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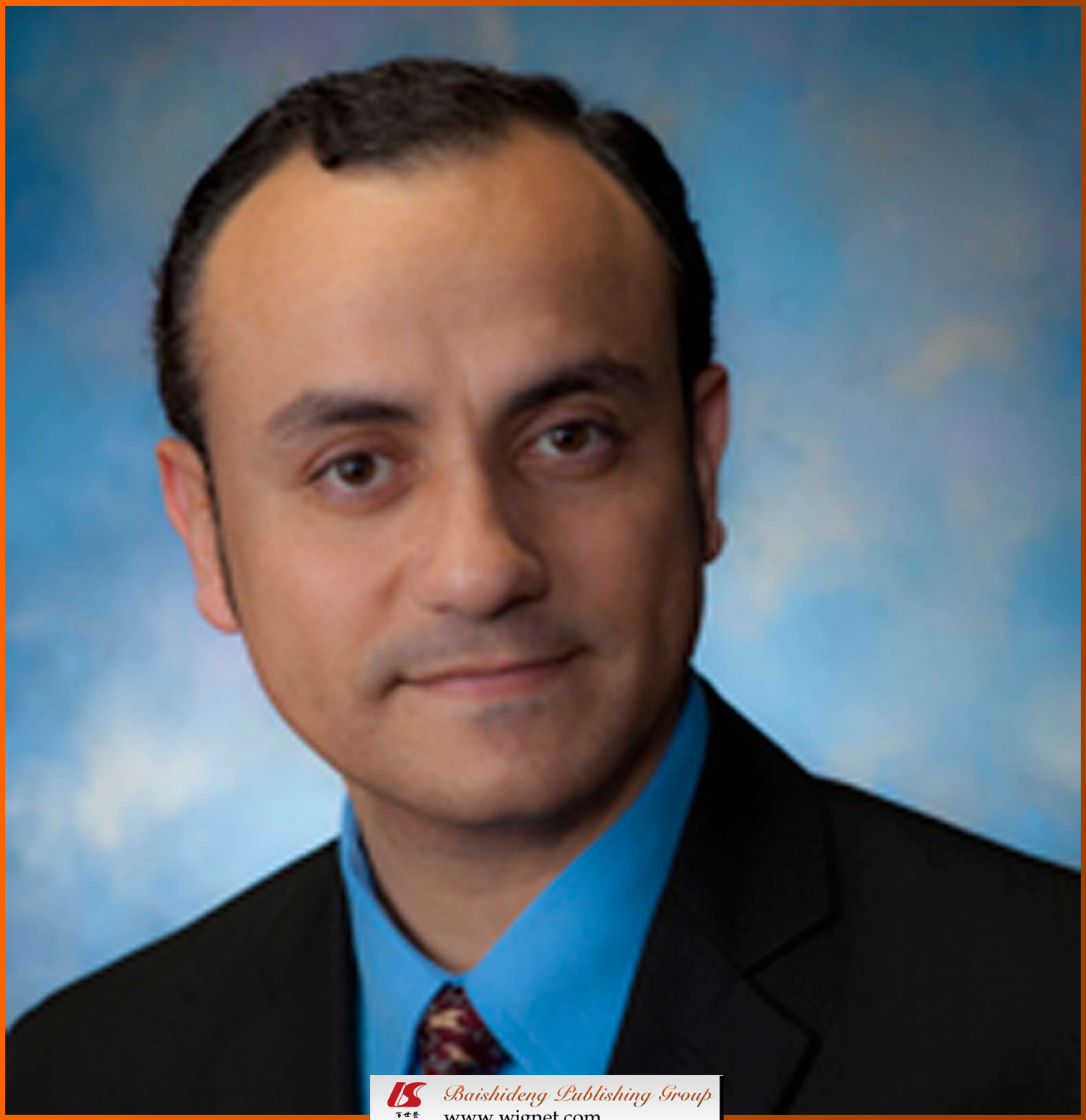

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EDITORIAL

Centers of excellence in minimally invasive gynecology: Raising the bar for quality in women's health

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Abstract

The "Center of Excellence" concept has been employed in healthcare for several decades. This concept has been adopted in several disciplines; such as bariatric surgery, orthopedic surgery, diabetes and stroke. The most successful model in surgery thus far has been the bariatric program, with a very extensive network and a large prospective database. Recently, the American Association of Gynecologic Laparoscopists has introduced this concept in gynecologic surgery. The "Center Of Excellence in Minimally Invasive Gynecology" (COEMIG) designation program has been introduced with the goals of increasing safety and efficiency, cutting cost and increasing patient awareness and access to minimally invasive surgical options for women. The program may harbor challenges as well, such as human and financial resources, and difficulties with implementation and maintenance of such designation. This commentary describes the COEMIG designation process, along with its potential benefits and possible challenges. Though no studies have been published to date on the value of this concept in the field of gynecologic surgery, we envision this commentary to provoke such studies to examine the relative value of this new program.

Key words: Excellence; Minimally-invasive; Gynecology; Surgery; American Association of Gynecologic Laparoscopists; Outcomes

Core tip: There are a number of benefits and potential challenges inherent to the "Center Of Excellence in Minimally Invasive Gynecology" (COEMIG) program. With an understanding of these challenges, organizations pursuing COEMIG may find advantages in efficiency, marketing and growth for both the institution and practice as a whole. There may also be reductions in complications, improvement in patient satisfaction and potentially reductions in cost that can arise as a result of COEMIG.

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INTRODUCTION

A program has recently been implemented whereby surgical facilities and gynecologic surgeons can earn the designation of "Center Of Excellence in Minimally Invasive Gynecology" (COEMIG). The COE programs are focused on improving the safety and quality of surgical care, and lowering the overall costs associated with successful treatment. They are designed to expand patient awareness of - and access to - surgical procedures per-

formed by surgeons and facilities that have demonstrated excellence in the specialty-specific techniques[1]. Under the direction of the American Association of Gynecologic Laparoscopists (AAGL) and administered by the Surgical Review Corporation (SRC), surgeons, hospitals and ambulatory surgery centers around the world that provide minimally invasive gynecologic surgical care may now pursue designation as a "Center of Excellence in Minimally Invasive Gynecologic"[2]. Though the nomenclature and its application vary, centers of excellence have been shown to improve outcomes and reduce costs[3]. The implementation of strict guidelines including procedure volumes, complication rates, readmissions, and mortality has helped to refine what exactly constitutes a standard center of excellence[4]. Recently, the University of Florida minimally invasive gynecologic surgery program has been designated as a COEMIG site. Herein we attempt to provide a concise description of the COEMIG program, including both its potential benefits and challenges. In doing so, we hope to stimulate research pertaining to this relatively new and uninvestigated process.

CENTER OF EXCELLENCE IN MINIMALLY INVASIVE GYNECOLOGY

COE concept dates back to the 1960s and generally describes a facility or organization which creates value that exceeds the norm in the locale of interest[3]. Similarly, the National Institutes of Health designate centers of excellence to institutes that have made concerted progress in a given area of research[5]. In the case of COEMIG and similar COE programs like that of bariatric surgery and cardiovascular service, COE refers to a specialty that works to incorporate the highest standards of practice into their entire scope of operations[6]. In the most fundamental sense of the term, a center of excellence should strive to fulfill several basic goals, including the presence of an integrated program, a comprehensive array of services, diverse ability to handle complications, high levels of patient satisfaction, a lower cost based on improved safety and efficiency, and a commitment to the continual measurement and comparison of care quality[7]. Our organization utilizes several methods for extracting patient satisfaction, including paper and electronic methods. Ideally, monitoring patient satisfaction scores and comparing data over time to the baseline scores before COEMIG designation may provide insight into the effect of the program on patient satisfaction.

The American Society for Bariatric Surgery (ASBS) recognized the need for this framework of care delivery and assessment in bariatric surgery and in 2003 they formed the nonprofit accreditation agency, surgical review corporation (SRC)[7]. The bariatric surgery center of excellence program has been shown to improve surgical outcomes[8]. This positive performance may be related in part to the fact that center of excellence programs are typically found in higher volume facilities (> 100 cases per year) with literature supporting volume as a metric by which accreditation occurs[9]. Compared to low volume facilities, patients who underwent gastric bypass at high-volume hospitals had a shorter length of hospital stay (3.8 d *vs* 5.1 d, $P < 0.01$), lower overall complications (10.2% *vs* 14.5%, $P < 0.01$), lower complications of medical care (7.8% *vs* 10.8%, $P < 0.01$), and lower costs ($10292 *vs* $13908, $P < 0.01$), further compounding this notion[10]. Additionally, centers of excellence in knee and hip replacement have also shown statistically significant lower risk of complications with an odds ratio of 0.80 ($P = 0.002$)[11].

The AAGL was inspired by the success of the bariatric and knee and hip center of excellence programs and partnered with SRC in 2010 to launch the COEMIG program. Like other center of excellence programs, COEMIG focuses on improving outcomes, reducing costs, increasing access to minimally invasive procedures and advancing the field.

The ten-year-old accreditation methodology used for the bariatric centers of excellence program has proven efficacious in improving surgical outcomes and lowering readmission rates[8,12]. COEMIG utilizes a similar system to promote a potentially transformative mechanism for surgeons, healthcare organizations and the discipline of minimally invasive gynecologic surgery as a whole[1]. SRC reports that this transformation includes processes to improve safety and efficacy, promote practice development, contain costs and improve patient satisfaction[1].

COEMIG adoption may also prove beneficial for the discipline of gynecologic surgery in general. For individual practices, SRC also asserts that through the effective marketing and communication of COEMIG status, healthcare organizations and surgeons may be able to use their position for personal and organizational benefit and likely impact contract negotiations, reimbursement rates and referral patterns[1].

SRC incorporates three committees, including boards for Standards, Review and Outcomes[13]. Each of these committees is comprised of a host of the industry's leading surgeons, each working to monitor and ensure an alignment of missions between the AAGL and organizations seeking COEMIG status. As of the date of this publication, 75 institutions and 282 gynecologic surgeons have earned the COEMIG designation. An additional 6 institutions and 45 surgeons are in the final stages of being designated[14].

