly described by cancer survivors include fear, uncertainty, anxiety, depression, insomnia, relationship challenges, employment discrimination, financial concerns, and loss of insurance[5-10]. Furthermore, due to disease and treatment specifics, gynecologic cancer survivors may frequently encounter issues with body image, sexuality, and fertility[11,12]. Compared to other populations of cancer survivors, relatively few studies have specifically investigated the long-term psychosocial outcomes and needs of gynecologic cancer survivors. Caution must be emphasized when generalizing amongst survivors as each population faces unique challenges and has specific supportive care needs.

It has been recognized that medical variables, while important, seem to play a lesser role than psychological adjustment in predicting long-term psychological health amongst survivors[8,13]. Studies have suggested that survivors with better social support systems experience less anxiety and depression[14,15], and that socioeconomic status may strongly contribute to overall wellbeing[16]. A recent longitudinal study investigating long-term survivors of gynecologic cancers revealed overall normal levels of quality of life and relationship adjustment, however increased levels of anxiety and post-traumatic stress disorder amongst survivors[8]. Overall, more research is needed in this area.

In general, cancer survivors as a whole have fortunately shown positive responses to psychosocial interventions[7]. Unfortunately, many survivors do not receive psychosocial care[17], representing missed opportunities. Thus, we recommend routine psychological screening and emphasize that screening should continue throughout a survivor's life, as a longer survivorship period does not necessarily correlate with decreased psychosocial concerns[8]. There are multiple brief psychosocial distress scales available for rapid in-office screening[18]. When psychological issues are identified, we recommend either treating or promptly referring for treatment.

Other interventions that have been associated with psychosocial well-being include healthy lifestyle interventions and management of menopausal symptoms. We recommend encouraging healthy lifestyle choices including healthy eating, regular exercise, and good sleep. Regular physical activity may positively affect survivors' psychosocial wellbeing and quality of life[19,20]. Menopausal symptoms, especially in premenopausal patients, have been associated with distress, depression, and sexual dysfunction[21]. While most gynecologic cancer survivors can be treated with hormone replacement therapy[22], consult with the patient's oncologist if there is concern about tumor hormonal response. The American College of Obstetricians and Gynecologists (ACOG) also recommends several non-hormonal options for management of menopausal symptoms that may be of benefit to these women[23].

In addition, it is important to address survivors' supportive care needs, as increased unmet needs correlate with increased distress and decreased quality of life[8]. Referral to a well-run local survivor support group may be helpful, and can often be located through local chapters of the American Cancer Society[24]. Relationship counseling may be beneficial, especially amongst younger survivors[9]. Finally, sexual dysfunction and infertility, to be discussed subsequently, may profoundly affect survivors' psychological health and social wellbeing[11,21].

Sexual health

Amongst cancer survivors in general, sexual dysfunction has been broadly identified as a common and often untreated problem[25]. Women treated for gynecologic malignancies are at risk for sexual dysfunction due to the nature, location, and treatment of their disease.

After all, patients with gynecological cancer often undergo pelvic surgery and/or pelvic radiation, which may have considerable effects on sexual function[26]. Research has indicated that sexual concerns amongst gynecologic cancer survivors may include physical, psychological, and social dysfunctions[6,11,12]. A recent abstract presented at the 2015 American Society of Clinical Oncologists found that young, premenopausal women, those who underwent chemotherapy, and those in committed relationships may be at greater risk for sexual dysfunction, and among those with sexual dysfunction, a greater decline in sexual activity was seen after cancer treatment[27].

Pelvic radiation therapy may contribute significantly to many of the physical effects described, including skin fibrosis, shortening and narrowing of the vagina, disruption in ovarian function and subsequent vaginal dryness, dyspareunia, and loss of interest in sexual activity[26,28-30]. Other concerns identified amongst gynecologic cancer survivors include altered body image, decreased libido, sexual performance anxiety, and perceived changes in partner interest[31-34].

When considering treatment options for cancer-related sexual dysfunction it is important to recognize that normal sexual functioning can vary markedly, and that sexual function may improve as time from treatment increases[25,35]. Therapies addressing sexual dysfunction may focus on physical or psychosocial components. Studies evaluating various interventions are few and have shown mixed results[36,37].

We recommend screening all gynecologic cancer survivors for sexual dysfunction and offering therapeutic suggestions to interested patients. Optimal evaluation and treatment often requires a multidisciplinary team. Physical concerns are often related to loss of ovarian function and anatomical changes resulting from treatment. Although conclusive evidence does not exist regarding the efficacy of vaginal dilator use[37], use of a graduated series of dilators with lubricant may improve vaginal compliance, dyspareunia, and sexual function. Vaginal dryness may be improved with use of a vaginal moisturizer or a local estrogen product[38]. We also recommend screening for underlying psychological disorders. In addition, relationship counseling or consultation with a sexual therapist may benefit some patients.

Fertility implications

While the majority of women diagnosed with gynecologic cancer are post-menopausal, a significant number are of reproductive age. Clinicians must be aware of the reproductive consequences of treatments, which can profoundly affect a woman's reproductive potential and overall wellbeing. Studies have shown that women with absent or impaired fertility resulting from gynecologic cancer treatment may experience depression, grief and stress resulting from infertility[11,19].

Gynecologic cancers are treated with some combination of surgery, radiation, and chemotherapy, any of which may negatively affect fertility. While surgery may remove part or all of a woman's reproductive organs, radiation and chemotherapy can significantly hinder ovarian function and subsequent ability to conceive. Pelvic irradiation and alkylating chemotherapeutic agents pose the greatest threats to ovarian function, but other chemotherapeutics may contribute. In addition, pelvic irradiation affects the uterus and may hinder pregnancy implantation and appropriate growth[39,40].

As fertility has emerged as such a significant quality of life issue amongst cancer survivors, fertility preservation in patients undergoing gynecologic cancer treatment is an emerging topic. Reproductive aged women with fertility desires and early stage endometrial, cervical, and ovarian cancers are increasingly being offered fertility-conserving treatment options[41-43]. The complicated medical, ethical, and legal details of such are beyond the scope of this article, however this trend will undoubtedly affect future gynecologic cancer survivors. Gynecologic cancer survivors with fertility concerns should be promptly evaluated by reproductive specialists in conjunction with their oncologists.

Premature loss of ovarian function

As discussed previously, premenopausal women may lose ovarian function as a result of gynecologic cancer treatment. While menopausal symptoms may be quite disruptive to a woman psychologically, sexually, and socially[21], early loss of ovarian function may also have significant long-term effects on cardiovascular function, bone health, neurological status, and overall wellbeing[44-47]. We recommend encouragement of healthy lifestyle habits, following with a primary care provider, and consideration of hormone replacement therapy when appropriate. Furthermore, it is important to regularly screen affected women for bone loss and encourage healthy eating, calcium supplementation, and regular weight-bearing exercise. Providers may refer to ACOG's published recommendations for management of osteoporosis[48].

Lymphedema

Lower-extremity lymphedema is a late effect experienced by some gynecologic cancer survivors, especially those treated with surgery or radiation involving the pelvic or inguinal lymph nodes[49]. Onset may occur immediately after therapy or be delayed many years[50]. Patients with lymphedema may complain of pain, heaviness, fullness, a tight sensation, or decreased flexibility in an affected limb. Simple activities of daily living may be affected, and ambulation may be difficult[51]. Physical exam findings may include non-pitting edema[52], and magnetic resonance imaging techniques are increasingly being used to diagnose early lymphedema[53].

Risk factors for developing lower extremity lymphedema include the extent of surgery or radiation to lymph nodes, removal of the circumflex iliac lymph nodes,

cellulitis, and delayed wound healing[52,53]. Lymphedema may be instigated by small traumas including cuts, bites, injections, and sunburns. It is important for patients with lymphedema to maintain good skin hygiene and to engage in simple, regular range of motion exercises[51]. Therapies which may help survivors suffering from lymphedema include: Lymphedema hosiery, manual massage, compression bandages, or consultation with a lymphedema therapist. Severe cases may require hospitalization and intravenous antibiotics[49,51-53]. Lymphedema therapists may be located on the Lymphology Association of North America's website, http://www.clt-lana.org.

Cognitive dysfunction

Furthermore, cancer patients may suffer from cognitive dysfunction, which may persist long after completion of treatment. The individual patient, type of cancer, and variety of treatment all combine to influence a survivor's cognitive state. Factors that may contribute to cognitive dysfunction include: Indirect effects of the cancer itself, brain metastases, chemotherapy, radiation therapy, medication effects, preexisting conditions and psychiatric issues[54]. Research exploring cognitive-related cancer dysfunction in survivors of gynecologic cancers is scant, as most literature in this area has focused on general or breast cancer survivors. However, cognitive decline has been identified amongst gynecologic cancer survivors and must be considered in survivor care plans[55,56].

Interestingly, the cognitive deficits commonly described by survivors tend to differ from those of neurodegenerative diseases. Cancer patients and survivors often describe problems with organization, attention, memory, multitasking, and efficiency, often causing problems with occupational or social responsibilities[57,58]. Standard tests such as the Mini Mental Status Exam are often not sensitive enough to detect the subtle cognitive deficits experienced by survivors, and perceived cognitive decline may be considered reason to explore potential intervention[56].

When assessing cancer survivors with perceived cognitive dysfunction it is important to address and treat fatigue, assess psychological health, assess for anemia, and encourage healthy lifestyle habits. Potential interventions include cognitive behavior therapy, coping strategies such as assisted technology or memory aids, compensatory strategy training, stress management, and energy management[56,59,60]. It is also important to remember that a new cognitive deficit in a cancer survivor could be an indication of recurrence and requires prompt evaluation.

SURVIVORSHIP ISSUES BY GYNECOLOGIC CANCER TYPE

Endometrial cancer

Endometrial cancer is both the most common and the most curable type of gynecologic cancer[61]. Fortunately, among the nearly 55000 women expected to be diagnosed with endometrial cancer in 2015, most will be diagnosed with early-stage disease and given an excellent prognosis. Approximately 67% of women have localized disease at diagnosis, with estimated 5-year survival at 95%. Overall 5-year survival for endometrial cancer patients is approximately 82%, the highest amongst gynecologic cancers[62]. Thus it is important to understand and address the unique needs of this population.

When caring for endometrial cancer survivors, providers must address adverse treatment effects and screen for disease recurrence and second primary cancers. Equally important is addressing cardiovascular health and lifestyle factors. Overall morbidity amongst endometrial cancer survivors is high, despite favorable cancer prognoses. This has been attributed to the strong association of endometrial cancer with obesity and its related co-morbidities including hypertension, diabetes, metabolic syndrome, and pulmonary disease[63,64]. Women with endometrial cancer are more likely to die from cardiovascular disease than from cancer[65], and obesity has been associated with increased morbidity and decreased quality of life in survivors[66,67]. Recent studies evaluating lifestyle programs that target endometrial cancer survivors have shown that various interventions may be able to increase physical activity levels, improve dietary habits, and influence weight loss in these patients[68-73]. Further study is needed in this area.

While the majority of women diagnosed with endometrial cancer are postmenopausal, an estimated 25% are premenopausal. Since 1988 the standard treatment for endometrial cancer has been hysterectomy and bilateral salpingoophorectomy, making loss of ovarian function amongst premenopausal women treated for endometrial cancer an important issue[61,74]. These women experience abrupt onset menopausal symptoms, which may exacerbate psychological difficulties and sexual dysfunction.

Traditionally, estrogen replacement therapy in survivors of endometrial cancer has been avoided since most endometrial cancers are estrogen dependent. Review of limited evidence suggests that estrogen replacement may be a reasonable option in premenopausal patients with a history of early-stage disease, and may be considered with appropriate risk-benefit counseling and oncology consultation[75,76]. Of note, some premenopausal women with endometrial cancer are choosing fertility preserving or ovarian preserving therapies[77,78]. The details of such treatments are beyond the scope of this review, however may influence the future composition of this population.

Furthermore, survivors of endometrial cancer are at increased risk for multiple subsequent cancers[64,79,80]. Breast and colon cancers are the most commonly identified second primary cancers in endometrial cancer

survivors and require regular screening[80]. Patients with endometrial cancer may have a genetic predisposition for development of other cancers, such as in Lynch syndrome, and should be offered genetic screening when personal or family history indicates[80,81].

When caring for endometrial cancer survivors we recommend: Yearly pelvic exams, imaging as clinically indicated, regular screening for second primary cancers, and genetic testing when indicated. We also recommend routine assessment of psychosocial wellbeing, sexual health, and adverse treatment-related effects, accompanied by treatment or referral as indicated. Furthermore, we recommend medical optimization of cardiovascular health and increased emphasis on healthy lifestyle choices. At minimum, obese endometrial cancer survivors should receive physician counseling regarding weight loss, physical activity, and healthy eating. Ideally these patients should be referred to weight loss and lifestyle intervention programs available within their medical communities. Finally, in order to provide optimal care to endometrial cancer survivors we recommend that these women follow with a gynecologist or gynecologic-oncologist as well as a primary care specialist familiar with the needs of this population.

Ovarian cancer

Ovarian cancer is the second most common gynecologic cancer in the United States, with an estimated 21000 diagnoses expected in 2015. Significant survival differences exist between women diagnosed with early stage disease and those diagnosed with advanced disease. Unfortunately, 60% have distant spread at diagnosis and 5-year survival at 28%. However women diagnosed with localized or regional spread have better prognoses with 5-year survival at 92% and 73%, respectively[82,83].

Importantly, notable survival differences exist between women diagnosed with epithelial ovarian cancer and those diagnosed with ovarian germ cell tumors. While the former are generally diagnosed at an advanced stage with limited survival potential, many women diagnosed with germ cell tumors face favorable prognoses. In these women, who are often diagnosed at a young age and make up a small proportion of overall ovarian cancer diagnoses, survival is common and treatment may frequently induce concerns related to fertility, premature loss of ovarian function, and disease recurrence[83-85].

Ovarian cancer is generally treated with surgery and/or chemotherapy, and survivors may additionally experience neuropathy, cognitive decline, psychosocial difficulties, and sexual dysfunction[55,86-88]. Fear of recurrence is of particular concern in this population and may contribute to significant anxiety and decreased quality of life. Studies have shown that psychosocial wellbeing can have the greatest influence on overall quality of life amongst ovarian cancer survivors[89]. Adequately powered longitudinal studies are needed to further qualify, quantify, and assess the specific survivorship needs of this population.

When providing care to survivors or ovarian cancer, we recommend: Routine exams at least yearly and imaging as clinically indicated. Evaluation of tumor markers should be directed by the patient's oncologist. We recommend screening for neuropathy and cognitive difficulties, psychological and sexual dysfunction, and referral for treatment when indicated. Similar to endometrial cancer survivors, survivors of ovarian cancer benefit from a healthy diet, maintaining supportive relationships, regular physical activity and maintaining a healthy weight. Survivors may carry *BRCA1*, *BRCA2*, or *HNPCC* mutations, and should be screened for such based on personal and family histories[90].

Cervical cancer

Cervical cancer is the third most common gynecologic cancer in the United States. Its incidence has decreased markedly in recent decades with the introduction of widespread screening and treatment of pre-invasive disease. The recent introduction of the HPV vaccine will hopefully further decrease cervical cancer incidence in coming decades[91].

Despite improved screening, an estimated 13000 women are expected to be diagnosed with this malignancy in 2015. Nearly half of these women will be diagnosed with local disease with 5-year survival at 90%. Overall, 5-year survival amongst cervical cancer patients is estimated at 68%[92]. Cervical cancer affects younger women when compared with other gynecologic cancers, with mean age at time of diagnosis approximately 50 years, resulting in longer post-treatment life expectancies. In addition, women of lower socioeconomic status and women of minority or immigrant groups are more likely to develop invasive cervical cancer[93,94].

Women diagnosed with very early stage disease are often treated exclusively with surgery. More advanced disease is generally treated with radiation and chemotherapy. Survivors may suffer from psychosocial difficulties, sexual dysfunction, long-term treatment side effects, and second primary malignancies. Studies have suggested that survivors who received treatment with radiation therapy are at increased risk of suffering from long-term physical effects and sexual dysfunction when compared to those treated with radical surgery alone[93,95,96].

Premenopausal women treated for cervical cancer may suffer from premature ovarian failure as a result of treatment. Estrogen replacement therapy is generally considered to be appropriate in this population and may be considered[22,97]. Women who have not completed childbearing at the time of diagnosis may suffer from psychological and social difficulties resulting from treatment-induced infertility. Fortunately, fertility preservation is increasingly being offered to women with

very early stage invasive disease[98-100], and ovarian-preserving efforts including pre-treatment ovarian transposition have been investigated with promising results[101,102].

Furthermore, women with a history of cervical cancer are at increased risk of developing subsequent cancers of the vulva, vagina, and rectum as well as tobacco-related malignancies including lung, esophageal, stomach, urogenital, pancreatic, and leukemia in those with a tobacco use history[103-105]. Thus, it is important to screen for potential second malignancies and to routinely address tobacco use.

When providing care to cervical cancer survivors we recommend: Yearly pelvic exams with pap screening, imaging as clinically indicated, and routine screening for second primary cancers. Furthermore, we encourage healthy lifestyle choices and regular tobacco prevention and cessation efforts, including referral to cessation programs for motivated patients. It is important to recognize that many of these patients may suffer from long-term psychological issues or have severe physical effects from cancer treatment. We also recommend educating these survivors on the importance of encouraging their family and community members to undergo routine cervical screening.

Vulvar cancer

Vulvar cancer is the fourth most common gynecologic cancer, with approximately 5000 women expected to be diagnosed in 2015[106]. Vulvar cancer diagnoses occur most frequently in women between the ages of 65-75, however vulvar cancer has increased in younger populations, likely due to increasing HPV prevalence[107]. As with cervical cancer, the introduction of the HPV vaccine will hopefully decrease vulvar cancer incidence in the coming decades[92]. Women with vulvar cancer are generally treated with pelvic surgery and/or radiation therapy[108].

Overall the literature assessing survivorship issues specific to vulvar cancer is limited. Patients treated with extensive surgery or radiation therapy seem to be at risk for decreased quality of life, including sexual dysfunction and psychosocial difficulties[108-110]. These patients may suffer from skin changes including changes in skin texture and color, thickening, contractures, fibrosis, decreased clitoral sensation, and painful intercourse. Patients treated with extensive lymph node surgery or radiation therapy often suffer from chronic lymphedema[111].

As vulvar cancer has increased among younger women who often present with less advanced disease, a trend toward less radical surgery has emerged. Wide local excision has been associated with higher quality of life amongst survivors when compared to radical vulvectomy[109], and sophisticated sentinel node mapping techniques are decreasing the need for radical lymph node surgery and the associated risk of lymphedema[112]. Overall, more research is needed to define and best meet the evolving needs of vulvar cancer survivors.

When treating these patients we recommend: Routine pelvic exams and screening for disease recurrence, as well as routine guideline-recommended screening for other cancers. In tobacco users we recommend an emphasis on cessation. Finally, we recommend approaching these patients with awareness that mental health or sexual counseling may be indicated, especially in patients with a history of extensive pelvic surgery or radiation therapy.

CONCLUSION

The number of gynecologic cancer survivors is expected to continue to increase in coming decades. While further research is warranted to better understand and meet the needs of this population, there are many things that the general gynecologists can do to manage the survivorship care of these women. Attention to the unique psychosocial symptoms, treatment related sequella, cancer type specific issues, and management of general health maintenance and other health issues would improve the health and quality of life of gynecologic cancer survivors.

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REVIEW

Cancer stem cells and early stage basal-like breast cancer

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Abstract

Ductal carcinoma *in situ* (DCIS) is a category of early stage, non-invasive breast tumor defined by the intraductal proliferation of malignant breast epithelial cells. DCIS is a heterogeneous disease composed of multiple molecular subtypes including luminal, HER2 and basal-like types, which are characterized by immunohistochemical analyses and gene expression profiling. Following surgical and radiation therapies, patients with luminal-type, estrogen receptor-positive DCIS breast tumors can benefit from adjuvant endocrine-based treatment. However, there are no available targeted therapies for patients with basal-like DCIS (BL-DCIS) tumors due to their frequent lack of endocrine receptors and HER2 amplification, rendering them potentially susceptible to recurrence. Moreover, multiple lines of evidence suggest that DCIS is a non-obligate precursor of invasive breast carcinoma. This raises the possibility that targeting precursor BL-DCIS is a promising strategy to prevent BL-DCIS patients from the development of invasive basal-like breast cancer. An accumulating body of evidence demonstrates the existence of cancer stem-like cells (CSCs) in BL-DCIS, which potentially determine the features of BL-DCIS and their ability to progress into invasive cancer. This review encompasses the current knowledge in regard to the characteristics of BL-DCIS, identification of CSCs, and their biological properties in BL-DCIS. We summarize recently discovered relevant molecular signaling alterations that promote the generation of CSCs in BL-DCIS and the progression of BL-DCIS to invasive breast cancer, as well as the influence of the tissue microenvironment on CSCs and the invasive transition. Finally, we discuss the translational implications of these findings for the prognosis and prevention of BL-DCIS relapse and progression.

Key words: Ductal carcinoma *in situ*; Invasive ductal carcinoma; Basal-like ductal carcinoma *in situ*; Basal-like invasive ductal carcinoma; Cancer stem cells

Core tip: Basal-like ductal carcinoma *in situ* (BL-DCIS) often lacks endocrine receptors and has a high rate of recurrence due to no available targeted therapies. BL-

DCIS is a precursor of invasive basal-like breast carcinoma, a malignant cancer prone to metastasis and drug-resistance. Therefore, targeting BL-DCIS to prevent transition into invasive cancer is of significant interest. The recent identification and characterization of cancer stem-like cells in BL-DCIS advance the understanding of BL-DCIS and their potential role in driving the progression of BL-DCIS to invasive basal-like breast cancer. These findings provide critical implications for the development of therapies that prevent the progression of BL-DCIS.

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INTRODUCTION

Breast cancer has been recognized as a complex, heterogeneous disease, encompassing multiple cell populations with different risk factors, histological features, clinical behaviors and responses to therapy[1-3]. While breast cancer diagnosis was initially based on tumor size, histological classification systems were later developed to categorize breast tumors into subgroups. Primary breast carcinomas are first classified as either *in situ* or invasive tumors. Ductal carcinoma *in situ* (DCIS) of the breast is an early stage, non-invasive breast tumor commonly diagnosed by mammography screening. DCIS accounts for 15%-20% of all newly diagnosed breast cancer cases, and is characterized by the intraductal proliferation of malignant epithelial cells without invasion through the basement membrane into the surrounding tissue[4]. In contrast, invasive breast carcinoma is able to invade through the basement membrane into the surrounding stroma. Invasive breast carcinomas have been extensively studied and found to be composed of numerous heterogeneous histological subtypes[5]. Similar to invasive breast carcinoma, divergent histological types of DCIS lesions have been recognized, and various classification systems have been developed to characterize DCIS tumors[6]. Approximately 15%-30% of DCIS patients relapse within 10 years after surgical lumpectomy[7], and it is of urgent clinical need to have an effective classification system to identify DCIS with a high-risk of tumor recurrence. Owing to subjective interpretation of lesion morphology by pathologists, inconsistency in DCIS classification cannot be avoided[8]. Histological classification of heterogeneous DCIS lesions is not sufficient to identify molecularly heterogeneous DCIS subgroups, and additional classification approaches are necessary for the pathological characterization of DCIS and identification of more effective therapeutic options.

Gene expression profiling has emerged as a useful system for breast cancer classification[9-11], and has been used to define five intrinsic molecular subtypes of invasive breast carcinoma: Luminal A, luminal B, HER2-enriched, normal- and basal-like[9,10]. Following this discovery, additional subgroups of breast cancer were identified, including the interferon-enriched[12], molecular apocrine[13] and claudin-low subgroups[14]. Given that these subtypes possess different molecular alterations, they display distinct clinical outcomes and therapeutic responses. The basal-like subtype is highly aggressive and therefore of particular clinical relevance. Basal-like breast cancers are more likely to occur in younger, African American women, and are associated with breast cancer susceptibility (*BRCA*) gene mutations. They are characterized by high tumor grade, proliferation rate, frequency of recurrence, and the presence of *p53* mutations. Patients with basal-like breast cancers frequently have poor prognosis, and are difficult to treat due to the lack of effective targeted therapies[10,11,15]. Breast tumors categorized as basal-like display gene expression signatures similar to normal basal/myoepithelial breast cells (myofibroblast-like breast epithelial cells located between breast ductal epithelial cells and the basement membrane), including high-molecular weight basal cytokeratins (CK5/6, CK14 and CK17)[16].

The majority of diagnosed basal-like breast cancer cases are triple-negative breast cancers (TNBC), which lack expression of hormone receptors [estrogen receptor (ER) and progesterone receptor (PR)] and overexpression/amplification of HER2[9,10,15]. Although there is significant overlap between basal-like breast cancers and TNBC, they are not identical. Approximately 70%-80% of basal-like breast cancers have been identified as triple-negative, basal-like breast cancer (TN-BLBC)[15,17,18]. The remaining non-triple-negative basal-like breast cancers share similar gene expression profiles with TN-BLBC, but might have gained additional genetic and/or epigenetic aberrations due to increased genomic instability[17,18]. Using gene expression profiling analysis, Lehmann *et al*[19] identified six distinct molecular subtypes of TNBC: Two basal-like (BL1 and BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like and luminal androgen receptor (LAR). Among these TNBC molecular subtypes, BL1, BL2, IM and M are predominantly basal-like[20]. This sub-classification of TNBC is clinically relevant due to the differential clinical outcome and chemotherapeutic response of each TNBC subtype[20,21]. Two lines of evidence indicate that distinct molecular subtypes of TNBC manifest differential responses to immunoediting, the process by which tumor cells escape the anti-tumor effect of immunosurveillance[22,23]. Similar to Lehmann's sub-classification of TNBC, Burstein *et al*[22] utilized RNA and DNA profiling analysis to define TNBC subtypes as: (1) LAR; (2) mesenchymal (MES); (3) basal-like immunosuppressed (BLIS); and (4) basal-like immune-activated (BLIA). BLIS tumors have the worst prognosis and BLIA tumors manifest the best[22], in part due to the ability of the immune system to target them. Similarly,

Jézéquel *et al*[23] sub-classified TNBC into three different subtypes *via* gene-expression profiles, including the C1 subtype (LAR, 22%), the C2 subtype (basal-like with a low immune response and high M2-like macrophages, 45%) and the C3 subtype (basal-enriched with a high immune response and low M2-like macrophages, 33%). They also found that basal-enriched C3 with a high immune response had a better prognosis than basal-like C2 with a low immune response[23]. While the molecular mechanisms leading to immune tolerance are not fully understood, two lines of study indicate that inactivation of tumor suppressor p53 and activation of CUL4A E3 ubiquitin ligase are involved in failure of tumor immunosurveillance[24,25].