COEMIG works to foster excellence in the field through the establishment of a live outcomes database, much like the bariatric outcomes longitudinal database (BOLD) of the BSCOE program. The goal of this database is to help establish a standard resource of information for the accumulation and analysis of improvements or areas of need within the field. This large, prospective database will also enable the development of new "standards" of care through monitoring outcomes for issues that have long been debatable due to the lack of large prospective trials. The BOLD is now the world's largest and most comprehensive repository of related clinical

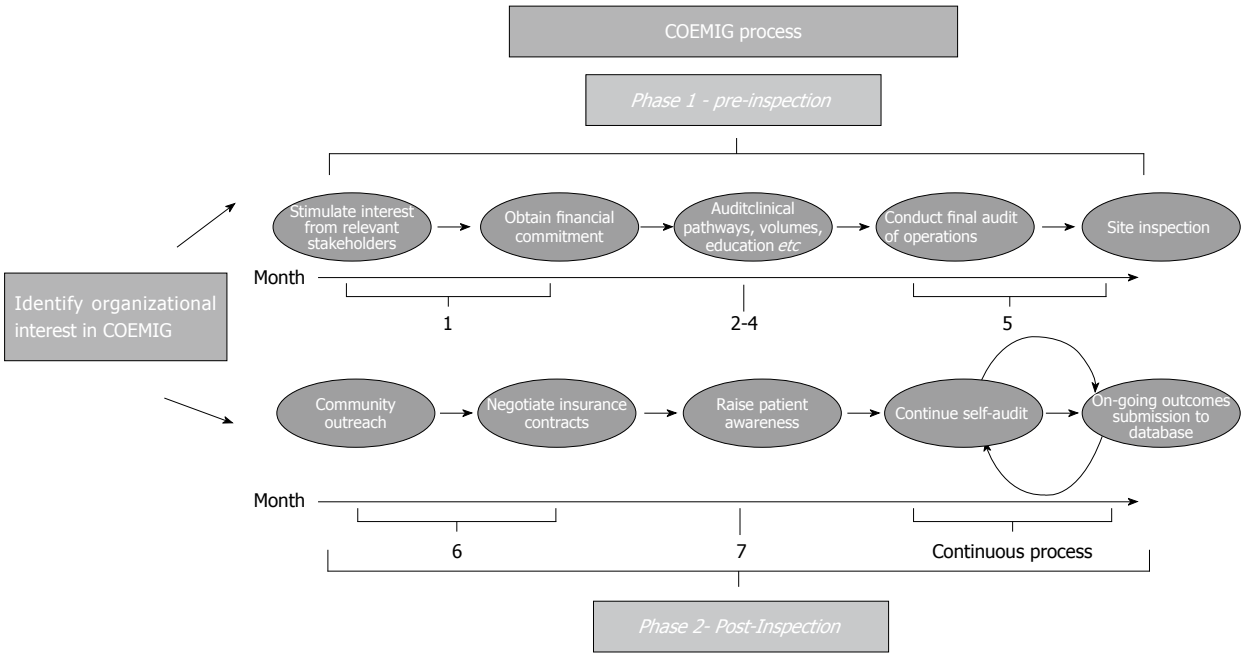

Figure 1 A visual depiction of the center of excellence in minimally invasive gynecology process. COEMIG: Center Of Excellence in Minimally Invasive Gynecology.

bariatric surgery patient information, a vital resource that the COEMIG database will likely try to emulate for minimally invasive gynecologic surgery[15].

COEMIG designation is promoted by the American Association of Gynecologic Laproscopists and the Surgical Review Corporation, through their website, e-mails, webinars, meetings, periodicals, journals and direct mail to the membership. Through the COEMIG initiative, the AAGL and SRC provide the opportunity to surgeons, practices, and hospitals of varying size and scope to pursue the designation and contribute to the potential growth and enhancement of the field.

The University of Florida Minimally Invasive Gynecologic Surgery (MIGS) program found it desirable to pursue designation, to strengthen the multidisciplinary team approach to the care of the minimally invasive surgical patient and to streamline our processes and procedures. The application process proved transformative for us and produced a level of organizational examination and introspection that have led to significant benefit. The process itself, outlined in Figure 1 was not a short one; a significant amount of effort and time was required for successful preparation and completion. In addition to workload, pursuit of COEMIG demanded a high level of consistent, clear communication among multiple units of the organization, displayed in Figure 2. Through an organized and focused approach, coupled with a fluid, communicative relationship among all involved, our pursuit of COEMIG was ultimately successful.

Certain aspects of the COEMIG application process in particular have encouraged a positive transformation in our practice. The augmentation of existing clinical pathways for example, has been an excellent method for analyzing organizational processes and ensuring their effectiveness, consistency and efficiency. Clinician and staff education requirements also provided an effective platform for bringing together the MIGS team and confirming and growing their knowledge base and synergy level. To maintain this synergy, quarterly staff education sessions on topics pertaining to minimally invasive gynecologic surgery, as well as in-services on equipment, are required for designation. Additionally, participating surgeons will need to maintain continued medical education credits in topics pertaining to minimally invasive surgery while also participating in staff education and quarterly team meetings.

Detailed review of volumes pointed out opportunities for improvement in coding and documentation, though formal percentages of error were not recorded. Some procedural volumes CPT codes provided by SRC were not congruent with the codes used within our organization. These challenges did not impact safety and efficiency; however they did add an additional layer of difficulty to the application process. The use of a prospective database will strive to alleviate this obstacle, as retrospective data collection will no longer be necessary. The creation of resource manuals for each unit that MIGS patients visit worked to ensure a consistent and reliable reference. Our resource manual includes call schedules, consultants, equipment specifications, patient education material, clinical pathways, standard operating procedures and consent information. Through the creation of these manuals, we were able to establish a more refined and identifiable source for information within our department.

The application process requires linked facility and surgeon(s) applications. Neither a surgeon nor a facility can apply independently. Hence, collaboration and building a unified goal between the facility and the applicant surgeon(s) are paramount. Surgeon requirements include demonstration of adequate surgical experience in lapa-

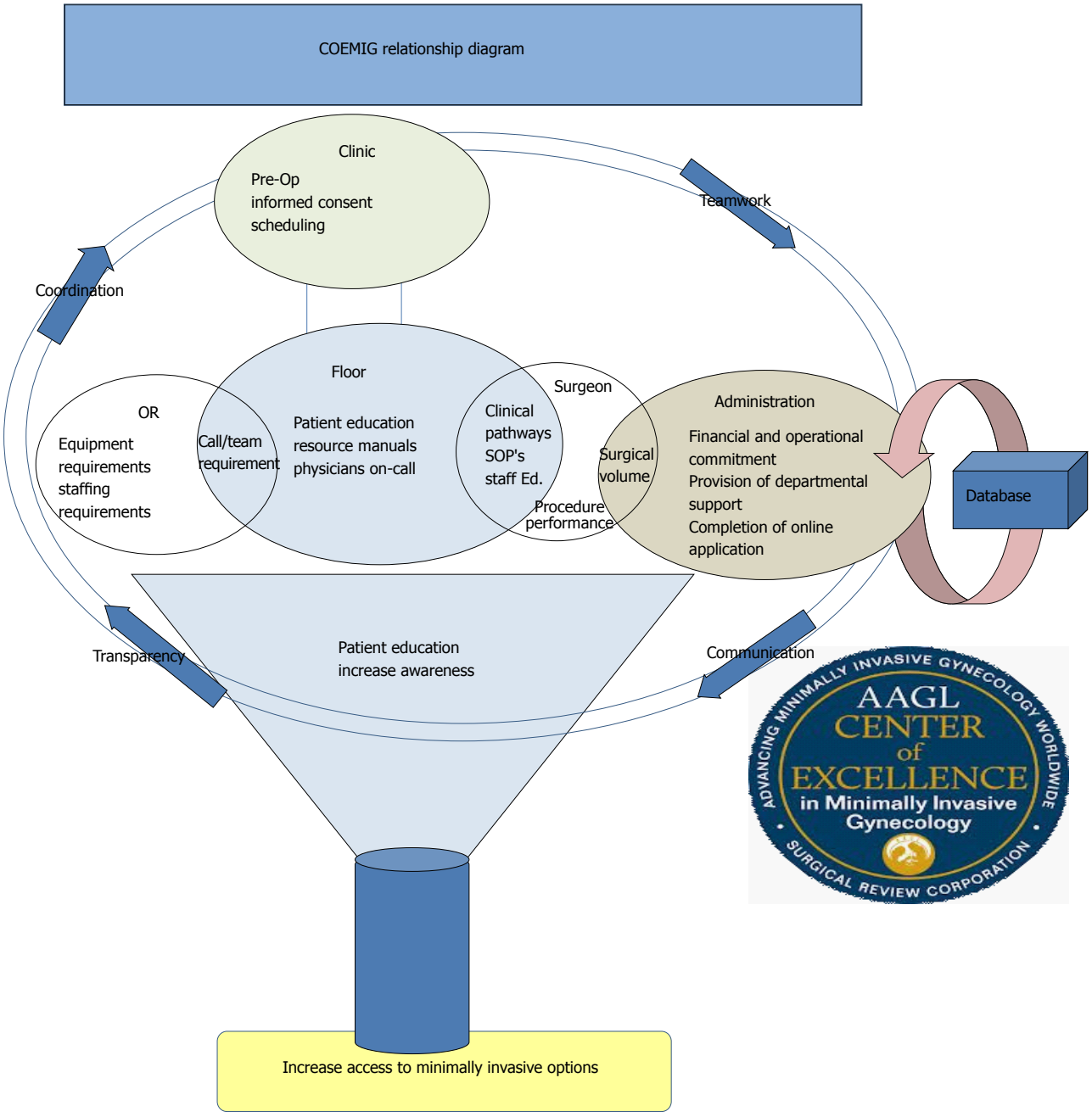

Figure 2 A visual depiction of the interconnected nature of the relationships within the center of excellence in minimally invasive gynecology process. COEMIG: Center Of Excellence in Minimally Invasive Gynecology.

roscopic and/or hysteroscopic procedures, a physician program director, qualified call coverage, consistent utilization of clinical pathways and standard operating procedures, informed patient decision making and consents for procedures commonly performed, and continuous assessment of quality goals[16]. The facility requirements include an institutional commitment to excellence in minimally invasive gynecology, surgical experience and volumes, a physician program director leading a multidisciplinary team, surgeons and qualified call coverage, and 24/7 consultant availability, advanced equipment and instruments, clinical pathways and standard operating procedures. Additional requirements include consistent, trained surgical team and support staff, documentation of informed patient decision making and consent and continuous assessment of quality and safety goals, defined by operative time, estimated blood loss, rate of complications, length of stay, reoperations, readmissions and mortality[17]. Specific difficulties in addressing these requirements within our organization dealt with the scope of the institution and the intricate navigation that occurs while trying to collect information and resources in a relatively short period of time. We found it beneficial and efficient to ensure brief but focused communication sessions at regularly scheduled intervals between a close group of relevant parties for the delegation and assurance of timely duty completion.

COEMIG requirements embrace similar criteria to

other quality programs such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). Staff education requirements and physician CME requirements foster the environment of safety that is promoted by other quality programs. It is important to note that an additional program is available in minimally invasive gynecologic surgery and is administered through the American Institute of Minimally Invasive Surgery (AIMIS). The requirements of this program are parallel to those of COEMIG. Individual institutions and surgeons can choose the program that fits their style or environment. The programs should be viewed as complimentary rather than competitive, with the overarching motivation to improve safety in a larger number of institutions and improve patient access to minimally invasive surgical procedures in institutions and by surgeons that have met minimum criteria for designation.

Additional surgeons in our organization began seeking COEMIG designation within 5 mo, interested in the potential benefits of our pursuit of designation as a center of excellence. Although all of the surgeons within an organization may not initially choose to pursue COEMIG, this is not a reflection of their quality of practice. Moreover, the overarching benefits to the entire institution help improve the organization as a whole and may stimulate other surgeons' interest in meeting the criteria to be designated. We envision this designation to incrementally increase volume, safety and efficiency of our processes and increase patient awareness and access to minimally invasive surgical options, and consequently, improve patient outcomes and satisfaction. Though a formal definition has not been implemented, efficiency will be monitored and measured through the recording of operative times, length of stay and complications. Each of these metrics coordinates directly with the cost of care and monitoring these changes over time may reflect changes in the level of efficient operation within a COEMIG applicant institution. These benefits illustrate a potentially positive transformational process within one organization, but the overarching implications of these changes may be considered for the practice of minimally invasive gynecologic surgery as a whole.

The execution of the center of excellence designation process does possess challenges and potential pitfalls. While physicians may foresee the possible benefits of creating a center of excellence, aligning the goals with hospital leadership may prove more challenging. A financial commitment is required for participation in the program, as with many other designation processes. The required fees include a COEMIG application fee of $7500, COEMIG surgeon application fee of $650 and site Inspection fee of $1850. Annual COEMIG institution participation fee of $3975 and an annual COEMIG surgeon participation fee of $650 are required. There are also significant effort, staffing and time commitments involved in the process. Staff education, standardized clinical pathways and operating procedures are some of the core requirements that can demand time, effort and consensus-building among participating surgeons. Another designation requirement is commitment to submit all surgical data into a prospective database, a task that will require ongoing support and accuracy, with potential added cost. It is conceivable that COEMIG pursuit may harbor personal interests and pose ethical issues; however, COEMIG designation is available to any facility that meets the requirements, including small and large practices, community and academic institutions as well as outpatient surgery centers[18].

COEMIG designation will vary based on the institution's size and practice type. In larger institutions, the disparate locations and motivations of departments and key stakeholders may make it challenging for the completion of certain aspects of the application. Conversely, smaller organizations may reach consensus easier, but may find it challenging to demonstrate adequate volume and to make the financial and personnel commitments required to achieve COEMIG designation. COEMIG applicants may also see a challenge in gaining interest from non-applicant surgeons; however, it is important to maintain that this does not mean those surgeons are not "excellent" in practice. It may be beneficial for organizations and the center's leadership to ensure that this fact is communicated to its surgeons so as not to create an exclusionary environment within their facility. Another foreseeable pitfall of designation is potentially misleading the patients to believe that every practicing surgeon in the facility is COEMIG-designated, while this is not true in most institutions. The Surgical Review Corporation has developed safeguards against this in the institutional agreements. Marketing of COEMIG will be important to the impact of its implementation. However, surgeons and organizational leaders must remain focused on the core purpose of COEMIG, which is to examine and improve the operations of an institution and ultimately improve patient care.

COEMIG designation remains in effect as long as the center is in good standing and verifiable compliance with all current requirements and program criteria, monitored every three years as part of a renewal cycle. At the three-year re-inspection visit, or sooner through monitoring the prospective database, surgeons who are not meeting the criteria will be moved back to a provisional status. Provisional status prohibits the surgeon from communicating his/her COEMIG designation in any fashion. If the surgeon is able to rectify the deficiency, she/he is moved back to the designated status. Conversely, if the deficiency is not rectified, the surgeon will lose his or her designation and is required to reapply in the future if she/he so desires. It is imperative for institutions interested in COEMIG to weigh the challenges and benefits when deciding whether this pursuit is appropriate for their organization.

It is important that COE programs make every effort to be inclusive, so that to build partnership with every institution and individual surgeon that can provide consistent, safe and efficacious minimally invasive surgi-

cal options for women. The driving purpose for this is to increase awareness and access to patients, and encourage the increased training of surgeons and staff and utilization of minimally invasive approaches. By elevating the level of practice, sharpening the operations of individual organizations and establishing an ongoing outcomes database for review and analysis, the COEMIG process generates a possible platform for advancing an entire arena of practice. The value of a large, prospective national and international database cannot be underestimated, not only for clinical research and advancing the field, but also for monitoring surgeons' and hospitals' progress over time and for anonymous comparison to peer surgeons and institutions. Though the COEMIG process is not without challenges, this incarnation of quality will and should serve to augment organizations, the field and most importantly, the standard of patient care.

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REVIEW

Desmopressin for the treatment of female storage lower urinary tract symptoms

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Abstract

Female storage lower urinary tract symptoms are prevalent and bothersome. They are usually attributed to an overactive bladder and treated with antimuscarinics. Nevertheless, failure of conventional treatment to alleviate nocturia in particular and epidemiological data suggesting that nocturnal polyuria is the only or a contributing factor to nocturia, has attracted interest in decreasing nighttime urine production as a method of managing nocturia. A reduction in urine production could also, at least temporarily, delay daytime storage symptoms by delaying bladder filling. Therefore, desmopressin, the synthetic analogue or naturally occurring antidiuretic hormone, could have a role in the management of female frequency, urgency and urgency incontinence. This work aims to review data on the use of desmopressin in females with storage symptoms. Available evidence indicates that desmopressin is efficacious in reducing nighttime urine production and episodes of nocturia, resulting in fewer sleep interruptions. This translates into improved quality of life. Desmopressin is also effective in postponing micturition, urgency and incontinence for several hours after being taken on demand. The tolerability profile of desmopressin is good and significantly improved compared to historical figures due to the introduction of new oral formulations, tailoring the dose according to gender and age and adhering to instructions for fluid restriction before administration. The incidence of hyponatremia, desmopressin's most important side-effect, is less than 3% in recent trials. The efficacy of desmopressin, combined with its improved safety profile, makes it an interesting method for treating female storage lower urinary tract symptoms.

Key words: Lower urinary tract symptoms; Storage; Nocturia; Overactive bladder; Desmopressin; Female; Nocturnal polyuria

Core tip: Recent data suggest that desmopressin in its oral formulations offers significant improvements in nocturia as well as daytime storage symptoms in female patients. The treatment rationale for nocturia is that nocturnal polyuria due to inadequate antidiuresis is a major contributing factor to nocturia. In the case of daytime storage symptoms, desmopressin taken on demand can postpone their manifestation by delaying bladder filling. Desmopressin is well tolerated and the risk of hyponatremia is low with appropriate dosing, based on a lower minimum effective dose in females compared to males.

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INTRODUCTION

Arginine vasopressin (AVP), a hormone produced by the neurohypophysis, is an integral part of the complex

mechanism regulating water homeostasis. AVP decreases urine production and increases its concentration by promoting osmotic reabsorption of solute-free water in the collecting tubules of the kidney[1] through activation of V2 receptors. AVP secretion is principally determined under physiological conditions by the osmotic pressure of plasma and mediated by specialized osmoreceptor cells in the hypothalamus.

Inadequate antidiuresis caused by a deficiency in AVP secretion or resistance to its action at the kidney level may lead to the development of clinical syndromes such as diabetes insipidus, primary nocturnal enuresis or nocturnal polyuria. Deficiencies or defects in vasopressin secretion can often be corrected by using desmopressin, a synthetic analogue of the naturally occurring hormone.

Desmopressin has increased potency and prolonged duration of action compared to AVP. Unlike AVP, desmopressin is V2-receptor specific so it reduces urine production without inducing pressor activity. It is the only available antidiuretic drug and has been used for over 30 years. Three different formulations of desmopressin have been available: nasal spray, hard oral tablet (0.1 and 0.2 mg) and since 2005 the desmopressin melt oral lyophylizate (administered sublingually without water) formulation (60 and 120 μg).

According to the International Urogynecological Association (IUGA) and the International Continence Society (ICS), female lower urinary tract symptoms (LUTS) include increased daytime urinary frequency, nocturia, urgency and urinary incontinence[2]. The symptom complex of urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology is defined as the overactive bladder (OAB) syndrome. The prevalence of female storage lower urinary tract symptoms is 59.2%, as shown in the EPIC study[3]. Nocturia in particular is a very common complaint in women. 54.5% of the female survey population had to wake up to void once or more per night and 24.0% at least twice.

The pathophysiology of OAB is not completely elucidated but detrusor overactivity, the finding of involuntary detrusor contractions during the filling phase of the micturition cycle, is still considered to play an important role. The symptom of nocturia from a pathophysiological point of view is as complex as overactive bladder; even although it is traditionally attributed to a decreased bladder functional capacity in the context of OAB, the role of nocturnal polyuria is increasingly recognized[4]. Nocturnal polyuria is defined as a nocturnal urine output greater than 20% of the total daily in young people and 33% in the elderly, with the value for middle age falling between the two extremes[5]. Fifty-seven percent to sixty-four percent of patients with nocturia have confirmed nocturnal polyuria with the percentage increasing to as high as 89% in patients treated with a blockers or anticholinergics for benign prostatic hyperplasia (BPH) or OAB[4,6,7].

Based on the current knowledge of the physiology of lower urinary tract and the pathophysiology of lower urinary tract dysfunction, the amount of urine produced cannot be an etiological factor but may exacerbate underlying pathology. Therefore, the rationale for the use of desmopressin in the treatment of OAB patients is that through a decrease in urine production, it will increase the time taken to reach functional bladder capacity between micturitions, thereby reducing frequency and urgency and offering symptomatic improvement. This is very similar to the rationale for use of desmopressin in nocturia patients. An inadequate antidiuresis may have an etiological role in cases where nocturnal polyuria is present and then the rational of using desmopressin is most obvious.

This review aims to investigate the use of desmopressin for the treatment of female storage LUTS. Only papers in peer-reviewed journals that reported results on female populations were considered.

DESMOPRESSIN FOR NOCTURIA

Prospective studies investigating the efficacy and safety of desmopressin in women with storage LUTS are summarized in Table 1.

In a phase-Ⅲ, randomized, double blind study investigating the safety and efficacy of oral desmopressin in the treatment of nocturia[8], women with at least 2 episodes per night and a nocturia index score of more than 1 (defined as the mean nocturnal volume divided by largest voided volume) entered a dose-finding phase starting at 0.1 mg orally administered desmopressin, with weekly dose increments to 0.2 and 0.4 mg, if necessary. Patients who experienced a complete response to any of the doses or a greater than 80% response on the maximum tolerated dose followed a one week washout. Provided that their washout voiding diary values returned to at least 78% of their baseline ones, they were randomized to receive their optimal desmopressin dose or placebo in a double-blind fashion for another 3 wk. Eighty patients withdrew during the dose-finding and washout phases (adverse events 27.5%, failure of diuresis to return to baseline values 37.5%, lack of response 10%) and 144 were finally randomized.