TN/BLBC are more sensitive to preoperative or neoadjuvant chemotherapy than luminal breast cancers. Current therapeutic options for TN/BLBC include cytotoxic (*e.g.*, combined treatment with anthracyclines or taxanes) and targeted (*e.g.*, PARP1 and EGFR inhibition) therapies[20,21,26]. Although cytotoxic therapeutics achieves good tumor regression rates in the neo-adjuvant setting, patients experience frequent recurrence in five years after treatment[26,27]. Targeted therapies have also encountered discrepancies in trial results and issues with resistance[26,27]. TN/BL drug resistance potentially involves several mechanisms including intrinsic therapy resistance by a minor cell population in tumors, therapy-induced senescence and polyploidy in tumor cells, acquired therapeutic resistance *via* upregulation of drug efflux transporters, and acquired resistance *via* genetic reversion[28]. It is well accepted that tumor-initiating cells [generally called cancer stem cells (CSCs), discussed in the following paragraph] have high intrinsic drug-resistance, and may lead to relapse[28]. In regard to cell-cycle-related mechanisms, Puig *et al*[29] reported that cisplatin treatment induced senescent giant polyploid cells *via* DNA endoreduplication. These giant, multi-nucleated cells were able to generate small-sized, diploid cells that started to proliferate and were increasingly cisplatin-resistant[29]. These findings suggest that the multistep drug-resistant progression in which cells undergo DNA endoreduplication, polyploidization, depolyploidization and then generation of clonogenic escape cells, can account for tumor relapse after initial efficient chemotherapy[29]. Another common mechanism of drug resistance in cancer is the upregulation of ATP-binding cassette (ABC) transporter family proteins, which increases the efflux of chemotherapeutic drugs[28]. Besides these mechanisms, genetic alterations to restore the function of DNA repair proteins (*e.g.*, BRCA1, BRCA2, FANCA, *etc.*) have been identified as a novel drug-resistant mechanism in DNA-repair-deficient cancers, which are initially sensitive to DNA-damaging agents (*e.g.*, cisplatin) and to PARP inhibitors[28]. In addition to these general resistance mechanisms, dysregulation of signal pathway regulators in basal-like breast cancers have recently been identified to be responsible for resistance to neoadjuvant chemotherapy and PARP inhibitor treatment. For example, basal-like breast cancers have low expression of dual specificity protein phosphatase 4 (DUSP4), which negatively regulates the Ras-ERK pathway, due to hypermethylation of the DUSP4 promoter. This results in activation of the Ras-ERK pathway and resistance to neoadjuvant chemotherapy[30]. Furthermore, over-expression of p38 mitogen-activated protein kinase in basal-like breast cancers enabled cancer cells to be resistant to the treatment of PARP inhibitors[31]. These results show the promise of increased molecular and functional characterization of TNBC subtypes. While the development of therapeutics to effectively treat TNBC still faces tremendous challenges, molecular targeting of TNBC based on molecular subtypes is a promising therapeutic strategy.

A conceptual model has been proposed that describes the developmental process of breast cancer as the progression of atypical hyperplasia into carcinoma *in situ* and finally to invasive carcinoma[32]. To better understand the relationship between DCIS and invasive breast carcinoma in breast cancer progression and to molecularly classify DCIS lesions, immunohistochemical and gene expression profiling analyses were used to define DCIS subtypes. The molecular subtypes of invasive breast cancer are also present at the DCIS stage, although their frequencies are varied between these two distinct breast cancer stages[33-35]. Furthermore, genetic studies of DCIS and invasive breast carcinoma have demonstrated that they have remarkable similarity in their genetic profiles when matched by histological grade and hormone receptor status[3,36-38]. These findings strongly support the theory that DCIS is a non-obligate precursor of invasive breast cancer. The distinct tumor subtypes may be generated from different cells of origin, by distinct tumor progression pathways, or a combination of both events. The ability of DCIS to progress to invasive disease is a complex biological phenomenon and depends on multiple factors, including genetic/epigenetic aberrations, genomic instability and the stromal microenvironment[3,32].

As poorly differentiated invasive ductal carcinomas (IDC), basal-like breast tumors presumably have a DCIS precursor with similar cytologic and immunophenotypic features. Several studies reported that the use of both gene expression profiling and immunohistochemical analysis of basal-specific protein markers identified DCIS tumors with molecular features of basal-like invasive breast cancer[33,39-43]. These basal-like DCIS (BL-DCIS) tumors are presumed to be precursors for basal-like IDC (BL-IDC)[39,44]. Identification of BL-DCIS sheds light on the possibility of preventing progression to malignant basal-like breast cancer through the therapeutic targeting of precursor DCIS lesions. This review summarizes the recent investigation of BL-DCIS characteristics and the potential precursor relationship between BL-DCIS and invasive basal-like breast carcinoma.

CSCs have been identified in many types of cancer

including breast cancer, and have significantly changed the strategy of cancer therapy. CSCs are a small tumor cell subpopulation that can be identified by several methods including fluorescence-activated cell sorting (FACS) analysis of stem/progenitor-cell-specific surface protein markers, aldehyde dehydrogenase (ALDH) activity assays, and FACS analysis of the "side population" indicated by Hoechst dye exclusion. CSCs have the unique ability to self-renew and to differentiate into heterogeneous tumor cell lineages *in vitro* and *in vivo*[45-48]. CSCs possess higher tumorigenic ability than non-CSCs, which can be measured by *in vivo* xenograft tumor formation assays involving the injection of enriched CSC fractions to immunodeficient mice[45-48]. Similar to normal stem cells, CSCs manifest stem-cell-specific gene expression signatures and can undergo symmetric as well as asymmetric cell division[45-48]. CSCs also exhibit high levels of drug resistance. Under the stress of chemotherapy they can become quiescent and resistant to drugs that target proliferating cells[49,50]. In addition, CSCs generally express high levels of multi-drug resistant ABC transporters and pump out anti-cancer drugs at high rates[51]. The stem-like characteristics of CSCs are due to dysregulation of stemness signaling pathways, such as the Notch, hedgehog, Wnt, TGF-β and pluripotent transcription factor (*e.g.*, SOX2, OCT4, KLF4, *etc.*) pathways[52,53]. Moreover, CSCs possess similar characteristics to cells that have undergone epithelial-to-mesenchymal transition (EMT), allowing CSCs to survive in circulation and contribute to the metastasis of invasive cancers[54,55]. Due to these traits, CSCs are believed to be necessary for tumor heterogeneity, relapse, metastasis, and drug resistance. Breast CSCs were first identified in primary breast carcinomas using the markers $CD44^+$/$CD24^-$[56]. This minor tumor cell subset can self-renew to form tumorspheres in *in vitro* suspension culture conditions, and exhibit stem-cell gene expression patterns[56]. Isolated $CD44^+/CD24^-$ cells have a higher capacity to initiate *in vivo* xenograft mammary tumors compared with other cell subsets and can differentiate into heterogeneous breast tumor cell lineages[56]. Furthermore, breast CSCs display a drug-resistant phenotype, and are able to better tolerate anti-cancer drug treatment than non-CSCs[57,58]. Enrichment of CSCs in breast cancer correlates with tumor aggressiveness, likely due to the characteristics described above. Among the molecularly-classified breast cancer subtypes, basal-like breast carcinomas tend to possess the highest proportion of CSCs compared with other subtypes, consistent with their heterogeneity and aggressiveness[59,60]. CSCs in basal-like breast cancer have emerged as a key target for cancer therapy.

These discoveries have prompted cancer researchers to investigate the existence of CSCs and their characteristics in BL-DCIS[61,62]. Studies employing *in vitro* cell line and *in vivo* xenograft tumor models have significantly propelled the understanding of CSC characteristics and their role in BL-DCIS. They also give new insights into the aberrant molecular mechanisms involved in regulating CSC formation in BL-DCIS and the BL-DCIS-to-IDC transition. This article will review recent advances in these topics and their translational implications to the prognosis and prevention of BL-DCIS progression to invasive basal-like breast cancer.

EXISTENCE AND FEATURES OF BASAL-LIKE-DCIS

Due to the lack of effective targeted therapies, invasive basal-like breast cancers have poor prognosis. This has prompted cancer researchers to investigate the existence of precursor DCIS lesions that can potentially develop into BL-IDC. If precursor DCIS lesions with the potential to develop into BL-IDC are identified, patients with these lesions can be treated earlier with more aggressive therapies to prevent tumor progression and recurrence. Precursor DCIS lesions are presumed to have cytologic and immunophenotypic features similar to BL-IDC. By characterizing protein markers such as ER, PR, HER2, basal cytokeratins (*e.g.*, CK5/6, CK14, and CK17), EGFR, c-kit and p63, about 6%-8% of DCIS cases were identified to be TN/BLBC[39-41,43]. In addition to immunohistochemical surrogates, Hannemann *et al*[33] performed microarray-based gene expression profiling to analyze and classify 40 *in situ* and 40 invasive breast cancer cases. Their two-dimensional hierarchical clustering analysis of microarray data showed that the luminal, HER2 and basal-like subtypes originally described in invasive breast cancer could also be identified in DCIS. A population-based cohort has shown that patients with BL-DCIS have a higher risk for local recurrence and development into invasive cancer compared with other molecular subtypes[63], demonstrating the need for further molecular characterization. The BL-DCIS subtype is associated with unfavorable prognostic variables such as high-grade nuclei, mutant p53 overexpression and elevated Ki-67 index[42]. In addition, through RNA deep sequencing analysis, Abba *et al*[64] subdivided high-grade DCIS into two subtypes, DCIS-C1 and DCIS-C2. The more aggressive DCIS-C1 (highly proliferative, basal-like, or $ERBB2^+$) had a molecular signature characteristic of activated regulatory T (Treg) cells ($CD4^+/CD25^+$/$FOXP3^+$) and $CTLA4^+/CD86^+$ complexes, indicative of a tumor-associated immunosuppressive phenotype[64]. This is the first evidence identifying mechanisms of immune evasion in BL-DCIS. Recently BL-DCIS tumors have also been associated with cell cycle-related biomarkers[65,66]. Over 80% of BL-DCIS cases were p16-positive, whereas over 90% of DCIS cases with the luminal A phenotype were p16-negative[66]. In addition to p16 expression, co-expression signatures of $p16^+/Ki67^+/COX2^+$ and $p16^+/Ki67^+/COX2^-$ were also found to be associated with the basal phenotype in DCIS and IDC[66]. These cell-cycle related profiles could be exploited to guide more aggressive treatment

strategies in patients with high-grade DCIS. According to studies by Tamimi *et al*[42], the frequency (7.7%) of BL-DCIS in diagnosed DCIS cases is slightly lower than that (10.7%) of BL-IDC in diagnosed invasive breast cancer cases. One plausible explanation for the slightly higher frequency of basal-like expression in high-grade invasive *vs in situ* tumors is either that BL-DCIS lesions rapidly progress, leading to the lower identifiable frequency, or that the basal-like phenotype is acquired during invasive progression. Studies investigating the precursor potential of comedo-DCIS tumors (comedo-DCIS), a type of high-risk *in situ* breast lesions, identified a novel p63/CK5/Her2/neu-expressing cell subpopulation with ER-/PgR-/EGFR-[67]. Given that p63 alone and p63/Her2/neu co-expression are both associated with microinvasion and the recurrence of clinical comedo-DCIS, the p63/Her2/neu-expressing precursor intermediate is considered a cellular basis for the emergence of $p63^+$/$Her2/neu^-$ or $p63^+$/$Her2/neu^+$ basal-like breast cancer, and thus may serve as a biomarker for identifying the BL-DCIS subgroup[67].

CSCS AND BASAL-LIKE-DCIS

Evidence of CSCs existing in DCIS

It has been proposed that CSCs are responsible for generating tumor heterogeneity and the malignant progression of cancer. To validate this hypothesis within breast cancer and investigate the mechanisms of the DCIS to IDC transition, researchers are seeking to identify the existence of CSCs in DCIS and characterize their cell properties. To study the heterogeneous tumorgenicity of cancer cells, Damonte *et al*[68] generated mammary intraepithelial neoplasia (MIN) outgrowth lines. Derived from premalignant atypical lesions from PyV-mT transgenic mice, the MIN outgrowth lines are able to grow orthotopically in cleared mammary fat pads, and form a mammary tumor structure similar to human DCIS.

The 6 MIN lines generated demonstrated a varied ability to progress to invasive carcinoma with pulmonary metastatic potential *via* serial transplantation[68], establishing the paradigm that pre-CSCs in DCIS are capable of self-renewal, multilineage differentiation, and serve as the origin of invasive cancer. Notably, their studies indicate that sequential genetic hits for malignant transformation are not required for this DCIS model to progress to invasive and metastatic mammary carcinoma, and the programmed potential for latency and metastasis might be predetermined in these pre-CSCs[68]. Moreover, Espina *et al*[69] studied *ex vivo* organoid culture of fresh human DCIS lesions without enzymatic digestion or sorting, and found that DCIS contains malignant precursor cells that were able to form spheroids and a duct-like 3D structure in *ex vivo* organoid culture and to exhibit tumorigenicity in NOD/SCID mice[69].

Evidence for the presence of CSCs in BL-DCIS

The two lines of evidence mentioned above raised the possible existence of tumorigenic CSCs in BL-DCIS, which may determine the phenotypes of BL-DCIS and the capability of BL-DCIS to progress into invasive cancer. To confirm this, our research group characterized the BL-DCIS cell model MCF10DCIS.COM, which is derived from the non-cancerous breast epithelial cell line MCF10A. This BL-DCIS-mimic cell model has a unique bipotent progenitor ability, and is able to generate both myoepithelial and luminal-type cells *in vivo*, giving rise to BL-DCIS with high similarities to human DCIS lesions[70-76]. In addition to the formation of DCIS-like tumor structures *in vivo*, these tumor lesions are able to spontaneously progress to invasive breast cancer[74,76]. In our studies of MCF10DCIS.COM, we identified a CSC population with enriched $ALDH1^+$ and the molecular signature $CD44^+$/$CD49f^+$/$CD24^-$[62]. Compared with the non-stem-like cell subset, these stem-like cells possessed enhanced migration, invasion and self-renewal capacity, and accelerated xenograft tumor growth in nude mice[62]. Pandey *et al*[61] have also identified CSCs in the MCF10DCIS.COM cell line using similar cell surface markers ($CD44^+$/ESA^+/$CD24^-$). In line with our result, CSCs isolated using this profile showed significantly higher DCIS tumor-initiating ability compared with non-stem-like cells[61]. The existence of CSCs in BL-DCIS raises the possibility that this CSC population serves as a malignant precursor necessary for the progression of BL-DCIS to BL-IDC.

DEREGULATED FACTORS INVOLVED IN THE GENERATION OF CSCS AND THE BL-DCIS-TO-BL-IDC TRANSITION

A challenging question in the breast cancer research field is how precursor DCIS lesions progress to invasive breast carcinomas. Attempts to address this critical question are hampered by the complexity of heterogeneous DCIS lesions. To overcome this barrier, the aforementioned MCF10DCIS.COM cell line has been extensively exploited as a unique model to study DCIS and explore molecular mechanisms involved in regulating the progression of DCIS to IDC. As MCF10DCIS.COM belongs to the BL-DCIS subtype, we review recent findings of deregulated factors implicated in the generation of basal CSCs in this cell model, and in enhancing malignancies as well as invasive progression of this BL-DCIS model *in vivo*. Further characterization of dysregulated signaling pathways involved in CSCs would advance insights into how BL-DCIS tumors progress to invasive cancer and propel the development of effective therapeutics to prevent this malignant progression.

The role of miR-140

MicroRNAs (miRNAs) are short non-coding RNA

molecules with a length of approximately 22 nucleotides that bind to the 3'-untranslated region of messenger RNAs and regulate mRNA stability and/or translation. miRNAs have been extensively investigated in cancer and other diseases, and regulate a variety of physiological and pathological processes at the post-transcriptional level. Although numerous miRNAs have been found to be involved in regulating CSCs in breast cancer[77], the miRNAs participating in basal CSC regulation and the tumorigenic development of BL-DCIS remain largely unknown. Through miRNA profiling of paired DCIS tumors, we identified downregulation of miR-140 as a hallmark of BL-DCIS lesions[78]. Our studies have shown that miR-140 is a tumor-suppressive miRNA which targets the stem-cell related factor SOX9 for degradation in in normal breast epithelial cells[78]. The degree of miR-140 downregulation positively correlates with the increased expression of SOX9 and the grade of DCIS lesions, implicating the critical role of the miR-140/SOX9 axis in the progression of DCIS[78]. Our studies also revealed that miR-140 was downregulated in cancer stem-like $CD44^+/CD24^-$ cells isolated from MCF10DCIS.COM cells compared with normal breast stem cells isolated from MCF10A cells[78]. Moreover, restoration of miR-140 expression in MCF10DCIS.COM cells suppressed CSC self-renewal, invasion and *in vivo* tumorigenicity[78]. This suggests that the miR-140/SOX9 regulatory circuit is pivotal for the self-renewal and invasive capacity of basal CSC and their tumor formation *in vivo*, and is a potential therapeutic target.

The role of the nuclear receptor coactivator amplified in breast cancer 1

Ory *et al*[79] found that expression of nuclear receptor coactivator amplified in breast cancer 1 (AIB1) was aberrantly upregulated in DCIS lesions compared with normal breast.

AIB1 activates NOTCH, HER2 and HER3 signaling pathways in MCF10DCIS.COM cells, and is required for the malignant phenotype of MCF10DCIS.COM in 3D culture and *in vivo* tumor formation and progression[79]. Critically, AIB1 inhibition led to a significant reduction in the $CD44^+/CD24^-$ CSC population and also resulted in decreased myoepithelial progenitor cells in DCIS lesions *in vitro* and *in vivo*[79]. These data indicate that activation of AIB1 is an aberrant mechanism that initiates and maintains DCIS *in vivo* by facilitating the development as well as maintenance of basal CSCs. It is likely that aberrantly activated AIB1 assists other deregulated factors to promote the transition of BL-DCIS to BL-IDC.

The role of the p63-membrane-type 1-matrix metalloproteinase axis

A critical step in the progression from DCIS to the invasive lesion is the crossing of the basement membrane and invasion into the stroma. This is achieved through degradation of extracellular matrix (ECM) proteins in the basement membrane by membrane-anchored matrix metalloproteinases (MMPs), including membrane-type 1 (MT1)-MMP[80]. MT1-MMP has been shown to be involved in invasive tumor growth and metastasis in several experimental cancer models[81-84]. Lodillinsky *et al*[85] analyzed expression of MT1-MMP in a large cohort of DCIS, IDC and microinvasive breast tumors, and found that MT1-MMP was significantly upregulated in the DCIS to IDC transition, and correlated with higher grade and hormone receptor-negative tumors. Functional analysis showed that silencing of MT1-MMP in MCF10DCIS.COM cells impaired the ability of this DCIS tumor model to progress into infiltrating lesions *in vivo*[85]. Additionally, Lodillinsky *et al*[85] identified p63 as an upstream positive regulator that increases MT1-MMP expression in DCIS, and is required for activating the basement membrane-invasive program of DCIS. Their findings suggest that aberrant activation of the p63/MT1-MMP axis in DCIS may contribute to the progression of DCIS to high-grade basal-like breast cancers. Although their studies did not address the role of the p63/MT1-MMP axis in MCF10DCIS.COM CSCs, p63 is a well-known basal-associated molecular marker, and has been recently found to be elevated in CSCs of HER2-type breast cancer and essential for their self-renewal as well as tumorigenicity[86]. Therefore, their results imply that aberrant activation of the p63/MT1-MMP axis in basal CSCs is a potential mechanism to trigger the progression of BL-DCIS to BL-IDC.

The role of Singleminded-2s

Recent work has demonstrated that the basic helix-loop-helix/PER-ARNT-SIM (bHLH/PAS) transcription factor Singleminded-2s (SIM2s) is critical for normal mammary gland development and promoting tumor cell differentiation[87]. SIM2s is inhibited by C/EBPβ and NOTCH, important promoters of EMT and cell differentiation. Loss of SIM2s enhances EMT in the mouse mammary gland, normal breast and breast cancer cell lines. Moreover, SIM2s is frequently downregulated in human breast cancer. When SIM2s expression was restored in human breast cancer cell lines, their proliferation and invasion were suppressed. These results suggest that SIM2s is a tumor suppressor gene that is crucial for maintaining epithelial integrity through inhibiting the EMT program and promoting cell differentiation. To address the role of SIM2s in the transition of DCIS-to-IDC, Scribner *et al*[87] analyzed SIM2s expression in MCF10DCIS.COM and found that it is downregulated in this DCIS cell model when compared with non-cancerous MCF10A cells. Moreover, their functional studies showed that reestablishment of SIM2s in MCF10DCIS.COM cells significantly impaired their growth and invasion both *in vitro* and *in vivo* by promoting tumor cell differentiation. This is characterized by increased expression of luminal markers, including β-casein, E-cadherin, keratin 18, and decreased expression of genes associated with stem cell maintenance and a basal/EMT phenotype, including smoothened, p63, Snail-2, keratin 14 and vimentin[87].

In contrast, abrogation of SIM2s in MCF10DCIS.COM-derived xenograft tumors led to a more invasive phenotype and increased lung metastasis, correlating with the elevated expression of Hedgehog signaling and MMP[87]. From our and other studies indicating that basal CSCs are the origin of the tumorigenic and invasive characteristics of MCF10DCIS.COM cells[61,62,79], it is likely that decreased expression of SIM2s promotes the development of basal CSCs in BL-DCIS and further reduction in its expression activates invasive features of CSCs to facilitate the invasive progression of BL-DCIS into invasive breast carcinoma.

The role of lipogenesis

Cancer cells have altered metabolisms in comparison to normal cells[88], and upregulation of lipogenic genes and increased lipogenesis are hallmarks of late-stage breast cancer[89]. Inhibition of key lipogenic enzymes results in suppression of tumorigenicity both *in vitro* and *in vivo* by blocking proliferation and inducing apoptosis[90-93]. Although the role of increased lipogenesis in late-stage breast cancer has been extensively studied, its role in early-stage breast cancer DCIS still remains elusive. Moreover, whether lipogenesis is engaged in regulating CSCs of DCIS is an interesting yet unexplored question. To address the role of lipogenesis in DCIS CSCs, Pandey *et al*[61] used the cell surface marker profile ($CD44^+$/ESA^+/$CD24^-$) to isolate CSCs from the MCF10DCIS.COM cell line for expression analysis of lipogenic genes. Their studies showed that expression levels of all lipogenic genes tested in the CSC population were significantly higher than the normal stem-like counterpart population isolated from non-cancerous MCF10A cells. To further investigate the role of sterol regulatory element-binding protein-1 (SREBP1), the master transcriptional activator of lipogenic genes, in CSCs, SREBP1 was ectopically overexpressed in MCF10A stem-like cells. Overexpression of SREBP1 caused enhanced lipogenesis, cell growth and mammosphere formation[61]. When upregulated in MCF10AT, a MCF10A-derived, premalignant cell line, SREBP1 promoted DCIS generation *in vivo* by increasing CSC survival[61]. These findings indicate that activation of lipogenesis is a prerequisite for basal CSC generation and DCIS formation, and is important for endowing increased cell survival capacity.

THE IMPACTS OF THE TISSUE MICROENVIRONMENT ON CSCS OF BL-DCIS

DCIS lesions are heterogeneous tumors encapsulated by the myoepithelium and basement membrane. When they progress to IDC, tumor cells cross the myoepithelial layer and basement membrane and invade into the stroma, comprised of stromal fibroblasts/preadipocytes, mature adipocytes, immune and endothelial cells. Therefore, these various tissue cells and the ECM that composes the tumor microenvironment can regulate CSC self-renewal and differentiation, DCIS formation, progression into invasive lesions, and metastasis[94-98]. Understanding the impact of the tumor microenvironment on basal CSCs and BL-DCIS could potentially enable the design of more effective diagnosis and intervention strategies to improve the survival of cancer patients. There are two lines of recent studies indicating the critical impacts of the tissue microenvironment on the tumorigenesis of BL-DCIS and their transition to BL-IDC, exosomal signaling and ECM dependent signaling.

Exosomal signaling from the tumor microenvironment

Exosomal secretion is a newly identified mechanism of paracrine signaling through which cells secret exosomes, microvesicles with a diameter usually less than 100 nm, which can contain cargo proteins, nucleic acids and nutrients[99]. Secreted exosomes can transduce their carried contents into surrounding cells *via* the cell internalization mechanism mediated by the heparan sulfate proteoglycan receptors[99]. The known roles of exosomes in tumorigenesis are to restructure the tumor tissue microenvironment, modulate tumor immune responses and directly regulate tumor cell behaviors *via* their delivery of proteins and genetic materials. miRNAs have been found to be one kind of nucleic acids carried by secreted exosomes[99,100]. Given that miRNAs are regulatory factors that can modulate protein expression, exosomal trafficking of miRNAs has been recognized to be a microenvironmental signal that can affect signaling networks at the post-transcriptional level[100]. From BL-DCIS studies, we found that the miRNA content in exosomes secreted from CSCs of DCIS was altered compared to exosomes from normal stem-like breast cells[62]. Notably, CSC-secreted exosomes carried less miR-140, an aforementioned tumor-suppressive miRNA, than those secreted from normal stem-like cells, suggesting that the tumorigenic process alters exosomal contents[62].

In addition to the role of exosomal trafficking in signaling among DCIS tumor cells, we recently found that exosomes secreted from preadipocytes, the precursors of mature adipocytes, could impact the stemness and tumorigenic properties of CSCs in BL-DCIS[101]. Preadipocyte-derived exosomes enhanced *in vitro* cell migration as well as self-renewal of BL-DCIS cells and facilitated the xenograft tumor formation of transplanted BL-DCIS cells *in vivo*[101]. The enhanced effect of preadipocyte-secreted exosomes on the tumorigenicity of BL-DCIS might be attributable to a number of growth-promoting cytokines identified within these exosomes[101]. Taken together, these findings demonstrate that exosomal signaling plays an important role in the tumor microenvironment.