After 3 wk of treatment, 46% of patients on desmopressin had a 50% or greater reduction in nocturnal voids compared with 7% on placebo ($P < 0.0001$). The mean number of nocturnal voids, duration of sleep until the first nocturnal void, nocturnal diuresis and ratios of nocturnal to 24 h and nocturnal to daytime urine volumes changed significantly in favor of desmopressin *vs* placebo ($P < 0.0001$).

As far as safety is concerned, headache and nausea were reported by 22% and 8% of patients during the dose titration. Clinically relevant hyponatremia was reported in 6% of the population but serum sodium levels were below the normal range during the study in 12%. All cases of hyponatremia occurred during the dose titration period. Two deaths occurred during the same period but neither could be directly associated with the study

Table 1 Summary of studies investigating desmopressin in female storage

Study	Indication	Design	Desmopressin dose/formulation	Comparator	*n*	Primary end-point	Result
Lose *et al*[8], 2003	Nocturia	RCT	0.1, 0.2, 0.4 mg oral, hard tablet	Placebo	144	Percent of patients with > 50% reduction in nocturia	Significant *vs* placebo
Weiss *et al*[9], 2012	Nocturia	RCT	10, 25, 50, 100 μg oral lyophylizate	Placebo	341	Reduction in no of voids, patients with > 33% reduction in nocturia	Significant *vs* placebo for both co-primary end-points
Yamaguchi *et al*[11], 2013	Nocturia	RCT	10, 25, 50, 100 μg oral lyophylizate	Placebo	58	Reduction in nocturia episodes	Significant *vs* placebo for 25 and 50 mg
Sand *et al*[13], 2013	Nocturia	RCT	25 μg oral lyophylizate	Placebo	261	Reduction in nocturia episodes, percent of responders (> 33% reduction)	Significant *vs* placebo
Hilton *et al*[14], 1983	Nocturia (MS)	RCT, crossover design	20 μg nasal	Placebo	16	Reduction in nocturia episodes	Significant *vs* placebo
Eckford *et a*[15], 1994	Nocturia (MS)	RCT	20 μg nasal	Placebo	22	Reduction in nocturia episodes	Significant *vs* placebo
Eckford *et al*[16], 1995	Nocturia (MS)	Open label, non-randomized, placebo controlled, incremental dose	20, 40 , 60 μg nasal	-	8	Nocturnal urinary volume and osmolarities	Significant *vs* placebo No significant for 40 and 60 *vs* 20 μg
Robinson *et al*[18], 2004	Daytime incontinence (any type)	RCT, crossover design	40 μg nasal	Placebo	60	4-h post-dose periods with no urine leakage	Significant *vs* placebo
Hashim *et al*[19], 2009	OAB	RCT, crossover design	0.2 mg oral, hard tablet	Placebo	41	Time to various OAB symptoms in 8 h post dose	Significant *vs* placebo
Han *et al*[20], 2011	OAB	Open label, randomized	Desmopressin 0.2 mg plus solifenacin 5 mg	Desmopressin 0.2 mg	68	Time to first frequency or urgency episode	Significant for combination *vs* desmopressin monotherapy

RCT: Randomized controlled trial; OAB: Overactive bladder.

drug. As was expected, adverse events associated with desmopressin treatment were usually mild and comparable with placebo in the selected population of women entering randomization for whom efficacy and safety were established during the uncontrolled dose titration. It is worth mentioning that overall, 50% of the patients were excluded during the study because of adverse events.

The authors of the study concluded that oral desmopressin is an effective and well-tolerated treatment for nocturia in women. Nine years later, in a 4 wk, randomized, double-blind study comparing 10, 25, 50 or 100 μg desmopressin orally disintegrating tablet (melt) *vs* placebo in adults with at least two episodes of nocturia per night but no formal requirement for documented nocturnal polyuria[9], 341 women were recruited. The study had two co-primary endpoints: change in mean number of nocturnal voids and proportion of subjects with > 33% reduction in mean number of nocturnal voids from baseline. The study also investigated the minimum effective dose (MED) of desmopressin.

A greater decrease in number of nocturnal voids and a greater increase in the proportion of subjects with > 33% reduction in nocturnal micturitions were observed with increasing doses of desmopressin. The effect was significant *vs* placebo for all desmopressin doses except the 10 μg for both the co-primary endpoints. Significant effects were also noted for the reduction of nocturnal urine volume and the increase in initial period of undisturbed sleep *vs* placebo. The improvements in quality of life outcomes, including self-rated sleep quality and the Nocturia Quality of Life questionnaire, were also significant.

The incidence of adverse events increased for increasing doses of desmopressin and was within the expected range. As far as hyponatremia is concerned, six women on active treatment had reductions in serum sodium to < 125 mmol/L, none in the 25 μg group. These drops all occurred within a week of treatment initiation.

The results of all analyses of voiding data in this study indicated that the MED for desmopressin orally disintegrating tablets is 25 μg in women and the 10 mg dose was sub-therapeutic. The MED for the 416 men also included in the study was 100 μg.

The influence of concurrent voiding dysfunction on the efficacy of desmopressin in the treatment of female nocturia was examined in a retrospective analysis of 84 women with more than 2 episodes of nocturia at initial evaluation[10]. Women were treated with 100 μg desmopressin for 1 mo and were escalated to 200 μg for another month in case of lack of effect of the initial dose. Among the 84 patients, 51 (60.7%) complained of concomitant OAB symptoms and were treated with anticholinergics. As far as nocturia etiology is concerned, 59 patients (70.2%) had nocturnal polyuria, 6 (7.1%) had reduced nocturnal bladder capacity, and 19 (22.6%) had both. A dose escalation in 39.3% women was required.

Overall, 73 women (86.9%) showed improvement of nocturia and the mean number of nocturia episodes (1.4 ± 1.5) was significantly reduced compared to baseline (3.7 ± 1.3) ($P < 0.05$). A ≥ 50% reduction in the number of nocturnal voids compared with baseline was observed in 41 of 84 women (48.8%). The 41 women with a ≥ 50% reduction in the number of nocturnal voids had a lower baseline urgency grade (according to the urinary sensation scale) compared to the 32 women who showed smaller improvements.

The authors concluded that lower urinary tract symptoms (other than nocturia) and urgency in particular may reduce the effect of desmopressin in the treatment of nocturia and should be adequately addressed in order to maximize the efficacy of antidiuresis.

In another randomized, double-blind study comparing 10, 25, 50 or 100 μg desmopressin orally disintegrating tablet (melt) *vs* placebo in Japanese patients[11], the dose-response relationship of pharmacodynamic variables measured after a single dose of desmopressin was investigated along with the mean reduction of nocturia episodes after 28 d of treatment. Among the 111 patients completing the protocol, 58 were female. More than 50% but not all patients had nocturnal polyuria.

In the female population of the trial, there was an increase in the duration of antidiuretic action (DOA) of desmopressin, defined as the time with urine osmolality > 200 MOsm/kg after dosing. The DOA for the 25, 50 and 100 mg doses was 3, 4.41 and 5.59 h respectively; all significant compared with placebo. As far as a reduction of nocturia episodes is concerned, a significant reduction was seen in the 25 and 50 μg groups (mean reduction 1.81 and 1.70 respectively) but not the 10 or 100 μg compared with placebo. Significant changes were also observed for desmopressin over placebo in the secondary study outcomes: prolongation of initial undisturbed sleep, reduction in nocturnal diuresis and the ratio of nocturnal to 24 h urine volume.

The incidence of adverse events was within the expected range. No patients on active treatment had serum sodium < 130 mEq/L during any treatment period. Only two patients had serum sodium levels below 135 mEq/L, both of whom were male and > 65 years of age.

After analyzing both the female and male subpopulations of the study, the authors concluded that male patients require approximately 58 mg of desmopressin to achieve the duration of antidiuretic action that females achieve with 25 mg.

Taking into consideration evidence from previous trials[9,11,12] indicating that the effective dose of desmopressin may be lower in females than in males, a 3 mo, randomized, double-blind, placebo controlled study was designed to assess the efficacy and safety of a 25 mg orally disintegrating tablet of desmopressin in the treatment of women with at least 2 episodes of nocturia per night without significant daytime symptoms[13]. In all, 261 women were randomized. Desmopressin achieved a statistically significant reduction from baseline in mean number of nocturnal voids compared to placebo (treatment effect -0.22 voids, $P = 0.028$). The other co-primary endpoint, the percentage of responders, defined as the patients with a decrease of at least 33% in the mean number of nocturnal voids at each study visit compared to baseline using a longitudinal analysis, was also met: the odds ratio of responding to desmopressin compared to placebo was 1.85 ($P = 0.006$). The treatment difference was similar for patients younger than 65 and 65 years old or older, was evident from 1 wk into the study and maintained throughout the 3 mo treatment period.

Desmopressin was also shown to significantly increase the mean time to first nocturnal void by 49 min compared to placebo and decrease nocturnal urine volume at 3 mo. Significant increases in health related quality of life and sleep quality were also observed. Nevertheless, the percentage of patients with a decrease of at least 33% in the mean number of nocturnal voids at the 3 mo visit compared to baseline was not significantly different between treatment arms.

Desmopressin was well tolerated overall. Adverse events with an incidence of 2% or more in either treatment group included dry mouth, headache, medication error, somnolence and rash, leading to a 3% discontinuation rate in the desmopressin arm compared to less than 1% for placebo. As far as hyponatremia is concerned, sodium levels remained greater than 125 mmol/L throughout the trial and 3 transient decreases to less than 130 mmol/L were recorded which recovered in 2-4 d without requiring discontinuation of treatment.

The authors concluded that at a dose of 25 μg, desmopressin orally disintegrating tablet is an effective and well tolerated treatment for women with nocturia and supported recommendations for gender specific desmopressin doses.

The efficacy of desmopressin in the treatment of nocturia in female patients with neurogenic bladder dysfunction due to multiple sclerosis has been assessed in a randomized, double-blind, placebo controlled, cross-over study of 16 women, published 30 years ago[14]. Twenty microgrammes of desmopressin were administered intranasally at bedtime. Desmopressin achieved significant changes in early morning urine osmolality and nocturia episodes.

Eleven years later, 22 women and 11 men, younger than 65 years of age with multiple sclerosis and nocturnal frequency, with or without enuresis, were recruited into a study assessing the efficacy and safety of desmopressin[15]. Following a two week placebo run-in to establish baseline values, patients entered a double-blind, placebo-controlled, cross-over study of 20 μg intranasal desmopressin at bedtime. Desmopressin achieved significant improvements in nocturia, reduced nocturnal urinary volume and the ratio nocturnal to 24 h urine volume. There were no cases of clinically significant hyponatremia and only two cases of asymptomatic hyponatremia were reported.