ECM-dependent regulatory signaling

High tumor heterogeneity correlates with poor prognosis due to its association with malignancies, recurrence, metastasis and anti-cancer drug resistance[102]. In-

tratumor heterogeneity could result from an intrinsic stochasticity in gene expression and from genetic and/or heritable epigenetic differences among tumor cells[103]. By studying the effect of ECM on an immortalized basal-like breast epithelial cell line, Wang *et al*[104] identified the ECM-dependent TGFBR3 (transforming growth factor β receptor 3)-JUND (jun D proto-oncogene)-KRT5 (keratin 5) regulatory circuit that generates heterogeneous gene expression among ECM-attached breast cells. This circuit is composed of two anticorrelated gene expression programs that negatively regulate each other. TGFBR3 signaling downregulates JUND mRNA levels, whereas JUND represses both TGFBR3 and JUND mRNA levels[104]. Perturbing this regulatory circuit in breast epithelial cells could lead to the formation of aberrant tissue lesions similar to high-grade DCIS[104]. Their studies also indicate that the TGFBR3-JUND circuit is the molecular mechanism responsible for the heterogeneous expression of KRT5 in some basal-like premalignant lesions[104]. These findings suggest that heterogeneous KRT5 expression patterns present in high-grade basal-like DCIS lesions are likely due to loss of tissue-level regulation of gene oscillatory networks rather than genetic selection. Disrupting the dependence of this regulatory circuit on ECM results in detachment of breast epithelial cells from the ECM, in turn leading to cell death[104]. However, some cells survive through activation of a juxtacrine tenascin C (TNC) deposition mechanism. TNC is a critical survival factor for detached cells that would otherwise be subjected to keratinization-induced or anoikis-dependent cell death, and participates in stabilizing the heterogeneous JUND-KRT5 expression[102,104]. These results are in line with the previous finding that metastasizing breast cancer cells express TNC to elicit and/or maintain their metastasis-initiating characteristics[105]. Particularly, it has been shown that TNC is able to increase the expression of stem-cell signaling proteins, suggesting its role in modulating the CSC population[105]. Their findings demonstrate that this ECM-dependent regulatory circuit program can maintain normal tissue architecture and function in addition to preventing cell outgrowth and migration when it is properly regulated. However, when dysregulated (*e.g.*, aberrant ECM signaling), this system enables cells to evade keratinization and anoikis, and allows them to metastasize.

THE IMPLICATIONS OF CSCS IN PROGNOSIS AND PREVENTION OF EARLY STAGE BASAL-LIKE BREAST CANCER

The identification of CSCs in BL-DCIS opens a window for cancer researchers to explore how BL-DCIS initiate and progress into invasive basal-like breast cancer. In addition to promoting our understanding of the role of basal CSCs in BL-DCIS, these research advances have tremendous translational implications for future prognostic and therapeutic applications. The dysregulated molecular factors which result in basal CSC generation could potentially be exploited as prognostic biomarkers for BL-DCIS. This would help identify and grade the probability of diagnosed DCIS developing into BL-IDC, and determine whether DCIS patients should be treated more aggressively. If this prognostic system can be established, it will substantially benefit patients with DCIS and lower their chances of basal-like invasive breast cancer recurrence. The therapeutic agents that can target these deregulated factors could be potentially exploited for targeted therapy of DCIS. This chemopreventive strategy would save breast cancer patients' lives, especially since there are currently no effective therapies to cure basal-like invasive breast cancer. Promising therapeutic agents have already been identified that are effective in targeting CSCs in BL-DCIS. The dietary compound sulforaphane (SFN) can restore miR-140 expression and downregulate the expression of miR-140 targets SOX9 and ALDH1, inhibiting the self-renewal of basal CSCs and DCIS formation *in vivo*[62]. Besides SFN, our studies of the chemopreventive agent Shikonin (SK), a bioactive compound found in the herbal plant shikon, showed that exosomes secreted from SK-treated preadipocytes lost the ability to promote BL-DCIS tumorigenicity both *in vitro* and *in vivo*. This is a novel chemopreventive mechanism for BL-DCIS, targeting the tumor microenvironment in place of the tumor itself[101]. Furthermore, a study from Watabe's research group shows that resveratrol, a therapeutic agent capable of blocking the lipogenic gene expression in basal CSCs, is able to significantly suppress DCIS formation in animals[61]. These exciting findings provide a strong rationale to propel the development of chemopreventive therapeutics for DCIS patients after surgical and radiological treatment.

CONCLUSION

Although the research efforts to combat invasive basal-like breast cancer have provided tremendous insights into this breast cancer subtype, we still have not identified effective therapeutic agents and strategies to cure this disease. Therefore, identifying and targeting the precursor of aggressive breast cancer is a promising direction to prevent the occurrence of this disease. BL-DCIS is an early stage breast cancer with a high risk of recurrence, and targeting it may prevent cancer recurrence and progression to invasive disease. As summarized and discussed in this review, numerous signaling pathways and factors have been identified as dysregulated in basal CSCs of BL-DCIS. Moreover, several chemopreventive agents have been tested to target these deregulated mechanisms. These studies suggest targeting CSCs in BL-DCIS as a potential strategy to inhibit the tumorigenicity of BL-DCIS and prevent the progression of BL-DCIS into BL-

IDC. However it is critical to test the proof-of-principle of these chemopreventive strategies in clinical trials. Developing reliable BL-DCIS biomarkers will allow clinicians to design effective targeted therapies that can prevent the recurrence and progression of early stage basal-like breast cancers.

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REVIEW

Risks and guidelines for the consumption of alcohol during pregnancy

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Abstract

Daily average intake of alcohol during pregnancy has consistently been associated with short term adverse outcomes such as miscarriage, preterm birth and intrauterine growth restriction, a large variety of malformations, as well as long term adverse outcomes such as foetal alcohol syndrome, mental retardation and general impairment of cognitive functions including intelligence, attention, learning abilities as well as social and behavioural functions. Weekly average consumption and alcohol binge drinking (usually defined as $\geqslant$ 5 drinks on a single occasion) independently of high daily average intake has not been consistently associated with short and long term adverse outcomes. Health authorities in most countries recommend that pregnant women completely abstain from alcohol. Even so, many health professionals including doctors, midwives and nurses do not provide information to pregnant women in accordance with the official recommendations, although a large proportion of women of child bearing age and pregnant women drink alcohol, especially before recognition of pregnancy. The discrepancy between guidelines and the information practice of health personnel is likely to continue to exist because guidelines of abstinence are not clearly evidence-based and not in line with current focus on autonomy and informed choice for patients, and because guidelines do not consider the everyday clinical communication situation.

Key words: Alcohol; Binge drinking; Pregnancy; Adverse pregnancy outcomes; Neuropsychological development

Core tip: Daily average consumption of alcohol during pregnancy has been systematically associated with short and long-term adverse outcomes, while lower weekly average consumption and alcohol binge drinking independently of high daily average intake has not. Health authorities in most countries recommend that pregnant women abstain from alcohol. Even so, many health professionals do not provide information to pregnant women in accordance with the official recommendations. The discrepancy between guidelines and the information practice of health personnel is likely to continue, because guidelines of abstinence are not clearly evidence-based

and not in line with current focus on patient autonomy.

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INTRODUCTION

It has been known for thousands of years that alcohol consumption may compromise human reproduction and harm the newborn baby. In his *Problems*[1], Aristotle described how alcohol may reduce semen quality and male potency ["…semen of drunkards (is) generally not reproductive…"]. In his *History of Animals* he described how breast milk from wine-drinking women may cause convulsions in the weaning baby[2]. During the first half of the 18th century, during the English gin epidemic, the English College of Physicians asked Parliament to re-introduce control with the distillation process, because gin was "a cause of weak, feeble and distempered children"[3].

Some one hundred years later a movement had been set in motion that called on women not to drink alcohol while pregnant or while breast-feeding, for as Aristotle had suggested, "alcoholic milk" might cause convulsions in the newborn[4], and children nursed on abstinence on the other hand escaped many common childhood disorders[4].

In 1848, a population based survey was carried out among 574 intellectually disabled people in Massachusetts, United States. Approximately half of the intellectually disabled people (then termed idiots) had parents who were "habitual drunkards"[5].

In 1899, in England, Sullivan[6] described 120 chronic alcoholic women in Liverpool Prison or their relatives and their approximately 600 children. Approximately one in ten children was stillborn, and 56% of the children had died within two years after delivery, usually because of convulsions. The longer the mother had been drinking the greater the risk. But if the mother was abstinent during imprisonment, the child's chance of survival was increased[6].

By the beginning of the 20th century, alcohol consumption during pregnancy had also been associated with miscarriage, malformations and preterm birth[3].

During the American Prohibition of the 1920s and 1930s alcohol was less accessible, and following the Prohibition the potentially damaging effects of alcohol consumption during pregnancy was hardly an issue. In fact, in the late 1960s and 1970s, a number of case series (inherently lacking a reference group) - mainly from the New York Hospital - even suggested that infusion of alcohol could potentially prevent preterm birth in women with threatening preterm delivery[7], although others had difficulties replicating these findings[8]. In 1975, a paper was published including several comparison groups, showing that the therapeutic effect of alcohol on preventing premature labour was no better than that obtained with placebo[9].

In retrospect, it is interesting that while experiments were being carried out using alcohol infusions as a treatment among pregnant women and published in high profile journals[7], the first modern description of the potentially harmful effects of high intake of alcohol during pregnancy was published in French and went almost unnoticed[10]. In fact, today's focus on the damaging foetal effects of high alcohol intake during pregnancy was started with the (re-) discovery of the Foetal Alcohol Syndrome (FAS) in 1973[11].

The aim of this paper was to assess the potentially damaging effects of alcohol intake during pregnancy at all intake levels, the attitudes and knowledge among pregnant women and health personnel towards the issue, drinking patterns, and how official recommendations are handled in everyday clinical practice by health personnel.

METHODOLOGY

A systematic literature search in PubMed was performed for each of the topics: Foetal/fetal damage, attitudes and knowledge, drinking patterns, and recommendations. Search terms may be obtained from the author. All identified records were screened for eligibility by article title. Abstracts were read if the study appeared to be relevant for inclusion. Full text of all cited papers were read. The computerized literature search was supplemented with a hand-search of the bibliography of all included papers. The study selection was done by the author.

A brief introduction to measurement of alcohol intake during pregnancy

A single measure of overall consumption does not necessarily give a sufficient picture of the actual pattern of consumption: Patterns of alcohol consumption are often complex, and much too often alcohol consumption is categorised in an oversimplified manner. In clinical and scientific practice, the alcohol consumption pattern of an individual is usually described by three components: Frequency, quantity, and variability[12], and a fourth component is now being assessed in more and more studies: Timing[13]. Most often a measure of the average number of standard drinks per day or per week at a more or less well-specified point in time during pregnancy is provided (measuring frequency and quantity, *i.e.*, the number of drinking episodes × the number of standard drinks on each episode). Many attempts have been made to include a measure of variability into measures of quantity and frequency, creating a quantity-frequency-variability measure[12]. Variability is often measured as binge drinking, usually defined as intake of ⩾ 4 or ⩾ 5 drinks on a single occasion. Binge drinking is incorporated into many of

these measures and indices. Binge drinking, however, is now often used as a separate exposure and timing of such episodes may be of importance.

Other aspects of alcohol consumption such as context (setting, *i.e.*, private *vs* public, *etc.*), unit size and type of alcohol are scarcely reported. However, the potentially harmful effects of alcohol on the foetus are most likely caused by ethanol itself, and hence the type of alcohol is unlikely to be of any importance, as suggested in some studies[14].

No reliable or valid biomarkers of alcohol intake during pregnancy have been found.

THE DAMAGING EFFECTS OF ALCOHOL DURING PREGNANCY - WHAT IS THE CURRENT EVIDENCE?

Average alcohol intake

FAS is a diagnostic entity with fairly well defined diagnostic criteria[15], but even so diagnostic criteria differ somewhat and the diagnosis may be difficult[16]. Confirmed prenatal alcohol exposure is not required to make a diagnosis, but all three of the following findings are required, although some differences in diagnostic criteria are observed within each category[15,16]: (1) Documentation of at least 2[16] or all 3[15] of the following facial features (smooth philtrum, thin vermillion border, and small palpebral fissures); (2) Documentation of growth deficits (Confirmed, age, sex, gestational age, and race or ethnicity adjusted prenatal or postnatal height or weight, or both, at or below the 10th percentile, documented at any one point in time); (3) Documentation of CNS abnormality [Ⅰ: structural (small head circumference or brain abnormalities observable through imaging)[15,16], Ⅱ: neurological (not due to a postnatal insult or fever)[15], or Ⅲ: functional][15]. Functional deficits may be either global cognitive or intellectual deficits representing multiple domains of deficit with performance below the 3rd percentile (2 standard deviations below the mean for standardized testing); or functional deficits below the 16th percentile (1 standard deviation below the mean for standardized testing) in at least three of the following domains: (1) cognitive or developmental deficits or discrepancies; (2) executive functioning deficits; (3) motor functioning delays; (4) problems with attention or hyperactivity; (5) social skills; and (6) other, such as sensory problems, pragmatic language problems, or memory deficits.

Apart from the diagnostic features mentioned above, FAS has been associated with a huge number of malformations, which are not specific for FAS, but still may be caused by the excessive, high average daily alcohol intake, *e.g.*, craniofacial such as microcephaly, ptosis, retrognathia, micrognathia/flat midface, maxillary hypoplasia, and short upturned nose; skeletal such as pectus excavatum, joint defects, radioulnar synostosis, hypoplastic fingernails and toenails; cardiac such as atrial- and ventricular septal defects; cleft lip and/or palate; ocular defects including myopia, strabismus and microphthalmia; dental such as dental malocclusion, hypoplastic/misaligned teeth and faulty enamel; hypospadias, hypoplastic/dysplastic kidneys and inguinal hernia[16-19].

FAS represents the severe end of the Foetal Alcohol Spectrum Disorders (FASD), a widely used term for a group of at least three types of conditions[16,20]: FAS, Alcohol-Related Neurodevelopmental Disorder (ARND), and Alcohol-Related Birth Defects (ARBD). Some have attempted to define ARBD (malformations) as a diagnostic entity including confirmed maternal alcohol exposure, ≥ 2 facial features as mentioned above, and a combination of structural defects/malformations[16], although this is not universally acknowledged. FASD and ARND (*e.g.*, intellectual disabilities, learning and behaviour problems), are umbrella terms and are not at this point diagnostic entities[15,16]. Some also include partial FAS as an additional entity[16].

FAS and all the characteristics associated with it is by definition caused by (high average daily) alcohol intake during pregnancy. To the extent that smaller amounts of alcohol are potentially harmful, the effects are likely to be the same but smaller.

Anthropometric measures and growth: A recent meta-analysis assessed the association of average alcohol consumption with low birth weight and being small for gestational age (SGA)[21]. The meta-analysis suggested a non-linear association[21]. The meta-analysis is interesting for several reasons: In an analysis of any alcohol use *vs* no alcohol use, including a total of 28 studies, alcohol users were at increased risk of having children with low birth weight (RR = 1.12, 95%CI: 1.04-1.20). Not surprisingly, studies with no confounder control (12 studies) showed a higher increased risk (RR = 1.27, 95%CI: 1.00-1.61), while studies adjusting for potential confounders (17 studies) showed an insignificantly increased risk of low birth weight (RR = 1.06, 95%CI: 0.99-1.13). The pooled odds ratio of SGA in all studies (11 studies) was 1.11 (95%CI: 0.95-1.30), and in studies that adjusted for confounders it was 0.99 (0.89-1.10).

However, looking at any alcohol intake, does not distinguish between low and high alcohol intake. In the study, meta-regression was carried out using linear as well as first-order and second-order fractional polynomial regression. For both low birth weight and SGA polynomial regression fitted the data better than linear regression. Intake of less than one drink a day on average showed no association with poor outcome, whereas intake of more than one drink per day on average was associated with a steadily increasing risk of low birth weight up to approximately 10-12 drinks per day (RR = 7.48, 95%CI: 4.46-12.55)[21].

Preterm birth

The same meta-analysis showed data on preterm

birth[21]. In an analysis of any alcohol use *vs* no alcohol use, including a total of 21 studies, alcohol users were not at increased risk of preterm birth (RR = 1.03, 95%CI: 0.91-1.16). Studies adjusting for potential confounders (11 studies) yielded an attenuated estimate (RR = 0.93, 95%CI: 0.86-1.01). Again, for preterm birth, polynomial regression fitted the data better than linear regression. Intake of less than 1½ drinks a day on average showed no association with preterm birth, whereas intake of more than 1½ drinks per day on average was associated with a steadily increasing risk of preterm birth with increasing alcohol intake. For women drinking three drinks per day on average, the risk of preterm birth was 23% more likely than in nondrinking mothers (RR = 1.23, 95%CI: 1.05-1.44)[21].

In general, the relative risks, but not necessarily the differences between the two risk estimates, for very preterm birth (before 32 wk of gestation) are higher than the relative risks for moderate preterm birth (32-36 wk of gestation)[14]. Mode of delivery does not seem to affect the risk[22].

Foetal death - spontaneous abortion and stillbirth

From a methodological point of view, spontaneous abortion is perhaps one of the most difficult pregnancy outcomes to assess, especially in the first trimester. To mention but a few: Variation in self-testing behaviour, *i.e.*, variations related to the different gestational ages at which different women choose to perform a pregnancy test - women testing themselves very early in pregnancy will appear to have higher abortion rates than women who do not[23]. Very early spontaneous abortions (*i.e.*, weeks 0-6) are usually not recognized, and hence these are not included in studies on spontaneous abortions. Most studies apply logistic regression analysis, and they will therefore tend to overestimate the risk of early spontaneous abortions because the odds ratio will overestimate the true risk ratio. This problem may be dealt with by applying survival analysis techniques with delayed entry or left truncation, so that women do not inappropriately contribute time at risk before recognition of pregnancy[23]. Survival analysis also allows pregnancies that end in induced abortion to contribute time at risk to the analyses, since such pregnancies are also at risk of spontaneous abortion until the day of the induced abortion[23]. Only few studies have previously addressed this problem by using Cox proportional hazard models with delayed entry[24-26].

Increased risk of early spontaneous abortion has been reported in alcoholics[27,28]. At lower intake levels, some studies show no association[29-33], while most studies seem to suggest an increased risk of first trimester spontaneous abortion with an intake of $\geqslant$ 1 drink/d on average[34-36]. Two studies with open ended high intake group of > 3[25] and $\geqslant$ 5[24] drinks/wk on average, respectively, suggested an increased risk within this group, but because of the open ended categorization it is unclear at what level the actual effect increases.

A recent (and much cited) study showed an increased risk of first trimester spontaneous abortion at intake levels of 2-3½ drinks/wk on average (Hazard ratio = 1.66, 95%CI: 1.43-1.92)[26]. As for second trimester spontaneous abortions, the majority of studies show no association, although two studies showed an increased risk at an intake of $\geqslant$ 1 drink/d on average[35,36]. Again, a recent study showed an increased risk of vey early second trimester spontaneous abortion (weeks 13-16) at intake levels of 2-3½ drinks/wk on average (Hazard ratio = 1.57, 95%CI: 1.30-1.90)[26].

Interestingly, the authors of the one study showing an association between average intake levels of 2-3½ drinks/wk on average and first and early second trimester abortions, found hardly any association between alcohol binge drinking and spontaneous abortion, as mentioned below[37]. It seems biologically implausible that in the same population 2-3 drinks/wk on average should increase the risk, while intake of $\geqslant$ 5 drinks on a single occasion does not.

The definition of stillbirth differs between studies, with gestational age usually varying between $\geqslant$ 22 wk or $\geqslant$ 28 wk of gestation. In most studies, the rate of stillbirth has ranged between 3 and 6 per thousand[26,38]. While children of alcoholics are probably at increased risk of stillbirth[28], in the majority of studies no association or even a slightly increased risk among abstainers compared with women with low intake has been described[26,38]. One study with an open-ended high intake group of $\geqslant$ 5 drinks/wk on average has suggested an increased risk within this group[39].

Malformations

As mentioned above, FAS has been associated with a large number of malformations in different parts of the body. Similar malformations have been described in children of alcoholics without other signs of FAS. At lower intake levels, intake of $\geqslant$ 3 drinks/d on average has been associated with craniofacial and genitourinary malformations[40,41], and intake of $\geqslant$ 1-2 drinks/d on average has been associated with musculoskeletal malformations and malformations of the sex organs and inguinal hernias[40,42]. A single study has shown increased risk of cryptorchidism among boys of women reporting intake of $\geqslant$ 5 drinks/wk on average, with increasing risk up to $\geqslant$ 9 drinks/wk on average[43]. Unfortunately, no estimate was reported separately for the 5-8 drinks/wk group, making it unclear where the actual effect started. One study, using different assessments of alcohol consumption, suggested a possible threshold for the risk of malformations. Although different measures yielded different thresholds, the lowest level at which an effect was observed was 0.5 ounces/d on average corresponding to approximately 1 drink/d on average[44].

While timing of alcohol consumption is likely to be an important issue when assessing the risk of malfor-

mations, few studies have studied this aspect.

Neuropsychological development

Daily average intake of alcohol during pregnancy may affect intelligence[45,46]. IQ may be reduced by up to 25 IQ points in children of alcoholics compared to children of women with no or very limited intake, whereas intake of 2-4 drinks/d on average may reduce IQ by 5-7 IQ-points[47,48].

Executive functions[49,50] and attention deficits in children are among the most commonly reported effects of daily drinking during pregnancy[51-53]. It has been suggested that the attention deficit potentially caused by high prenatal alcohol exposure may constitute a specific subtype of Attention Deficit Hyperactivity Disorder[54]. Cerebral structural changes after prenatal alcohol exposure have been observed in several areas considered to be involved in attention processes[55].

Daily average prenatal alcohol exposure has also been associated with deficits in, *e.g.*, speed of information processing[56], memory[52], learning[57], spelling, and behaviour[57]. Children of alcoholics have also been reported to have more psychiatric and psychopathological symptoms[58].

Based on > 30 studies a recent systematic review showed that among studies reporting maternal intake of more than four drinks per day on average, only one study showed no effect on motor function, while among all studies reporting intake levels of less than 10 drinks/wk on average, only one study showed deficits[59] in gross and fine motor function. Intake of 1-7 drinks/wk on average was not associated with such deficits[59].

In a recent meta-analysis, the association between average alcohol intake of 0 - ⩽ 6 drinks per week on average and neuropsychological development was assessed as follows: (1) > 0 - ⩽ 3 drinks per week and visual and motor function, cognition, behaviour, language and verbal function; (2) 3- ⩽ 6 drinks per week and visual and motor function, attention, cognition, behaviour, language and verbal function; and (3) > 0 - ⩽ 6 drinks per week and visual and motor function, cognition and behaviour was evaluated[60]: Overall, no significant associations were observed between any of the exposure categories and the included neuropsychological outcomes (*i.e.*, visual and motor function, attention, cognition, behaviour, development, and language skills). When restricting analyses to studies of high quality (as determined by Newcastle-Ottawa-assessment-scale score), two significant results appeared, one showing a negative and one showing a positive effect: Three studies with approximately 11900 children aged 9 mo to 5 years yielded a statistically significant detrimental association between intake of 3 - ⩽ 6 drinks per week on average and child behaviour (P = 0.01)[60], while 7 studies with approximately 26100 children, yielded a small, statistically significant, beneficial association between intake of > 0 - ⩽ 6 drinks per week on average and child cognition (P = 0.03). It should be noted that cognition was measured by different IQ-tests in three studies (WPSSI-R, WISC, Raven), the Bayley Scales, Mental Development Index, in three studies, and the Bracken School Readiness Assessment in one study[60].

It is possible, however, that the effect of alcohol on child IQ may be modified by genetic predisposition[61], but very little evidence on this issue has been published. A recent study on behaviour not included in the meta-analysis showed no effect of average weekly intake of alcohol on behaviour in 5-year-old children[62].

In conclusion, average daily intake of alcohol during pregnancy has been associated with intrauterine growth restriction, preterm birth, foetal death throughout pregnancy, malformations, poor neurocognitive development and may cause deficits in psychomotor function, attention, memory, executive function, intelligence, behaviour and learning. However, less than average daily average consumption has not been systematically associated with any of these outcomes. With respect to early spontaneous abortion, however, the many methodological problems inherent in such studies should warrant caution in the interpretation of the results. Overall, the results suggest that if any, the potential effect of average weekly alcohol consumption is likely to be small.

BINGE DRINKING INDEPENDENTLY OF HIGH DAILY AVERAGE INTAKE

Pregnancy and birth outcomes: The risk of foetal death in clinically recognized pregnancies has been assessed in one study[37]. Binge drinking, including number of binge episodes and timing of binge drinking, was not associated with overall risk of foetal death or risk of miscarriage in the first or early second trimester (until pregnancy week 21)[37]. Women reporting ⩾ 3 binge episodes had an increased risk of stillbirth (week 22 or later, OR = 1.56, 95%CI: 1.01-2.40), but timing of binge drinking was not associated with stillbirth[37].

Few studies have assessed the association between alcohol binge drinking and anthropometric measures: In studies adjusting for potential confounders, no significant or clinically relevant associations were described between binge drinking and weight, length or head circumference at birth[63-67]. Only two studies reported an adjusted difference in birth weight, respectively -41 g 95%CI: -92; 10[65] and -41 g 95%CI: -108; 27 for ⩾ 2 binge episodes[67]. The remaining studies either did not show the adjusted results[63,66], or showed no measures of association, but simply stated that no differences were observed[64]. Number of binge episodes was not associated with anthropometric measures[67], while timing of binge drinking has not been reported.

Few studies, mainly of poor quality, have assessed birth defects including features of FAS[68]. One study reported that newborn children of binge drinkers had slightly shorter palpebral fissures, but no association

was reported with other facial features[69]. Two subsequent studies not included in the above systematic review[68] showed no association between binge drinking and cryptorchidism[43] or between number or timing of binge episodes and congenital heart defects, in particular atrial and ventricular septal defects[70].

A systematic review of the effects of alcohol binge drinking suggested that prenatal binge drinking might be associated with impaired neurodevelopment[68]. Based on five studies with different definitions of binge drinking, another systematic review concluded that the issue of whether prenatal alcohol binge drinking was potentially associated with motor dysfunction in children was unsettled[59].

These issues were updated in a recent meta-analysis including nine outcomes (visual and motor function, attention, memory, executive function, cognition, behaviour, language and verbal, academic reading performance, and academic math performance)[60]: When including all eligible studies irrespective of quality, a significant detrimental association between binge drinking and child cognition was observed (Cohen's d -0.13; 95%CI: -0.21, -0.05). The analysis included 8 studies on children aged 6 mo to 14 years. However, the results of this meta-analysis were no longer significant when limited to data from studies of high quality[60]. Analyses of motor function (6 studies), executive function (3 studies), attention (3 studies) and behaviour (5 studies) showed no significant or clinically relevant associations[60].

In conclusion, prenatal alcohol binge drinking independently of high, average daily intake does not seem to be systematically associated with short or long term adverse outcomes to a clinically relevant degree. However, timing of binge drinking is not well studied.

RECOMMENDATIONS

Official recommendations and guidelines from health authorities are meant to guide clinical practice and health behaviour among patients and the population at large. Many guidelines and recommendations are based on scientific evidence, but evidence evolves and changes over time, and the interpretation of the evidence may vary depending on the cultural setting. For example, the Gin Epidemic in England was following by a petition to Parliament to more strict control with the distillation process, while the Prohibition in the United States was followed by direct denial that alcohol during pregnancy might be harmful[3].

OFFICIAL RECOMMENDATIONS

In the 1990s, health authorities and health professionals in most countries recommended that pregnant women should abstain from alcohol during pregnancy[17,71-73]. However, in some countries, recommendations on alcohol during pregnancy have changed considerably over the past two decades.

In Australia, for example, the 1992 guidelines suggested that pregnant women should abstain from alcohol[73]. However, the 2001 guideline modified this view to suggest that while pregnant women should consider not drinking at all and should never become intoxicated, "if they choose to drink, over a week, should have less than seven standard drinks, and, on any one day, no more than two standard drinks" [74]. Two years before, in 1999, a comparable recommendation was issued by the Danish Health and Medicines Authority (previously Danish National Board of Health): "Avoid alcohol in pregnancy if possible; if you drink, drink no more than one drink per day; do not drink every day"[75]. In the United Kingdom, the recommendation from the Department of Health suggested that intake of up to 1-2 United Kingdom units once or twice a week may be acceptable.

In 2007, the Danish Health and Medicines Authority again changed its recommendation to: "If you are pregnant: Avoid alcohol. If you are trying to conceive: Avoid alcohol, to be on the safe side"[76]. Around the same time, a draft guideline was made available in Australia, leading to the 2009 guideline: "not drinking is the safest option" [77]. Only in the United Kingdom, the Department of Health and National Institute for Health and Clinical Excellence and RCOG still condone low levels of alcohol intake (as of November 2015): "Women who are pregnant or trying to conceive should avoid alcohol altogether". However, if they do choose to drink, to minimize the risk to the baby, we recommend they should not drink more than 1-2 units once or twice a week and should not get drunk"[78,79].

ACTUAL RECOMMENDATIONS FROM HEALTH PROFESSIONALS

While health authorities in most countries recommend abstinence from alcohol during pregnancy, little is known about the actual information practice of health professionals.

Doctors

In 2002-2003, in Australia, a postal survey among health professionals showed that only 57%-67% of general practitioners and obstetricians routinely asked pregnant women about alcohol use[80]. The complex recommendation (consider not drinking/do not become intoxicated/have < 7 drinks over a week/on any one day have no more than 2 standard drinks) was provided in its entirety by only 5% of obstetricians and 17% of GPS[80].

A Danish study among GPs in 2000 and 2009 showed that in 2000, when a complex recommendation was used, only 5% spontaneously mentioned all three statements that made up the recommendation (avoid alcohol in pregnancy/if you drink, drink no more than one drink per day/do not drink every day) and 26% explicitly said they did not know the recommendation. In 2009, when the recommendation had been

Table 1 Potential advantages and disadvantages of recommending abstinence *vs* a more condoning approach

	Abstinence	Condoning approach
Advantages	Simple message	Little evidence that a low intake is harmful
	No alcohol = no alcohol induced adverse effects	
	Safest choice considering potential uncertainties related to interpretation of the scientific evidence	
Disadvantages	Little evidence that a low intake is harmful	Complex message
	May cause guilt in women who have been drinking a few drinks, especially in early pregnancy	To regard recommendations as guidance rather than an absolute limit may increase alcohol consumption among pregnant women
	What are health professionals going to tell women who have been drinking a few drinks, especially in early pregnancy?	May be regarded as guidance rather than an absolute limit
	Disagreements between health authorities and health professionals may lead to confusion and worry among pregnant women	Alcoholics may have difficulties stopping after intake of only small amounts

changed into complete abstinence, 87% knew the new recommendation. Even so, only 53% recommended abstinence to pregnant women in 2009[81].

The fact that many doctors do not provide information to pregnant women in accordance with the official recommendations seems to be in accordance with the attitudes of many doctors. American gynaecologists have been shown not to consider a mean intake of 4-5 drinks/wk to be harmful[82], and only 51% of Danish GPs believed that pregnant women should completely abstain from alcohol[81].

Midwives and community nurses

Danish midwives have reported attitudes and information practice comparable with GPs: Thus, in 2009, only 46% recommended abstinence, even though more than 90% knew the official recommendation of abstinence, and only 48% believed that pregnant women should completely abstain from alcohol[83]. Among Australian community nurses caring for pregnant women 41% reported routinely asking about alcohol use[80].

ARGUMENTS FOR AND AGAINST DIFFERENT RECOMMENDATIONS

Some of the advantages and disadvantages of recommending abstinence *vs* a more condoning approach are listed in Table 1.

A general recommendation about alcohol intake during pregnancy may be based on two different arguments, both based on the existing literature[75]: (1) essentially, intake of small amounts of alcohol has not been consistently associated with adverse effects; (2) It has not been proved that intake of small amounts of alcohol in pregnancy is not harmful, hence pregnant women should abstain from alcohol - or as it is often phrased: No safe level of alcohol consumption has been established.

A recommendation of abstinence is based on the latter argument. However, most scientific studies are based on the (statistical) hypothesis that intake of small amounts of alcohol are not harmful to the foetus. But a hypothesis of no harm can never be proved, as it is impossible to prove that something does not exist.

ALCOHOL DRINKING AMONG PREGNANT WOMEN

Drinking patterns

Alcohol consumption among women of child bearing age is often high. This is concerning since many pregnancies are unplanned[84]. In the United Kingdom, approximately 85% of women of child bearing age drink alcohol[85], and in Denmark, Norway and Sweden as many as 89%-95% of pregnant women admit to drinking alcohol before pregnancy[86-88]. In the United Kingdom, the average consumption of women aged 16-44 years was approximately 10-11 drinks/wk in 2011[89], virtually unchanged since 2007[85]. In the United States, binge drinking prevalence (28.2%) and intensity (9.3 drinks per occasion) has been reported to be highest among persons aged 18-24 years[90] and this is in line with a general observation that, *e.g.*, college students in many countries report particularly high intake[91]. In Sub-Saharan Africa ten countries are among the 22 countries worldwide with the highest increase in per capita alcohol consumption in the recent years[92]. While the proportion of female abstainers is generally high in this region, the proportion of binge drinkers is high[92].

Even so, most people who binge drink are not alcoholics or alcohol dependent[93].

Among pregnant women, reported consumption is considerably lower, but with huge variation from one country to another. In Denmark and Norway, 85%-90% of pregnant women have been reported to reduce alcohol consumption after recognition of pregnancy[86,87].

In a Danish study, approximately 70% of pregnant women admitted to drinking alcohol during the second trimester, *i.e.*, after recognition of pregnancy[86]. Even so, the actual consumption level was low with an average of 1 drink/wk, and 92% of the women reported a maximum intake of 3 drinks/wk[86], comparable to a report from Sweden[88]. Approximately 1% admitted to drinking $\geqslant$ 7 drinks/wk[86]. In Norway, only 23%

report alcohol consumption after pregnancy week 12[87], comparable to new Danish data on current levels of alcohol intake, and in the United States, 15% reported any alcohol consumption, including 3.5% who admitted to either intake of ⩾ 7 drinks/wk or binge drinking[94].

Interestingly, while 25% in Denmark reported intake of 2 or more drinks on a single occasion in the 2nd trimester in the late 1990s[86] none did so in Sweden[88].

Interestingly, new up-to-date information on prevalence of alcohol consumption is difficult to find.

In Denmark, approximately 50% of pregnant women admit to alcohol binge drinking during pregnancy[12,86]. The majority do so before recognition of pregnancy with a peak in week 3 after the last menstrual period around the time of ovulation, and hence around the time of conception for most women[12]. In Norway, 25% admit to binge drinking in weeks 0-6, *i.e.*, before recognition of pregnancy[87]. In the United States, only 3% have previously admitted to binge drinking during pregnancy[95].

There may be several explanations for these differences. As opposed to studies investigating the association between an exposure (*e.g.*, alcohol consumption) and adverse outcomes[96], analyses of prevalence of consumption are likely to be much more influenced by selection bias. For example, the above study showing that nearly 70% of pregnant women drink alcohol during pregnancy, and that 50% binge drink in early pregnancy, was based on a sample of 92% of eligible pregnant women[86]. A large, prospective cohort study from the same period showed that only 27% of pregnant women in Denmark reported binge drinking in early pregnancy[97], but the participation rate was lower, approximately 30%[97,98]. While the former study used personal interviews the latter used telephone interviews, but the questions on binge drinking were essentially identical. Hence, the discrepancy in proportions of binge drinkers was most likely due to selection bias. Previous studies have suggested a North-South difference in drinking pattern in Europe, but especially among young (non-pregnant) people, this difference is diminishing[99]. Therefore, reported differences in consumption patterns should be interpreted with great caution.

CHARACTERISTICS OF ALCOHOL DRINKERS DURING PREGNANCY

With a view to identifying alcohol drinkers during pregnancy, only few studies have attempted to assess risk factors associated with average alcohol intake and binge drinking during pregnancy[86,94,95,100].

Even so, the pattern of risk factors is fairly consistent across different populations: Smoking and being single are consistent risk factors for high average alcohol intake, while employment and high income are less consistent findings[86,94]. Consistent risk factors for binge drinking are smoking and being single[86,95,100]. Nulliparity and employment/high income are less consistent findings[86,95,100]. One study has assessed risk factors for binge drinking before and after recognition of pregnancy and found somewhat different patterns[100]: Age 25-29 years, nulliparity, ⩽ 12 mo's time to achieve a pregnancy, late recognition of pregnancy at week 6 or later, being a lower grade professional compared to being unskilled or unemployed, smoking, being single and some average alcohol intake were risk factors in the period before recognition of pregnancy. Multiparity, overweight and obesity, unplanned pregnancy, early recognition of pregnancy, self-reported mental disorders, smoking, being single and some average alcohol intake were risk factors after recognition of pregnancy[100].

Characteristics associated with alcohol-related admissions (based on ICD-10 codes) in pregnancy have been studied in Australia: Residence in a remote/very remote area, being Australian-born, having had a previous pregnancy, smoking in the current pregnancy, and presenting late to antenatal care[101].

These findings would suggest that while many smokers and single women may not have a problem with alcohol, health professionals should perhaps be more aware of potential alcohol problems among these groups and actively ask them about alcohol consumption. To the extent that nulliparous women engage in binge drinking before recognition of pregnancy more often than multiparous women health authorities should focus their information on binge drinking to young women and women planning their first pregnancy.

ATTITUDES AND COMPLIANCE WITH OFFICIAL RECOMMENDATIONS

While it is clear that many health professionals do not seem to recommend abstinence to pregnant women, few studies have assessed what pregnant women actually believe or do, and whether their attitudes and drinking habits are influenced by official recommendations and advise from health professionals.

In a Danish study, 76% of the women considered some alcohol intake during pregnancy to be acceptable, mostly on a weekly level[102]. Binge drinking, however, was considered to be harmful by 85%[102]. These attitudes were not associated with knowledge about the official recommendation or with discussions between the woman and her general practitioner or midwife about alcohol during pregnancy[102]. These results seem to be in line with data from Australia, showing that 72% of pregnant women did not comply with the recent 2009 recommendation of alcohol abstinence during pregnancy[103].

A few studies have evaluated the potential change in alcohol consumption in relation to changes in guidelines, allowing some alcohol intake in pregnancy: Both in Australia[104] and in Denmark[97] no significant or clinically relevant changes in drinking habits were found among pregnant women after relaxation of the

guidelines for sensible drinking during pregnancy.

Most Danish women had received information on alcohol from the mass media or relatives, but most women believed that information about alcohol during pregnancy could best be communicated to them by health personnel[102]. Only 21% were aware of the official recommendation from the Danish Health and Medicines Authority[102]. One third had discussed alcohol with their general practitioner or midwife, but these women had mostly been advised that some alcohol intake was acceptable[102].

THE ROLE OF RANDOM ERROR AND BIAS

It is evident that an average daily intake of alcohol during pregnancy is potentially harmful and should be avoided. However, it is less clear if average weekly intake of alcohol may have adverse effects on foetal development and later child development, since the vast majority of studies show no association. If indeed low, average weekly amounts of alcohol during pregnancy are harmful, the effects are likely to be small. When planning and carrying out studies looking for potentially small differences, the methodological challenges are inherently greater, and assessment of the influence of random error and systematic bias becomes paramount, and this assessment may lead different researchers to different views.

The results of any epidemiological study can potentially be due to random error or bias. Considering the increasing number of studies on the association between prenatal alcohol consumption and adverse pregnancy outcomes, the role of chance becomes an ever more important factor to consider when assessing the evidence. In the case of multiple statistical tests, one or more significant findings - positive or negative - may be expected because of chance alone, even in the absence of a true effect. For example, multiple tests may be conducted and reported in a single paper[105], or in a meta-analysis, for example the cited review on child neuropsychological development involving numerous studies[60], where a few significant findings would be expected.

Many of the studies, particularly those with long-term follow-up of children, are hampered by potential selection bias because of low participation rates, or missing information on key variables including key confounders; and because participants and non-participants in some studies differed substantially with respect to a large number of important potential confounders[106]. One way of dealing with this problem is multiple imputation, which has been used in recent studies[13].

Publication bias is a potential problem, and if so studies showing no association between alcohol intake and adverse outcomes are most likely to remain unpublished.

Information bias is a possibility in all studies of alcohol during pregnancy[107]. Generally, it is usually assumed that pregnant women probably tend to underestimate their alcohol intake, whereas overestimation - while not impossible - is unlikely. In prospective cohort studies, non-differential misclassification would be expected, because the outcome is unknown at the time of reporting alcohol consumption. Hence, with two exposure categories, as seen in some studies, results will most likely be biased towards the null, *i.e.*, no effect. Even so, with several exposure categories, non-differential misclassification due to underreporting could be expected to lead to bias away from the null value[107].

Confounding from important confounders was not accounted for, especially in many studies from the 1980s and early 1990s. Residual confounding is therefore likely to be a problem in many studies, and may explain both findings of adverse as well as beneficial effects.

As suggested by the Newcastle-Ottawa-Assessment-Scores in the recent meta-analysis on child neuropsychological development[60], few studies achieve very high scores, suggesting ample room for methodological improvement in future studies.

DISCUSSION

Is it possible to reach a common consensus on everyday praxis?

The main arguments for abstinence from alcohol during pregnancy is that no safe level of drinking has been established, and that alcohol induced adverse effects cannot occur in the absence of alcohol intake. While the latter argument is indisputable, the former may be challenged. As suggested above, there is no clear, systematic evidence that intake of a few alcohol containing drinks a week will harm the foetus to any measurable degree.

It is particularly interesting that medical ethics have moved in the direction of increased autonomy and informed choice for patients. The British Medical Association advices that "Doctors should respond honestly to direct questions from patients and, as far as possible, answer questions as fully as patients wish"[108]. It has been suggested that where the available evidence does not suggest a clear and unambiguous answer to the question "how much is safe to drink during pregnancy?", an honest response would be to communicate this uncertainty to the pregnant woman[109].

While health authorities generally favour informed choice in many circumstances, based on impartial and neutral information, this principle does not seem to apply when it comes to alcohol in pregnancy. If it did, health personnel should convey to pregnant women the potential harmful but also the potential beneficial effects and the potential uncertainty related to individual vulnerability at low intake levels. No health authorities advocate this, probably based on the assumption that the risk of harming an otherwise healthy foetus (non-

maleficence) should be prioritized over the risk of failing to do good (beneficence)[109]. For example, in an editorial from 2011, a representative of The Danish Health and Medicines Authority wrote that "it seems that alcohol, especially in the first 3 mo of pregnancy, may increase the risk of miscarriage, low birth weight, preterm birth and delayed development in the uterus - even at low intake levels"[110], referring to a study on the risk of preterm delivery[14]. This study showed a significantly increased risk of preterm delivery only for nulliparous women drinking ⩾ 7 drinks/wk (OR = 2.91, 95%CI: 1.29-6.55), but a significantly reduced risk for all women drinking 2-3½ drinks/wk (OR = 0.80, 95%CI: 0.68-0.96)[14].

At the same time it is evident from the few relevant studies that many health professionals do not believe that pregnant women must totally abstain from alcohol[80-83]. Also, pregnant women in Australia and Denmark did not seem to change their drinking habits, even when less restrictive recommendations were issued[97,104]. Hence, it seems that the mere existence of an official guideline or recommendation concerning alcohol in pregnancy has not been enough to standardize the information provided to pregnant women and to modify their behaviour in relation to alcohol.

In some cases, guidelines from health authorities are written by civil servants and epidemiologists with no or very limited clinical experience. In Denmark, the literature review and guideline from 1999 allowing a small, weekly intake, was written mainly by clinicians[75]. The 2007 recommendation of abstinence and the arguments supporting it was written solely by representatives of The Danish Health and Medicines Authority[76] and two epidemiologists[111].

Perhaps this is the real issue: Guidelines issued by many health authorities do not take into account the everyday clinical communication, where pregnant women turn up admitting to some alcohol intake, often one drink per week or even less. Health personnel have to advise pregnant women in these situations, and telling the pregnant woman that a single drink may have harmed the foetus is not in line with current evidence. But if one drink is unlikely to harm the foetus, where is the limit? This question is asked every day, and if health authorities do not supply health personnel with an answer, each clinician will have to come up with a responsible answer in line with current evidence.

The Danish Health and Medicines Authority write that "General practitioners and midwives will meet pregnant women, who have a bad conscience, because they have been drinking alcohol, before recognition of pregnancy. These women should be met with a risk assessment based on the existing evidence that intake of one drink a day is associated with a small risk for the child"[76]. It is left to the health personnel to decide if the focus of the information should be "there is a (small) risk" or "the risk is negligible, so do not worry".

Most likely the discrepancy between guidelines and recommendations from health authorities and the information practice of health personnel will continue to exist. Mainly because guidelines of total abstinence are not clearly evidence based and not in line with current focus on autonomy and informed choice for patients, and because guidelines may be written by non-clinicians, who do not consider and have no experience with the everyday communication between health personnel and pregnant women.

There is little evidence to support a guideline or recommendation of total abstinence, and considering the vast number of studies already published on the topic, it is perhaps surprising that so few studies suggest a risk at low intake levels. Guidelines recommending abstinence may seem an obvious choice because the message is simple. However, simplistic messages that are not clearly evidence-based do not necessarily answer the specific and detailed questions of pregnant women. Health personnel are faced with an increasing amount of information that they are expected to pass on to pregnant women, including messages about lifestyle, and the information must be given within the context of the individual woman. In the absence of clear evidence that abstinence from alcohol is the only right choice, many clinicians will probably continue to focus on other important aspects of pregnancy rather than insisting that a drink a week or less is potentially harmful.

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Laparoscopic surgery in pregnancy

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Abstract

Each year, roughly 2% of pregnant women will undergo non-obstetrical abdominal surgery. Appendicitis, symptomatic cholelithiasis and adnexal masses are some of the common diagnoses encountered. Pregnancy poses challenges in the diagnosis and surgical management of these conditions for several reasons. Since the 1990's, laparoscopic surgery has gained popularity and in the past few years has become the standard of care for pregnant women with surgical pathologies. The advantages of laparoscopic surgery include shorter hospital stay, lower rates of wound infection, and decreased time to bowel function. This brief review discusses key points in laparoscopic surgery during pregnancy and highlights studies comparing laparoscopic and open approaches in common surgical conditions during pregnancy.

Key words: Pregnancy; Laparoscopy; Surgery

Core tip: Laparoscopic surgery is increasingly common in pregnancy. The indications for surgery are similar to non-pregnant patients in the same age population. The benefits of laparoscopic surgery include decreased length of staying, lower rates of wound infection and ventral hernia apply to pregnant patients as well. This brief review highlights studies comparing laparoscopic surgery to open approach in common clinical scenarios.

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INTRODUCTION

Roughly two percent of pregnant women require nonobstetric surgical procedures each year[1]. The common indications for surgery are similar to an age-matched, non-pregnant population and include appendicitis, symptomatic cholelithiasis, breast masses and trauma. However, changes in maternal-fetal physiology and

maternal organ placement can obscure the diagnosis and make treatment in these patients challenging since even common physiologic changes in pregnancy can present as an acute. The physical examination of a pregnant female change with the gestational age and the usual workup of a surgical abdomen using laboratory tests and imaging is also of limited value considering the physical and chemical changes that take place during pregnancy[2]. Furthermore, for many years, laparoscopic surgery was considered hazardous and was contraindicated during pregnancy. With the increasing use and development in surgical and laparoscopic techniques, the advantages of laparoscopy were evident in pregnant patients. In order to understand the concerns and risks of laparoscopic surgery in pregnancy and avoid them, one should be familiar with the difference in physiology and anatomy in a pregnant patient. This review article will evaluate the benefits and use of laparoscopic surgery in pregnancy in comparison to contemporary approaches.

RESEARCH

A systematic literature search was conducted in the PubMed, Cochrane, MEDLINE with the following individual and combined key words: Pregnancy, surgery, laparoscopy, minimally invasive surgery, appendectomy, cholecystectomy, adnexal disease, randomized, meta-analysis. References cited in the articles retrieved were also searched in order to identify other potential sources of information. The results were limited to human studies available in English.

DIFFERENCES IN ANATOMY AND PHYSIOLOGY

There are numerous anatomic and physiologic changes in pregnant woman that affect the clinical presentation and the decisions made when planning surgery and anesthesia.

Cardiovascular

Circulating volume in the pregnant patient can increase by up to 40% and cardiac output can increase by as much as 45%[3,4]. These changes occur gradually over the course of the pregnancy to a peak at around 32 wk gestational age. Overall systemic vascular resistance is decreased to accommodate the increased load of circulating volume. While the circulating volume is increased, only a percentage is erythrocyte volume and mass, creating a physiologic anemia of pregnancy. The minute ventilation in pregnant women is 50% higher than that in non-pregnant women. This change results in a marked decrease in arterial carbon dioxide concentration, and a resulting mild respiratory alkalosis. There is also increase in heart rate and oxygen consumption due to increased demands by the fetus and placenta.

Gastrointestinal

There is a decrease in gastrointestinal motility caused by mechanical changes in the abdomen from an enlarging uterus as well as from smooth muscle relaxation caused by the increased production of progesterone. The uterine fundus at the end of the first trimester is at the level of the pubic symphysis, but by the end of the second trimester it is at the level of the umbilicus. Furthermore, the decrease in lower esophageal sphincter competence caused by mechanical shifting from the gravid uterus combined with increased intra-abdominal pressure leading to an increase in reflux and dyspepsia[5]. These changes have led to a recommendation of rapid induction anesthesia in pregnant women undergoing surgery.

Hepatobiliary

Hepatic and biliary changes include elevated liver enzymes as well as a relative decrease in concentration of plasma proteins from dilution[4,5]. This leads to higher free levels of protein bound drugs, which adds another level of consideration to anesthetic techniques. Throughout pregnancy, there is an increase in gallbladder volume and delayed emptying, which lead to a higher incidence of gallstones[6]. Portal pressures are higher due to increased abdominal pressure, which lead to an increased incidence of both gastric and esophageal varices as well as symptomatic hemorrhoids.

Renal/hematologic

In the kidney, there is an increase in the glomerular filtration rate by 50% with a concurrent decrease in plasma values of creatinine, urea, and uric acid. There are changes in the coagulation factors during pregnancy[3]. These changes include an increase in fibrinogen, factor Ⅶ, and factor Ⅻ, and a decrease in antithrombin Ⅲ. All of these changes result in an increased risk of venous thromboembolism.

Even knowing the physiological changes occurring in pregnancy, distinguishing between abdominal pain caused from normal pregnancy and abdominal pain caused by a pathophysiologic cause is challenging. Abdominal pain, nausea and vomiting are common in pregnancy. Tachycardia, mild hypotension and low grade fever are also common. Changes in the position and orientation of the abdominal organs from the enlarging uterus can change the physical examination expected in some abdominal pathologies. Take for instance that the average pregnant patient with radiographically diagnosed appendicitis presents with rigidity in only 55% of cases and rebound tenderness in only 60%[2]. The progressive rise in the leukocyte count throughout pregnancy and the imaging limitations can often delay diagnosis. To illustrate the harm that a confusing diagnostic picture can play, delaying surgery up to 24

h in patients with suspected appendicitis can increase perforation rate by 14%-43%[7,8].

LAPAROSCOPIC SURGERY IN PREGNANCY

In 1989, Mazze *et al*[9] published data from three Swedish healthcare registries between the years 1973 to 1981 and investigated adverse outcomes of non-obstetrical operations during pregnancy. Five thousand, four hundred and five operative cases were evaluated, 16.1% of which were diagnostic laparoscopies. They reported no increase in stillbirths or congenital anomalies in the pregnant patient who underwent surgery. However, there was an increase in low birth weight infants, premature delivery, and infants who died within 168 h from delivery compared with women who did not require surgery. There was, however, no difference in adverse outcomes between the laparoscopy and open surgery groups. Diagnostic laparoscopies were normally done to diagnose ectopic pregnancies before converting patients to laparotomies, but by the mid 1970's, many adnexal surgeries were being fully done laparoscopically.

For many years, pregnancy was considered a relative contraindication for laparoscopic surgery. The lack of information and experience with laparoscopy in these patients raised concerns about the effect of CO_2 pneumoperitoneum used on venous return, cardiac output, uterine perfusion and fetal acid base status. Furthermore, there was a concern about the risk of injury to the uterus with laparoscopy. Starting in the late 1990's, more and more laparoscopy was being performed for diagnosis and management of abdominal pain in the pregnant patient. In 1997, Reedy *et al*[10] retrospectively reviewed 413 laparoscopic procedures performed during pregnancy in the first report to specifically address the safety and complications of laparoscopy in pregnancy. They concluded that there is no difference in maternal or fetal complication rate between patients that had laparoscopic surgery and patients that had open surgery. In 2008, Jackson *et al*[11] comprehensively reviewed the literature which supported the safety and efficacy of laparoscopy in cholecystectomy, appendectomy, solid organ resection and oophorectomy in the gravid patient. The authors made their recommendations based on existing data, or consensus of expert opinion when little or no data were available. This and other publications have led to the adoption of laparoscopic surgery as a safe technique during pregnancy when used selectively and carefully.

Similar to the non-pregnant patient, decreased pain is one of the main benefits of laparoscopic surgery. The need for less narcotic pain control in laparoscopic surgery may decrease fetal depression. Other advantages include lower rates of wound infection and incisional hernia, decreased manipulation of the uterus, diminished postoperative maternal hypoventilation, decreased risk of thromboembolic events, faster recovery with early return to normal function and decreased risk of ileus[10,12,13]. Laparoscopy may have special advantage during pregnancy since abdominal organs may shift, and their exact location may be difficult to predict. The appendix for instance, may significantly shift from the right lower quadrant owing to the gravid uterus. Laparotomy for appendiceal disease may require large incision during pregnancy to localize the appendix. Diagnostic laparoscopy is safe and effective when used in selected patients and can be an alternative to radiologic imaging[10,11,14,15]. It avoids fetal radiation, provides direct visualization of the pathology, and allows rapid surgical treatment of the problem at the time of diagnosis. On the other hand, the potential hazards of laparoscopy include uterine injury during trocar placement, decreased uterine blood flow, preterm labor due to increased intra-abdominal pressure, and decreased visualization with the enlarged uterus.