The same study team conducted an open-label, incre-

mental-dose safety and efficacy study of desmopressin in women with multiple sclerosis and nocturia[16]. Neither a significant decrease in nocturnal urinary volumes nor an increase in urinary osmolality was achieved by doses of desmopressin larger than 20 mg. A dose of 60 μg was associated with a decreased serum sodium level at the end of the 24 h period post administration. The authors concluded that as there were no benefits and a possibility of clinical hyponatremia with doses higher than 20 μg, these doses cannot be recommended.

A pooled analysis of data from three short-term, randomized, controlled efficacy studies of desmopressin orally disintegrating tablet or solid tablet, with treatment extension periods of 40-56 wk in patients with nocturia[17], indicated that efficacy was maintained and in some cases increased after long-term treatment compared with short-term for females as well as in males. This analysis also showed that long-term efficacy is not a result of early discontinuation of dissatisfied patients.

DESMOPRESSIN FOR DAYTIME STORAGE SYMPTOMS

The efficacy and safety of 40 μg doses of desmopressin nasal spray in managing daytime female urinary incontinence was explored in a multicenter, randomized, double-blind, placebo-controlled study with a cross-over design published in 2004[18]. Sixty women with mixed (32), predominantly urge (13), or predominantly stress (15) incontinence received study medication. The primary efficacy endpoint was the number of periods with no leakage for 4 h after dosing.

There was a significantly higher incidence of periods with no leakage in the first 4 h after dosing with desmopressin compared to placebo (62% *vs* 48%). There were no differences in outcome when analyzed according to type of incontinence. There was also a higher frequency of dry days on desmopressin than on placebo; 36% of patients had no leakage on virtually all treatment days for 4 h after dosing. The time from dosing to first incontinence episode was longer on desmopressin (6.3 *vs* 5.2 h), whilst the volume leaked per incontinence episode was lower on desmopressin than placebo. The total volume voided over the 24 h period after administration was consistently lower on desmopressin (1180 *vs* 1375 mL).

There were no serious or severe adverse events reported despite the relatively high dose used in the study and those most commonly reported on desmopressin were headache (36%) and nausea (10%). Three percent of women withdrew from the study because of mild adverse events.

A phase Ⅱb, double-blind, randomized, placebo-controlled study with cross-over design investigated the efficacy of 0.2 mg of oral desmopressin in patients with idiopathic OAB[19]. The rationale behind this "proof of concept" study was that desmopressin would postpone OAB symptoms by reducing the speed at which the bladder fills. Female and male patients were given 3 doses of 0.2 mg desmopressin on alternate days and 11 doses of placebo on all other days during the 2 wk double-blind phase. The primary endpoint was the time to the first OAB symptom episode (micturition, urgency, urge incontinence) during the first 8 h following treatment.

Forty-seven male and 41 female patients were randomized and results were not presented separately for each gender. There was an 8 min delay in the first post-dose micturition for desmopressin compared to placebo (92 min *vs* 84 min) which was not statistically significant. The delay in the second and third micturitions was statistically significant, resulting in one less micturition in the first 8 h post dosing for desmopressin compared to placebo. The time to the first and second urgency episodes was statistically significant on the drug compared to placebo. As far as urge incontinence was concerned, the majority of patients (78%) did not experience any leakage in the first 8 h following treatment, but no significant difference was found between drug and placebo days with regards to the number of UUI episodes in the first 8 h following dosing. However, if incontinence frequency was classified as severe (≥ 2 episodes/3 d) or mild (≤ 1 episodes/3 d), there was significantly less incontinence episodes with desmopressin in severe cases compared to placebo.

According to the authors, this proof-of-concept study showed that desmopressin reduces OAB symptoms by increasing the time to the first OAB episode, with an overall improvement in QoL and minimal and tolerable side-effects, and therefore it represents a feasible method for symptomatic relief at least in the short-term. Its use as a per-needed tablet for management of OAB merits further assessment.

The use of a combination of anticholinergics and desmopressin in the treatment of overactive bladder was investigated in an open-label, randomized study[20]. Female patients with OAB and at least four voids in the first 8 h of the day after waking-up, excluding the first morning void, were recruited. Patients were randomly assigned to receive 5 mg of solifenacin (anticholinergic group) or 5 mg of solifenacin and 0.2 mg of desmopressin (combination group) for 2 wk. Patients were instructed to take the tablets after the first morning void. The primary efficacy endpoint was the increase in time to each of the first frequency or urgency episode. Thirty-one women in the anticholinergic group and 37 in the combination group completed the study.

Time to first micturition was 12 min later for the combination group compared to anticholinergic group (117 *vs* 105 min). This difference was not statistically significant in contrast to the difference in times to the second and third voids and time to the first urgency episode which were significant for the combination treatment compared to anticholinergic monotherapy. Combination treatment was also significantly better in reducing the total number of urinary frequency and urgency episodes during the first 8 h of the day as well as in improving quality of life scores. Age > 65 years and voided volume > 150 mL were predictors of improvement with combination treatment.

The authors concluded that the combination of desmopressin and an anticholinergic could be considered a feasible method for relief of symptoms in female patients with OAB.

CONCLUSION

Our review of the literature has revealed a renewed interest in the use of desmopressin for the treatment of female LUTS. Indeed, the majority of relevant trials have been published during the past 3-5 years.

Desmopressin has been available for over thirty years in the intranasal formulation for most of this period. Multiple reports of hyponatremia in elderly patients as well as in children have led to an increased awareness of this particular risk associated with desmopressin and have restricted its further clinical development. Due to this safety issue, desmopressin nasal spray lost Food and Drug Administration approval in 2007, leading to its worldwide withdrawal for the indication of nocturnal enuresis in children. Despite this, newer formulations of desmopressin are a well-established treatment in the management of childhood enuresis[21]. Drug dosing, variable absorption and misuse were major problems with the intranasal spray[22].

The switch to desmopressin tablet and more recently to the orally disintegrating formulation has been associated with a decrease in the incidence of hyponatremia[23,24]. Indeed, in all the recently reviewed trials for the role of desmopressin in the management of female storage LUTS, the incidence of hyponatremia and more specifically of clinically relevant hyponatremia was low. The superior pharmacokinetic and pharmacodynamic properties of the orally administered formulations are only one of the reasons for this observation[25-27]. Another reason is the identification of age and low baseline plasma sodium concentration as important risk factors for hyponatremia[23]. Finally, the awareness of a lower minimum effective dose in female patients compared to males[12] has led to more appropriate dosing.

The incidence of hyponatremia is currently less than 3%[23]. Evidence in this review suggests that desmopressin is currently a well-tolerated and safe treatment for females with LUTS.

Apart from the improved safety of oral formulations of desmopressin, another factor leading to a recent increase in the number or trials conducted in female populations is increased awareness of the prevalence and pathophysiology of nocturia. Nocturia in women was for many years attributed to OAB and was treated mainly with anticholinergics. The association of age with a reduction in the sensitivity of the osmoregulatory system resulting in inadequate production of AVP and a disturbance in the circadian rhythm of urine production has brought focus on nocturnal polyuria as an etiological factor of nocturia. Indeed epidemiological studies have found nocturnal polyuria in the vast majority of females with nocturia.

In our review, desmopressin administration achieved significant reduction in nocturia episodes and nocturnal urine production, which in most trials was translated to improvements in sleep and quality of life.

Trials conducted in females with daytime symptoms have confirmed that desmopressin is effective in at least postponing the development of storage symptoms and may be a useful on-demand medication for the management of OAB symptoms, particularly in combination with other treatments that address them around the clock.

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Peritoneal carcinomatosis from advanced ovarian cancer: To treat or not to treat ethical issues suggested by a case study

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Abstract

This article provides a brief description of an epithelial ovarian cancer (EOC) case (stage Ⅳ) treated with the association of complete CytoReductive Surgery and hyperthermic intraPEritoneal chemotherapy (HIPEC). The use of HIPEC in EOC makes theoretic sense in view of the high rates of recurrence following standard treatment, but there are no randomized clinical trial to date and HIPEC for these patients still represents a radical treatment where the choice of no treatment may be acceptable since definitive cure is unlikely. We reviewed the entire decision making process considering the risk/benefit of the procedure in term of mortality/morbidity, the quality of life and the psychological profile of the patient 1 year after surgery. The platform World Health Organization-International Classification of Functioning, Disability and Health that permits evaluation of the person in relation to the psycho-social context is presented. A person-centred approach and assessment of health-related quality-of-life and disability in EOC survivors are of central importance for decision making.

Key words: Advanced epithelial ovarian cancer; Peritoneal carcinomatosis; Platform World Health Organization-International Classification of Functioning, Disability and health; Ethical issues; Hyperthemic intraperitoneal chemotherapy; Health related quality of life

Core tip: This paper addresses the topic of "treating the untreatable". Advanced epithelial ovarian cancer with peritoneal carcinomatosis is not susceptible of definitive treatment. Anyway we can gain time. To achieve this goal the patient undergoes extensive treatment that has a significant burden of morbidity and mortality with decrease in quality of life in the postoperative period. This manuscript is the report of the bioethical conference held in our institution between the multidisciplinary team that take care of these complex patients and the bioethical philosopher and the clinical psychologist. Aim of the conference was to seek for bioethical

counsel in this cohort of patients highlighting the relationship of medical counseling, terminal state, the patient's individual preferences, psychological evaluation and health related quality of life. The case is evaluated by a patient-centered approach through the platform World Health Organization-International Classification of Functioning, Disability and Health that is presented into the article text.

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INTRODUCTION

The standard treatment for patients with advanced epithelial ovarian cancer (EOC) (stage Ⅲ or Ⅳ) is surgical debulking followed by platinum/paclitaxel-based adjuvant therapy. Although high rates of patients respond well to this therapy, about half of the patients relapse within 5 years[1] and long-term survival is achieved in only 10%-20% of patients[2]. Intraperitoneal route with the intravenous administration in primary stage Ⅲ ovarian cancer has been consequently studied in large randomized trials[3] and demonstrated that bidirectional chemotherapy using intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel significantly improved survival in patients with optimally debulked stage Ⅲ disease[4]. Despite these convincing data, intraperitoneal chemotherapy with normothermia still presents several limits, basically consisting of the inability of this technique to penetrate into tumor nodules larger than 3 mm[5].