Historically, it was believed that laparoscopic surgery should not take place in the first trimester of pregnancy since the fetus is still undergoing organogenesis, but it has been shown that laparoscopy can be performed safely during any trimester with minimal morbidity to the fetus and the mother. There have been no studies showing long term negative cognitive or motor defects in child after mother undergoes laparoscopic surgery. Postponing necessary operations may increase the rates of complications[10,13,15,16]. It has also been suggested that laparoscopic surgery should not be attempted after 28 wk of pregnancy due to the size of the uterus, but several studies showed that laparoscopic cholecystectomy and appendectomy have been successfully performed late in the third trimester[15,17].

Laparoscopic surgery can be safely performed with the help of several modifications of surgical technique. When the pregnant patient is placed in a supine position, the gravid uterus places pressure on the inferior vena cava resulting in decreased venous return to the heart, decreased cardiac output with concomitant maternal hypotension, and decreased placental perfusion. Hence, the patient should be positioned in the left lateral decubitus whenever possible to minimize compression of the vena cava[3,18].

The open technique for abdominal access can reduce the risk for uterine and other abdominal organ injury. However, using a Veress needle for insufflation or optical trocar can be done safely if the site of initial abdominal access is adjusted according to fundal height and the abdominal wall is elevated[15,17,19].

Adjustments in trocar placement must be made to avoid uterine injury and improve visualization. An angled laparoscope may help in better viewing of areas around the uterus.

Pneumoperitoneum remains a concern amongst surgeons because of its effect on uterine blood flow and pulmonary function. It is recommended that intraabdominal insufflation pressures be maintained at less than 12 mmHg to avoid worsening pulmonary physiology in the pregnant women[3]. However, insufflation less

than 12 mmHg may not provide adequate visualization of the intra-abdominal cavity. Furthermore, pressures of 15 mmHg have been used during laparoscopy in pregnant patients without increasing adverse outcomes to the patient or her fetus[20]. Because CO_2 exchange occurs with intraperitoneal insufflation there has been concern for deleterious effects to the fetus from CO_2 absorption. However, despite the large experience with the use of laparoscopy pregnancy, there are no data showing detrimental effects to human fetuses from CO_2 pneumoperitoneum. Additionally, pneumoperitoneum promotes lower extremity venous stasis already present in pregnant woman, and along with the hypercoagulable state that is induced by pregnancy and associated hormones, there is an ever further increased risk of Deep Vein Thrombosis. Therefore, pneumatic compression devices are used whenever possible and DVT prophylaxis should be considered when indicated[21].

Fetal respiratory acidosis with subsequent fetal hypertension and tachycardia has been observed in gravid animal models, but the effect was lessened by maintaining maternal respiratory alkalosis[22]. Fetal acidosis with insufflation has not been documented in the human fetus, but concerns over potential detrimental effects of acidosis have led to the recommendation of intra-operative maternal CO_2 monitoring. That can be done either by maternal blood gas or end-tidal carbon dioxide monitoring[23].

A preoperative obstetrics consultation should be obtained for all pregnant women who will be undergoing surgical therapy, but should not delay definitive surgical treatment as that may increase the risk of morbidity to the mother and fetus. It is recommended to perform preoperative and postoperative monitoring of the fetal heart rate when possible[17]. It is generally recommended that post-operative patients should undergo cesarean sections for delivery of child so as not to disrupt any surgically placed materials such as sutures or staples[9]. The role of the obstetrician post-operatively is to monitor the fetus in a strict setting until both the mother and fetus are stable with sufficient pain control, care of wounds, and fetal monitoring.

COMMON SURGICAL PROCEDURES IN SURGERY

Appendectomy

Acute appendicitis is the most common non-obstetric indication for surgical intervention in pregnant women occurring as often as 1 in 500 pregnancies per year and most commonly presents in the 2nd trimester[5,6,24]. Accurate and timely diagnosis of appendicitis in the gravid patient may minimize the risk of fetal loss and optimize outcomes. Rupture of the appendix during pregnancy increases the risk for perinatal morbidity and mortality. Therefore, it is crucial to make an early diagnosis and proceed with timely surgical intervention.

Presentation of appendicitis in pregnancy is similar to the nonpregnant population with a few caveats. Most common complaints are anorexia, emesis, nausea, fever, and pain, which depending on the gestational age of the fetus can be right lower quadrant, right upper quadrant or flank, as the pain migrates further superior as the appendix gets displaced upwards secondary to the growing uterus. Also since there is an increased separation of the peritoneum from the abdominal organs, peritoneal signs such as rebound tenderness and involuntary guarding are less likely to be present.

Multiple retrospective studies consistently showed it is safe to use the laparoscopic approach with very low rates of preterm delivery and, in most series, no reports of fetal demise[16]. In 2010, a large hospital-based series evaluated laparoscopic *vs* open approach for pregnant patients with presumed acute appendicitis in which the authors concluded that laparoscopy is a safe, feasible, and efficacious approach for pregnant women[25]. A meta-analysis by Walsh *et al*[26] published in 2008 using 27 studies, looked at 637 women undergoing laparoscopic appendectomy and 4193 women undergoing appendectomy by open approach. There was an increased risk of fetal loss using laparoscopy, with fetal loss rate of 5.6% (35/624) in the laparoscopic group and 3.1% (128/4193) in the open group, which was statistically significant (P = 0.001). Preterm delivery was however increased in the open group with a risk of 8.1% (346/4193) *vs* 2.1% (13/624) in the laparoscopic group, also statistically significant. A population-based study published in 2007 by McGory *et al*[27] retrospectively reviewed all cases of women undergoing appendectomy between the years 1995 and 2002. Four hundred and four pregnant patients underwent laparoscopy and 2679 underwent laparotomy for suspected appendicitis. Once again, there was significantly higher rate of fetal loss (7%, 31/454) with laparoscopy compared with laparotomy (3%, 88/2679) (OR = 2.31). Preterm birth was 1% (1/454) in the laparoscopic group *vs* 8% (216/2679) in the laparotomy group. Another meta-analysis published in 2012 by Wilasrusmee *et al*[28] evaluated eleven studies comparing laparoscopic and open appendectomy in pregnancy from January 1990 to July 2011. A total of 3415 women (599 in laparoscopic and 2816 in open group) were included in the analysis. After weighted and pooled analysis fetal loss was significantly worse in those who underwent laparoscopy compared with open appendectomy (pooled RR = 1.91). No significant difference was found for wound infection, birth weight, preterm labor, length of hospital stay, duration of operation or Apgar score. Preterm birth is a very morbid condition which if extreme (23-27 wk GA) can lead to high rates of infant mortality, autism and low educational attainment (Table 1).

CHOLECYSTECTOMY

Presentation of acute cholecystitis, similar to appendiceal

Table 1 Comparing laparoscopy and open appendectomy fetal loss and preterm birth rates

Ref.	Fetal loss rate laparoscopic	Preterm delivery rate laparoscopic	Fetal loss rate open	Preterm delivery rate open
Sadot *et al*[25]	2.0% (1/41)	29% (12/41)	0.0% (0/16)	19% (3/16)
Walsh *et al*[26]	6.0% (35/624)	2.1% (13/624)	3.1% (128/4193)	8.1% (346/4193)
Mcgory *et al*[27]	7.0% (31/454)	< 1.0% (1/454)	3.0% (88/2679)	8.0% (216/2679)

disease, is similar to the nonpregnant population. Unlike the nonpregnant population however, most gallstones are found incidentally without symptoms during routine imaging for obstetric health maintenance. There are no confounding differences in location of pain or symptoms between the two populations, but there are many alternative diagnoses in patients with right upper quadrant pain and pregnancy, so a thorough differential of diagnoses must be done.

Up to 10% of women have been shown to have gallstones on routine imaging during pregnancy[29-31]. However, the incidence of symptomatic cholelithiasis during pregnancy is similar to the incidence in age-related non-pregnant woman. Early surgical management of gravid patients with symptomatic gallstones is supported by data showing that 92% of patients managed non-operatively have recurrent symptoms after presenting in the first trimester, 64% of patients who present in the second trimester, and 44% of patients who present in the third trimester[32]. The incidence of gallstone pancreatitis is 13% in any pregnant patient diagnosed with gallstones at any point during their pregnancy. Studies comparing conservative to operative management for biliary disease, find that up to 50% of patients conservatively managed will have recurrent symptoms *vs* roughly 10% in the surgically treated group. Considering that up to 60% of cases of gallstone pancreatitis in the pregnant patient lead to fetal demise it is generally agreed that surgery should be performed. A delay in surgical management by way of conservative therapy results in increased rates of hospitalizations, spontaneous abortions, preterm labor, and preterm delivery compared to those undergoing cholecystectomy.

The advantages of laparoscopic surgery were mentioned before and apply here as well. There have been no reports of fetal demise for laparoscopic cholecystectomy performed during the first and second trimesters and decreased rates of spontaneous abortion and preterm labor have been reported in laparoscopic cholecystectomy when compared to laparotomy. Laparoscopy is generally agreed to be technically easier during the first and second trimester owing to the fact that there is less of a distorting effect from the uterus on the rest of the viscera and that anatomy is still maintained in regular position without the effect of the gravid uterus.

If an intra-operative or endoscopic cholangiogram is done it is recommended to shield the lower abdomen with lead[15].

ADNEXAL DISEASE

During the course of pregnancy, the incidence of adnexal masses is 1%-2%[33]. Most of the masses discovered during pregnancy are functional cysts and resolve spontaneously by the end of the pregnancy. These patients can be observed as long as they are asymptomatic, the mass is smaller than 6 cm, there are no concerning ultrasound findings, and tumor markers are within acceptable ranges (CA-125 normally elevated slightly during pregnancy). However, 5%-20% of masses do not resolve or are symptomatic and require operative intervention[33,34]. The use of laparoscopy for removal of any of these lesions has the same outcome in all trimesters of pregnancy[35]. A retrospective review of 88 pregnant women undergoing surgical intervention for adnexal pathology demonstrated equivalent maternal and fetal outcomes in adnexal masses managed laparoscopically compared to laparotomy and concluded that laparoscopy is safe for gynecologic surgery and should be considered if technically feasible[36].

DISCUSSION

It is not uncommon that a pregnant woman requires a surgical procedure. The etiologies and indications for surgery still usually just the ones common for the patient's age group and are unrelated to pregnancy. The clinical presentation and physical examination of these patients may be atypical and the evaluation of the patient can be challenging. Changes in the anatomy and physiology of the pregnant woman and the care for the fetus need to be considered when deciding whether or not to perform surgery on these patients. In the past, laparoscopic surgery was considered hazardous and was contraindicated for a number of reasons. The significant developments in laparoscopic techniques encouraged surgeons to seek advancements in the surgical treatment of the pregnant woman. The advantages of laparoscopic surgery in the pregnant patient are similar to non-pregnant, with the additional advantage of rapid localization of abdominal organs that may shift during pregnancy, and the ability to manage conditions through smaller incisions and less organ manipulation. Current literature comparing laparoscopy and open techniques for surgical management of common diseases lacks randomized trials, but consistent outcomes seen in the available studies show that minimally invasive surgery in the pregnant woman is feasible and safe in any trimester and should not be postponed when indicated.

Patient selection and surgeon experience are important for successful laparoscopic surgery and a consultation with an obstetrician is recommended when available. It is also important to look long term after the fetus has been delivered but there are few studies looking at outcomes after surgery. A study looking at 29 patients undergoing laparoscopic appendectomy show that there was no motor, sensory or social deficits in the child by age 3[37]. As laparoscopy is further adopted, even longer follow up is possible to examine the effects of laparoscopic surgery on the fetus' development.

CONCLUSION

Laparoscopy is emerging as the standard approach for pregnant patients requiring surgery. While it is essential to have a thorough discussion with the patient regarding the risks and benefits of surgical intervention, the current literature suggests that laparoscopy for pregnant patients is a safe and favorable technique when performed by an experienced surgeon.

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Urinary incontinence following obstetric fistula repair

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Abstract

Prolonged and/or obstructed labour is the most common cause of genital tract fistula world-wide, in particular, sub-Saharan Africa and parts of Asia where emergency obstetric services are unavailable or suboptimal to afford timely delivery of the baby. This results in pressure necrosis by the fetal presenting part at the level of the obstruction in the maternal pelvis. Other reasons for obstetric fistula include trauma from vaginal deliveries (spontaneous or instrumental) and iatrogenic from cesarean section/hysterectomy. The majority of women develop the fistula during their first labour and most babies are stillborn. Women with a fistula suffer from leakage of urine and/or faeces from the vagina and surgery is the treatment for an established fistula. Long-term complications of fistulas include recurrent fistula, urinary incontinence, reproductive dysfunction, sexual dysfunction, mental health dysfunction, social isolation and orthopaedic complications such as footdrop. Ongoing urinary symptoms are not uncommon after successful fistula closure. There are various reasons for residual urinary incontinence following obstetric fistula repair including urinary stress incontinence, overactive bladder, mixed urinary incontinence and voiding dysfunction. Urinary incontinence after fistula repair requires careful evaluation prior to further surgery, as in some diagnoses, continence surgery is unlikely to treat and may worsen the condition. Initial results from educational and physiotherapy programs demonstrated a positive impact on post-fistula incontinence.

Key words: Urinary incontinence; Obstetric fistula

Core tip: About one quarter of women suffer from residual urinary incontinence after surgical closure of genito-urinary fistula. Women with ongoing urinary incontinence usually complain of continuous urinary leakage and recurrent fistula requires exclusion. Women with fistulas involving the urethra are more likely to have ongoing urinary symptoms. Causes of ongoing urinary incontinence after fistula closure include urodynamic stress incontinence, detrusor overactivity (DO) and voiding dysfunction. Synthetic slings have a high rate of complications in these cases. Suboptimal success from surgery may be due to undiagnosed or untreated DO and marked reduction in urethral function.

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INTRODUCTION

Obstetric fistula is the most common cause of female genito-urinary fistula world-wide. Prolonged or obstructed labour results in pressure necrosis of the genital tract and surrounding tissues and this creates abnormal communications between the vagina and lower urinary tract and/or vagina and rectum/anus. Uncontrolled leakage of urine and/or faeces from the vagina ensues.

Iatrogenic injuries at time of cesarean section/hysterectomy may also result in fistulas, including ureterovaginal fistulas. Other causes include vaginal injury from spontaneous or instrumental vaginal deliveries.

The management of an established fistula is surgical. However, inspite of anatomical closure of the genito-urinary fistula, ongoing urinary incontinence may persist. Other complications of obstetric fistula include vaginal stenosis, sexual dysfunction, anal incontinence, infertility, ameorrhoea, chronic pain, calculi (vaginal/renal tract), social isolation and mental health dysfunction.

The aim of this paper is to review post-fistula urinary incontinence, its risk factors, possible causes and treatment.

OBSTETRIC FISTULA - DEMOGRAPHICS

Obstetric fistula from pressure necrosis occurs as a result of the lack of effective emergency obstetric services. It is a common condition in low-income countries, in particular sub-Saharan Africa. The true rate of obstetric fistula is unknown. Women, especially in remote areas, may have limited access to health care due to the lack of infrastructure and poverty or may not have permission from their family/husband to seek assistance[1]. Under-reporting may also occur because women are too embarrassed and socially isolated by their condition, do not realize that treatment is available or do not know where to go for treatment[2,3]. In 2011, the Ugandan Bureau of Statistics Demographic and Health Survey demonstrated that 2% of Ugandan women complained of symptoms of genital tract fistula[3]. Other reported risks of obstetric fistula include early age of marriage/childbearing and poor nutritional status.

The average length of labour for the woman with an obstetric fistula is 3-4 d and the majority developed the fistula during the first delivery[4,5]. During the delivery that was associated with the development of the fistula, over 90% of babies delivered were stillborn[4]. It is often difficult to ascertain the true age of the women. Many do not know their date of birth and age due to illiteracy and the tendency to relate time to significant events in their lives rather than the calendar.

COMPLICATIONS FOLLOWING OBSTETRIC FISTULA

Anatomical closure of the genital tract fistula should no longer be considered a "cure" as many other functional, social and mental health issues require consideration. McConnachie *et al*[6] in 1958 suggested that cure should only be considered when there is complete urinary continence. Complications of obstetric fistula include ongoing incontinence (urinary/faecal), mental health dysfunction, sexual dysfunction, reproductive dysfunction, social isolation and orthopaedic considerations (such as footdrop).

Over 95% of women with obstetric fistula screened positive for mental health dysfunction in a validated mental health screening test[7]. Factors such as the constant leakage of urine and/or faeces with limited access to continence pads or water together with the delivery of a stillborn baby and social isolation contribute to mental health dysfunction. Following fistula repair, if the woman is continent, the results from mental health screening improved significantly and returned to general population rates[8].

It is not uncommon for women with obstetric fistulas to suffer from vaginal stenosis due to loss of tissue from pressure necrosis and scarring[9]. This will in turn affect sexual and reproductive function and may further contribute to the woman's social isolation and affect her re-integration into the community after fistula surgery. The prolonged obstructed labour may also increase the risk of significant blood loss and intrauterine infections, further complicating reproductive function by intrauterine/pelvic adhesions and/or pituitary dysfunction.

URINARY INCONTINENCE FOLLOWING SUCCESSFUL CLOSURE OF OBSTETRIC GENITO-URINARY FISTULA

In a prospective follow-up of over 900 women with obstetric fistulas, ongoing urinary incontinence occurred in 23.9% of women after successful fistula closure[4]. Fistulas associated with significant scarring and the circumferential fistulas were less likely to achieve anatomical closure. A circumferential fistula usually involves the urethra and at times the bladder neck. It is thought to be due to a highly significant obstructed labour as the whole circumference of the urethra is lost to pressure necrosis. Commonly, a genito-urinary fistula involves the anterior vaginal wall and posterior aspect of the urethra/bladder. In the circumferential fistula, however, the anterior vaginal wall, posterior aspect of the urethra plus the anterior portion of the urethra is lost. In other words, the urethra is completely transected, with the distal portion of the urethra

Table 1 Summary of Classification according to Goh[10] with the 3 parameters

Type: distance from fixed reference point (external urinary meatus)
Type 1 – distal edge of fistula > 3.5 cm from external urinary meatus
Type 2 – distal edge 2.5-3.5 cm
Type 3 – distal edge 1.5-2.5 cm
Type 4 – distal edge < 1.5 cm
Size: Largest diameter in centimetres
Size a < 1.5 cm
Size b 1.5-3 cm
Size c > 3 cm
Special considerations
Special considerations i – none or mild fibrosis and/or vaginal length > 6 cm, normal capacity
Special considerations ii – moderate or severe fibrosis and/or marked reduction in vaginal length and/or capacity
Special circumstances iii – *e.g.*, post-irradiation, ureteric involvement, circumferential fistula, previous repair

completely separated from the proximal part.

Several classification systems have been proposed for genital tract fistulas. A comparison of 2 classification systems demonstrated the Goh system[10] had a significantly better ability to predict fistula closure[11]. Using the Goh system in a prospective follow up of over 900 women, it was demonstrated that those with the Type 1 fistula (Table 1) were most likely to be continent and those with the Type 4 fistula were least likely to be continent after successful fistula closure. Those with significant vaginal scarring, the circumferential fistula and larger fistulas were also less likely to be continent[4]. There is no association between length of time with obstetric fistula prior to closure and risk of urinary incontinence[12].

There is a paucity of data on urodynamic studies in women following obstetric fistula closure[5,13]. In 2002, Murray *et al*[13] published the first known paper on urodynamic studies following obstetric fistula in a low-income country. Thirty women with persisting urinary incontinence underwent urodynamic studies with subtracted cystometry. This demonstrated 57% with pure urodynamic stress incontinence (USI), 37% with mixed incontinence and 7% with detrusor overactivity (DO). Thirteen percent of women had voiding dysfunction and on physical examination, 85% had a fixed bladder neck. Continence surgery on a subset of the women with severe stress incontinence demonstrated significant retropubic adhesions with a "drain-pipe" urethra[14].

In 2013, Goh *et al*[5] published urodynamic studies on a series of 149 women with residual urinary incontinence after closure of obstetric genito-urinary fistula. Most of the women (77%) complained of continuous urinary incontinence. A fistula was excluded on examination and dye test. Fifteen percent complained of stress urinary incontinence only, 4% complained of overactive bladder only, 3% complained of mixed incontinence and 1% complained of incomplete bladder emptying. Urodynamic testing demonstrated that 49% of these women had USI only, 3% had DO only, 43% had mixed incontinence and 5% had neither USI nor DO. Seven percent of women had post-void residual urine volumes of 150 mL or more. Uroflowmetry was unable to be performed as the women could not use the commode but preferred to squat on the floor to void. One third (50 women) required digital para-urethral compression to fill the bladder. In other words, 1 in 3 women leaked per urethra in the early stages of filling cystometry without detrusor pressure rise or provocation. Forty-two of these 50 women (84%) complained of continuous urinary incontinence. Another interesting finding was that urethral closure pressures often did not reflect the severity of urinary incontinence. The authors postulated that the pressures may be generated by scarring of a functionless urethra.

MANAGEMENT OF POST-FISTULA URINARY INCONTINENCE

Unfortunately, many women with post-fistula urinary incontinence have been treated with surgery only, with little consideration given to non-surgical options or diagnoses that are not treated surgically. In other words, the women may be subjected to surgeries that are unlikely to treat and may worsen their urinary symptoms.

As with the management of female urinary incontinence around the world, conservative approaches must be considered. Castille *et al*[15] demonstrated a positive impact on post-obstetric fistula incontinence with pre- and post-surgery pelvic floor rehabilitation and educational programs.

DO and voiding dysfunction may also be neglected or misdiagnosed[5]. The management of the overactive bladder is primarily with pelvic floor rehabilitation including bladder training/behavior modification and pharmacological agents such as anticholinergic medication. Continence surgery is unlikely to treat and may worsen these conditions.

Goh *et al*[16] described the use of urethral plugs for post-fistula urinary incontinence. This has been a useful adjunct in the management of post-fistula urinary incontinence. Women are taught how to use and self-manage the plugs.

Ideally, a multidisciplinary team is required to optimize the management of women with residual urinary incontinence following obstetric genito-urinary fistula repair. Unfortunately, continence nurses and pelvic floor physiotherapists are not readily available even in established fistula units. Pharmacological agents to assist women with overactive bladder symptoms are also limited or unavailable in many instances.

Numerous operations have been described to treat women with residual urinary incontinence following obstetric fistula. Women with Goh Type 4 fistulas (involving the urethra) have been shown to be least likely to be continent[4]. Unfortunately, surgeries to treat urinary incontinence following these fistulas have

frustrated fistula surgeons for many years. Mahfouz[17] and Moir[18] were in agreement that when the fistula involves the whole urethra, functional outcomes were extremely poor. Hamlin *et al*[19] employed the gracilis muscle to reinforce the urethra in an attempt to achieve continence.

McConnachie[6] first described using bulbocavernosus and levator ani cross-strut muscular slings to treat post-fistula urinary incontinence. This was re-popularised by Browning[20] in more recent times.

Carey *et al*[14] described the use of rectus fascia pubovaginal sling with retropubic urethrolysis and omental graft to treat women with proven USI. Follow up of a small group of women demonstrated continence in 67% at 14-mo. These women were found to have a fixed bladder neck and open "drain-pipe" urethras and hence the rational for retropubic urethralysis and omental graft to reduce the risk of retropubic re-adherence of the urethra.

In a larger group of women treated with slings for residual stress incontinence after obstetric fistula, it was concluded that synthetic slings have a 20% risk of erosion and are not indicated in this group of women and the overall risk of iatrogenic fistula is high at 17%[21].

Krause *et al*[22] described the use of periurethral polyacrylamide hydrogel for a small group of women with post-fistula stress urinary incontinence. The immediate post-operative results were promising but longer term follow-up is required. It is often difficult to obtain follow up due to a number of reasons including the cost of returning for follow-up and in many places in Africa, violence against women is common and hence follow-up is challenging for fear of personal safety.

Various techniques for urinary diversion have also been described in the literature to treat women with ongoing urinary incontinence. These women however, require ongoing long-term follow up due to the risk of long-term complications such as infections, metabolic abnormalities, ureteral strictures, and stones[23]. Therefore, there is much debate about the practicalities and safety aspects of urinary diversion in the low resource setting.

CONCLUSION

Residual urinary incontinence continues to be a major health issue following the repair of obstetric genito-urinary fistula. There are various reasons other than USI for ongoing urinary incontinence such as DO and voiding difficulty, where continence surgery is unlikely to treat and may worsen the problem. Fistula surgeons should be aware of these other conditions and should carefully select women for further surgery in the treatment of ongoing urinary incontinence.

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ORIGINAL ARTICLE

Observational Study

Gynecologic oncologists involvement on ovarian cancer standard of care receipt and survival

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Abstract

AIM: To examine the influence of gynecologic oncologists (GO) in the United States on surgical/chemotherapeutic standard of care (SOC), and how this translates into improved survival among women with ovarian cancer (OC).

METHODS: Surveillance, Epidemiology, and End Result (SEER)-Medicare data were used to identify 11688 OC patients (1992-2006). Only Medicare recipients with an initial surgical procedure code (n = 6714) were included. Physician specialty was identified by linking SEER-Medicare to the American Medical Association Masterfile. SOC was defined by a panel of GOs. Multivariate logistic regression was used to determine predictors of receiving surgical/chemotherapeutic SOC

and proportional hazards modeling to estimate the effect of SOC treatment and physician specialty on survival.

RESULTS: About 34% received surgery from a GO and 25% received the overall SOC. One-third of women had a GO involved sometime during their care. Women receiving surgery from a GO *vs* non-GO had 2.35 times the odds of receiving the surgical SOC and 1.25 times the odds of receiving chemotherapeutic SOC ($P < 0.01$). Risk of mortality was greater among women not receiving surgical SOC compared to those who did [hazard ratio = 1.22 (95%CI: 1.12-1.33), $P < 0.01$], and also was higher among women seen by non-GOs *vs* GOs (for surgical treatment) after adjusting for covariates. Median survival time was 14 mo longer for women receiving combined SOC.

CONCLUSION: A survival advantage associated with receiving surgical SOC and overall treatment by a GO is supported. Persistent survival differences, particularly among those not receiving the SOC, require further investigation.

Key words: Ovarian neoplasms; Gynecologic oncologist; Guidelines-based care; Surveillance, Epidemiology, and End Result Medicare

Core tip: A significant survival advantage is associated with receiving surgical standard of care (SOC), yet still some women had lower odds of receiving surgical SOC.

Rim SH, Hirsch S, Thomas CC, Brewster WR, Cooney D, Thompson TD, Stewart SL. Gynecologic oncologists involvement on ovarian cancer standard of care receipt and survival. *World J Obstet Gynecol* 2016; 5(2): 187-196 Available from: URL: http://www.wjgnet.com/2218-6220/full/v5/i2/187.htm DOI: http://dx.doi.org/10.5317/wjog.v5.i2.187

INTRODUCTION

Women in the United States with advanced stage epithelial ovarian cancer (OC) have an overall 5-year survival rate of about 30%[1]. As with many cancers, survival is closely linked with the stage of diagnosis, such that women with localized (stage Ⅰ) disease have a relative 5-year survival rate of 92%; the prognosis however declines with late stage disease and metastases[2]. Without an adequate early detection strategy, ensuring that women receive appropriate, standard of care (SOC) treatment is a very important intervention that has demonstrated reduction in OC mortality[3].

National Comprehensive Cancer Control Network (NCCN) current treatment recommendations for women with epithelial OC include an evaluation prior to initiating chemotherapy along with accurate surgical staging and primary debulking surgery/cytoreduction performed by a gynecologic oncologist (GO)[3]. In most but not all cases, at least six cycles of platinum and taxane-based chemotherapy administration is recommended for advanced epithelial OCs[3]. Appropriate care not only constitutes the receipt of SOC treatment, but also quality care from an experienced GO, who is trained to both perform the surgery and administer chemotherapy[3,4]. The evidence supporting better guideline-adherent care and outcomes among patients seen by a GO has been previously examined[5-8], and prior studies suggest only 30%-40% of women with OC are treated by a GO[5,9-11]. While NCCN cancer center patients tend to receive guideline-adherent care[12], there is potential in exploring whether differences in SOC treatment are affected across patient-level demographic and clinical subgroups.

To date, few studies have jointly considered surgical and chemotherapeutic SOC indicators in examining survival in OC patients[13-17]. In this study, we examine predictors of both SOC receipt (surgical and chemotherapeutic) and adherence to these treatments among women treated by GOs compared to non-GOs. We further quantified the survival advantage of SOC treatment receipt among OC patients.

MATERIALS AND METHODS

Data source and study population

The study included all women in the Surveillance, Epidemiology, End Results (SEER)-Medicare database[18] diagnosed with OC from January 1, 1992 to December 31, 2006 (n = 38972). We excluded women who did not have a primary epithelial OC diagnosis (n = 6175); were Medicare age-ineligible (age < 66) at date of diagnosis (n = 11716); had an invalid month of diagnosis (n = 166); had diagnoses based on autopsy or death certificate only (n = 543); had a non-epithelial ovarian malignancy (n = 3198); and were not continuously enrolled in both Medicare Part A and B or were enrolled in an Health Maintenance Organization plan during the course of treatment (n = 5486). A total of 11688 OC patients met the inclusion criteria for the study.

Definition of variables

Patient-level covariates included age, race, stage at diagnosis, marital status, year of diagnosis, geographic region of SEER registry, and cancer histology. The Charlson-Klabunde comorbidity index score was determined using Medicare claims data for 12 mo prior to and 4 mo after cancer diagnosis date, per prior studies[19,20].

We examined all procedure codes in the Medicare claims data falling within a treatment window (defined as two months prior to and one year after the diagnosis date) to determine if a patient received surgical or chemotherapeutic SOC. Since only month and year of

diagnosis are reported in the SEER database, the 15th day of the month was assigned as the day of diagnosis for each patient.

SOC definitions

Per recommendation from an experienced group of GOs, consulted specifically for this project (W. Brewster, R.E. Bristow and D.K. Singh), the International Federation of Gynecologists and Obstetricians (FIGO) stage of disease categories were grouped as: ⅠA/ⅠB, ⅠC/Ⅱ, ⅢA/ⅢB and ⅢC/Ⅳ based on similarities in current surgical and chemotherapeutic treatment regimens. FIGO stage Ⅲ NOS and stage Ⅳ were grouped into stage ⅢC/Ⅳ group, given that a high proportion of all stage Ⅲ cases were stage ⅢC.

Among the women who met the inclusion criteria (*n* = 11688), we examined receipt of SOC among women receiving any initial surgical care. Thus, we further excluded women who received treatment outside of the treatment window (*n* = 28), those who had no procedure codes of interest for any surgical care (*n* = 2464), and women who received neoadjuvant chemotherapy (*n* = 2482) (given the difficulty of cancer staging for women who are eligible for neoadjuvant chemotherapy) to examine differences in guideline-adherent treatment and survival. We also excluded all OC patients diagnosed with stage Ⅰ NOS or who were unstaged at diagnosis since minimum SOC parameters are not well defined for these groups.

The GO group defined minimum surgical SOC as lymph node dissection, omentectomy and oophorectomy for all patients with FIGO stage ⅠA/IB, ⅠC/Ⅱ or ⅢA/ⅢB at diagnosis, but omentectomy and oophorectomy only for women with stage ⅢC/Ⅳ at diagnosis. Minimum chemotherapy SOC definition depended on: (1) stage of disease at diagnosis; (2) number of chemotherapy cycles received; and (3) type of chemotherapy agent received. For analysis, chemotherapy SOC was defined as an individual receiving the defined number of cycles (three cycles of chemotherapy for stage ⅠC/Ⅱ and six cycles for stage Ⅲ/Ⅳ), with at least one multi-agent cycle (defined as one platinum based and one non-platinum based agent) using either intravenous or intraperitoneal modes of administration. One cycle of chemotherapy was equal to three weeks of treatment, given that chemotherapy is usually administered every 3-4 wk[3,21]. Patients were documented as receiving overall SOC if they received both surgical and adjuvant chemotherapeutic SOC.

The GO group recommended surgical and chemotherapy procedure codes for use in determining SOC for each FIGO stage category. Procedure codes included both International Classification of Diseases, Ninth revision, clinical modification codes and American Medical Association (AMA) Current Procedural Terminology codes.

Surgeon specialty definition

Self-reported, physician specialty information from the SEER-Medicare claims file was linked with and verified against the AMA Physician Masterfile using the unique provider identification number (UPIN) for physicians performing (or those in attendance) of an OC procedure of interest. If the operating physician UPIN was not available, but the attending physician UPIN was available, AMA specialty was assigned to the attending physician. If the UPIN for an operating and attending physician was unavailable, the self-reported physician specialty variable found in the Medicare data set was used to define specialty. When a patient received treatment from multiple physicians, care was attributed to the most specialized physician (most to least specialized: GO, gynecologist, general surgeon, and other physician). For analytic purposes, physician specialty was grouped as GO and non-GO.

Statistical analysis

We examined predictors associated with receipt of surgical and chemotherapeutic SOC. A forward selection logistic regression model was used to examine each question. Comparisons of the distribution of OC patients receiving the SOC by physician specialty was examined using the Pearson χ^2 test.

Cox proportional hazard methods were used to determine differences in survival time from date of OC diagnosis to date of death. The proportional hazards assumption was examined by testing interactions between time and each covariate in the model. The final models (Model 1 and 2) exclude women (*n* = 1003) who died within 4.5 mo after diagnosis (*i.e.*, women who did not live long enough to receive chemotherapy SOC). Due to a common category in the chemotherapy variables (chemotherapy SOC and chemotherapy physician specialty), we examined two different models. The first model (Model 1) examined surgery physician specialty and receipt of both SOC measurements, while the second model (Model 2) examined both surgery and chemotherapy physician specialty and receipt of surgery SOC, adjusting for patient-level and clinical factors. All final models were adjusted for covariates that had a statistically significant association from the bivariate analysis or were of importance in the literature. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, United States).

RESULTS

Among the 11688 OC patients, 57.4% (*n* = 6714) received an initial surgical procedure code of interest. Table 1 shows the patient and tumor characteristics by the type of physician performing the initial surgery. The mean age of patients was mid to late-70s; most women were white, married or widowed, had no comorbidities, had FIGO stage ⅢC/Ⅳ disease, and serous histology. More women received an initial surgical procedure from OB/GYNs (*n* = 3088) than GOs (*n* = 2254), general surgeons (*n* = 914), or other non-GO/unknown specialties (*n* = 419).

Table 1 Characteristics of ovarian cancer patients who received any initial surgical procedure by physician specialty (*n* = 6714)

Characteristic	Surgeon specialty[1]			
	GO	Non-GO		
		OBGYN	General surgeon	Other[2]
No. of patients	2254	3088	914	419
Mean age at diagnosis (stddev)	74.6 (5.9)	74.8 (6.1)	77.0 (6.8)	75.5 (6.2)
Race *n* (%)				
White	1995 (88.5)	2844 (92.1)	827 (90.5)	379 (90.5)
African American	121 (5.4)	104 (3.4)	49 (5.4)	26 (6.2)
Hispanic	35 (1.6)	31 (1.0)	[3]	[3]
Asian	53 (2.4)	66 (2.1)	[3]	[3]
Other[4]	47 (2.1)	37 (1.2)	[3]	[3]
Marital status				
Married	1052 (46.7)	1424 (46.1)	327 (35.8)	170 (40.6)
Single	159 (7.1)	221 (7.2)	53 (5.8)	31 (7.4)
Divorced	148 (6.6)	166 (5.4)	58 (6.3)	29 (6.9)
Widowed	799 (35.4)	1168 (37.8)	458 (50.1)	176 (42.0)
Separated/unknown	96 (4.2)	109 (3.5)	[3]	[3]
Charlson-Klabunde comorbidity score				
0	1521 (67.5)	2133 (69.1)	605 (66.2)	266 (63.5)
1	498 (22.1)	644 (20.9)	188 (20.6)	93 (22.2)
2	175 (7.8)	189 (6.1)	78 (8.5)	38 (9.1)
3	45 (2.0)	80 (2.6)	29 (3.2)	[3]
4 or more	[3]	42 (1.4)	[3]	[3]
FIGO treatment stage				
ⅠA/ⅠB	200 (8.9)	383 (12.4)	66 (7.2)	43 (10.3)
ⅠC/Ⅱ	276 (12.2)	516 (16.7)	90 (9.8)	40 (9.5)
ⅢA/ⅢB	119 (5.3)	179 (5.8)	59 (6.5)	[3]
ⅢC/Ⅳ	1580 (70.1)	1898 (61.5)	660 (72.2)	308 (73.5)
Unstaged/NOS	79 (3.5)	112 (3.7)	39 (4.2)	[3]
Histology				
Serous	1460 (64.8)	1897 (61.4)	554 (60.6)	254 (60.6)
Endometrioid	238 (10.6)	381 (12.3)	73 (8.0)	46 (11.0)
Mucinous	129 (5.7)	235 (7.6)	79 (8.6)	25 (6.0)
Clear cell	84 (3.7)	127 (4.1)	[3]	[3]
Adenocarcinoma	275 (12.2)	344 (11.1)	175 (19.1)	66 (15.8)
Other[5]	68 (3.1)	104 (3.3)	20 (2.2)	[3]

[1]Surgeon specialty was categorized according to the most specialized care received during the course of the treatment window; [2]39 women received a surgery procedure code during the treatment window (defined as a period of two months prior and one year after a patient's diagnosis date in which procedures were performed) but surgeon specialty could not be identified; [3]Denotes cell size suppression of less than 20; [4]Other race includes designation of "Other" or Native American; [5]Other histology includes Transitional. GO: Gynecologic oncologists; FIGO: International Federation of Gynecologists and Obstetricians; NOS: Not otherwise specified.

Among women treated by a GO, 79.2% received the surgical SOC and 52.8% received the chemotherapy SOC (Figure 1). Regardless of stage at diagnosis, women more frequently received surgical and chemotherapeutic SOC from a GO than from a non-GO.

Table 2 reports the factors associated with receipt of surgical SOC after adjusting for other covariates. Surgery performed by a GO was strongly associated with receiving surgical SOC [odds ratio (OR) for GO = 2.35; 95%CI: 2.03-2.71]. Other factors associated with greater odds of surgical SOC receipt included: More advanced stage of disease, white *vs* African-American race, younger age at diagnosis, serous *vs* adenocarcinoma not otherwise specified histologic type, being married *vs* not married, and diagnosis during the later years of the study period.

Table 2 also reports factors associated with receipt of the minimum chemotherapy SOC after adjusting for other covariates. Women who obtained chemotherapy from a GO had a higher odds of receiving chemotherapeutic SOC (OR = 1.25, 95%CI: 1.07-1.47). Other statistically significant factors for higher odds of chemotherapeutic SOC included: Less advanced stage of disease, younger age at diagnosis, histologic type (serous compared with endometrioid/mucinous/clear cell), being married compared with unmarried, living in the SEER Midwest region (compared to the SEER Northeast), and diagnosis during more recent years.

Table 3 shows the Cox regression model of time to death among the sample of OC patients who received a primary surgery procedure who did not die within 4.5 mo after diagnosis. In Table 3 (Model 1), women who did not receive surgery SOC had increased mortality compared to women who did [hazard ratio 1.22 (95%CI: 1.12-1.33)]. Similarly, women who did not receive any chemotherapy SOC had a higher risk of earlier death compared to women who received the full contingent of chemotherapy [hazard ratio 1.29 (95%CI: 1.14-1.46)]. Increasing age, late stage disease, higher number of comorbidities, and

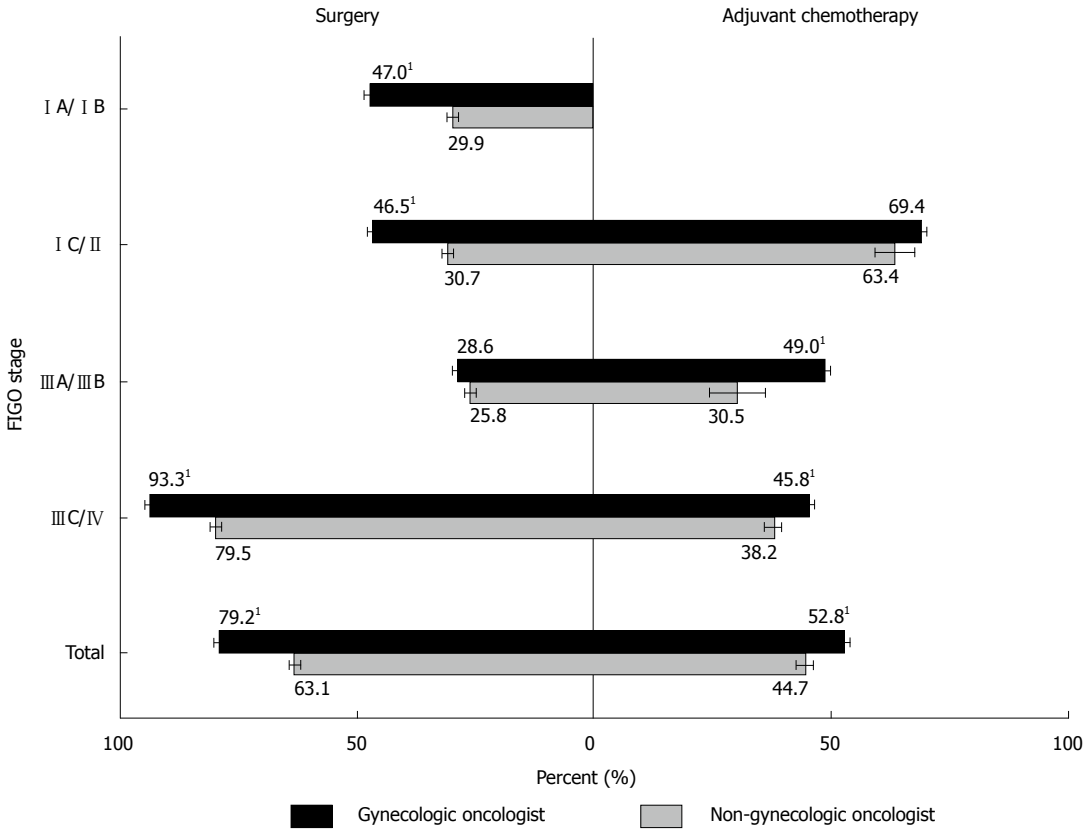

Figure 1 Surgical standard of care (*n* = 4434) and adjuvant chemotherapy standard of care (*n* = 2595) receipt by physician specialty and International Federation of Gynecologists and Obstetricians stage. (1) Surgery SOC treatment was based on ovarian cancer patients receiving surgery prior to chemotherapy (*n* = 6714); (2) Stages 1, not otherwise specified and Unknown/unstaged were removed from analysis; (3) Surgeon specialty and chemotherapy specialty was categorized according to the most specialized care received during the course of the treatment window; (4) Women who received surgery SOC by a surgeon specialty who could not be identified are not shown (*n* = 17); (5) There were 177 women who received a chemotherapy procedure code of interest but for whom physician specialty could not be identified and 1238 women who did not receive a chemotherapy procedure code of interest. [1]Denote that the estimate is statistically significantly higher for GO compared to Non-GO. SOC: Standard of care; GO: Gynecologic oncologist.

mucinous histology compared to serous histology were all associated with increased death (Table 3, Model 1). Similar patterns were observed in Table 3, Model 2 after controlling for chemotherapy physician specialty (as opposed to chemotherapy SOC). For Model 2, women who received surgery from a GO had better survival. Although there was no significant difference in survival between chemotherapy treatment from a GO compared to non-GO, those not receiving any chemotherapy had a significantly shorter survival time (Table 3, Model 2). The median survival time for women who received the overall SOC was 52 mo compared to 38 mo for women that did not receive the overall surgical and chemotherapeutic SOC (Figure 2).

DISCUSSION

Our findings show that among OC patients receiving initial surgical treatment, only 25% of women received the overall SOC as defined by our panel of GOs. Few women (approximately one-third of women receiving a surgical procedure) had a GO involved at any point during their care. Women who obtained surgery from a GO however, were more likely to receive the surgical SOC and chemotherapeutic SOC than women who obtained treatment from a non-GO. The median survival time was 14 mo longer for women who received the overall SOC compared to women who did not receive overall SOC.

Our results are consistent with prior studies that suggest that appropriate surgical treatment in the United States is more frequently performed when a GO is the treating physician[5]. Data from a single state cancer registry study by Chan *et al*[14] showed that women with OC under the care of GOs were more likely to receive appropriate staging and chemotherapy treatments, controlling for age, stage, and grade of disease. Also similar to previous studies, our results suggest that greater utilization of GOs in the care of OC patients would be beneficial[22]. Although the level of detail in our analysis is unable to discriminate the factors underlying the low utilization, it is likely that our results reflect a complex interaction of both preference and access-relevant effects, such as the influence of a patient's choice in receipt of GO care *vs* a shortage of available GOs in some areas.

While patient treatment preferences can independently and significantly affect chemotherapy receipt[23],

Table 2 Predictors of receipt of minimum surgical and chemotherapeutic standard of care[1]

	Surgical standard of care[2]		Chemotherapeutic standard of care[2]	
	Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value
Physician specialty[3]				
Gynecologic oncologist	2.35 (2.03-2.71)	< 0.01	1.25 (1.07-1.47)	0.006
Non-gynecologic oncologist	1.00		1.00	
Age at diagnosis				
66-69	1.00		1.00	
70-74	0.80 (0.67-0.96)	0.017	0.93 (0.78-1.09)	0.393
75-79	0.83 (0.69-1.0)	0.053	0.79 (0.66-0.94)	0.008
80-84	0.58 (0.47-0.71)	< 0.01	0.61 (0.48-75)	< 0.001
⩾ 85	0.40 (0.31-0.51)	< 0.01	0.31 (0.21-0.48)	< 0.001
Race[4]				
White	1.00			
African American	0.67 (0.50-0.91)	0.01	-	
Other	0.83 (0.62-1.10)	0.208	-	
Treatment stage[5]				
ⅠA/ⅠB	0.08 (0.07-0.10)	< 0.01	NA	NA
ⅠC/Ⅱ	0.08 (0.07-0.10)	< 0.01	3.46 (2.86-4.18)	< 0.001
ⅢA/ⅢB	0.05 (0.04-0.07)	< 0.01	0.83 (0.64-1.09)	0.182
ⅢC/Ⅳ	1.00		1.00	
Charlson-Klabunde comorbidity score				
0	1.00		1.00	
1	0.84 (0.72-0.98)	0.029	0.84 (0.71-0.99)	0.029
2	0.81 (0.63-1.02)	0.084	0.78 (0.60-1.03)	0.078
3	0.65 (0.44-0.97)	0.039	0.49 (0.31-0.80)	0.005
4 or more	1.09 (0.60-1.97)	0.771	0.63 (0.29-1.37)	0.247
Histology				
Serous	1.00		1.00	
Endometrioid	1.10 (0.90-1.35)	0.356	0.70 (0.56-0.89)	0.003
Mucinous	0.95 (0.74-1.35)	0.67	0.49 (0.34-0.70)	< 0.001
Clear cell	1.29 (0.93-1.78)	0.13	0.62 (0.41-0.93)	0.026
Transitional	0.70 (0.27-1.79)	0.454	0.76 (0.30-1.97)	0.572
Adenocarcinoma (NOS)	0.44 (0.37-0.54)	< 0.001	1.04 (0.86-1.27)	0.695
Other	1.05 (0.70-1.56)	0.813	0.74 (0.47-1.13)	0.168
Marital status				
Married	1.00		1.00	
Not married	0.83 (0.72-0.95)	0.007	0.75 (0.66-0.86)	< 0.001
Unknown	1.03 (0.69-1.52)	0.87	0.73 (0.48-1.09)	0.127
Year of diagnosis				
1993-1997	0.62 (0.52-0.73)	< 0.01	0.28 (0.23-0.33)	< 0.001
1998-2002	0.79 (0.68-0.92)	0.003	1.09 (0.94-1.26)	0.261
2003-2006	1.00		1.00	
SEER region[4]				
Northeast	-		1.00	
Midwest	-		0.76 (0.62-0.93)	0.009
South	-		1.09 (0.88-1.37)	0.424
West	-		0.93 (0.78-1.10)	0.391

[1]Minimum SOC treatment was based on patients receiving surgery prior to chemotherapy (n = 6714); [2]Surgery SOC (n = 4434) and chemotherapy SOC (n = 2595); [3]Physician specialty was categorized according to the most specialized care received during the course of the treatment window; there were 39 and 177 cases where physician specialty could not be identified for surgery or chemotherapy procedures, respectively (results for this group not shown); [4]Race was not entered into the chemotherapy SOC model based on forward selection entry criteria ($P \leqslant 0.10$); Region was not entered into the surgery SOC model based on forward selection entry criteria ($P \leqslant 0.10$); [5]Stage I NOS, Stage IA/IB (for chemotherapy SOC) and unknown/unstaged were removed from the analysis since current guidelines recommend early stage patients not receive chemotherapy treatment. NOS: Not otherwise specified; SOC: Standard of care; SEER: Surveillance, Epidemiology, and End Result; NA: Not applicable.

geographic access may also play an important role in (both chemotherapeutic or surgical) treatment receipt from a GO. For example, a previous analysis reported on the unequal distribution of GOs in the United States[24]. A recently published study suggested that OC mortality may be a function of distance to a practicing GO as counties located more than 50 miles from a gynecologic oncology practice had almost 60% increased likelihood of OC mortality than those physically closer to a practice location[25]. While earlier research efforts have indicated that treatment of OC can be improved by early referral to a GO[5,10], referral and consultation from GOs have generally been low, with only about 39% of family physicians and 51% of general internists self-reporting referrals to a GO[26]. Given that surgery is an important determinant of outcomes for OC patients, receiving surgery/treatment from surgeons with specialized training in pelvic surgery

Table 3 Cox proportional hazard model of time-to-death among ovarian cancer patients

Predictor	Model 1[1]		Model 2[1]	
	Hazard ratio (95%CI)	*P* value	Hazard ratio (95%CI)	*P* value
Received surgery SOC[2]				
Yes	1.00		1.00	
No	1.22 (1.12-1.33)	< 0.01	1.21 (1.11-1.31)	< 0.01
Received chemotherapy SOC[2]			[4]	
Yes	1.00		[4]	
No, but received some chemotherapy	0.95 (0.89-1.02)	0.18	[4]	
Received no chemotherapy	1.29 (1.14-1.46)	< 0.01	[4]	
Age at diagnosis				
66-69	1.00		1.00	
70-74	1.07 (0.98-1.17)	0.13	1.05 (0.97-1.15)	0.24
75-79	1.23 (1.12-1.34)	< 0.01	1.21 (1.10-1.32)	< 0.01
80-84	1.52 (1.37-1.69)	< 0.01	1.48 (1.33-1.65)	< 0.01
⩾ 85	1.96 (1.70-2.26)	< 0.01	1.92 (1.67-2.21)	< 0.01
Race				
White	1.00		1.00	
African American	1.11 (0.95-1.29)	0.18	1.13 (0.97-1.32)	0.12
Other	0.90 (0.78-1.05)	0.17	0.88 (0.75-1.02)	0.09
Year of diagnosis				
1993-1997	1.27 (1.17-1.38)	< 0.01	1.24 (1.14-1.35)	< 0.01
1998-2002	1.18 (1.09-1.27)	< 0.01	1.17 (1.08-1.27)	< 0.01
2003-2006	1.00		1.00	
Treatment stage				
ⅠA/ⅠB	0.20 (0.18-0.23)	< 0.01	0.17 (0.15-0.20)	< 0.01
ⅠC/Ⅱ	0.35 (0.32-0.40)	< 0.01	0.36 (0.32-0.40)	< 0.01
ⅢA/ⅢB	0.61 (0.53-0.71)	< 0.01	0.62 (0.54-0.71)	< 0.01
ⅢC/Ⅳ	1.00		1.00	
Charlson-Klabunde comorbidity score				
0	1.00		1.00	
1	1.28 (1.18-1.38)	< 0.01	1.26 (1.17-1.36)	< 0.01
2	1.38 (1.22-1.56)	< 0.01	1.37 (1.21-1.55)	< 0.01
3	1.64 (1.34-2.00)	< 0.01	1.64 (1.34-2.01)	< 0.01
⩾ 4	2.33 (1.73-3.15)	< 0.01	2.27 (1.67-3.09)	< 0.01
Histology				
Serous	1.00		1.00	
Endometrioid	0.76 (0.68-0.85)	< 0.01	0.75 (0.68-0.84)	< 0.01
Mucinous	1.22 (1.06-1.41)	< 0.01	1.22 (1.06-1.41)	< 0.01
Clear cell	0.83 (0.69-1.00)	0.05	0.83 (0.69-1.00)	0.05
Transitional	0.79 (0.47-1.31)	0.36	0.79 (0.48-1.32)	0.37
Adenocarcinoma (NOS)	1.07 (0.98-1.18)	0.14	1.07 (0.97-1.17)	0.2
Other	1.02 (0.82-1.28)	0.85	1.02 (0.82-1.28)	0.85
Marital status				
Married	1.00		1.00	
Not Married	1.07 (1.00-1.14)	0.05	1.07 (1.00-1.14)	0.05
Unknown	1.00 (0.82-1.23)	0.97	0.99 (0.80-1.21)	0.89
Surgeon specialty[3]				
Non-GO	1.00		1.00	
GO	0.90 (0.84-0.96)	< 0.01	0.90 (0.84-0.97)	< 0.01
Chemotherapy specialty[3]				
Non-GO	[4]		1.00	
GO	[4]		0.98 (0.89-1.08)	0.68
Did not receive chemotherapy	[4]		1.33 (1.19-1.47)	< 0.01

[1]Model 1 and Model 2: Includes OC patients who did not have an unknown FIGO stage at diagnosis, and survived at least 4.5 mo after diagnosis; [2]Minimum SOC procedure codes for surgery; [3]Missing surgeon and physician specialty excluded from analysis; [4]Excluded from the model based inclusion criteria. Chemotherapy SOC and chemotherapy physician specialty cannot be included in the same model because the common level of "did not receive chemotherapy" would introduce a singularity and prevent model convergence. OC: Ovarian cancer; SOC: Standard of care; GO: Gynecologic oncologist; FIGO: International Federation of Gynecologists and Obstetricians; NOS: Not otherwise specified.