On the other hand a significantly higher rates of treatment-related toxicities, side effects, complications[6-20] and a temporary reduction in quality of life[21-23] have been observed. All these adverse events could moreover lead to a potentially higher resource use[24,25]. To overcome these problems, intraperitoneal chemotherapy can be supplied intraoperatively, improving the tumor response to cancer chemotherapy drugs through the combination of drugs with hyperthermia[26,27]. Hyperthermia added to intraperitoneal chemotherapy might enhance the antimitotic effect by several mechanisms as known since the second half of the 90s[28,29].

The association of complete cytoReductive surgery (CRS) and hypertermic intraperitoneal chemotherapy (HIPEC) has shown to improve survival in patients with pseudomyxoma peritonei, malignant peritoneal mesothelioma or peritoneal carcinosis from advanced abdominopelvic tumors with high level of evidence[30-33]. EOC has no definitive data upon the effectiveness of the association of CRS and HIPEC[34] but some ongoing randomized clinical trials are meant to assess the clinical efficacy of this therapeutic approach[35].

Two recently published systematic reviews, which analysed almost all the available international literature, concluded that this comprehensive treatment modality is a viable option in the management of patients with advanced EOC (stage Ⅲ e Ⅳ disease), with potential benefits comparable with the current standard of care (conventional secondary cytoreduction or systemic chemotherapy)[3,4].

Practical implications at the basis of CRS and HIPEC has been presented on previously published studies focused on the quality of life (QoL) post procedure[23,24,36-40]. All of these studies, however, are limited by the fact that disability was not measured according to the conceptualization of disability endorsed by World Health Organization (WHO)'s International Classification of Functioning, Disability, and Health (ICF)[41] which defines disability as the relationship between one's health condition and environmental factors expressed in activity limitations and/or participation restrictions.

No article was found regarding the use of an ethical advice for decision making in case of advanced EOC. Few physicians sought external ethical advice and decisions were entirely taken by the medical team. Direct involvement of family and treating physician was limited[42]. The main goal of this paper is to offer ethical consideration useful for decision making for advanced EOC, when HIPEC represents a radical treatment for patients where the choice of no treatment may be acceptable since definitive cure is unlikely.

RESEARCH

In this article we presented one case of advanced EOC (stage Ⅳ) treated with CRS and HIPEC with favourable outcome (grade 1) in term of Common Terminology Criteria for Adverse Events (CTAE)[43] classification after 1 year of follow-up. The patient gave written informed consent to this case presentation.

We discussed the case after 1 year with the main specialists involved in the care process: surgeon, oncologist, anaesthetist and intensivist.

We reviewed the entire decision making process taking into consideration the risk/benefit of the procedure in term of mortality/morbidity, quality of life and psychological profile of the patient 1 year after surgery.

A clinical psychologist and a bioethicist philosopher took part at the discussion.

CASE PRESENTATION

Clinical picture

The patient was a 64-year-old woman. Twenty-seven years ago she had a breast cancer, initially treated with quadrantectomy and chemotherapy and after a relapse treated with mastectomy and chemotherapy in 2001; consecutive follow-ups were negative.

In December 2011, an advanced EOC (FIGO stage Ⅳ) was diagnosed. She underwent total body computed

tomography-scan that showed a pelvic mass with massive ascites and pleural effusion positive for tumor cells. The diagnosis of an EOC serous type was made by transvaginal biopsy. Markers were elevated (CA125: 500 U/mL). She had 6 cycles of neoadjuvant chemotherapy with carboplatin (CDDP) and paclitaxel (PTX) with partial clinical response according with Response Evaluation Criteria In Solid Tumors criteria: the CA125 concentration was significantly diminished (75 U/mL); positron emission tomography scan was negative.

In June 2012, a month since chemotherapy, the patient underwent cytoreductive surgery with HIPEC: the Peritoneal Cancer -Index score was 5 and at the end of surgery no macroscopic residual disease was detected (Completeness of Cytoreduction 0[29]). She was discharged after 19 d: during the hospital stay she developed a severe thrombocytopenia (platelets < 20000). After two months from the surgery she underwent 3 cycles of adjuvant chemotherapy with CDDP and PTX. At the bioethical conference (12 mo since surgery) she was alive with no evidence of relapse.

Decision making: A surgical point of view

When the patient received the communication of the advanced EOC, she lived the diagnosis as a sentence that triggers the sense of the end.

Patient simplified a lot her condition. The main question was: "How much time remains and will I suffer from it?" She asked for a longer life and does not ask for quality of life. Surgeon spoke with her clearly. "Advanced EOC lead the patient to die with bowel occlusion without treatment. CRS and HIPEC allows a five years cancer-free in 15%-20% of the patients". He proposed this option as an experimental treatment conducted in a clinical trial. Patient and her family had two weeks to decide what to do. The crucial problem was the level of invasive treatment proposed. This consultation has the difficulty to balance the incidence of EOC recurrence and post-operative complications of CRS and HIPEC against the optimal front-line chemotherapy including a combination of platinum analogue and taxane.

Psychological profile one year after procedure

The patient accessed the interview willingly. Lucid and oriented over space and time, reality testing was intact. Attention, memory and concentration appeared to be adequate. Psychopathology history was negative. She constructs her history anchoring the events of illness that saw her, a 39-year-old woman with two young daughters, dealing with the cancer disease.

Her narration shows the presence of a lively temperament and determined character. When the disease and other tragic events, such as the loss of their first child at the end of pregnancy, have taken place in her life, she dealt with confidence in the doctors and her resources, but, at the same time, aware of the risks present.

She describes her husband as a person of few words, but with which she has a solid relationship characterised by the sharing of everyday life. Even the daughters, both married and with children, along with extended families, are a significant landmark and, even in the event of illness, were present and supportive.

When she dwells on the surgical procedure repeats several times: "if I had known that this recovery would have been so hard..." but then she concludes, "but my daughter says that I would have done the same".

In particular, she recalls the fear experienced in the post-intervention linked to the perception of a body that did not respond to commands and a shooting time that it seemed very long. Scar tissue are frequently emphasised in her speeches to husband that minimizes, and through some ironic joke, contributes to the acceptance the lady is building towards a change in her body.

She complains a strong weakness on the afternoon during which she stays in a chair for a long time. On the morning she perceives herself, in continuity with her whole life, as active and energetic; on the afternoon she seats throughout the rest of the day in an armchair because of fatigue. This situation forces her to a lifestyle in which she does not recognize. People do not always understand this fatigue, but the spur of the others makes her nervous.

ETHICAL CONSIDERATIONS

CRS is associated with morbidity and mortality and it is difficult to determine whether mortality and morbidity occurring after major CRS and HIPEC is caused by the surgery or the HIPEC or by the natural history of the EOC disease. Chua *et al*[4] reviewed 19 studies including CRS and HIPEC and found mortalities between 0% and 10% from any cause within 30 d of surgery. Postoperative events are common but mostly grade I (self-limiting) or grade Ⅱ, requiring only medical treatment for resolution[35]. Grade 1 events occurred in 22 of 30 (73%), including transient nausea and vomiting, diarrhea, thrombocytopenia, and pleural effusion. One or more grade 2 events occurred in 27 patients (90%), including nausea and vomiting, cardiac arrhythmia, hypertension, diarrhea, pleural effusion, line sepsis, and increased creatinine. Twelve patients (40%) experienced 1 or more grade Ⅲ complications that required invasive intervention, including anemia, pleural effusion, pneumothorax, fascial dehiscence, diarrhea, ileus, and pancreatic leakage.

The use of HIPEC in EOC is aimed at reduction of the high rates of recurrence following standard treatment. CRS and HIPEC allows a five years cancer-free in 15%-20% of the patients with EOC. Experience reported in the literature is increasing, but there are no randomized clinical trial to date[34] and HIPEC still represents a radical treatment for patients where the choice of no treatment may be acceptable since definitive cure is unlikely.

For this reason HIPEC in EOC should ideally be performed on a research protocol or their data prospectively collected in registries such as the Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer registry[35]. Every study should always be functional to the patient. It's important to ensure that the patient does not become sub-

ordinate to a research protocol because the feasibility of a treatment does not exhaust the question. Medical code of ethics states "Every treatments that affect the integrity and the mental and physical strength of the patient may be implemented, following an assessment of care needs, and only in order to obtain a real clinical benefit to the patient or alleviate their suffering. The doctor, also taking into account the patient's wishes if expressed, must refrain in diagnostic and therapeutic treatments from which we can't reasonably expect a benefit to the health of the patient and/or an improvement in quality of life"[44].

Even if the case presented had a good outcome (grade I as defined by CTAE classification), the patient has a strong weakness one year after CRS and HIPEC that forces her to a lifestyle in which she does not recognize herself. She says "if I had known that this recovery would have been so hard..."

In this complex situation the bioethical question is crucial.

Bioethics should be meant as the critical conscience of technological civilization that moves philosophical questions on the significance of the construction of human identity within the technological action. In this context the need to think of the technological process, involves the whole person and belongs to each person[45]. This "critical" enterprise should be participated by all those who, from different perspectives and with different cultural backgrounds, are interested in understanding the historical condition of contemporary human being. The field of bioethics is not derived solely from the fact that what is being discussed is theoretically and practically complex, but for the reason that the truth is an ethical judgment from the empirical data of other sciences. Bioethics loses its specificity if it does not examine the historical condition in which it addressed the question of life today: the binomial life-ethics placed inside the filter with which the experimental sciences think and govern the phenomena of life[45].

For this reasons the ethical data can never be an element that arises at the end of a process. We can't move the ethical question only when the evidence based medicine is uncompleted, as in EOC, because the wellness of the patient is not a clinical judgment. The ethical aspect can never be separated from the clinical practice because every human act has an ethical value and its lawfulness does not end in an appropriate technical gesture. It's necessary to make explicit the anthropological aspect that influences clinical decisions.

A help to the analysis of the situation of the patient can came from the platform World Health Organization-International Classification of Functioning, Disability and Health (WHO-ICF), that permits evaluation of the person in relation to the psycho-social context[41]; it also should help researchers and clinicians to reinterpret terminology or expressions they use daily, such as quality-of-life, proportionality, informed consent, rights, autonomy, vulnerability, discrimination, participation, from the perspective of ethics[46].