(*i.e.*, GOs)[27], who see a high volume of cases[10,28] at high volume facilities treating more than 20 OC cases per year[28,29], might help improve outcomes.

It is important to note that there are still subgroups that require further research. Although African-American women were more likely than their white counterparts to receive their initial surgical procedure from a GO (data not shown), they had lower odds of receiving the surgical SOC and there was no difference in survival after adjusting for physician specialty, surgical SOC, and other tumor and sociodemographic characteristics. The increased risk of death among African American women

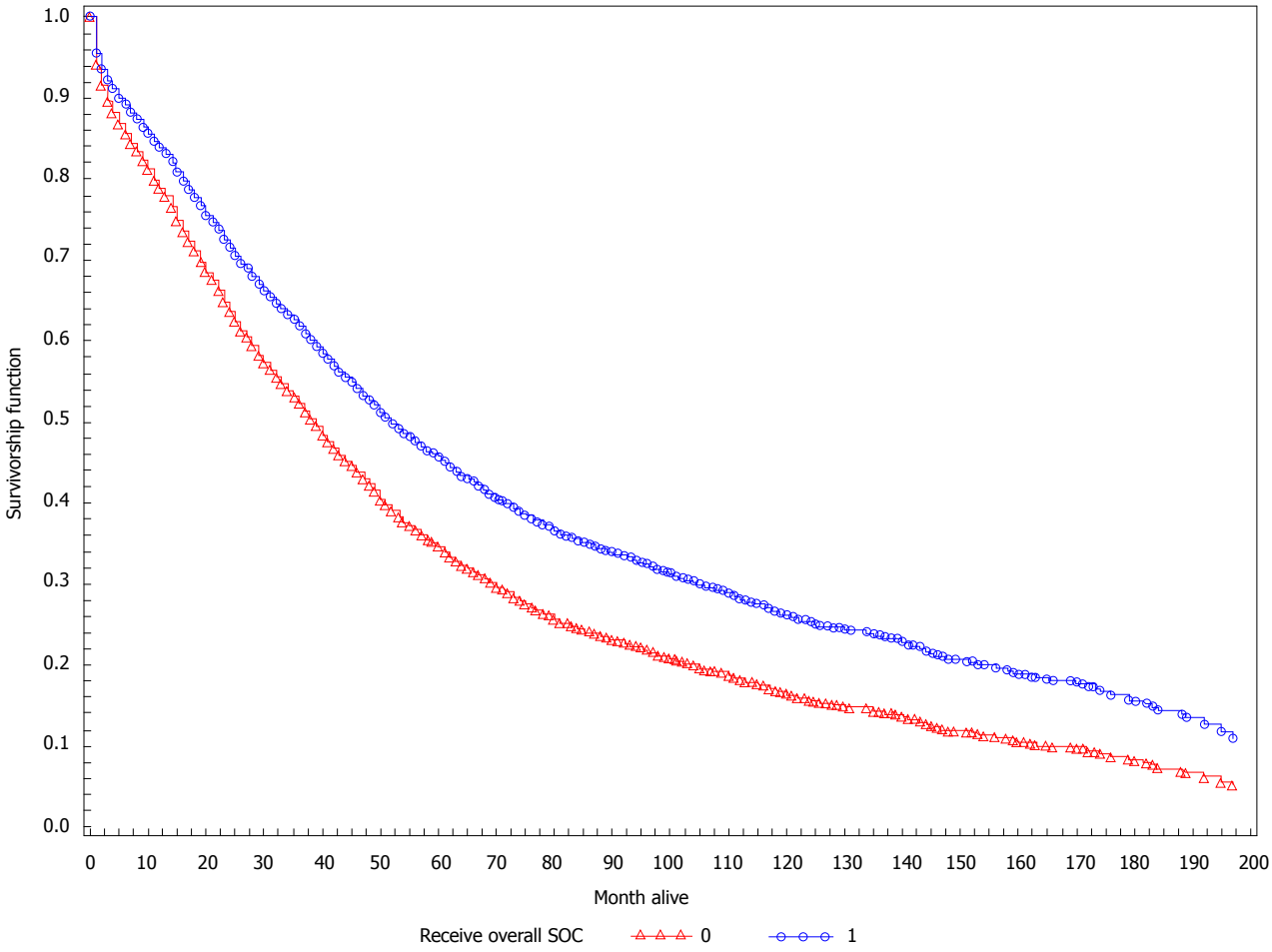

Figure 2 Ovarian cancer survivor curves[1] by receipt of overall standard of care[2] (*n* = 1678). [1]All covariates held at the reference level noted in Table 3; [2]0 = Did not receive overall standard of care; 1 = Did receive overall SOC. SOC: Standard of care.

noted in other studies, when controlling for receipt of chemotherapeutic SOC, suggests that there may be some important nuanced differences in the definitions of chemotherapeutic SOC[30,31], chemotherapeutic agents, and/or interaction effects between age, comorbidity, stage, and race that have not been adequately explored. Bristow *et al*[32] have previously suggested similar differences in survival between African-American and white OC patients and the complexity of examining race-based survival associations[33,34].

The findings in this study should be considered in light of several limitations: (1) our analysis was focused on fee for service Medicare; women who received treatment under managed care were not included because the managed care cases did not include codes to identify specific treatment procedures; (2) neoadjuvant chemotherapy cases, which could have later received surgical SOC, were excluded; and (3) it is a challenge to operationalize NCCN recommendations into an analytic/computer program because the recommendations are relatively complex, and some information required for the NCCN decision algorithms is not available in claims data. However, our panel of experienced GOs developed a simpler, but accurate definition of the SOC so that recommendations could be converted into analytic code. Similarly, since SOC definitions were varied for each stage at diagnosis, if claims data were not available for the full contingency of treatment procedures, it is possible that there was an underestimation of patients identified as receiving overall SOC in that subgroup. Fourth, given the limitations of Medicare data, inaccuracies or incomplete data in billing, drug, or procedure codes could have resulted in an underestimate or overestimate of the total number of surgeries and/or chemotherapy procedures performed, thus biasing the estimate. Previous studies have noted some concerns in the validation of chemotherapeutic agents within Medicare claims data[30,31]. Fifth, there is potential for misclassification of physician specialty, given the use of multiple data sources including operating physician, attending physician, and self-reported physician specialty[35]. Furthermore, in our analysis, receipt of treatment from a GO was designated as such if a GO had been seen at any point during the care. Lastly, since we assumed each cycle of treatment lasted three weeks, we calculated that it would take at least 4.5 mo for women diagnosed with stage ⅢC or Ⅳ to complete the chemotherapy SOC as defined in our study. Thus, women who died within five months of the diagnosis date would not have had the opportunity

to receive chemotherapy SOC. Our definition of chemotherapy SOC may have been too rigorous and potentially introduce selection or survival bias.

Our study showed that GOs more often provided the surgical and chemotherapeutic SOC. The receipt of surgical standards was associated with better survival outcomes, even after adjusting for provider specialty. As such, these two NCCN-recommendations (*i.e.*, treatment from a GO and receipt of SOC) continue to be critical points of intervention for improving survival time and reducing deaths from OC. Although it is difficult to determine when adjuvant chemotherapy is warranted based on sound clinical judgement (*i.e.*, taking into consideration the patient's comorbidities, toxicities, age, *etc.*) or patient refusal, one area that has not been carefully examined is the potential that race/ethnicity-based differences in patient and caregiver preferences may have for OC care. Future research may further explore this and the interaction effects of race, age, comorbidities on survival.

ACKNOWLEDGMENTS

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

COMMENTS

Background

Ovarian cancer (OC) is the deadliest gynecologic cancer among women. Standard treatment for OC consists of extensive surgery and chemotherapy. Gynecologic oncologists (GOs) more often adhere to standard treatment guidelines among OC patients, resulting in longer patient survival.

Research frontiers

Low survival rates from OC may be related to lack of GO involvement in surgery or chemotherapy and/or lack of standard treatment receipt. Research measuring receipt of standard of care and its effect on survival can help reveal areas for intervention to improve OC mortality.

Innovations and breakthroughs

These results among over 6000 OC patients aged 65 and older indicate that a low proportion received standard treatment. Not having seen a GO, African American race, and being older (80+) were associated with not receiving standard treatment. Women who received standard treatment survived over one year longer than those who did not receive standard treatment.

Applications

Ensuring appropriate referral of OC patients to GOs for treatment will likely increase survival rates from OC. Education of primary care providers and/or health systems changes that promote referral would be beneficial to increase referral rates. Research is needed into patient factors and other potential reasons underlying lack of referral.

Terminology

GOs are subspecialists trained to administer both surgical and chemotherapeutic treatment to OC patients.

Peer-review

The authors investigated the influence of GO in the United States on surgical/chemotherapeutic SOC, and how this translates into improved survival among women with OC. The authors claimed that a survival advantage is associated with receiving surgical SOC and overall treatment by a GO. This manuscript provides useful information to the medical students, clinicians, and researchers in this field.

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Single incision slings: Are they ready for real life?

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open-access home for the dataset.

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Abstract

AIM: To review of the efficacy and safety outcomes of different single incision slings (SIS) systems, also in comparison with traditional slings.

METHODS: A literature search was conducted in PubMed/MEDLINE database. The research was restricted to randomized and/or prospective trials and retrospective studies, published after 2006, with at least 20 patients with non-neurogenic stress urinary incontinence (SUI). The studies had to assess efficacy and/or safety of the SIS with a minimum follow-up of 12 mo. All the paper assessing the performance of tension free vaginal tape secur were excluded from this review. The final selection included 19 papers fulfilling the aforementioned criteria. Two authors independently reviewed the selected papers.

RESULTS: Four different SIS systems were analysed: Ajust®, Ophira®, Altis® and MiniArc®. The average objective cure rate was 88%. Overall no statistically significant differences were found between SIS and traditional mid-urethral slings (MUS) in terms of objective cure (all $P > 0.005$). Only one paper showed a statistically lower success rate in MiniArc® *vs* Advantage® slings (40% *vs* 90%) and higher rates of failure in the SIS group. Since there was a great variability in terms of tests performed, it was not possible to compare subjective cure between studies. The vast part of the studies showed no major complications after SIS surgery. We also observed very low reported pain rates in SIS patients. The RCTs on Ajust® and MiniArc®, showed better outcomes in terms of post-operative pain compared to MUS. None of the patients reported long-term pain complains.

CONCLUSION: SIS showed similar efficacy to that of traditional slings but lower short-term pain, complication and failure rates.

Key words: Female urological diseases; Urinary stress

incontinence; Pelvic floor disorders; Minimally invasive surgery; Mid-urethral slings

Core tip: This review shows an average objective cure rate of 88% in minisling patients and underlines their comparable efficacy with traditional slings. Short term pain, complication and failure rates are lower in the minisling group.

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INTRODUCTION

Stress urinary incontinence (SUI) is the involuntary leakage of urine associated with effort on exertion, sneezing or coughing. The estimated prevalence is roughly 30% in women aged > 40 years. The annual incidence increases with age (aged > 65 years, annual incidence rates approximately 9%)[1-3]. Several treatment options for SUI exist, including physical therapy, urethral bulking injections, and surgery.

Surgery traditionally consisted of Burch urethropexy or pubovaginal slings[3]. These procedures were found to give adequate results but were also associated with long recovery time and complications such as frequent post-operative voiding dysfunction[4].

Mid urethral slings (MUS) were developed as a less invasive approach to the treatment of SUI. Since the introduction in 1996 of retropubic tension free vaginal tape (TVT), the use of synthetic MUS has grown to become the most common surgery performed for SUI in women.

These procedures have evolved and multiple types of MUS have been launched on the market, enabling treating physicians to offer different therapeutic options to patients with SUI. The single-incision slings (SIS) are one of the latest innovations for female SUI. They were introduced with the concept of using a shorter tape through a single vaginal incision providing a similar "suburethral hammock" to classical MUS[5].

Their anchoring mechanism (to the obturator membrane or muscle) avoids the passage of trocars through the obturator foramen[6]. SIS represent a minimal invasive innovation for the surgical treatment of SUI. Some studies have already proven their efficacy on the short, medium and long term[5,7-9].

The purpose of this study is to review the evidence for different SIS systems, to compare this relatively new system with traditional MUS and to give the reader an overview on the principal SIS currently available, defining their efficacy and safety. Moreover we aim at giving the physician a tool to simplify the clinical decision-making on the base of the existing literature.

MATERIALS AND METHODS

Evidence acquisition

The literature search was conducted on PubMed in June 2015. The search strategy included the following terms: "SUI" AND "mid urethral slings", AND "SISs" AND "female".

Our research was restricted to randomized and/or prospective trials and retrospective studies with at least 20 patients with non-neurogenic SUI, published after 2006 in English. To be included in the review the studies had to assess efficacy and/or safety of the SIS and have a minimum follow-up of 12 mo. It is important to underline that all the paper assessing the performance of TVT secur were excluded from this review. The reason is the worldwide withdrawal of this sling from practice in March 2013.

Two independent researchers evaluated the articles with one researcher making the final decision.

Evidence synthesis

Using the aforementioned research strategy, 102 studies were identified. After applying the eligibility criteria a total of 19 papers were included in the review. Of these, 8 reported efficacy and/or safety outcome on Ajust® (C.R. Bard, Inc., Murray Hill, NJ, United States), 2 on Ophira® (Promedon, Cordoba, Argentina), 2 on Altis® (Coloplast), and 7 on MiniArc® (American Medical System, Inc., Minnesota, United States) (Figure 1). The statistical review of the study was performed by a biomedical statistician.

RESULTS

Ajust® (Figure 2)

Method of action/working mechanism: The Ajust® sling provides a strong insertion into the obturator muscle/membrane and allows immediate post insertion adjustment of the tape. A 1 cm incision is made and a bilateral tunnel is created as far as the posterior margin of the inferior pubic ramus. The trocar with the fixed anchor is then introduced and pivoted slowly in the obturator internus and membrane. The adjustable anchor is subsequently placed at the contralateral side and the tape tension is adjusted. A flexible "sylet" is used to lock the adjustable anchor[10].

Population: A total of 8 studies assessing efficacy and/or safety of Ajust® slings have been included in the review[11-18]. All patients included presented with SUI or MUI with predominant stress symptoms. In all the studies, patients with concomitant organ prolapse, predominant overactive bladder symptoms or patients

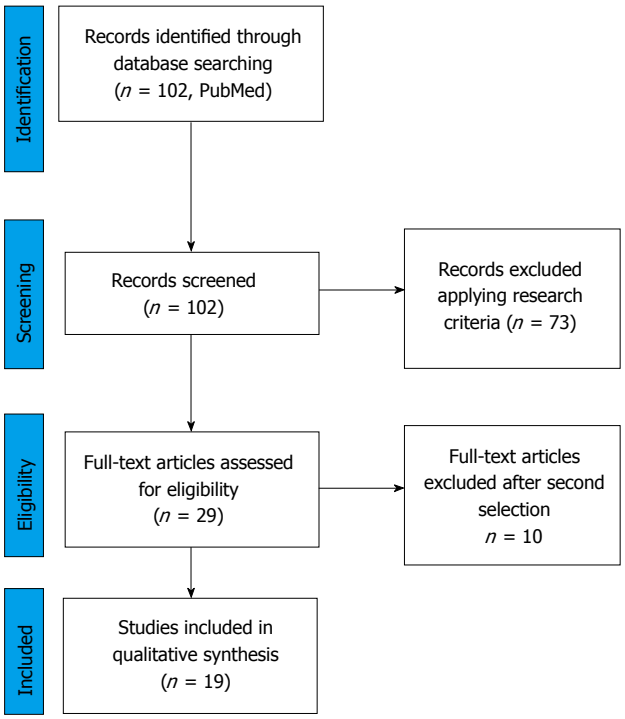

Figure 1 Prisma flow chart.

with a history of previous incontinence and/or anterior vaginal wall surgery were excluded. The majority of the studies included do not differentiate the severity of the incontinence. Overall severity information were available for a total of 374 patients who showed moderate to severe SUI[11,15,16].

Evidence efficacy (Table 1): Ajust® sling efficacy was investigated in a total of 3 randomized controlled trials (RCT)[9,11,12].

Two of them compared the efficacy of the adjustable sling system with the classic MUS TOT in a total of 293 patients. At 1-year follow-up, both studies demonstrated no difference between groups in terms of objective cure (assessed with cough stress test - CTS): 90.8% *vs* 88.6%[11] and 81.2% *vs* 82.3%[9] in Ajust® and TOT respectively, all $P > 0.05$. Subjective cure was also assessed. In the paper by Schweitzer *et al*[11], subjective cure was defined as a negative answer to the UDI-6 question: "do you still experience any leakage related to physical activities?". In the paper by Mostafa *et al*[9], it was assessed using the patient global impression of improvement (PGI-I) questionnaire. Using the aforementioned criteria, neither RCT showed any difference in subjective cure rate between the two groups. Failure was defined as any surgical re-treatment for urinary incontinence. Schweitzer *et al*[11] showed a failure rate of 2.2% and 2% in Ajust® and TOT slings at 1-year. Mostafa *et al*[13] showed a 7.2% and 4.4% failure rate in Ajust® and TOT respectively. These differences between groups were not statistically significant in both papers[9,11].

The third RCT is a comparison between three

Figure 2 Ajust sling.

SISs, namely TVT Secur®, MiniArc® and Ajust®[12]. As mentioned before, we did not include the results concerning TVT Secur. The other two arms (namely MiniArc® and Ajust®) did not show any difference in terms of subjective and objective cure rates at 6, 12, 18 and 24 mo follow-up. It is important to underline that both objective and subjective cure rates decreased significantly in each arm between 6 and 24 mo. At 24 mo, no difference was found between groups in total failure rates: 60% in the Ajust® group and 55% in MiniArc® group.

In the matched paired study performed by Grigoriadis *et al*[14] on 171 patients diagnosed with urodynamic SUI, we observed similar results in terms of objective and subjective cure rates at 22 mo follow-up for both thr Ajust® and TOT group. Failure rate varied between 8.1% and 10.6%[14].

We also collected data of 4 prospective studies assessing the efficacy of Ajust® slings up to 1-year follow-up. The results were comparable with those of the RCTs: Objective cure varied from 82.4% to 83.7%. Patient reported cure varied from 80% to 83%[15-18]. However, it has to be underlined that each study used different objective and subjective parameters to assess continence after surgery. Failure of the procedure defined as persisting SUI or need of other types of incontinence surgery vary widely from 0.0% to 14%.

Evidence safety (complications and pain) (Table 2): No major complications were observed in all the studies analysed. In a cohort study, Cornu *et al*[17] described a post-operative vaginal bleeding managed surgically 8 h after the initial surgery. Also a total of 2 mesh erosions (on 95 patients) requiring surgery were observed after a mean follow-up of 21 mo[17].

In the RCT comparing Ajust® and MiniArc® the number of patients using analgesic tablets during the first 30 d from surgery ($P = 0.349$) and the number of analgesic tablets used ($P = 0.124$) were similar among both groups.

Complications occurred in 7 (17.5%) and 2 (5.0%), cases from the Ajust® and MiniArc® groups respectively. All post-operative complications were Dindo grade 1,

Table 1 Efficacy

Ref.	Design	Participants	Intervention (*n*)	Comparison	Follow-up	Cure assessment	Cure rate	Assessment of improvement or success	Improv. rate	Success rate	*P*
Schweitzer *et al*[11]	RCT	156	Ajust: 100	TOT	12 mo	OC: CST	OC: 90.8% *vs* 88.6%		-	-	OC: 0.76
			TOT: 56			SC: UDI-6	SC: 77.2% *vs* 72.9%				SC: 0.57
Palomba *et al*[12]	RCT (Multi)	80	Ajust: 40	MiniArc	24 mo	OC: CST	OC: 47% *vs* 55%		-	-	$P > 0.05$
			MiniArc: 40			SC: % dry? Or improved?	SC: 52.5% *vs* 65%				$P > 0.05$
Mostafa *et al*[13]	RCT (Multi)	137	Ajust: 69	TOT	12 mo	OC: CST	OC: 81.2 *vs* 82.3%				$P = 1$
			TVT-O: 68			SC: PGI-I	SC: 85.5% *vs* 84%				$P = 1$
Grigoriadis *et al*[14]	Prosp matched controlled	171	Ajust: 85	TOT	22.3 mo (mean)	OC: CTS	OC: 84% *vs* 86%	-			
			TOT: 86			SC: Patient impression	SC: 81.2% *vs* 82.6%				
Natale *et al*[15]	Prosp. (Multi)	92	Ajust: 92	-	24 mo	OC: CST SC: PGI-I	OC: 83.7% SC: 81.5%		-	-	-
Naumann *et al*[16]	Prosp. (Multi)	51	Ajust	-	25.2 ± 2.24 mo (mean)	OC: CTS	82.4%	Ingelmann-Sundberg scale	3.9%	86.3%	-
Cornu *et al*[17]	Prosp.	95	Ajust		21 ± 6 mo (mean)	OC: Pad usage SC: Subjective reports of leakage	OC: 80% SC: 83%	-	-	80%	-
Abdel-fattah *et al*[18]	Prosp. (Multi)	90	Ajust	-	12 mo	-	-	PGI-I	86%	80%	-
Palma *et al*[19]	Prosp. (Multi)	124	Ophira		12 mo	OC: 1 h-PWT	OC: 85.3%	Leakage < 50%	6.30%		
Djehdian *et al*[20]	RCT	120	Ophira: 64	TOT	12 mo	OC: CST/	OC: 68.1% *vs* 81.9% (ITT) and 73% *vs* 89% (PP)	-	-	-	$P = 0.43$ and 0.54
			TOT: 56			20 min pad test					
						SC: Patient satisfaction	SC: 81.1% *vs* 88.5% (ITT) and 87.5% *vs* 96.4% (PP)				$P = 0.11$ and 0.10
Dias *et al*[21]	Prosp.	50	Altis	-	12 mo	CST ICIQ-SF = 0	OC: 90.2% SC: 84%	ICIQ-SF lower than pre-op or > 0	8%		
Kocjiancic *et al*[22]	Prosp. (Multi)	101	Altis	-	12 mo	OC: PWT (< 50% pad weight compared to baseline) and CST SC: PGI-I	OC: 90% OC: 90.1% SC: 89.3%	-	-	-	-
Lee *et al*[25]	RCT	206	MiniArc: 103	Monarc	12 mo	CST (negative)	OC: 94% *vs* 97%	-	-	-	OC: 0.78
			Monarc: 103			SC: Negative reply to ICIQ 3 and 5 and UI-SF	SC: 92% *vs* 94%				SC: 0.50
Schellart *et al*[26]	RCT	173	MiniArc: 86	Monarc	12 mo	OC: CST	OC: 89% *vs* 91%				$P = 0.65$
			Monarc: 87			SC: PGI-I	SC: 83% *vs* 86%				$P = 0.46$
Basu *et al*[27]	RCT	71	MiniArc: 38 Advantage: 33	Advantage	36 mo			KHQ	48% *vs* 90%		All $P < 0.05$

Oliveira *et al*[23,30]	Prosp.	71	MiniArc	-	12 mo	SC: No leakage and no protection	77%	Use of protection decreased > 50% and affirmative reply to the question: are you satisfied with the results?	11%	88%	
Deole *et al*[29]	Prosp.	59	MiniArc		12 mo	OC: CST SC: ICIQ-SF PGI-I	OC: 66% SC: median score 6 64%	-	-	-	-
Presthus *et al*[24]	Prosp.	31	MiniArc		24 mo	OC: CST and PWT	93.5% 90.3%				
Kennelly *et al*[31]	Prosp. (Multi)	142	MiniArc		24 mo	OC: CST and PWT SC: UDI-6	84.5% 80.1% 92.9%	-	-	-	-

RCT: Randomized controlled trial; TOT: Trans obturator tape; OC: Objective cure; SC: Subjective cure; PGI-I: Patient global impression of improvement; CST: Cough stress test; PWT: Pad weight test; ITT: Intention to treat; PP: Per protocol; ICIQ-SF: International Consultation on Incontinence Questionnaire - Short Form; UI-SF: Urinary incontinence-Short form; UDI-6: Urogenital Distress Inventory; Prosp.: Prospective; Multi: Multicentric.

and they were not significantly different among the groups (P = 0.897).

Schweitzer *et al*[11] showed a significantly lower pain score in the Ajust® group *vs* the TOT group during the first week. However no differences were found after day 6 between both groups (P = 0.75).

OAB symptoms: In the RCT by Shweitzer only women with moderate to severe SUI were included. Seven out of 100 women in the Ajust® group and four out of 56 in the TOT group reported new onset of OAB. Both the RCT by Mostafa *et al*[13] and Palomba *et al*[12] included also patients with mixed urinary incontinence. In the first paper the authors showed a trend toward higher rates of *de novo* urgency and/or worsening of the pre existing urgency in the Ajust® group during the first 4 mo (although it was found not to be statistically significant) but this finding was not retained at 1-year. Moreover there was no significant difference between the two groups (6.5% *vs* 8.7% in TOT *vs* Ajust®, P = 0.74)[12].

De novo or worsened urgency UI was noted in 5 patients, in the paper by Palma *et al*[19], occurring in 3/40 (7.5%) and 2/40 (5.0%) cases in the Ajust® and MiniArc® groups, respectively[16].

In the study by Grigoriadis *et al*[14], there was a total of 10/85 (11.6%) *vs* 8/86 (9.4%) patients that complained of early post-operative symptoms of frequency and urgency in the TOT group *vs* Ajust® groups respectively (P < 0.05). No DO was demonstrated on urodynamic investigation[14].