The ICF introduces a new conceptual and operational model that promotes a new vision of health and disability, and it is based on the definition of disability as a "difficulty in functioning at the body, person, or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors"[47]. Usually, physicians hypothesize the existence of a strict relationship between the patient's health related quality of life (HRQoL) and disability: the higher the disability is, the more impaired the HRQoL. All of these studies, however, are limited by the fact that disability was not measured according to the conceptualization of disability endorsed by WHO's ICF[41,48]. Therefore, changes in HRQoL or in disability profiles are again only explained by changes in a person's intrinsic health state. Patients reporting worse health status also reported higher levels of disability and lower quality-of-life. This finding shows that not only an objective, namely medically assessed, health status is related to quality-of-life and disability, but also health status perceived by patients is an important aspect to understand quality-of-life and disability[49]. A person-centered approach and assessment of health-related quality-of-life and disability in EOC survivors are of central importance. In fact, persons who experienced CRS and HIPEC, including those who are not severely affected anymore, report a substantial impact of the disease on some areas of participation[22,23,36-40]. For this reason, the identification of participation areas that are mostly affected by the disease can provide useful inputs to guide rehabilitation and care. For example, younger people not only have different rehabilitation needs and personal resources compared with older persons but also encounter different opportunities in tackling daily life difficulties in their workplace, community, and other settings. They experience the environment in different ways. In this sense, seeing the person in the interaction with the environment might explain why self-reported levels of health, disability, and HRQoL change among persons. Exploring the HRQoL in term of ICF's concept allows to evaluate the person in relation to the psycho-social context and to define the proportionality of the treatment. There is a strictly clinical judgment on the proportionality which defines the cost-benefit of the treatment, but also the patient point of view determines the proportionality. The tolerability of the condition takes part in the determination of proportionality, which has not to be confused with the expectations of the patient. Tolerability must be evaluated in term of pain but also in term of feeling of suffering. Treatment planning with the patient helps to assess the tolerability. The evaluation of feasibility of CRS and HIPEC considering the concept ICF "of disability and functioning" can help both doctor and patient to decide not only in term of survival, but also in term of HRQoL. The final decision must come from a doctor-patient negotiations (and not from a contractual process), in which the doctor has to be aware that the decision making is never equal.

The informed consent stays at the end of this com-

munication process and requires enough time to create an adequate relational context. The patient's informed decision not exhaust the relationship, but still remains a working progress where the patient should have the chance to change his decision, because the psico-social context may change.

Some data suggest that when patients fully understand their situation as a "terminal state" they are less likely to submit to extensive, life-threatening or QoL-threatening therapies[50,51].

It is likely that any treatment will impair QoL, at least in the short-term. However, like health, quality-of-life as well is the result of the interaction of many elements. Consequently, both the attribution of a complete subjective meaning to this concept and its transformation into a mere quantitative parameter should be avoided[46]. On the one hand, emphasizing the concept of the quality-of-life by drawing on people's subjective experience (desires, expectations, projects, *etc*.) involves the loss of the intersubjective perspective, which establishes the relationship between rights and duties. On the other hand, focusing on the quantitative parameters, that are more easily measured, may determine misunderstandings in the assessment of the relevance of the quality-of-life for the individual. All of that implies a new idea of well-being: the quality of life also derives from the quality of relationships[46].

The aim of the article was not to suggest an interventional protocol to guide the decision, but an EOC patient-centered ethical approach through the platform WHO-ICF that permits evaluation of the patient in relation to the psycho-social context. This approach may improve the decision making process of both patient and doctor without removing individual responsibility.

CONCLUSION

The need to raise the subject of disability as a relationship between environment and pathological condition derives from a single fact: the changes in the living conditions in Western societies resulting from scientific and technological progress made it possible for an ever increasing number of people to live with their disease, with their impairments. The recognition of this fact is useful in addressing, not only issues related to the disease (which can be only partially addressed), but also for environmental intervention planning and it is therefore crucial to think of the treatment relationship as a question of justice[52].

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CASE REPORT

Metastasis to a uterine leiomyoma originating from lung cancer: A case report

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Abstract

The uterus is an uncommon site of metastasis especially from a primary lung adenocarcinoma. More frequently, extragenital primary tumours, including lung cancer, metastasize to the ovaries. In the literature, lung cancer metastasizing to the uterus is rare and has been reported to involve the endometrium and uterine serosa. Here, we report an unusual case of a 58-year-old woman who had a history of lung adenocarcinoma with subsequent metastasis to a single uterine fibroid only. The patient was known to have a long history of asymptomatic fibroids. In 2008, she was diagnosed with lung adenocarcinoma which was treated with primary surgery and adjuvant chemotherapy. Four years later, a routine abdominal computerised tomography scan showed an enlargement of the fibroid and she underwent a hysterectomy and bilateral salpingo-oophorectomy. Pathology reported a lung adenocarcinoma metastatic to the uterine leiomyoma with a similar morphology to the original pulmonary malignancy and this was confirmed with immunohistochemical staining. She had no evidence of metastatic disease elsewhere. The final diagnosis was metastasis of a primary lung adenocarcinoma confined to a uterine leiomyoma. Our patient also fulfilled the criteria for a phenomenon called tumour-to-tumour metastasis in this case a primary malignancy having metastasized to a benign tumour. In conclusion, metastasis of a primary lung cancer to the female reproductive tract has been documented, but clinicians should also be aware that metastasis to benign gynaecological tumours such as fibroids can also occur, especially in the setting of tumour-to-tumour metastasis. In addition, the clinical history and use of immunohistochemistry are invaluable in reaching a diagnosis.

Key words: Uterine metastasis; Lung cancer; Metastasis to leiomyoma; Tumour-to-tumour metastasis; Lung adenocarcinoma metastasis; Metastasis to female genital tract

Core tip: Our paper describes a rare occurrence of metastasis from a lung cancer to a uterine leiomyoma only without involvement of the endometrium, serosa or adnexae. This has not been reported in recent literature. We also describe the utility of immunohistochemistry in reaching a diagnosis which was essential in our patient who was asymptomatic-unlike those previously reported. The phenomenon of "tumour-to-tumour" metastasis, which not many gynaecologists have heard of, is also described in our report. The importance of knowing that the formation of metastasis to the female genital tract, although uncommon, is highlighted.

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INTRODUCTION

Lung cancer metastasizes most frequently to the regional lymph nodes, the surrounding pulmonary structures, the liver, adrenal glands, bones and brain. Metastasis of this common malignancy to the female genital tract is unusual and specifically to the uterus, is rare. A review of the literature shows that the commonest site in the female genital tract to be affected by pulmonary metastasis is the ovary, with several cases documented so far[1-4]. Lung metastasis to the uterus is much rarer. To our knowledge, there have been only two cases of non-small cell lung cancer (NSCLC) with metastasis to the uterus reported in recent years - one to the uterine serosa and the other to the endometrium[5,6].

Here we report a rare case of an asymptomatic postmenopausal woman with lung cancer metastasis to a uterine leiomyoma.

CASE REPORT

In July 2008, a 54-year-old postmenopausal Chinese woman, para 3, was diagnosed to have a non-small cell lung cancer. She had presented only with a cough of a six weeks' duration and a computed tomography (CT) scan of the thorax, abdomen and pelvis showed a 22 mm × 20 mm upper lobe left lung lesion. An incidental 150 mm × 150 mm uterine fibroid was also noted (Figure 1A). After a left upper lobectomy and lymphadenectomy her recovery was uneventful. Histology confirmed a poorly differentiated adenocarcinoma with 2 out of 3 left hilar lymph nodes involved. The resection margins were free on tumour and the inferior pulmonary ligament lymph nodes were not involved. The tumour cells were positive for thyroid transcription factor-1 (TTF-1). She was staged as ⅡA NSCLC (T1N1M0). She received adjuvant chemotherapy with cisplatin and vinorelbine and remained disease free at subsequent follow-ups. The patient was a non-smoker whose only medical history was that of uterine fibroids which she had had since her first pregnancy, 23 years earlier. For her subsequent visits, a metastatic surveillance for the primary lung cancer was carried out with yearly CT scans of the thorax, abdomen and pelvis. No further imaging, *e.g.*, ultrasonography was performed for the uterine fibroid.

In September 2012, the patient was referred to our Department of Obstetrics and Gynaecology. The uterine fibroid had increased slightly in size (170 mm × 160 mm) causing bilateral hydronephrosis noted on the annual CT scan done for metastatic surveillance (Figure 1B). There was no evidence of disease recurrence and the patient remained completely asymptomatic. Clinically, she had a firm, regular, mobile 22-cm uterine mass palpable. Transabdominal and transvaginal ultrasonography revealed a cystic degenerative uterine mass (137 mm × 123 mm × 104 mm) with no increased vascularity demonstrated on Doppler studies suggesting a uterine leiomyoma (Figure 2). The ovaries were not visualised and endometrium was thin. Pap smear and renal function were normal. She underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy in October 2012. Intra-operatively, a 24-wk size uterus was found with atrophic tubes and ovaries, all of which were removed intact to avoid any disease dissemination. The specimen was then cut open intra-operatively to confirm the impression was that of a degenerated fibroid with a cystic cavity filled with brownish fluid and some calcifications (Figure 3). The patient recovered uneventfully. The final histology report showed a poorly differentiated carcinoma consistent with metastatic lung cancer showing similar morphology to the previous pulmonary malignancy. Immunohistochemical staining was strongly positive for TTF-1 and cytokeratin (CK) 7. The lesion was confined to the leiomyoma with no involvement of the endometrium, cervix or adnexae (Figure 4). The resection margins were free of tumour.

Subsequent metastatic survey with CT and bone scans was performed and did not show any disease. At her last follow-up in May 2013, she remained in remission with no evidence of recurrence and was clinically well.

DISCUSSION

The most common extragenital primary sites resulting in metastases to the uterine corpus are the breast (42.9%), colon (17.5%), stomach (11.1%) and pancreas (11.1%). The lung accounts for less than 5% of extragenital primary tumours and most of these are adenocarcinomas, the most frequent subtype of NSCLC[7].