In the prospective study by Mostafa *et al*[13], the authors assessed post-operative urgency in a group of pure SUI and mixed incontinence patients, using the urgency perception scale (UPS). Pre operative assessment of urgency showed 53/90 patients (59%) to have urgency symptoms. Of them, 35/53 (66%) reported post-operative improvement of urgency (29 of them reported total cure). However, 18/53 (20%) patients reported no improvement or even worsening of the symptoms. No data on *de novo* urgency was described by the authors[18].

Cornu *et al*[17] also showed a decreasing trend in OAB symptoms after surgery compared to the pre-operative assessment (35% *vs* 25%). Of them 12/95 (12.6%) had *de novo* urgency and 12/95 (12.6%) reported persistent OAB symptoms[17].

Natale *et al*[15] reported a rate of post-operative urgency of 5.4% (5/92), 9.8% (9/92) of which *de novo* urgency. In the group of patient with pre-operative OAB symptoms (n = 36, 39.1%), 27 reported persistence of urgency and of them 18 had a good response to pharmacotherapy (30%)[15].

Naumann *et al*[16] reported on 6/51 patient (12%), having a preoperative patient perception of intensity of urgency scale higher than 1 (*i.e.*, at least moderate urgency). However, 3 of them (60%) reported improvement of urgency compared to their situation before surgery and 2 (40%), reported severe urgency (2/5: 4%)[16].

Ophira® (Figure 3)

Method of action/working mechanism: Ophira®, has blue loosening sutures inserted in the base of both fixation arms, giving the ability to correct tension during the procedure. The fixation system has multiple fixation points along its self-fixating arms.

The system includes a "Retractable Insertion Guide" to improve control and ease when inserting the sling and releasing it in the correct position. The connectors located at the ends enable the Retractable Insertion Guide to be inserted easily and safely.

Table 2 Safety

Ref.	Design	Participants	Intervention	Comparison	Timing	Assessment	Pain rate/ complications	*P*
Schweitzer *et al*[11]	RCT	156	Ajust: 100 TOT: 56	TOT	Immediatepost-op and up to week 6	VAS	Median score week 1: Ajust: 0.2 TOT: 1.0 Median score week 2: Ajust: 0.0 TOT: 0.5	< 6 d: 0.01 > 6 d: > 0.05
Palomba *et al*[12]	RCT (Multi)	80	Ajust: 40 MiniArc: 40	MiniArc	24 mo follow-up	VAS	Pain score Ajust: 5.3 ± 3.8 Pain score MiniArc: 5.0 ± 3.5 Complications: Ajust: 17.5% MiniArc: 5% 1 mesh erosion in Ajust group (no surgical revision)	All *P* > 0.05
Grigoriadis *et al*[14]	Prosp. matched controlled	171	Ajust: 85 TOT: 86	TOT	Post-op and during follow-up	Patient's impression	3.5% *vs* 5.8%	-
Natale *et al*[15]	Prosp. (Multi)	92	Ajust *n* = 92	-	Post-op and during follow-up	Patient's impression	1 leg pain, 3 mesh extrusion (of which 1 mesh removal)	-
Naumann *et al*[16]	Prosp. (Multi)	51	Ajust	-	1 d after surgery and at during follow-up	VAS	1 patient day 1	-
Cornu *et al*[17]	Prosp.	95	Ajust		1-6 and 12 mo and yearly thereafter	Use of pain medication and surgeon's and patient's reports	1 vaginal bleeding managed surgically 8 h after surgery. At last follow-up 2 patients still complained of tight and vaginal pain respectively	-
Abdel-fattah *et al*[18]	Prosp. (Multi)	90	Ajust	-	Intra-op., after 30 min and 3 h pot-surgery or at the time of discharge	10 point Likert scale	1 case had to be converted in standard MUS (kit fault). Median pain rate at the time of the discharge was 0 and didn't change during follow-up	-
Palma *et al*[19]	Prosp. (Multi)	124	Ophira	TOT	1-yr and 2 yr	Patient's impression	1 patient severe intraoperative painà sedation. 2 mesh resection: 1.6%	*P* > 0.05
Djehdian *et al*[20]	RCT	120	TOT: 56 Ophira: 64		Day 1 and after 4-6 wk	VAS	0% *vs* 1.7%	*P* = 0.04
Dias *et al*[21]	Prosp.	50	Altis	-	12 mo	Patient's report	1 mesh erosion treated surgically (2%)	
Kocjiancic *et al*[22]	Prosp. (Multi)	101	Altis	-	During 12 mo follow-up	Patient's and surgeon's reports	Non-pelvic pain: 9 (8%) 3 serious adverse events (1 bleeding, 2 mesh extrusion requiring surgery)	
Lee *et al*[25]	RCT	206	MiniArc: 103 Monarc: 103	Monarc	24 h after surgery and 12 mo follow-up	Patient's and surgeon's reports	Women requiring analgesia: 0.5 *vs* 2 tablets) and groin pain 9.7% *vs* 33% 1 mesh erosion in the MiniArc group at 1 yr follow-up	*P* = 0.02 *P* < 0.01
Schellart *et al*[26]	RCT	173	MiniArc: 86 Monarc: 87	Monarc	3 d and 4 wk	VAS Use of pain medications	2 *vs* 3 8% *vs* 3%	*P* = 0.90 *P* = 0.37

Basu *et al*[27]	RCT	71	MiniArc: 38 Advantage: 33	Advantage	During follow-up	Patient's response on late adverse events	No late adverse events	-
Oliveira *et al*[23,30]	Prosp.	71	MiniArc	-	First 24 h	VAS	1.0 ± 1.4 (one patient had pain for 6 mo)	-
Deole *et al*[29]	Prosp.	59	MiniArc	-	Intra and post-op	Surgeon's and patient's reports and Wong-Baker score	No major intraoperative complications Wong-Baker score: 2 ± 1.5	-
Presthus *et al*[24]	Prosp.	31	MiniArc	-	Intra and post-op	Surgeon's and patient reports and Wong baker faces	No major intraoperative complications Pain rate 9.6%	-
Kennelly *et al*[31]	Prosp. (Multi)	142	MiniArc	-	At discharge and at 7 d post-op	Surgeon's and patient's reports and Wong-Baker score	No major complications Median pain score 0	-

RCT: Randomized controlled trial; TOT: Trans obturator tape; Prosp.: Prospective; Multi: Multicentric.

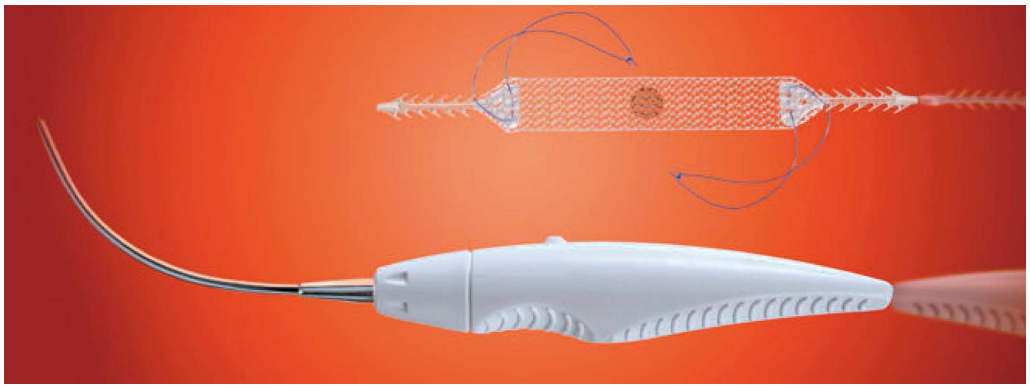

Figure 3 Ophira sling.

The delivery trocar is inserted in the small vaginal incision and guided by the surgeon toward the obturator internus. When half of the mesh is within the incision, the deployment button on the needle is pressed and the sling is kept in place by the self-anchoring fishbone columns.

Population: A total of two studies on Ophira® slings have been included in the review. One study is a prospective cohort study (n = 124) that includes women older than 18 years with a urodynamically confirmed diagnosis of SUI in absence of neurological disease[19]. The second one is a RCT including also women (n = 120) older than 18 years but with positive CST, urine leakage greater than 2 g (measured by a standardized pad test with 250 mL bladder volume) and urodynamic stress incontinence[20].

Evidence efficacy (Table 1): In the prospective cohort study by Palma *et al*[19] 124 women were included in the study to assess efficacy, safety and predictors of failure of Ophira® slings. The authors compared also the results at 1 and 2 years after surgery. Objective cure at 24 mo was 85.3% and improvement 6.3%. Overall 8.4% patient had failure and the only predictor of failure was previous incontinence surgery (P = 0.04)[19].

In the randomized prospective trial by Djehdian *et al*[20] comparing Ophira® and TOT, the efficacy at 12 mo was analysed using a non-inferiority test. They demonstrated no differences in terms of objective and subjective cure rates between the two slings in both intention to treat and per protocol analyses (all P > 0.5).

Overall failure rate was 19%. In the Ophira® group 5/64 patients (7.8%) did not achieve an objective and subjective cure, and were submitted to a second surgery. In TOT group, 1/56 (1.8%) of patients were submitted to a second surgery for failure. However no statistically significant differences have been found between groups[20].

Evidence safety (complications and pain) (Table 2): No major complications were reported in both studies. In the prospective randomized paper there was no difference in terms of complications between the two

Figure 4 Altis sling.

groups. However the number of patients complaining of tight pain resulted to be significantly higher in the TOT group compared to the Ophira® group (7.1% *vs* 0% respectively; $P = 0.04$). Two patients in the Ophira® group had the tape cut for voiding obstruction[20].

OAB symptoms: In the prospective cohort study, *de novo* urgency was reported in 9/124 patients (7.3%)[19]. In the prospective randomized study comparing Ophira® slings with TOT, symptoms of urgency were determined by patient's self reported response to urogenital distress inventory short form 1 and 2. The authors reported a significant reduction of in urge symptoms in both surgeries; Ophira®: 35.9% *vs* 3.1% and TOT 15.7% *vs* 3.5% (all $P < 0.01$) but no statistically significant difference was found between groups[20].

Altis® (Figure 4)

Method of action/working mechanism: The Altis® SIS is a low elasticity sling. The dynamic adjustability of the sling allows for accurate tensioning and placement of the sling in relation to the urethra. Its low elasticity and adjustability allows tensioning, placement and positioning of the sling under the urethra without compression.

The introducers are curved in shape and come as a set for the inside-out approach. They are designed for holding the anchor on the tip until insertion into the obturator membrane complex.

A monofilament suture is attached to the sling body and extends over the sides of the sling. The suture is connected to a dynamic anchor, which allows tensioning of the sling after placement. Positioning of the sling should be without tension to the urethra as the Altis® sling has a low 7.5% elasticity.

The surgical procedure is similar to the others single incision approaches. Using the introducer, the static anchor is placed through the obturator membrane. The dynamic anchor is then placed on the other side to be sure not to have tension. The suture extending from the sling and through the dynamic anchor is designed for two-way adjustability (metti Erwin). In all the studies included, a CST was performed to adequately tension the sling. The dynamic anchors holding force and suture design prevents sling movement during the tissue ingrowth period. This also eliminates the need for a locking mechanism. Following the procedure, the excess suture is cut and discarded.

Population: In the prospective observational study by Dias *et al*[21], a total of 50 women completed the 1-year follow-up and were included in the analysis. All women had SUI or MUI (mixed urinary incontinence) with predominant stress component, a positive cough test and a previous failure of conservative treatments[21]. The same inclusion criteria were used in the prospective multicentre study of Kocjancic *et al*[22] ($n = 101$) where they demonstrated pre-operative incontinence also with urodynamic exam.

Evidence efficacy (Table 1): In the small observational prospective study by Dias *et al*[21] the patient's reported subjective cure is 84% at 12 mo with an additional 8% of reported improvement. The objective cure, assessed with a standard CST is 92%. Failure was defined as the indication for mesh removal or absence of cure or improvement. Overall failure rate was 8%[21].

In the prospective study of Kocjancic *et al*[22] the overall objective cure tested with 24 PWT was 90% and CST was negative in 90.1% of patients. PGI-I was 89.3%. At 12 mo, 1 patient reported no changes compared to baseline and 2 patients reported the situation to be a little bit worse. Overall 2.9% of patients were not satisfied with the results[22].

Evidence safety (complications and pain) (Table 2): Dias *et al*[21] demonstrated no major complications in their observational study. The authors report none of the patients to require significant analgesics (only oral ibuprofen and/or acetaminophen in the first few days were used), however we have no clear data on pain because of the lack of validated scale in this study[21].

Kocjancic *et al*[22] registered three serious adverse events: One included a pelvic hematoma after revision surgery for urinary obstruction, the second one was a mesh extrusion categorized as a serious adverse event because the patient withdrew the study before revision surgery. The third event was a mesh extrusion for which the sling was trimmed on two separate surgeries. No cases of persistent pelvic pain were reported[22].

OAB symptoms: Just one of the included studies on Altis® sling analysed also the new onset of OAB symptoms. Dias *et al*[21] reported *de novo* urge incontinence rate to be 5.9% (3/50 patients).

MiniArc® (Figure 5)

Method of action/working mechanism: One of the most widely used and studied SIS is the MiniArc®. It has been used to treat female SUI since 2007, when the original MiniArc® Single-Incision Sling System was

Figure 5 Miniarc sling.

introduced.

As the others, this is a minimally invasive procedure using a small (1.5 cm) vaginal incision and a sharp dissection to the inferior pubic ramus in order to create the trajectory for the needle. The tip of the needle is keyed to the sling extremity so that the mesh lay on the convexity of the needle. The sling is advanced through the trajectories created with the scissors bilaterally and its self anchoring tip pushed along the posterior surface of the of the ischio-pubic ramus, taking care not to perforate the obturator membrane[23].

Population: A total of 7 studies analysing efficacy and/or safety of MiniArc® slings were included in the review[23-29]. A total of 753 patients had a follow-up ⩾ 12 mo. All studies included women with SUI or mixed incontinence with predominant complains of stress. Only in one study women with mixed incontinence were excluded and only women with documented pure SUI were included[23]. Women with a story of previous incontinence surgery, previous sling operation, concomitant pelvic prolapse ⩾ 2, neurogenic bladder, or predominant urodynamic detrusor overactivity, were excluded from the analysis in the majority of the studies.

Evidence efficacy (Table 1): Our selection of papers on MiniArc®[25-27] slings includes two randomized clinical trials comparing MiniArc® and Monarc slings and one comparing MiniArc® and Advantage sling. In the RCT by Lee *et al*[25] 103 patients in each group reached 1-year follow-up. There was no statistically significant difference in terms of subjective and objective cure rates between groups. Failure rate was 2.7% *vs* 1.8% in the MiniArc® group and in the Monarc group respectively; $P = 0.68$)[25].

In the RCT by Schellart *et al*[26], comparing MiniArc® and Monarc women, subjective cure was similar between both groups. The objective cure rate, defined as negative CST during follow-up, was also not statistically different between groups. Overall a total of 4 failures requiring a second surgery for SUI were identified: 3 in the Monarc group and 1 in the MiniArc® group[26].

Basu *et al*[27] in 2013 published the three-years results from their randomized trial comparing Advantage™ slings and MiniArc®™. They reported a success rate of 48% for MiniArc®™ with a failure rate of 52% (combining subjective failures with the need for repeat continence surgery). Moreover the MiniArc® were associated with a higher rate of persistent SUI (34% *vs* 9%)[27].

Overall 5 prospective studies on MiniArc® slings were included in the review[23,24,28,29]. Oliveira *et al*[23,30] reported 12 mo follow-up of patients with pure SUI. The intention to treat analysis showed a subjective cure rate of 80% and an improvement of 11%. The same group updated the analysis at 45 mo and showed 70 patients of the 77 responders to maintain the initial improvement/cure rate (91%).

All the other cases were reported as failures (7% in patients with 1-year follow-up)[23,30].

Deole *et al*[29] showed lower rates of objective and subjective cure at 1-year compared to other studies (66% and 64% respectively). They did demonstrate a statistically significant difference in post-operative subjective cure rates (defined as mean ICIQ-SF scores) compared to pre-operative scores (mean 8.6% ± 6.6% *vs* 16% ± 3.7% respectively, $P < 0.001$). Failure was reported in a total of 3/59 patients (5%) of which 1 was lost at follow-up but included in the analysis as failure. The other 2 patients reported persistent obstructive symptoms (requiring transection) and erosion of the mesh respectively[29].

In the prospective cohort study by Presthus *et al*[24] the objective cure ranged between 90% and 93% at 24 mo. Moreover patients reported a statistically significant improvement in UDI-6 and Ⅱ Q-7 compared to baseline. The percentage of patients with improvement in UDI-6 and IIQ-7 scores was 90.3% and 100% respectively. Failure rate was 9.6% (a total of 3 patients at 24 mo)[24].

Kennelly *et al*[28,31] in 2012 reported objective and subjective cure to be 84.5% and 93% respectively. Moreover a significant improvement occurred in UDI-6 and Ⅱ Q-7 compared to baseline. In their first paper of 2010, a total of 4 patients were reported to have surgical failures within the first year of follow-up. However no additional cases of surgical failure or adverse events have been reported from 12 to 24 mo[28,31].

Evidence safety (complications and pain) (Table 2): No major complications were reported in all the studies assessing MiniArc® safety. Lee *et al*[25] reported a statistically significant higher rate medication use and groin pain in Monarc group (all $P < 0.05$). Schellart *et al*[26] demonstrated a statistically significant difference pain score in the first 3 d after surgery in favour of MiniArc® patients.

No late side effects, pain or complications were registered by Basu *et al*[27], at 3-year follow-up[25-27].

Overall low pain scores were registered also in the prospective studies included in this review. Only one patient reported groin pain for more than 6 mo after

MiniArc® implant. Pain rates were generally very low either using VAS or patient reported impressions during the entire follow-up[23,24,28,29].

OAB symptoms: In the RCT by Lee *et al*[25] there was no difference in terms of post-operative OAB symptoms between the two groups at 1-year follow-up (median ICIQ OAB scores: 3 *vs* 3 in MiniArc® and monarc respectively; $P = 0.48$). However a difference was registered in terms of use of anticolinergic medications (5.5% *vs* 15.8% in MiniArc® and Monarc respectively; $P = 0.034$)[25]. On the other end Schellart *et al*[26] did not show any difference in terms of UDI-6 domain score for irritative symptoms between the two groups at 1-year follow-up.

Oliveira *et al*[30] showed a new onset of OAB symptoms in a total of 7 patients (6%). However the symptoms were classified as mild to moderate and solved spontaneously or were well controlled with anticholinergics. Deole *et al*[29] reported a 24% of *de novo* urgency symptoms of which 9% required anticholinergics at 3 mo follow-up. *De novo* urgency incontinence rate was reported to be 10% at 24 mo by Kennelly *et al*[31]. Presthus *et al*[24] reported only one patient to have *de novo* urge incontinence after surgery (3.2%) and of 10 patients witheline OAB symptoms, 90% reported no more symptoms at 24 mo.

DISCUSSION

The European Association of Urology Guidelines, concerning the treatment of female SUI, report that MUS, inserted by either the transobturator or retropubic route, give equivalent patient-reported outcome at 12 mo[7].

SIS represent the last modification to the MUS for SUI. They require very limited dissection and might further increase safety of sub-urethral slings. Many options have been proposed on the market but despite the increasing interest in SIS and their widespread use, there are still conflicting results on their effectiveness and safety.

Many recent reviews and meta-analysis on effectiveness and complications of SIS *vs* standard MUS have shown better outcomes for SIS in terms of operating time, better recovery and less intraoperative bleeding[5,13,32]. However there is still a lack of standardized characteristics for the ideal candidate for minisling surgery. There exist several different types of SIS systems with different characteristics that show different outcomes. The results of a particular SIS system cannot be transposed to another. In this review we report efficacy and safety of SIS and their effect on OAB symptoms, in patient with more than one year follow-up. We didn't focus our research on the advantages of SIS in terms of operating time or intraoperative bleeding already extensively assessed in previous reviews.

In our review we analysed different SIS systems, namely: Ajust®, Ophira®, Altis® and MiniArc®. Given that 63% of the studies included in the review are prospective or retrospective studies (level of evidence 3) we have to conclude that the evidence for SIS remains quite weak[7].

Nevertheless 2 randomized studies including 293 patients and comparing Ajust® sling with traditional TOT sling demonstrated high objective and subjective cure rates (ranging between 81% and 91% for objective cure and between 77% and 85% for subjective cure) and no difference between groups. Failure rate ranged between 2.2% and 7.2% but no difference was found between groups[9,11].

A third randomized study including Ajust® and MiniArc® slings showed no differences between the two slings in objective and subjective cure on the short term (OC: 80% *vs* 82.5% and SC: 90% *vs* 92.5%). However, a statistically significant difference was found when comparing the results at 6 mo with the results at 24 mo (OC: 47% *vs* 55% and SC: 52.5% *vs* 65%) in Ajust® and MiniArc® respectively, with lower rates of objective and subjective cure compared to the short term follow-up and other studies[12]. This decline, in OC and SC rates, has not been demonstrated in other studies by several other groups. The reason for this inferior resulted in this particular study is not clear.

Data from prospective studies analysing the efficacy of Ajust® sling on a total of 328 patients showed an objective cure rate between 80% and 84% and a subjective cure between 81% and 83%. However there was a variability between studies in terms of failure rates (range 0.02% and 14%).

In the RCT study comparing Ophira® slings and TOT, no difference was found in objective and subjective cure either in intention to treat analysis and per protocol analysis[20]. Palma *et al*[19] in their prospective study on Ophira®, showed higher rates of objective cure with a 6.3% improvement at 2 years but also higher rates of failure compared to the RCT (8.4% *vs* 7.8% respectively).

We found no RCT assessing the efficacy of the Altis® sling. Two prospective cohort studies on 151 patients with 12-mo follow-up did show similar results in terms of objective cure compared to the other RCTs (90.2% and 90%)[15,21,22].

One of the most widely used SIS is the MiniArc® sling. Our review includes a total of 3 RCT comparing MiniArc® to traditional MUS (namely Monarc and Advantage) including data on 450 women. The objective cure assessed with standard CST in the studies by Lee and Schellart was respectively 94% and 92% in MiniArc® slings and no difference was found between groups in both alayses. In this case, the MiniArc® sling was not inferior to monarc with respect to both objective and subjective cure. Failure was 1.8% and 0.5 % in Lee and Schellart paper respectively.

Basu *et al*[27] recently published the three years results of their RCT comparing MiniArc® to advantage sling. They reported a success rate of 48% in MiniArc®

slings and a failure rate of 52% (combining subjective failures with the need of repeat continence surgery). Moreover the MiniArc® slings were associated with a higher rate of persistent SUI.

Oliveira *et al*[30] described a success rate for MiniArc® slings of 88%, analysing only patients completing the 1 year follow-up visits. Failure rate however was higher compared to the two RCT (7%). The other prospective studies included in the paper showed results in line with the aforementioned RCT: The objective cure varied between 77% and 93%. Failures rates ranged between 3% and 7%. It is to underline that Deole *et al*[29] showed lower rates of cure compared to the other authors but a statistically significant difference compared to baseline.

We would like to underline that objective cure rates have been assessed using the standard cough stress test with 200 mL in the bladder in the majority of the studies, so it was possible to compare the different studies in terms of objective cure with an average objective cure rate of 88%.

It was not possible to compare subjective cure between studies since there was a great variability in terms of test performed (the majority of them were patient reported improvement or impression).

The vast part of the included studies did not show any major complication for minisling surgery. However Cornu *et al*[17] reported 1 post-operative vaginal bleeding requiring surgery and Kocjancic a serious pelvic hematoma and a mesh extrusion causing the abandoning of the study before second surgery and Dias showed 1 mesh erosion requiring surgery in the Altis® group. Two mesh erosions requiring surgery were registered also in the Ajust® group. In the Ophira® group two patients had the mesh cut for post-operative voiding obstruction.

Pain rate is another parameter difficult to compare because of the lack of standardized questionnaires or examinations. The majority of data obtained on pain were assessed by patient reports or VAS scale (also a subjective scale). However we can observe very low reported pain rates.

None of the patients reported persistent pelvic pain at long term follow-up. Both RCTs on Ajust® and MiniArc®, showed better outcomes in terms of immediate post-operative pain compared to traditional slings[25,26].

Again due to variability in the used parameters, it was not possible to systematically assess the new onset of OAB or worsening of the pre-existing OAB symptoms in all patients. It is of notice that all studies except 1 included also women with pre-existing mixed symptoms.

Some studies showed a trend toward higher rates of *de novo* urgency or worsening of pre-existing symptoms in the first months after surgery. We can assess that an average rate of 10% of de novo OAB symptoms or worsening of the pre-existing incontinence were reported in the minisling studies. On the other hand, Mostafa, Cornu and Djehdian showed a decrease in post-operative urgency in patients with baseline OAB symptoms. Moreover Presthus *et al*[24] demonstrated a 90% improvement in OAB symptoms after MiniArc® slings in patients with pre-operative urgency.

This review shows an average objective cure rate of 88% in minisling patients and underlines their comparable efficacy with traditional slings. Short-term pain, complication and failure rates are lower in the minisling group. In general we showed good results of minislings on the short and medium follow-up compared to traditional MUS. However this result supports the need of long-term follow-up, prospective, randomized trials, with adequate numbers and validated questionnaires to identify the best candidate for this type of procedure.

COMMENTS

Background

Single incision slings (SIS) represent a minimal invasive treatment for stress urinary incontinence (SUI). Some SIS have proven their efficacy on the short, medium and long-term follow in comparative studies with traditional mid urethral slings (MUS). The final purpose of this study is to guide the physician into the correct management of incontinent patient in order to give them a correct counselling in terms of surgical treatment of SUI.

Research frontiers

MUS were developed as a less invasive approach to the treatment of SUI. Nowadays the use of synthetic MUS is the most common surgery performed for SUI in women. The SIS are one of the latest innovations for female SUI. Their anchoring mechanism avoids the passage of trocars through the obturator foramen. Some studies have already proven their efficacy on the short, medium and long term.

Innovations and breakthroughs

The purpose of this study is to review the evidence for different SIS systems and to compare them with traditional MUS. The authors give an overview on the principal SIS currently available, defining their efficacy and safety.

Applications

This review can give the physician a tool to simplify the clinical decision-making on the base of the existing literature.

Terminology

SUI: Stress urinary incontinence; MUS: Midurethral slings; SIS: Single incision slings; TOT: Trans obturator tape; TVT: Tension free vaginal tape; RCT: Randomized controlled trial; OC: Objective cure; SC: Subjective cure; OAB: Overactive bladder; UPS: Urgency perception scale; PGI-I: Patient Global Impression of Improvement; CST: Cough stress test; PWT: Pad weight test; ITT: Intention to treat; PP: Per protocol; ICIQ-SF: International Consultation on Incontinence Questionnaire - Short Form; UI-SF: Urinary incontinence-Short form; UDI-6: Urogenital Distress Inventory.

Peer-review

This is a nice review.

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