In recent literature, there have been two reported cases of NSCLC with metastasis to the uterus. The first case involved a patient who presented with postmenopausal bleeding and a uterine lesion on surveillance positron emission tomography/CT imaging. She had had previous lung resection for NSCLC 3 years earlier. Sixteen months post-operatively, she developed suspicious mediastinal lymphadenopathy. An endometrial sampling showed uterine carcinosarcoma and subsequent hysterectomy and bilateral salpingo-oophorectomy revealed that besides the carcinosarcoma, there were other neoplastic foci in the uterine serosa, adenexae and cervix consistent with metastatic lung cancer[5]. The second case described a patient with advanced stage NSCLC treated with primary chemotherapy. Ten months after completing treatment, she complained of vaginal bleeding and ultrasonography showed an endometrial thickness of 10 mm. An endometrial biopsy confirmed endometrial metastasis from the primary lung cancer. A hysterectomy was not performed for this patient due to her clinical condition and advanced disease[6]. In both these cases, the patients had clinical symptoms (abnormal vaginal bleeding) and radiological abnormalities suggestive of a uterine malignancy. Differently from these reports, our patient was completely

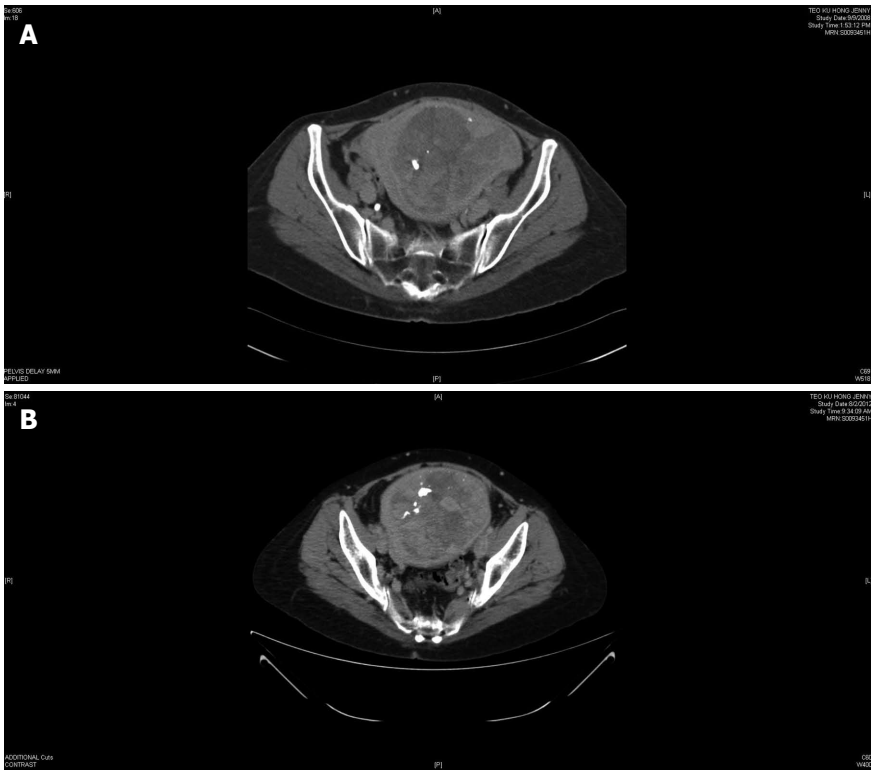

Figure 1 Computed tomography scan of the pelvis showing fibroid uterus. A: August 2008; B: September 2012.

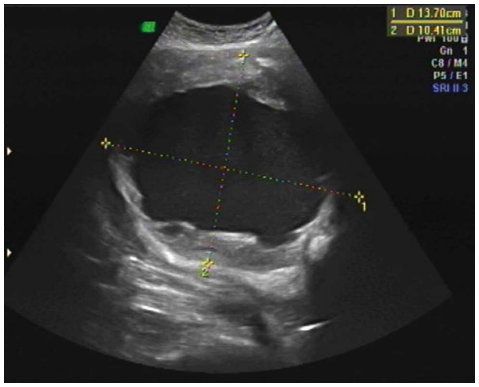

Figure 2 Transabdominal ultrasound showing fibroid with cystic degeneration.

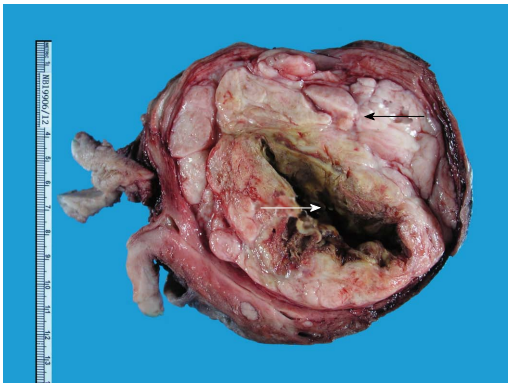

Figure 3 Hysterectomy specimen showing myometrial fibroid (black arrow) with cystic cavity (white arrow).

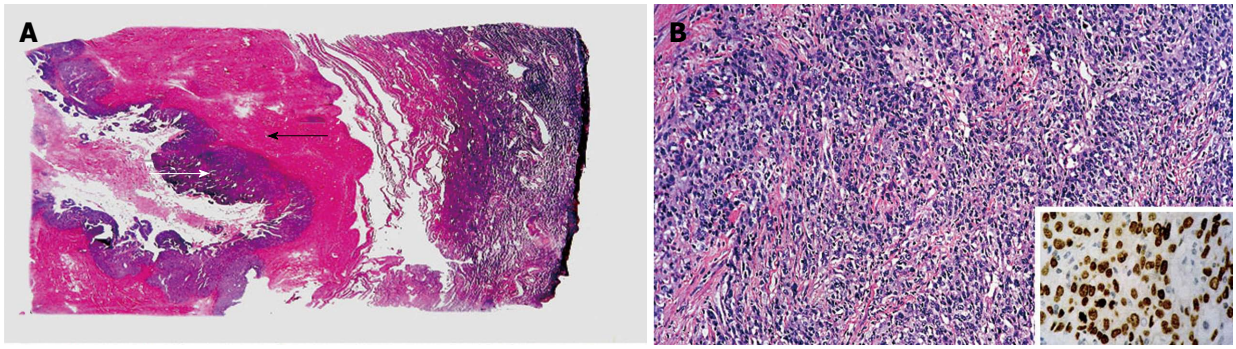

Figure 4 Histopathology. A: Tumour cells (white arrow) surrounding cystic cavity and the leiomyoma (black arrow); B: Sheets of malignant cells and those staining positive for thyroid transcription factor-1 (inset).

asymptomatic, had no evidence of disease progression or recurrence for 4 years since her initial diagnosis of lung cancer, had a long history of fibroids and there was no radiological suspicion of metastatic disease. She had not

experienced any abnormal vaginal bleeding and the endometrium was thin thus an outpatient endometrial sampling was not performed unlike the previous cases. As the overall pre- and intra-operative impressions were that of a leiomyoma only, we performed an extrafascial hysterectomy and salpingo-oophorectomy without surgical staging. The clinical picture here was neither consistent with a primary uterine malignancy nor with metastasis of a lung malignancy.

Although pathological examination did reveal leiomyoma, the final diagnosis was clinched by immunohistochemistry which is valuable in proving the primary origin of the malignant component. TTF-1 is a protein which stains positively in pulmonary adenocarcinomas and is sensitive and specific for respiratory and thyroid malignancies[8]. In this patient, her initial histology showed a lung cancer which stained for TTF-1 and the subsequent pathology report of the hysterectomy specimen also showed tumour cells similarly positive for TTF-1, ascertaining the pulmonary origin of the lesions in the leiomyoma. CK staining with CK7 and CK20 is also useful in distinguishing primary and metastatic lung adenocarcinomas from other malignancies, *e.g.*, colorectal tumours. Primary and metastatic pulmonary adenocarcinomas show a typical $CK7^{+}/CK20^{-}$ staining pattern which was comparable in our case, corroborating the diagnosis of lung cancer with metastasis and excluding a primary uterine malignancy[9].

Other metastatic sites in the female genital tract originating from the lung that have been reported include the cervix and vagina and these are rare too. In their analysis of 325 cases with metastasis to the female genital tract, Mazur *et al*[1] found that in 149 cases, the origin of the primary tumour was extragenital, the remainder being intragenital metastases. The ovaries and vagina were the most frequent sites of metastasis and most of these extragenital primaries were adenocarcinomas of the gastrointestinal tract.

Tumour-to-tumour metastasis was described by Campbell *et al*[10] by the following strict criteria: there must be > 1 primary tumour, the recipient tumour being either benign or malignant (a leiomyoma in our case); the donor tumour must be a proven malignancy (lung adenocarcinoma in our case) and this must metastasize with an established growth in the recipient tumour. Finally, a pre-existing lymphoma must be excluded should metastatic lymphadenopathy occur. Our patient fulfils all the criteria for this uncommon phenomenon and to date, about 60 cases of metastasis from a malignancy to a benign tumour have been reported[11].

In conclusion, metastasis from a lung adenocarcinoma to the female genital tract is uncommon and to a uterine leiomyoma only is rare. Even in an asymptomatic patient with a long-standing history of a benign condition like fibroids and with no clinical evidence of disease recurrence for a few years, one should be aware that the formation of metastases can occur. The history of the initial disease and the use of immunohistochemical markers like TTF-1 and CK7 are essential in distinguishing between a primary versus metastatic uterine adenocarcinoma and localizing the pulmonary origin. Although there are not enough data to quote a prognosis for this patient, it would seem optimistic at this point as the metastatic survey post-operatively was negative and the metastatic tumour was completely resected with clear margins.

COMMENTS

Clinical diagnosis

The clinical findings were that of a firm, regular, 22-cm uterine mass on abdominal and pelvic examination with a normal cervix and no adnexal masses.

Differential diagnosis

The possible differential diagnoses of the pelvi-abdominal mass were a uterine fibroid, which was the most likely given the long-standing history and lack of symptoms, a uterine sarcoma or an ovarian pathology, which were less likely in view of the history, lack of symptoms and clinical findings.

Laboratory diagnosis

Laboratory testing did not contribute greatly in this case and the main methods were a full blood count, renal function test and Pap smear cytology which were all normal.

Imaging diagnosis

A computed tomography scan of the thorax and abdomen was done which showed no recurrent lung disease but slight enlargement of the uterine fibroid causing upper urinary tract dilatation - this was confirmed on ultrasonography which was suggestive of degenerating uterine leiomyoma.

Pathological diagnosis

The gross pathological finding was that of a degenerated fibroid with a cystic cavity and the microscopic findings were that of metastasis of the original lung cancer to the uterine leiomyoma which was confirmed with immunohistochemical staining for thyroid transcription factor-1 (TTF-1) and cytokeratin (CK) 7.

Treatment

The treatment for the primary lung cancer was left upper lobectomy and lymphadenectomy with adjuvant chemotherapy and for the metastatic disease to the uterus, the treatment was total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Related reports

Other contents would include the pattern of metastasis of primary lung cancer, *i.e.*, mainly to the regional lymph nodes and liver/brain and the possibility of haematogenous spread to more distant organs like the uterus in this case.

Term explanation

TTF-1 is a protein nuclear transcription factor that is expressed in lung and thyroid tissue and is used in anatomic pathology as a marker to determine if a tumour arises from the lung or thyroid. CK7 is a protein found in the glandular epithelium of thyroid and breast tissue but not in others like the colon or prostate. It is commonly used in conjunction with CK20 to distinguish between colon cancer and other types *e.g.* ovarian.

Experiences and lessons

Large uterine masses in the presence of a known primary malignancy may be associated with secondary (metastatic) disease rather than the commonly assumed primary uterine pathology.

Peer review

The article reminds us that when clinicians encounter pelvic masses, it is important to think beyond the commoner gynaecological pathologies, especially in the setting of a known primary malignancy. The authors also aim to increase awareness of the phenomenon of "tumour-to-tumour" metastases and the value of immunohistochemistry in reaching a diagnosis to educate readers on these less commonly used but essential methods.

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

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

Volume with supplement

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No volume or issue

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

Books

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Electronic journal (list all authors)

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

Patent (list all authors)

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

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